

PRINCIPLES OF NEUROLOGY

Edited by
Sławomir Budrewicz, Justyna Chojdak-Łukasiewicz,
Anna Pokryszko-Dragan, Magdalena Koszewicz,
Krzysztof Słotwiński



Principles of Neurology

Script for Medical Students

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WROCLAW
MEDICAL UNIVERSITY

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e-ISBN 978-83-7055-707-2

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Wrocław 2026

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PART 1
BASICS

1. Neurological examination with interpretation

Magdalena Koszewicz, Konstanty Gurański

The neurological examination in everyday practice consists of:

- 1) Observation of the patient, establishing verbal contact, and taking a medical history;
- 2) A physical examination, which includes:
 - assessment of the general medical condition,
 - assessment of the neurological condition,
 - assessment of cognitive function (neuropsychological examination).

Observation, Verbal Contact, and Medical History

First impression

At the first encounter, careful observation of the patient's gait, posture, use of the limbs, and any involuntary movements provides insight into their general condition and possible neurological disorders. The clinical importance of these features in diagnosing neurological diseases will be discussed in later sections. The presence of a companion may indicate reduced independence due to physical disability or cognitive impairment.

Interview/medical history

The basis for choosing the right diagnostic algorithm is the skillful establishment of contact with the patient and a properly taken, targeted medical history. However, in some patients, a medical history may be impossible to take. This applies to patients with disorders of consciousness or speech impairments. A complete history should include:

- **Personal data:** information about family status, social and living conditions, use of stimulants or additive substances, occupation, and potential occupational exposures;
- **Current illness:** present complaints, and the immediate reason for reporting to a neurologist;
- **Past medical history:** previous neurological and general medical conditions, surgeries, hospitalizations, and treatments received;
- **Family history:** with special attention to hereditary or familial neurological diseases.

Physical Examination

General medical examination

This part of the assessment follows the basic standards given in internal medicine textbooks and includes:

- **General appearance:** body habitus, nutritional status, condition of the skin and appendages, developmental anomalies;
- **Cardiorespiratory system:** auscultation of the lungs and heart, blood pressure (RR), heart rate (HR), and assessment of peripheral circulation;
- **Palpation:** abdomen, thyroid gland, lymph nodes;
- **Additional investigations, if abnormalities are found:** laboratory tests, imaging studies, or electrophysiological examinations.
- **Assessment of skin color and temperature,** sweating, cutaneous reflexes (dermographism), together with assessment of pupil size and reactivity, blood pressure, heart rate, and respiratory rhythm, form the basis of autonomic nervous system function testing.

Neurological Examination

Cranial nerves

Before examining the cranial nerves (CNs), the head and face should be carefully inspected. Attention is paid to the shape and symmetry of the skull, head position, condition of the skin and hair, and facial expressions. Palpation of the head may reveal anatomical abnormalities. Auscultation of the head and neck can help detect vascular bruits. Each cranial nerve must be examined separately on the right and left sides, and the results compared.

Olfactory nerve (cranial nerve I, CN I)

The olfactory nerve consists of 15–20 olfactory filaments. Its examination includes:

- **Exclusion of local causes:** assessment of the nasal mucosa and exclusion of obstruction of the nasal passages;
- **Subjective testing of smell:** with the patient's eyes closed, familiar odors (e.g., coffee, soap, or standardized test substances in tubes or markers) are presented to each nostril separately, while the opposite nostril is occluded. The patient is asked to describe the smell.

Optic nerve (cranial nerve II, CN II)

Although called a “nerve”, CN II is developmentally an outgrowth of the prosencephalon and lacks the typical features of a peripheral nerve. Its examination includes:

- **Visual acuity:** assessed by counting fingers at a distance of ~6 m or using a Snellen chart;
- **Visual fields:** initially by confrontation (orientation test) comparing the patient’s perception of moving fingers in horizontal and vertical planes with that of the examiner. Abnormalities must be confirmed with perimetry or eye-tracking methods;
- **Fundoscopy:** ophthalmoscopic evaluation of the optic disc, noting its color, margins, degree of elevation, vascular pattern, presence of hemorrhages, or pigmentary changes.

Oculomotor, trochlear, and abducens nerves (cranial nerves III (CN III), IV (CN IV), and VI (CN VI))

These three nerves innervate the external and internal muscles of the eyeball and are therefore examined together. Their examination includes:

- **Position of the eyes:** alignment and symmetry of the eyeballs;
- **Palpebral fissures:** width and symmetry;
- **Eye movements:** the patient follows the examiner’s finger in horizontal and vertical directions. Smoothness and range of motion are evaluated. Nystagmus, if present, is usually most evident in extreme gaze positions;
- **Pupillary responses:** assessment of pupil size, shape, and symmetry, as well as their reactions to light and accommodation.
- **Double vision (diplopia):** a subjective symptom of paresis of the extraocular muscles. It typically worsens when the patient looks in the direction of the impaired ocular movement.

Trigeminal nerve (cranial nerve V, CN V)

The trigeminal nerve consists of 3 branches:

- ophthalmic nerve (v1) – sensory;
- maxillary nerve (v2) – sensory;
- mandibular nerve (v3) – mixed (sensory and motor).

The trigeminal nerve exits the brainstem at the cerebellopontine angle. Its examination includes:

- **Palpation of Valleix pressure points (trigger zones)** at the exit of the ophthalmic, maxillary, and mandibular branches, assessing tenderness;
- **Superficial sensation** (touch, pain, and temperature) tested in areas supplied by each branch;

- **Deep sensation:** assessed by examining the arrangement of skin folds on the cheeks; the patient identifies whether folds are horizontal or vertical;
- **Corneal and conjunctival reflexes:** touching the cornea or conjunctiva elicits a blink response;
- **Taste testing (optional):** assessment of taste in the anterior two-thirds of the tongue;
- **Motor assessment:** inspection and palpation of the masseter and temporalis muscles for atrophy and strength;
- **Jaw mobility:** checking for deviation of the mandible on opening, and testing the jaw jerk reflex.

Deliberation signs

Additionally, deliberation signs, which are atavistic in nature, must be examined. They reappear in adults with bilateral corticobulbar tract lesions. These include:

- **Palmomentary reflex:** stroking the patient's palm causes contraction of the mentalis (chin) muscle;
- **Corneomentary reflex:** touching the cornea induces contraction of the chin muscles;
- **Snout reflex:** tapping near the lips with a reflex hammer causes puckering or protrusion of the lips.

Facial nerve (cranial nerve VII, CN VII)

The facial nerve exits the brainstem at the cerebellopontine angle. It is primarily a motor nerve, innervating the muscles of facial expression, the stapedius muscle, and the platysma. It is accompanied by the intermediate nerve, which carries sensory fibers (taste from the anterior two-thirds of the tongue) and parasympathetic fibers (to the lacrimal, submandibular, and sublingual glands).

Facial nerve (CN VII): lesions and examination

Facial nerve lesions can be classified as peripheral or central:

- **Peripheral lesion** (damage to the nerve or its nucleus in the pons) is manifested by muscle paresis of the entire half of the face on the side of the lesion, sometimes with hypersensitivity to sound stimuli and impaired secretion of tears and saliva, and taste disturbances in the anterior two-thirds of the tongue;
- **Central (supranuclear) lesion** (damage to corticonuclear fibers) – paresis affects the muscles of the lower half of the face contralateral to the damage.

Examination includes:

- observation of the face at rest and while speaking;
- examination of symmetry and strength of forehead creasing;

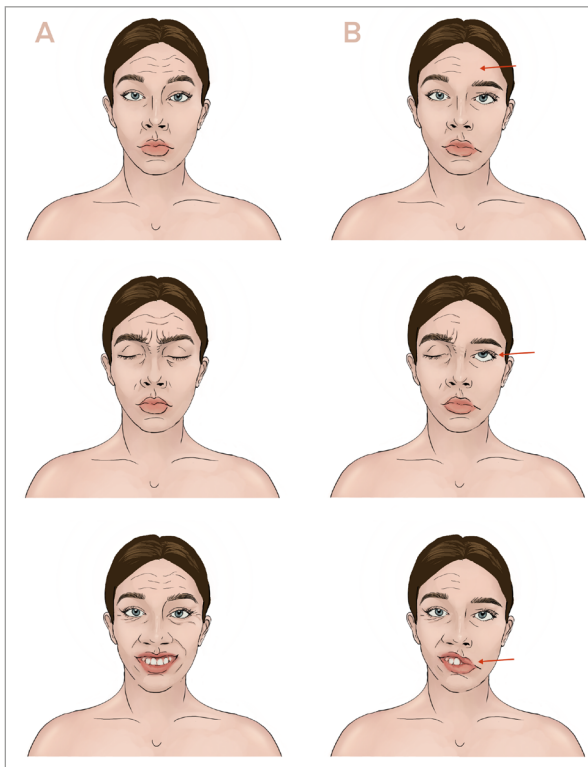


Fig. 1.1. Facial nerve.
A. Correct function of the nerve.
B. peripheral paresis of the facial nerve

- assessment of symmetry and strength of eye closure;
- assessment of symmetry and strength of showing the teeth (smiling).

Additionally, **Chvostek's sign** should be tested. A light tap with a reflex hammer over the facial nerve, just anterior to the tragus (at the “goose foot”), may induce reflex contraction of the facial muscles. A positive sign indicates tetany.

Vestibulocochlear nerve (cranial nerve VIII, CN VIII)

Examination depends on the part being assessed.

Vestibular part

- **Romberg's test:** The patient is instructed to stand with their feet together and their upper limbs stretched out in front of them. They are then asked to maintain this position first with their eyes open and then with their eyes closed. This test assesses the patient's ability to maintain balance and the direction of any potential falls;

- **Walking in a straight line:** Abnormal test involves deviation while walking in a designated straight line;
- **Unterberger's stepping test:** When taking steps alternately forward and backward (with eyes closed) there is a tendency to rotate toward the damaged labyrinth ("star gait");
- **Bárány pointing test:** The patient stretches their arms out in front of them and, with their eyes closed, makes several movements in the vertical plane. They then return their index fingers to the forefingers extended in front of them, pointing at the fingers of the person sitting opposite the examinee. In vestibular damage, both hands of the examinee symmetrically deviate toward the damage side. In cerebellar hemisphere damage, one limb deviates toward the side of the damaged cerebellar hemisphere;
- **Vestibular nystagmus:** horizontal, fine, beating away from the side of the lesion.

Cochlear part: hearing tests

- **Whispered voice test:** With one ear occluded, the patient should hear whispered words (e.g., "net", "hat") from ~6 meters. Alternative stimuli include a tuning fork, ticking watch, or finger rub;
- **Tuning fork tests** (rarely used today but of historical/educational value):
- **Weber test:** assesses lateralization,
- **Rinne test:** compares air vs bone conduction,
- **Schwabach test:** compares the duration of bone conduction in patient vs. examiner.

Glossopharyngeal (CN IX) and vagus (CN X) nerves

Glossopharyngeal nerve and vagus nerve have mixed motor, sensory, and autonomic functions. They share nuclei in the brainstem and have partially overlapping areas of innervation. The vagus nerve innervates all internal organs. Its examination includes:

- **Palatal symmetry:** observation of the palatal arches and uvula at rest and during phonation. In paresis, the affected palatal arch hangs lower, and the uvula deviates toward the healthy side;
- **Palatal reflex:** elevation of the palatal arch after stimulation with a spatula;
- **Pharyngeal (gag) reflex:** touching the posterior pharyngeal wall with a spatula elicits a gag response;
- **Taste:** optional testing of taste sensation in the posterior one-third of the tongue;
- **Voice:** assessment of resonance and vocal strength; dysphonia or dysarthria may be present;
- **Swallowing:** evaluation of swallowing difficulties (dysphagia), mainly from patient history;
- **Vital signs:** monitoring of heart rate and blood pressure, as vagal dysfunction may affect autonomic regulation.

Accessory nerve (cranial nerve XI, CN XI)

The accessory nerve consists of cranial and spinal roots (C2–C5). The cranial part, together with cranial nerves IX and X, innervates the pharyngeal and laryngeal muscles. The spinal part innervates the sternocleidomastoid muscle and the upper part of the trapezius muscles. Its examination includes:

- **Head position:** inspection for abnormal posture;
- **Muscle appearance:** evaluation for atrophy of the sternocleidomastoid or trapezius;
- **Strength of head rotation:** tested against resistance to assess the sternocleidomastoid muscle;
- **Shoulder shrug:** tested against resistance to assess trapezius function.

Hypoglossal nerve (cranial nerve XII, CN XII)

The hypoglossal nerve provides motor innervation to the tongue. A **peripheral lesion** of the hypoglossal nerve causes atrophy of the muscles of the ipsilateral half of the tongue with fasciculations, as well as weakness with deviation of the tongue toward the side of the lesion.

A **supranuclear (central) lesion** is manifested only by contralateral tongue deviation. Its examination includes:

- **Observation:** inspection of the tongue for atrophy, tremor, fasciculations, and deviation;
- **Assessment of tongue mobility;**
- **Syndrome differentiation:** distinguishing bulbar syndrome (peripheral lesion) from pseudobulbar syndrome (central lesion).

Examination of the Upper and Lower Limbs

The examination of the upper and lower limbs should include an analysis of these body parts:

- **Skin:** blood supply, temperature, color, discolorations, scars, rashes, peeling, keratoses, hemangiomas, subcutaneous nodules, etc.;
- **Structure:** symmetry, developmental disorders, muscular atrophy (diffuse or limited, e.g., related to a single peripheral nerve lesion), fasciculations;
- **Position:** normal, free or forced position of limbs, contractures, or typical postures seen in central or peripheral nervous system diseases (excluding orthopedic causes);
- **Involuntary movements:** tremor, chorea, dystonia, ballismus, myoclonus.

Limb mobility

- **Passive mobility:** the examiner assesses the ability to perform movements in each joint when the patient is relaxed;
- **Active mobility:** assessing the patient's active performance of movements in each joint.

Muscle tone

During passive movements, the resistance of relaxed muscles is assessed as an indicator of muscle tone.

- **Increased muscle tone:** typically seen in central nervous system disorders;
- **Spasticity** (also known as “clasp-knife” type) in pyramidal lesions;
- **Rigidity** (also known as “plastic” type), sometimes with cogwheel phenomenon in extrapyramidal disorders.
- **Decreased muscle tone:** typically seen in peripheral nervous system disorders, but also in central nervous system disorders such as cerebellar lesions or certain extrapyramidal disorders (hypotonic-hyperkinetic syndromes).

Muscle strength

Muscle strength is tested by having the patient perform active movements in all directions against resistance, with side-to-side comparison. Weakness of muscle strength is called **paresis**, lack of movements – **plegia**.

Paresis/plegia may affect:

- one limb (monoparesis/monoplegia);
- two limbs on one side of the body (hemiparesis/hemiplegia);
- two lower limbs (paraparesis/paraplegia);
- all 4 limbs (tetraparesis/tetraplegia).

Exceptionally, there may be muscle weakness in both upper limbs, as well as weakness of one upper limb and the contralateral lower limb, which is called **hemiplegia cruciata**.

Tests for subtle paresis:

- **Barre's test (upper limbs):** the patient makes symmetrical movements of the upper limbs up and down with eyes closed. The paretic limb moves lower and lags behind the healthy limb;
- **Barre's test (lower limbs):** the patient lies on their back with limbs bent at an angle at the hip and knee joints; the weaker limb moves down faster or falls onto the bed.

Deep tendon reflexes (muscle stretch reflexes)

Tested with a reflex hammer, always comparing both sides. Reflexes may be:

- normal – brisk and symmetrical;
- exaggerated – typical of central lesions;
- diminished or absent – typical of peripheral lesions.

Clonus (repetitive rhythmic contractions) may appear with very brisk reflexes (e.g., patellar or ankle clonus) – also typical of central lesions.

Upper limb reflexes

- **Biceps reflex (C5–C6):** tapping the biceps tendon → elbow flexion;
- **Triceps reflex (C6–C7):** tapping the triceps tendon → elbow extension;

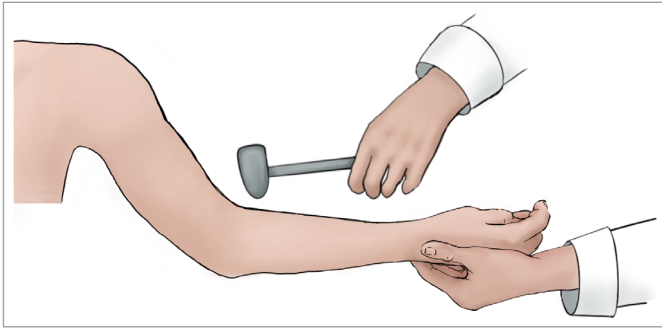


Fig. 1.2. Reflex from the biceps muscle

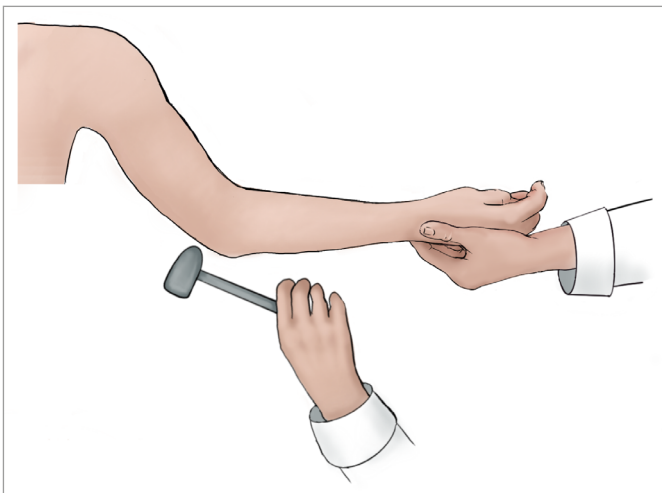


Fig. 1.3. Reflex from the triceps muscle

- **Radial (brachioradialis) reflex (C5–C6):** tapping over the radial styloid process → elbow flexion and forearm supination;
- **Ulnar reflex (C6, accessory):** rarely performed; tapping the ulnar styloid process → pronation of the forearm.

Lower limb reflexes:

- **Knee (patellar) reflex (L2–L4):** tapping the quadriceps tendon → leg extension.
- **Achilles (ankle) reflex (S1–S2):** tapping the Achilles tendon → plantar flexion of the foot.

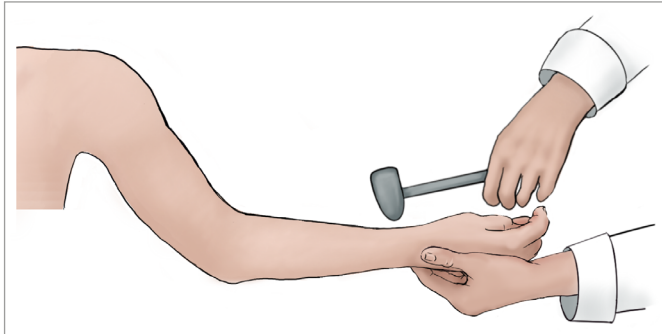


Fig. 1.4. Radial reflex

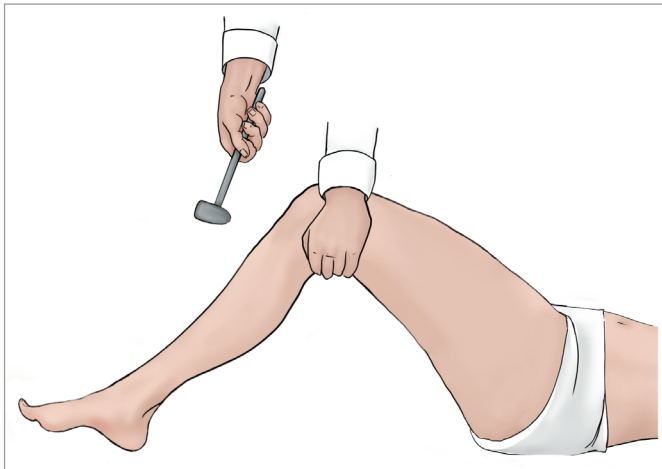


Fig. 1.5. Knee reflex

Superficial (skin) reflexes

These reflexes are polysynaptic and involve cortical pathways in addition to their spinal centers.

- **Plantar reflex (S1–S2):** stroking the sole of the foot → plantar flexion of all toes;
- **Cremasteric reflex (L1–L2):** stroking the inner thigh in males → elevation of the ipsilateral testicle.

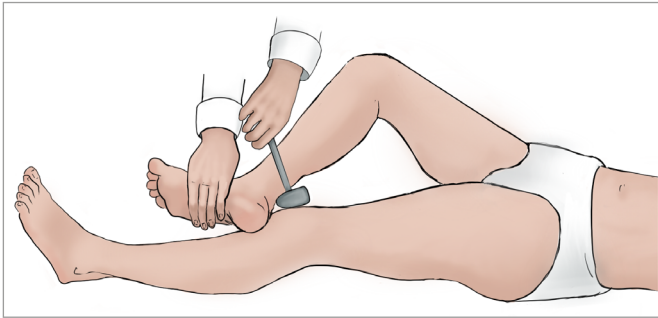


Fig. 1.6. Achilles tendon reflex

Pathological pyramidal reflexes

This group of reflexes indicates pyramidal tract (corticospinal) damage. Of greatest clinical importance is the Babinski sign and its variants.

Babinski's sign: stroking the lateral border of the sole from heel to toes → dorsiflexion (extension) of the great toe, often with fanning of the other toes (Fig. 1.7);

Oppenheim's reflex: firm stroking/pressure along the anterior surface of the tibia → great toe extension (Babinski-like) (Fig. 1.8);

Chaddock's reflex: stroking around the lateral malleolus → great toe extension (Fig. 1.9).

Gordon's reflex: strong compression of the calf muscles → great toe extension;

Rossolimo's reflex: tapping the plantar surface of the toes → flexion of the toes (Fig. 1.10);

Jacobsohn's sign (upper limb): during elicitation of the radial reflex, the fingers flex rapidly at the same time.

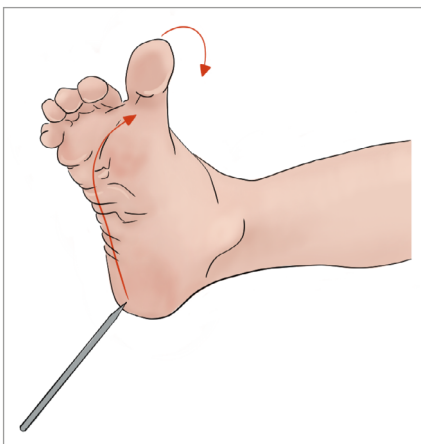


Fig. 1.7. Babinski's reflex

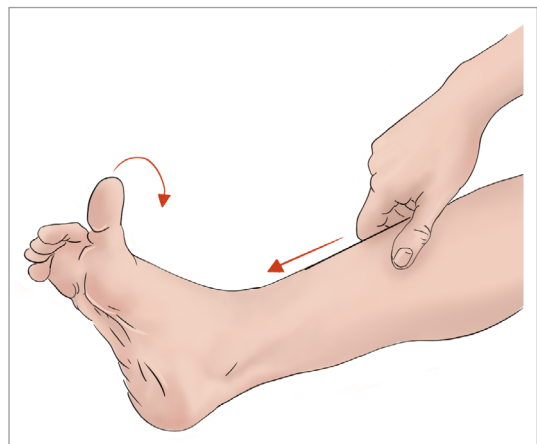


Fig. 1.8. Oppenheim's reflex

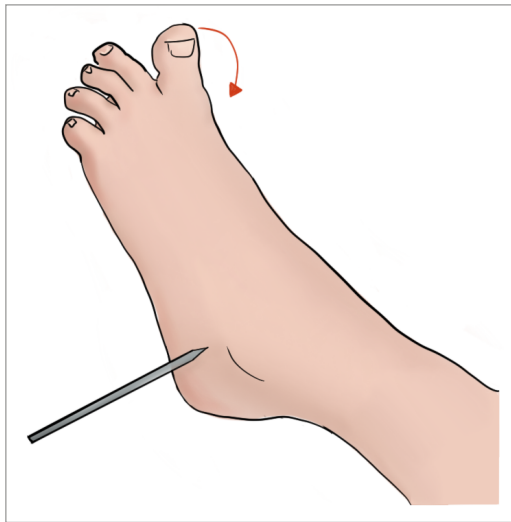


Fig. 1.9. Chaddock's reflex

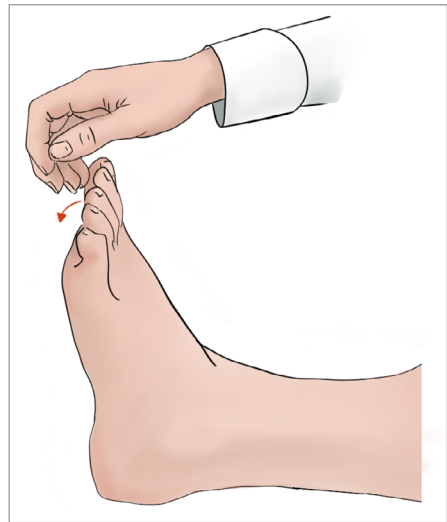


Fig. 1.10. Rossolimo's reflex

Other pathological reflexes in CNS lesions

Spinal reflexes:

- Withdrawal (shortening) reflex – flexion withdrawal of a limb in response to painful stimulus;
- Mass reflex (Riddoch's reflex) – generalized flexor response in spinal cord injury;
- Phillipson's crossed extensor reflex – extension of the contralateral limb when the ipsilateral limb is flexed.

Frontal release signs (seen in frontal lobe syndromes):

- Grasp reflex – involuntary grasping when the palm is touched;
- Bulldog reflex – forced closure of the jaw when the examiner tries to open the patient's mouth;
- Kral's sign – oral automatisms triggered by tactile stimuli around the mouth;
- Tonic plantar reflex and other deliberation signs.

Ataxia

Proper coordination of movements and their precision are controlled mainly by the cerebellum and deep sensory pathways. To differentiate cerebellar and posterior funiculus ataxia, tests are performed with eyes open and closed: closing the eyes reveals or exacerbates posterior funiculus ataxia.

Tests of coordination

- **Finger-to-nose test (or finger-to-finger test):** the patient touches the tip of their nose with the index finger (or the examiner's index finger or own fingers), first with eyes open, then closed (Fig. 1.11);
- **Heel-to-knee test:** the patient places the heel of one leg on the opposite knee and slides it down the tibia, first with eyes open, then closed (Fig. 1.12);

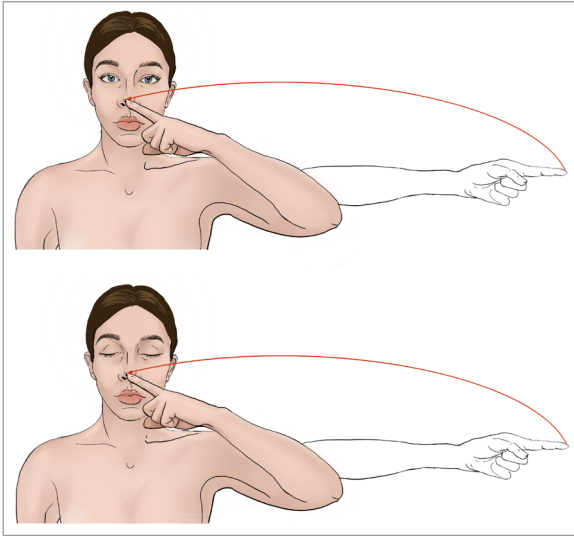


Fig. 1.11. Finger to nose test

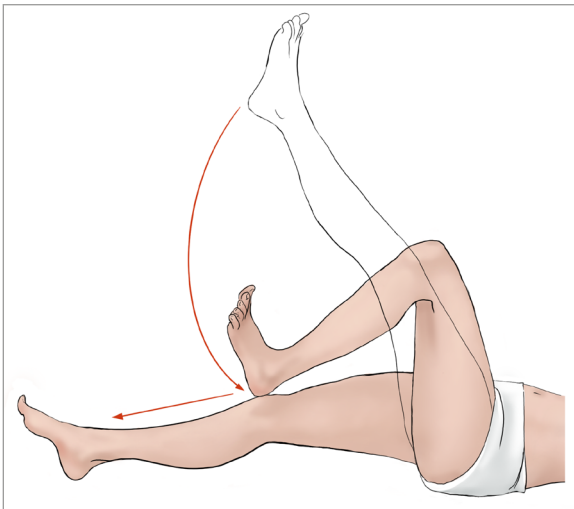


Fig. 1.12. Heel to knee test

- **Hypodiadochokinesis/adiadochokinesis:** making rapid alternating movements of turning the hands reveals their slowing down or complete inability to make such movements;
- **Rebound phenomenon (Steward–Holmes sign):** the release of the test subject's grip on the forearm should cause an almost immediate deceleration of the flexion movement by the triceps muscle antagonistic to the biceps muscle;
- **Bárány test:** see vestibulocochlear nerve examination (CN VIII).

Sensory Examination

- **Superficial sensation:** temperature, pain, touch – the examiner touches symmetrical parts of the body on the right and left sides (hemisensory disturbances) and in proximal and distal parts of the limbs (sensory disturbances of the polyneuropathic type – “gloves and socks”).
- **Deep sensation:** feeling for positioning, displacement, vibration, deep pressure:
 - **position and displacement sensing** – define the individual fingers (e.g., thumb – first finger) and the direction of movement, the patient is to determine the tested finger and in which direction it was moved;
 - **vibration sensation** is tested using a vibrating camertone (set on the bones lying just under the skin), comparing the corresponding limb regions on the right and left sides;
 - **deep pressure sensation** – the test involves stimulation of proprioceptors that respond to pressure, usually by applying strong pressure to the Achilles tendon.
 - Cortical sensation assessment (done with closed eyes):
 - **topognosis:** location of the stimulus: the examinee points to the place, where he/she felt the sensory stimulus;
 - **stereognosis:** the ability to recognize objects by means of touch;
 - **sensory discrimination:** the ability to discriminate between two acting simultaneous stimuli;
 - **dermolexia:** the ability to read letters or numbers written on the skin.

Observation of the Trunk and Trunk Reflexes

Observation of the trunk: assessment of trunk structure, skin, muscles, respiratory chest mobility.

Superficial reflexes of the trunk:

- **Abdominal skin reflexes:** irritation of the abdominal skin from the outside to the inside along the rib arches (upper abdominal reflexes, Th8–9), at the level of the navel (mid-

dle abdominal reflexes Th10–11) and along the inguinal ligaments (lower abdominal reflexes Th11–12) causes contraction of the rectus abdominis muscles;

- **Sling reflex (L1/L2):** as above;
- **Anal reflex:** irritation of the anal area causes contraction of the external sphincter muscle and retraction of the anus (S4–S5).

Sensory examination on the trunk: surface sensory testing on the trunk is performed on both sides of the body and is designed to determine the level of damage (the limit of sensation is usually 2 segments below the level of damage). Landmarks – consecutive ribs, rib arch = Th8, navel height = Th10, groin = L1.

Gait and Posture

Characteristic gaits:

- **Hemiparetic (“mowing” gait):** pyramidal hemiparesis;
- **Paraparetic gait:** spastic – pyramidal lesions, flaccid – peripheral lesions;
- **Cerebellar gait:** cerebellar disorders, gait on a wide base;
- **Posterior funiculus gait:** deep sensation disorders;
- **Shuffling gait:** in parkinsonism;
- **Waddling gait:** in myopathies;
- **Stork’s gait:** in polyneuropathies;
- **Choreic gait (“dancing” gait):** extrapyramidal, hypotonic-hyperkinetic syndromes.

Characteristic postures:

- Wernicke–Mann posture: in capsular hemiparesis;
- Bent posture, with a flexed position of the upper limbs, a roof-shaped position of the hands and resting tremor: in parkinsonism;
- Excessive lumbar lordosis: in myopathy.

Examination of the Unconscious Patient

Coma is a quantitative disturbance of consciousness. Not all elements of the neurological examination can be performed in an unconscious patient; this applies to tests that require the patient’s cooperation. Examination includes:

- Vital signs: respiratory pattern, rate, heart rate, blood pressure, temperature;
- Signs of trauma: CSF or blood leakage from nose/ear, skin appearance, odor of breath, limb posture;
- Meningeal signs.

Cranial nerves:

- Fundoscopy (papilledema, hemorrhages);
- Pupils: size, symmetry, reactivity; spontaneous movements; oculoccephalic (“doll’s eye”) reflex;
- Corneal reflex;
- Bell’s palsy (facial nerve palsy).

Limb examination:

- Spontaneous or pain-induced movements;
- Weakness/paresis: paretic limbs drop faster when lifted;
- Muscle tone, reflexes, pathological reflexes (as described above).

Assessment scales: e.g., Glasgow Coma Scale (GCS).

Nerve Root Tension Signs

Nerve root tension signs occur in patients with **radiculopathy**, which consists of sensory, motor, and less commonly, autonomic symptoms caused by nerve root pathology.

Tests to assess L4–S1 roots tension are listed below:

Lumbar (L4–S1):

- **Lasègue’s sign (Straight Leg Raise):** passive leg raising with knee extended reproduces radicular pain between 30–70°;
- **Crossed Lasègue (Fajersztajn–Krzemicki):** lifting the opposite leg causes pain on the affected side;
- **Bragard’s test:** dorsiflexion of the foot during SLR increases pain;
- **Flip (sitting root) test:** passive knee extension while seated causes the patient to “flip” backward due to pain;
- **Neri’s bowing test:** during forward bending, the patient flexes the knee to reduce pain;
- **Neri’s sign:** neck flexion in supine position provokes pain;
- **Naffziger’s test:** jugular compression reproduces radicular pain.

Femoral (L2–L4):

Mackiewicz sign (reverse Lasègue): patient prone; knee flexion with hip extension produces anterior thigh pain.

Cervical roots:

- **Spurling's test:** cervical extension with ipsilateral rotation and axial compression reproduces radicular pain;
- **Shoulder abduction (relief) sign:** abduction of the arm relieves symptoms.

Common causes of radiculopathy:

- Disc herniation (most common);
- Spondylolisthesis;
- Spinal stenosis;
- Spondylosis;
- Trauma;
- Tumors (primary or metastatic);
- Infections (spondylodiscitis, Lyme disease, herpes zoster);
- Diabetes mellitus;
- Guillain–Barré syndrome.

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2. Basics of neuropsychological examination

Krzysztof Słotwiński

Neuropsychological examination is used to assess the level of functioning of cognitive functions, higher nervous functions and thinking, as well as emotional and motivational functions. The most important elements of a neuropsychological assessment are:

- getting to know the history of the disease;
- conducting an initial anamnesis (aimed at a general assessment of the state of consciousness);
- collecting the most important information about the patient's socio-professional situation, their emotional state, and general well-being in the event of illness.

Test methods include:

The psychometric method is based on the use of tests, questionnaires, or scales that enable determining the efficiency of performing the tested function and relating the obtained results to the population average. Clinical method based on symptom analysis (syndromological) and on diagnosis of a set of neuropsychological symptoms using a clinical neuropsychological examination, which includes the assessment of cognitive functions, determining the basic disorder, and its impact on other activities that affect human behavior. The mixed psychometric and clinical method is a study in which a clinical neuropsychological examination is supported by a psychometric analysis.

Assessment of cognitive activities

Assessment of cognitive activities such as:

- **Memory** – the process of recording, storing, and reproducing experiences, events, knowledge, and acquired skills. The structural basis of memory is more or less permanent changes in synapses, modulating neurotransmission in the brain's neuronal networks, which create complex, interacting systems.

Types of memory include:

- species;
- individual;
- short-term;
- long-lasting;
- declarative (memory of facts and events);

- non-declarative (memory of learned activities and reactions to more or less complex stimuli and situations).

Selected memory tests are listed below:

- **Auditory Verbal Learning Test (AVLT)**, a so-called test for learning new words. The subject is presented with a list of 15 words (list A) in 5 separate trials, and then asked to repeat all the words they memorized in each learning trial (direct recall). After completing 5-word learning trials, a new list of 15 words is presented (list B). The subject is then asked to reproduce the remembered words from the previously presented list A (direct recall after distraction). After 15–20 min, the subject recalls the words from list A again (deferred recall).
- **Wechsler Memory Scale (WMS)** consists of 9 subtests:
 - 1) Orientation test in place, time, etc.;
 - 2) Attention test, in which the participant counts backward from 20 to 1, lists the letters of the alphabet, and counts in steps of 3 at time intervals of 30 to 45 s;
 - 3) Figure memory test, during which an abstract figure is demonstrated and then recognized in a larger set;
 - 4) A logical memory test using 2 stories told immediately and 30 min later;
 - 5) Non-verbal pairs test, testing colors, and abstract figures;
 - 6) Verbal pairs test using 8 pairs of words;
 - 7) A test of reproduction of non-verbal material, in which 4 drawings are drawn from memory;
 - 8) A test in which numbers are repeated;
 - 9) A test of repetition of spatial patterns, where a system of 8 squares is used, which must then be touched following the pattern set by the examiner.
- **Key-Osterrieth Complex Figure test (CFT)**, which involves copying a drawing of a complex figure and reproducing it from memory after 3 or 15 min.
- **Attention** – the state of activity of the sense organs and the associated cortical-subcortical areas, enabling targeted, optimal reception of stimuli with a specific meaning. The structural basis is the activation of the prefrontal cortex, parietal lobe, and thalamus. The brain centers involved in attention processes are functionally and anatomically independent of each other, although they form a network and actively interact with each other.

The following methods are used to test the concentration of attention:

- **Trial Making Test – (TMT)**, where in part A, the participant's task is to connect points marked 1–25 with a line as quickly as possible, in numerical order. In part B, the person being tested must connect the numbers with alternating letters of the alphabet with a line as quickly as possible, in the order 1–A–2–B–3–C–4–D.
- **Concentration Endurance Test – d2**, consisting of 14 lines containing 47 letters each. The participant's task is to mark the letter “d” contained in a specific graphic sign as quickly as possible, with a time limit of 20 s for each line.

- **Paced Auditory Serial Addition Test (PASAT)** in which single digits are presented every 3 s, and the patient must add each new digit to the previous one heard immediately before. Intervals between stimulations are 3 or 2 s.
- **Visuospatial functions** – the ability to perceive, analyze, synthesize, manipulate, and transform visual patterns and images. They are involved in recalling and manipulating images to maintain orientation in space and track location, the ability to determine the position of objects in space, as well as their relative position to each other, and to determine the distance of objects from each other.
Selected methods for testing visuospatial functions are:
 - **Key–Osterrieth Complex Figure Test (CFT)**, i.e., copying a complex figure according to the definition mentioned above;
 - **The Clock Drawing Test (CDT)** is used to assess visuospatial functions and enables the initial diagnosis of dementia. The participant's task is to complete the clock face with all the hours and draw hands for a specific time.
- **Executive functions** – involve the control of cognitive processes, enabling the formulation of goals, planning how to achieve them, and providing cognitive flexibility in thinking and selecting optimal strategies for solving mental tasks. They require the involvement of wide cortical and subcortical fields, neuroanatomically related to the frontal lobes, especially the prefrontal cortex. Selected executive function assessment tools are listed below:
 - **Wisconsin Card Sorting Test (WCST)** involves guessing successively changing rules for selecting cards showing patterns of geometric figures;
 - **Repeating Digits Backwards** is a part of the Wechsler Intelligence Scale. It involves repeating an increasing quantitative series of digits in the opposite order to that heard by the examinee;
 - **Ridley Stroop test**, where part I is to read the names of colors written in black font as quickly as possible. Part II is to read the names of the colors as quickly as possible, ignoring the font color they are written in;
 - **Controlled Oral Word Association (COWA)**, i.e., the Verbal Fluency Test, involves the examined person saying as many words as possible from a specific semantic category (the so-called semantic fluency) and starting with a specific letter (so-called phonetic fluency).
- **Thinking** – one of the most complex mental activities, involving extensive cortical-subcortical areas, based on concepts and images. The study of the thinking process is based on the Wechsler Intelligence Scale (WAIS) and the Raven's Progressive Matrices (RPM) test, which involves accurate completion of the presented pattern by selecting the appropriate element.
- **Higher nervous activities** – complex neural processes based on associative processes of the secondary and tertiary association cortex of individual brain lobes, with the participation of the emotional and memory system (limbic). The higher nervous activities

include speech, praxia, and gnosis. Damage to the structures responsible for higher nervous activities and/or impairment of the mechanisms of these activities results in disorders such as aphasia, apraxia, and agnosia.

Speech enables precise communication between people using appropriately ordered sound, graphic, or gesture symbols denoting a specific object, situation, or phenomenon. We specify aphasic speech disorders related to disorders of the central mechanisms shaping speech processes and dysarthric speech disorders related primarily to disorders of speech executive functions.

Aphasia – an acquired disorder in the reception of language content, its manipulation, and/or its expression in the field of language activities, caused by damage to the cortical and/or subcortical areas of the dominant hemisphere of the brain, accompanied by impairment of the central programming mechanisms of previously mastered speech activities.

The structural basis of aphasic disorders is damage to strategic areas of the dominant hemisphere of the brain for speech, located near the Sylvian fissure (Broca's areas, Wernicke's areas, temporo-parieto-occipital junction), in the peripheral areas adjacent to them, and some subcortical structures, especially the thalamus and basal ganglia, as well as the cerebellum.

Test methods for assessing the type and depth of aphasic disorders include:

- Boston Diagnostic Aphasia Examination (BDAE), Boston Aphasia Diagnostic Battery
- Aachen Aphasia Test (AAT), Aachen Aphasia Battery;
- Western Aphasia Battery (WAB);
- Goodglass–Kaplan Scale, a verbal communication scale, assesses the patient's ability to communicate in everyday situations.

Attention does not differentiate between types of aphasia.

Dysarthria – an acquired speech disorder caused by damage to the central and/or peripheral nervous system, with impairment of motor functions related to phonation, articulation, and speech fluency. The structural basis of dysarthria is damage to the primary motor cortex, corticonuclear tracts, pontine nuclei, and/or medulla oblongata. When assessing dysarthric disorders, attention should be paid to the clarity of spoken sounds, syllables, words, and sentences, the selection of which by the examiner should take into account the appropriate level of difficulty. Routine assessment of dysarthric speech disorders is usually performed subjectively – by hearing, and their characteristics are described descriptively. The value of such an examination is limited and largely depends on the doctor's experience.

Selected clinimetric methods for testing dysarthria are:

- **Susan Jane Robertson profiles** are a 5-level assessment of intelligibility in speaking and reading tests, performed by a speech therapist, relatives, and strangers.

The following are examined here:

- respiration;
- phonation;
- facial muscles;

- diadochokinesis;
- articulation;
- prosody;
- speech clarity;
- communication competences;
- swallowing.
- **Perceptual speech dimensions** by Helen J. Chenery and Bruce E. Murdoch is a 4-level assessment of speech intelligibility within the norm:
 - barely noticeable reduction in intelligibility where listener effort is required;
 - moderate lowering, which requires a lot of effort from the listener;
 - completely reduced intelligibility, where the symptom is barely recognizable speech.
 Speech disorders, both **aphasic** and **dysarthric**, are revealed already during the anamnesis, while their quantitative and qualitative assessment requires the use of appropriate methods, taking into account individual executive activities, i.e., articulation and language activities, listed below:
 - spontaneous speech (verbal fluency) – fluency, the correctness of sentence construction, melody, and accent, presence of pathological elements (perseverations, paraphasias, neologisms, etc.);
 - linear speech (automated word or numerical sequences) – mentioning days of the week, months of the year, numbers);
 - naming objects known to the patient, paying attention to possible amnesic disorders (anomia), and trying to describe the purpose of the object, without being able to give its proper name;
 - repetition of letters, syllables, and sentences of varying difficulty;
 - reading individual letters, words, and sentences (the assessment should take into account possible vision disorders, e.g., visual field defects);
 - writing, where you can use the same set with which we assess reading, but taking into account hand impairments (paresis, apraxia, ataxia);
 - understanding, where the examination gives the patient the following simple and complex verbal commands (e.g., please close your eyes; please close your eyes and raise your hand; before raising your hand, please close your eyes).

Praxia is the ability to efficiently perform complex movements according to a plan learned and consolidated in the neural network. As a result of damage to the association cortex of the frontal or parietal lobe, most often the left (dominant) hemisphere of the brain, movement disorders called apraxia may occur.

Apraxia is the inability to perform learned movement sequences according to a specific plan. The strength and mobility of the limbs are fully preserved; there is no paresis, as well as no disturbances of sensation, attention, or understanding. Simple, spontaneous movements can be performed correctly, but clumsiness occurs when performing complex movement tasks on command. The following activities are performed:

- examination of elementary movements, consisting of clenching fists, wrinkling the forehead, clapping, or sticking out the tongue;
- examination of complex movements, i.e., negation, giving military honors, gesture of farewell;
- imitating activities such as pretending to play the piano or screwing in a screw; imitation of movements performed by the examiner;
- observation of complex motor activities, including dressing, opening doors, lighting a cigarette;
- performing alternating movements, e.g., copying the positions of the examiner's fingers; using imaginary objects, performing movement sequences shown by the examiner.

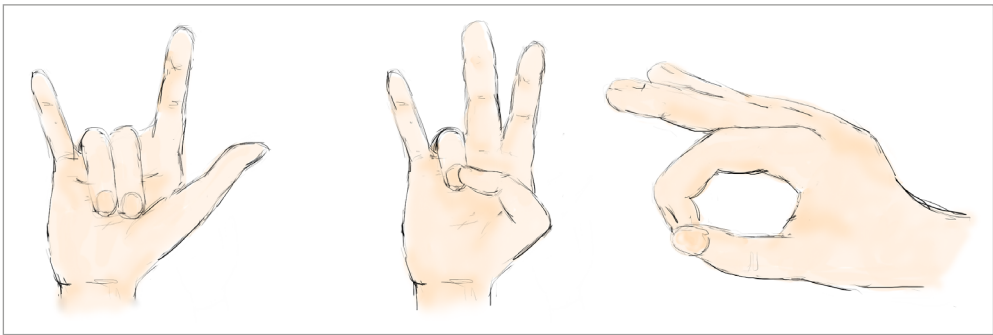


Fig. 2.1. Copying subsequent positions of the examiner's fingers

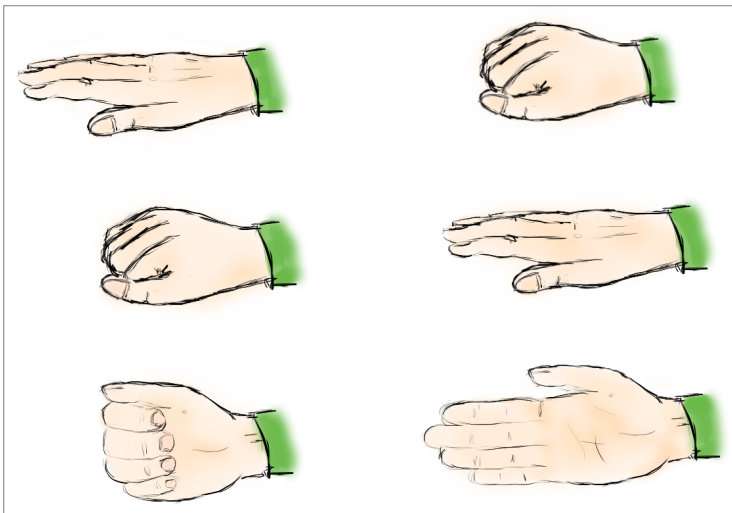


Fig. 2.2. Performing movement sequences shown by the examiner: A. First sequence; B. Second sequence

Gnosis is a complex activity enabling the recognition of known people, objects, phenomena, parts of one's own body, signs, etc., using individual senses. As a result of damage to the secondary and tertiary association cortex of the temporal, parietal, and/or occipital lobes, often in the dominant hemisphere, while maintaining normal perception, dependent on receptors, specific afferent pathways, and cortical projection fields, gnostic dys-

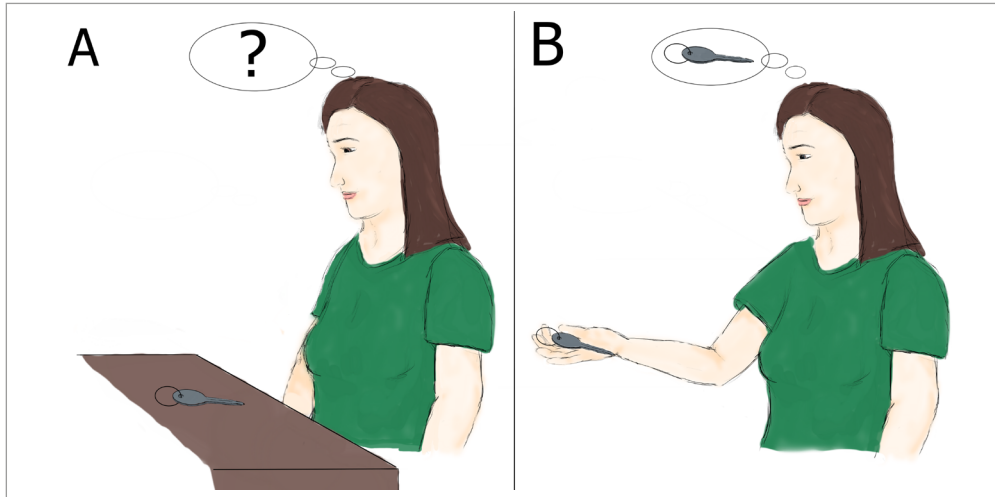


Fig. 2.3. Visual recognition of objects: A. Failure to identify correctly; B. Correct identification using a different modality, in this case sensory

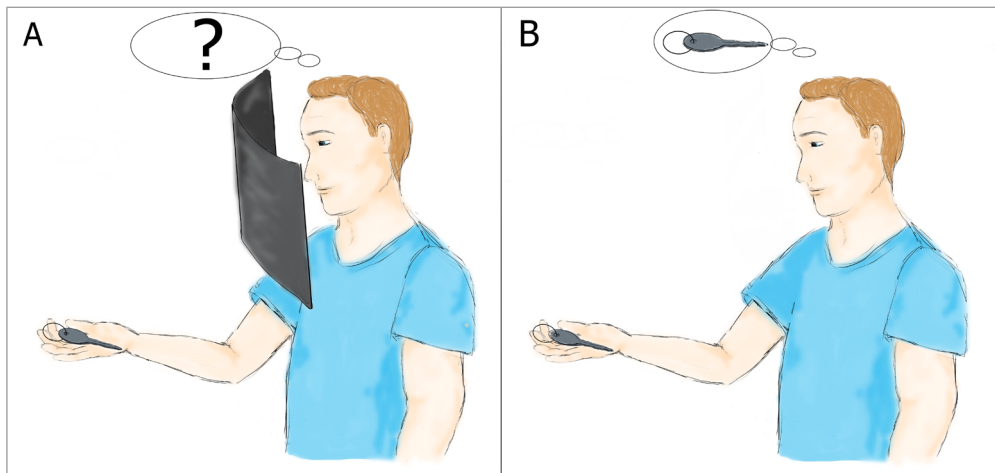


Fig. 2.4. Sensory recognition of objects: A. Failure to correctly identify when the field of view is obscured; B. Correct identification using another modality, in this case, visual

functions may occur, called agnosia, consisting of on the inability or limitation of recognition in particular modalities: visual, auditory or sensory.

Gnosis tests include:

- recognizing objects or photos of famous people through the visual modality;
- recognizing objects known to the examined person through the sensory modality;
- the examinee's copying of simple drawings (house, clock, butterfly, etc.);
- visual search using an eye tracker.

Screening tests

In a situation where we cannot perform a complete neuropsychological examination, we can perform an examination using screening tests. The American Academy of Neurology recommends performing simple tests and screening scales to assess cognitive functions in people, especially in older ones. The roles of screening tests include:

- answering the questions IF, WHAT, and HOW to investigate further;
- confirming or not cognitive disorders;
- tracking the progression of cognitive disorders.

Screening methods for assessing cognitive functions:

- **Mini-Mental State Examination (MMSE)** is one of the most frequently used screening tests for an approximate assessment of the depth of cognitive disorders. The maximum score that can be obtained in the test is 30 points; the abnormal result is below 27 points. The test consists of 20 questions or tasks assessing cognitive activities such as:
 - orientation in time and place;
 - memorizing;
 - attention;
 - counting;
 - recall;
 - language skills;
 - construction praxis.
- **Montreal Cognitive Assessment (MoCA)**, where the maximum number of points is 30. A score of 26 or more is considered normal. This test allows to assess:
 - concentration of attention;
 - executive functions;
 - memory;
 - language skills;
 - visual-spatial functions;
 - thinking;
 - orientation;
 - calculia.

- **Addenbrooke Cognitive Examination-III** is a test with a maximum score of 100, which assesses:
 - attention;
 - orientation;
 - memory;
 - verbal fluency;
 - language skills;
 - visuospatial functions.
- **The Frontal Assessment Battery (FAB)** The sum of the sub-scores from each of the six components are added up to generate total score out of 18. To administer and consists of 6 tasks assessing:
 - concept formation and abstract reasoning (similarities);
 - mental flexibility (phonemic verbal fluency);
 - motor programming (Luriamotor sequences);
 - sensitivity to interference (conflicting instructions);
 - inhibitory control (go-no-go);
 - environmental autonomy (prehension behavior).

The selection of tests in neuropsychological screening should take into account the leading clinical symptoms. For mild cognitive impairment, the MoCa is recommended. For suspected frontotemporal dementia FAB, the MMSE combined with CDT is recommended for symptoms of dementia.

Emotional and motivational functions

Emotional and motivational functions involve many structures of the central nervous system (primarily the structures of the limbic system) through extensive neuronal networks, and fundamentally influence the level of cognitive functioning. Disturbances of these functions may be exogenous (related to structural changes in the central nervous system resulting from damage to this system) or endogenous (related to the situation of a person suffering from a disease with all its consequences). The assessment of depression and anxiety requires special attention in neuropsychological examination.

Selected research methods:

- **The Geriatric Depression Scale (GDS)** is one of the most frequently used scales for screening self-assessment of depression in the elderly. It consists of 30 questions that must be answered yes or no. If the examinee has trouble understanding the questions (e.g., due to intellectual function disorders), assistance in reading and completing the scale is allowed. The scoring is as follows:
 - 0–9 points = no depression;
 - 10–19 points = mild depression;
 - 20 or more points = deep depression.

- **Beck's Depression Inventory (BDI)** is a self-report scale used to screen for symptoms of depression. The test result can be a clue to the diagnosis if the answers given during the test are honest. It consists of 21 statements, and each of them is assigned 4 answers, from which the respondent chooses one. Result:
 - 0–11 points = no depression;
 - 12–19 points = mild depression;
 - 20–25 points = moderate depression;
 - 26–63 points = severe depression.
- **The Hamilton Depression Rating Scale (HDRS)** is a method for assessing the severity of depression symptoms in diagnosed patients, as well as examining changes in the patient's condition over time. The main purposes of using the Hamilton Depression Rating Scale are to assess the severity of depressive disorders and to assess the impact of possible therapies on each of the components that the tool assesses. The Hamilton Depression Rating Scale is not intended for diagnosis, but for assessing the condition of a patient who has previously been diagnosed with depression. However, the scale is also used to assess the presence of depressive symptoms, other problems, and disease states.
- **The State-Trait Anxiety Inventory (STAI)** is a tool for examining anxiety understood as a transient and situationally conditioned state of an individual, and anxiety understood as a relatively permanent personality trait. It contains 40 statements, each of which is assigned 4 answers, allowing the assessment of the intensity of the respondent's emotions. Point values range from 20 to 80. High numerical values indicate a high level of anxiety.
- **Hamilton Anxiety Rating Scale (HARS)** is a scale assessing anxiety as a syndrome and its physiological, psychological, and behavioral symptoms. On this scale, the patient's response is assigned points from 0 to 4 for each of the 14 questions. The total number of points that can be obtained is 56. The scoring is as follows:
 - 18–24 points = mild anxiety level;
 - 25–30 points = moderate level of anxiety;
 - 30–56 points = severe anxiety level.

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3. Diagnostic imaging of the nervous system

Marta Nowakowska-Kotas, Krystian Obara

Diagnostic imaging is a crucial tool in neurology, enabling detailed visualization of the structure and function of the nervous system. Several imaging modalities can be used, each with its strengths and limitations.

Computed Tomography (CT)

Computed tomography uses X-rays to obtain cross-sectional brain images (scans). Cross-sections are reconstructed from measurements of attenuation coefficients of X-ray beams passing through the skull, intracranial structures, and vertebral column during rotation of the emitter around the head or trunk. They are often used in emergency settings to quickly diagnose conditions such as stroke or brain injury.

Computed tomography scans are less detailed than MRI but are faster and more accessible (Fig. 3.1). The possible CT modalities include:



Fig. 3.1. Head CT: subtle bilateral SAH more pronounced on the left side albo R&L, small intracerebral hematoma within the right hemisphere, hematoma of the extracranial soft tissues

- **CT Angiography (CTA):** uses an iodine contrast injection and CT imaging to visualize the blood vessels. They are used to assess ischemic strokes, subarachnoid and intracerebral hemorrhages, unruptured aneurysms and dissections of arteries (Fig. 3.2).
- **CT Perfusion (CTP):** a method that measures blood flow to assess the perfusion of tissues and is often used in the acute setting of a stroke to determine areas of core of infarction (region where Cerebral Blood Flow – CBF is lower than 30% of one found

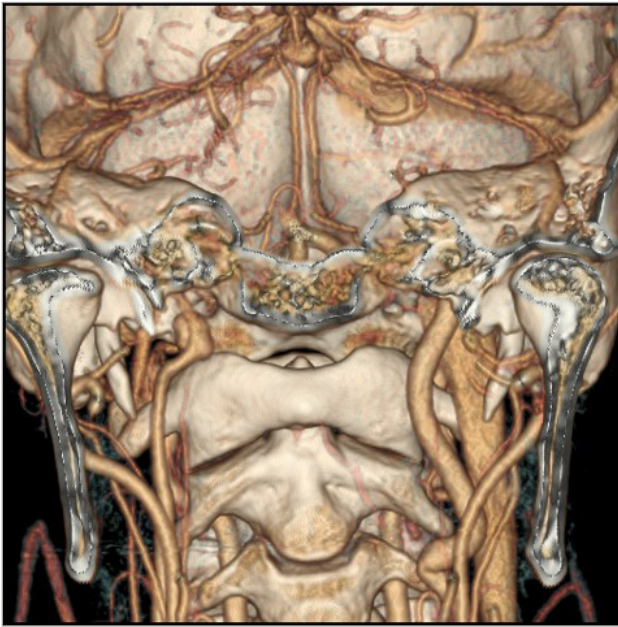


Fig. 3.2. CT angiography of the neck, 3D volume rendering (VR) reconstruction: left ICA dissection with secondary aneurysm of the proximal ICA

in the other hemisphere) and penumbra (measured as region, where delay of the maximum contrast enhancement – $T_{max} > 6$ s, reduced by area of region, where CBF is lower than 30%); Fig. 3.3.

- **Spectral (multi-energy) CT:** uses different X-ray energies to acquire multiple sets of data from the same scan. This can provide better differentiation of materials and more accurate tissue characterization, i.e., differentiate contrast from hemorrhage.

Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging uses strong magnetic fields and radio waves to create detailed brain and spinal cord images. It is often used to diagnose and monitor neurological conditions like degenerative diseases, multiple sclerosis, strokes, tumors, and pathologies of nerve roots and intervertebral discs. Magnetic resonance imaging can provide very high-resolution anatomical images, significantly superior to images obtained with CT, especially of the posterior cranial fossa and spinal cord (Fig. 3.4).

MRI modalities:

- **Functional MRI (fMRI):** detects changes in blood flow related to neural activity, which allows for the study of brain activity, which, for the moment, is mainly applicable to research, but also allows to detect early stages of cognitive impairment and evaluate patients with chronic disorders of consciousness.

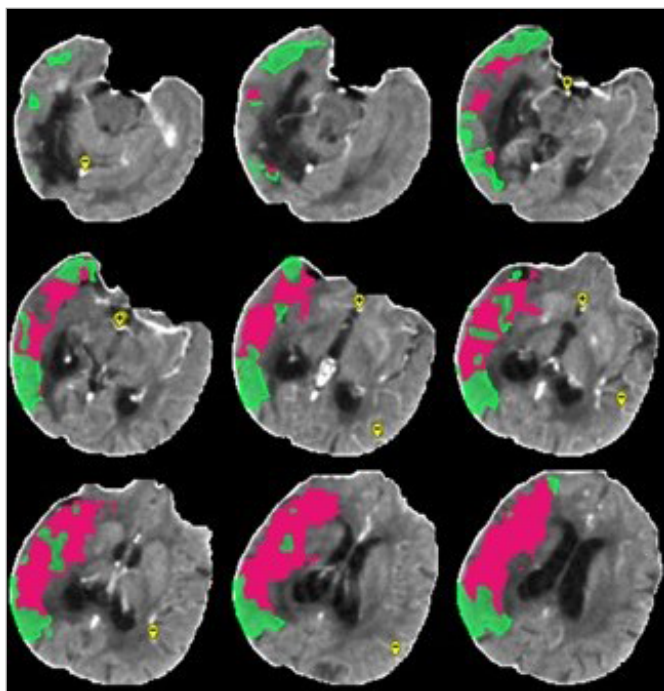


Fig. 3.3. CT brain perfusion: Ischemic stroke within right hemisphere with extensive core (red) and small penumbra (green)



Fig. 3.4. Brain MRI: Hot cross bun sign within the pons typical for MSA-C, hyperintense lesions within the middle cerebellar peduncles, cerebellar atrophy

- **MRI spectroscopy:** a method that creates a spectrum of biochemical metabolites instead of creating images, measuring their concentrations in the region of interest in the brain. It has been used in studying a range of neurological conditions, such as tumors (by detecting increased levels of certain chemicals like choline), Alzheimer's disease (by detecting decreased N-acetylaspartate), and multiple sclerosis (by evaluating the integrity of neurons and axons).

- **Diffusion tensor imaging (DTI):** uses the movement of water molecules to image white matter tracts in the brain. It allows the study of neural connectivity and can be helpful in conditions like traumatic brain injury, motor neuron disease, and tumors.
- **Magnetic resonance angiography (MRA):** an examination of arteries, which can also be performed without contrast (TOF technique). It can identify issues like aneurysms, vascular malformations, dissections, and stenosis.
- **Magnetic resonance venography (MRV):** an assessment of veins. Especially useful for the detection of intracerebral venous thrombosis.

Limitations: are related to the presence of various electronic or metal components in the patient's body (e.g., heart pacing systems, metal bone joints, metal filings that are stuck in the body); also, the patient's claustrophobia and inability to lie down during a lengthy examination.

Digital Subtraction Angiography (DSA)

Digital subtraction angiography is a diagnostic imaging technique used in neurology to visualize blood vessels within the brain and spinal cord. It involves the injection of a contrast agent into the patient's bloodstream and capturing X-ray images before and after the contrast administration. While DSA is considered an invasive procedure due to the use of contrast agents and catheterization, it remains a golden standard in stating the diagnosis of many vascular pathologies since images are of high resolution and the technique is very sensitive.

Positron Emission Tomography (PET)

Positron emission tomography uses a radioactive tracer to show how tissues and organs function. In neurology, they are often used to diagnose and monitor conditions such as Alzheimer's disease, Parkinson's disease, and epilepsy.

Ultrasonography

Ultrasonography uses sound waves to produce images of the body's internal structures. Applications in neurology:

- **Transcranial Doppler ultrasound (TCD):** measures the blood flow velocity through the brain's blood vessels. It helps diagnose the causes of such conditions as stroke, vasospasm (blood vessel narrowing), and other vascular abnormalities. It is also used to monitor blood flow in patients undergoing surgery for vascular abnormalities, such as aneurysms (Fig. 3.5).

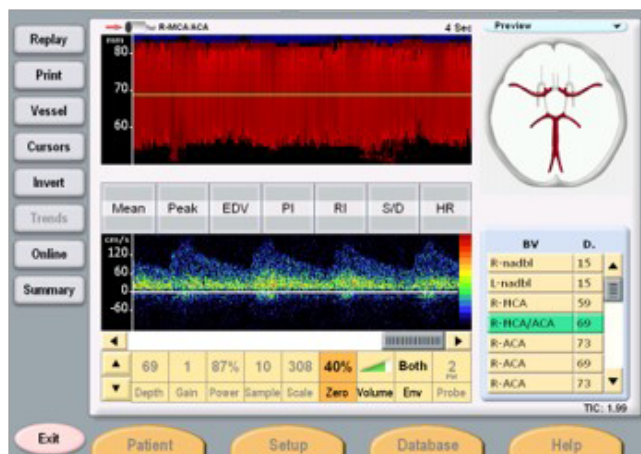


Fig. 3.5. TCD showing cerebral flow parameters in the middle cerebral artery

- **Transcranial Color Doppler (TCCD):** visualizes the course of intracranial vessels and blood flow parameters (Fig. 3.6).
- **Transorbital ultrasonography:** assesses the optic nerve and the eyeball in search of edema of the optic nerve or stenosis in the ophthalmic artery (Fig. 3.7).
- **Transcranial sonography (TCS):** evaluates subcortical structures, such as the black matter in the midbrain (hyperechogenic in, i.e., Parkinson's disease), enlarged 3rd ventricle (in subcortical dementia), or nucleus lenticularis (hyperechogenic in case of some neurodegenerative diseases caused by accumulation of iron).
- **Carotid/vertebral Doppler ultrasound:** allows visualization of the vessels and measurements of blood flow parameters. It is a primary tool in assessing the risk of stroke, as it can reveal stenosis in these arteries (Fig. 3.8).
- **Peripheral nerve ultrasound:** evaluates the peripheral nerves, which can be used to diagnose various peripheral nerve disorders, including carpal tunnel syndrome, peripheral neuropathy, and nerve entrapments or injuries (Fig. 3.9).
- **Intraoperative ultrasound:** used during brain surgery to guide the surgeon in real time. It can help locate tumors, distinguish between normal brain and tumor tissue, and confirm complete tumor removal.

• **Neuromuscular ultrasound:** evaluates muscles and other parts of the neuromuscular system. It can aid in diagnosing conditions like muscular dystrophy and other neuromuscular disorders. It can also guide therapeutic interventions such as injections.

Ultrasound is non-invasive, does not involve ionizing radiation, and provides real-time imaging, making it very useful for:

- diagnostic;
- monitoring;
- intraoperative applications.

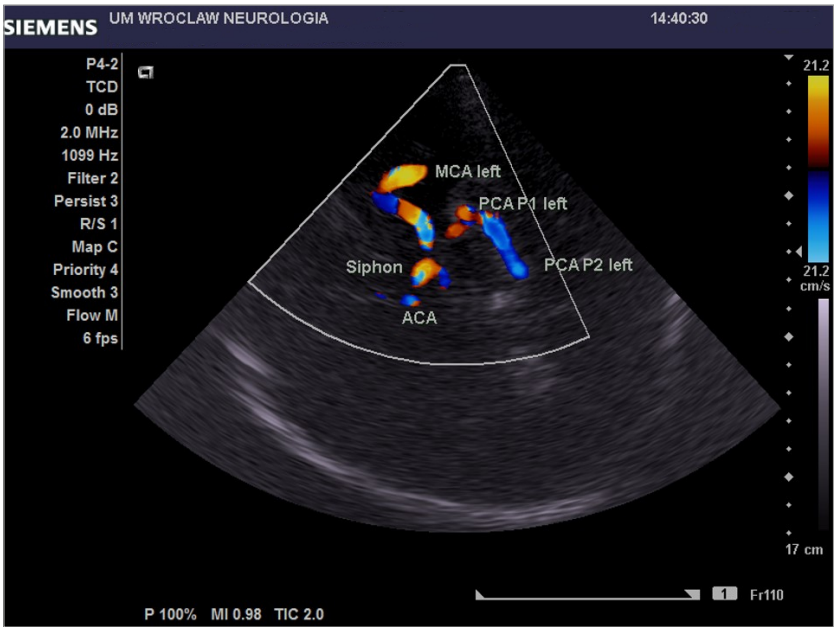


Fig. 3.6. Circle of Willis via temporal window

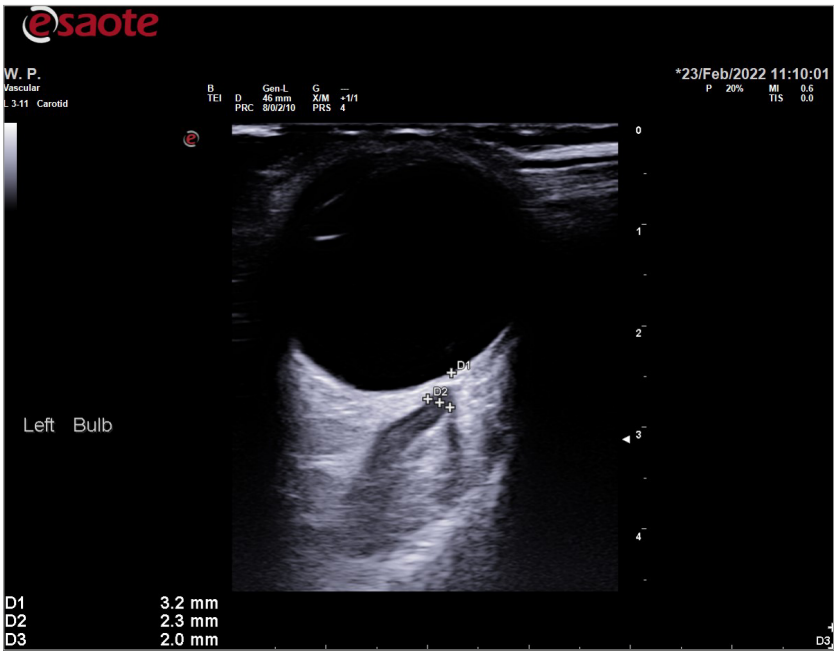


Fig. 3.7. Transorbital ultrasonography of the optic nerve – normal appearance

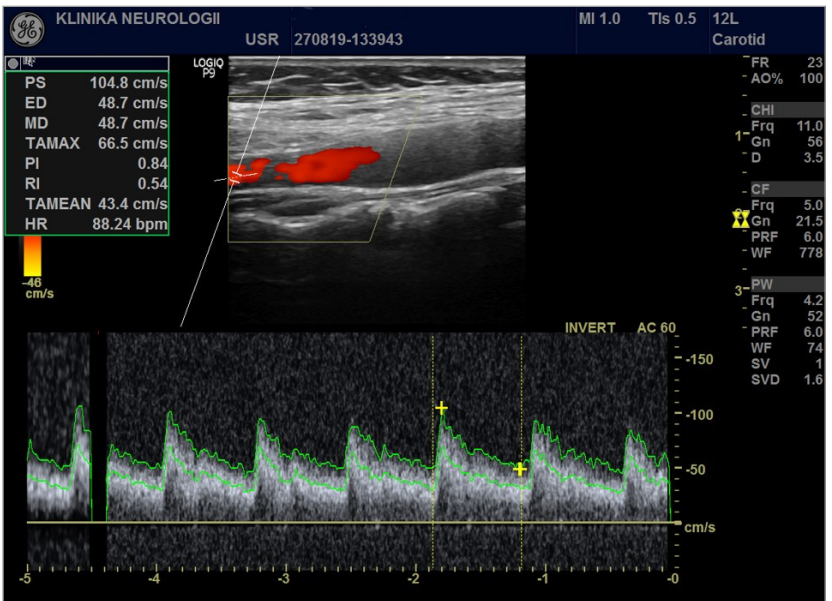


Fig. 3.8. Carotid Doppler ultrasonography

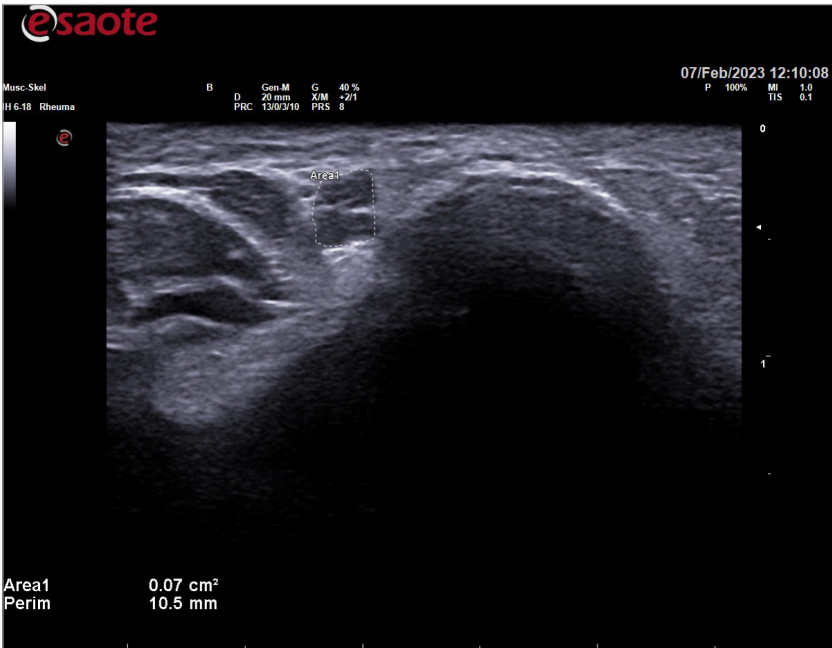


Fig. 3.9. Ultrasonography of nervus ulnaris in ulnar groove. The cross-sectional area of the nerve is marked

However, its use in neurology is somewhat limited because ultrasound waves cannot penetrate bone, limiting their ability to image specific parts of the nervous system, especially the adult brain.

Optical Imaging Techniques

Optical imaging techniques such as **diffuse optical tomography (DOT)**, **near-infrared spectroscopy (NIRS)**, and **optoacoustic imaging** offer non-invasive ways of imaging the brain using light. While they do not currently provide the same level of detail as methods such as MRI scanning, they have the advantage of being safe, relatively inexpensive, and portable.

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4. Electrophysiological examinations of the nervous system

Edyta Dziadkowiak

Electrophysiological examinations allow for a non-invasive assessment of the bioelectrical activity of the nervous system. They are used both in the initial diagnostic process and in monitoring the course of a disease, along with dynamic evaluation of treatment effectiveness.

The main electrophysiological examinations include:

- **electroencephalography (EEG)**, which reflects spontaneous brain activity,
- **evoked potentials (EPs)**, which arise in response to a specific modality of stimulus,
- **nerve conduction studies**, assessing the ability of motor and sensory fibers of peripheral nerves to conduct impulses,
- **electromyography (EMG)**, which records the bioelectrical activity of muscles.

Electrophysiological examinations are also used to assess the function of the autonomic nervous system, enabling analysis of heart rate variability and respiratory rate, as well as evaluation of the sympathetic skin response.

Electroencephalography (EEG)

Electroencephalography is a diagnostic method that allows recording the activity of the cerebral cortex using surface electrodes placed on the scalp according to the international “10–20” system. The electrodes are marked with a number and a letter. Even numbers indicate the right hemisphere, and odd numbers indicate the left hemisphere. The letter “Z” denotes the midline. Letters denoting different brain areas:

- F – frontal;
- Fp – frontopolar;
- C – central;
- P – parietal;
- T – temporal;
- O – occipital.

There are 4 basic frequency bands of brain waves in the EEG recording. In adults, the basic component is the alpha rhythm (8–13 Hz), which in healthy adults is recorded during wakefulness with the eyes closed and is most prominent in the occipital region. Beta waves (>13 Hz) are also common in normal adult EEGs, with the greatest ampli-

tude observed in the frontal–central areas. Theta waves (4–7 Hz) are present only in small amounts in healthy adults, typically in the midline and temporal leads; an increased number or focal distribution of theta waves is considered pathological. Delta waves (<4 Hz) are not usually recorded in the EEG of an awake adult.

Electroencephalography is a fundamental tool for detecting and recording pathological bioelectrical activity characteristic of epilepsy, both during initial diagnosis and in treatment monitoring. Paroxysmal discharges between clinical seizures, often invisible to a competent observer, can confirm the diagnosis of epilepsy. However, the absence of such discharges does not rule out epilepsy.

When epilepsy is suspected, epileptic discharges are detected in 30–50% of patients during the first resting EEG and in 60–90% during the 3rd (control) examination. It is estimated that in 10–40% of patients with epilepsy, no seizure discharges are recorded. A total of 2.7% of adults with various diseases, including neurological ones, but without a history of clinical seizures, may experience seizure discharges.

During the interictal period and epileptic seizures, EEG captures various bioelectric phenomena, whose morphology depends on the type of epilepsy or seizure form. If present, interictal epileptic activity can primarily be detected when the cortical epileptiform focus is located on the superior–lateral surface of the cerebral hemisphere, whereas foci in the uncus, insula, or hippocampus are not directly reflected in the recording. EEG reflects bioelectrical changes that are influenced not only by the location and size of the epileptiform focus, but also by the conditions that determine how pathological excitation spreads to neighboring areas.

Epileptiform graphoelements include the following:

- sharp waves;
- spikes;
- multi-spikes;
- series of high-frequency spikes;
- spike–slow wave complexes.

In epilepsy with primary generalized tonic–clonic seizures, interictal EEG recordings may show paroxysmal, symmetric discharges of spike–slow complexes at a frequency of 3.5–4.5 Hz, which are synchronous and generalized. Electroencephalography patterns recorded during an epileptic seizure are characterized by rhythmic or repetitive graph elements that may evolve into postictal patterns (e.g., decreased recording amplitude or polymorphic slow activity). The bioelectrical picture of a generalized epileptic seizure is characterized in the initial phase by generalized depression of activity, followed by spikes of gradually increasing amplitude and decreasing frequency. After a few seconds, spike–slow wave complexes are recorded, with an increasingly longer duration. During the tonic phase of a seizure, muscle and motor artifacts can mask the signals. These artifacts can also occur during the clonic phase. After the seizure, there is a depression of bioelectrical activity, and polymorphic slow waves appear, typically with a frequency below 1 Hz and low amplitude.

A normal resting EEG does not exclude epilepsy. Seizure-related changes, or their enhancement, can sometimes be achieved by using activation methods, such as:

- the stopping reaction (opening the eyes) – the safest, but also the least effective method of activation;
- hyperventilation (HV) – involves taking deep breaths for 3 min at a rate of approx. 20 breaths per min. In 1–2% of healthy adults, hyperventilation (HV) may reveal spike–slow wave complexes, isolated spikes, or slow waves. In patients with syncope of various etiologies, HV can induce a prolonged slowing of the basic function, while in patients with vascular diseases, e.g., moyamoya disease, high-amplitude slow waves may be recorded. Prolongation of EEG normalization beyond 1 min after the end of HV may indicate pathology. A positive HV test typically reveals, especially in the frontal areas, spikes, sharp waves, spike–slow wave complexes, and sharp wave–slow wave complexes. Clear lateralization of changes or focal slowing of bioelectrical activity can also be observed.

Photostimulation using a stroboscopic lamp involves the use of rhythmic, intermittent light stimuli. The best results are obtained with flash frequencies of 10–18 Hz, and at 3 Hz when focal-onset seizures are suspected. The stimulation effect can be increased by the priming phenomenon, achieved by pairs of light stimuli delivered at an interval of approx. 70 ms. Stimulation with an intermittent light stimulus in healthy people may evoke occipital rhythms consistent with the frequency of the light stimulus. Two types of frequency responses are distinguished:

- harmonics (with a frequency 2–3 times higher than the flash frequency);
- subharmonics (with a frequency 2 times lower than the flash frequency).

Photostimulation may also induce a **photomyoclonic response**, consisting of multi-peak spikes at the frequency of the light stimulus, accompanied by myoclonus of the oculomotor or facial muscles, or by generalized myoclonus. In healthy individuals, this response occurs for approx. 1 s after the end of light stimulation and is not considered a positive activation result. At low frequencies, e.g., 1 flash per second, so-called “on” responses correspond to visual evoked potentials. Lack of response to photostimulation is not considered pathological. In 20–30% of patients with epilepsy, during the presentation of rhythmic light flashes, discharges of slow waves, spikes, multi-spikes, or spike–slow wave complexes appear, mainly in the occipital leads. These discharges may persist for several seconds after the end of photostimulation and are sometimes accompanied by a clinical epileptic seizure. If generalized multi-spike discharges appear during the activation test, photostimulation should be discontinued.

Sleep deprivation is used in patients with suspected epilepsy when the resting EEG is normal or shows only minor changes after standard activation tests (hyperventilation, photostimulation). In the EEG recording, after a sleepless night, paroxysmal changes most often appear during sleep onset, sleep, and awakening. In clinical practice, EEG recording is also used for the diagnosis of encephalitis and for assessing treatment effective-

ness. Electroencephalography changes during neuroinfection are non-specific and involve disruption of basic activity with paroxysmal discharges. Electroencephalography analysis is also used in neuropsychiatric disorders, including systemic lupus, liver cirrhosis, advanced chronic kidney disease, and inflammatory and degenerative of the central nervous system, e.g., prion diseases, or subacute sclerosing panencephalitis.

Evoked potentials (EP)

Evoked potentials (EP) are brain responses elicited by stimuli of a specific modality. Abnormalities of EP consist of pathological extension (less often shortening) of the response latency, reduction or excessive increase in potential amplitude, or complete lack of a response. Evoked potentials testing enables the verification of disorders that are ambiguous or clinically silent. The main types of EPs include:

Visual evoked potentials (VEP) assess signal conduction throughout the entire visual pathway and are primarily indicative of myelin integrity. They reflect the response of the visual system, including the optic nerves, visual pathways, and visual cortex, to a visual stimulus, which may consist of a uniform light flash or a structural stimulus, most often in a reversible checkerboard with the conversion of black and white fields.

Visual responses obtained at a stimulus frequency of up to 4.5 Hz are classified as transient VEPs and consist of a complex of waves. The most important component is the repeatable, positive deflection with a latency of about 100 ms (P100), preceding the negative deflection with a latency of approximately 75 ms (N75).

The value of the P100 wave, assessed in transient VEPs, is influenced by the following physiological factors:

- **Age:** amplitude is higher in children than in adults, while latency increases slightly after 60 years (by approx. 3 ms per 10 years);
- **Gender:** men have slightly longer latency and lower amplitude than women;
- **Attention status:** lack of attention on the stimulus and poorer visual fixation may lead to a change in the morphology of the potential, reduced amplitude, and prolonged latency;
- **Visual acuity:** if visual acuity is significantly reduced, the latency time increases – visual acuity correction is required during the examination;
- **Hyperventilation:** causes a slight reduction in latency;
- **Medications:** certain drugs, e.g., carbamazepine reduce the amplitude and prolong latency of VEPs.

Visual evoked potentials can reveal abnormalities in individuals who report visual symptoms despite a normal clinical examination, as well as in those who exhibit no visual complaints. Since the clinical introduction of pattern-reversal VEPs for diagnosing optic

neuritis, these potentials have proven especially valuable in assessing patients with suspected multiple sclerosis (MS). Furthermore, VEPs may support the diagnostic consideration of neuromyelitis optica spectrum disorders (NMOSDs), especially in AQP4-antibody-negative cases.

Brainstem auditory evoked potentials (BAEPs) arise because of stimulation of the initial section of the auditory pathway with a high-frequency acoustic stimulus (approx. 20/s). Auditory stem responses are recorded during the first 10 ms after the stimulus occurs. It is a complex of 7 waves, the most reproducible of which are waves I, III, and V.

The origin of BAEPs is as follows:

- Wave I – from the peripheral part of the auditory nerve;
- Wave II – mainly from the proximal part of the auditory nerve, as well as from the cochlear nucleus;
- Wave III – from the lower part of the pons, from the area of the dorsal olivary nucleus and trapezius body;
- Wave IV – from the sideband;
- Wave V – is generated at the level of the midbrain, near the inferior colliculus;
- Wave VI – in the thalamus (medial geniculate body);
- Wave VII – comes from the auditory radiance.

Clinical interpretation of BAEPs is most often based on the parameters of waves I, III, and V (latencies of individual waves and inter-latencies, i.e., the time measured between individual waves, and the amplitude of wave V). Abnormal BAEPs are found in patients with acoustic neuroma or other tumors of the cerebellopontine angle, as well as in focal lesions of the auditory pathway in the brainstem.

Somatosensory evoked potentials (SSEPs) are elicited by transcutaneous electrical irritation of peripheral nerves, most often the median nerve or tibial nerve, and are recorded along the sensory pathway, initially in the peripheral and then in the central nervous system. Somatosensory evoked potentials enable the objectification and determination of sensory disorders.

Clinical neurophysiology (neurography and electromyography)

Neurography is a diagnostic test used to evaluate disorders of peripheral nerves, nerve plexuses, and spinal roots. This method allows the assessment of:

- function of the examined nerve;
- the nature of abnormalities (axonal, demyelinating);
- the location of the lesion;
- dynamics of a given disease process.

Axonal damage is characterized by reduced potential amplitude, while demyelinating damage is characterized by slowed conduction velocity. As the disease progresses, axonal and demyelinating degeneration overlap. Another diagnostic difficulty is the differentiation of axonopathy (primary axonal damage) from neuronopathy (primary degeneration of alpha motor neurons).

Electrophysiological diagnosis of neuromuscular junction diseases is important in:

- myasthenia gravis;
- Lambert–Eaton syndrome;
- myasthenic syndrome in botulism.

The electrostimulation test for numbness involves delivering a series of supramaximal stimuli of various frequencies to the nerve under examination and recording the motor response from the innervated muscle. The amplitude and area of subsequent responses are then analyzed. A characteristic feature of postsynaptic block in myasthenia gravis is a decrement (decrease) in the amplitude of subsequent potentials of more than 10%. Presynaptic block (Lambert–Eaton syndrome) is indicated by the phenomenon of priming, i.e., an increase in the amplitude of subsequent potentials by over 50% during stimulation with higher frequency stimuli (10–20–50 Hz).

Electromyography (EMG) enables the recording of the bioelectric activity of skeletal muscle using a needle electrode. An EMG recording consists of:

- assessment of resting activity,
- assessment of the activities of individual motor units with weak voluntary movement,
- assessment of interference during maximal muscle contraction.

Electromyography (EMG) allows for the differentiation between neurogenic and primarily muscular damage. In the case of neurogenic damage, EMG makes it possible to determine the level of damage (peripheral nerves, neural plexuses, spinal roots, alpha motor cells). Chronic neurogenic recording is characterized by an increase in the amplitude, duration, and area of the motor unit, instability of the motor unit, recruitment disorder, and disturbance of exercise recording interference. The potentials of the motor unit are complex, the number of phases and turns increases, and they are unstable, depending on the variability of conduction in muscle fibers and reinnervation. Large multiphase potentials are recorded in the neurogenic recording, and the so-called giants are characteristic of damage at the level of alpha motor neurons. The exercise recording is poor, and the motor unit potentials show high amplitude with reduced interference pattern.

Specific criteria for diagnosing myopathy include shortening the duration and potential area of the motor unit, and excessive interference with the exercise recording obtained from a weak, atrophied muscle. The non-specific criteria of primary muscle damage include the presence of fibrillations, positive slow waves and pseudo-myotonic phases in the resting recording, and an increase in the percentage of polyphasic potentials.

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5. Cerebrospinal fluid examination

Justyna Chojdak-Łukasiewicz

Cerebrospinal fluid (CSF) surrounds the internal and external surfaces of the brain and spinal cord. It is produced by the choroid plexus of the lateral, 3rd, and 4th ventricles and is absorbed through the villi of the arachnoid granulations that project into the dural venous sinuses. Cerebrospinal fluid is produced continually at a rate of about 0.5 mL per min (20 mL per h). The total CSF volume is 90–200 mL, with approx. 20% of the CSF contained in the ventricles; the rest is contained in the subarachnoid space in the cranium and spinal cord (Fig. 5.1).

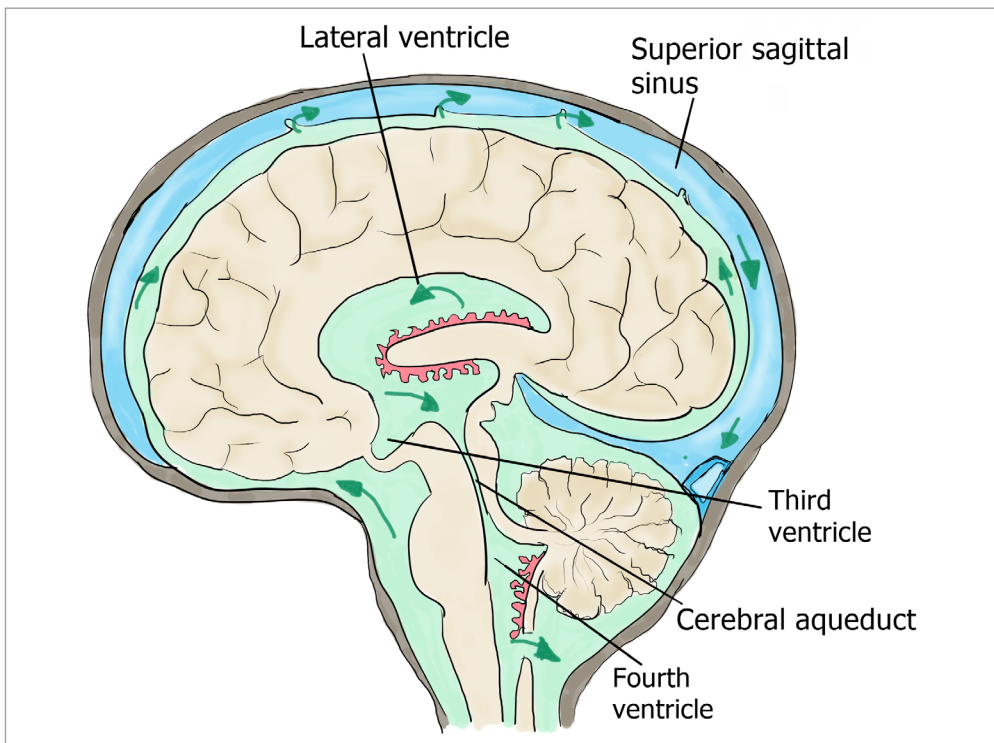


Fig. 5.1. Cerebrospinal fluid circulation

Lumbar puncture (LP)

Lumbar puncture (spinal tap) with cerebrospinal fluid (CSF) analysis is an important diagnostic tool for a variety of infectious and noninfectious neurological conditions.

Indications:

- neuroinfections;
- autoimmune diseases (e.g., multiple sclerosis, acute and chronic polyneuropathies, autoimmune encephalitis);
- subarachnoid hemorrhage;
- paraneoplastic disorders;
- neurodegenerative diseases;
- suspected abnormalities of intracranial pressure.

Additional uses of lumbar puncture

Beyond its role in diagnosing infections, autoimmune, hemorrhagic, and degenerative conditions, LP is also used to:

- measure and fractionate CSF proteins in suspected immunologic diseases, especially in multiple sclerosis.
- support the differential diagnosis of some neuropathies, such as Guillain–Barré syndrome (albuminocytologic dissociation).
- serve as a therapeutic or diagnostic procedure in: spinal anesthesia, intrathecal administration of chemotherapy or antibacterial agents; injection of contrast media for myelography or cisternography.

Preparation before lumbar puncture:

Exclude contraindications such as increased intracranial pressure (assessed by fundoscopy, neuroimages studies). Laboratory tests: complete blood count, coagulogram. Obtain written informed consent for the procedure.

Contraindications to lumbar puncture

Lumbar puncture has several contraindications, which can be categorized as absolute and relative ([Table 5.1](#)).

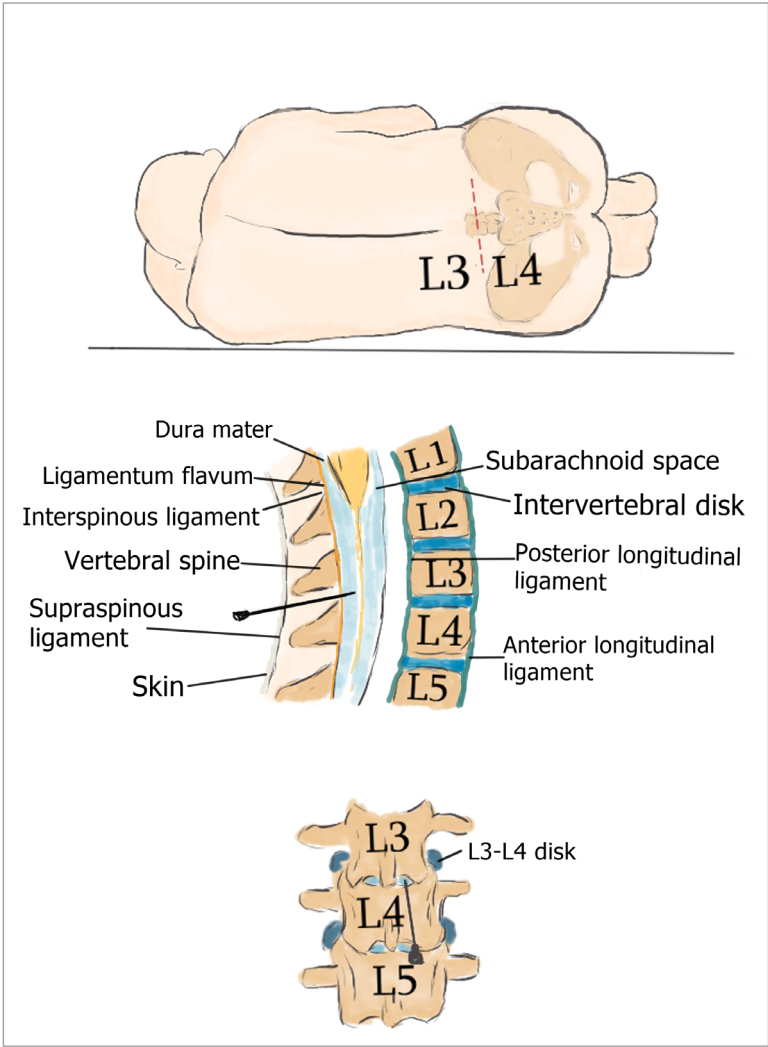
Technique of lumbar puncture

Optimal positioning is essential for a successful and atraumatic LP. The patient, lying on their side with the spine maximally flexed and the knees drawn toward the chest. The spinous processes should be horizontal, with the 2 iliac crests forming perpendicular lines. The needle is usually inserted in the L3–L4 or L4–L5 interspace. The subarachnoid space is identified by a characteristic “give” as the needle passes through the dura mater. CSF pressure can then be measured using a manometer, followed by collection of the samples ([Fig. 5.2](#)).

Table 5.1. Contraindications for lumbar puncture

Absolute	Relative
– signs of increased intracranial pressure such as: bradycardia, increased blood pressure, breathing disturbances, optic disc edema – coagulopathy-platelet level <50,000/mm³ or INR >1.6 or DIC – cardiorespiratory failure, shock – regional skin infection in the lumbar area	– coagulopathy-platelet level 50,000–100,000/mm³ or INR 1.4–1.6 – deformation of the lumbar spine – significant dehydration

Fig. 5.2. Technique of lumbar puncture



Normal cerebrospinal fluid

The examination of CSF includes:

- evaluation of physical properties (color, turbidity);
- cytological assessment;
- other biomarkers: tau protein, amyloid-β1-40, amyloid beta-β1-42, 14-3-3 protein, neurofilament proteins.

Basic examination of cerebrospinal fluid (CSF)

The standard CSF analysis includes:

- assessment of CSF appearance;
- quantitative estimation of total protein;
- quantitative estimation of glucose;
- cell count and differential profile.

Normal CSF is clear and colorless. Cell count is fewer than 5 cells/μL, predominantly lymphocytes. The glucose is usually around 60 mg/dL or 60% of the serum glucose level. Protein concentration is usually ≤40–50 mg/dL. CSF pressure, measured with a manometer in a lateral decubitus position with legs extended, ranges from 6 to 25 cm H₂O. Table 5.2 shows normal CSF values.

Table 5.2. Normal cerebrospinal fluid

Constituent	Value
Glucose	40–70 mg/dL
Lactate	10–20 mg/dL
Total protein	15–50 mg/dL
Albumin	6.6–44.2 mg/dL
IgG	0.9–5.7 mg/dL
IgG index = CSF IgG (mg/dL) × serum albumin (mg/dL)/serum IgG (mg/dL) × CSF albumin (mg/dL)	0.29–0.59
serum IgG (mg/dL) × CSF albumin (mg/dL)	25–80 ug/dL
Ammonia	0
Red blood cells	0–5 mononuclear cells per mm ³
Leukocytes:	
Lymphocytes	60–70%
Monocytes	40–50%
Neutrophils	None

Further examination of CSF may include:

- Estimation of IgG, IgA, IgM, and albumin in both serum and CSF to assess intrathecal synthesis of immunoglobulins and the degree of blood-CSF barrier impairment.
- Isoelectric focusing for the detection of IgG oligoclonal bands.
- Other examinations, such as measurement of other proteins in CSF and serum.
- Special staining of cytological preparations (Table 5.3).

Table 5.3. CSF parameters in selected conditions

????????	Color and clarity	Pressure	Cells	Glucose level	Protein level
Bacterial	yellow, cloudy	increased	>1000 polymorphs	low	↑↑>100
Viral	clear	normal or increased	5–1000 lymphocytes	normal	normal or ↑ (50–200)
Tuberculosis	clear/opalescent	increased	5–1000 lymphocytes	very low	↑↑>100
Fungal	clear	normal or increased	20–500 lymphocytes	normal	normal or ↑ (50–200)
Subarachnoid hemorrhage	xanthochromia	increased	lymphocytes and many RBCs	normal	may be high

Lumbar puncture complications

Lumbar puncture is a relatively safe procedure, but complications may occur even when standard technique is used. The most common complications include:

Positional headache:

- in 40% of examined patients;
- usually appears within 3 days;
- symptoms contain: bilateral fronto-occipital, non-throbbing pain, worse in the upright position (better with supine), photophobia, nausea, stiff neck;
- treatment includes lying in a flat position, providing fluids, especially caffeinated beverages; and epidural blood patches are rarely needed.

Localized back pain:

- a) in 30% of patients.

Rare complications:

- a) in less than 0.5% of patients;
- b) symptoms include: CSF infections, spinal hematoma, bleeding, brainstem herniation, epidermoid tumor.

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6. Other diagnostics in neurology

Justyna Chojdak-Łukasiewicz

Neurogenetic tests in neurology diagnostics

Many neurological disorders have a genetic etiology that can be diagnosed and/or confirmed by chromosomal or molecular testing. Due to advances in technology, genetic technology has improved in recent years. We have a range of testing options used in diagnostic procedures.

The selection of a genetic test depends on the clinical features, family history and probable site of the defect. Genetic counselling is required before diagnostic and predictive gene testing (Table 6.1).

Table 6.1. Diagnosis of hereditary neurological diseases.

First phase	
Disease characterization:	neurological history and examination family history test evaluation: relevant blood work (CK), electrophysiological tests (EMG/NCV), imaging (if needed) nerve or muscle biopsy
Second phase	
Sample collection:	sources of DNA extraction: white blood cells (EDTA tube), saliva, or tissue stable at room temperature very small amount needed sampling from family members may be helpful
Third phase	
DNA testing (which leads to diagnosis)	

Many neurological disorders appear to be inherited through a single gene mutation. Others have multifactorial origin, with one or more genes involved as part of their etiology. The clinical evaluation involves obtaining a detailed family history to identify the inheritance patterns. Recognizing a specific inheritance pattern can help focus the clinical differential diagnosis and guide clinical testing. The most important inheritance patterns are summarized below:

- **Chromosomal disorders** are caused by structural mutations of one of several chromosomes. The most common chromosomal abnormalities encountered clinically involve sporadic aneuploidy, either a deletion leaving one chromosome (a monosomy), or a duplication leaving three chromosomes (a trisomy). Chromosomal abnormalities are a common cause of developmental disorders. The most common chromosomal disorders include:
 - Turner syndrome (monosomy X, XO);
 - Klinefelter syndrome (XXY);
 - Down syndrome (trisomy 21);
 - Edwards syndrome (trisomy 13);
 - Patau syndrome (trisomy 18).
- **Monogenic disorders** are caused by a (missense, nonsense) mutation in a single gene according to Mendelian inheritance. We distinguish:
- **Autosomal dominant inheritance** – diseases involving autosomal genes require mutation of only one allele. This group includes:
 - neurofibromatosis type 1 (neurofibromin on chromosome 17, caused by point mutations, frameshifts, and splicing mutations);
 - CMT type 1B (myelin protein zero on chromosome 1, often caused by missense mutations);
 - early-onset familial AD (presenilin-1, often caused by missense mutations).
- **Autosomal recessive inheritance** – diseases involving autosomal genes require mutation of both alleles. Both parents are carriers of the disease and usually are not affected with the disease. Most of the metabolic single-enzyme deficiency disease states are inherited through autosomal recessive transmission, for example: Gaucher's disease, which is caused by a deficiency of the lysosomal enzyme beta glucocerebrosidase.
- **X-linked dominant inheritance** – a single mutation occurring on the X chromosome causes this disease state. Males and females with a mutation are equally likely to have the disease. An example of the X-linked dominant inheritance pattern is Rett's syndrome.
- **X-linked recessive inheritance** is characterised by the presence of disease in males only. Some examples include:
 - Duchenne muscular dystrophy (dystrophin, commonly caused by deletions),
 - Emery–Dreifuss muscular dystrophy-1 (emerin, often caused by nonsense mutations),
 - Menkes disease (ATPase, Cu²⁺-transporting, alpha-polypeptide, commonly caused by frameshifts, nonsense mutations, and splicing mutations),
 - Fabry disease (alpha-galactosidase A, commonly caused by point mutations, gene rearrangements, and splicing mutations).
- **Multigenic disorders** are syndromes that are inherited through a complex interaction between several genes and/or the environment. The genetics of these disorders is more difficult to determine. Examples of these multifactorial disorders are:

- Alzheimer's dementia;
- Parkinson's disease;
- dystonia.

Neurogenetic disorders are characterised by phenotypic variability. Some diseases can have remarkable inter- and intrafamilial variability in severity of symptoms, type of symptoms, age of onset, and disease course. Typical for neurological conditions is genetic heterogeneity. Some diseases, like Huntington's disease (HD), spinocerebellar ataxias (SCAs), fragile X-associated tremor ataxia syndrome (FXTAS) or myotonic dystrophies are connected with anticipation. The age of onset for these diseases roughly correlates with the number of repeats of the polynucleotide. Expansion of the allele size occurs during gamete formation so that the repeat number can increase, and therefore, the age of onset of disease can decrease with next generations. Also, many of the genes arranged in neurological conditions can cause dysfunctions in other organs as well. Other forms of genetic condition are mitochondrial disorders. Mitochondria contain their own DNA and are maternally inherited.

Genetic tests can be divided into:

- those that assess structural variants;
- those which test at the individual base level for genes.

Chromosomal and sub-chromosomal pathologies can be identified by cytogenetics, whereas molecular methods are required for exon/gene level and single-base pair mutations. Many types of genetic tests are useful in neurological evaluation. We list some of them below:

- **Sanger sequencing** is a method of single-gene sequencing in which DNA is sequenced in short fragments to detect point mutations, as well as small deletions and insertions of a few nucleotide base pairs. The method is used clinically when the sequence of a specific gene is being tested.
- **Next-generation sequencing (NGS)** is a technology that is based on the simultaneous execution of thousands of PCRs and sequencing reactions. NGS is useful to determine the sequences of multiple genes. NGS can be used as a targeted panel sequencing, such as whole-exome sequencing (WES) and whole-genome sequencing (WGS).
- **Targeted gene panel sequencing** is a method to examine all the exons on a pre-specified number of genes. It is useful to determine sequences of many genes. WES is a method to assess sequences of all protein-coding regions (exomes) of the genome. WGS is the most comprehensive sequencing method that covers the entire genome.
- **Chromosomal microarray** is a comparative genomic hybridization method used for detecting deletion, duplications and copy number variations. It is used in the diagnosis of congenital anomalies, developmental and intellectual disorders, and autism spectrum disorders.
- **FISH and high-resolution analyses** are used to find genetic changes (detection of aneuploidies, gene translocations, deletions of chromosomal regions) at the level of an entire chromosome or chromosome segment.

- **Testing for polynucleotide repeat disorders** is assessing the sample for trinucleotide repeats that can be directly sequenced after PCR.

Molecular diagnosis

Molecular diagnosis can be defined as the clinical application of molecular technologies to:

- elucidate;
- diagnose;
- monitor neurological disorders.

The basic morphological examination is based on observation of microscopic changes. These tests fall within the scope of neurohistopathology. Based on histopathological examination, microscopy, electron beam, we can diagnose the neurological disorder. The assessment of tissue is based on classical histopathologic examination stained with H&E for screening purposes, and examined microscopically. The H&E stain allows for visualisation of the cytoarchitecture and all the cellular types in the tissue, including neurons and glia.

The assessment of proliferation markers such as:

- antigen carcinoembryonic (CAE, carcinoembryonic antigen);
- alpha-fetoprotein;
- cytokeratin (marker of epithelial tumors);
- leukocyte antigen (marker of lymphomas).

It is important to establish the degree of malignancy of the tumor. In case of lymphoma consideration, flow cytometry on fresh brain tissue can be performed to characterize the neoplastic population.

Immunocytochemical methods are useful in the diagnosis of amyloid deposits in Alzheimer's disease, ubiquitin in Lewy bodies, dementia and detections of antigens in case of neuroinfection.

Assessment of enzymes (e.g. dehydrogenases, phosphatases, ATPases, acetylcholinesterases), occurring in mitochondrial or lysosomal dysfunctions and in differentiating the components of enzymatic defects is possible.

Immunocytochemical tests involving the detection of individual components or based on the reaction of an antigen with an effect (mono- or polyclonal). Marking the presence of an enzyme or fluorochrome allows them to be visible at the site of binding. The method is used in the assessment of:

- neuronal enolase;
- synaptophysin;
- MAP-tau behavior (neuronal markers);
- vimentin;
- epithelial membrane antigen (EMA – characteristic of astroglia);

- myelin basic protein (MBP);
- myelin-associated glycoprotein (MAG – characteristic of oligodendroglia);
- S-100 competitor (present in cell tires and cell lining);
- lots of neurotransmitters.

Biopsies

Brain biopsy

Brain biopsy is a surgical procedure used to obtain a histopathological diagnosis and guide the management of patients with suspect neoplasms. Limited data indicated using brain biopsy to determine a diagnosis in human immunodeficiency virus (HIV)-positive patients with neurological symptoms, cerebral angiitis, Creutzfeldt–Jakob disease, or dementia. Brain biopsy is an invasive procedure, with a risk of complications.

Tissue sections from formalin-fixed brains are mounted on glass slides and stained with H&E. In the assessment, other stains are also used, for example variations of the Bielschowsky silver stain (to visualize neuronal processes) and trichrome, reticulin, or van Gieson stains (to look for vascular pathology). For visualizing amyloid, Congo red and thioflavin are used. Microbiological tests include Gram, Gomori methenamine silver, and Ziehl–Neelsen stains. In the case of a tumor, NGS technology is used for classification.

Muscle biopsy

Muscle biopsy is an investigation used in the diagnosis of suspected myopathy. Histopathologic examination of a muscle biopsy can indicate whether the weakness is neurogenic or myopathic.

In neurogenic disorders, atrophic fibers occur in groups, adjacent to groups of larger uninvolved fibers. In myopathies, atrophy occurs in a random pattern; the nuclei of muscle cells may be centrally situated, rather than in their normal peripheral location; and fibrosis or fatty infiltration may also be found. Examination of a muscle biopsy specimen may also permit certain inflammatory diseases of muscle, such as polymyositis, to be recognized and treated.

Recommended for biopsy are muscles moderately affected by the disease. The most commonly investigated muscles are deltoid, biceps, vastus lateralis, anterior tibialis or gastrocnemius. Metabolic enzymes or mitochondrial DNA analyses can be performed.

Evaluation of muscle tissue includes a lot of techniques – below are the most popular:

- light microscopy;
- histochemistry;

- immunocytochemistry with a battery of antibodies;
- electron microscopy.

For accurate morphological diagnosis, formalin-fixed tissues are used. Histochemical staining techniques applied on cryosections help classify the fiber types (e.g. myosin adenosine triphosphatase) and delineate cytologic abnormalities. A neurogenic disease can demonstrate fiber-type grouping and/or target/targetoid fibers, best demonstrated by myosin adenosine triphosphatase and nicotinamide adenine dinucleotide tetrazolium reductase, respectively.

In metabolic myopathy, the lack of enzymatic functions can be histochemically demonstrated. These tests are useful in the diagnosis of glycogenosis type V (myophosphorylase deficiency), glycogenosis type VII (phosphofructokinase deficiency) or mitochondrial myopathy (myoadenylate deaminase deficiency, cytochrome c oxidase). In diagnostic procedure aetiology of myopathy genetic defects of dystrophin, sarcoglycan proteins, dysferlin, caveolin-3, emerin, merosin, collagen VI.

Nerve biopsy

Nerve biopsy is required to establish a diagnosis of the causes of neuropathy for some cases. Some diseases such as metachromatic leukodystrophy, adrenoleukodystrophy, Krabbe disease, Lafora disease, neuronal lipofuscinosis, lysosomal storage diseases, infection, vasculitis or neoplasm may clinically involve the peripheral nerve. The nerve biopsy can establish the diagnosis of giant axonal neuropathy and neuroaxonal dystrophy. The sural nerve is the most recommended for biopsy.

For morphologic diagnosis, the nerve is divided into three parts: buffered formalin-fixed for paraffin-embedded sections; buffered glutaraldehyde-fixed for epoxy resin sections, teasing fiber analysis, and electron microscopic assessment; and frozen for potential immunofluorescent study.

The routine histology of nerves demonstrates features of vasculopathy (vasculitis, arteriolosclerosis, embolus, intravascular malignancy, etc.), amyloid deposition, sarcoidosis, inflammation, infiltration of nerve by hematologic neoplasia, leprosy, giant axon neuropathy, and polyglucosan body disease.

Electron microscopic examination is useful to find the pathology of axons, myelin, Schwann cells, or interstitial tissue (e.g. accumulation of neurofilaments, organelles, or protein aggregation in axon; widened, uncompacted, or irregularly folded myelin lamellae; various intracellular inclusions or deposits) and is essential for the assessment of unmyelinated fibers.

In the case of autoimmune polyneuropathies, many serum autoantibodies directed against peripheral nerve have been identified as putative targets to date, and the direct immunofluorescent study using nerve frozen sections could be used to demonstrate possible immunoglobulin and complement deposits within the myelin sheath.

Skin biopsy

Skin biopsy may be performed to evaluate mainly cutaneous sensory and autonomic nerves. It is useful in the probability of hereditary or acquired small-fiber neuropathy. Skin biopsy may be performed to determine the number, density, and length of small nerve fibers in the epidermis. Morphologic abnormalities in the epidermal axons (e.g., short length, small diameters, swelling, and complicated branching patterns) may precede the actual dropout of the epidermal axons.

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PART 2
GENERAL NEUROLOGY

1. Symptoms of cranial nerve lesions

Mariusz Szydło

Symptoms of cranial nerve lesions, divided into individual nerves, are as follows:

CN I olfactory nerve

The diagnosis of olfactory nerve disorders is based on patient history and testing with various scent markers (e.g., vanilla, lemon, mint, coffee). The diagnosis of neurogenic olfactory disorders requires the exclusion of nasal mucosa diseases. Detailed examinations are carried out in specialized Ear, Nose and Throat (ENT) departments.

Smell can be:

- normal on both sides;
- weakened on 1 or both sides (hyposmia);
- abolished (anosmia).

Less common:

- hypersensitivity to olfactory stimuli (hyperosmia);
- abnormal sense of smell (parosmia).

Impaired smell disorders may be caused by:

- trauma with a fracture of the ethmoid bone causing damaging olfactory sensory neurons (often accompanied by CSF rhinorrhea);
- slowly growing supraorbital meningioma;
- neurodegenerative brain diseases, such as Alzheimer's disease and Parkinson's disease;
- epilepsy: paroxysmal perception of unpleasant odors (cacosmia) is a characteristic feature of epileptic seizures, with the focus located in the hippocampus.

CN II optic nerve

Clinical manifestations of optic nerve or visual pathway lesions:

- reduced visual acuity and color vision disorders;
- visual field defects;
- blindness;
- optic disc abnormalities on fundus examination.

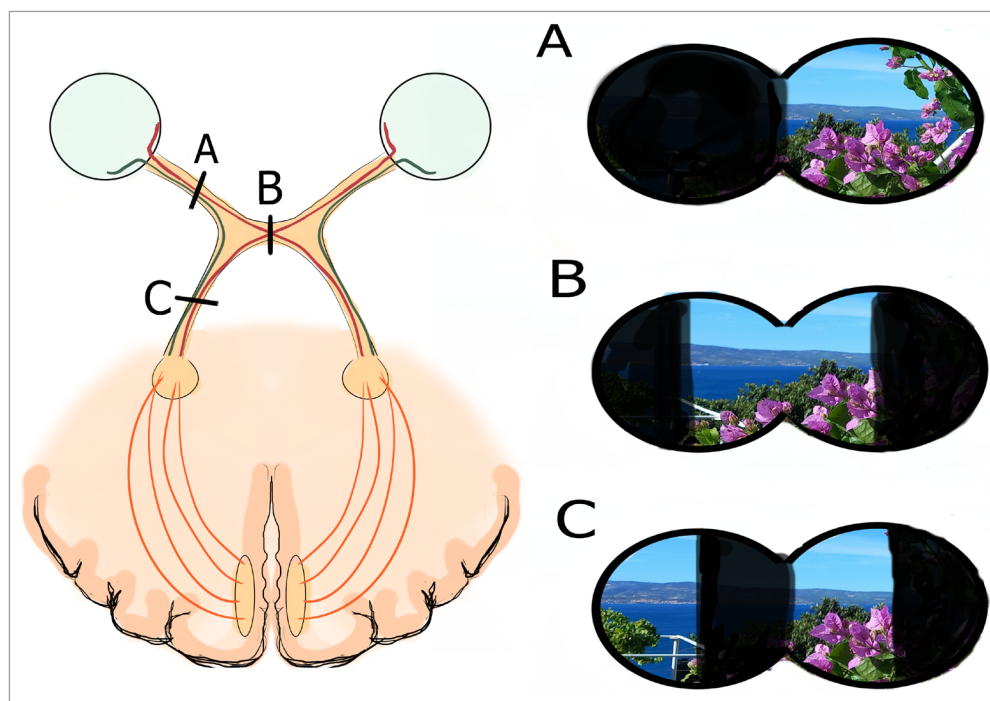


Fig. 1.1. Visual field defects due to lesions of the visual pathway. A. In front of the optic chiasm – blindness; B. In the area of the optic chiasm – bitemporal amblyopia; C. Behind the optic chiasm – monomial hemianopia

In clinical practice, lesion to the optic nerve is diagnosed when the patient is unable to read a newspaper (text written in small font or headlines), state the number of fingers shown by the examiner, perceive hand movements, or perceive light. Ophthalmoscopic examination may show swelling of the optic nerve disc, indicating increased intracranial pressure. In such cases, the disc is elevated, its margins are blurred, venous vessels are dilated, and petechiae may appear on the ocular fundus. In a normal condition, the optic nerve disc has sharp margins, is flat – at the bottom level, and has a distinct depression in the middle.

Sudden monocular blindness (amaurosis fugax) may be a symptom of narrowing or occlusion of the internal carotid artery, the origin of ophthalmic artery. A bitemporal hemianopia indicates a lesion in the optic chiasm area, most often due to a pituitary tumor. Monocular hemianopia is caused by a lesion to the visual pathway posterior to the optic chiasm.

CN III oculomotor nerve

Lesions of the oculomotor nerve may lead to:

- lower position or drooping of the upper eyelid;
- diplopia (double image) in binocular vision;
- divergent position of the eyeball;
- impaired eyeball movements medially, upward, and downward;
- pupil asymmetry;
- impaired pupil reaction to light, convergence, and accommodation.

Potential causes include:

- inflammatory mononeuropathy;
- metabolic mononeuropathy;
- ischemic mononeuropathy;
- brain aneurysm;
- tumors involving the cavernous sinus area;
- injury;
- increased intracranial pressure.

Lesion to the CN III may be:

- external – only when eyeball mobility is impaired;
- internal – dysfunction restricted to parasympathetic nerve fibers;
- complete – paralysis of ocular movements and lack of pupil response.

Syndromes associated with oculomotor disorders

- **Horner's syndrome** – characterized by drooping of the eyelid (ptosis), constriction of the pupil (miosis), posterior displacement of the eyeball (enophthalmos), resulting from lesions of the cervical sympathetic ganglion (e.g., brachial plexus avulsion, or cervical cord tumors), brainstem involvement (posterior inferior cerebellar artery syndrome), or as a developmental anomaly of no clinical significance.
- **Internuclear palsy** – characterized by impaired adduction of 1 eye and nystagmus in the abducted eye when looking binocularly to the side. It occurs in lesions of the medial longitudinal fasciculus in the brainstem, most commonly caused by multiple sclerosis. Paralysis of paired lateral gaze or deviation of the eyeballs may be caused by lesions in the pons (the patient looks to the side opposite to the focus and the paresis) and the cortical center of the brain in the frontal lobe (the patient looks to the focus, opposite to the paresis).
Paralysis of vertical and circular eye movements results from lesions of the subcortical movement centers in the midbrain.
- **Parinaud's syndrome ("sunset sign")** is characterized by the position of the eyeballs downwards (the lower part of the iris is covered by the lower eyelid; a fragment of the white layer is visible above the iris). The pupils are dilated and unrespon-

sive to light, while the accommodation response is preserved. The vestibulo-ocular reflex is also preserved, i.e., allowing upward movement of the eyeballs when the head is quickly bent toward the chest.

CN IV trochlear nerve

Lesions of the trochlear nerve result in upward and outward deviation of the affected eye. Patients are unable to look at the nose, and they report double vision when looking down (e.g., when going downstairs), and experience compensatory head tilt. The causes of lesions of the trochlear nerve are similar to those of the oculomotor nerve.

CN V trigeminal nerve

Lesion of the sensory branches of the trigeminal nerves I, II, and III results in sensory disorders in the cranial region, including the meninges, blood vessels, and facial skeleton. Peripheral trigeminal nerve lesions usually affect 1 of its 3 branches, while a semicircular loss of sensation around the angle of the mouth is typical of lesions affecting the nucleus in the spinal cord region at the C1–C2 level. An objective symptom of trigeminal sensory fiber involvement is the lack of corneal and conjunctival reflexes – failure to close the eye when irritated by a sensory stimulus. In contrast, inability to close 1 eye indicates a facial nerve lesion.

Lesions of the motor fibers of branch III results in:

- impaired jaw movements;
- weakness of teeth clenching;
- reduced tone or atrophy of the masseter and temple muscles;
- diminished jaw reflex.

Trigeminal neuropathy may be caused by:

- injury;
- tumor;
- varicella zoster virus infection.

CN VI abducens nerve

Lesion to the abducens nerve leads to:

- convergent positioning of the eyeball;
- impaired or absent abduction of the eyeball;
- horizontal diplopia when looking towards the lesion.

The causes are similar to those of oculomotor nerve lesions.

CN VII facial and intermediate nerve

Lesion to the facial nerve leads to:

- weakness or paralysis of facial expressions;
- inability to close the eyelids;
- hypersensitivity to sound stimuli;
- weakness of the platysma muscle.

Peripheral facial nerve lesion

A peripheral lesion of the facial nerve occurs when the nucleus of the facial nerve in the pons or its motor fibers, after leaving the nucleus, are damaged on their way to the facial muscles. It presents with paresis or paralysis of all muscles on the ipsilateral side of the face, characterized by smoothing of the forehead and nasolabial fold, and inability to close the eyelids and grin.

A central lesion of the facial nerve affects the supranuclear motor fibers of the facial nerve running from the cortex of the opposite hemisphere of the brain to the lower part of the facial nerve nucleus. It manifests as paresis of the lower part of the face on the side

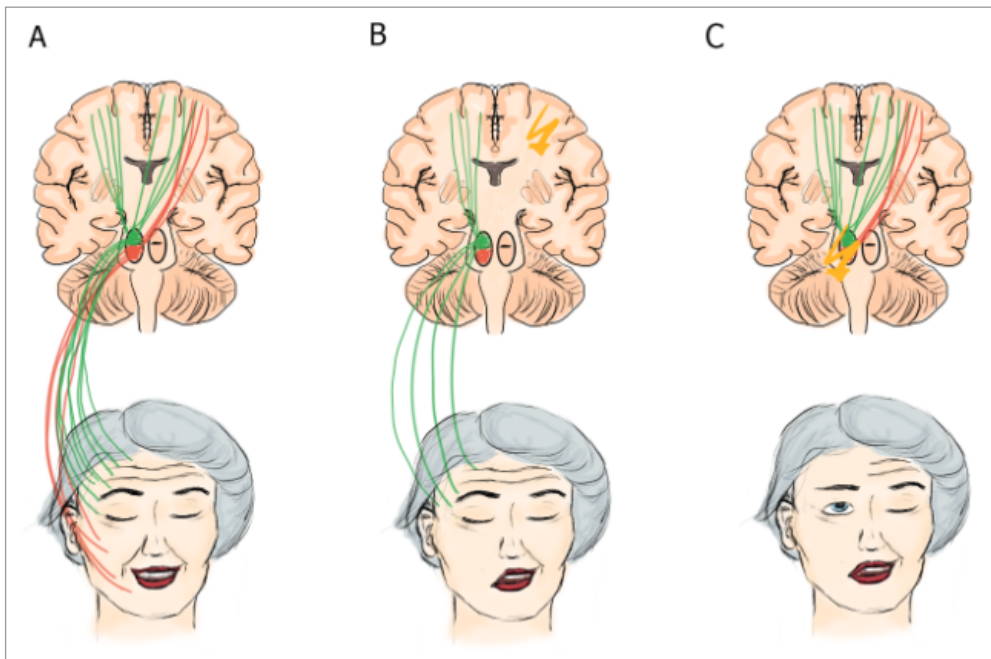


Fig. 1.2. Innervation of facial muscles in normal conditions (A), in central lesion of the right facial nerve (B) and in peripheral lesion of the right facial nerve (C)

Table 1.1. Differentiation of nystagmus

?????	Peripheral nystagmus	Central nystagmus
Type:	horizontal	horizontal, vertical, multidirectional
Direction:	unidirectional towards the healthy side, quick phase	may be unidirectional, usually towards the affected side, multidirectional (direction may change depending on the direction of gaze)
Intensification: 1 st degree – only when looking to the side 2 nd degree – when looking to the side and straight ahead 3 rd degree – when looking in all directions	decreases after visual fixation, usually 1 st degree	does not decrease after visual fixation, I, II and III degree
Accompanying symptoms:	nausea, vomiting, dizziness, no symptoms of lesion to other structures of the central nervous system	other symptoms of lesion to the central nervous system, e.g., brain stem, cerebellum

opposite the lesion (drooping of the mouth corner, inability to grin, and so-called “pipe sign”).

The upper part of the facial nerve nucleus, innervating the muscles of the upper part of the face, is supplied by cortico-nuclear fibers from both brain hemispheres. In contrast, the lower part of the facial nerve nucleus, supplying fibers to the muscles of the lower part of the face, is supplied exclusively by fibers from the contralateral hemisphere. Hence, damage to the supranuclear fibers results in paresis or paralysis of the lower part of the face and preserved innervation of the upper part of the face.

A lesion of the intermediate nerve, which is a part of the facial nerve, leads to:

- a) sensory disorders involving the outer ear, ear canal, and external surface of the eardrum:
 - outer ear;
 - ear canal;
 - outer surface of the eardrum.
- b) taste disturbances in the anterior 2/3 of the tongue (which indicates severe damage to the facial nerve);
- c) impaired secretion of tears and saliva by the sublingual and submandibular glands.

CN VIII vestibulocochlear nerve

A lesion of the cochlear nerve leads to hearing impairment observed during:

- inability to perceive whispered speech from a distance of 6 m;
- inability to hear finger rubbing at the same distance from the ears.

Conductive hearing loss results from impaired conduction of stimuli in the outer and middle ear. It can be detected using the Rinne tuning test, in which bone conduction lasts longer than air conduction. Normally, air conduction is approximately twice as long as bone conduction.

Nervous hearing loss results from damage to the cochlea and can be detected by Weber's tuning test in which the patient hears sounds louder in the healthy ear. For a more accurate hearing assessment, audiometric testing and auditory evoked potentials are used.

A lesion of the vestibular nerve is manifested by:

- nystagmus (fine-wave nystagmus – fine-beat, binocular, horizontal, towards the healthy ear);
- balance disorders and positive Romberg test;
- unsteady gait;
- deviation towards the lesion when trying to walk in place (Unterberger test);
- reduced response to caloric stimulation with cold and warm water.

CN IX glossopharyngeal nerve

A lesion of the glossopharyngeal nerve results in paresis or paralysis of the palatal and pharyngeal muscles.

On the side of the lesion, it is stated:

- lower position of the palate at rest or when phonating the letters “a” and “e”;
- deviation of the uvula to the healthy side during phonation;
- sensory disturbances in the area:

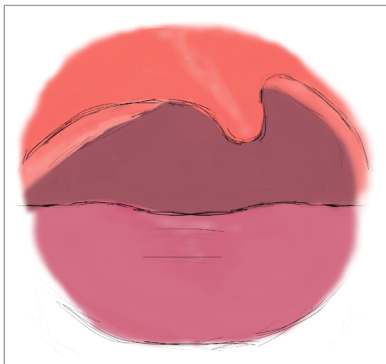


Fig. 1.3. Deviation of the uvula in a lesion of the right glossopharyngeal nerve

- palate;
- throat;
- middle ear;
- esophagus;
- larynx.
- taste disturbances in the back 1/3 of the tongue and parotid gland secretion;
- asymmetry of palatal and pharyngeal reflexes in response to irritation with a spatula;
- dysphagia;
- dysarthria.

CN X vagus nerve

A lesion of the vagus nerve may lead to:

- paresis of the palatal and pharyngeal muscles;
- sensory disturbances involving the palate, pharynx, middle ear, esophagus, and larynx;
- paresis or paralysis of the vocal cords causing hoarseness;
- symptoms of parasympathetic autonomic dysfunction, including orthostatic hypotension, cardiac arrhythmias, dry skin, and constipation.

CN XI accessory nerve

A lesion of the accessory nerve results in paresis of the trapezius muscle, leading to weakness in lifting the shoulder, and paresis of the sternocleidomastoid muscle, causing reduced strength of head rotation to the opposite side of the lesion.

CN XII hypoglossal nerve

A lesion of the hypoglossal nerve leads to:

- ipsilateral atrophy and weakness of the tongue muscles;
- limitation of tongue movements;
- reduced ability to press the cheeks outward with the tongue;
- deviation of the protruding tongue towards the affected side;
- sometimes:
 - fasciculations of the tongue, e.g., in amyotrophic lateral sclerosis;
 - tremor of the tongue, e.g., in parkinsonism;
 - waving of the entire tongue in neurotic disorders.

Note. Symptoms of cranial nerve lesions may also result from damage to the cranial nerve nuclei in the brainstem:

- in the midbrain – CN III, IV;
- in the pons – CN V, VI, VII, VIII;
- in the medulla oblongata – CN IX, X, XI, XII.

Eye movement disorders may result not only from lesions of the cranial nerves (III, IV, VI), but also from neuromuscular transmission disorders (e.g., myasthenia gravis) or myopathies.

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2. Disorders of upper and lower motor neurons

Mieszko Zagrajek

The central nervous system (CNS) consists of:

- a) the brain;
- b) the spinal cord.

The peripheral nervous system (PNS) consists of:

- a) nerves;
- b) ganglia

and can be divided into:

- a) the somatic nervous system;
- b) the visceral nervous system.

The main function of the PNS is to connect the CNS with the limbs and organs.

Upper motor neurons (UMNs) are located in the cerebral cortex and brainstem. They transmit impulses to activate interneurons and lower motor neurons (LMNs), exerting direct or indirect supranuclear control over them. In the cerebral cortex, UMNs are responsible for voluntary motor activity.

Lower motor neurons (LMNs) are located in the anterior horn of the spinal cord, the anterior nerve roots (spinal LMNs), and the cranial nerve nuclei in the brainstem. Lower motor neurons directly innervate skeletal muscles.

Neuroanatomy of the UMNs

The motor cortex consists of:

- a) the primary motor cortex, containing giant pyramidal neurons:
 - Betz's cells;
 - Brodmann's area 4;
- b) the premotor area:
 - Brodmann's area 6.

Premotor area is further divided into:

- a) the supplementary motor area (SMA);
- b) and the premotor cortex.

The entire motor area controls voluntary muscle movement.

The corticospinal and corticobulbar tracts are formed by axons from cortical motor areas. Corticospinal fibers (75–90%) decussate in the lower part of medulla oblongata

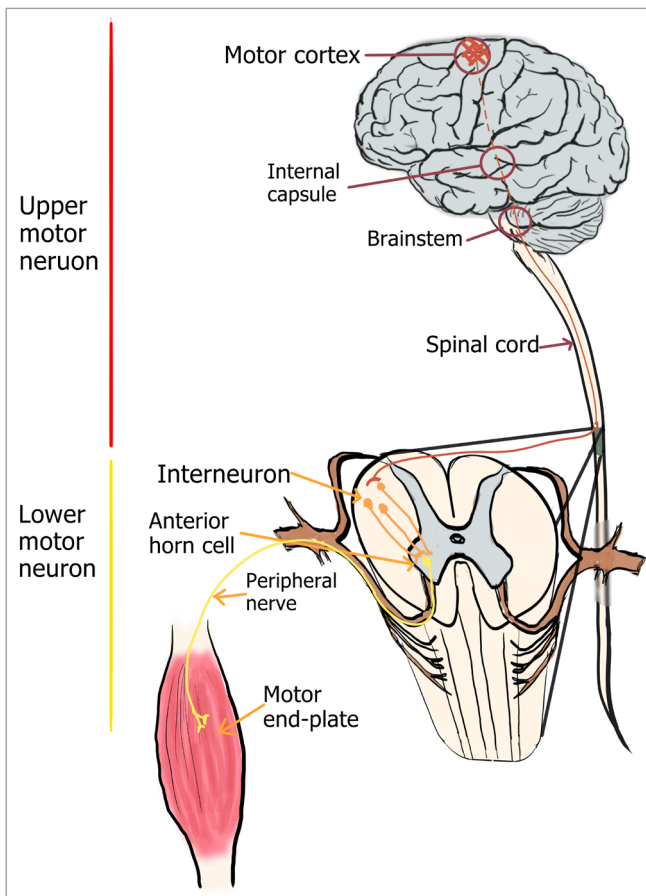


Fig. 2.1. Upper and lower motor neurons

in the area known as pyramidal decussation, forming the lateral corticospinal tract (pyramidal tract), which has an excitatory input to alpha motoneurons.

The extrapyramidal system is responsible for modulating motor function without direct input to LMNs. The basal ganglia are important for the creation of complex motor strategies. The cerebellum directly regulates mechanical execution of movement.

Furthermore, there is also brainstem control – several brainstem nuclei (e.g., Deiter's nucleus) and brainstem reticular formation exert supranuclear on LMNs.

The structures of the limbic system have many different functions, influencing:

- a) motivation;
- b) emotions;
- c) memory;
- d) sensory processing;

- e) the endocrine system;
- f) the autonomic nervous system;
- g) motor behavior.

Thanks to the limbic system, a person's emotional state also has a significant impact on somatic motor neuron activity.

Symptoms of UMN dysfunction are as follows:

- a) less precise and slowed movements;
- b) paresis (loss of muscle strength) – generally mild comparing to LMNs;
- c) spasticity with a clasp-knife response (increased muscle tone);
- d) pathological hyperreflexia (very brisk deep tendon reflexes);
- e) presence of pathological signs, such as:
 - Babinski's sign,
 - Chaddock's sign,
 - Oppenheim's sign,
 - Gordon's sign,
 - Rossolimo's sign;
- f) pseudobulbar palsy (dysfunction of the corticobulbar tracts).

UMNs disorders include:

- a) primary lateral sclerosis;
- b) hereditary spastic paraplegia;
- c) adrenomyeloneuropathy.

Neuroanatomy of the LMNs

The majority of LMNs are located in the anterior horn of the spinal cord and in the brain-stem. They have supranuclear inhibitory and excitatory motor control from different structures of the central nervous system. Motor axons from LMNs directly innervate skeletal muscle fibers.

Large spinal cord LMNs (alpha motoneurons) are the principal motor neurons innervating muscle fibers. Medium-sized spinal cord LMNs (beta motor neurons) integrate both muscle fibers and spindle muscles, whereas small spinal cord LMNs (gamma motoneurons) innervate only spindle muscle fibers. A single alpha motor neuron and its group of skeletal muscles form a motor unit. Motor axons typically mix with sensory and autonomic nerve fibers to form peripheral nerves.

Symptoms of LMN dysfunction include:

- a) paresis/paralysis (partial or complete loss of muscle strength);
- b) muscle atrophy (reduced muscle volume);
- c) hyporeflexia/areflexia (decreased or absent deep tendon reflexes);

- d) muscle hypotonicity or flaccidity (reduced or absent resistance of muscles to passive manipulation);
- e) fasciculations (painless, rapid, spontaneous contractions of muscle fibers).

Examples of disorders affecting LMNs:

- a) poliomyelitis;
- b) progressive post-poliomyelitis muscular atrophy;
- c) multifocal motor neuropathy;
- d) spinal muscular atrophy;
- e) Kennedy's disease;
- f) post-radiation LMN syndrome.

There are also disorders affecting both UMNs and LMNs. The most common and clinically most important of these is amyotrophic lateral sclerosis (ALS).

Other diseases affecting both motor neurons include:

- a) ALS with dementia;
- b) SOD-1 mutation;
- c) paraneoplastic motor neuron disease;
- d) Machado–Joseph disease.

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3. Sensory abnormalities

Monika Służewska-Niedźwiedź

The most important sensory abnormalities include:

- Dysesthesia – an unpleasant or abnormal perception of a stimulus (e.g., pressure provoking tingling or pain).
- Paresthesia – abnormal, spontaneous sensations (e.g., tingling, prickling) occurring without an external stimulus; may resemble dysesthesia but arises spontaneously.
- Neuropathic pain – pain resulting directly from damage to, or disease of, the somato-sensory system.
- Hyperesthesia – increased sensitivity to sensory stimuli.
- Hyperpathia – an exaggerated painful response to stimulation, often with an elevated threshold, delayed perception, and prolonged after-sensation.
- Sensory ataxia – impaired coordination due to loss of proprioceptive input from large-fiber sensory pathways.

Localization of sensory abnormalities

The distribution of sensory disorders is a crucial indicator for locating nervous system damage. When examining sensory abnormalities, it is important to consider motor signs such as weakness, muscle atrophy, and fasciculation, as well as tonus and tendon reflexes. This will help to determine the location of the lesion, whether it is in the central nervous system, spinal cord, nerve root, or peripheral nerve.

Peripheral sensory lesion

Peripheral nerve and plexus lesions produce sensory loss that follows the peripheral anatomical distribution. Distal sensory loss or pain in more than 1 limb suggest peripheral neuropathy. Sensory loss in a restricted portion of 1 limb suggests a peripheral nerve or plexus lesion. Sensory loss affecting the entire limb suggests a central lesion.

Spinal sensory lesion

Depending on the extent and location of the spine damage, we distinguish following sensory syndromes:

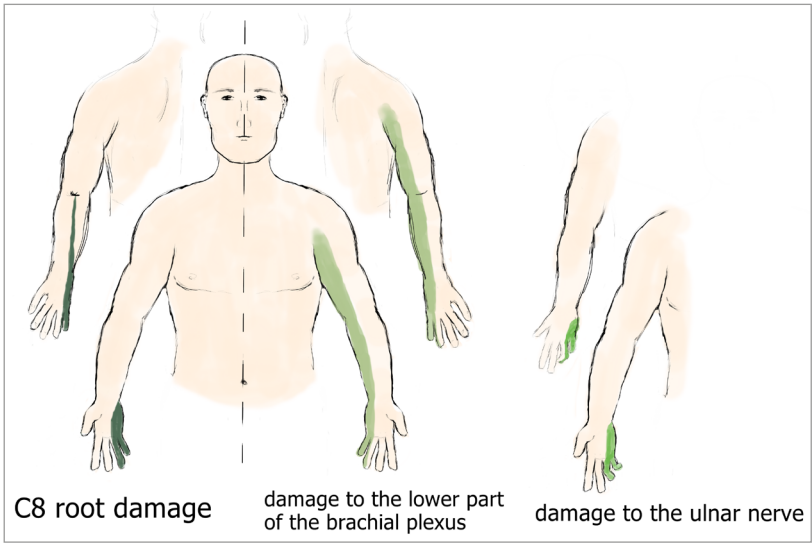


Fig. 3.1. Examples of anatomical distribution of sensory loss in the upper limb

Table 3.1. General guidelines to sensory abnormality localization

Level of lesion	Features and location of sensory loss
Cortical	– sensory loss in contralateral body, restricted to the portion of the homunculus affected by the lesion
Internal capsule	– sensory symptoms in the contralateral body, which usually involve head, arm, leg to an equal extent, – motor findings commonly present, though not always
Thalamus	– sensory symptoms in the contralateral body, including the head, may split the midline, – sensory loss without weakness – suggestive of lesion here
Spinal transection	– sensory loss at or below segmental level, which may be slightly different for each side – motor examination is also key for localization
Spinal hemisection	– sensory loss ipsilateral for vibration and proprioception (dorsal columns), contralateral for pain and temperature (spinothalamic tract)
Nerve root	– sensory symptoms follow dermatomal distribution
Plexus	– sensory symptoms span two or more adjacent root distribution, corresponding to the anatomy of the plexus
Peripheral nerve	– distribution follows peripheral nerve anatomy or involves nerves symmetrically

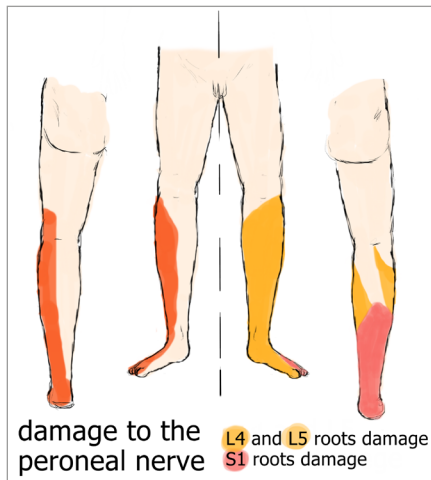


Fig. 3.2. Examples of the anatomical distribution of sensory loss in the lower limb

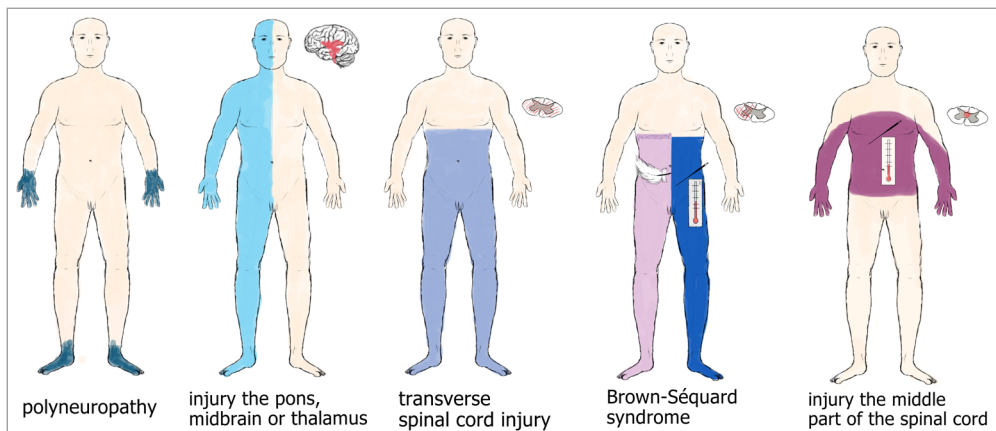


Fig. 3.3. Sensory disturbance syndromes

a) Sensory level:

- spinal transection – sensory loss at or below segmental level.

b) Dissociated sensory loss:

- Spinal hemisection – loss of vibration and proprioception ipsilateral to the lesion, with loss of temperature and pain sensation contralateral to the lesion.

c) Central spinal lesion:

- Bilateral loss of pain and temperature sensation.

Cerebral Sensory Lesion

- a) **Thalamic lesion** – pure sensory deficit of cerebral origin, thalamic pain syndrome (spontaneous pain localized to the distal arm and leg, exacerbated by contact or stress).
- b) **Cortical lesion** – a lesion of the postcentral gyrus produces sensory rather than motor symptoms.

Posterior lesions may spare primary modalities but impair higher sensory functions, such as:

- graphesthesia;
- two-point discrimination;
- perception of double simultaneous stimuli.

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4. Spinal cord anatomy

Karol Marschollek

The spinal cord, along with the cerebrum, is a part of the central nervous system. It is a cylindrical structure that extends from the brainstem and runs within the spinal canal, protected by the vertebral column. In adults, the spinal cord usually ends at the level of the L1/L2 vertebrae, terminating in the filum terminale. It is divided into 5 parts; each composed of a specific number of segments:

- 1) Cervical (8 segments);
- 2) Thoracic (12 segments);
- 3) Lumbar (5 segments);
- 4) Sacral (5 segments);
- 5) Coccygeal (1 segment).

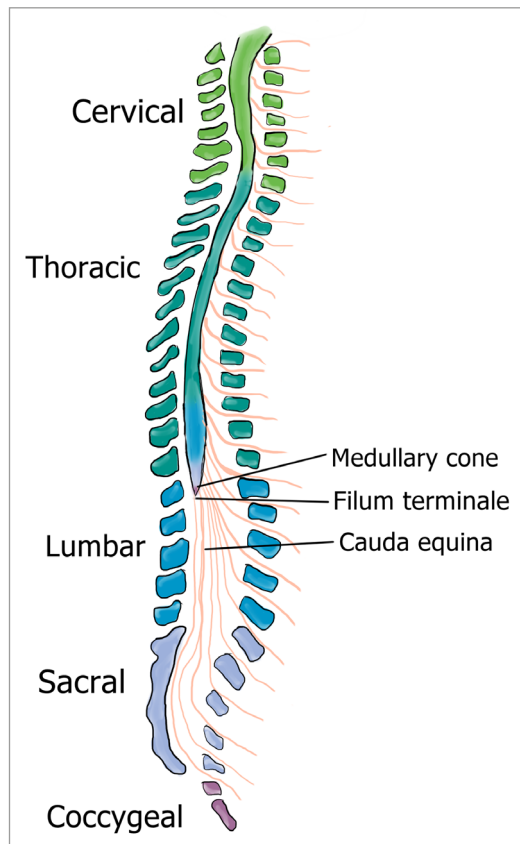


Fig. 4.1. Spinal cord anatomy

From each segment of the spinal cord, on both sides, a ventral root (motor) and a dorsal root (sensors) separate and then fuse to form the spinal nerve, leaving the spinal canal through the corresponding intervertebral foramen. The elongated roots of the lumbar and sacral nerves form a structure called the cauda equina, which runs parallel to the filum terminale to reach the appropriate intervertebral foramina.

The relative positioning of the white and gray matter in the spinal cord is different from that in the cerebrum. The peripherally located white matter is divided into 3 funiculi on each side of the spinal cord: anterior, lateral, and posterior. They comprise the ascending and descending fibers of the neuronal tracts.

The gray matter is located centrally and has the shape of the letter H in cross-section. There are columns (or horns) on each side: anterior, posterior, and lateral. They contain the nuclei of cells that are elements of neural pathways. The efferent (descending) pathways are divided into the corticospinal tract and the extrapyramidal system tracts. The corticospinal (pyramidal) tract is responsible for voluntary motor function. It starts in the motor cortex and leads to the alpha motor neurons located in the anterior gray horns. Fibers that cross at the pyramidal decussation (70–90% of all fibers) form the lateral corticospinal tract, while the remaining fibers form the anterior corticospinal tract.

The most important extrapyramidal pathways include:

- vestibulospinal tract;
- tectospinal tract;
- rubrospinal tract;
- reticulospinal tract;
- olivospinal tract.

Afferent (ascending) pathways transmit the information of different modalities from receptors to the central nervous system.

The posterior column–medial lemniscus pathway carries sensory input from neuromuscular spindles and Golgi tendon organs and is responsible for conscious proprioception and touch discrimination. This pathway divides into the **fasciculus gracilis** (fibers from the lower extremities and trunk) and **fasciculus cuneatus** (fibers from the upper extremities).

The **anterior spinothalamic tract** carries information of touch and pressure, whereas the **lateral spinothalamic tract** is responsible for the sensation of pain and temperature.

The **anterior and posterior spinocerebellar tracts** transfer sensory information from muscles and joints to the cerebellum in order to coordinate muscle tone and movement precision.

Spinal cord syndromes:

Injury of the spinal cord can be either acute or progress gradually. Clinical symptoms will depend on the level of the lesion, such as:

a) Complete cord transection:

- Sensory loss (all modalities) below the level of the lesion.
- Radicular pain or segmental paresthesias may be present at the level of the lesion.
- Muscle weakness below the lesion reflects upper motor neuron damage (spasticity, hyperreflexia, presence of pathological signs). Acute damage to the spinal cord may result in an initial phase of spinal shock – with lower motor neuron signs (flaccid paresis, areflexia).
- Urinary and rectal sphincter dysfunction are present.
- Most common causes: tumor, infectious, multiple sclerosis.

b) Central cord syndrome:

- Dissociated sensory loss – impaired sensation of pain and temperature with preserved sensation of touch and position.
- In acute cervical spine injury – disproportionate upper extremity weakness and less severe lower extremity weakness.
- Urinary and rectal sphincter dysfunction may be present.
- Most common causes: injury, syringomyelia, intramedullary spinal cord tumors.

c) Brown–Séquard syndrome:

- Hemisection of the spinal cord.
- Loss of proprioception below the level of the lesion ipsilaterally.
- Loss of pain and temperature sensation contralaterally (usually 1 or 2 segments below the level of the lesion).
- Radicular pain or segmental paresthesia may be present at the level of the lesion.
- Muscle weakness below the lesion ipsilaterally – upper motor neuron damage (spasticity, hyperreflexia, presence of pathological signs).
- Most common causes: injury, intramedullary spinal cord tumors.

d) Anterior cord syndrome:

- most commonly caused by occlusion of the anterior spinal artery (which supplies the anterior two-thirds of the spinal cord);
- muscle weakness (with flaccid muscle tone) at and below the level of the lesion;
- loss of pain and temperature sensation at and below the level of the lesion, with preserved sensation of touch and position;
- urinary and rectal sphincter dysfunction may be present;
- may manifest as an isolated flaccid paralysis (anterior horn cell syndrome), e.g., spinal muscular atrophy or poliomyelitis.

e) Posterior cord syndrome:

- loss of proprioception below the level of the lesion with preserved sensation of pain, temperature, and motor function – sensory ataxia;
- most common causes: vitamin B12 deficiency, neurosyphilis, compressive extramedullary tumors, and cervical spondylosis.

f) Conus medullaris syndrome:

- sensory deficit of saddle distribution, usually with no dissociation of sensation;
- symmetric and mild motor weakness of the lower limbs (mixed upper and lower motor neuron dysfunction);
- early symptoms of urinary and rectal sphincter dysfunction;
- spontaneous pain is not common;
- onset is usually sudden and bilateral;
- most common cause: injury.

g) Cauda equina syndrome:

- sensory deficit in a saddle distribution, usually with dissociation of sensation;
- asymmetric and more prominent motor weakness of the lower limbs (lower motor neuron dysfunction with flaccid paresis);
- symptoms of urinary and rectal sphincter dysfunction may be present;
- spontaneous pain is common and prominent – usually severe and radicular, radiating to the perineum, thighs and back;
- onset is more gradual than in conus medullaris syndrome;
- most common cause: injury, disc herniation, burst fractures.

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5. Cerebellar syndrome

Konstanty Gurański

Anatomy of the cerebellum

Major parts of the cerebellum:

- a) vermis;
- b) two cerebellar hemispheres;
- c) cerebellar peduncles (superior, middle, and inferior);
- d) tonsils.

Internal structures:

- a) cortical gray matter;
- b) cerebellar white matter;
- c) deep cerebellar nuclei.

Cerebellar lobes:

- a) anterior lobe (regulation of muscle tone);
- b) posterior lobe (coordination of voluntary motor activity);
- c) flocculonodular lobe (maintenance of posture and balance; connected to the vestibular nuclei).

Main cerebellar tracts:

- a) vestibulocerebellar tract;
- b) anterior spinocerebellar tract;
- c) posterior spinocerebellar tract;
- d) corticopontocerebellar tract;
- e) cerebro-olivocerebellar tract;
- f) cerebro-reticulocerebellar tract;
- g) cerebro-pontocerebellar tract.

Vascular supply to the cerebellum:

- a) posterior inferior cerebellar artery (PICA);
- b) anterior inferior cerebellar artery (AICA);
- c) superior cerebellar artery (SCA).

Main functions of the cerebellum:

- a) maintenance of posture and balance;
- b) control of muscle tone;
- c) coordination of voluntary motor activity;
- d) other: respiratory movements, motor learning, cognitive functions.

Functions of various parts of the cerebellum:

- a) **Vermis:** proximal limb and trunk coordination;
- b) **Flocculonodular lobe:** balance and vestibulo-ocular reflexes;
- c) **Lateral hemispheres:** motor planning for extremities;
- d) **Intermediate hemispheres:** distal limb coordination.

Symptoms of cerebellar lesion

- Vertigo (often accompanied by nausea and vomiting) or dizziness;
- scanning dysarthria (words are broken down into separate syllables and spoken with varying force).

Oculomotor signs:

- a) dysmetric saccades;
- b) nystagmus:
 - horizontal, direction-changing, bilateral gaze-evoked nystagmus (more prominent when the eyes move toward the side of the cerebellar lesion);
 - rebound nystagmus (transient nystagmus that appears on returning to straight-ahead gaze after prolonged eccentric gaze);
 - vertical nystagmus may also be present.

Appendicular ataxia (hemisphere lesion):

- a) dysmetria (finger–nose and heel–shin test);
- b) dysrhythmia (e.g., finger tapping, foot tapping);
- c) intention tremor (finger–nose/finger–finger and heel–shin test);
- d) postural tremor;
- e) dysdiadochokinesia/adiadochokinesia: inability to perform rapid alternating movements; movements are slow and irregular,
- f) muscular hypotonia;
- g) rebound phenomenon (Stewart–Holmes sign);
- h) macrographia.

Limb ataxia is ipsilateral to the side of the cerebellar lesion.

truncal ataxia (vermis lesion):

- a) wide-based, unsteady gait: patients tend to fall or deviate toward the side of the lesion;
- b) head and/or trunk titubation;
- c) ataxia of stance/astasia: the patient has problems sitting or standing unsupported (Romberg test is helpful in differentiating cerebellar ataxia from sensory ataxia).

Etiology of cerebellar ataxia

Acute causes:

- Stroke;
- Toxic (ethanol; anticonvulsants; other medications, heavy metals);
- Traumatic injury;
- Demyelination (multiple sclerosis, acute disseminated encephalomyelitis);
- Infectious (acute viral cerebellitis, postinfectious cerebellitis, Lyme disease);
- Metabolic disorders (Wernicke's encephalopathy, hepatic encephalopathy; pontine and extrapontine myelinolysis).

Subacute and chronic causes:

- Tumors;
- Demyelination (multiple sclerosis);
- Autoimmune disorders (Miller Fisher syndrome, Bickerstaff encephalitis, GAD antibody-associated ataxia, systemic immune disorders);
- Chronic toxin exposure;
- Inherited and degenerative disorders (SCA, MSA-C, FXTAS, Friedreich's ataxia, Wilson's disease, mitochondrial syndromes, CANVAS);
- Creutzfeldt–Jakob disease;
- Arteriovenous malformations;
- Paraneoplastic syndromes;
- Nutrient-related diseases (vitamin E deficiency, celiac disease).

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6. Extrapyramidal syndromes

Ewa Koziorowska-Gawron

Basal ganglia (substantia nigra, putamen, caudate nucleus, globus pallidus, subthalamic nucleus) are responsible for the initiation and continuation of voluntary movements. Impairment of basal ganglia and their connections manifests as extrapyramidal syndromes, which can be divided into 2 main groups:

a) Hypertonic–hypokinetic syndrome

- increased muscle tone with diminished movements;
- also referred to as akinetic–rigid syndrome;
- parkinsonism is a form of hypertonic–hypokinetic syndrome.

b) Hypotonic–hyperkinetic syndrome

- decreased muscle tone with involuntary movements (dyskinesias);
- main symptoms: chorea, athetosis, dystonia, ballism, and tics;
- myoclonus is often included here; however, it may result from dysfunction of other nervous system structures, not only the basal ganglia.

Hypertonic–hypokinetic syndrome

Parkinsonism (parkinsonian syndrome) consists of:

a) Rigidity

- constantly increased muscle tone, equally affecting flexor and extensor muscles of the limbs and trunk;
- also called stiffness or plasticity, often compared to “lead-pipe”;
- when accompanied by resting tremor, jerks called the “cogwheel sign” may appear.

b) Resting tremor

- rhythmic, biphasic oscillatory movements with a frequency of 4–7 Hz, present at rest;
- increases with emotions, improves during movements, disappears during sleep;
- affects distal parts of the limbs, especially the hands;
- due to the movement of the thumb against the fingers, it is compared to “pill-rolling” or “counting money”.

c) Bradykinesia

- slowness and paucity of movements with difficulties in initiation, continuation, and performing alternating activities.
- Together with rigidity and resting tremor, it manifests as:
- immobile face;
- hypophonic and monotonic dysarthria;

- deterioration of limb motor skills with spidery writing and micrographia;
- stooped posture with a shuffling gait;
- reduced arm swing;
- postural instability.



Fig. 6.1. Patient with parkinsonism

Types of parkinsonism

- a) Primary idiopathic parkinsonism – Parkinson's disease (PD).
- b) Primary atypical parkinsonism (parkinsonian-plus syndromes):
 - multiple system atrophy (MSA);
 - Lewy body dementia (LBD);
 - progressive supranuclear palsy (PSP);
 - cortico-basal degeneration (CBD).
- c) Secondary parkinsonism:
 - vascular parkinsonism (small-vessel disease with multifocal lacunar subcortical infarcts);
 - drug-induced parkinsonism (neuroleptics);
 - parkinsonism in the course of normal pressure hydrocephalus (NPH).

Hypotonic–hyperkinetic syndrome

Chorea

- a) irregular, brief, jerky, unpredictable “dance-like” movements;
- b) flitting movements affecting different parts of the body, interfering with speech, voluntary movements, posture, and gait.

Types of chorea:

- a) Primary, idiopathic and hereditary – Huntington’s disease (HD).
- b) Secondary (acquired):
 - pregnancy;
 - systemic lupus erythematosus (SLE);
 - Sydenham’s chorea;
 - levodopa-induced chorea.



Fig. 6.2. Patient presenting choreic movements

Athetosis

- a) slow, convoluted, writhing movements;
- b) frequently accompanied by chorea (choreoathetosis);
- c) may also be associated with dystonia;
- d) typically affects the face and distal parts of the limbs (fingers, hands, toes, feet);
- e) appears due to impairment of the basal ganglia region in the course of:
 - cerebral palsy;
 - stroke;
 - trauma.

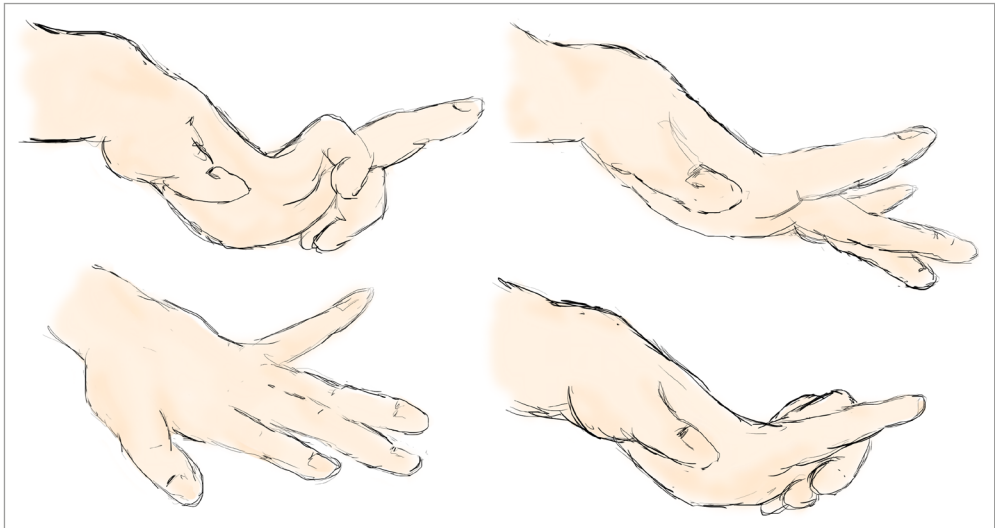


Fig. 6.3. Patient presenting athetotic movements

Dystonia

- a) repetitive, twisting movements with sustained muscle contractions;
- b) may be painful and lead to abnormal posture.

Types of dystonia (according to localization):

- Focal dystonia (one part of the body):
 - blepharospasm;
 - oromandibular dystonia.
- Segmental dystonia (two or more adjacent regions):
 - cervical dystonia;
 - Meige syndrome.

- Generalized dystonia (whole body):
 - Oppenheim's dystonia (DYT1);
 - Dopa-responsive dystonia (DYT5; Segawa's dystonia).
- Action-induced dystonia interfering with specific tasks, e.g.:
 - writer's cramp.

Causes of dystonia:

- a) idiopathic, genetically conditioned dystonias (e.g., DYT5);
- b) symptomatic dystonias:
 - Wilson's disease;
 - cerebral palsy;
- c) drug-induced dystonia:
 - levodopa;
 - metoclopramide;
 - neuroleptics.

Ballism

- a) sudden, violent, large-amplitude flinging movements;
- b) typically affects proximal limb segments and is almost ceaseless;
- c) may involve:
 - a single limb (monoballism);
 - both limbs on one side (hemiballism);

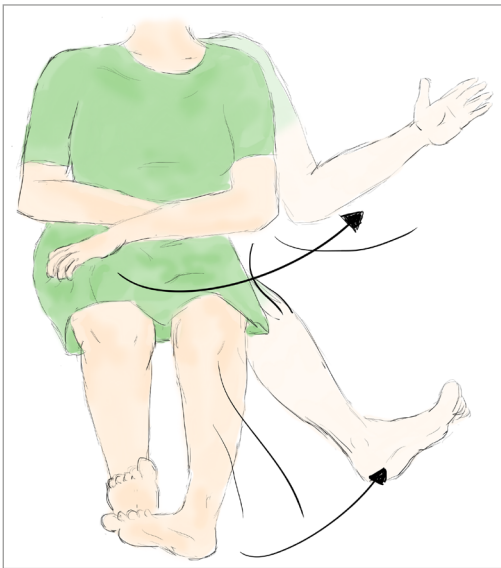


Fig. 6.4. Patient with ballism

- d) extremely rare;
- e) appears due to the impairment of basal ganglia in the course of:
 - stroke;
 - trauma;
 - tumor;
 - non-ketotic hyperglycemia.

Tics

- a) Motor tics
 - brief, repetitive, non-rhythmic contractions of a muscle or a group of muscles;
 - can be simple or complex.

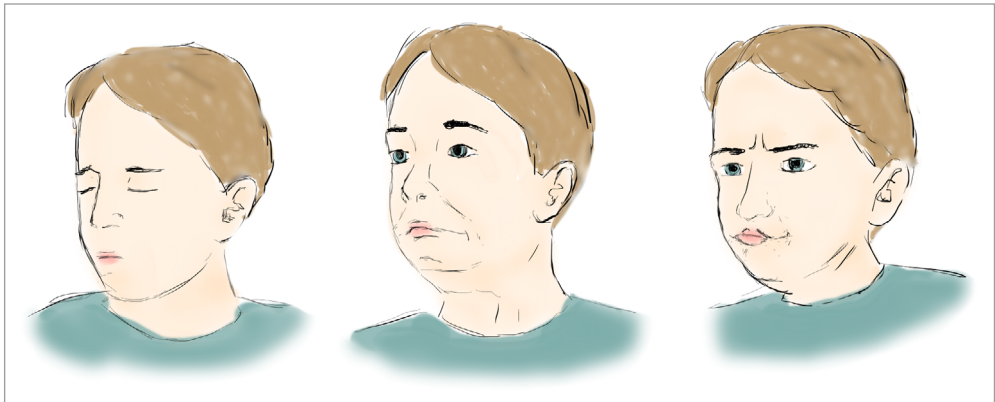


Fig. 6.5. Patient presenting motor tics

- b) Vocal tics
 - sudden, explosive sounds such as snorting, grunting, verbal obscenities;
 - can be simple or complex.
- c) Very common and usually benign.
- d) They are the main symptom of Gilles de la Tourette syndrome.

Myoclonus

- a) shock-like, irregular twitching of a muscle or a group of muscles;
- b) may occur alone or in sequence, either patterned or without a pattern;
- c) various stimuli may precipitate myoclonic jerks (noise, light, touch).

Type of myoclonus (according to etiology):

- a) physiologic;
- b) essential;
- c) epileptic;
- d) symptomatic.

Type of myoclonus (according to anatomical origin):

- a) cortical;
- b) brainstem;
- c) spinal;
- d) peripheral.

Causes of myoclonus:

- normal sleep startle;
- hypnagogic myoclonic jerks;
- essential myoclonus;
- myoclonic epilepsy;
- subacute sclerosing panencephalitis (SSPE);
- Creutzfeldt–Jakob disease (CJD);
- hepatic or uremic encephalopathy;
- lipid storage diseases (e.g., Gaucher’s disease).

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7. Gait disturbance

Justyna Chojdak-Łukasiewicz

Gait is the term used to describe the pattern of a person's walking. Normal gait is a cyclical and symmetric process. The gait cycle begins when the heel of one foot contacts the ground and ends when the other heel does the same. This cycle sets an individual in motion.

The gait process depends on neuronal circuits and pathways from the entire central and peripheral nervous system. The gait engages sensory and motor inputs (visual, vestibular, proprioception, premotor planning, upper and lower motor neurons, cerebellum, basal ganglia, and spinal cord). Observation of gait is an important part of the neurological examination that may provide information about several musculoskeletal and neurological conditions.

The most important types of gait disturbances are:

a) Hemiplegic gait

The patient stands with unilateral weakness on the affected side, arm flexed, adducted, and internally rotated. The leg on the same side is extended with plantar flexion of the foot and toes. During walking, the patient holds the affected arm close to the body and makes a semicircular (circumduction) movement with the affected leg.

The most common cause of hemiplegic gait is stroke, which results in unilateral weakness and spasticity.

b) Diplegic gait (scissoring gait)

The patient has bilateral involvement with spasticity. The lower extremities are more affected than upper extremities. The hips and knees are flexed and adducted, while the ankles are extended and internally rotated.

Diplegic gait is characterized by leg stiffness, a narrow base, and often some circumduction during the forward swing due to difficulty lifting the foot sufficiently.

The most common cause is cerebral palsy.

c) Cerebellar gait (ataxic gait)

Clumsy, staggering movements with a wide-based gait. Patients are unable to walk from heel-to-toe or in a straight line. When standing, the patient's body may sway back and forth or side to side. Patients with ataxia have a significant risk for falling.

The most common cause of cerebellar gait is cerebellar dysfunction.

d) Neuropathic gait (steppage gait)

Lifting the leg higher than normal by elevating the hip. The foot may appear floppy when it drops, and toes usually point downward and scrape the ground during the walk.

Neuropathic gait is caused by weakness of distal limb muscles (typically the dorsiflexors of the foot).

The most common causes include peripheral neuropathies with peroneal nerve injuries.

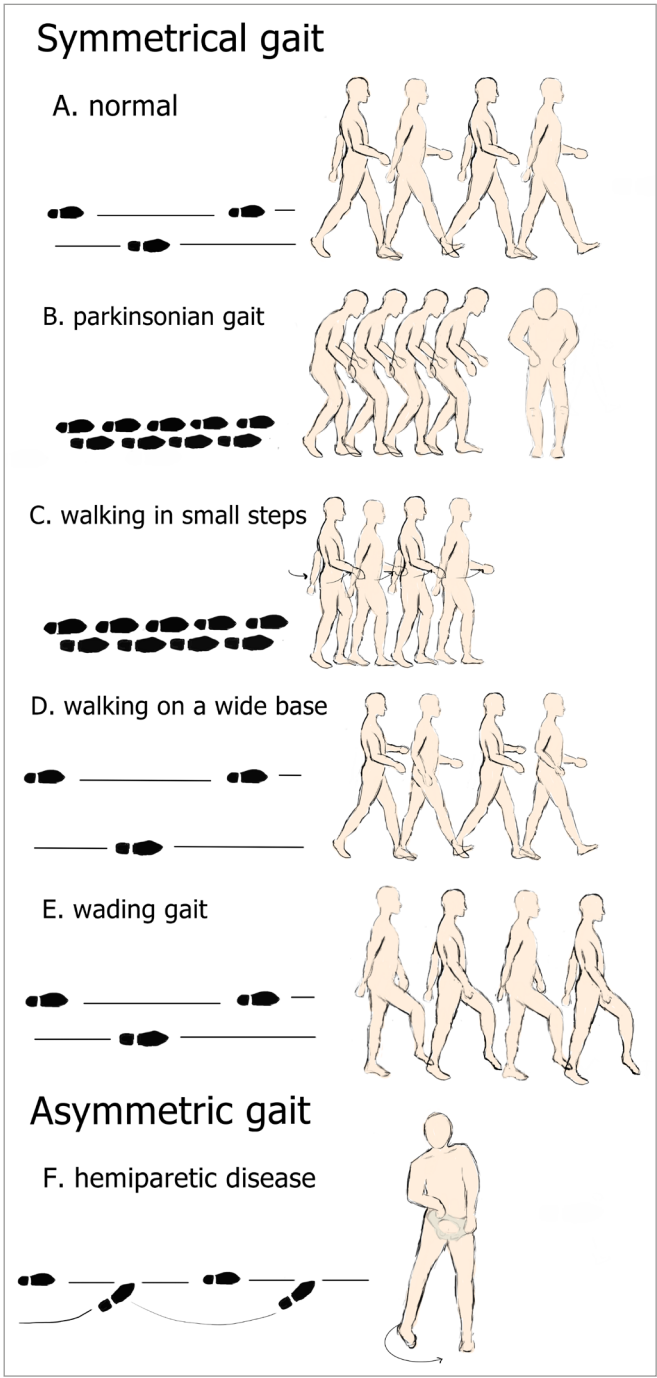


Fig. 7.1. Different types of gait

e) Myopathic gait (waddling gait)

The patient presents an inability to stabilize the pelvis during the stance phase. As a result, the pelvis tilts downwards toward the unsupported side during the swing phase of the gait cycle.

This gait results from weakening of the muscles that abduct the hip joint, producing a waddling (duck-like) appearance.

The gait is characteristic for myopathies.

f) Parkinsonian gait

The patient walks slowly with little steps and a stooping, rigid posture, with head and neck bent forward. In some patients, freezing episodes and slow turning are observed. Parkinsonian gait is a result of stiffness and rigidity.

g) Choreiform gait (hyperkinetic gait)

The patient walks with irregular, jerky, involuntary movements affecting all extremities. Walking may accentuate the underlying movement disorder.

The most common causes are basal ganglia disorders such as Huntington's disease and other forms of chorea, athetosis, or dystonia.

h) Antalgic gait

Walking is secondary to pain that causes a limp, whereby the stance phase is shortened relative to the swing phase.

Antalgic gait develops as a result of pain, especially lower limb pain.

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8. Meningeal syndrome

Ewa Koziorowska-Gawron

Meningeal syndrome (meningism) is caused by irritation of the meninges, mainly in the course of neuroinfections (meningitis) or hemorrhages (subarachnoid hemorrhage), less frequently from neoplastic processes.

Meningeal syndrome consists of:

- **Subjective symptoms**

- headache;
- nausea;
- vomiting;
- photophobia;
- hyperacusis;
- hyperesthesia.

- **Objective symptoms**

Examined by the physician in a patient lying on their back and include:

- a) Eyeballs tenderness: Pressure applied to the eyeballs through closed eyelids causes pain.
- b) Neck stiffness:
 - resistance occurs during flexion of the neck toward the sternum;
 - the distance between the chin and the sternum (due to this resistance) can be measured or expressed as the number of fingers that fit between them.
- c) Upper Brudzinski's sign:
 - flexion of the neck toward the sternum triggers flexion of the lower limbs at the hips and knees.
- d) Lower Brudzinski's sign:
 - pressure applied to the lower abdomen (over the pubic symphysis) elicits flexion of the lower limbs at the hips and knees.
- e) Kernig's sign:
 - elevation of a straightened lower limb results in reflex flexion at the hip and knee;
 - elevation of the lower limb flexed at the knee and an attempt to straighten it causes resistance.
- f) Flatau's sign:
 - flexion of the neck toward the sternum causes pupillary dilatation.
- g) Herman's sign ("neck-big toe" sign)
 - flexion of the neck toward the sternum causes dorsal flexion of the big toes.

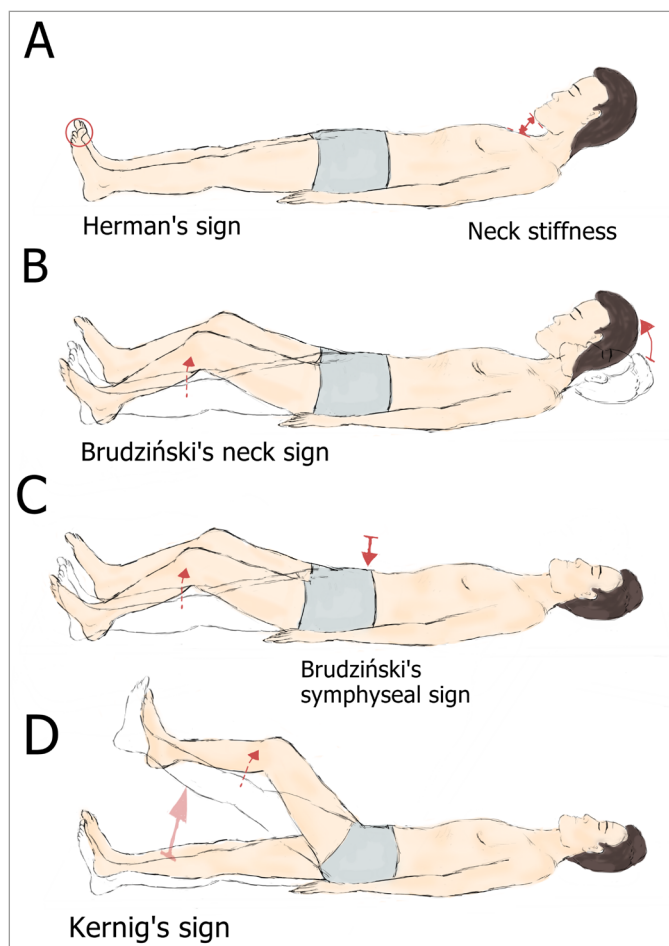


Fig. 8.1. Examination of meningeal signs

h) Amoss's sign ("Amoss tripod"):

- when rising from a supine to a sitting position, the patient supports the trunk with straightened upper limbs.

i) Opisthotonus:

- abnormal supine position with backward arching of the head, neck, and trunk.

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9. Disorders of higher brain functions

Krzysztof Słotwiński

Higher nervous activities include:

- **Speech** – a human way of expressing one's thoughts and communicating through language. The anatomical basis for these activities, mediated by associative processes, is located in the secondary and tertiary association cortices of individual brain lobes, with participation of the limbic system (responsible for emotion and memory), as well as the phonatory, respiratory, and articulatory systems. The quaternary cortex of the anterior part (prefrontal) of the frontal lobe is involved in integrating and coordinating these processes.
 - **Praxia** – the ability to efficiently perform complex movements according to an acquired and consolidated motor plan. The neurophysiological basis of praxia is the activity of a widely branched neuronal network.
 - **Gnosia** – the ability to recognize known people, objects, phenomena, and body parts, while using spatial orientation. The structural substrate is the secondary and tertiary association cortex, often in the dominant hemisphere, involving the parietal and occipital lobes.
- Damage to the structures responsible for higher nervous activities and/or disruption of the functions of these areas causes disorders known as:

- a) aphasia;
- b) apraxia;
- c) agnosia.

Aphasia

Aphasia is an acquired disorder of language comprehension, processing, and/or expression, caused by damage to the cortical and/or subcortical regions of the dominant cerebral hemisphere. It is accompanied by impairment of the central programming mechanisms of previously mastered speech functions.

Functional neuroimaging studies using PET have shown that the process of language formation involves:

- homologous cortical regions in the non-dominant hemisphere (responsible for prosody: melody, rhythm, intonation, emotional tone);
- subcortical structures, especially the thalamus and basal ganglia;
- and, likely, the cerebellum.

Aphasic disorders may be caused by:

- stroke;
 - craniocerebral trauma;
 - intracranial proliferative processes;
 - degenerative brain diseases;
 - less frequently, inflammatory or parasitic brain diseases.
- Transient aphasic events may occur during TIAs or partial epileptic seizures.

Types of aphasia

- **Motor aphasia (Broca's aphasia)** – caused by a lesion in the posterior-inferior premotor area of the dominant frontal lobe (area 44B). Speech is non-fluent, effortful, with grammatical errors, impaired naming and repetition. Comprehension is preserved;
- **Sensory aphasia (Wernicke's aphasia)** – caused by a lesion in the posterosuperior temporal lobe of the dominant hemisphere (area 22B). Speech is fluent but filled with paraphasias and neologisms, producing an incomprehensible message. Comprehension, repetition, naming, reading, and writing are impaired;
- **Mixed (sensory-motor) aphasia** – the most common form after stroke, containing elements of both motor and sensory aphasia;
- **Amnesic (anomic) aphasia** – typically related to lesions in the temporo-parieto-occipital junction (areas 39B, 40). Naming is impaired while comprehension and repetition remain preserved;
- **Conductive aphasia** – due to arcuate fasciculus lesion. Fluent speech with paraphasias, impaired repetition, preserved comprehension;
- **Global aphasia** – extensive damage to frontal, temporal, and parietal regions. Speech and comprehension are profoundly impaired or absent;
- **Primary progressive aphasia (PPA)** – a neurodegenerative form of aphasia preceding other symptoms of dementia. Three variants:

Non-fluent/agrammatic variant (nfvPPA)

Characteristics:

- impaired word retrieval;
- articulation difficulties;
- grammatical errors;
- preserved awareness of deficits.

Two forms:

- a) **Dominant syntactic deficit** – simplified sentences, grammatical errors;
 - b) **Dominant apraxia of speech** – impaired articulation, dysprosody.
- MRI: atrophy of left posterior frontal region at the border with the insula.

Semantic variant (svPPA)

Gradual loss of semantic knowledge:

- difficulties naming and recognizing objects;
 - fluent but semantically impoverished speech;
 - replacement of lost words with more general or prototypical terms.
- MRI: predominant atrophy of the anterior temporal lobe.

Logopenic variant (lvPPA)

A linguistic variant of Alzheimer's disease, characterized by:

- slow speech with pauses;
- impaired word retrieval;
- phonological errors;
- impaired repetition of long phrases.

MRI: atrophy around the posterior Sylvian fissure and parietal region (left).

Transcortical aphasia

- **Transcortical motor aphasia** – lesion anterior/superior to Broca's area; similar to Broca's aphasia but milder; preserved repetition;
- **Transcortical sensory aphasia** – lesion in temporo-parietal region; similar to Wernicke's aphasia but with preserved repetition;
- **Transcortical mixed aphasia** – impaired spontaneous speech, naming, comprehension, reading, writing; preserved repetition.

Subcortical aphasia

Can follow lesions of the left thalamus, basal ganglia, or internal capsule. Speech is fluent with paraphasias, but less severe than cortical aphasia.

Speech executive dysfunction

Speech execution involves:

- supplementary motor area (initiation);
- primary motor cortex;
- corticobulbar tracts;
- brainstem nuclei;
- cranial nerves and articulatory muscles.

The extrapyramidal and cerebellar systems coordinate tone and rapid alternating movements. The limbic system and non-dominant hemisphere mediate emotional prosody.

Damage to these structures causes:

- **aphonia or dysphonia**;
- **dysarthria**;
- or, in psychogenic cases, **mutism**.

Types of dysarthria

- **Cortical dysarthria** – exaggerated, uncoordinated articulatory movements; disturbed prosody; irregular breathing.
- **Supranuclear (spastic, pseudobulbar) dysarthria** – hoarse, strained voice; monotony; slow speech; distorted vowels.
- **Flaccid (peripheral) dysarthria** – weakness and flaccidity of articulatory muscles; hypernasality; short phrases; imprecise consonants.
- **Subcortical (extrapyramidal) dysarthria**:
 - a) **Hypertonic form** – stiff, slow, unclear speech.
 - b) **Hyperkinetic form** – irregular articulatory movements; variable nasality; strained voice.
- **Cerebellar dysarthria** – irregular rhythm, “scanning” speech, impaired coordination of articulators.
- **Mixed dysarthria** – combination of types, typical in diffuse/multifocal brain disorders.

Apraxia

Apraxia = inability to perform learned motor sequences despite preserved strength, sensation, attention, and comprehension.

Types of apraxia

- **Kinetic (limb-kinetic) apraxia** – loss of kinesthetic memory patterns; clumsy, imprecise movements; difficulty with fine hand tasks;
- **Ideational apraxia** – impaired conceptual plan of a multi-stage act; patient cannot complete a sequence of actions;
- **Constructional apraxia** – inability to assemble elements (puzzles, blocks); parietal-dominant hemisphere lesions;
- **Ideo-motor apraxia** – inability to imitate or perform gestures on command despite understanding; lesion in supramarginal gyrus.

Agnosia

Agnosia = inability to recognize stimuli despite intact sensory pathways.

Types of agnosia

- **Adermolexia** – inability to recognize letters “written” on the skin;
- **Color agnosia** – difficulty identifying colors;
- **Auditory agnosia** – inability to recognize familiar sounds;
- **Visual agnosia** – impaired recognition of objects by sight;
- **Anosognosia** – neglect of one side of the body (usually left);
- **Autotopagnosia** – impaired identification of body parts;
- **Prosopagnosia** – impaired recognition of familiar faces;
- **Stereoagnosia** – impaired tactile object recognition.

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10. Syndromes resulting from lesions of the cerebral lobes

Konstanty Gurański, Krzysztof Słotwiński

Frontal lobe

The prefrontal cortex has a six-layered structure and is one of the evolutionarily youngest regions of the cerebral cortex. Its basic role is related to the initiation and organization of voluntary movements and the integration of diverse brain activities.

Structure (functional architecture of the frontal lobe)

- **Primary motor cortex (area 4):** located in the precentral gyrus; responsible for voluntary movements.
- **Secondary motor cortex (area 6):** situated in the posterior portions of the superior and middle frontal gyri; responsible for planning limb movements. This region includes:
 - supplementary motor area (SMA),
 - premotor area (PMA).
- **Frontal eye field (area 8):** located in the superior and middle frontal gyrus; responsible for voluntary eye movements.
- **Prefrontal cortex (areas 9–12):** located in the superior and middle frontal gyri; responsible for consciousness, thinking, and higher nervous activities.
- **Motor speech cortex (Broca's area, areas 44–45):** located in the inferior frontal gyrus; responsible for speech production.
- **Prefrontal association cortex (area 46):** located in the middle frontal gyrus; responsible for behavior, thinking, and planning eye movements.

Motor cortex – clinical manifestations of lesions

- **Paresis:** usually limited to one limb (monoparesis) or part of a limb, with low muscle tone (in the absence of extrapyramidal signs). Pathological reflexes may appear (e.g., Babinski sign).
- **Paroxysmal convulsions:** typically involving hands and/or face; consciousness preserved. This is a form of Jackson's motor seizure.

Premotor cortex (areas 6B and 8B) – clinical manifestations of lesions

- **Kinetic (limb-kinetic) apraxia:** movements are imprecise, uncertain, clumsy, and ineffective.
- **Non-fluent motor aphasia:** impaired speech fluency with preserved comprehension (damage to Broca's area 44) in the dominant hemisphere.
- **Adverse symptoms:** paroxysmal deviation of the eyeballs, and sometimes the head and trunk, to the opposite side (adversive epileptic seizure).
- Frontal ataxia:
 - astasia (inability to maintain a standing position),
 - abasia (inability to walk).

Prefrontal cortex (areas 9–12)

The youngest and least differentiated part of the frontal lobe. It has extensive connections with the motor cortex, other cortical areas, the reticular system, thalamic nuclei, and limbic structures.

Unilateral lesions cause mild, easily compensated disturbances. Bilateral lesions lead to behavioral changes:

- apathy, loss of interests, psychomotor slowing (dorsolateral prefrontal area),
- or disinhibition, jocularity, and loss of social restraint ("moria").

Notable clinical syndrome

- **Foster–Kennedy syndrome:** ipsilateral anosmia and optic atrophy with contralateral papilledema due to an anterior cranial fossa tumor. The cortical manifestations arise from compression of adjacent structures, not direct cortical injury.

Other prefrontal signs

- Palmar grasp reflex and the "bulldog sign" (forceful biting of a spatula placed between the teeth – a primitive oral reflex).
- Motor perseveration – inappropriate repetition of previously initiated movements.
- Herman's tonic plantar reflex – persistent plantar flexion of the toes in response to plantar stimulation.
- Delayed reaction disorders – difficulty maintaining an active stimulus in memory once it ceases.
- Retrieval disturbances – difficulty accessing stored long-term information (**oryginalny sens zachowany, ujednolicona forma**).
- Working memory deficits – especially concerning spatial location.
- Disorders of voluntary activity – reduced motivation and initiative.
- Disorders of abstract and analytical thinking – rigid, simplified reasoning.

Temporal lobe

The lateral surface consists of:

- superior temporal gyrus;
- middle temporal gyrus;
- inferior temporal gyrus.

Functions

- perception and processing of auditory and olfactory stimuli;
- comprehension;
- emotional and memory functions of limbic structures.

Unilateral lesions usually do not cause hearing or smell loss. Damage to higher-order cortical areas causes auditory agnosia and association disturbances between auditory, memory, emotional, and visual stimuli.

Clinical manifestations

- Homonymous visual field defects – usually upper quadrantanopia from optic radiations injury; occasional visual illusions (macropsia, micropsia).
- Wernicke's sensory aphasia: fluent, unintelligible speech with impaired comprehension (dominant hemisphere).
- Auditory agnosia – inability to recognize familiar sounds.
- Memory impairment: bilateral medial temporal injury leads to anterograde amnesia.
- Partial epileptic seizures: complex symptoms, déjà vu, déjà vécu, jamais vu, cacosmia, psychomotor automatisms, sensory hallucinations.
- Klüver–Bucy syndrome: hyperreactivity, loss of fear, hypersexuality, hyperorality.
- Symptomatic trigeminal neuralgia: irritation of the trigeminal ganglion by a lesion at the skull base.

Parietal lobes

Lesions of the parietal lobe cause disturbances involving:

- sensation,
- body schema,
- visuospatial integration.

Clinical manifestations (dominant & non-dominant hemisphere)

- Impaired contralateral tactile discrimination, weight discrimination, and agrophesthesia
Lesion: primary somatosensory cortex (areas 3, 1, 2).
- Astereognosis
- a) primary (morphognosis) – impaired recognition of physical object features (weight, texture),
- b) secondary – impaired object recognition despite preserved primary features.
Lesion: areas 5 and secondary somatosensory cortex.
- Contralateral homonymous hemianopia or inferior quadrantanopia
Lesion: parietal optic radiations.
- Mild hemiparesis.

Lesion of the dominant parietal lobe

- **Gerstmann syndrome:**
 - a) left–right disorientation,
 - b) finger agnosia,
 - c) dysgraphia/dyslexia,
 - d) dyscalculia.Lesion: angular gyrus (area 39).
- **Apraxias:**
 - a) ideomotor,
 - b) ideational,
 - c) facial.Lesion: supramarginal gyrus (area 40).
- **Anomic aphasia**
Lesion: angular gyrus (area 39).
- **Conduction aphasia**
Lesion: supramarginal gyrus (area 40).

Lesion of the non-dominant parietal lobe

- Hemispatial neglect
- Anosognosia
- Asomatognosia
- Constructional apraxia
- **Dressing apraxia** – impaired ability to dress oneself due to visuospatial disorganization (e.g., putting on clothes inside out, confusing left and right).
Lesion: supramarginal and angular gyri.

Bilateral parietal lesions – Balint syndrome

Triad:

- a) **Optic ataxia** – impaired visually guided reaching,
- b) **Oculomotor apraxia** – inability to voluntarily shift gaze,
- c) **Simultanagnosia** – inability to perceive more than one object at a time.

Occipital lobe

Primary cortical center for visual processing.

Occipital lobe syndromes

- a) **Contralateral homonymous hemianopsia with macular sparing** – lesion: area 17.
- b) **Visual hallucinations** – lesion: areas 18–19.
- c) **Cortical blindness**: bilateral lesion of area 17.
- d) **Anton syndrome (Anton–Babinski)**: cortical blindness with unawareness and confabulation.
- e) **Color agnosia**: lesion of left occipitotemporal region.
- f) **Visual agnosia**: inability to recognize objects visually; lesion of occipitotemporal cortex.
- g) **Prosopagnosia**: inability to recognize faces; lesion of left or bilateral occipitotemporal cortex.
- h) **Dyslexia**: impaired recognition of written words; lesion of left occipitotemporal cortex.

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11. Comas and criteria for brain death

Edyta Dziadkowiak

Definitions

Consciousness determines the ability to respond appropriately to stimuli. Disturbances of consciousness can be classified quantitatively (e.g., different levels of coma).

Consciousness is defined as the ability to correctly perceive oneself and the surroundings and requires maintaining wakefulness. Consciousness refers to mental activities related to cognitive abilities, thoughts, and emotions. Disorders of consciousness may be:

- **quantitative** – referring to the degree of decreased wakefulness;
- **qualitative** – referring to the type of disturbances in mental (including cognitive) functions.

Quantitative disorders of consciousness:

- Somnolence;
- Sopor;
- Coma

Qualitative disorders of consciousness

- Stupor
- Delirium
- State of disorientation

Qualitative disturbances of consciousness usually do not affect the level of wakefulness. The only physiological form of consciousness disorder is sleep.

Coma

Disturbances of consciousness constitute a continuum, from wakefulness to coma. Within this continuum, the following are distinguished:

- **Pathological drowsiness (somnolence):**

Sleep is not related to the circadian rhythm; the patient falls asleep easily regardless of the time of day but can be woken and establish logical contact for a short time, after which the patient falls asleep again.

- **Semi-coma or pathological deep sleep (semi-coma, sopor, stupor):**
No reaction to the environment; defensive reflexes are preserved; arousal is possible as a reaction to strong, repeated stimuli.
- **Coma:**
A deep disturbance of consciousness lasting for at least 1 hour, without a sleep–wake cycle. Subtypes include:
 - a) **Simple (coma simplex) or mild coma (stages I and II):** preserved reflexes and trace, usually undirected reaction to painful stimuli.
 - b) **Deep coma (coma profundum) or severe coma (stages III and IV):** variable or absent defense reflexes (e.g., pupillary reaction to light); reactions to pain may be flexor, extensor, or absent; respiratory disorders may occur.
 - c) **“Exceeded” coma (coma dépassé):** abolished reflexes and reaction to pain, with associated respiratory failure.

Quantitative disturbances of consciousness are acute, life-threatening conditions and require stabilization of vital parameters, urgent diagnostics, and treatment (especially for reversible causes).

Etiology

Coma may develop:

- during the progression of an existing disease (e.g., enlargement of an acute ischemic lesion in the brainstem, excessive oxygen supplementation in COPD exacerbation),
 - as a complication (e.g., cardiac arrest in a patient with arrhythmia),
 - in the course of status epilepticus, including nonconvulsive forms.
- Causes of coma/consciousness disorders can be divided into:
- **non-structural,**
 - **structural** (with primary or secondary CNS involvement).

Non-structural causes

- **Toxins**, including:
 - carbon monoxide,
 - mushrooms,
 - methanol,
 - ethylene glycol.
- **Medicines and chemicals**, including:
 - salicylates,
 - barbiturates,
 - drugs,
 - other alcohols.

- **Infections**, including:
 - primary CNS infections (meningitis, encephalitis, meningoencephalitis),
 - sepsis,
 - malaria,
 - typhus,
 - other systemic infections.
- **Metabolic causes**, including:
 - adrenal crisis,
 - Wernicke's encephalopathy,
 - hepatic encephalopathy,
 - uremia,
 - porphyria,
 - hyper- and hyponatremia,
 - hyper- and hypocalcemia,
 - hypoglycemia,
 - diabetic ketoacidosis,
 - nonketotic hyperglycemic coma,
 - lactic acidosis,
 - hyper- and hypothermia,
 - hypoxia.
- **Endocrine causes**, e.g.:
 - adrenal crisis,
 - severe hypo- or hyperthyroidism,
 - other acute endocrine crises.

Structural causes

- Supratentorial or infratentorial brain injury with mass effect/impaction
- Traumatic subdural or epidural hematomas
- Spontaneous intracranial hemorrhages
- Thalamic hemorrhage
- Pituitary infarction
- Subdural abscess
- Cerebral venous sinus thrombosis
- Proliferative processes of the CNS
- Acute hydrocephalus
- Increased intracranial pressure
- Cerebral hypoxia
- Brainstem stroke

Clinical picture/diagnostics

In a comatose patient, basic vital functions should be assessed:

- blood pressure,
- heart rate,
- body temperature,
- respiratory rate and rhythm.

Examples:

- Cheyne–Stokes breathing – associated with generalized forebrain damage,
- ataxic breathing – associated with damage to the dorsomedial reticular formation of the medulla.

Skin and general examination

It is important to search for skin changes and rashes, e.g.:

- Petechiae – DIC
- Cherry-red skin – carbon monoxide poisoning
- Petechial–purpuric rash – meningococcal sepsis
- Maculopapular rash – staphylococcal/streptococcal toxic shock, scrub typhus, subacute bacterial endocarditis, autoimmune diseases (SLE, dermatomyositis)
- Multiple bruises – trauma, chronic steroid therapy, liver failure, anticoagulant therapy, coagulation disorders
- Linear subungual hemorrhages – endocarditis, leukemia, anemia, sepsis
- Injection marks – insulin, drugs, other substances

Glasgow Coma Scale

The Glasgow Coma Scale (GCS) ([Table11.1](#)) is used to assess:

- eye opening,
- verbal response,
- motor response.

Neurological examination

Includes assessment of:

- Resting posture
- Reflex reaction to stimuli
- Spontaneous movements
- Focal neurological deficits
- Pupil size and reactivity

Table 11.1. Glasgow Coma Scale

Glasgow Coma Scale	
Eye response (1–4)	No eye opening
	Eye opening to pain
	Eye opening to verbal command
	Eyes open spontaneously
Verbal response (1–5)	No verbal response
	Incomprehensible sounds
	Inappropriate words
	Confused
	Oriented
Motor response (1–6)	No motor response
	Stereotyped extension to pain
	Stereotyped flexion to pain
	Withdrawal from pain
	Localizing to pain
	Obeys command

- Eye movements:
 - resting eye position,
 - spontaneous movements,
 - reflex eye movements.

Downward and lateral deviation of one eyeball suggests ipsilateral third nerve palsy due to midbrain damage or extrinsic brainstem compression.

Sixth nerve palsy (medial deviation of the eye) has lower localizing value, as the nerve is long and susceptible to pressure from generalized increased intracranial pressure.

Vertical gaze and special eye signs

- Impaired downward gaze – lesions in midbrain tegmentum at the level of the inferior colliculi.
- Impaired upward gaze – lesions in the pretectal region/anterior commissure area.

Upward deviation of the eyes may occur in:

- Hemorrhage into the cerebellar vermis
- Brainstem ischemia
- Apnea phase of Cheyne–Stokes respiration

Damage to the **basilar part of the pons** and the medial longitudinal fasciculus may cause the “**see-saw phenomenon**”, where one eye is deviated upward and the other downward.

Spontaneous eye movements:

- Roving eye movements – slow, conjugate horizontal eye excursions; typical of metabolic/toxic coma or bilateral hemispheric lesions above the brainstem.
- Ocular bobbing – rapid downward movement with slow return upward; associated with pontine lesions.

Other neurological signs

- “Pipe-stem” rigidity
- Defensive reflexes, e.g.:
 - corneal and conjunctival reflexes,
 - cough reflex.

In patients with fluctuating consciousness, a **continuous performance test** may be used (raising the hand upon hearing a specific letter in a sentence). Another tool is the **hand position test** (praxia) – the patient imitates three different hand positions demonstrated by the examiner.

Diagnostics

To determine the cause of consciousness disorders, the following should be performed:

- Laboratory tests:
 - CBC with smear,
 - coagulation profile,
 - blood gases,
 - glucose and electrolytes,
 - kidney, liver, thyroid parameters,
 - urea nitrogen,
 - cortisol,
 - creatine phosphokinase,
 - screening for drugs and toxins.
- ECG
- Neuroimaging (CT/MRI of the head)
- EEG

Additionally, **evoked potentials (EPs)** may help assess brainstem integrity and prognosis. **Intracranial pressure (ICP) monitoring** is useful particularly in severe head trauma after neurosurgical treatment.

Differential diagnosis

Some chronic disorders of consciousness or mental illnesses may mimic coma. Coma itself may evolve into brain death or into chronic disorders of consciousness. Differentiation is crucial for treatment and prognosis.

We distinguish:

- conditions that are not disorders of consciousness (e.g., locked-in syndrome),
- chronic disorders of consciousness (e.g., vegetative state, minimally conscious state).

Conditions that are not disorders of consciousness

a) Locked-in syndrome

The patient is conscious and alert but has quadriplegia and lower cranial nerve palsies. Voluntary movements are limited to vertical eye movements and/or blinking. Causes: bilateral lesion of the ventral pons (most often basilar artery thrombosis/embolism, less often central pontine myelinolysis or compressive brainstem lesions).

b) Similar states

Can be seen in:

- patients after neuromuscular junction–blocking agents,
- myasthenia gravis,
- Guillain–Barré syndrome (AIDP).

c) Myasthenic crisis

Severe exacerbation of myasthenia gravis with respiratory muscle weakness leading to respiratory failure and need for ventilatory support. Consciousness is preserved; the picture may mimic coma because of immobility and lack of verbal response.

d) Abulia

Marked loss or impairment of will and initiative; severe apathy with blunted behavior, thought, motivation, and emotions. The patient does not move spontaneously and does not initiate speech but remains awake and aware (distinct from akinetic mutism).

e) Catatonia

The patient does not establish verbal contact and shows reduced or stereotyped motor activity. Most often seen in psychiatric illnesses, but may also result from frontal lobe lesions or exposure to toxins.

Vegetative state and minimally conscious state

In a **persistent vegetative state (PVS)**:

- there is no evidence of cognitive activity,
- the sleep–wake cycle and vegetative functions (respiration, heart rate, blood pressure) are preserved,
- reflex reactions are present, but the patient cannot consciously interact with the environment.

PVS typically follows coma and is due to extensive damage to the gray matter of the cortex or subcortical white matter, with relative preservation of the brainstem.

Some patients may progress from vegetative state to **minimally conscious state (MCS)**, depending on preservation of structures supporting cognition and motor functions.

Table 11.2. Parameters differentiating coma, vegetative state, and minimally conscious state

Condition	Definition	Main clinical characteristics
coma	unarousable state of unresponsiveness	absence of eye opening (even after intense stimulation), no evidence of awareness of the self or environment, condition protracted for more than one hour
vegetative state	wakefulness accompanied by the absence of any sign of awareness	presence of eye opening and closing, absence of any reproducible purposeful behaviour including: no evidence of non-response to sensory stimulation, no evidence of awareness of self or environment, no evidence of language comprehension or expression
minimally conscious state	wakefulness accompanied by inconsistent but reproducible signs of awareness	presence of eye opening and closing, presence of inconsistent but reproducible purposeful behaviour including (any of): non-reflexive response to sensory stimulation, awareness of the self or the environment, language comprehension or expression, lack of functional communication or object use

Based on: Monti MM, Laureys S, Owen AM. The vegetative state. *BMJ*. 2010;341(aug02 1):c3765–c3765. doi:<https://doi.org/10.1136/bmj.c3765>

In MCS:

- simple eye contact, gestures, or facial expressions may occur (MCS–),
- in some cases, the patient can follow simple verbal commands (MCS+).

Brain death

At an expert meeting in Montreal (2012), death was defined as: permanent loss of consciousness and permanent loss of all brainstem functions, resulting from permanent cessation of circulation or severe brain damage.

“Permanent” means loss of function that cannot return spontaneously and will not be restored by intervention.

Brain death = permanent and irreversible cessation of brainstem function.

National regulations define detailed criteria. In Poland, these are specified in the **Announcement of the Minister of Health of December 4, 2019** on the method and criteria for determining permanent irreversible cessation of brain function (under the Act of December 5, 1996 on the Profession of Physicians and Dentists).

Core clinical criteria (general)**1. Coma – irreversible condition**

- Catastrophic brain injury (supra- or infratentorial) of known cause.
- Lesion is irreversible; no effective treatment is possible.
- Confounders excluded: hypothermia, hypotension, metabolic/endocrine disturbances, intoxication, sedatives, muscle relaxants, etc.
- No response to external (including painful) stimuli.
- Trunk areflexia (spinal reflexes may persist).

2. Permanent apnea

- Apnea test in mechanically ventilated/ECMO patients to verify lack of respiratory drive in response to hypercapnia (rise in PaCO_2).

3. Absence of brainstem reflexes:

- no pupillary response to light,
- absent corneal reflexes,
- no spontaneous eye movements,
- absent oculocephalic reflex (“doll’s eyes”),
- no eye movements during caloric testing,
- no motor response to painful stimuli in cranial nerve distribution,
- no facial motor response to painful stimuli in spinally innervated areas,
- absent cough and gag reflexes.

Additional diagnostics

Brain death diagnosis is primarily clinical. Doubts may arise in:

- massive facial trauma,
- infratentorial lesions,
- intoxication,
- severe metabolic/endocrine disorders,
- unusual reflex phenomena.

In such cases, one of the following **confirmatory tests** is used:

- Electrophysiological tests:
 - EEG,
 - multimodal evoked potentials.
- Cerebral blood flow tests:
 - cerebral angiography,
 - CT angiography,
 - CT perfusion,
 - transcranial Doppler ultrasound,
 - perfusion scintigraphy.

Once the appointed medical commission confirms that all criteria have been fulfilled according to the protocol, **brain death is declared**, which is equivalent to **legal death**. From that moment, therapeutic obligation toward the patient ceases.

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PART 3
NEUROLOGICAL DISORDERS

1. Cerebrovascular diseases

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Ischemic stroke

Cerebral ischemic stroke is a set of clinical symptoms associated with the sudden occurrence of focal brain damage with no other cause than vascular. A similar definition applies to the spinal cord or retinal ischemia.

Additionally, at least one of the following criteria must be met:

- Demonstration of acute focus of ischemia in the brain, spinal cord, or retina in neuroimaging or pathological examination
- Persistence of clinical symptoms for at least 24 h, or earlier death of the patient (after excluding other causes)
- Resolution of neurological symptoms of the brain, spinal cord, or retina as a result of reperfusion treatment (in such a case, it is not necessary for clinical symptoms to persist for a period of 24 h or to show signs of fresh ischemia of the brain, spinal cord or retina in neuroimaging examination).

Ischemic stroke is the 2nd leading cause of death worldwide and the 3rd leading cause of death and disability combined. Each year, about 17 million people suffer from stroke. The 90-day mortality due to ischemic stroke is estimated at 22%, and for intracerebral hemorrhage – at 48%. The global economic burden of stroke is over 721 billion USD (Table 1.1).

Table 1.1. Risk factors for ischemic stroke

Unmodifiable	Modifiable
• age • male gender • genetic factors • previous stroke	• hypertension • heart diseases • diabetes • dyslipidemia • lifestyle: – smoking; – alcohol; – lack of physical activity. • medicines: – oral contraceptives; – hormone replacement therapy

Transient ischemic attack

A **transient ischemic attack (TIA)** is defined as a transient event of brain injury caused by focal ischemia of the brain, spinal cord, or retina, without changes on neuroimaging. Symptoms usually last a few to several minutes, usually up to an hour. A TIA is an important risk factor for subsequent cerebral ischemic events and should be treated as a condition requiring immediate diagnosis and the implementation of secondary prevention ().

Etiology of ischemic stroke:

- thromboembolism:
 - atherosclerosis:
 - carotid arteries,
 - vertebral arteries,
 - intracranial arteries,
 - aortic arch,
- cardioembolism:
 - atrial fibrillation,
 - myocardial infarction
 - mitral valve stenosis,
 - artificial heart valves,
 - atrial myxoma,
 - bacterial endocarditis,
 - dilated cardiomyopathy,
- small vessel disease:
 - lacunar strokes,
- aortic dissection,
- inflammatory diseases of the vessels:
 - inflammation of large vessels,
 - systemic diseases,
 - primary intracranial vasculitis,
- hematological diseases:
 - antiphospholipid syndrome,
 - sickle cell anemia,
 - thrombophilia,
- genetic disorders:
 - cerebral autosomal dominant arteriopathy with subcortical infarcts,
 - leukoencephalopathy – CADASIL,
 - mitochondrial myopathy,
 - encephalopathy,
 - lactic acidosis,
 - stroke-like episodes MELAS,

- infections:
 - meningitis,
 - human immunodeficiency viruses – HIV
- other:
 - migraine,
 - cerebral venous thrombosis,
 - vascular spasm in the course of subarachnoid hemorrhage,
- cryptogenic stroke.

The clinical symptoms of ischemic stroke include

- anterior vascular area (carotid artery area):
 - monocular blindness,
 - associated eye deviation,
 - paresis,
 - hemihypoesthesia,
 - features of central facial nerve damage,
 - hemianopia,
 - dysphasia,
 - dysarthria,
 - hemineglect syndrome.

A stroke involving the vascular area of the middle cerebral artery (MCA) usually manifests itself with contralateral faciobrachial paresis. In contrast, occlusion of the anterior cerebral artery (ACA), greater paresis is observed in the contralateral lower limb.

- posterior vascular area (area of vertebral arteries and basilar artery):
 - ataxia,
 - dizziness,
 - features of peripheral facial nerve damage,
 - double vision,
 - hemifacial hypoesthesia,
 - dysphagia,
 - dysarthria,
 - Horner's syndrome,
 - paresis and hemi-hypoesthesia (may be bilateral),
 - hemianopia, cortical blindness (involvement of the occipital lobes),
 - circulatory, breathing, and consciousness disorders,
 - locked-in syndrome,
 - sudden weakness of the lower limbs (drop attacks).

In lacunar stroke resulting from occlusion of small perforating vessels, even a small ischemic lesion may cause advanced symptoms of neurological deficit. Typical locations include the vascular area of the internal capsule, thalamus, basal ganglia, and brainstem.

Management of the acute phase of ischemic stroke:

- **pre-hospital phase:**

- a) the anamnesis must include:
 - determining the onset of the event when the patient was seen without any symptoms,
 - medications taken (oral anticoagulants, heparins, etc.), time of taking the last dose,
 - past surgical procedures, serious injuries, recent bleeding,
 - co-existing and past diseases,
 - contact telephone number for the family, witness of the event,
- b) assessment of basic vital functions (blood pressure, heart rate, breathing), neurological examination, insertion of a peripheral catheter,
- c) electrocardiogram – ECG, blood glucose measurement,
- d) transporting the patient to the nearest emergency department.

Apart from special cases (shock, hypertensive crisis, hypoglycemia), it is not recommended to administer drugs that may complicate further treatment or diagnosis, including antihypertensives, anticoagulants, psychotropic drugs, etc.

- **hospital phase or diagnostic phase:**

- a) neurological assessment using the NIHSS scale (National Institute of Health Stroke Scale):
 - level of consciousness,
 - answer to the question about age and month,
 - following commands,
 - eyeball mobility,
 - field of view,
 - facial nerve palsy,
 - muscle strength of the upper limbs,
 - muscle strength of the lower limbs,
 - ataxia of limbs,
 - sensations,
 - aphasia,
 - dysarthria,
 - hemineglect syndrome
- b) Complete blood count, coagulation, electrolyte concentration, creatinine, C-reactive protein, liver enzymes, arterial blood gas analyses, and blood group. Routine catheterization of the patient and subsequent ECG are not indicated due to the delay in specific treatment. In the case of a non-incriminating anamnesis, we do not wait for the results of laboratory tests before applying specific treatment.

- c) Neuroimaging studies in the acute phase include:
 - Computed tomography (CT) of the head without contrast – the basic examination in the diagnosis of acute stroke, with the highest sensitivity in detecting intracranial blood (alternatively, magnetic resonance imaging (MRI) of the head with T2 sequences)
 - MRI of the head in a protocol containing inversion and reversion sequences fluid-attenuated inversion recovery (FLAIR), diffusion MRI diffusion-weighted imaging – DWI/apparent diffusion coefficient – ADC). These studies qualify for intravenous thrombolytic treatment.
 - angio-CT or angio-MRI of cephalad and intracranial arteries – searching for vascular malformation,
 - with a possible additional perfusion CT or perfusion MRI in patients with an unknown time of onset – wake up stroke.
 - **hospital phase** – the stage of intravenous thrombolytic treatment with recombinant tissue plasminogen activator (ang. recombinant tissue-type plasminogen activator – rt-PA, alteplase):
 - a) the gold standard treatment for acute ischemic stroke,
 - b) rt-PA administered at a dose of 0.9 mg/kg body weight (10% of the total dose as a bolus, then an hourly infusion) within 4.5 h of the onset of symptoms; in the research phase, tenecteplase administered as a single dose,
 - c) the optimal time from the patient's admission to the hospital to the administration of rt-PA should be 45 min,
 - d) conditions necessary for the use of rt-PA:
 - confirmed ischemic stroke,
 - determining the exact time of illness,
 - exclusion of intracranial bleeding based on neuroimaging (CT/MRI),
 - determination of glycemia level,
 - qualification for thrombolytic treatment,
 - e) rt-PA treatment is associated with a 5- to 7-fold increase in the risk of secondary hemorrhage. In each patient, before starting an antiplatelet drug, a follow-up CT scan of the head should be performed 22–36 h after the treatment ([Table 1.2](#)).
- Secondary symptomatic hemorrhage after rt-PA treatment is defined as a deterioration in the patient's neurological status by at least 4 points on the NIHSS, accompanied by radiological evidence of a hemorrhagic focus involving more than 30% of the infarcted area within 22–36 hours after treatment (according to SITS criteria).
- **hospital phase** – mechanical thrombectomy (MT):
 - a) Mechanical thrombectomy, using new generation systems (stent-retrievers or aspiration systems) is the most effective method of treating ischemic stroke in large vessel occlusion. Mechanical thrombectomy should be performed on a patient who meets all the following criteria:

Table 1.2. Absolute contraindications to rt-PA administration

Absolute contraindications to rt-PA administration:	
–	visualization of a hemorrhagic focus on neuroimaging
–	symptoms suggesting subarachnoid hemorrhage
–	prolonged clotting times (aPTT >40s, PT >15 s, INR >1.7),
–	platelet count (<100,000/mcl)
–	recent intake of new oral anticoagulants (<48 h)
–	unfractionated heparin with prolonged aPTT (<48 h)
–	low molecular weight heparin in a therapeutic dose (<24 h)
–	bleeding diathesis
–	severe liver disease
–	treatment-resistant hypertension (BP >185/110 mmHg)
–	previous intracranial bleeding in the last 3 months
–	significant bleeding from the gastrointestinal or urinary tract in the last month
–	large size of unruptured cerebral aneurysm (>10 mm)
–	previous damage to the central nervous system within the last 3 months (neurosurgical procedure, brain contusion)
–	active acute pancreatitis
–	active bacterial endocarditis
–	presence of cancer with a high risk of bleeding
–	vaginal delivery in the last 2 weeks.

- score on the modified Rankin scale before stroke 0–1,
 - cause of the stroke: occlusion of the common carotid, internal carotid, middle, anterior, posterior cerebral, vertebral, and basilar arteries (possible occlusion of several vessels),
 - age ≥18 years,
 - NIHSS score ≥6,
 - ASPECT (Alberta Stroke Program Early CT Score) ≥6,
 - the procedure can be started (counting from the moment of puncture of the femoral artery) within 6 h from the beginning of the stroke;
- b) Patients meeting the qualification criteria for IV rt-PA treatment should also receive this drug if endovascular treatment is considered;
- c) Administration of rt-PA IV should not delay the use of MT;
- d) As part of the qualification for MT in the 6-hour therapeutic window, there is no need to perform additional MRI diffusion and perfusion or CT perfusion tests;

- **hospital phase** – general pharmacological treatment:
 - a) cardiovascular function:
 - maintaining normal cardiac output and heart rate,
 - correcting hypovolemia and hypotension (fluid therapy, catecholamines),
 - treatment of comorbidities such as AF (antiarrhythmic drugs, cardioversion), heart failure (avoiding patient's overhydration), and myocardial infarction; if necessary, cardiology consult,
 - b) glycemia:
 - maintaining glycemia within the range of 140–180 mg%,
 - in the acute phase of ischemic stroke, it is recommended to treat hyperglycemia with intravenous insulin injection (bolus, then continuous infusion),
 - avoiding hypoglycemia,
 - c) respiratory system function:
 - breathing disorders often occur in:
 - brainstem stroke,
 - in extensive hemispheric stroke,
 - pneumonia,
 - pulmonary embolism,
 - exacerbation of circulatory failure,
 - treatment of respiratory failure (oxygen therapy, intubation, ventilator therapy). In patients with disorders of consciousness and a Glasgow Coma Scale (GCS) <8 points, intubation is recommended as a prevention of aspiration pneumonia.
 - treatment of pneumonia (empiric antibiotic therapy, then targeted after obtaining a culture from bronchial secretions),
 - d) body temperature:
 - antipyretics, cold compresses, determining the source of infection,
 - e) prevention and treatment of deep vein thrombosis of the lower limbs and pulmonary embolism according to general principles,
 - f) blood pressure:
 - patients not eligible for thrombolytic treatment systolic blood pressure – SBP diastolic blood pressure – DBP), SBP $\leq$ 220 mmHg, and DBP $\leq$ 120 mmHg – do not treat, except for the accompanying:
 - new heart attack,
 - aortic dissection,
 - pulmonary edema
 - hypertensive encephalopathy,
 - acute kidney failure,
 - SBP > 220 mmHg and/or DBP 121–140 mmHg – reduce the initial value by 15–25% (further reduction in the following days). If one drug is ineffective, another medication can be additionally used:

- Urapidil:
10–50 mg IV as a bolus, then, if necessary, 5–40 mg/h as a continuous infusion,
- Labetalol:
10–20 mg IV for 1–2 min, can be repeated every 10 min up to a maximum dose of 300 mg,
- Nicardipine:
5 mg/h IV in continuous infusion; can be increased every 5–15 min by 2.5 mg/h (max. dose 15 mg/h) until the desired effect is achieved; then reduce to 3 mg/h,
- DBP >140 mmHg:
 - Sodium nitroprusside:
0.5 µg/kg/min by intravenous infusion with continuous blood pressure monitoring,
 - Nitroglycerin:
5 mg IV, then 2–8 mg/h IV in the infusion,
- patients qualified for thrombolytic treatment with BP >185/110 mmHg:
 - Urapidil:
10–50 mg IV in a bolus,
 - Labetalol:
10–20 mg IV for 1–2 min,
 - Nicardipine:
5 mg/h IV in continuous infusion; can be increased every 5–15 min by 2.5 mg/h (max dose 15 mg/h) until the desired effect is achieved; then reduce to 3 mg/h,
- g) correcting water and electrolyte imbalances (it is not recommended to administer hypotonic solutions, including 5% glucose or hypotonic saline),
- h) nutrition:
 - in case of dysphagia, nutritional treatment through a nasogastric tube or percutaneous gastrostomy is recommended 14–28 days from the beginning of the ischemic stroke.
- i) antiplatelet treatment:
 - acetylsalicylic acid: 160–300 mg,
 - clopidogrel, ticagrelor in case of ineffectiveness or contraindications to the use of aspirin,
- j) anticoagulation treatment:
 - heparins or heparinoids should be used in the acute phase of ischemic stroke only in the context of prevention of venous thrombosis and pulmonary embolism in patients with deep limb paresis or active treatment of the mentioned thrombotic complications,
- k) neuroprotection:
 - intravenous administration of cerebrolysin at a dose of 30 mL daily, started within 24–72 h of the onset of symptoms of at least moderately severe hemispheric stroke

(manifested by upper limb paresis and aphasia) and continued for 21 days in combination with intensive rehabilitation, has a positive effect on the limb's function.

Treatment of neurological complications of stroke is as follows:

- **brain swelling:**

- a) cytotoxic cerebral edema usually reaches its greatest severity within the first 3–4 days from the onset of symptoms,
- b) mainly in patients with hemispheric or posterior cranial fossa stroke,
- c) treatment:
 - hyperthermia, hyperglycemia, hypoosmolar fluids should be avoided,
 - lifting the head and torso to 30 degrees,
 - administration of mannitol IV (0.25–0.5 g/kg body weight every 6 h), concentrated NaCl solution,
 - controlled hyperventilation (target $p\text{CO}_2$ 30–34 mmHg),
 - steroids are not recommended,
 - indications for decompressive hemicraniectomy (hole with a diameter of min 12 cm):
 - malignant cerebral edema (infarction focus covering $\geq 50\%$ of the extent of MCA vascularization in head CT or a focus with a volume $>145 \text{ cm}^3$ with involvement of deep structures in patients with worsening neurological condition);
 - up to 48 h from the beginning of ischemic stroke,
 - in patients ≤ 60 years of age,
 - in patients with a stroke in the posterior cranial fossa, suboccipital craniectomy should be considered,

- **epileptic seizures:**

- a) seizures are distinguished:
 - early (up to 2 weeks from the beginning of ischemic stroke),
 - late (later than 2 weeks from the beginning of ischemic stroke),
 - b) indication for treatment is status epilepticus and recurrent seizures,
 - c) the risk of recurrence of seizures is much higher in the case of late seizures.
- A single early seizure is not an indication for long-term antiepileptic treatment.

Secondary ischemic stroke prevention includes:

- tests aimed at determining the etiology of ischemic stroke, such as:
 - a) lipid profile, fasting blood glucose, ESR, TSH, complete blood count with smear, screening for connective tissue diseases, indicators of damage to the heart muscle, kidneys, liver, diagnosis of hypercoagulable states (protein C, S, mutation in the factor V Leiden gene, mutation in prothrombin gene),

- b) ultrasound of carotid, vertebral and intracranial arteries,
 - c) prolonged ECG monitoring,
 - d) Transthoracic, transesophageal cardiac ultrasound (assessment of the patency of the foramen ovale, thrombus in the left atrial appendage),
 - e) classic angiography of cerebral vessels (vasculitis of the central nervous system – CNS),
 - f) examination of cerebrospinal fluid – CSF (suspected SAH, inflammatory processes of the CNS),
- **antiplatelet treatment:**
 - a) ASA (160–300 mg) taken within 48 h of the onset of ischemic stroke reduces the risk of recurrence of ischemic stroke or death in the first weeks after stroke,
 - In patients with recurrent ischemic stroke who were taking aspirin, changing, or adding another antiplatelet drug (e.g., clopidogrel 75 mg); there is no justification for increasing the dose of ASA.
 - In the case of non-cardiogenic ischemic stroke with a minor neurological syndrome (0–3 points in NIHSS) or TIA with a high risk of early recurrence (≥ 4 points in ABCD2) (Table 1.3), dual antiplatelet therapy may be considered according to the following scheme:
 1. for the first 21 days of clopidogrel (single loading dose of 300–600 mg, then 75 mg/day) in combination with ASA (75–150 mg/day),
 2. for the next 69 days, monotherapy with clopidogrel (75 mg/d) or aspirin (75–150 mg/d),

Table 1.3. ABCD2 score: Assessment of patients with TIA in terms of the risk of stroke

Letters for every criterion	Criterion	Number of points
A	age ≥ 60 ; female gender	1
B	blood pressure $\geq 140/90$ mmHg	1
C	clinical symptoms such as: • unilateral muscle weakness, • speech disorders without muscle weakness	2 1
D	duration of symptoms: • 10–59 min • ≥ 60 min	1 2
D	diabetes	1
D ¹	another TIA episode – at least 1 TIA incident in the 7 days preceding the diagnosed TIA episode	2

¹additional factor in the ABCD3 score compared to the ABCD2 score.

3. 90 days after initiation of treatment, switch to conventional long-term secondary prevention of ischemic stroke.
- treatment with oral anticoagulants (OAC) – in case of embolic etiology of stroke:
 - a) atrial fibrillation (AF):
 - the risk of ischemic stroke in patients with non-valvular AF is assessed based on the CHA₂DS₂-VAS_c score (Table 1.4),
 - the risk of bleeding in patients under anticoagulation treatment is determined based on the HAS-BLED score (score ≥ 3 points. indicates a high risk of bleeding) (Table 1.5),
 - oral anticoagulants that are vitamin K antagonists (acenocoumarol, warfarin) (Table 1.6),

Table 1.4. CHA₂DS₂-VAS_c score

Risk factor	Points
Heart failure/left ventricular dysfunction (EF ≤40%)	1
Hypertension	1
Age >75 years	2
Diabetes	1
Previous stroke or TIA	2
Vascular disease (heart attack, peripheral atherosclerosis, atherosclerotic plaques in the aorta)	1
Age 65–74 years	1
Female gender	1

EF – ejection fraction.

Table 1.5. HAS-BLED score

Risk factor	Points
Hypertension	1
Abnormal kidney or liver function	1 or 2
Stroke	1
Bleeding	1
Unstable INR values	1
Old age (>60 years)	1
Medications (antiplatelet agents, NSAIDs) or alcohol	1 or 2

NSAIDs – non-steroidal anti-inflammatory drugs.

Table 1.6. Advantages and disadvantages of oral anticoagulants (acenocoumarol, warfarin)

Disadvantages	Advantages
– interactions with other drugs and food – complicated dosing with INR control – delayed effect – higher risk of bleeding complications	– price – INR index allowing monitoring drug activity – possible reversal of the drug's effect – possibility of use in renal failure – skipping one dose does not have a significant impact on drug concentration, – recommended in valvular AF

Table 1.7. Advantages and disadvantages of NOAC

Disadvantages	Advantages
– no indicator to monitor drug activity – no antidote¹ – skipping one dose may significantly reduce the effect of the drug – not recommended in renal failure² – not recommended in valvular AF	– no interactions with other drugs and food³ – simple dosage – quick effect – more effective in secondary prevention of stroke⁴ – lower risk of bleeding complications⁵

¹idarucizumab – an antidote for dabigatran; andexanet – an antidote for xabans; ²mainly regarding dabigatran; ³it is recommended to take rivaroxaban with food, which increases its bioavailability; ⁴dabigatran, apixaban; ⁵apixaban, edoxaban.

- new anticoagulants novel oral anticoagulants (NOACs): dabigatran, rivaroxaban, apixaban, edoxaban) (Table 1.7),
- the duration of initiation of anticoagulant drugs depends on the severity of the neurological syndrome and/or the extent of the ischemic focus and ranges from 3 to 14 days; in the case of TIA, treatment can be started on the next day,
- an alternative to long-term OAC treatment may be a left atrial appendage closure system,
- b) other indications for the use of OAC in the secondary prevention of ischemic stroke:
 - myocardial infarction/dilated cardiomyopathy complicated by a thrombus in the left ventricle (at least 3 months),
 - rheumatic mitral valve disease (INR 2–3), mechanical mitral valve (INR 2.5–3.5), aortic valve (INR 2–3),
 - carotid/vertebral artery dissection (OAC vs ASA),
- **modification of risk factors:**
 - a) hypertension:
 - diuretics, calcium antagonists, angiotensin-converting enzyme inhibitors, sartans, less effective beta-blockers,

- target BP values: <140/90 mmHg (lacunar stroke <130 mmHg SBP),
- BP lowering in the acute phase of ischemic stroke should be gradual,
- b) lipid metabolism disorders:
 - statins are recommended in patients with ischemic stroke or TIA accompanied by atherosclerosis,
 - recommended LDL cholesterol level <70 mg/dL or drop >50%,
 - in patients with ischemic stroke, we continue to use statins if the lipid metabolism is well-controlled,
- c) optimal glycemic control,
- d) lifestyle modification (regular physical activity, giving up smoking, drinking alcohol, appropriate diet),
- e) discontinuation of hormone replacement therapy (HRT), oral contraceptives (OCP).
- f) carotid endarterectomy (CEA) and angioplasty – carotid artery stenting (CAS) in the treatment of symptomatic carotid artery stenosis,
- g) recommended in patients with symptomatic carotid stenosis (70–99%), without profound neurological deficit in a surgical center where the risk of all perioperative complications (stroke or death) <6% within 2 weeks of the occurrence of ischemic stroke/TIA.

Carotid angioplasty is recommended for:

- a surgically inaccessible site,
- restenosis after CEA,
- condition after major neck surgery,
- artery narrowing after radiotherapy,
- contralateral carotid artery occlusion,
- contralateral laryngeal nerve damage,
- severe heart/lung disease.

Hemorrhagic stroke

Hemorrhagic stroke – intracerebral hemorrhage (ICH) – is a condition caused by rupture of an intracerebral vessel, leading to extravasation of blood directly into the brain and the formation of an intracerebral hematoma that damages the brain and causes neurological symptoms. Intracerebral hemorrhage accounts for 10–17% of all strokes and has a worse prognosis than ischemic stroke. The 90-day mortality caused by ICH is estimated at 48%, substantially higher than that of ischemic stroke.

Etiology of hemorrhagic stroke:

- small vessel disease due to hypertension;
- amyloid angiopathy;
- arteriovenous malformations;

- tumors;
- cerebral venous thrombosis;
- medications (anticoagulants, antiplatelet drugs, thrombolytic therapy);
- coagulopathies;
- cirrhosis;
- chronic kidney failure;
- drugs (cocaine, amphetamine);
- smoking;
- alcohol;
- low cholesterol;
- pregnancy-induced hypertension.

Cerebral amyloid angiopathy (CAA) is one of the main risk factors for ICH in older people. It is characterized by the accumulation of beta-amyloid in the walls of arterioles, capillaries, and venous vessels located in the cerebral cortex and dura mater. CAA may occasionally coexist with Alzheimer's disease or with certain genetically determined syndromes.

Clinical symptoms of hemorrhagic stroke:

- based on the clinical picture, ischemic stroke cannot be differentiated from ICH (see clinical symptoms in stroke);
- hemorrhagic stroke is indicated by:
 - a) sudden, severe headache accompanied by vomiting;
 - b) rapidly increasing disturbances of consciousness and breathing;
 - c) epileptic seizures.

Table 1.8. Intracerebral hemorrhage (ICH) scale- score assessment for patients with ICH (the higher the score, the higher the mortality)

Component		ICH score points
GCS ¹ score:	3–4	2
	5–12	1
	13–15	0
ICH volume (cm ³):	≥30	1
	<30	0
IVH:	Yes	1
	No	0
Infratentorial origin:	Yes	1
	No	0
Age:	≥80	1
	<80	0
Total ICH score		0–6

¹Glasgow Coma Scale.

Treatment in the acute phase of ICH:

- death risk factors:
 - a) older age;
 - b) severe disturbances of consciousness upon admission to the hospital;
 - c) larger volume of the hemorrhagic focus, presence of blood in the ventricular system;
 - d) hemorrhage into deep brain structures and infratentorial hemorrhage;
 - e) use of OACS (oral anticoagulants).CT angiogram shows punctate enhancement manifested as a spot sign is a marker of active bleeding.
- **the management of ICH** is in many respects analogous to that of ischemic stroke, it should be carried out simultaneously with the diagnostic process (see management in the acute phase of ischemic stroke),
- **general procedure:**
 - a) hypertension:
 - in the case of SBP 150–220 mmHg, intravenous, short-acting antihypertensive drugs (urapidil, labetalol, furosemide) should be used, aiming to achieve a value of approx. 140 mmHg,
 - in patients with pre-existing hypertensive disease, antihypertensive treatment should be carried out more carefully,
 - in the case of SBP ≥ 230 mmHg, a drop in SBP >90 mmHg may contribute to acute renal failure,
 - b) brain swelling:
 - invasive monitoring of intracranial pressure has no advantage over repeated assessment of the clinical condition and performing follow-up CT scans of the head,
 - the treatment is analogous to that of hemorrhagic ischemic stroke,
 - c) epileptic seizures:
 - treatment analogous to ischemic stroke,
 - d) deep vein thrombosis of the lower limbs and pulmonary embolism:
 - the use of OACs or heparins is associated with an increased risk of recurrent bleeding,
 - recommended intermittent pneumatic compression, possibly implantation of a filter into the inferior vena cava,
- **specific treatment:**
 - a) in case of deficiency of one of the coagulation factors or severe thrombocytopenia, it is advisable to supplement the missing factor, administer fresh frozen plasma, concentrate prothrombin complex factors, or transfusion of platelet concentrate,
 - b) with an increased INR (≥ 1.3), it is recommended to administer vitamin K 10 mg IV,
 - c) in people taking dabigatran or xabans, 50 g of activated charcoal should be administered (up to 2 h after taking dabigatran, up to 6 h after taking xabans), and idarucizumab at a dose of 5 g IV, for xabans there is an antidote – andexanet alfa, for heparins – protamine,

d) surgery:

- surgical decompression is recommended mainly in cerebellar hemorrhages >3 cm in diameter in patients with deteriorating neurological condition,
- decompressive hemicraniectomy, including suboccipital – recommendations as in hemorrhagic ischemic stroke,
- in case of bleeding from an aneurysm, embolization or clipping should be performed; in case of bleeding from a vascular malformation, embolization, surgical removal, and stereotactic radiotherapy should be considered.

Cerebral venous thrombosis

Cerebral venous thrombosis (CVT), i.e., brain dysfunction caused by clotting of cerebral veins and/or venous sinuses of the dura mater, most often the superior sagittal sinus. Increased pressure in the cerebral venous system leads to disruption of the blood–brain barrier and elevated intracranial pressure. These changes decrease cerebral blood flow and impair function of the sodium–potassium pump resulting in mixed vasogenic and cytotoxic edema, as well as vascular damage and blood extravasation – producing a venous stroke.

Cerebral venous thrombosis is responsible for 0.5–1.0% of all cerebral strokes, most often in young people, with a higher prevalence in women. Due to the variety of symptoms and their non-specificity, as well as the multitude of causes, CVT remains an important diagnostic and therapeutic problem. The disease is often diagnosed with delay, which worsens prognosis, so it is important to know its clinical and radiological symptoms. Risk factors for CVT are as follows:

- pregnancy and puerperium, antiphospholipid syndrome;
- medicines (OCP, HRT, glucocorticosteroids – glucocorticoids, intravenous immunoglobulins), drugs;
- inflammatory diseases around the nose, ear, throat, meningitis, acquired immunodeficiency syndrome – AIDS;
- inflammatory and autoimmune diseases (systemic lupus erythematosus, Behcet's disease, granulomatosis with polyangiitis, Buerger's disease, sarcoidosis);
- cancer;
- congenital and acquired thrombophilias;
- hematological disorders (polycythemia, severe anemia, thrombocytopenia, paroxysmal nocturnal hemoglobinuria, thrombocytopenia after heparin administration);
- dural arteriovenous fistulas;
- dehydration and cachexia;
- neurosurgical operations, jugular vein catheterization, head injuries;
- congenital heart defects.

Clinical picture:

- features of increased intracranial pressure:
 - a) swelling of the optic nerve discs;
 - b) headaches;
 - c) nausea, vomiting;
 - d) defects in the field of vision;
 - e) damage to the VI nerve.
- focal symptoms:
 - a) paresis;
 - b) hemihypesthesia;
 - c) aphasia;
 - d) dysarthria;
 - e) focal epileptic seizures.
- symptoms of encephalopathy with impaired consciousness, epileptic seizures, multifocal neurological deficit;
- in the case of cavernous sinus thrombosis:
 - a) damage to cranial nerve III, IV, VI, V¹;
 - b) redness and pulsating proptosis of the eyeball.

Diagnostic tests:

- Laboratory tests:
 - a) increased D-dimer concentration may be useful in making the correct diagnosis, although a normal result does not exclude the diagnosis; there is a correlation between the extent of thrombosis and the concentration of D-dimer; D-dimer concentration decreases with the duration of the disease;
 - b) the diagnosis of thrombophilia in all patients diagnosed with CVT does not seem justified;
 - c) cerebrospinal fluid (CSF) examination in case of suspected meningitis;
 - d) diagnosis of diseases causing CVT (see etiology).
- neuroimaging studies:
 - a) Head CT without contrast medium is characterized by low sensitivity in diagnosing CVT (30%); the clot is visible as an area of increased density (empty triangle) after contrast administration in the case of thrombosis of the posterior section of the superior sagittal sinus);
 - b) visualization of dural vein/sinus occlusion is possible thanks to CT angiography, MRI angiography with a venous option; classic angiography – the method with the highest sensitivity;
 - c) MRI in the SWI sequence (Susceptibility weighted imaging) is particularly helpful in detecting cortical vein thrombosis and differentiating the thrombus from sinus hypoplasia – the clotted vessel is hypointense.

Treatment:

- anticoagulation treatment:
 - a) the advantage of low-molecular-weight heparins in the therapeutic dose has been demonstrated low-molecular-weight heparin (LMWH) over unfractionated heparin (UFH), also in the presence of concomitant bleeding into the central nervous system;
 - b) in secondary prevention (after about 1–3 weeks), acenocoumarol or warfarin should be used for 3–6 months (established etiology of CVT), 6–12 months (idiopathic thrombosis), for life (recurrent thrombosis, severe thrombophilia);
 - c) mechanical thrombectomy, thrombolysis (disease progression despite anticoagulation treatment);
 - d) treatment of increased intracranial pressure, neurosurgical decompression, and treatment of epileptic seizures (see ischemic stroke complications).

Subarachnoid hemorrhage

Subarachnoid hemorrhage (SAH) is a pathological extravasation of blood into the subarachnoid space and may result from traumatic or non-traumatic causes. Subarachnoid hemorrhage is characterized by high mortality of approx. 50%. Among survivors, about 1/3 remain dependent. In every patient with sudden fulminant headache, SAH should be considered in the differential diagnosis, and rapid diagnosis should be performed. Immediate securing of the aneurysm significantly affects the survival of patients (Table 1.9).

Table 1.9. Hunt–Hess score – stratification of the risk of death in patients with SAH

Score	???????
1	– asymptomatic – mild headache – slight stiffness of the neck
2	– moderate or severe headache – noticeable stiffness of the neck – damage to cranial nerves
3	– slight disturbances of consciousness, – slight symptoms of neurological deficit
4	– stupor – moderate or severe hemiparesis
5	– coma – decerebrate posturing – decorticate posturing

Etiology:

- most often the result of rupture of a saccular aneurysm (95%);
- other reasons:
 - arteriovenous malformations;
 - artery dissection;
 - coagulopathies;
 - alcohol abuse, cigarette smoking, cocaine, amphetamines;
 - pituitary hemorrhage;
 - mycotic aneurysms (bacterial endocarditis, fungal infections);
 - vasculitis;
 - brain tumors.

Non-aneurysmal perimesencephalic SAH most often occurs in people in the 6th decade of life with mild hypertension. It usually does not recur, and the extravasated blood is limited to the cisterns surrounding the midbrain.

Clinical picture:

- a) sudden thunderclap headache (sometimes preceded by a warning headache);
- b) nausea, vomiting;
- c) diplopia;
- d) disturbances of consciousness;
- e) epileptic seizures;
- f) meningeal symptoms;
- g) pain in the sacrum area.

Diagnostic tests include:

- physical examination (meningeal symptoms, retinal examination – vitreous hemorrhage, diplopia),
- imaging tests:
 - a) Head CT, the basic test for detecting SAH, CT sensitivity decreases in the following days,
 - b) angio-CT, angio-MRI, classic angiography (gold standard) to determine the source of bleeding,
- other exams:
 - a) examination of CSF should be performed in every patient with symptoms suggestive of SAH in whom no bleeding was detected on head CT,
 - b) transcranial Doppler ultrasound (detection of vascular spasm – see complications of SAH).

Treatment:

- securing of the aneurysm:
 - a) early surgical intervention is recommended (preferably within 72 h), which helps reduce the mortality rate,

- b) surgical treatment of aneurysm (vascular clips) vs endovascular embolization,
- treatment of complications:
 - a) repeated bleeding in the case of an unprotected aneurysm – immediate surgical treatment,
 - b) in the case of increasing hydrocephalus, external ventricular drainage is indicated,
 - c) cerebral edema (see: neurological complications of ischemic stroke),
 - d) epileptic seizures should be treated temporarily,
 - e) vascular spasm:
 - the contraction usually occurs between the 3rd day and the 2nd–4th week of illness,
 - the most serious complication is ischemic stroke,
 - the basis of treatment is to maintain a high BP, hypervolemia, and hemodilution (3H rule) – immediate administration of a colloidal solution, treatment of hypoxemia, fluid supply of 3 L per day, treatment of hyponatremia,
 - for the prevention of vascular spasm, nimodipine is used orally at a dose of 60 mg every 4 h; parenteral administration is not recommended.

Spinal vascular diseases

Spinal vascular diseases (ischemia or hemorrhage) occur much less frequently than cerebral strokes. Spinal dural arteriovenous fistula (SDAVF) is the most common malformation of the spinal cord (70%), occurring mainly in the thoracolumbar section and is most often diagnosed in people between the 5th to 6th decade of life (more often in men). The underlying mechanism of SDAVF involves the formation of a pathological arteriovenous connection, most often between the meningeal branch of the radicular artery and the spinal venous system.

Sudden neurological symptoms in the form of para- or quadriplegia with sphincter dysfunction should raise suspicion of a spinal cord vascular disease. Patients with spinal stroke must be regarded as life-threatening cases and closely monitored in a hospital setting. The low specificity of the clinical picture of SDAVF means that patients are usually diagnosed in the late stage of the disease with symptoms of paraparesis and sphincter disorders.

Spinal ischemic and hemorrhagic stroke:

Etiology:

- spinal ischemic stroke:
 - a) dissecting aortic aneurysm resulting from atherosclerosis, surgical reconstruction of abdominal/thoracic aortic aneurysm,

- b) significant hypotension,
- c) cardiogenic emboli,
- d) systemic connective tissue diseases, vasculitis,
- e) cocaine,
- f) thrombophilia,
- spinal hemorrhagic stroke is most often associated with vascular malformations or coagulation disorders.

Clinical picture:

- spinal ischemic stroke:
 - a) radicular back pain,
 - b) tetraplegia, sometimes breathing disorders, split sensory disorders below the level of the lesion at which the damage occurs (stroke affecting the vascularization of the anterior spinal artery),
 - c) paraplegia, urinary and fecal incontinence, level of sensation below the level of damage (vascularization of the Adamkiewicz artery)
- spinal hemorrhagic stroke (usually around the central canal):
 - a) at the level of the damage (flaky paresis, muscle atrophy, split sensory disorders),
 - b) below the damage (spasmodic paresis with sphincter disorders).

Diagnostic tests:

- CT, MRI of the spinal cord, if a malformation is suspected, angiographic examinations,
- CSF examination helpful in differential diagnosis (e.g., inflammatory processes of the spine).

Treatment:

- mainly symptomatic treatment, as in patients with para- and quadriplegia,
- no data on the effectiveness of antiplatelet drugs, anticoagulants, or intravenous thrombolytic treatment.

SDAVF:**Etiology:**

- the cause is usually unclear,
- history of spinal injury is considered a risk factor.

Clinical picture:

- pain in the lumbosacral spine, sometimes radiating to the lower limbs, accompanied by gait disturbances and paresthesia with weakness of one limb (less often paraparesis/paraplegia),
- features of lower and upper neuron damage in neurological examination,
- urination and stool disorders,
- late period impotence.

Diagnostic tests:

- spinal MRI shows spinal edema and dilated, tortuous venous vessels,
- whole-spinal MRI/CT angiography confirms the presence of SDAVF, allowing the scope of classical angiography to be reduced.

Treatment:

- operational closure,
- embolization.

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2. Central nervous system tumours

Justyna Chojdak-Łukasiewicz

Brain tumors

Brain tumors are a diverse group of neoplasms arising from different cells within the central nervous system (CNS) or from systemic cancers that have metastasized to the CNS. Intracranial tumors are the 6th most common neoplasm in adults and the most common solid tumors in children. The incidence of all primary brain tumors is 14–21 cases per 100,000 population per year. Primary brain tumors grow within the brain regions and do not spread out. These types of tumors can be benign or malignant and can occur at any location within the intracranial or spinal space.

Metastatic brain tumors evolve from primary neoplasms located outside the central nervous system. In adults, 70% of primary brain tumors are supratentorial, and of those, 80–90% are gliomas and meningiomas. The remaining 30% are infratentorial, including schwannomas, hemangioblastomas, and meningiomas. In children, approx. 70% of primary brain tumors are infratentorial, most commonly medulloblastoma, cerebellar astrocytoma, brainstem glioma, and ependymoma.

Brain tumors generally originate from genetic dysregulation within cells, causing them to bypass normal growth regulatory mechanisms, with simultaneous immune system evasion. The etiology of brain tumors is unknown. While numerous hypotheses about the pathogenesis of primary tumors have been proposed, no specific etiologic factor has been identified. The vast majority of brain tumors are sporadic, though some are associated with familial cancer predisposition syndromes. To date, only two established risk factors for brain tumors have been: ionizing radiation (meningiomas, gliomas, and schwannomas) and immunosuppression (primary CNS lymphoma). The association with other risks remains unproven (Table 2.1).

There are many types of primary brain tumors. In 2021, the World Health Organization (WHO) published updated versions of the classification system for CNS tumors, based on histo-molecular data (Fig. 2.1).

Clinical presentation depends on tumor site. Onset can be abrupt (stroke-like) or indolent, with gradual development of focal deficits. Patients may present with seizures or non-specific symptoms from increased intracranial pressure.

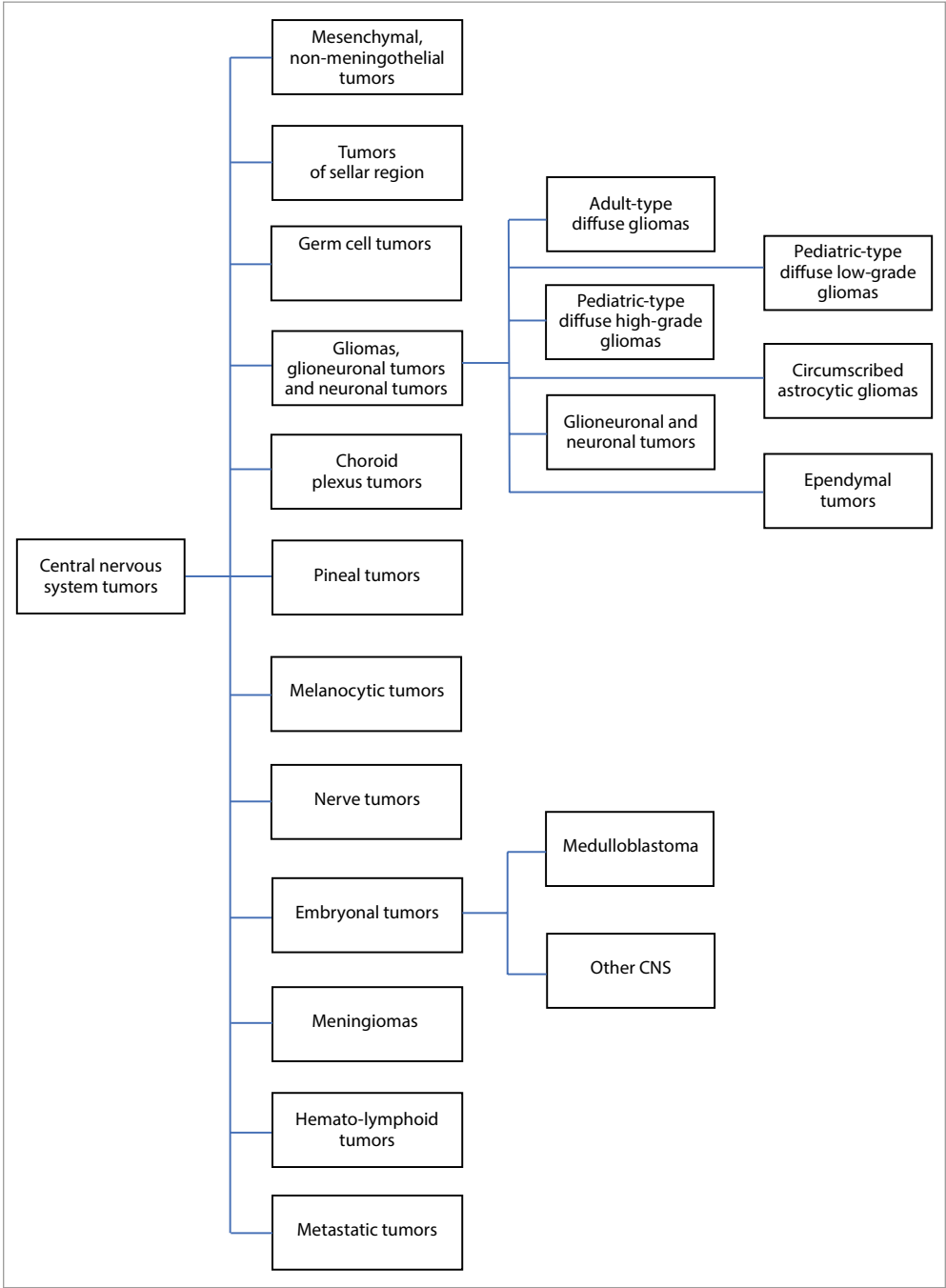


Fig. 2.1. Tumors’ classification (WHO classification of CNS tumors modified by the author)

Table 2.1. Risk factors for brain tumor

Validated risk factors	Unverified risk factors
environmental	
– prior exposure to high dose ionizing radiations	– cell phones – alcohol – virus-induced infections – smoking – exposure to vinyl chloride, pesticides, rubber, etc. – dietary – N-nitroso compounds – exposure to aspartame – exposure to electromagnetic fields
genetic	
– neurofibromatosis types 1 and 2 – Li–Fraumeni syndrome – Von Hippel–Lindau disease – tuberous sclerosis – Turcot syndrome – Cowden disease – Gorlin syndrome	– genetic polymorphisms (e.g., XRCC1)

Clinical features:

There are no specific clinical symptoms or signs of brain tumors. Patients may be asymptomatic or present with generalized and/or focal neurological manifestations ([Table 2.2](#)).

Diagnosis

- physical and neurologic examination,
- CT with contrast (useful for calcifications),
- MRI with gadolinium (preferred),
- MRI spectroscopy,
- MRI perfusion,
- arteriography,
- EEG (in case of seizures),
- lumbar puncture **NOT** recommended (except in suspected meningeal involvement),
- laboratory testing.
- CT chest/abdomen to search for primary neoplasm (in metastases),
- stereotactic biopsy in inoperable tumors.

Table 2.2. Clinical symptoms of brain tumor

Generalized symptoms	Focal symptoms
– headache (most common early morning) – nausea and vomiting – disturbed consciousness – diplopia – obscured vision – papilledema – Cushing reflex: A triad of clinical signs, including: increased systolic pressure bradycardia respiratory irregularity	frontal lobe: – personality and behavior changes – cognitive impairment – memory loss – contralateral motor loss parietal lobe: – spatial disorientation – writing, naming – drawing difficulties – aphasia occipital lobe: – unilateral/bilateral vision loss – visual field defects – illusions – hallucinations – blurred vision temporal lobe: – short and long-term memory problems – speech and language deficits – emotional changes, e.g., aggressiveness – difficulty in understanding words cerebellum: – ataxia – cerebral signs brainstem: – difficulty in swallowing – facial paresis – tingling – double vision

Treatment

Treatment depends on:

- location and type of tumor,
- patient's general condition.

Main therapeutic approaches:

- surgery,
- radiotherapy,
- chemotherapy.

Radiotherapy may be teletherapy or brachytherapy. Chemotherapy efficacy is limited by the blood–brain barrier. Temozolomide is commonly used for gliomas. Intrathecal chemotherapy is useful in lymphoma and leukemia.

Newer approaches include immune checkpoint inhibitors and CAR-T therapy.

Supportive care includes:

- corticosteroids,
- opioids,
- antiepileptic drugs,
- spasticity management,
- nutritional support,
- psychosocial care.

Prognosis varies widely by tumor type.

Gliomas

Gliomas are the most common type of primary brain tumors, arising from glial cells. In the United States, there are 6 cases of gliomas diagnosed per 100,000 people every year. The incidences of glioblastoma (the most common type of glioma) increase with age. Gliomas are more common in men across all age groups and histologies.

Gliomas are classified based on involved cell types into three groups:

- astrocytomas;
- ependymomas;
- oligodendrogliomas.
- In addition, WHO classification divides gliomas into 2 groups:
- low-grade glioma;
- high-grade glioma.

The classification of gliomas is based on histological findings, including cellular pleomorphism and the presence or absence of nuclear atypia, mitosis, endothelial/microvascular proliferation, and necrosis. About 80% of gliomas are high grade, while only 20% are low grade. Low-grade gliomas (LGGs) are typically slow-growing, and dissemination into cerebrospinal fluid (CSF) is rare. In contrast, high-grade gliomas (HGGs) are characterized by rapid, infiltrative growth, with cerebrospinal fluid dissemination occurring in 25–55% of cases (Table 2.3).

Astrocytomas arise from astrocytes and are typically slow-growing, infiltrative tumors. Low-grade astrocytomas are more common in children, whereas high-grade astrocytomas are more often diagnosed in adults.

Ependymomas arise from ependymal cells, which are found lining the ventricular cavities and the central canal of the spinal cord. They account for about 5% of all brain tumors and are common in the pediatric population.

Table 2.3. WHO classification of gliomas

WHO classification of gliomas	
low-grade glioma (LGG)	high-grade glioma (HGG)
I. pilocytic astrocytoma	III. anaplastic astrocytoma
I/II. mixed astrocytoma	IV. glioblastoma multiforme (GBM)
II. fibrillary astrocytoma	

Oligodendrogliomas account for 5% of all gliomas and originate from oligodendrocytes. These tumors grow slowly, typically arising in childhood or early adulthood (ages 20–40), and are twice as common in men as in women. Oligodendrogliomas are less infiltrative than astrocytomas.

Other tumors

Acoustic neuroma (vestibular schwannoma) is a relatively common benign tumor that originates from the vestibulocochlear nerve sheath. Vestibular schwannomas account for 8–10% of intracranial tumors and 25–30% of spinal tumors, with an estimated 2% incidence in the general population. They may develop at any age, with peak incidence between the 4th and 6th decades of life, with women affected twice as often as men. Unilateral tumors are usually sporadic, whereas bilateral acoustic schwannomas can be associated with neurofibromatosis type II (NF2).

Schwannoma grows slowly and can be asymptomatic in early stages. The typical clinical presentation is progressive sensorineural hearing loss with involvement of the trigeminal (V) and facial (VII) cranial nerves, as well as ipsilateral cerebellar signs. They may be associated with compression of the brainstem, characterized by symptoms such as:

- headache,
- vertigo,
- nystagmus,
- vomiting,
- visual changes.

Medulloblastoma is a primitive neuroectodermal tumor of the cerebellum, arising from neuronal stem or progenitor cell populations early in life. Medulloblastoma most often develops in the roof of the fourth ventricle. The peak age at diagnosis is 6–8 years, and the tumor is rare in adults. It is characterized by rapid growth with infiltration of surrounding tissue and extension toward the fourth ventricle, often leading to hydrocephalus. Medulloblastoma may spread via cerebrospinal fluid, both intracranially and into the spinal cord, producing “drop metastases”.

Meningiomas arise from meningotheelial cells of the dura mater or arachnoid. They occur most commonly in the parasagittal falx, cerebral convexities, tuberculum sel-

lae, sphenoidal ridge, tentorium, foramen magnum, and olfactory groove. They present as spherical, well-circumscribed masses or as irregular infiltrating *en plaque* lesions. Meningiomas are the second most common primary brain tumor, with an annual incidence of approx. 6 per 100,000 per year. They may remain asymptomatic or grow slowly for years.

Pituitary adenoma is a primary neuroendocrine neoplasm of the pituitary gland, accounting for 10–15% of all intracranial tumors. They are classified according to whether they are endocrinologically active. Active tumors secrete hormones, most commonly prolactin. Non-functioning adenomas present with mass-effect symptoms, typically bitemporal hemianopia due to optic chiasm compression. Active tumors are often treated medically (e.g., bromocriptine), whereas macroadenomas are generally treated surgically.

Brain metastases are the most common brain tumors, originating from malignant neoplasms outside the CNS. They occur up to ten times more frequently than primary brain tumors. Brain metastases occur in 15–40% of patients with systemic cancer (approx. 12 per 100,000 inhabitants per year). The most frequent primary sites are lung, breast, melanoma, colorectal, and renal cancer.

Hematological neoplasms constitute about 10% of brain metastases and primarily involve the leptomeninges.

Spinal cord tumors

Definition

An abnormal tissue growth within or next to the spinal cord. Spinal tumors can occur in all levels of the spine and are divided into primary tumors and secondary spine tumors. Primary cord tumors are rare, they account 10–15% of CNS neoplasms. The incidence is estimated about 10 cases per 100 000 per year young and middle-aged adults predominantly. Primary spine tumors arise from the spine itself and/or its adjacent structures. The most common primary spinal tumors are astrocytomas or ependymomas. The secondary tumors originate in the distant organ. The metastatic extradural lesions are the most common tumors of the spine.

Classification

Anatomically, spinal tumors can be classified as extradural tumors, intradural-extramedullary tumors and intramedullary tumors by their with the dura and spinal cord [Fig. 2.2].

- 1) **Extramedullary:** the tumor is located outside the dura, which is the thin covering surrounding the spinal cord. These tumors may be either intradural or extradural (epidural). They are common, account 45–55% of tumors, especially in adults. They arise from a range of tissues, such as nerves, blood vessels, meningeal layers

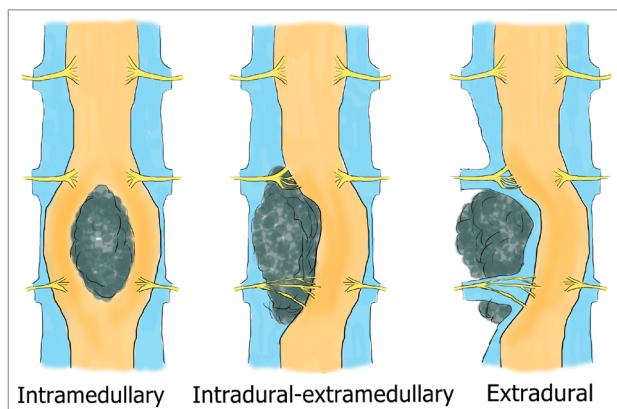


Fig. 2.2. Localization of spinal tumor

- 2) **Intradural-extramedullary:** the tumors outside the spinal cord but beneath the dura, i.e. in the leptomeninges or roots. They account 40–50% of tumors. The most common are neurofibromas, schwannomas, and meningiomas. Also leptomeningeal metastasis and drop metastases of intracranial tumors involve in the intradural space.
- 3) **Intramedullary:** the tumors grow inside the spinal cord. They account for about 5% of tumors, more common in children. Typically arise from glial or ependymal cells. The most common types are ependymomas and astrocytomas. Primary intramedullary tumors may extend over many segments of spine, causing dilatation of the spinal cord and sometimes syringomyelia. The most common intramedullary metastases are lung cancer or breast cancer.

Symptoms

Clinical signs and symptoms are variable and nonspecific. The most common symptom is pain, which is present in 85% of patients. Other symptoms include: progressive weakness, numbness, paraesthesia, reflex abnormalities, radicular signs, sphincter dysfunction. The clinical signs and symptoms associated with spinal tumor are related to the level of the lesion along the spinal column (cervical, thoracic, lumbar, sacral) as well as tumor location within the dura and spinal cord (extramedullary, intramedullary). Symptoms of spinal tumors may be mistaken for the more common degenerative spine disease, thus leading to a delay in diagnosis.

Diagnosis

- MRI with contrast: the most sensitive imaging modality for detection of vertebral metastases and other spinal lesions;
- X-ray of spine;
- CT-myelography (when MRI impossible) in tumors of the spinal canal, determination of focal widening, erosion of the spinal canal and of intervertebral foramen and of changes within the cerebral fluid;

- lumbar puncture: elevated level protein in CSF (Froin syndrome: xanthochromia with clotting of CSF, due to isolation or location of the CSF below the site of the tumor which has blocked the circulation of CSF from above);
- laboratory tests;
- screening for neoplasm in case of metastases.

Treatment

Corticosteroids should be started immediately to reduce spinal cord edema and preserve functionality. The general approach to treatment of spinal cord tumors versus intramedullary spinal cord tumors consist of combination surgery, radio- and chemotherapy. The method of treatment depend on the histologic diagnosis and localization. Some tumors, if well-localized, can be excised surgically. Bening intradural-extramedullary spinal cord tumors can be successfully resected in most patients. Radiotherapy or chemotherapy is generally reserved for tumors with malignant histologic characteristics and recurrent tumors.

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3. Headache and craniofacial pain

Marta Waliszewska-Prosół

Headache is the most common symptom in medicine and may account for up to 40–50% of medical consultations. According to epidemiological studies, up to 30% of the population suffers from frequent or recurrent headaches. Migraine is the most common neurological disease, affecting more than 1 billion people worldwide. The current International Classification of Headache Disorders (ICHD-3), published in 2018, divides headaches into the following categories (Table 3.1):

- Primary headaches – independent clinical entities, caused by their own pathomechanisms rather than by other disorders.
- Secondary headaches – occur as a symptom of another disorder known to cause headache.
- Neuropathies and facial pain – caused by lesions or diseases of the somatosensory nervous system. Neuralgia is a type of pain occurring within the distribution of a specific cranial nerve or nerves.

The primary headaches

Migraine affects approx. 12–16% of the population and is 3 times more prevalent in women. The initial symptoms may manifest in childhood or adolescence, typically before the age of 25. The disease is characterized by severe, throbbing headaches that are usually unilateral (although in up to 40% of cases, the pain can be bilateral). Attacks are commonly accompanied by photophobia, phonophobia, nausea, vomiting, and other vegetative symptoms. They occur with varying frequency and can last from 4 to 72 h (Fig. 3.1).

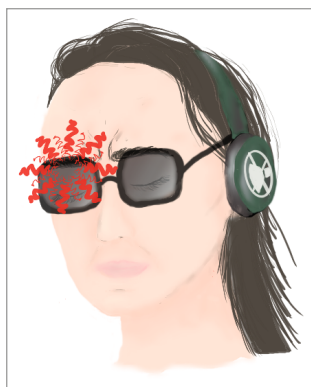


Fig. 3.1. Clinical picture of the patient during a migraine attack

Table 3.1. International classification of headache disorders (ICHD-3)

The primary headaches • Migraine: – migraine without aura; – migraine with aura; – chronic migraine. • Tension-type headache (TTH); • Trigeminal autonomic cephalalgias (TACs): – cluster headache, – paroxysmal hemicrania, – short-lasting unilateral neuralgiform headache attacks (SUNCT, SUNA), – hemicrania continua, • Other primary headache disorders: – primary cough headache; – primary exercise headache; – primary headache associated with sexual activity; – primary thunderclap headache; – cold-stimulus headache; – nummular headache; – hypnic headache; – new daily persistent headache (NDPH).
The secondary headaches • Headache attributed to: – trauma or injury to the head and/or neck; – cranial or cervical vascular disorder; – non-vascular intracranial disorder; – a substance or its withdrawal; – infection; – disorder of homoeostasis; – disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cervical structure; – psychiatric disorder.
Neuropathies and facial pains and other headaches

Migraine is divided into:

- migraine without aura – the most common (about 80% of cases) (Table 3.2);
- migraine with aura (10–15% of cases) (Table 3.3);
- chronic migraine (Table 3.4).

In over 90% of individuals with migraine aura, the manifestations are visual. These symptoms are often reversible and may appear as flashes, lights, spots, lines, visual field defects, or fortifications, typically affecting one half of the visual field (Fig. 3.2).

Table 3.2. Migraine without aura: Diagnostic criteria

- A.** At least 5 attacks fulfilling criteria B–D.
- B.** Headache attacks lasting 4–72 h (untreated or unsuccessfully treated)
- C.** Headache has at least 2 of the following 4 characteristics:
 - unilateral location;
 - pulsating quality;
 - moderate or severe pain intensity;
 - aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs).
- D.** During headache at least 1 of the following:
 - nausea and/or vomiting;
 - photophobia and phonophobia.
- E.** Not better accounted for by another ICHD-3 diagnosis.

Table 3.3. Migraine with aura: Diagnostic criteria

- A.** At least 2 attacks fulfilling criteria B and C.
- B.** One or more of the following fully reversible aura symptoms:
 - visual;
 - sensory;
 - speech and/or language;
 - motor;
 - brainstem;
 - retinal.
- C.** At least 3 of the following 6 characteristics:
 - at least 1 aura symptom spreads gradually over ≥ 5 min;
 - 2 or more aura symptoms occur in succession;
 - each individual aura symptom lasts 5–60 min;
 - at least 1 aura symptom is unilateral;
 - at least 1 aura symptom is positive;
 - the aura is accompanied, or followed within 60 min, by headache.
- D.** Not better accounted for by another ICHD-3 diagnosis.

Table 3.4. Chronic migraine: Diagnostic criteria

- A.** Headache (migraine-like or tension-type-like¹) on ≥ 15 days/month for >3 months, and fulfilling criteria B and C.
- B.** Occurring in a patient who has had at least 5 attacks fulfilling criteria B–D for [Table 3.2](#). Migraine without aura and/or criteria B and C for [Table 3.3](#). Migraine with aura.
- C.** On ≥ 8 days/month for >3 months, fulfilling any of the following:
 - criteria C and D for [Table 3.2](#). Migraine without aura;
 - criteria B and C for [Table 3.3](#). Migraine with aura;
 - believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative.
- D.** Not better accounted for by another ICHD-3 diagnosis.

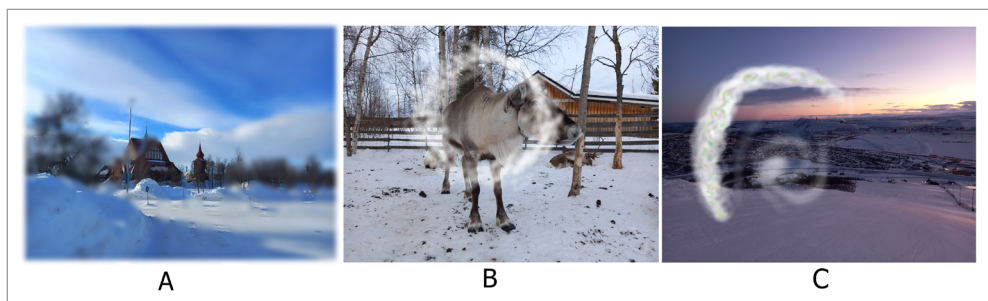


Fig. 3.2. A–C. Visual aura

Motor, sensory, or speech disturbances are less common. A typical migraine aura lasts from 5 to 60 minutes, usually about 15 min. The headache may occur during or after the aura. A rare form of migraine is acephalgic migraine – patients experience only migraine aura attacks without subsequent headache. In such patients, an epileptic and vascular background to the symptoms should be ruled out. Migraines with aura and migraines without aura can coexist.

The pathogenesis of migraine is unknown. Most likely, it is a polygenetically determined channelopathy, characterized by a predisposition to increased vasomotor reactivity on the basis of paroxysmal events in the central nervous system. The theory of a functional trigemino-vascular system, which includes the brain, cerebral vessels, and trigeminal nerve with nuclei in the brainstem, has been developed. This system is activated during a migraine attack, resulting in the release of a number of neuropeptides from the sensory endings, such as:

- calcitonin gene-related peptide (CGRP);
- substance P;
- pituitary adenylate cyclase activating polypeptide 38 (PACAP38);
- vasoactive intestinal peptide (VIP);
- neurokinin A;
- nitric oxide synthase (NOS).

The released neuropeptides lead to the initiation of neurogenic inflammation (edema around the arachnoid vessels), arterial vasodilation, and increased cerebral flow.

Complications of migraine

Chronic migraine, which is diagnosed when the headache occurs at least 15 days a month for at least a quarter.

Medication-overuse headache (MOH) – overuse of abortive medications, particularly those containing codeine and caffeine in their composition.

Status migrainosus – pain attack lasts longer than 72 h, often with dehydration and does not subside despite treatment;

Migrainous infarction – aura symptoms do not resolve for 7 days; neuroimaging studies of the brain show a cerebral infarct usually in the posterior area (Table 3.5).

Table 3.5. Medication-overuse headache: Diagnostic criteria

- A. Headache on ≥ 15 days/month in an individual with a pre-existing headache disorder.
- B. Regular overuse for >3 months of 1 or more drugs that can be taken for acute and/or symptomatic treatment of headache (regular intake of 1 or more non-opioid analgesics on ≥ 15 days/month for ≥ 3 months or any other acute medication or combination of medications on ≥ 10 days/month for ≥ 3 months).
- C. Not better accounted for by another ICHD-3 diagnosis.

The only role for neuroimaging (MRI is a preferred modality) in the diagnosis of headache is to confirm or exclude causes of secondary headaches that are suspected on the basis of red-flag features in the medical history and/or physical examination. Pharmacotherapy can be distinguished between abortive and prophylactic treatment; the latter being indicated in patients with frequent attacks. The choice of therapy must be individualized, taking into account many factors such as possible side effects, contraindications, comorbidities, and patient's preferences (Table 3.6, Table 3.7).

Tension-type headache (TTH) is the most prevalent neurological disorder worldwide and is characterized by recurrent headaches of mild-to-moderate intensity, bilateral location, pressing or tightening quality, and no aggravation by routine physical activity. It is the most common form of spontaneous headache. The incidence per year is 30–78%, with a predominance in women.

Potential pathophysiological mechanisms of TTH can be divided into 3 broad categories:

- genetic factors;
- musculoskeletal mechanisms (including nociception);
- chronification mechanisms (including central sensitization and altered pain modulation).

The latest ICHD classification distinguishes 3 forms of tension-type headache:

- infrequent episodic TTH (episodic tension-type headache (ETTH); headaches for <1 day/month on average or <12 days/year);
- frequent ETTH (headaches for 1–14 days/month or ≥ 12 and <180 days/year);
- chronic TTH (CTTH) (headaches for ≥ 15 days/month or ≥ 180 days/year).

Tension-type headache is diagnosed based on a clinical history and exclusion of other disorders that may mimic this type of headache. Anxiety, depression, and sleep disorders (including insomnia) are more prevalent in people with TTH than in the general population without headache, and their prevalence is also related to the frequency and severity of TTH attacks. Tension-type headache coexists with migraine, neck pain, and back pain (Fig. 3.3).

Table 3.6. Acute migraine treatment

Drug class	Drug	Dosage and route	Contraindications
First-line medication			
NSAIDs	acetylsalicylic acid	900–1000 mg p.o.	gastrointestinal bleeding, heart failure
	ibuprofen	400–600 mg p.o.	
Other simple analgesics	paracetamol	1000 mg p.o.	hepatic disease, renal failure
Antiemetics (when necessary)	metoclopramide	10 mg p.o.	Parkinson’s disease, epilepsy, mechanical ileus
Second-line medication			
Triptans	sumatriptan	50 or 100 mg p.o. or 6 mg s.c. or 10 or 20 mg intranasal	cardiovascular or cerebrovascular disease, uncontrolled hypertension, hemiplegic migraine, migraine with brain-stem aura
	zolmitriptan	2.5 or 5 mg p.o.	
	almotriptan	12.5 mg p.o.	
	eletriptan	20, 40 or 80 mg p.o.	
	frovatriptan	2.5 mg p.o.	
	naratriptan	2.5 mg p.o.	
	rizatriptan	10 mg p.o.	
Third-line medication			
Gepants	rimegepant	75 mg p.o.	hypersensitivity, hepatic impairment
Ditans	lasmiditan	50, 100 or 200 mg p.o.	pregnancy, concomitant use with drugs that are p-glycoprotein substrates



Fig. 3.3. Clinical picture of the patient during tension-type headache

Table 3.7. Preventive migraine treatment

Drug class	Drug	Dosage and route	Contraindications
First-line medication			
Beta blockers	bisoprolol	5–10 mg p.o. once daily	asthma, cardiac failure, Raynaud disease, atrioventric- ular block, depression
	metoprolol	50–100 mg p.o. twice daily	
	propranolol	80–160 mg p.o. once or twice daily	
Angiotensin II-receptor blocker	candesartan	16–32 mg p.o. per day	co-administration of aliskiren
Anticonvulsant	topiramate	50–100 mg p.o. daily	nephrolithiasis, pregnancy, lactation, glaucoma
Second-line medication			
Tricyclic antidepressant	amitriptyline	10–100 mg p.o. at night	age <6 years, heart fail- ure, co-administration with monoamine oxidase inhibi- tors and SSRIs, glaucoma
Calcium antagonist	flunarizine	5–10 mg p.o. once daily	parkinsonism, depression
Anticonvulsant	sodium valproate	600–1500 mg p.o. once daily	liver disease, thrombocytope- nia, female and of childbear- ing potential
Third-line medication			
Botulinum toxin	onabotulinumtoxinA	155–195 units every 12 weeks	infection at injection site
Calcitonin gene- related peptide (CGRP) monoclo- nal antibodies	erenumab	70 or 140 mg s.c. once monthly	not recommended in patients with a history of stroke, subarachnoid hemorrhage, coronary heart disease, inflammatory bowel disease, chronic obstructive pulmo- nary disease or impaired wound healing
	fremanezumab	225 mg s.c. once monthly or 675 mg s.c. once quarterly	
	galcanezumab	240 mg s.c., then 120 mg s.c. once monthly	
	eptinezumab	100 or 300 mg iv. quarterly	

Treatment of tension-type headache (TTH) is difficult and complex. In acute treatment, acetylsalicylic acid and paracetamol have been shown to be most effective, followed by other non-steroidal anti-inflammatory drugs (NSAIDs). For prophylactic treatment, amitriptyline, mirtazapine, or venlafaxine are recommended, preferably in a single daily dose. In some patients, a beneficial effect can be obtained by using drugs that block serotonin reuptake (fluoxetine, sertraline). Behavioral, physical and/or occupational therapies and various relaxation techniques are very important as adjunctive treatments.

Cluster headache (CH) occurs in about 0.1% of the population, with a marked male predominance (male-to-female ratio about 3:1). Periods of repeated pain attacks (clusters) last 2–12 weeks and usually occur 1–2 times a year, sometimes at the same time – usually in spring and/or autumn. In most cases, these clusters are followed by remission periods, which last from a year to several years. Cluster headache is widely described as the most painful condition a human can experience.

There is no consensus on the pathophysiology of CH. Most likely, during attacks the trigeminovascular system and trigeminal-autonomic reflex become activated via a trigeminal-hypothalamic pathway under fluctuating control from central pain-processing regions and the hypothalamus.

Unilateral pain attacks are very severe and involve the orbital, supraorbital or temporal regions; typically lasting 15–180 min. The pain is accompanied by unilateral autonomic symptoms, and attacks are usually accompanied by agitation and restlessness.

Cluster headaches are often associated with the rapid eye-movement (REM) sleep phase, with patients awakening with pain about 60–90 min after falling asleep. Common provoking factors include alcohol, strong smells, exercise, warm environments, and nitrates (Fig. 3.4).

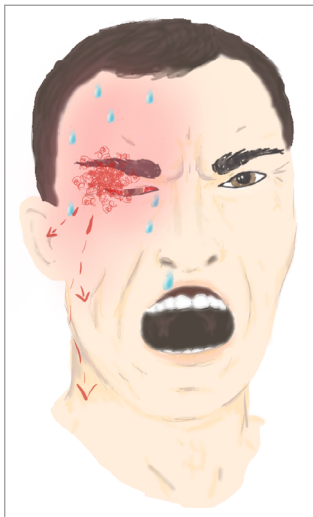


Fig. 3.4. Clinical picture of the patient during cluster headache attack

Table 3.8. Cluster headache: Diagnostic criteria

- A.** At least 5 attacks fulfilling criteria B–D.
- B.** Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15–180 min (when untreated).
- C.** Either or both of the following:
 - at least 1 of the following symptoms or signs, ipsilateral to the headache:
 - conjunctival injection and/or lacrimation;
 - nasal congestion and/or rhinorrhea;
 - eyelid oedema;
 - forehead and facial sweating;
 - miosis and/or ptosis;
 - a sense of restlessness or agitation.
- D.** Occurring with a frequency between 1 every other day and 8 per day.
- E.** Not better accounted for by another ICHD-3 diagnosis.

The management options in CH are divided into:

- acute,
- preventive,
- transitional treatments.

Nonsteroidal anti-inflammatory drugs are ineffective in the treatment of cluster headache. Interruption of the attacks can be achieved by administering sumatriptan (6 mg subcutaneously or 20 mg intranasally), intranasal zolmitriptan (5 mg), or with high-flow oxygen (12–15 L/min) administered by face mask. For preventive treatment, recommended options include verapamil 360–960 mg/day (ECG is necessary before administration), lithium preparations, topiramate, steroids (e.g., prednisone), or greater occipital nerve (GON) blocks.

The secondary headaches:

Secondary headaches occur in the course of many nervous system diseases, primarily in vascular diseases such as:

- hemorrhagic stroke,
- subarachnoid hemorrhage,
- in developmental disorders of the vessels:
 - aneurysms,
 - hemangiomas,

but also in systemic diseases (such as giant cell arteritis), in infections, metabolic or psychiatric disorders. Headache is the primary symptom of increased intracranial pressure in the course of brain tumors. It most often occurs in the early morning hours and

Table 3.9. Secondary headache disorders: Red flags

Secondary headache • Red flags: – focal neurological symptoms, – headache onset >50 years of age – headache associated with weight loss and/or change in memory or personality – impaired memory and/or altered consciousness or personality
Meningitis • Red flags: – neck stiffness – unexplained fever
Intracranial hypertension or hypotension • Red flag: – headache aggravated by posture or maneuvers that raise intracranial pressure,
Subarachnoid hemorrhage • Red flag: – neck stiffness

is accompanied by vomiting. In cases of chronic diffuse headache, with nausea, vomiting, and papilledema on fundus examination, after ruling out an intracranial proliferative process, the possibility of idiopathic intracranial hypertension (IIH) should be considered. IIH is often associated with endocrine disorders, obesity, or excessive intake of certain vitamins.

Headache can be the result of diagnostic measures (iatrogenic), as in post-puncture syndrome with cerebrospinal fluid negative pressure. In the diagnosis of secondary headaches, the primary objective is to quickly determine the underlying causes, since some of them can be seriously life-threatening for the patient (Table 3.9).

The following elements are important in the assessment:

- a thorough medical history;
- an internal and neurological examination, with particular attention to signs of focal neurological deficits, and meningeal symptoms;
- focal or secondarily generalized epileptic seizures.

Neuropathies and facial pain

Trigeminal neuralgia (TN) is a highly disabling disorder characterized by very severe, brief and electric shock-like recurrent episodes of facial pain. The lifetime prevalence is estimated to be 0.2% and it is more prevalent in women than in men (F:M ratio 3:2). The incidence increases with age, with a mean age of onset of 55 years (Table 3.10).

Table 3.10. Diagnostic criteria for trigeminal neuralgia

- A.** Recurrent paroxysms of unilateral facial pain in the distribution(s) of one or more divisions of the trigeminal nerve, with no radiation beyond, and fulfilling criteria B and C.
- B.** Pain has all of the following characteristics:
- lasting from a fraction of a second to 2 min;
 - severe intensity;
 - electric shock-like shooting, stabbing or sharp in quality.
- C.** Precipitated by innocuous stimuli within the affected trigeminal distribution.
- D.** Not better accounted for by another ICHD-3 diagnosis.

Trigeminal neuralgia is further subclassified into:

- classical type – 75% of cases, there is trigeminal neurovascular compression with morphological changes ipsilateral to the side of the pain, demonstrated either on MR imaging with appropriate trigeminal sequences or during surgery; simple trigeminal contact without morphological changes is not sufficient to underpin such a diagnosis as this is a common neuroimaging finding in healthy people,
- secondary type – 15% of cases, is attributable to an identifiable underlying neurological disease (except trigeminal neurovascular compression) that is known to cause TN, such as cerebellopontine angle tumor, arteriovenous malformation and multiple sclerosis,
- idiopathic type – 10% of cases, no apparent cause for TN can be found.

The pain of TN most frequently affects the distribution of the maxillary (V2) and mandibular (V3) divisions of the trigeminal nerve, though approximately a quarter of the cases have ophthalmic (V1) division involvement.

The frequency and duration of TN attacks are highly variable. The pain usually lasts from less than a second up to 2 min in the majority; a significant minority reports attacks lasting 2–10 min. The number of attacks is highly variable even in the same patients and ranges from a few attacks to several hundred attacks daily. Trigeminal neuralgia follows a relapsing–remitting pattern in approx. 2/3 of patients, but has a chronic pattern in the remaining 1/3.

One of the hallmark clinical features of TN is the triggerability of the attacks by innocuous mechanical stimulation of the face and intraoral mucosa ipsilateral to the side of the pain and these are often considered to be pathognomonic of TN.

Around 95–99% of patients report triggered attacks by:

- light touch;
- talking;
- chewing;
- brushing teeth;
- washing or drying;
- drinking;
- shaving.

The physical and neurological examinations are generally normal, though approx. 30% of cases can have sensory changes including mild hypoesthesia (Fig. 3.5).



Fig. 3.5. Localization of pain depending on divisions of the trigeminal nerve

The gold-standard investigation to exclude secondary causes of TN is MRI of the brain. Detailed trigeminal MR brain scan sequences are pivotal to detecting the presence of a trigeminal neurovascular conflict, the type of vascular structure (artery or vein or both) and the degree of compression.

Abortive treatments are not useful in the management of TN due to the brevity of the attacks. The mainstay of management is pharmacological preventive treatments (Table 3.11).

Table 3.11. Preventive treatments in trigeminal neuralgia

Drug	Initiating dose	Titration	Dose range
Carbamazepine	200 mg	200 mg every 3 days	200–1200 mg
Oxcarbazepine	300 mg	300 mg every 3 days	300–1800 mg
Lamotrigine	25 mg	25 mg for 2 weeks, 50 mg for 1 week, then increase by 50 mg every week	25–400 mg
Gabapentin	300 mg	300 mg every 3 days	300–3600 mg
Pregabalin	150 mg	150 mg every 7 days	150–600 mg
Baclofen	15 mg	15 mg every 7 days	15–90 mg
Botulinum toxin type A	25–195 units	NA	25–195 units

Surgical interventions are only for patients who fail to respond to or adequately tolerate medical therapies. Currently, we distinguish:

- invasive, non-ablative (microvascular decompression);

- invasive, ablative (controlled lesioning of the trigeminal ganglion), thermal (radiofrequency thermocoagulation), chemical means (glycerol rhizolysis), separation of trigeminal nerve fascicles in the posterior fossa (internal neurolysis);
- non-invasive, ablative (stereotactic radiosurgery).

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4. Neuroinfections

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Neuroinfections are infectious diseases of various etiology that involve the nervous system. Infections of the central nervous system (CNS) are varied in their causes, presentation, and prognosis. Many etiologic factors determine the incidence of different neuroinfections across geographical regions (Table 4.1).

Table 4.1. Classification of neuroinfections

Localization • Diffuse: – meningitis-inflammation of meninges – encephalitis-brain inflammation – myelitis spinal cord inflammation • Limited: – brain abscess – subdural empyema – epidural abscess	Etiology – bacteria – virus – fungus – protozoa – prion
Clinical course: – acute – subacute – chronic	Results of cerebrospinal fluid: – purulent – non-purulent (aseptic)

Route of entry:

The most common:

- a) blood entry;
- b) local infection (middle ear, sinusitis);
- c) neuronal transmission;
- d) penetrating wound;
- e) contaminated surgical procedures;
- f) through congenital or acquired defects in the skull or spine.

Diagnostics:

Clinical features:

- a) meningeal signs:
 - neck stiffness;
 - Kernig's sign;
 - Brudzinski's sign.

Cerebrospinal fluid (CSF) examination:

bacteriology methods:

- a) Gram stain;
- b) culture;
- c) radioimmunoassay (RIA);
- d) latex particles agglutination (LPA);
- e) co-agglutination (Co-A);
- f) enzyme-linked immunosorbent assay (ELISA);
- g) polymerase chain reaction (PCR);

neuroimaging studies:

- a) MRI;
- b) CT;

Blood tests:

- a) complete blood count (CBC);
- b) procalcitonin;
- c) C-reactive protein (CRP);
- d) glucose level;
- e) coagulation;
- f) liver and kidney function;
- g) blood culture;

EEG; other:

- a) echocardiography,
- b) body fluid cultures,
- c) chest X-ray,
- d) urinalysis (this analysis may be undertaken as necessary to evaluate suspected coexistent disease).

Meningitis

Meningitis is an acute inflammation of the meninges (pia and arachnoid mater), caused by a primary infection within the subarachnoid space. It may be caused by a variety of microorganisms, which vary in frequency according to the age of the host and other risk factors.

Etiology includes:

Bacteria:

The incidence of bacterial meningitis is estimated at 2–6 cases per 100,000 population per year, with peaks in infancy, adolescence, and the elderly. The most common organisms causing bacterial meningitis vary depending on the patient's age. Under 2 months

of age, group B streptococcus is the most common bacterial agent, and in those 11–17 years of age, *Neisseria meningitidis* is the most common bacterial agent. In all other pediatric age groups and in adults, *Streptococcus pneumoniae* is the most common bacterial agent.

A number of risk factors predispose to bacterial meningitis, including:

- a) penetrating head trauma;
- b) CSF shunt (*Staphylococcus*);
- c) immunosuppression;
- d) splenectomy (*Streptococcus pneumoniae*);
- e) skull base fracture.

Viruses:

Viruses, especially enteroviruses, are the most common cause of aseptic meningitis.

Other viral causes of meningitis include:

- a) arboviruses (including West Nile virus),
- b) herpesviruses (herpes simplex virus type 2),
- c) acute HIV infection,
- d) lymphocytic choriomeningitis virus.

Fungi:

Candida species, *Cryptococcus neoformans*, *Coccidioides immitis*, and *Aspergillus* are the most common causes of fungal meningitis, especially in patients with depressed cell-mediated immunity.

Other causes:

Spirochetes such as *Treponema pallidum* (syphilis), *Borrelia* species (early neuroborreliosis), and *Leptospira* can cause meningitis, but are rather subacute or chronic. Parasitic infections, including *Angiostrongylus*, *Baylisascaris*, *Taenia solium*, and *Gnathostoma*, which are endemic in some regions of the world, can present as meningitis. Among the zoonotic infections, the most important causes are *Brucella* spp. and *Coxiella burnetii*.

Typically, clinical features of bacterial meningitis include: headache, fever, neck stiffness, photophobia; additional symptoms:

- a) focal neurologic deficits;
- b) seizures (20–30%, especially *H. influenzae*, *S. pneumoniae*);
- c) cranial nerve palsies (III, IV, VI, VII).

More than 90% of patients with meningitis present with at least 2 of the following symptoms: headache, fever, neck stiffness, and altered consciousness. Rash may occur in meningococcal meningitis. Immunocompromised patients may lack some of the cardinal features of meningitis, such as fever.

Bacterial meningitis may present as:

- **Acute** – symptoms evolve rapidly over 1–24 h;
- **Subacute** – symptoms evolve over 1–7 days;
- **Chronic** – symptoms evolve over more than 7 days.

In viral meningitis, the clinical presentation may be very similar to that of acute bacterial meningitis.

The characteristic CSF profile in acute bacterial meningitis includes an elevated white blood cell (WBC) count with a predominance of polymorphonuclear leukocytes, elevated protein, and low glucose. Viral meningitis usually features a lymphocytic predominance of WBCs (although polymorphonuclear leukocytes may be present in the early phase) and an elevated protein concentration without a concomitant significant lowering of CSF glucose. Testing the blood and CSF for virus-specific serologies and PCR assays can help identify the viral etiology.

Empiric antibiotic therapy needs to be administered promptly upon the diagnosis of acute bacterial meningitis, with specific drugs initially chosen on the basis of the most likely organisms and subsequently modified. In addition to antibacterial therapy, some adjunctive therapies may also be helpful in certain situations. Viral meningitis is typically a self-limited syndrome and does not require treatment. Antiviral therapy is reserved for cases in which herpes simplex virus type 1 (HSV-1) infection is suspected (Table 4.2).

Table 4.2. Empirical antibiotic therapy for suspected bacterial meningitis

Age group	Pathogen	Empiric treatment
Neonate (<1 months)	– <i>Streptococcus agalactiae</i> – <i>Listeria monocytogenes</i> – <i>Escherichia coli</i>	ampicillin + cefotaxime or gentamicin
1–24 months	– <i>Streptococcus agalactiae</i> – <i>Escherichia coli</i> – <i>Streptococcus pneumoniae</i> – <i>Neisseria meningitidis</i>	cefotaxime or ceftriaxone + vancomycin
2–50 years	– <i>Streptococcus pneumoniae</i> – <i>Neisseria meningitidis</i>	cefotaxime or ceftriaxone + vancomycin
Elderly	– <i>Streptococcus pneumoniae</i>, <i>Neisseria meningitidis</i> – <i>Listeria monocytogenes</i>	cefotaxime or ceftriaxone + vancomycin + ampicillin
Immuno-suppression	– <i>Streptococcus pneumoniae</i> – <i>Neisseria meningitidis</i> – <i>Listeria monocytogenes</i> – <i>Salmonella</i> spp.	cefotaxime or ceftriaxone + vancomycin + ampicillin

Neurological complications of meningitis

- increased intracranial pressure and cerebral edema;
- seizures;
- focal neurologic deficits (cranial nerve palsy, especially III, IV, VI, VII; hemiparesis);
- brain abscess;
- disseminated intravascular coagulation (DIC);
- cognitive impairment.

Antimicrobial prophylaxis

The risk of developing meningococcal meningitis is increased 400 to 800 times in individuals with close contact with an infected person. Antimicrobial prophylaxis should be initiated within 24 h after exposure (prolonged contact, close proximity, or direct exposure to the patient's oral secretions). Prophylaxis against meningococcal meningitis includes rifampin given twice a day (600 mg every 12 h), or 1 dose of ciprofloxacin (500 mg) or ceftriaxone (250 mg). In the case of tuberculosis, isoniazid is used.

Rifampin prophylaxis (600 mg for 4 days) is recommended for contacts of patients with *H. influenzae* meningitis in the case of immunocompromised children (including unvaccinated ones) or children younger than 4 years who have not completed their vaccination schedule. There are no current recommendations for chemoprophylaxis in pneumococcal meningitis.

Currently, some neuroinfections and their neurological complications can be prevented by vaccination:

- *N. meningitidis* types A, B, C, Y and W-135;
- *Haemophilus influenzae* type b (Hib);
- *S. pneumoniae* (several serotypes);
- anti-rotavirus, anti-tick-borne encephalitis, anti-influenza vaccine, tuberculosis, mumps, measles, rubella, polio.

Encephalitis

Encephalitis is an inflammation of the brain parenchyma associated with clinical evidence of neurological dysfunction. Encephalitis is usually a result of viral infection. Concomitant meningitis that can occur with encephalitis is known as meningoencephalitis. The worldwide incidence of encephalitis is estimated at 0.07–12.6 cases per 100,000 population.

The spectrum of causative agents is very broad and depends on immune status, geographical factors, season, and exposure. Viruses cause more than 90% of encephalitis cases. Herpes simplex type 1 virus is the most common cause of encephalitis. The esti-

mated worldwide incidence of herpes encephalitis is between 2 and 4 cases per 1,000,000. Other causes of encephalitis include:

Other viruses: arboviruses, cytomegalovirus, varicella-zoster virus, adenovirus;

Spirochetes: *Treponema pallidum*, *Borrelia burgdorferi*;

Parasites: toxoplasmosis, *Plasmodium falciparum*;

Fungi: *Cryptococcus neoformans*.

The presentation of encephalitis is very similar to meningitis and includes:

- headache;
- fever;
- nausea;
- vomiting;
- altered mental status accompanied by seizures and focal neurological signs.

Other common symptoms include behavior changes and disorientation. Patients often present with prodromal symptoms, which vary depending on the infectious agent and may include parotitis (in mumps virus infection) or fever, malaise, and myalgias (in arbovirus infections). HSV-1 encephalitis typically manifests with altered mentation and level of consciousness lasting more than 24 h, fever, new-onset seizures, and/or focal neurologic deficits. The most common manifestations are personality changes, dysphasia with progressive behavioral disturbances, and sometimes psychotic symptoms.

Diagnosis:

- CT: normal in the early stage. In HSV-1, hypodensities in temporal lobes with mild mass effect and hemorrhage may be seen in the later phase.
- MRI with contrast: in HSV-1, high-signal areas of unilateral focal edema on T2 images in the medial and inferior temporal lobes, extending into the insular cortex and frontal lobe.
- EEG: periodic discharges or focal slowing in frontotemporal leads in patients with HSV-1 encephalitis.
- CSF: typically lymphocytic pleocytosis, normal glucose level, and moderately elevated protein. CSF examination for specific virus antibodies and PCR tests.
- blood tests.

Intravenous acyclovir (10 mg/kg every 8 h) is the first-line treatment for HSV-1 encephalitis and should be continued for 14–21 days. Other cases of viral encephalitis are treated with supportive care, depending on the symptoms.

Encephalitis is a serious condition with a high rate of mortality. The prognosis is dependent on the causative organism. In the case of rabies, mortality is about 100%. In addition, approximately two-thirds of patients develop significant neuropsychiatric complications, including cognitive impairment, personality and behavioral changes, or epilepsy.

Brain abscess

A brain abscess is a focal intracerebral infection that begins as a localized area of cerebritis and develops into a collection of pus surrounded by a well-vascularized capsule. It is a rare condition, with the incidence estimated to be 0.3–0.9 per 100,000 population per year in developed countries.

Bacteria, especially *Streptococcus* species, are the most common causative agents, followed by *Staphylococcus* species and Gram-negative bacteria. The most common predisposing condition is the presence of contiguous foci of infection:

- otitis;
- mastoiditis;
- sinusitis;
- meningitis.

Brain abscess may be secondary to hematogenous dissemination in 30–40% of cases, especially in infective endocarditis, in patients with predisposing conditions associated with pulmonary circulation shunts, or as a consequence of distant infectious foci (e.g., dental infection, pulmonary abscess).

The presentation of brain abscess depends on the pathogen and concomitant conditions, including focal mass expansion, increased intracranial pressure, and tissue destruction. The clinical symptoms are varied and include:

- subacute fever;
- headache;
- focal signs;
- seizures;
- signs of increased intracranial pressure.

In most cases, a brain abscess is single and located in the frontal or temporal lobes.

Diagnostics include:

- CT and MRI: show a peripherally ring-enhancing lesion with a hypodense center (central necrosis), surrounded by a variable hypodense area (edema);
- lumbar puncture is not recommended and may be contraindicated due to increased intracranial pressure;
- laboratory tests are not specific;
- chest X-ray.

Management of brain abscesses:

neurosurgical drainage;

prolonged administration of parenteral antibiotics tailored to culture results;

eradication of the primary site of infection.

Subdural empyema

Subdural empyema is a loculated collection of purulent material in the subdural space between the dura mater and arachnoid. It accounts for 15–22% of all intracranial infections. Subdural empyema may arise as a complication of sinusitis or otitis media. Other common etiologies include penetrating trauma. *Staphylococci* and Gram-negative bacilli are the most common causative agents.

The clinical features include:

- seizures;
- focal deficits;
- fever;
- vomiting;
- progressive neurologic deterioration.

Diagnostics are:

- laboratory tests;
- CSF examination: moderate pleocytosis with a predominance of granulocytes (40% of patients have lymphocyte predominance); CSF culture may be negative;
- CT and MRI: presence of characteristic lesions in the subdural space, accumulation of liquid matter, and meningeal enhancement.

The recommended management includes surgical drainage and antibiotic therapy. Empiric treatment consists of vancomycin plus a fourth-generation cephalosporin (i.e., cefepime).

Spinal epidural abscess

Spinal epidural abscess is an infectious process usually confined to the adipose tissue of the dorsal epidural space, which contains a rich venous plexus. Abscesses that form in this space are limited by the bony structures of the spinal column.

Risk factors include:

- prior spinal surgery or trauma;
- injection drug use;
- diabetes mellitus;
- renal dysfunction;
- comorbid conditions: immunosuppression, malignancy, alcohol use.

The thoracolumbar spine is the most frequent site of infection.

In more than two-thirds of cases, *Staphylococcus aureus* is the causative agent. Other possible infective agents include *Pseudomonas aeruginosa* or *Escherichia coli*. Anaerobic or fungal causes are rarely identified. *Mycobacterium tuberculosis* is a possible cause of epidural abscess.

The first symptoms include localized back pain at the level of the affected spine, often associated with tenderness on percussion. Symptoms usually progress over days to weeks.

A typical triad of symptoms includes:

- back pain;
- fever;
- progressive neurological symptoms.

Diagnostics include:

- MRI with contrast;
- myelography or CT when MRI cannot be performed;
- laboratory tests:
 - a) increased inflammatory markers,
 - b) blood cultures;
- lumbar puncture is relatively contraindicated (CSF results show elevated protein and increased cell count).

Empiric antibiotic therapy typically includes vancomycin and cefepime, but whenever possible, it should be delayed until surgical cultures are obtained. Therapy should be refined once cultures confirm a causative pathogen. Emergency neurosurgical intervention is considered mandatory in cases of spinal abscess with neurological compromise.

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5. Movement disorders

Sławomir Budrewicz

Parkinson's disease (PD)

Parkinson's disease is a progressive neurodegenerative disorder with impaired activity of the dopaminergic system. The disease affects approximately 0.15–0.3% of the general population and is more common in men. The incidence of PD increases with age, reaching 2–3% of the general population by the age of 80.

The etiology of PD is multifactorial. It belongs to the group of alpha-synucleinopathies, diseases characterized by the accumulation of abnormal alpha-synuclein protein in the form of Lewy bodies within neuronal cytoplasm. In a small group of patients (about 5–10%), a genetic basis can be identified.

The neuropathological substrate of the motor symptoms of PD is atrophy of dopaminergic cells of the pars compacta of the substantia nigra in the midbrain. In addition to dopaminergic dysfunction, disturbances of the serotonergic and cholinergic systems are also present.

The modern diagnosis of the disease is based on the 2015 Movement Disorders Society clinical criteria (MDS Clinical Diagnostic Criteria for Parkinson's Disease, Postuma RB et al., 2015). On physical examination, signs of parkinsonian syndrome are present, with predominant bradykinesia in combination with either muscle rigidity, resting tremor (with a frequency of 4–6 Hz), or both. The described symptoms are initially asymmetric.

Patients exhibit a range of motor symptoms, including:

- hypomimia;
- ocular bradykinesia;
- abnormal postural reflexes;
- stooped posture;
- gait abnormalities with step shortening;
- narrow gait base with limited or absent upper limb co-movement.

Patients also have nonmotor symptoms:

- constipation;
- weakness or absence of the sense of smell;
- drooling;
- arterial hypotonia;
- behavioral disturbances during REM sleep (these may precede the onset of motor symptoms).

Psychiatric symptoms such as depression, anxiety, apathy, and, in the late stages of the disease, psychotic disorders and cognitive impairment may also be found.

The diagnosis is based on clinical symptoms and the patient's response to levodopa treatment. The nuclear medicine imaging procedure with DaTSCAN (dopamine transporter tracer SPECT study) can be used primarily to differentiate psychogenic parkinsonism from essential tremor. However, this method cannot distinguish PD from progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), or multiple system atrophy (MSA).

An important argument for confirming the diagnosis is the demonstration of a significant reduction in motor symptoms following levodopa.

Treatment of PD is symptomatic and should be started immediately once the diagnosis is established. The medications in the treatment of motor symptoms include:

- dopamine precursor – levodopa (LD) administered with an aromatic amino acid decarboxylase inhibitor, also in the form of extended-release preparations;
- dopaminergic agonists in the form of extended-release preparations, e.g., ropinirole, pramipexole, rotigotine (transdermal system), apomorphine (administered subcutaneously);
- NMDA receptor antagonist – amantadine;
- MAO-B inhibitors, such as rasagiline;
- COMT inhibitors, e.g., entacapone, opicapone;
- cholinolytics, e.g., biperiden, pridinol.

In the advanced stages of PD, surgical treatment with deep brain stimulation (DBS) with implantation of electrodes into the subthalamic nucleus may be used, as well as drugs administered by enteral infusion – Duodopa – or subcutaneous infusion – apomorphine. Apomorphine may also be administered as intermittent subcutaneous injections using a pen device. Treatment of postural symptoms is also symptomatic.

Summary

Parkinson's disease is the most common disease that runs with parkinsonian syndrome. In addition to motor symptoms, it is characterized by numerous nonmotor symptoms. In the initial period of the disease, pharmacological treatment provides substantial clinical improvement. In advanced PD, device-assisted methods can be used (DBS, continuous subcutaneous apomorphine infusion (CSAI), levodopa–carbidopa intestinal gel (LCIG) infusion, foslevodopa/foscarbidopa subcutaneous infusion (FLFCI) administered via pump or pen, or Duodopa infusion).

Atypical parkinsonism (AP)

This is a group of sporadic conditions with parkinsonian syndrome dominating in the clinical picture. In addition, patients often exhibit other symptoms, such as:

- dysarthria;
- dysphagia;
- gait disorders with falls;
- abnormalities of postural reflexes;
- disorders of the vegetative system and cognitive function;
- cerebellar symptoms.

The diagnosis of atypical parkinsonism is based on clinical criteria established for each specific disease. Nuclear magnetic resonance (NMR) examination also plays an important role in the diagnosis, in which abnormalities typical of individual forms of AP can be observed.

Multiple system atrophy (MSA)

This disease belongs to alpha-synucleinopathies, and occurs with a frequency of about 1.6–4.9 cases per 100,000 people in the general population. It is characterized by motor symptoms (mainly parkinsonian syndrome, cerebellar syndrome, and sometimes pyramidal signs) together with vegetative system dysfunction (including constipation, orthostatic hypotonia, dysuric disturbances, and sexual dysfunction).

In cases where symptoms of parkinsonian syndrome coexist with symptoms of vegetative dysfunction, the condition is referred to as MSA–P (in the European population about 80% of cases). If predominant symptoms are cerebellar and vegetative, the condition is referred to as MSA–C (about 20% of cases). The criteria are based on the Movement Disorder Society's MSA diagnostic criteria (Wenning GK et al., 2022) (Fig. 5.1, Fig. 5.2).

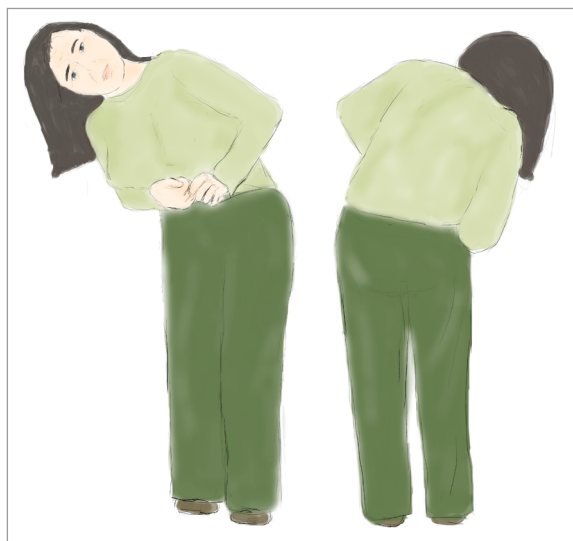
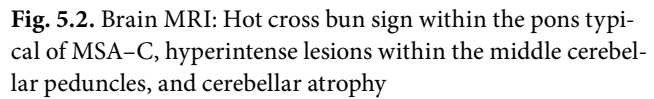
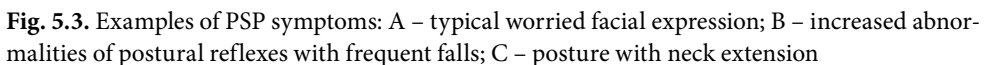


Fig. 5.1. Patient with MSA–P showing postural disturbance (Pisa sign)



This disease is classified among the tauopathies and occurs with a frequency of about 6 cases per 100,000 people in the general population. The condition is characterized by the coexistence of a parkinsonian syndrome with other motor and nonmotor symptoms as defined in the Movement Disorder Society PSP diagnostic criteria (Höglinger GU et al., 2017) (Fig. 5.3, Fig. 5.4).



These include:

- abnormal vertical eye movements;
- bradykinesia and stiffness mainly in the axial muscles;
- typical worried facial expression;
- increased abnormalities of postural reflexes with frequent falls;
- loss of criticism;
- motor inattention;
- posture with straightening of the neck;
- dysarthria;
- dysphagia;
- cognitive disorders with predominant executive function disturbances.

Corticobasal degeneration (CBD)

This rare condition belongs to the group of tauopathies, with an incidence of 5 people per 100,000 in the general population. The disease is characterized by symptoms of asymmetric parkinsonism, with cortical sensory disturbances, apraxia (usually affecting the upper limb), and dystonia. In addition, patients are found to have abnormal postural reflexes, frequent falls, dysphagia and dysarthria, and cognitive impairment. Diagnostic criteria were defined by Armstrong MJ et al. in 2013 (Fig. 5.5).

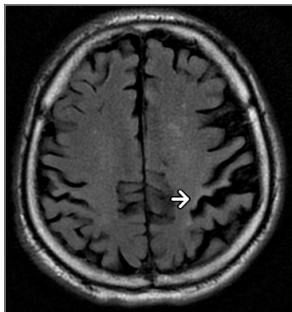


Fig. 5.5. Brain MRI: CBD. Asymmetric bilateral cortical atrophy in the region of the central sulcus on the left side (arrow)

Lewy body dementia (LBD)

This disease belongs to alpha-synucleinopathies. It affects 5% of people in the general population. It is the 2nd cause of dementia after Alzheimer's disease, accounting for 30% of dementias due to neurodegenerative disorders. Diagnostic criteria were outlined by McKeith IG et al. in 2017.

The condition is characterized by the occurrence of a parkinsonian syndrome and other symptoms, such as:

- cognitive impairment with early onset (unlike PD, where cognitive impairment occurs late in the disease);
- fluctuations in cognitive function in the early stages of the disease;
- symptoms of parkinsonian syndrome (with bradykinesia, rigidity, tremor, and gait disturbances);
- hallucinations – usually visual;
- overreactions to neuroleptics, primarily classic ones.

Treatment of atypical parkinsonian syndromes is symptomatic and based on experience gained in the treatment of Parkinson's disease. For parkinsonian symptoms such as bradykinesia and rigidity, levodopa preparations may be attempted, but usually with little or no response to the drug. Dysautonomia symptoms and psychiatric disorders require symptomatic treatment.

Huntington's disease

Huntington's disease (HD) is a genetically determined neurodegenerative disorder with an incidence of about 1.6–1.9 per 100,000 population.

The main symptoms are:

- hyperkinetic-hypotonic syndrome;
- psychiatric disorders.

The disease is caused by a mutation in the IT15 gene on chromosome 4, which encodes the huntingtin protein. The mutation involves a multiplication of CAG triplet nucleotide repeats.

The first clinical manifestations of HD appear between 35 and 40 years of age. There is also a distinction between the juvenile form (Westphal's variant) – with onset around the age of 20 – which is characterized by bradykinesia and rigidity without choreiform movements. In the typical adult form, movement disorders are dominated by choreiform movements with decreased muscle tone. Patients may develop dysarthria and dysphagia.

Later in the course of the disease, cognitive dysfunction develops, including impairments of executive functions, attention deficits, and dementia. Depression can be an early symptom (with an increased risk of suicide attempts), or later in the disease, often accompanied by behavioral disorders. Anxiety and psychotic disorders are also observed in patients.

The diagnosis is based on the result of genetic testing and the presence of the clinical syndrome described above. A thorough family history should always be obtained. Magnetic resonance imaging of the head shows atrophy of the caudate nuclei, resulting in dilatation of the lateral ventricles, producing the characteristic “butterfly wings” image (Fig. 5.6).

Treatment is symptomatic. For movement disorders, tetrabenazine is mainly used, as well as tiapride, risperidone, olanzapine, and haloperidol. In the treatment of depression – SSRIs, mirtazapine, or tricyclic antidepressants. For psychotic disorders – quetiapine and clozapine are used.

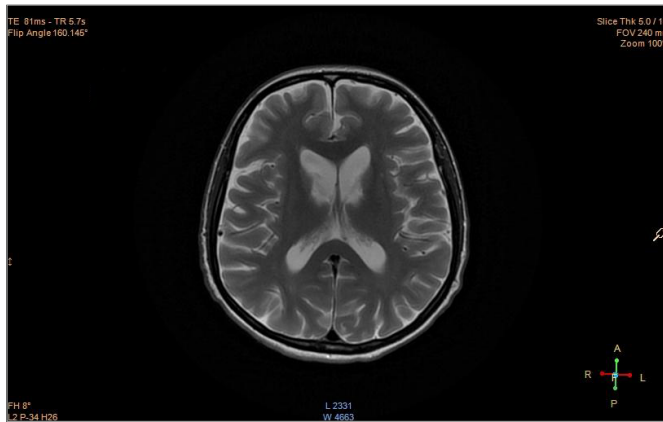


Fig. 5.6. Brain MRI: bilateral atrophy of the caudate nuclei heads with secondary enlargement of the lateral ventricles (“butterfly wings” sign) in a patient with Huntington’s disease

Summary

Huntington’s disease is an inherited neurodegenerative disorder that significantly impairs quality of life. Diagnosis is based on genetic testing, neuroimaging, and psychological as well as psychiatric evaluation.

Other chorea

Involuntary choreatic movements, which are the main motor symptom in HD, can also occur in other conditions. Selected conditions in which choreiform movements may be observed are listed below:

- Sydenham’s chorea;
- systemic lupus erythematosus;
- AIDS;
- neuroacanthocytosis;
- advanced stage of Parkinson’s disease.

Essential tremor (ET)

Essential tremor is the most common movement disorder presenting with tremor. In people over 65 years of age, it can occur in about 5% of the population. The disease can begin at different ages, and in about 50% of cases, it can be familial.

The tremor is intentional and positional, usually bilateral, and primarily affects the upper extremities, head, and voice. Severe intention tremor can significantly limit the patient’s ability to perform daily activities.

The basis for diagnosis is the physical examination. Patients should be tested for handwriting (which is significantly distorted by intention tremor) and for drawing the so-called Archimedes spiral or a ladder. Most patients show a temporary reduction in tremor severity after consuming a small amount of strong alcohol. In the DaTSCAN test, unlike in Parkinson's disease, no changes are found. In Parkinson's disease, by contrast, there is a decrease in uptake of the dopamine transporter marker (Fig. 5.7).

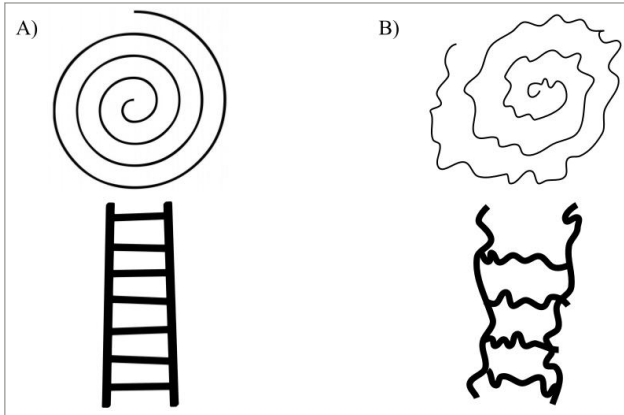


Fig. 5.7. Archimedes spiral and drawing of the ladder in a healthy person (A) and in a patient with ET (B)

Treatment is symptomatic. The first-choice drug is the beta-blocker propranolol. Other beta-blockers – metoprolol or atenolol – can also be used, although they are usually less effective. Another treatment option is primidone. Gabapentin, topiramate, and clonazepam are also used. In tremor of significant severity, surgical treatment can be undertaken with DBS by implanting an electrode into the ventral intermediate nucleus of the thalamus.

Summary

Essential tremor is the most common movement disorder that occurs with tremor. It can be familial in about 50% of cases.

Generalized dystonia (GD)

Generalized dystonia (GD) is a group of conditions in which dystonic movements affect multiple areas, e.g., face, neck, limbs, and trunk, significantly impairing the patient's functioning. Dystonic muscle spasms are accompanied by pain. In most cases, they have a genetic basis.

Examples of generalized dystonias include:

- Dystonia 1 (DYT 1):

Dystonia 1 is a rare disease caused by a mutation in the TOR1A gene, which encodes the protein torsin. The incidence of the disease is about 17–26 cases per 100,000 people in the general population. It usually manifests early in life, initially affecting one limb. Symptoms may then extend to the other limbs, the trunk, and the neck (Fig. 5.8).

In the early stages, symptomatic treatment may include high doses of cholinolytic drugs (e.g., pridinol, biperiden). In patients with severe symptoms of dystonia, surgical treatment with deep brain stimulation (DBS) is performed, in which the target of stimulation is the internal segment of the globus pallidus.



Fig. 5.8. A patient with generalized dystonia type 1

- Dystonia 5 (DYT 5), Segawa dystonia, dopa-responsive dystonia:

Segawa dystonia (DYT 5) is a rare dystonia that is genetically conditioned. Two mutations are responsible for the disease symptoms: DYT5a, involving a mutation in the gene on chromosome 14 encoding the enzyme GTP cyclohydrolase 1, and DYT5b, caused by a mutation in the tyrosine hydroxylase gene located on chromosome 11. The incidence is 0.5 per 1,000,000 people in the general population. The first clinical symptoms usually occur in childhood, in the form of dystonia of one lower limb, then involving the trunk, upper limbs, and neck. Symptoms of parkinsonian syndrome may also be present. Therapy includes levodopa administration, which at low doses (usually up to 400 mg per day), significantly reduces the symptoms of dystonia.

Cervical dystonia

Cervical dystonia is a focal dystonia that can occur at any age, more often in women. The symptoms of dystonia involve the muscles of the neck. The following types of cervical dystonia are distinguished:

- torticollis – dystonia with twisting of the head to one side;
- laterocollis – dystonia with bending of the head to one side;
- retrocollis – dystonia with backward bending of the neck;
- anterocollis – dystonia with forward bending of the neck.

Other mixed forms, involving flexion or torsion of the head relative to the neck, are also possible (COL-CAP new classification). Sometimes, patients present with coexisting head tremor, known as dystonic tremor. Muscle spasms causing dystonic movements are usually accompanied by pain. In symptomatic treatment (in addition to oral drugs – cholinolytics and benzodiazepines), local administration of botulinum toxin to dystonic muscles is used. In severe forms, deep brain stimulation (DBS) may also be used (Fig. 5.9).

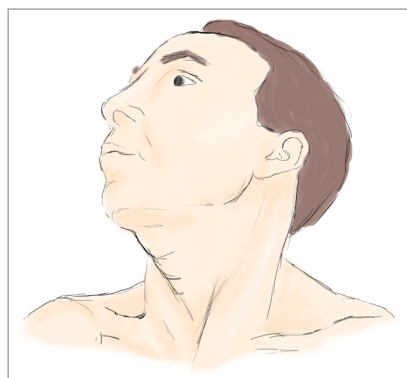


Fig. 5.9. Patient with cervical dystonia

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6. Dementia and cognitive decline

Mieszko Zagrajek

According to DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition), the diagnosis of dementia requires the development of multiple cognitive deficits that are sufficiently severe to cause impairment in occupational or social functioning. The cognitive deficits must involve memory and other cognitive domains, represent a decline from premorbid function, and cannot be attributed to delirium.

Age-Associated Memory Impairment (AAMI) is a natural process closely related to advancing age, resulting in memory decline with age. It is estimated that nearly 40% of people aged 65 and older experience gradual memory loss.

Mild Cognitive Impairment (MCI) is an intermediate stage between normal age-related cognitive changes and dementia. It is usually defined by the presence of objective memory impairment with preserved ability to function in daily life. Patients with MCI are at increased risk of developing dementia. Approximately 15–20% of people aged 65 or older are affected. There are 2 main types of MCI:

- amnesic MCI, primarily affecting memory (~15% annual conversion to AD);
- non-amnesic MCI, affecting cognitive functions other than memory (e.g., the ability to make decisions, executive functions).

Dementia can be grouped into 4 major categories:

- neurodegenerative diseases;
- cerebrovascular diseases;
- infectious diseases;
- metabolic diseases.

Neurodegenerative diseases

The most common neurodegenerative disease is Alzheimer's disease (AD), named after Alois Alzheimer. The clinical course of the disease is progressive, although plateaus may occasionally occur. The usual initial complaint is memory impairment for newly acquired information, while memory for remote events remains preserved at the onset. The prevalence of AD before the age of 65 is less than 1%, but it rapidly increases to 5–10% at age 65, and to 30–40% at age 85 and older.

In the early stages of AD, the neurological examination is usually normal. In later stages, patients show symptoms of extrapyramidal syndrome (e.g., bradykinesia, rigidity, postural changes). Delusions, psychotic behavior, agitation, and major depression are also common.

The diagnosis of AD is based on:

- neuropsychological testing (detect subtle cognitive impairment early in the disease, document global impairment, follow the course of the disease);
- neuroimaging (particularly MR of the brain – dilatation of the lateral ventricles and widening of the cortical sulci, especially in the frontal and temporal regions);
- functional imaging (PET, SPECT or fMRI – hypometabolism in the temporal and parietal areas);
- cerebrospinal fluid (CSF) examination: change in biomarker levels – reduction of beta-amyloid 1-42 (A β 42) and an increase of total Tau (t-Tau) and phosphorylated Tau 181 (p-Tau181);
- genetic tests.

In AD there are deterministic mutations in 3 genes responsible for the autosomal dominant form of the disease beginning as early as the third decade of life:

- amyloid precursor protein (APP);
- presenilin 1 (PS1);
- presenilin 2 (PS2).

Additionally, polymorphisms in 2 genes are associated with increased risk of AD in people over the age of 65 – ϵ 4 polymorphism of the APOE gene and alpha2-macroglobulin protein.

Risk factors for AD may also be:

- smoking;
- traumatic head injury;
- lower education level;
- parental age at the time of birth;
- the presence of neurodegenerative disease in a first-degree relative.

The main pathology in AD is rapidly progressive atrophy of the cerebral cortex. The earliest loss of neurons occurs in the entorhinal region of the medial temporal lobe. Histopathological markers of AD are argentophilic senile plaques and neurofibrillary tangles. Biochemically, AD is characterized by a 50–90% reduction in choline acetyltransferase activity in the cerebral cortex and hippocampus.

Symptomatic treatment can slow down disease progression by an average of 18 months. The medicines of choice are acetylcholinesterase inhibitors (donepezil, rivastigmine) and NMDA receptor antagonists (memantine). It is also often necessary to administer second-generation antipsychotics (e.g., quetiapine) and antidepressants (especially SSRI or SNRI).

Other neurodegenerative diseases with dementia include:

- frontotemporal dementias (mainly Pick disease; other than Pick disease are rare and associated with mutations on chromosome 17 in the tau gene);
- progressive supranuclear palsy (PSP);
- corticobasal ganglionic degeneration (CBD);
- familial progressive subcortical gliosis;

- Parkinson's disease (PD);
- Huntington's disease (HD).

Lewy body dementia (LBD) is now considered the second most common type of dementia after Alzheimer's disease. It is clinically distinct from dementia associated with PD and AD. Patients present with fluctuating cognitive decline (episodes of confusion alternating with lucid intervals), complex visual hallucinations and delusions, symmetrical Parkinson's motor symptoms, rapid eye movement (REM) sleep behavior disorder, recurrent falls, and sensitivity to neuroleptics.

Cerebrovascular diseases

Cerebrovascular diseases often result in dementia. Risk factors for developing dementia after stroke are:

- advancing age;
- diabetes;
- history of prior stroke;
- size and location of the stroke ("strategic" infarcts);
- cerebral hypoperfusion;
- fluctuations in systemic blood pressure;
- carotid atherosclerosis.

There are 2 main types of cerebrovascular dementia:

- **cortical syndrome** – typical of patients with repeated atherothrombotic or cardioembolic strokes and manifests with sudden onset of cognitive failure, focal sensorimotor signs, and more severe aphasia;
- **subcortical syndrome** – found in people with deep white matter lesions; clinical symptoms are pseudobulbar palsy, emotional lability, depression, executive dysfunction, and isolated pyramidal signs.

Dementia after stroke is predominantly of the mixed type – a combination of AD and stroke. The survival of patients with cerebrovascular dementia is shorter than that of other forms of dementia, including AD.

The most common hereditary disorder accompanied by cerebrovascular dementia is CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy). The disease is caused by mutations in the *Notch3* gene on chromosome 19. Typical clinical presentations of CADASIL include:

- recurrent transient ischemic attacks (TIA) or multiple deep infarcts;
- pseudobulbar palsy;
- urinary incontinence;
- gait imbalance;
- bilateral pyramidal signs.

Infectious diseases

Infectious diseases of the central nervous system leading to cognitive decline and dementia may have a viral, bacterial, fungal, parasitic, or prion etiology. The most important infectious causes of dementia are:

- herpes virus (HSV-1, HSV-2);
- toxoplasmosis (parasite *Toxoplasma gondii*);
- cryptococcus (yeast *Cryptococcus neoformans*);
- cytomegalovirus (CMV);
- neurosyphilis (spirochete *Treponema pallidum*);
- borrelia (spirochete *Borrelia burgdorferi*, Lyme disease);
- cysticercosis (tapeworm *Taenia solium*, particularly in developing countries).

Prion diseases are a group of transmissible spongiform encephalopathies characterized by a similar histopathology: spongy brain degeneration with neuronal loss and astrocytic proliferation. This pathology can be inherited, acquired, or sporadic, and is associated with abnormal protease-resistant prion protein (PrP^{Sc}) accumulation in the brain. Human prion diseases include:

- Creutzfeldt–Jakob disease (CJD);
- Gerstmann–Sträussler–Scheinker disease (GSS);
- fatal familial insomnia (FFI);
- Kuru.

The incidence of the most common prion disease – sporadic CJD (sCJD) – is 0.5–1.5 cases per million per year.

Human immunodeficiency virus (HIV) type 1-associated dementia complex (HIV dementia) is mainly a subcortical dementia associated with neuropathological changes located in the basal ganglia. Typical clinical features include psychomotor slowing, depressed mood, apathy, memory loss, and impaired executive functions.

Metabolic diseases

The last group of diseases associated with cognitive decline and dementia are inherited metabolic disorders. Although they are rare causes of dementia in adults, they are important because some of them may be potentially curable. The inherited metabolic diseases are typically characterized by an early onset of dementia and the involvement of other areas of the nervous system (e.g., cerebellum, visual pathways, peripheral nerves, muscles) and the body (e.g., skin, skeletal and visceral organs).

These diseases include the following:

- mitochondrial disorders (e.g., MELAS, MERRF);
- lysosomal disorders (e.g., Gaucher, Niemann–Pick, Fabry, Krabbe);

- Wilson disease;
- pantothenate kinase-associated neurodegeneration (PKAN);
- Fahr syndrome;
- adreno-myeloneuropathy.

Reversible causes of cognitive impairment/DEMENTIA

- D – drugs;
E – emotional/depression;
M – metabolic (hypothyroid);
E – eyes and ears declining;
N – normal pressure hydrocephalus (NPH);
T – tumor or other space-occupying lesions;
I – infection (syphilis/AIDS);
A – anemia (vitamin B₁₂ or folate deficiency).

Rapidly Progressive Dementias (RPD)

- cerebrovascular – stroke (“strategic” location, huge areas, multifocal);
- infectious – encephalitis, PML (progressive multifocal leukoencephalopathy), SSPE (subacute sclerosing panencephalitis);
- toxic – electrolyte disturbances, hypoxia, iatrogenic (medications), central pontine myelinolysis;
- autoimmune – Hashimoto encephalopathy, CNS vasculitis (e.g., SLE), sarcoidosis;
- neurodegenerative – CJD;
- paraneoplastic syndromes;
- systemic – hypertensive encephalopathy, delirium, mitochondrial.

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7. Multiple sclerosis and other demyelinating disorders

Anna Pokryszko-Dragan

Multiple sclerosis

Multiple sclerosis (MS) is a chronic, immune-mediated disease of the central nervous system (CNS). Multifocal damage to myelin sheaths and axonal loss, disseminated throughout the brain and spinal cord, impair the velocity and efficiency of conduction within neuronal pathways. As a result, there are a variety of symptoms of neurological deficit, which accumulate in the course of the disease.

Epidemiology:

- prevalence: 5–30/100,000 (dependent on geographical regions), incidence 2.1 per 100,000 persons/year;
- 2.8 million people worldwide are estimated to live with MS;
- female : male ratio approx. 2 : 1;
- disease onset is usually between 20 and 35 years of age (rare but possible early onset in childhood or late onset – after 50 years of age).

Etiology of MS is complex, and some of its aspects have not yet been explained. The key elements of MS background include interactions between genetic and environmental risk factors, which contribute to development of the disease.

- genetic risk factors (approx. 30%) are associated with polymorphism of several genes, mainly HLA–DR and DQ alleles;
- environmental risk factors comprise, e.g., infections (Epstein–Barr virus, Herpesvirus), smoking, obesity, deficiency of vitamin D3, and stress. Some additional factors (changes in hormonal activity – puberty, pregnancy and delivery; gut microbiome composition) are supposed to trigger and modify processes directly involved in disease initiation.

Auto-immune inflammatory process:

A pool of autoreactive T-cells develops in the peripheral circulation. Assisted by several factors (adhesive molecules, enzymes), they enter the CNS through a disrupted blood–brain barrier and initiate a cascade of inflammatory events, resulting in multifocal injury

of the myelin sheath. Apart from T-cells and cytokines, B-cells producing antibodies, macrophages, and glial cells take part in this process. Inflammatory demyelination fluctuates with exacerbations and is most active at an early stage of the disease.

Neurodegeneration with axonal loss:

Parallel to the inflammatory process, direct injury to neurons occurs, associated with oxidative stress, dysfunction of mitochondria, and apoptosis. Neurodegeneration is slowly expanding from the disease onset, increasing during its late stages.

Symptoms and signs of MS are multifocal and fluctuating, due to disseminated lesions in the CNS and long-lasting, polyphasic course of the disease. The first clinical manifestation of MS is often called “clinically isolated syndrome” (CIS) and subsequent attacks with new or recurrent symptoms – relapses. A relapse is characterized by subacute onset (sometimes triggered by provoking factors: heat, infection, stress, etc.), followed by stable intensity of symptoms (lasting at least 24 h) and complete or partial recovery (spontaneous or as a result of treatment). During remission (between relapses), the condition of the patient is stable, but short-term, transient fluctuation of symptoms may occur.

Most typical symptoms and signs:

- optic neuritis – diminished visual acuity (rarely, complete blindness), impaired central and color vision, sometimes pain of the eye;
- brainstem syndrome (nystagmus, n. VI palsy, internuclear ophthalmoplegia, trigeminal neuralgia);
- cerebellar syndrome (vertigo, disturbed balance and gait, ataxia, nystagmus, slurred speech – dysarthria);
- motor deficit – weakness of limbs with exaggerated reflexes, pyramidal signs and spasticity, resulting in disturbance of gait and/or manual dexterity;
- sensory loss (numbness) and/or paresthesia (tingling, burning sensation), Lhermitte sign – an electric shock-like sensation radiating down the spine that occurs on flexion of the neck;
- dysfunction of bladder (urinary urgency, incontinence, or retention) and bowels (constipation or incontinence);
- central symptoms: cognitive impairment, fatigue;
- associated symptoms: mental health issues (depression, anxiety), sleep problems.

Distribution of symptoms may vary, with the most common being incomplete transverse myelitis, cerebellar or brainstem syndrome, and less frequent hemispheric involvement.

In the majority of patients (85%), the course of disease is relapsing–remitting (RRMS), with bouts of symptoms and periods of stable condition between them. After several years,

RRMS usually turns into a secondary progressive course (SPMS), with relapses replaced by a gradually increasing disability. In a small percentage of patients (10–15%), primary progressive course (PPMS) is observed, with gradual increase in disability from the onset. The types of MS may be partially overlapping (e.g., active progressive type with relapses superimposed on disability progression).

There are significant individual differences in type and severity of symptoms, and in dynamics of the disease course in the MS population, which makes the disease hardly predictable.

Diagnostic tests

- Magnetic resonance imaging (MRI) of the brain and spinal cord (Fig. 7.1, Fig. 7.2):
 - a) hyperintense small, oval lesions shown on T2-weighted and FLAIR images;
 - b) typical regions: periventricular, juxtacortical, infratentorial (cerebellum, brainstem, spinal cord); mainly in white matter but also in cortex and subcortical gray matter;
 - c) active lesions – presenting gadolinium contrast enhancement;
 - d) “black holes” in T1-weighted images.
- CSF:
 - a) general assessment usually normal (protein >60 mg%, cell count >30; increased albumin level should be considered atypical and suggest differential diagnosis);
 - b) oligoclonal bands of IgG detectable in CSF but not in serum (due to intrathecal synthesis of Ig);
 - c) increased Link index (proportion of Ig and albumin in CSF and serum);

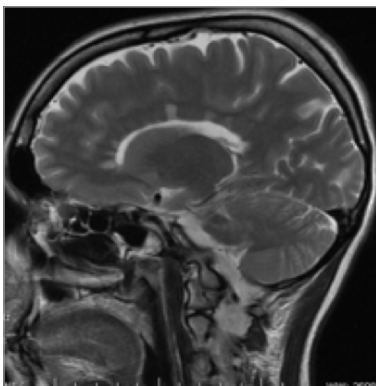


Fig. 7.1. Brain MRI: Dawson fingers type lesions in the corpus callosum in a patient with MS



Fig. 7.2. Cervical spine MRI: dorsally located lesion in the cervical spine in a patient with MS

- Evoked potentials:
 - a) abnormal parameters (prolonged latency, lowered amplitude) of visual, brainstem auditory, and somatosensory evoked responses may correspond with clinical symptoms (e.g., optic neuritis) or reveal subclinical damage to CNS structures.

McDonald’s diagnostic criteria

The guidelines to diagnose MS – McDonald’s criteria – were first proposed in 2001 and then have been regularly updated (recent version published in 2017). Their core elements include dissemination of lesions in space and time (Table 7.1).

Table 7.1. McDonald’s diagnostic criteria for RRMS: 2017 revision

Clinical presentation	Additional data needed for diagnosis
≥2 clinical attacks and objective evidence of ≥ lesions	none
≥clinical attacks and objective evidence of 1 lesion	DIS: An additional attack implicating a different CNS site OR by MRI ¹
1 clinical attack and objective clinical evidence of ≥lesions	DIT: An additional clinical attack OR by MRI ² CSF-specific oligoclonal bands
1 clinical attack and objective evidence of 1 lesion	DIS: An additional clinical attack implicating a different CNS site OR by MRI ¹ OR DIT: An additional clinical attack OR by MRI ² OR CSF-specific oligoclonal bands

DIS – dissemination in space; DIT – dissemination in time; ¹DIS in MRI: ≥1 lesion in ≥2 areas including cortical/juxtacortical/periventricular/infratentorial or spinal; ² DIT in MRI: New lesions on follow-up imaging or concomitant Gd-enhancing and non-enhancing lesions in single imaging.

According to McDonald’s criteria, PPMS may be diagnosed in those who have experienced worsening disability for ≥1 year (based on previous symptoms or ongoing observation), and who exhibit ≥2 of the following:

- ≥1 lesion in the MRI of the brain;
- ≥2 lesions in MRI of the spinal cord;
- CSF – specific oligoclonal bands of IgG.

The use of McDonald’s criteria is aimed at early and reliable diagnosis of MS. It is essential to integrate the history, examination, imaging, and laboratory evidence, preferably by an experienced clinician. In any atypical or doubtful cases, extended diagnostics and follow-up may be necessary.

Differential diagnosis

Differential diagnosis of MS should include other diseases with multifocal CNS involvement:

- other autoimmune demyelinating disorders:
 - a) neuromyelitis optica spectrum disorders (NMOSD),
 - b) anti-MOG antibodies-associated disease (MOGAD);
- inflammatory CNS disorders:
 - a) infectious:
 - Lyme disease,
 - tuberculosis,
 - b) non-infectious:
 - sarcoidosis,
 - Susac syndrome;
- CNS vasculitis – primary or in connective tissue diseases:
 - a) lupus,
 - b) antiphospholipid syndrome,
 - c) Behcet disease;
- small vessel disease;
- hereditary diseases associated with angiopathy (CADASIL), metabolic deficit (Fabry disease, leukodystrophies) or progressive neurodegeneration (hereditary spastic paraparesis).

Treatment of relapse

In acute relapse, early administration of high-dose corticosteroids is recommended to relieve the symptoms and hasten recovery. The standard schedule is methylprednisolone 0.5–1 g given iv. for 3–5 days; short-term (several days) oral administration may be an alternative option.

Side effects of corticosteroids include:

- high blood pressure;
- diabetes;
- insomnia;
- psychiatric disturbances;
- gastrointestinal problems.

In severe relapses not responding to corticosteroids, therapeutic plasma exchange (PLEX; 5–7 exchanges every other day) can be considered. There is less evidence for the effectiveness of iv. immunoglobulins in treatment of MS relapse.

Disease-modifying treatment (DMT)

Long-term immunomodulating or immunosuppressive therapies are used to suppress and control disease activity. The goals of such treatment include: reduction/prevention of relapses, accumulation of disability, and occurrence of new lesions in MRI (optimal status: NEDA – no evidence of disease activity). According to their potential, DMTs are classified as moderate- or high-efficacy ones (Table 7.2).

The majority of DMTs are approved for RRMS, except for ocrelizumab which can also be used in PPMS. Siponimod (p.o., SP1 modulator) is the only medication approved for SPMS.

Non-selective immunosuppressants, such as mitoxantrone, azathioprine, cyclophosphamide, despite few evidence-based recommendations, may be used when other options have failed – mostly in progressive or severe forms of the disease.

Table 7.2. Disease modifying treatment used in MS

Moderate efficacy DMT (1 st line)		High efficacy DMT (2 nd /3 rd)	
interferon beta (IFN-β): – pleiotropic immunomodulatory effect	s.c. every other day s.c. 3 times a week i.m. every 7 or 14 days	natalizumab: – monoclonal antibody anti-α4integrin	iv. or s.c. every 4 (6) weeks
glatiramer acetate (GA): – competes with myelin antigens targeted by T cells	s.c. 3 times a week	fingolimod, ozanimod, ponesimod: – sphingosine receptor – SP1 modulators	p.o. 1 × 1
dimethylfumarate (DMF): – modulates expression of genes associated with inflammatory response	p.o. 2 × 1	ocrelizumab, ofatumumab: ublituximab – monoclonal antibodies anti-CD20	iv. or s.c. every 6 months s.c. every 4 weeks iv. every 6 months
teriflunomide (TFL): – inhibits pyrimidine synthesis and proliferation of T cells and B cells	p.o. 1 × 1	cladribine: – causes reduction of T cells and B cells, followed by their selective repopulation)	p.o. 2 treatment courses (1–2 tablets for 4–5 days) in 2 consecutive years
		alemtuzumab: – monoclonal antibody anti-CD52	iv. 2 treatment courses (3–5 days) in 2 consecutive years

DMT should be initiated as soon as the definite diagnosis of MS has been established. The choice of DMT is based on analysis of disease activity, concomitant disorders, patient's preferences (pregnancy plans, lifestyle issues) as well as safety profile, with evaluation of benefit-to-risk ratio. The treatment is continued long-term and requires regular follow-up, with the assessment of efficacy and safety.

Side effects of DMT are:

- associated with drug administration (e.g., flu-like symptoms or site reactions after injectable drugs, gastrointestinal problems after oral administration);
- associated with immunosuppression:
 - leuko/lymphopenia – potentially increased susceptibility to infections (e.g., respiratory or urinary tract),
 - opportunistic infections (caused by HSV, VZV, JCV – progressive multifocal leukoencephalopathy) or reactivation of latent infections (HBV, HCV, tuberculosis),
 - potentially increased risk of neoplasms;
- organ-specific: affection of liver, bradycardia or heart conduction block, macular degeneration.

According to the escalation approach, the treatment starts with a moderate-efficacy DMT and is continued as long as there are no signs of disease activity. In case of poor response (active disease despite treatment) or side effects impeding further therapy, DMT should be switched to another one (more effective/better tolerated). In case of rapidly evolving onset of MS, an induction approach is recommended, with initial use of strong immunosuppressive DMT to control or eliminate disease activity. With greater availability of highly effective DMTs and more reassuring data on their safety profile, there is a trend for their early initiation to achieve the best possible long-term outcomes (HETA – high efficacy therapeutic approach).

Symptomatic treatment

Particular symptoms of MS can be relieved at any stage of the disease.

- Spasticity:
 - baclofen (p.o., in severe cases also intrathecally);
 - tizanidine;
 - tolperisone;
 - botulinum toxin.
- Neuropathic pain, paresthesia:
 - gabapentin;
 - pregabalin;
 - amitriptyline;
 - duloxetine.

- Bladder dysfunction:
 - oxybutynine;
 - tolterodine;
 - solifenacin – for urinary urgency or incontinence;
 - distigmine – for urinary retention;
 - myorelaxants – for urinary retention.
- Fatigue:
 - amantadine;
 - modafinil.
- Gait problems:
 - fampridine.

Complex therapeutic strategies in MS in severely disabled patients should include:

- exercise;
- physiotherapy;
- dietary recommendations (balanced diet, rich in polyphenols, PUFA, vit. D);
- prevention of complications.

Interdisciplinary care, with medical, psychological, and social support is crucial for improving patients' general condition and quality of life. Considering variability of MS course and progress in therapeutic options, an individualized treatment approach is recommended in management of the disease.

Summary

Multiple sclerosis (MS) is a chronic, immune-mediated disease which affects the CNS, leading to its long-lasting and disseminated damage. Demyelinating lesions and axonal loss within the brain and spinal cord cause multifocal symptoms and signs of neurological deficit. The diagnosis is based on McDonald's criteria, integrating clinical, radiological, and laboratory findings. Recent progress in early diagnosis and therapeutic opportunities has substantially improved long-term outcomes of the disease. A complex and individualized therapeutic approach is recommended in MS management.

Neuromyelitis optica spectrum disorder

Neuromyelitis optica spectrum disorder (NMOSD) is a chronic autoimmune disease of the CNS, characterized by inflammatory lesions primarily in the optic nerves and the spinal cord. An exacerbating course of the disease results in severe and often persistent neurological deficits.

Epidemiology:

- prevalence of 0.05–13 per 100,000 people;
- strong preponderance in women (9 : 1 female : male ratio);
- a typical age at onset is between 30 and 40 years old; it may occur later (>50 years old), rarely in childhood and adolescence.

The major element of NMOSD background is an autoimmune humoral response. Specific B-cells produce IgGs which target aquaporin 4 (AQP4) – a protein which constitutes a water channel, found abundantly in astrocytes, forming part of the blood–brain barrier in the CNS.

In a small percentage of cases, other autoreactive IgGs are found, targeted against myelin oligodendrocyte glycoprotein (MOG), a protein located within the myelin sheath and on the oligodendrocyte surface (see: MOGAD). Inflammatory processes mediated by antibodies involve activation of complement, macrophages, and cytokines (mainly IL-6). In addition, excitotoxic compounds and free radicals contribute to injury of astrocytes, oligodendrocytes, and neurons.

Core clinical characteristics of NMOSD reflect the involvement of optic nerve and spinal cord (30–40% of patients) and, less frequently, of the brain (<10%):

- Optic neuritis:
 - unilateral or bilateral impairment of visual acuity (often severe, up to complete blindness);
 - pale temporal part of the optic disc;
 - common ocular pain worsened by eye movement.
- Transverse myelitis:
 - bilateral, moderate/severe para- or tetraparesis;
 - sensory loss below level of lesion;
 - typically, neuropathic pain within trunk and limbs: radiculopathy, painful paresthesia or itching, Lhermitte sign, painful tonic muscle spasms;
 - urinary dysfunction.
- Area postrema syndrome:
 - intractable vomiting;
 - hiccups.
- Acute brainstem syndrome:
 - vertigo;
 - nystagmus;
 - trigeminal neuralgia.
- Symptomatic narcolepsy or acute diencephalic syndrome:
 - gluttony;
 - sleepiness;
 - other hormonal dysfunctions.

- Cerebral syndrome:
 - headache;
 - cognitive impairment;
 - rarely epileptic seizures.

During a relapse, the symptoms subacutely increase to reach a plateau phase and then gradually subside, usually with incomplete recovery. Occasionally the disease is monophasic, but in 90% relapses occur (especially in patients seropositive for AQP4-IgG). Severity of relapses and their frequency may vary, but residual disability after subsequent attacks tends to accumulate quickly in the course of the disease.

Diagnostic tests

- MRI:
 - a) lesion of the optic nerve (over at least half of the length), often bilateral and/or involving the optic chiasm;
 - b) longitudinally extensive lesions of the spinal cord (along three or more vertebral segments), usually in the cervical and upper thoracic region; Gd-enhancement on T1 imaging;
 - c) MRI of the brain with no abnormalities or minimal changes including specific areas: area postrema, III and IV ventricles, periaqueductal grey matter, hypothalamus (Fig. 7.3, Fig. 7.4).

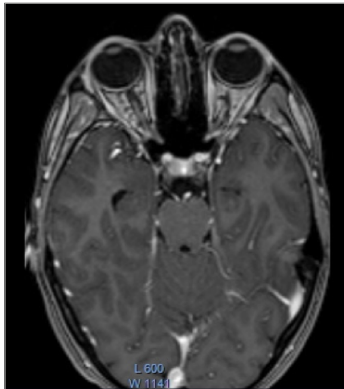


Fig. 7.3. Brain MRI: bilateral optic nerve contrast enhancement in patient with NMOSD



Fig. 7.4. Cervical spine MRI: long segment hyperintense lesion in the cervical spine in patient with NMOSD

- CSF:
 - a) elevated cell count, less frequently protein level – mainly during a relapse;
 - b) oligoclonal bands of IgG uncommon (10–20%) and transient.
- IgG anti-AQP4:
 - a) assessed in serum, preferably with cell-based assays, before initiation of immunosuppressive treatment.

Diagnostic criteria (Table 7.3):

Table 7.3. Diagnostic criteria for NMOSD

Diagnosis according to AQP4 – IgG –seropositive status	Diagnosis according to AQP4 –IgG –seronegative status
– ≥1 core clinical characteristic – positive test for AQP4-IgG – exclusion of alternative diagnosis	– ≥2 different core clinical characteristics as a result of ≥1 clinical attack and meeting all following requirements: – ≥1 core clinical characteristic must be ON1, LETM2 or area postrema syndrome – dissemination in space (≥2 different core clinical characteristics) – fulfillment of additional MRI requirements – negative test for AQP4-IgG – exclusion of alternative diagnosis

¹optic neuritis; ²longitudinal extensive transverse myelitis; ³aquaporin 4.

Differential diagnosis

- Other demyelinating CNS disorders: MS, MOGAD;
- Connective tissue diseases with CNS involvement: lupus, Sjogren disease, Behcet disease.
- Sarcoidosis;
- Vitamin B12 deficiency;
- CNS lymphoma or neoplastic infiltration of meninges;
- Autoimmune encephalitis;
- Hereditary: adrenomyeloneuropathy, hereditary spastic paraparesis, Leber hereditary optic neuropathy.

Treatment of relapse

The standard treatment includes high-dose iv. corticosteroids (methylprednisolone 0.5–1 g given iv. for 5–7 days). Therapeutic plasma exchange (PLEX) may be an alternative or additive option (5–7 exchanges, every other day). There is less evidence for the effectiveness of iv. immunoglobulins.

Maintenance treatment: preventing disease relapses

So far, oral corticosteroids and/or non-selective immunosuppressants such as azathioprine and mycophenolate mofetil have been used for long-term maintenance treatment. Another apparently effective therapeutic option has been rituximab (an anti-CD20+ monoclonal antibody), administered at regular 6-month intervals.

Since 2019, 3 targeted therapies have been approved for the treatment of NMOSD seropositive for anti-AQP4 IgG antibodies:

- eculizumab – monoclonal antibody against C5 component of the complement system, iv. every 2 weeks;
- inebilizumab – monoclonal antibody that targets CD-19 expressing B-cells, iv. every 6 months;
- satralizumab – monoclonal antibody which binds IL-6 receptors, blocking IL-6 signaling pathways; administered subcutaneously every 4 weeks.

The treatment requires follow-up with assessment of efficacy and safety (prevention and treatment of infections, occasional adverse reactions to drug administration).

Important!

Disease-modifying therapies (DMTs) approved for MS are ineffective – or even harmful – in NMOSD.

Symptomatic treatment

- Spasticity, tonic spasms of muscles:
 - myorelaxants: baclofen, tizanidine, botulinum toxin.
- Neuropathic pain:
 - carbamazepine;
 - pregabalin;
 - gabapentin;
 - amitriptyline;
 - duloxetine.
- Bladder dysfunction:
 - oxybutynine;
 - tolterodine;
 - solifenacin – for urinary urgency or incontinence;
 - distigmine – for urinary retention;
 - myorelaxants – for urinary retention;
 - catheterization often necessary.

Summary

Neuromyelitis optica spectrum disorder is an immune-mediated disease of the central nervous system that primarily affects the optic nerves and the spinal cord. The recurrent course of the disease, with severe exacerbations and incomplete remissions, leads to cumulative neurological disability. The discovery of antibodies against AQP4 and their leading role in NMO etiology has improved appropriate recognition of the disease and led to an increasing range of treatment options.

Myelin oligodendrocyte glycoprotein antibody-associated disease

Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is a diverse group of CNS inflammatory/demyelinating disorders, predominantly targeting the optic nerves, brain, and spinal cord and defined by the presence of anti-MOG IgG as their pathological hallmark.

Epidemiology

- estimated annual incidence 1.6/million person-years (limited population-based data);
- female-to-male ratio approximately 1 : 1;
- the relative frequency is higher in children (<18 years of age).

Etiology:

- MOG is a minor component of the CNS myelin sheath, expressed on its outermost layers and on the surface of oligodendrocytes;
- antibodies targeted at MOG initiate an inflammatory cascade, with contribution of CD4+ T-cells and complement activation, which result in multifocal demyelination (see: NMOSD).

The clinical manifestations of MOGAD are heterogeneous, partially overlapping with NMOSD. The most typical presentations include:

- optic neuritis – uni- or bilateral (diminished visual acuity, often accompanied with pain, characterized by optic disc oedema on fundoscopic examination);
- transverse myelitis – severe paraparesis with gait disturbances, sensory impairment, and bladder dysfunction (typical involvement of conus medullaris);
- acute disseminated encephalomyelitis (ADEM) – headache, altered consciousness, meningeal signs, multifocal signs of neurological deficit (pyramidal, cerebellar, brainstem);

- cerebral cortical encephalitis (CCE) – headache, aphasia, stroke-like episodes, altered behavior, refractory seizures;
- brainstem encephalitis – dysarthria, dysphagia, ocular movement disturbances, trigeminal neuralgia.

In more than 50% of cases, the course is monophasic (single attack without recurrence), with a tendency of symptoms and lesions to resolve completely. However, some patients with MOGAD may experience relapses.

Diagnostic tests

- MRI (Fig. 7.5, Fig. 7.6):
 - extensive involvement of the optic nerve for most of its length, with contrast enhancement;
 - longitudinally extensive lesions of the spinal cord (along 3 or more vertebral segments), often with involvement of the ventral part and gray matter;
 - brain MRI: multiple large lesions throughout white and gray matter, often with concomitant contrast enhancement (ADEM); unilateral hyperintensity of cortex with leptomeningeal enhancement (CCE).

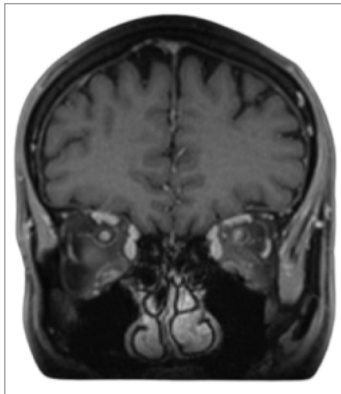


Fig. 7.5. Brain MRI: bilateral retrobulbar optic nerve contrast enhancement in patient with MOGAD



Fig. 7.6. Lumbar spine MRI: hyperintense lesion in the conus medullaris in patient with MOGAD

- CSF:
 - moderate increase in protein level and cell count;
 - oligoclonal bands of IgG rarely present (15%).
- Anti-MOG IgG:
 - assessed in serum, preferably with cell-based assays, before initiation of immunosuppressive treatment.

Diagnostic criteria (Table 7.4):

Differential diagnosis: see NMOSD.

Table 7.4. Proposed diagnostic criteria for MOGAD

Diagnosis of MOGAD (requires fulfillment of A, B and C)		
A. core clinical demyelinating event		– optic neuritis – transverse myelitis – ADEM – cerebral monofocal or polyfocal deficits – brainstem or cerebellar deficits – cerebral cortical encephalitis
B. positive MOG – IgG test		
C. exclusion of better diagnoses		
Supporting clinical or MRI features	optic neuritis transverse myelitis brain/brainstem syndromes	– bilateral, simultaneous – >50% of the nerve length involved – optic sheath enhancement – optic disc oedema – longitudinal extensive myelitis (>3 segments) – central cord lesion – conus terminalis involvement – multiple ill-defined lesions in white matter – deep gray matter involvement – involvement of pons, cerebellar peduncle and medulla – cortical/leptomeningeal involvement

Treatment

Treatment of relapses includes high-dose corticosteroids (methylprednisolone iv. 1,000 mg once daily for 5 days, usually with good response). Tapering oral corticosteroids can be continued for 2–3 months (or even longer), depending on the clinical and serological status. In severe relapses, a combination of intravenous corticosteroids and PLEX is recommended. For prevention of relapses, iv. infusions of immunoglobulins, azathioprine, mycophenolate mofetil, or rituximab can be considered (no clear recommendations).

Summary

Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is recognized to be a distinct CNS disorder, defined by MOG-IgG as a highly specific biomarker. Clinical presentation is heterogeneous, with involvement of the optic nerves, spinal cord, or brain. The prognosis is generally favorable, due to monophasic course and good response to corticosteroids. However, the risk of subsequent relapses and residual disability may require long-term immunosuppressive treatment.

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8. Epilepsy

Monika Służewska-Niedźwiedź

Epilepsy is a disorder of brain function characterized by a permanent predisposition to generate seizures, as well as the neurobiological, cognitive, psychological, and social consequences of this condition. Up to 1% of the population is affected – about 400,000 in Poland and 60–70 million worldwide.

Seizures are transient neurological symptoms due to abnormal, excessive, or synchronous activity of brain neurons (Table 8.1).

Table 8.1. Different types of seizures

Focal onset seizure		Generalized onset seizure	Unknown onset seizure
Aware	Impaired awareness	Motor: – tonic-clonic – clonic – tonic – myoclonic – myoclonic-tonic- clonic – myoclonic-atonic – atonic Nonmotor (absence): – typical – atypical – myoclonic – eyelid myoclonia	Motor: – tonic-clonic Nonmotor: – behavior arrest – unclassified
With motor onset: – automatism – atonic – clonic – hyperkinetic – myoclonic – tonic With nonmotor onset: – autonomic – behavior arrest – cognitive, emotional – sensory			
Focal evaluating to bilateral tonic-clonic seizure			

We can divide seizures into:

- **Focal onset seizure**, where abnormal neuronal activity is limited to one region of the brain:
 - focal aware (Fig. 8.1),
 - focal with impaired awareness (Fig. 8.2),
- **Generalized onset seizure**, where abnormal neuronal activity affects the entire brain (Fig. 8.3);
- **Unknown onset seizure**, when we do not know how/where the seizure starts.

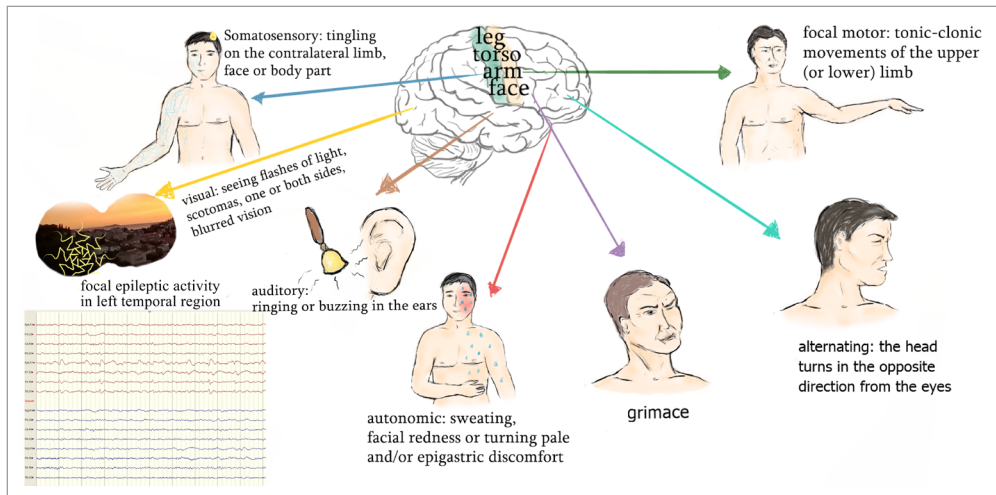


Fig. 8.1. Focal aware seizure symptoms

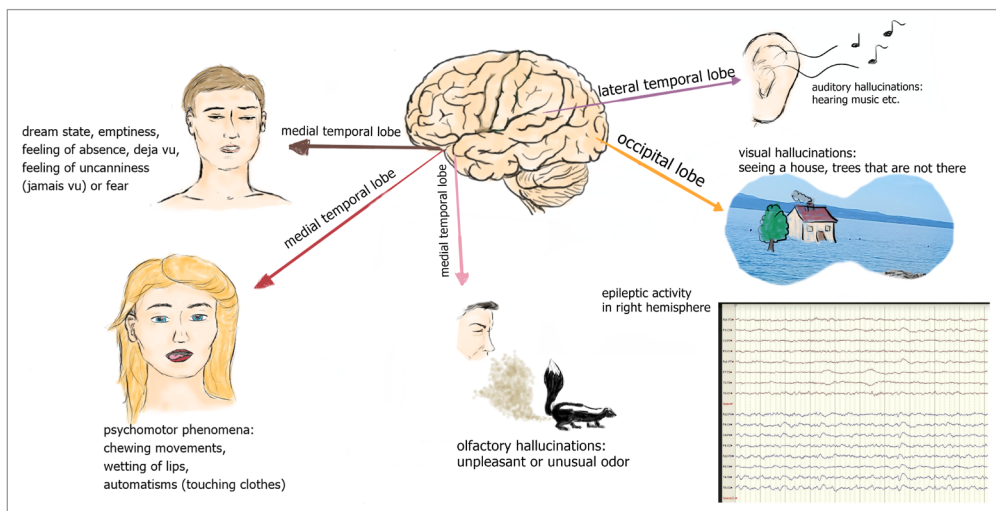


Fig. 8.2. Focal seizures with impaired awareness

Clinical definition of epilepsy

We can diagnose epilepsy when:

- at least 2 unprovoked seizures occur more than 24 h apart, or
- one unprovoked seizure occurs and there is a high (at least 60%) risk of recurrence of the seizure within the next 10 years, or
- there is a diagnosis of an epileptic syndrome.

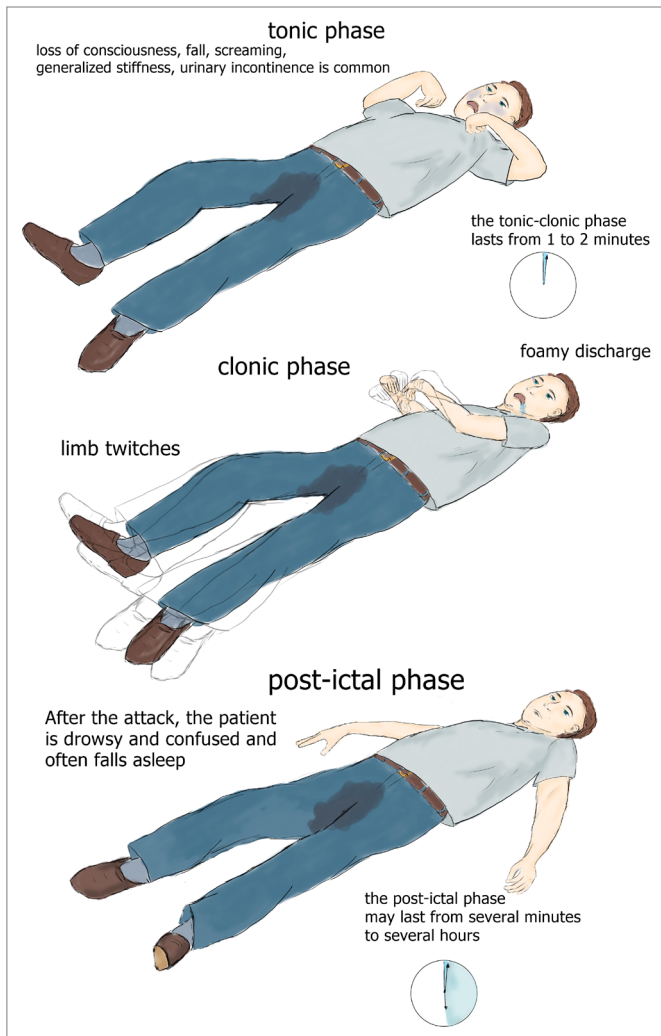


Fig. 8.3. Generalized onset seizure

Clinical factors that increase the risk of another seizure are:

- previous trauma or brain injury that may have caused the seizure;
- "epileptic" abnormalities in electroencephalography (EEG);
- significant abnormalities in neuroimaging;
- night seizure.

The term unprovoked means the absence of any temporary or reversible factor lowering the seizure threshold and triggering a seizure at that point in time. For example: seizures occurring after a concussion, with fever, or in association with hypoglycemia or alcohol withdrawal are considered provoked seizures and do not lead to a diagnosis of epilepsy.

After a single unprovoked seizure, we can diagnose epilepsy if there is a high risk of seizure recurrence, based on the patient's history and additional tests.

We can also diagnose epilepsy if we identify an epilepsy syndrome, which refers to a cluster of features incorporating seizure types, EEG changes, and a defined age of onset (e.g., juvenile myoclonic epilepsy, Lennox–Gastaut syndrome). Such syndromes have prognostic and therapeutic implications and may be associated with distinctive comorbidities, such as intellectual and psychiatric dysfunctions.

- Juvenile myoclonic epilepsy:
 - a) onset of symptoms at 12–17 years of age;
 - b) 3 types of seizures (absence, myoclonic, generalized tonic–clonic);
 - c) EEG: generalized polyspike-and-slow-wave complexes (3.5–4 Hz);
 - d) treatment: valproic acid (VPA), lamotrigine (LMT).

Epilepsy is considered to be resolved in individuals who had an age-dependent epilepsy syndrome but are now past the relevant age range, or in those who have remained seizure-free for the last 10 years and have not taken antiseizure medications for the last 5 years.

A range of etiologic categories regarding epilepsy has been recognized, with emphasis on those that influence treatment decisions. We can distinguish the following categories:

- **Structural** – focal brain injury of any etiology; examples:
 - trauma;
 - stroke;
 - tumor;
 - congenital malformation;
- **Genetic** – examples:
 - abnormalities in the structure of ion channels in neurons (such as sodium or potassium channels) or subunits of GABA receptors and nicotinic receptors.

It is important to note that genetic does not equate with inherited, as there is an increasing number of de novo mutations. If an individual has a de novo dominant mutation, their offspring will have a 50% risk of inheriting it, but it does not mean that their children will develop epilepsy, as its clinical expression will depend on the penetrance of the mutation and various environmental factors.

- **Infectious** – examples:
 - neurocysticercosis,
 - tuberculosis,
 - cerebral malaria,
 - subacute sclerosing panencephalitis,
 - cerebral toxoplasmosis,
 - congenital infections such as cytomegalovirus,

- **Metabolic** – examples:
 - porphyria,
 - uremia,
 - aminoacidopathies,
 - pyridoxine-dependent seizures,
- **Immune** – autoimmune encephalitis; examples:
 - anti-NMDA receptor encephalitis,
 - anti-LGI1 encephalitis,
- **Unknown** – cause of the epilepsy is not yet known.

Diagnostics

In the emergency department, when treating a patient who has experienced a first episode of loss of consciousness or seizures, the following steps should be taken:

- a) Differentiate whether we are dealing with syncope or an epileptic seizure;
- b) Exclude symptomatic seizures due to an acute neurological condition (neuroinfection, stroke);
- c) Determine whether the seizure was provoked or unprovoked (e.g., by alcohol, fever, hypoglycemia).

Next steps of diagnosis include:

History:

Obtain a detailed account of the episode, asking the patient and, if possible, direct witnesses about the course of the event.

Determine: Was it syncope or a seizure? If a seizure – was the onset focal or generalized? Could it have been a psychogenic seizure? Were there other neurological symptoms? An inadequate or faulty description is the leading cause of misdiagnosis. A home video recording of the event may even establish the diagnosis.

- Chronic diseases;
- Head trauma;
- Alcohol;
- Drugs;
- Fever;
- Infection;
- Occurrence of epilepsy in the patient's family;
- Pregnancy and perinatal history.

Neurological examination:

- State of awareness,
- Confusion,
- Focal neurological signs,
- Meningeal signs.

Blood tests:

- Metabolic disorders, such as hypo- or hyperglycemia,
- Electrolyte disturbances,
- Toxicological studies.

ECG, cardiological consultation (to exclude cardiogenic syncope).

Lumbar puncture with examination of cerebrospinal fluid (only in suspected symptomatic seizures due to neuroinfection or subarachnoid bleeding – SAH).

Neuroimaging:

- Computed tomography (CT) – used in emergency settings to confirm or exclude a symptomatic cause of the epileptic seizure, e.g., stroke (including SAH) or brain tumors with edema (Fig. 8.4).

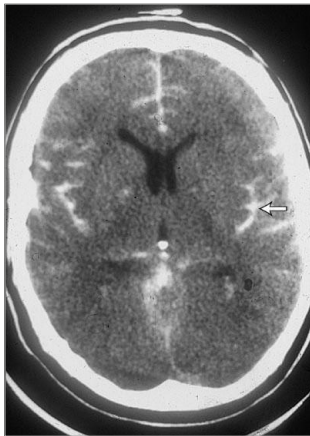


Fig. 8.4. Head CT: Bilateral subarachnoid hemorrhage

- Magnetic resonance imaging (MRI) – indicated in cases of epilepsy with focal seizures, as it allows visualization of small cortical malformations, scars, vascular malformations, or inflammatory lesions (Fig. 8.5A,B).

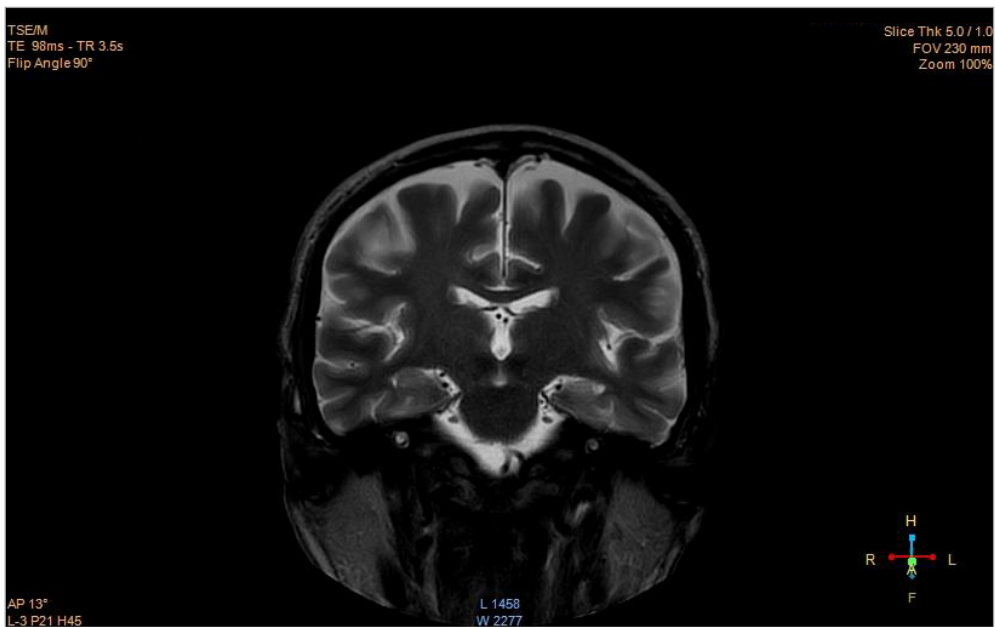


Fig. 8.5.A. Brain MRI: left hippocampal sclerosis

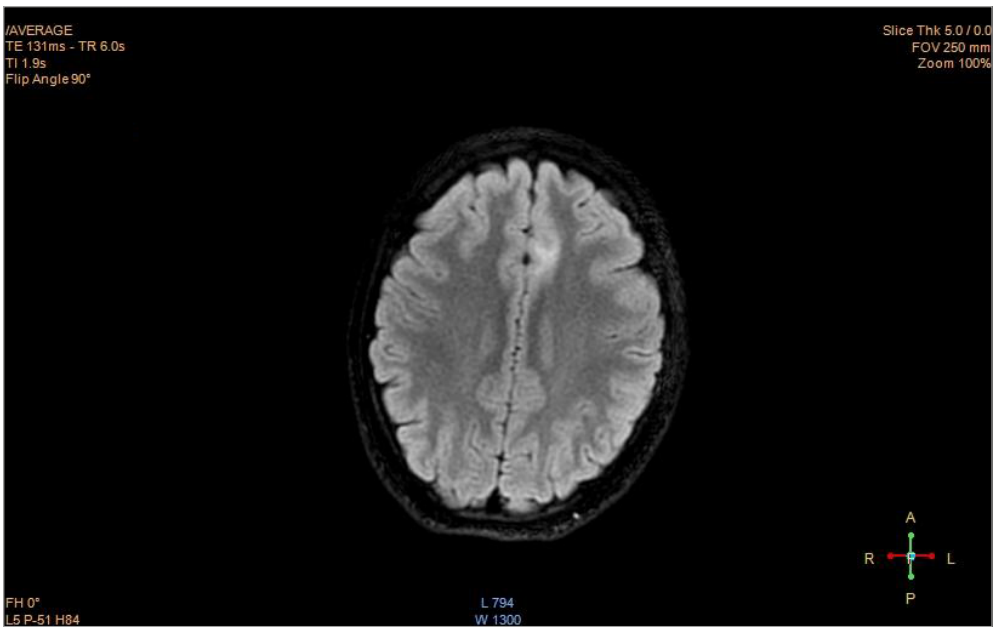


Fig. 8.5.B. Focal cortical dysplasia in the medial part of the left frontal lobe

- Functional studies – positron emission tomography (PET) and single-photon emission computed tomography (SPECT) can reveal hypometabolic areas in the interictal period, which often correlate with the seizure onset areas (Fig. 8.6).

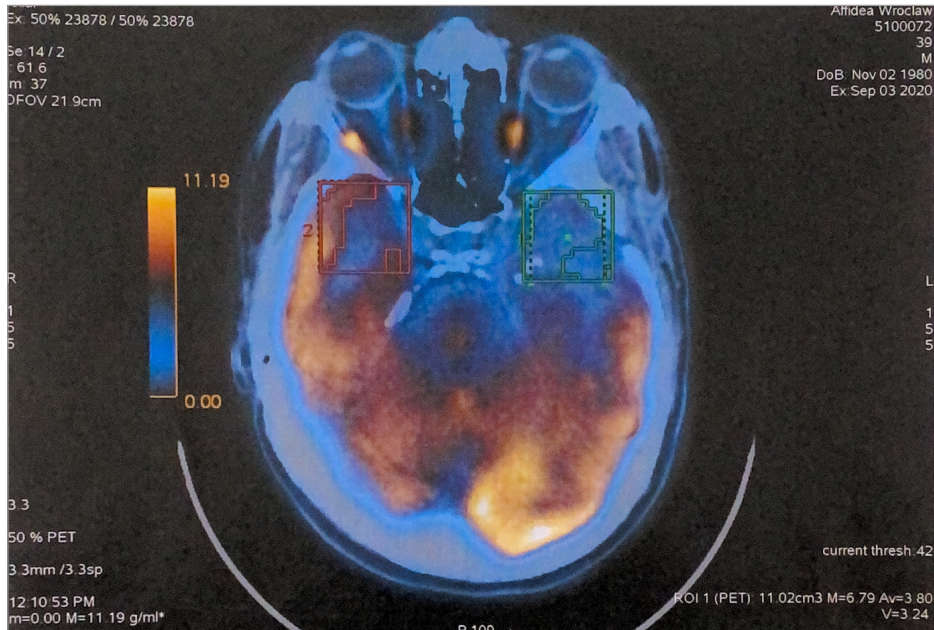


Fig. 8.6. Head PET/CT – decreased glucose metabolism in the left temporal lobe in a patient with focal cortical dysplasia

Electroencephalography (EEG) – recording of the bioelectrical activity of the brain (Fig. 8.7):

- Its diagnostic value applies only to patients with seizures.
- Epileptic changes in the EEG can confirm the diagnosis of epilepsy – this diagnostic test helps in distinguishing the type of seizure or epilepsy syndrome as well as in localization of the epileptogenic focus.
- The occurrence of paroxysmal changes in the EEG in patients without seizures does not confirm epilepsy.
- Some patients with recurrent seizures can have a normal EEG recording – this does not exclude epilepsy (Fig. 8.8).

We can perform:

- a) resting EEG with activation tests (hyperventilation and photostimulation),
- b) EEG during sleep (children),
- c) EEG after a night of sleep deprivation,



Fig. 8.7. EEG: Generalized paroxysmal changes in the form of 3 Hz spike-slow wave complexes

- d) long-term video-EEG monitoring (recording of clinical and electrophysiological features of a seizure),
- e) stereo-EEG (implantation of depth electrodes to localize the epileptogenic focus in drug-resistant epilepsy).

Psychiatric consultation (in suspicion of psychogenic non-epileptic seizure; comorbidities – psychiatric dysfunction).

Neuropsychological evaluation (comorbidities – intellectual dysfunction).

Genetic tests.

Treatment

After 2 or more subsequent seizures, antiepileptic therapy should be initiated, as the risk of further episodes is very high – 57% after 1 year and 73% after 4 years. The risk increases

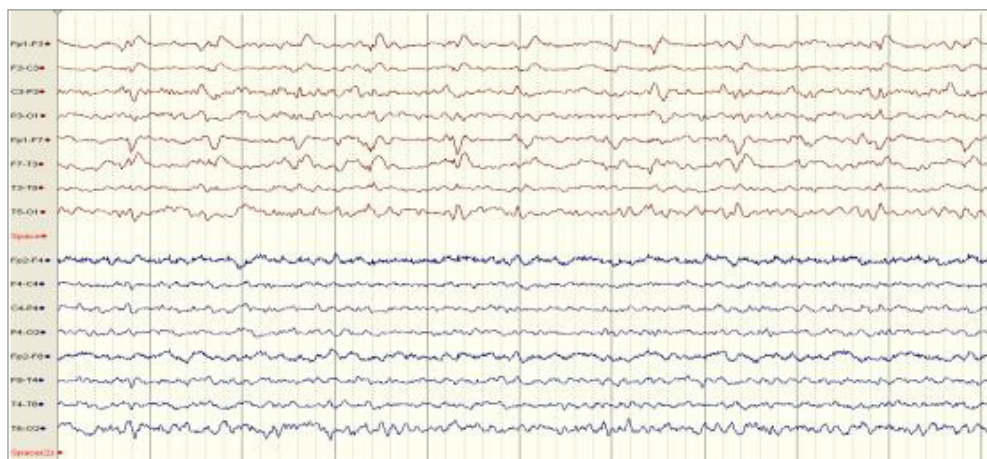


Fig. 8.8. EEG: focal epileptic changes in the left frontotemporal region

proportionally after each subsequent seizure and with shorter intervals between them. Recurrences of seizures can cause serious medical, psychological, and social consequences. Therefore, accurate identification of the seizure type and epilepsy syndrome is critical to the choice of treatment.

Pharmacological treatment uses antiepileptic drugs (AEDs), which do not treat the cause of the disease, but only prevent the occurrence of epileptic seizures. In about 2/3 of patients, after using a properly selected drug, complete cessation of epileptic seizures can be achieved. However, in 30–40% of cases, seizures cannot be controlled with available AEDs.

Surgical treatment in drug-resistant epilepsy

- **Focal cortical resection** – removal of the part of the brain where the epileptic focus is located (in drug-resistant patients with focal seizures, after presurgical evaluation). Surgical treatment is also considered when the cause of epilepsy is a life-threatening lesion, such as a brain tumor or hemangioma.
- **Ablation techniques** – radiofrequency ablation, laser interstitial thermal therapy (ablation of the epileptic focus).
- **Hemispherectomy** – performed when the seizure focus is not localized but is limited to one hemisphere.
- **Corpus callosotomy** – to interrupt the pathway of seizure activity.

Neurostimulation techniques

Used in drug-resistant patients who are not good candidates for surgery:

- Vagus nerve stimulation (VNS);
- Deep brain stimulation (DBS);
- Responsive neurostimulation (RNS).

Ketogenic diet

A diet high in fats and low in sugars, used in cases of drug-resistant epilepsy syndromes in children.

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9. Balance disorders

Mariusz Szydło

Vertigo

Vertigo is a common problem in people over 65 years of age and represents the 3rd most common reason for seeking medical attention.

Maintaining balance requires the cooperation of the vestibular system, cerebellum, proprioceptive pathways, and vision. A lesion in any of these components may cause vertigo. The simplest classification divides vertigo into central and peripheral, which allows for the approximate localization of the lesion.

Peripheral vertigo usually results from a lesion of the vestibule, vestibular nerve, or its nucleus in the brainstem. It involves the sensation of movement of the surroundings or one's own body, most often in the form of spinning or falling to one side. The episodes are usually paroxysmal and worsen when moving the head or changing body position, e.g., when turning from one side to the other in a lying position or when standing upright. They are often accompanied by nausea, vomiting, and a sense of anxiety.

The physical examination reveals:

- a) gait disturbances;
- b) positive Romberg test;
- c) fine-wave nystagmus;
- d) horizontal nystagmus;
- e) binocular nystagmus;
- f) nystagmus in the direction opposite to the lesion;
- g) hearing loss;
- h) other ear disturbances, e.g., ear pain, tinnitus.

Central vertigo mainly results from lesions of the central nervous system, in particular the brainstem and cerebellum. It is characterized by balance disorders with a feeling of postural instability, usually without a sensation of spinning. Severe nausea and vomiting are less common.

The physical examination reveals:

- a) balance and gait disorders;
- b) coarse-wave nystagmus;
- c) horizontal nystagmus;
- d) vertical nystagmus;
- e) torsional nystagmus;
- f) nystagmus with changing direction;

g) coexistence of other symptoms of brain lesion, such as:

- headache;
- diplopia;
- ataxia;
- dysarthria;
- dysphagia;
- limb paresis;
- disturbances of sensation in the face.

The causes of vertigo are divided into:

- Neurological:
 - a) inflammation of the vestibular nerve (neuritis vestibularis);
 - b) failure of the posterior circulation;
 - c) multiple sclerosis;
 - d) craniocerebral injuries;
 - e) neuroma of the VIII nerve and other brain tumors;
 - f) paraneoplastic syndromes;
 - g) basilar migraine;
 - h) meningitis and encephalitis;
 - i) hereditary ataxia;
 - j) autonomic neuropathy.
- ENT (ear, nose, throat):
 - a) acute and chronic inflammation of the outer, middle, and inner ear;
 - b) Ménière's disease;
 - c) motion sickness;
 - d) labyrinth injuries;
 - e) iatrogenic ear lesion – drug-induced.
- Other:
 - a) cervicogenic;
 - b) presyncope;
 - c) syncope;
 - d) dehydration;
 - e) electrolyte disorders;
 - f) hypoglycemia;
 - g) anemia;
 - h) respiratory failure;
 - i) hypothyroidism;
 - j) infection outside the nervous system;
 - k) heart arrhythmia;
 - l) heart failure;

- m) neurosis with panic attacks;
- n) hyperventilation attacks;
- o) somatization.

Important!

Acute vertigo may also occur as a result of a sudden lesion to the cerebellum or brainstem.

Vertigo diagnosis

A thorough medical history and neurological examination are crucial. Important auxiliary tests include computed tomography (CT) or magnetic resonance imaging (MRI) of the brain, as well as an otolaryngological examination, including the assessment of vestibular excitability, i.e., videonystagmography/vestibuloneurography (VNG).

Treatment of vertigo

Treatment should be primarily causal. Vascular/vestibular drugs such as betahistine and cinnarizine are used for symptomatic treatment. If necessary, antiemetics can be administered: metoclopramide, ondansetron. In cases of significant anxiety, anxiolytics such as hydroxyzine or benzodiazepines may be helpful.

In patients with vestibular lesions, vestibular rehabilitation using kinesitherapy plays an important role in accelerating vestibular compensation and improving everyday functioning.

Selected types of peripheral vertigo are listed below:

Benign paroxysmal positional vertigo (BPPV)

BPPV is one of the most common causes of vertigo, accounting for approx. 50% of cases in elderly people. It is most often idiopathic, but may also result from injuries, infections, or degenerative changes occurring in the labyrinth. Symptoms occur when the head moves in the plane of the affected semicircular canal.

It is characterized by short-lasting episodes of vertigo, lasting from a few to several seconds, triggered by a change in head position when lying down, standing up, bending over, or turning the head quickly. In severe cases, vertigo may be accompanied by nausea and vomiting.

In most patients, it resolves spontaneously, but in many cases, it tends to recur. The diagnostic test confirming BPPV is the Dix–Hallpike test. Treatment of BPPV originating from the posterior semicircular canal involves the use of the Epley repositioning maneuver.

Inflammation of the vestibular nerve (neuritis vestibularis)

Neuritis vestibularis is the 2nd most common cause of peripheral vertigo after BPPV. It is believed that the disease most often develops after activation of latent infection with the herpes simplex virus type 1 (HSV-1).

The main symptoms include:

- a) vertigo;
- b) horizontal–rotational nystagmus with a fast phase towards the healthy ear;
- c) instability in the Romberg test with a tendency to fall on the side of the affected ear.

Symptoms disappear gradually after 3–7 days and do not cause hearing problems. Caloric tests are useful in diagnostics, as they reveal decreased excitability of the labyrinth affected by the disease. The treatment involves glucocorticosteroids (prednisone, methylprednisolone).

Ménière's disease

Ménière's disease is characterized by paroxysmal vertigo accompanied by fluctuating hearing loss, tinnitus, and a sensation of fullness in the ear. Most often, it develops spontaneously, but in 2.6–12% of patients, it has a genetic basis and is inherited in an autosomal dominant manner.

The etiology is not well understood, but it is suggested to be related to an inner ear abnormality – a hydrops of the labyrinth – resulting from degenerative changes. It often co-occurs with migraine. Vertigo lasts from several minutes to 24 h, most often several hours. Its occurrence is usually preceded by a sensation of pressure or fullness in the ear and is accompanied by nausea and vomiting.

Hearing loss is sensorineural in nature. Tinnitus worsens the quality of life. The onset of the disease is generally unilateral; with time, lesions occur in both ears in as many as 50% of patients. In 5–10% of patients, paroxysmal drop attacks may occur, most likely because of acute irritation of one of the otolith organs.

Diagnostics include audiometric testing, which shows variable sensorineural hearing loss in the lower frequency range, and videonystagmography (VNG), which shows decreased labyrinth excitability in caloric tests. In addition, vestibular evoked myogenic potentials (VEMP) are examined – they show asymmetry of responses in unilateral disease.

All patients should undergo high-field (3T) magnetic resonance imaging of the head and ear with the administration of a contrast agent. Computed tomography of the temporal bone has limited diagnostic value. To exclude other causes of vertigo, blood tests should be performed, including complete blood count with smear, TSH, electrolytes, ESR, CRP, and antibodies for autoimmune diseases.

Due to the unexplained etiology of Ménière's disease, no causal treatment has been developed yet.

Emergency treatment in patients with an acute attack includes:

- neuroleptics;
- antihistamines;
- anxiolytics;
- antiemetics.

Long-term treatment involves:

- betahistine;
- diuretics such as hydrochlorothiazide, acetazolamide;
- glucocorticosteroids: methylprednisolone, prednisone, dexamethasone;
- gentamicin.

Preventive measures are recommended, including limiting salt consumption, avoiding caffeine, alcohol, and chocolate, stopping smoking, and avoiding stress whenever possible. In some countries, Meniett® low-pressure pulse generators are used in drug-resistant patients. If none of the treatment methods alleviate the symptoms, surgical treatment involving decompression of the membranous labyrinth or sectioning of the vestibular nerve may be considered.

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10. Head trauma

Konstanty Gurański

Traumatic brain injury

Traumatic brain injury (TBI) is an injury to the brain caused by an external mechanical force, leading to temporary or permanent impairment of neurological function.

Epidemiology

Traumatic brain injury is a major cause of death and disability worldwide, particularly in children and young adults. Globally, the incidence of TBI is estimated at 27 to 69 million cases. In Europe, about 2.5 million people sustain a TBI every year, of whom 1 million need hospitalization, and about 75,000 people die as a result of their injuries.

In most developed countries, the incidence of emergency department attendance is around 270–330 per 100,000 people annually. Approximately 60% of patients have significant permanent deficits, including cognitive impairment.

The main causes include:

- a) transportation accidents/motor vehicle accidents;
- b) construction/industrial accidents;
- c) sports (1.6–3.8 million per year in the US);
- d) violence;
- e) falls – children and older people (aged ≥ 65 years);
- f) firearms and blast injuries in war zones.

Mechanisms of traumatic brain injury are as follows:

- a) Penetration – the brain may be directly affected by the force of the trauma, leading to contusions (bruising) or lacerations (tearing) of the brain tissue that occur when an object penetrates the skull.
- b) Coup–contrecoup injury – this occurs when the force of the impact leads to the brain colliding with the inner surface of the skull at the site of impact (coup) and then rebounding to strike the opposite side of the skull (contrecoup). This mechanism may result in damage to the frontal or temporal lobes, and possibly to the posterior parts of the brain.
- c) Acceleration–deceleration injury – this occurs when the head undergoes rapid acceleration or sudden deceleration, such as in a car accident or sudden stop, causing the brain to move inside the skull. Rapid acceleration and deceleration forces can cause shearing, which is the tearing of axons and blood vessels. This mechanism is often associated with diffuse axonal injury (DAI).

- d) Blast injuries – explosions or blasts can lead to TBI, even without direct head impact. In a blast, energy from explosive shock waves is transmitted to the brain, causing internal injuries, such as vascular and neuronal damage and contusion.
- e) Hemorrhage – trauma can cause rupture of blood vessels, resulting in bleeding within the intracranial space. Such hemorrhages can cause further damage by increasing pressure within the skull and affecting the surrounding brain structures.

Classification of traumatic brain injury

Traumatic brain injury (TBI) can be classified into different categories based on its severity and clinical features. The most commonly used classification systems are as follows (Table 10.1):

- a) Classification according to physical mechanisms:
 - open or penetrating head injury (the skull is fractured or penetrated in an open head injury),
 - closed head injury (the skull remains intact, without penetration or fracture),
 - explosive blast injury (explosions or blasts can lead to TBI, even without a direct impact on the head; the powerful shock waves generated by the explosion can cause rapid changes in pressure and result in brain injury).
- b) Classification by severity based on the Glasgow Coma Scale (GCS):
 - mild traumatic brain injury – GCS score 13–15 points. This category includes concussions and typically involves a brief loss of consciousness (less than 30 min), alteration of consciousness, or confusion. Post-traumatic amnesia lasts up to 24 h.
 - moderate traumatic brain injury – GCS score 9–12 and a more prolonged loss of consciousness (from 30 min to 24 h), as well as significant neurological deficits and cognitive impairments. Post-traumatic amnesia persists from 24 h to 7 days. Recent studies suggest that patients with GCS 13 should be treated as having a moderate injury.
 - severe traumatic brain injury – GCS score 3–8 and prolonged loss of consciousness (more than 24 h), extensive neurological deficits, and potentially life-threatening injuries, with post-traumatic amnesia lasting more than 7 days.

Table 10.1. Severity rating for TBI using Glasgow Coma Scale (GCS), post-traumatic amnesia (PTA) and loss of consciousness (LOC)

Severity level	GCS	PTA	LOC
Mild	13–15	<1 day	0–30 min
Moderate	9–12	1–7 days	30 min–24 h
Severe	3–8	>7 days	>24 h

Post-traumatic amnesia usually refers to events immediately before head trauma (retrograde amnesia) and after head trauma (anterograde amnesia).

The GCS clinical classification assesses only the severity of symptoms and does not take into account findings from computed tomography (CT). Structural lesions on CT scan occur in about 5–15% of patients with mild traumatic brain injury (mTBI) and should be recognized as “complicated mTBI”, and the diagnosis should be verified according to CT findings (e.g., cerebral contusion, intracranial hemorrhage).

The Mayo Traumatic Brain Injury Classification, on the other hand, proposes excluding patients with traumatic lesions on head CT scan from the mTBI category.

c) Classification by pathophysiology and area of involvement:

Primary brain injury:

- diffuse brain injury: concussion, diffuse axonal injury (DAI);
- focal brain injury: contusion, hematoma (subdural, epidural and intracerebral), subarachnoid hemorrhage.

Both types of injuries are common in patients with moderate to severe TBI.

Secondary brain injury:

- excitotoxicity;
- mitochondrial dysfunction;
- oxidative stress;
- lipid peroxidation;
- neuroinflammation;
- axon degeneration;
- apoptotic cell death.

Complications of traumatic brain injury:

- a) cerebral edema;
- b) increased intracranial pressure;
- c) hemorrhage progression;
- d) seizures;
- e) ischemia;
- f) infection;
- g) traumatic venous sinus thrombosis.

Long-term consequences of traumatic brain injury:

- a) post-concussion syndrome;
- b) post-traumatic epilepsy;
- c) post-traumatic encephalopathy;
- d) post-traumatic hydrocephalus;
- e) post-traumatic hormone disturbances.

Types of traumatic brain injuries

Concussion is a traumatic alteration of brain function that occurs without identifiable abnormalities on structural imaging. The term “concussion” is often used interchangeably with mild TBI (mTBI); however, mTBI is a more general term, and concussion can be treated as one of the clinical forms of mTBI. One of the major differences between the two is that mTBI can show abnormal imaging changes (e.g., contusion or hemorrhage), whereas in concussion, imaging studies are normal.

The concept of concussion assumes the presence of functional brain impairment without structural changes. Traumatic neuronal dysfunction is probably due to the release of excitatory neurotransmitters and impaired axonal transport secondary to a disrupted neurofilament organization. However, more precise imaging techniques, such as diffusion tensor magnetic resonance imaging and postmortem studies, have shown that some patients with concussion or mTBI may exhibit focal changes in white matter axons and the corpus callosum.

The main symptoms of concussion, which occur immediately after injury, include confusion and amnesia, with or without loss of consciousness. Loss of consciousness is not required for diagnosis. Sometimes confusion is unnoticed by the patient. Amnesia usually refers to events immediately before (retrograde amnesia) or after (anterograde amnesia) head trauma. Other typical acute symptoms of concussion include:

- headache;
- dizziness;
- nausea;
- vomiting;
- hypersensitivity to sound and light;
- autonomic signs such as facial pallor, bradycardia, sluggish pupillary reaction.

In the following hours and days, neuropsychological symptoms usually appear:

- impaired concentration;
- impaired memory;
- sleep disturbances;
- fatigue;
- irritability;
- lowered mood.

Neurological examination reveals no signs of focal neurological deficits. Computed tomography or MRI images are normal and are usually performed to exclude structural traumatic injuries. Most symptoms resolve within 7–10 days and do not require specific treatment.

Diffuse axonal injury

Diffuse axonal injury, also known as **traumatic axonal injury (TAI)**, is characterized by widespread damage to the white matter of the cerebral hemispheres, corpus callosum, and brainstem, with clinically predominant disturbances of consciousness, including coma. Rotational acceleration/deceleration head injury results in shear and tear of axonal fibers, diffuse hemorrhagic foci, and injury to axons. Focal lesions may only be identified microscopically. Typical lesion locations:

- corpus callosum;
- brainstem;
- white matter of cerebral hemispheres;
- occasionally the cerebellum.

The Adams classification of diffuse axonal injury (DAI):

- Grade 1: mild diffuse axonal injury with microscopic white matter changes in the cerebral cortex, corpus callosum, and brainstem.
- Grade 2: moderate diffuse axonal injury with gross focal lesions in the corpus callosum.
- Grade 3: severe diffuse axonal injury with findings as in Grade 2 and additional focal lesions in the brainstem.

Diffuse axonal injury presents with a disturbance of consciousness, including coma, resulting from axonal damage within the brainstem and diencephalon. Loss of consciousness lasting >6 h in the absence of intracranial traumatic injury on CT scans usually suggests DAI. The majority of patients with DAI are classified into the group of severe TBI with less than 8 points on the Glasgow Coma Scale (GCS). Focal neurological deficits depend on the area of injury. Later, the coma may evolve into a prolonged vegetative state. In patients with less extensive damage, cognitive impairment often remains.

A CT scan has low value in the diagnosis of DAI and can reveal only larger hemorrhagic lesions or generalized cerebral edema. Small diffuse white matter lesions, typical of DAI, are readily visible on MRI. Susceptibility-weighted imaging (SWI) has high sensitivity for hemorrhage detection. Diffusion-weighted imaging (DWI) can accurately demonstrate focal brain edema. Diffusion tensor imaging (DTI) can detect areas of white matter with reduced anisotropy, highly sensitive to axonal damage. Magnetic resonance spectroscopy (MRS) can reveal neurochemical changes after axonal injury.

The main goal in managing patients with diffuse axonal damage is to prevent secondary brain injuries, particularly cerebral edema and intracranial hypertension.

Contusion is a type of focal severe TBI with bruising of the brain parenchyma. The main mechanism of cerebral contusion is coup–contrecoup damage, caused by the collision of the brain with the surrounding skull bones. Contusion lesions are usually located in the inferior frontal and temporal lobes, although they can occur at almost any site, including the cerebellum and brainstem. Lesions can be multifocal – on the side of the impact (coup injury) and on the opposite side (contrecoup injury).

Bruising of the brain parenchyma comprises swelling and hemorrhagic lesions. Focal neurological symptoms depend on the location of the contusion and on the extent of the lesions. Progression of cerebral contusions occurs in up to 75% of patients over the first 48 h after trauma, resulting in subsequent clinical deterioration and the need for surgical intervention.

A CT scan shows isodense, hypodense, or mixed-density areas often surrounded by perilesional hypodense areas. Multiple focal contusions may have a “salt and pepper” appearance. Magnetic resonance imaging is more sensitive than CT in detecting contusions, especially small or non-hemorrhagic lesions.

Conservative therapy consists of the management of increased intracranial pressure. Indications for surgical treatment include:

- progressive neurological deterioration;
- signs of mass effect on brain CT;
- unresponsive increased ICP;
- midline deviation of more than 5 mm;
- cistern compression evidenced on brain CT;
- temporal contusions of greater than 20 cc in volume.

Epidural hematoma

Epidural hematoma (EDH) is characterized by bleeding between the dura and the skull. It is usually associated with a skull fracture (75–95% of patients). Sources of bleeding include:

- lacerated middle meningeal artery (85% of cases);
- ruptured veins: meningeal vein, diploic veins, venous sinuses.

Symptoms of increased intracranial pressure include:

- headache;
 - vomiting;
 - decreased consciousness;
- and focal neurological signs such as:
- hemiparesis;
 - aphasia;
 - pupillary dilation;
 - seizures.

A lucid interval, usually lasting for several hours, occurs in about 50% of patients. After regaining consciousness following a head injury, the patient again develops impaired consciousness.

A CT scan reveals a lens-shaped hyperdense lesion in the epidural space, usually with a mass effect. In a small percentage of patients, the first CT scan performed within the 1st hours after the trauma, before blood collects in the epidural space, may not show bleeding.

Most patients require urgent surgical evacuation. Indications for surgical treatment include:

- focal signs or symptoms attributable to acute EDH;
- GCS score <9 and pupillary abnormalities due to acute EDH;
- large hematoma volume (>30 cm³);
- hematoma growth causing elevated intracranial pressure or neurologic deterioration.

Subdural hematoma

Subdural hematoma (SDH) occurs between the dura mater and the arachnoid mater. The source of bleeding is the bridging veins that connect the brain with the dural venous sinuses. Common locations are the frontal and parietal convexities. In older people taking anticoagulants, subdural bleeding can occur even with minor head trauma.

Symptoms of increased intracranial pressure include:

- headache;
- decreased consciousness;
- and focal neurological signs such as hemiparesis, aphasia, pupillary dilation, and seizures. Lucid intervals often occur.

Depending on the time of symptom onset, SDH is divided into 3 groups:

- acute – 1 to 2 days after onset;
- subacute – 3 to 14 days after onset;
- chronic – 15 or more days after onset.

Up to 50% of patients with chronic SDH do not remember a head injury. Risk factors for chronic SDH include:

- older age;
- use of anticoagulants;
- alcoholism.

Clinical signs of chronic SDH usually progress slowly. Patients often present with symptoms of increased intracranial pressure, cognitive impairment, behavioral disturbances, and epileptic seizures. Focal neurological symptoms are less common than in acute and subacute SDH.

A CT scan shows concave-shaped hyperdense (acute SDH) or isodense-to-hypodense (chronic SDH) blood collection along the brain convexity. Acute subdural hematomas of more than 10 mm in thickness or associated with a midline shift >5 mm on CT must be surgically evacuated, regardless of the patient's GCS score.

Traumatic subarachnoid hemorrhage (SAH) is a hemorrhage into the subarachnoid space caused by ruptured small vessels. It is typically associated with moderate and severe head trauma, often accompanied by brain contusion or diffuse axonal injury (DAI). Post-traumatic SAH should be differentiated from bleeding resulting from a ruptured aneurysm.

Patients with traumatic SAH and mTBI have a very low risk of clinical deterioration. A CT scan shows hyperdense areas in the superficial brain sulci. Complications may include post-traumatic vasospasm (in 30–40% of patients) with cerebral ischemia, dyselectrolytemia, pituitary or hypothalamic dysfunction, and hydrocephalus. Neurosurgical treatment may be required in patients with a significant increase in intracranial pressure.

Skull fracture is classified as:

- closed (simple fracture) or open (compound fracture);
- fractures of the vault (linear or depressed) and skull base (basal skull fracture).

Most linear skull fractures have no clinical significance. Clinical presentation and complications of basal skull fractures include:

- postauricular ecchymosis (Battle's sign);
- periorbital ecchymosis (raccoon's eyes) in the absence of direct orbital trauma;
- hemotympanum;
- cranial nerve damage;
- leakage of cerebrospinal fluid (CSF);
- pituitary gland injuries;
- traumatic carotid–cavernous fistula.

Cranial nerve damage associated with basal skull fractures:

- I, II: anterior fossa skull fracture;
- III, VI: fractures through the clivus;
- VII, VIII: temporal bone fracture.

A CT scan is the most sensitive method for diagnosing skull fractures, especially basal fractures. X-rays should be performed if CT is unavailable. As for treatment of basal skull fractures, most patients do not require specific therapy, except in cases complicated by CSF leakage or meningitis.

Management of traumatic brain injury

Prehospital, using the A B C D E method:

- A – airway and cervical spine control (clear airway, cervical spine protection);
- B – breathing and ventilation (achieve adequate oxygenation of tissues);
- C – circulation and hemorrhage control (assess the likelihood of blood loss, correct hypotension);
- D – dysfunction of CNS (GCS);
- E – exposure (to ensure that no injuries are missed).

Prehospital management focuses on the prevention and treatment of hypoxia and hypotension, which can lead to the progression of post-traumatic brain injury. Indications for endotracheal intubation include:

- low GCS (<9);
 - SpO₂ <90% despite the use of supplemental oxygen.
- Prevention of hypotension: administer isotonic crystalloids. Manage pain to decrease intracranial pressure.

Role of the Emergency Department:

- a) Evaluation of vital signs, such as:
 - heart rate;
 - blood pressure;
 - respiratory status;
 - temperature.
- b) Level of consciousness:
 - GCS.
- c) Skull and face examination, looking for:
 - external signs of head trauma such as scalp abrasions, contusions, lacerations, open depressed skull fractures;
 - evidence of basal skull fracture: Battle's sign (postauricular ecchymoses), raccoon eyes (periorbital ecchymoses), CSF otorrhea or rhinorrhea.
- d) Neurological examination:
 - signs of meningeal irritation;
 - cranial nerves;
 - focal neurological signs in the limbs;
 - symptoms of increased intracranial pressure and cerebral herniation (pupillary asymmetry, disturbances of consciousness, decorticate or decerebrate posturing, Cushing triad).
- e) Basic blood tests, coagulation parameters, toxicological tests (ethanol level as a main test); blood-based biomarkers, particularly GFAP and UCH-L1, may help predict patient outcomes after TBI.
- f) Neuroimaging.

Neuroimaging

- a) Computed tomography (CT) – the preferred radiologic test in the emergency setting; it is quick, accurate, and widely available. CT can detect areas of cerebral contusion, intracranial bleeding, brain edema, and skull fractures.

Indications for CT:

- GCS <15;
- clinical suspicion of skull fracture;
- vomiting (especially if recurrent);
- focal neurological deficit;

- coagulopathy;
 - age >65 years;
 - seizures;
 - prolonged post-traumatic amnesia (>30 min);
 - potentially high-impact head injury;
 - intoxication;
 - severe headache;
 - abnormal behavior.
- b) Magnetic resonance imaging (MRI), including diffusion tensor imaging and volumetric analyses, is more useful for imaging diffuse axonal injury. MRI should be performed in patients whose neurological deficits cannot be explained by CT findings. Disadvantages of this method:
- lower availability;
 - longer examination time;
 - less useful for imaging of bleeding and skull bone fractures.
- c) X-ray can be used in the diagnosis of skull fractures, but its accuracy is lower than CT. Administration of tranexamic acid in the emergency department is recommended for patients who present with moderate TBI within 3 h of injury.

Indications for admission include:

- Glasgow Coma Scale (GCS) <15;
- abnormalities on CT (e.g., intracranial hemorrhage, ischemia, mass effect, midline shift);
- seizures;
- abnormal bleeding parameters due to underlying bleeding diathesis or oral anticoagulation;
- focal neurologic deficit;
- recurrent vomiting.

Potential indications for neurosurgical treatment include:

- epidural hematoma;
- subdural hematoma;
- intracerebral hematoma;
- refractory intracranial hypertension;
- penetrating and depressed skull fracture.

Management of post-traumatic brain edema and raised ICP

Intracranial hypertension is suspected when one major or 2 minor criteria are present (Table 10.2).

Table 10.2. Diagnosis of intracranial hypertension

Major criteria
– Compressed cisterns (CT classification of Marshall diffuse injury III); – Midline shift greater than 5 mm (Marshall diffuse injury IV); – Non-evacuated mass lesion.
Minor criteria
– Glasgow Coma sum motor score of 4 or less; – Pupillary asymmetry; – Abnormal pupillary reactivity; – CT classification of Marshall diffuse injury II (i.e., basal cisterns are present with midline shift 0–5 mm or a high density or mixed-density lesion of 25 cm³ or less, or both).

Table 10.3. Marshall CT classification of traumatic brain injury

Category	Definition
Diffuse injury I	– no visible intracranial pathology
Diffuse injury II	– midline shift of 0 to 5 mm – basal cisterns remain visible – no high or mixed density lesions >25 cm³
Diffuse injury III (swelling)	– midline shift of 0 to 5 mm – basal cisterns compressed or completely effaced – no high or mixed density lesions >25 cm³
Diffuse injury IV (shift)	– midline shift >5 mm – no high or mixed density lesions >25 cm³
Evacuated mass lesion V	– any lesion evacuated surgically
Non-evacuated mass lesion VI	– any lesion evacuated surgically

For patients with severe TBI and a CT scan showing evidence of mass effect (Table 10.3), ventriculostomy and ICP monitoring are recommended for the treatment of elevated ICP to target pressures below 22 mmHg. Measures to decrease brain swelling include:

- adequate oxygenation and ventilation;
- head of bed elevation to 30° to permit adequate venous drainage;
- fluid and electrolyte balance;
- temperature control;
- hyperosmolar agents (mannitol 0.25–1.0 g/kg every 4 to 6 h or 23.4% NaCl 30 to 60 mL iv.);
- external ventricular drainage of CSF.

Treatment of refractory ICP elevation:

- decompressive craniectomy;

- barbiturate coma;
- induced hypothermia.

Uncertain or no benefit with:

- glucocorticoids;
- neuroprotective agents.

Long-term consequences of traumatic brain injury

Post-concussion syndrome is a common consequence of mild TBI that occurs in 10–15% of concussed individuals. Post-traumatic organic brain dysfunction and psychological factors are the causes. The most common symptoms are:

- headache;
- dizziness;
- memory impairment.

Other typical symptoms:

- somatic: blurred vision, tinnitus, anosmia, fatigue;
- cognitive and emotional: poor concentration, sleep disturbance, irritability, anxiety, depression, behavioral changes.

Symptoms generally disappear within a few weeks or months. Patients with persistent symptoms may require neurologist, psychiatrist, and/or psychologist care.

Post-traumatic seizures are divided into:

- a) Early seizures (<7 days after injury):
 - risk factors: moderate/severe injury, cortical lesion;
 - emergency medication to interrupt a seizure is the treatment for this type of seizures;
 - short-term prophylactic anticonvulsants can be considered in specific cases: extradural, subdural or intracerebral hematoma on CT, depressed skull fracture on CT, early post-traumatic seizure in the hospital (especially if focal or prolonged), severity of head injury (low initial GCS/prolonged coma/prolonged PTA), any suspicion of penetrating injury.
- b) Late seizures (>7 days after injury) – post-traumatic epilepsy:
 - risk factors: evacuated intracranial hematoma, depressed skull fracture, early seizure, dural tear, focal neurological signs, post-traumatic amnesia for more than 24 h;
 - long-term prophylactic anticonvulsants are the treatment.

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease, commonly caused by repetitive traumatic brain injuries. Neuropathological findings are abnormally phosphorylated tau accumulation in cerebral sulci and perivascular regions, microgliosis, and astrogliosis.

Clinical features include:

- a) Cognitive:
 - mental slowing;
 - memory deficits.
 - b) Emotional and behavioral changes:
 - depression;
 - anxiety;
 - agitation;
 - aggression;
 - violence;
 - poor impulse control;
 - socially inappropriate behavior;
 - apathy;
 - pathological alcohol intoxication;
 - paranoia.
 - c) Motor:
 - cerebellar dysfunction;
 - parkinsonism symptoms;
 - pyramidal tract dysfunction;
 - gaze disturbance.
- MRI reveals signs of diffuse atrophy with abnormal axonal changes.

Post-traumatic hydrocephalus:

- a) Risk factors:
 - subarachnoid hemorrhage;
 - intraventricular blood;
 - meningitis.
- b) Treatment:
 - ventriculoperitoneal shunt.

Post-traumatic pituitary dysfunction:

- a) Risk factors:
 - severe injury;
 - anterior skull base fracture.
- b) Treatment:
 - endocrine replacement therapy.

Traumatic spinal cord injury

Traumatic spinal cord injury is a condition that mainly affects young adult men (80–85%, usually 16–30 years old). With the aging of the population, the proportion of elderly people with traumatic spinal cord injury has been increasing, mainly because of fall-related injuries.

Causes:

- motor vehicle crashes;
- falls;
- violence;
- recreational/sporting activities;
- other.

Most spinal cord injuries are associated with damage to the vertebral column, such as:

- fracture of one or more bony elements;
- dislocation at one or more joints;
- tearing of ligaments;
- disruption or herniation of the intervertebral disc.

Pathophysiology of traumatic spinal cord injury:

- primary injury (immediate effect of trauma): compression, laceration, contusion, shearing, cord transection, hemorrhage;
- secondary injury (minutes and hours after trauma): ischemia, hypoxia, inflammation, edema, excitotoxicity, disturbances of ion homeostasis, apoptosis.

Following secondary damage, spinal cord edema develops within hours of injury, peaks between the 3rd and 6th days, and begins to resolve after the 9th day after injury.

Symptoms of spinal cord injury include:

- motor: paresis or paralysis of the limbs;
- sensory loss;
- autonomic: bowel or bladder incontinence, sexual dysfunction;
- pain associated with vertebral column injury.

The type of focal neurological deficits depends on the level and severity of the spinal cord injury (see symptoms of spinal cord injury).

Neurogenic shock is a temporary loss of the autonomic function of the cord at the level of injury, which controls cardiovascular function, lasting 4–6 weeks. Symptoms include:

- hypotension;
- bradycardia;
- anhidrosis;
- hypothermia.

Spinal shock refers to the sudden and temporary depression of neural function below the level of an acute spinal cord lesion after injury, which usually subsides in hours to weeks. Symptoms include:

- flaccid paralysis;
- no motor tone;
- total or near-total areflexia;
- complete loss or suppression of sensation distal to the anatomical lesion;
- flaccid sphincters.

Management of the injury includes:

- evaluation of vital signs;
- immobilization of the cervical spine when a fracture is suspected;
- neurologic examination;
- urinary catheter insertion.

Plain spine X-rays and CT scan are used in the diagnosis of bone injuries. Computed tomography has significantly higher sensitivity and specificity than plain radiographs. If it is not available, spine X-ray is recommended. Magnetic resonance imaging is better for evaluating cord, nerve roots, soft tissue and ligament pathology.

Treatment for traumatic spinal cord injury includes:

- a) Glucocorticoids: no clinical evidence exists to definitively recommend the use of steroid therapy, especially in patients with penetrating injury, multisystem trauma, moderate to severe traumatic brain injury. In other patients who present within 8 h of isolated, non-penetrating spinal cord injury, administration of intravenous methylprednisolone can be considered with knowledge of potential risks and uncertain benefits.
- b) Surgical intervention: decompression and stabilization.
- c) Rehabilitation.

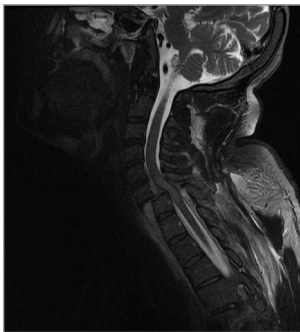
Fig. 10.1–10.5

Fig. 10.1. MRI: cervical spine (vertebral body dislocation)



Fig. 10.2. Head CT: epidural hematoma



Fig. 10.3. Head CT: brain contusions



Fig. 10.4. Head CT: SAH



Fig. 10.5. Head CT: subdural hematoma

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11. Neuromuscular disorders

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Neuromuscular diseases include disorders affecting alpha motor neurons, peripheral nerves, the neuromuscular junction, and muscles. We use the concept of a motor unit, which consists of: one motor neuron, all its axons, and all the muscle fibers innervated by individual axons. Between the axon (nerve) and the muscle lies the neuromuscular junction, consisting of pre- and postsynaptic components and the synaptic cleft (Fig. 11.1).

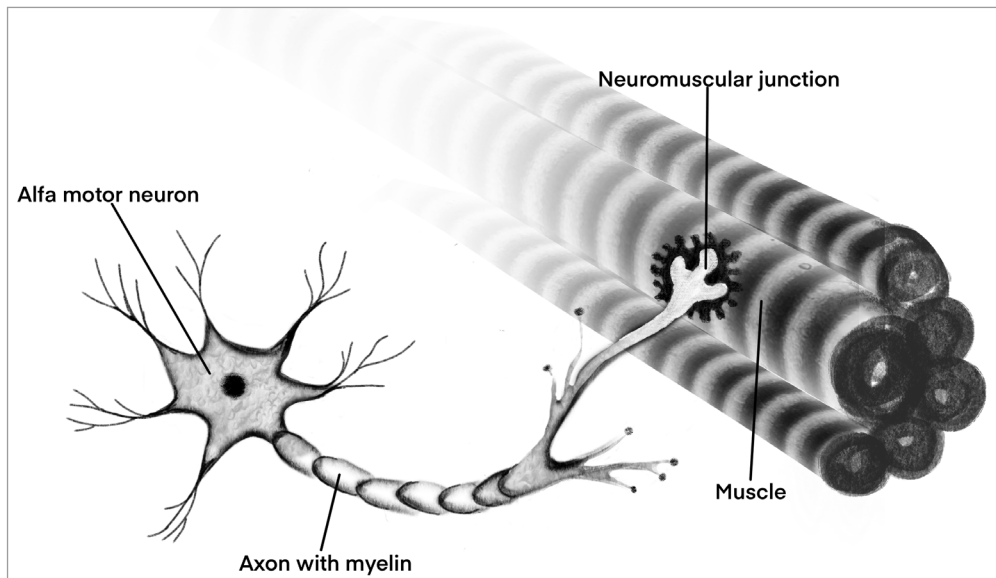


Fig. 11.1. Motor unit

All neuromuscular diseases can be divided into genetic and acquired diseases. Genetic neuromuscular diseases may begin at any age – in childhood, adulthood or even older age. Most acquired neuromuscular diseases have an autoimmune basis.

The clinical manifestations of neuromuscular diseases can be similar, making a correct diagnosis often challenging. The diagnosis of neuromuscular disorders is based on clinical examination, laboratory, electrophysiological, and imaging studies. Muscle or nerve–muscle biopsy is an established diagnostic method. However, due to its invasive nature, it is currently performed only in cases of diagnostic difficulty. The most common neuromuscular disorders are presented below.

Motor neuron diseases

Hereditary motor neuron disease

Spinal muscular atrophy (SMA) – a genetic disorder caused by a mutation in the *SMN1* gene (5q11.2–13.3) with autosomal recessive inheritance, seen in about 90% of cases. A second gene, *SMN2*, may have 1–4 copies. The protein produced by the second gene is unstable, degrades rapidly, and therefore fails to serve its purpose.

Clinical symptoms include:

- muscular atrophy;
- more proximal, mainly lower limb weakness;
- flaccidity;
- lack of deep reflexes;
- in more severe cases:
 - dysarthria;
 - dysphagia;
 - breathing problems;
 - scoliosis.

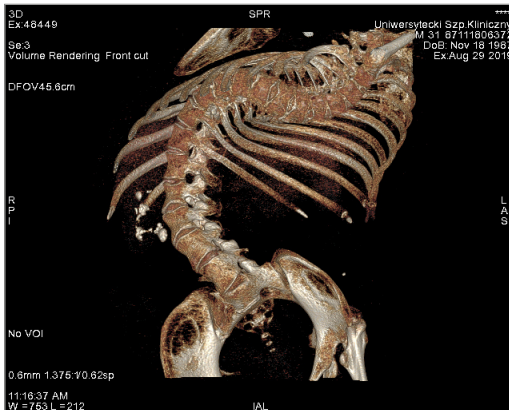


Fig. 11.2. 3D VR reconstruction of the spine CT: severe scoliosis in a 26-year-old woman with type 2 SMA

Historically SMA was divided into 4 types:

- a) SMA1 – severe – patient is not able to sit, death before 2 years of age;
- b) SMA2 – less severe – the child can sit without help but cannot walk;
- c) SMA3 – mild – the child can walk; patients lose mobility over time;
- d) SMA4 – onset in adulthood (around 20 years of age); patients lose mobility over time.

Diagnosis

- genetic testing with assessment of *SMN2* gene copy number; newborn screening;
- neurophysiological testing: ENG – normal, EMG – very high-amplitude potentials.

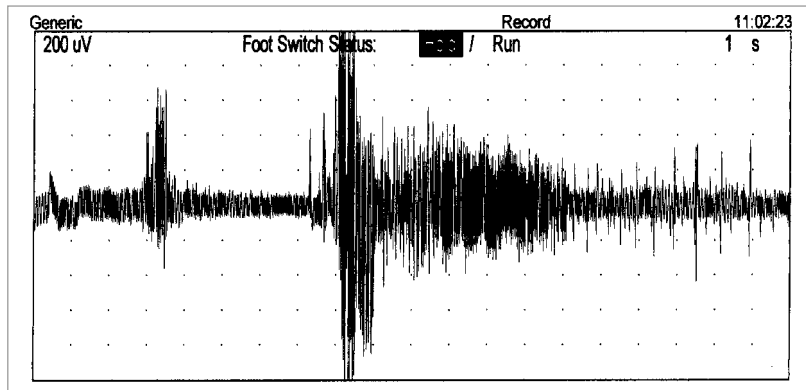


Fig. 11.3. Giant potentials in SMA, amplitude above 10,000 μV

Treatment

- Nusinersen (Spinraza), an antisense oligonucleotide given intrathecally, increases the level of SMN protein by modifying splicing of the *SMN2* gene;
- Risdiplam – oral medication with a similar mechanism of action;
- Onasemnogene abeparvovec (Zolgensma) – gene therapy using a viral vector (iv.).

Acquired motor neuron disease

Amyotrophic lateral sclerosis (ALS) – “motor neuron disease” (MND) is a broader concept, including similar disease entities or atypical syndromes. The pathogenesis remains unclear. Several altered signaling pathways, such as mitochondrial dysfunction, glutamate excitotoxicity, oxidative stress, and neuroinflammation, together with some genetic mutations (e.g., *SOD1*) seem to be involved in the pathological process.

Clinical symptoms include:

- progressive muscular weakness;
- atrophy with fasciculations in bulbar and spinal regions;
- dysphagia;
- dysarthria;
- loss of ability to walk;
- respiratory insufficiency in the late stages of the disease.

Diagnosis consists of:

- clinical examination: upper and lower motor neuron signs, localized in bulbar and spinal regions;
- neurophysiological testing: ENG – normal, EMG – acute denervation, very high-amplitude potentials (as in SMA);
- neuroimaging: MRI of the brain and cervical spinal cord (DWI, DTI – tractography) – lesions of the pyramidal tract (Fig. 11.4, Fig. 11.5).

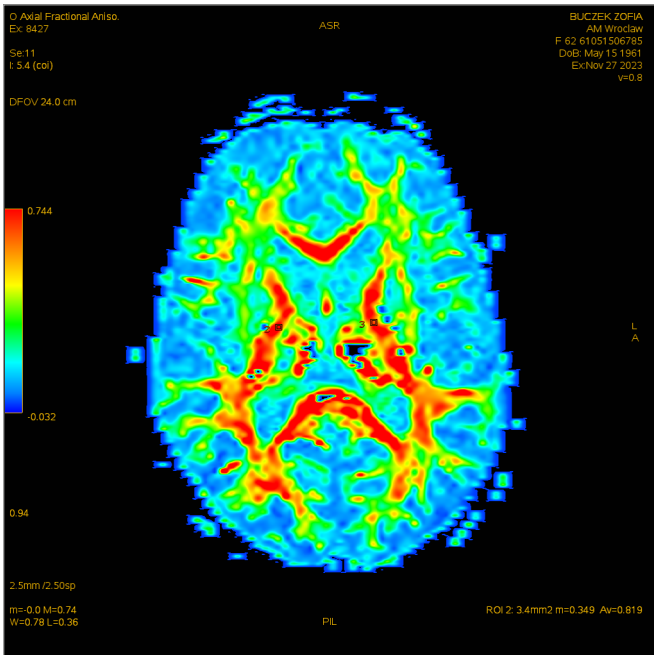
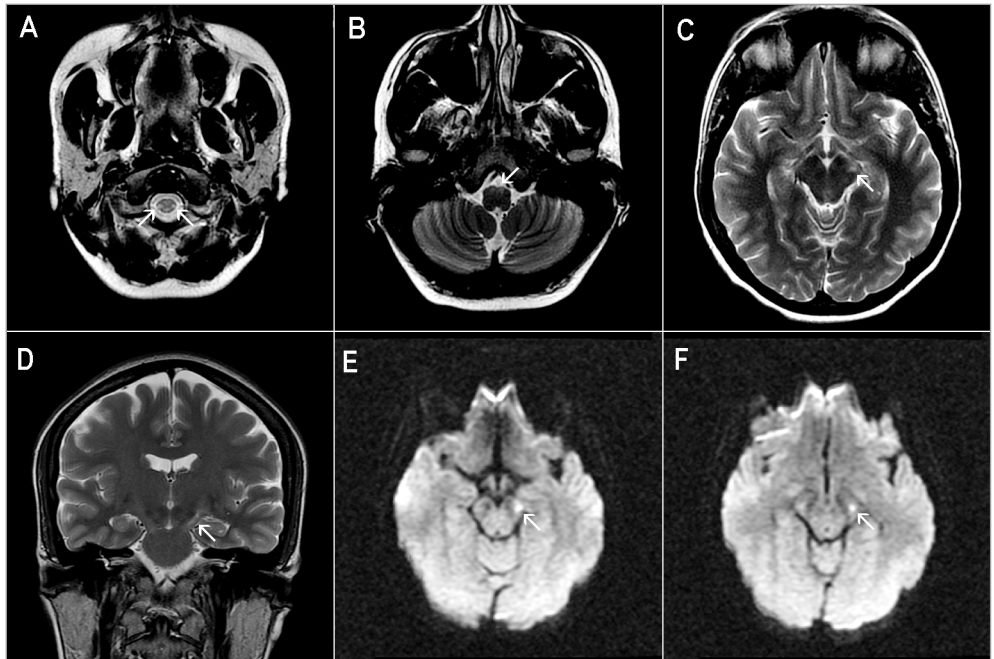


Fig. 11.4. DTI map of white matter tracts in a patient with ALS

Fig. 11.5. Brain MRI in a patient with ALS: A–C. T2-weighted images – bilateral high signal within corticospinal tracts (arrows); E–F. DWI images – diffusion restriction within the corticospinal tract at the level of the left cerebral peduncle



Treatment is only symptomatic:

- Riluzole – probably a glutamatergic inhibitor;
- Edaravone (Radicava) – diminishes oxidative stress as a free-radical scavenger.

In the future, potential therapies may include gene therapy, antisense oligonucleotides (e.g., tofersen – approved only for ALS with *SOD1* mutation), and fingolimod. Supportive therapies for ALS include physical therapy and speech therapy.

Polyneuropathies

Peripheral nerve damage can include damage to a single nerve, leading to loss of movement, sensation, and autonomic dysfunction (mononeuropathy); isolated damage to at least 2 separate nerve areas (mononeuritis multiplex); or simultaneous malfunction of multiple peripheral nerves (polyneuropathy).

Depending on the type of damage found in electrophysiological examination and nerve biopsy, a distinction is made between axonal and demyelinating polyneuropathies.

The condition can also be subdivided according to the type of nerve fibers damaged:

- motor polyneuropathy – motor fibers are damaged;
- sensory polyneuropathy – sensory fibers are damaged;
- autonomic polyneuropathy – autonomic nervous system fibers are damaged;
- mixed sensory–motor polyneuropathy.

According to their etiology, polyneuropathies are divided into hereditary and acquired.

Hereditary motor–sensory polyneuropathies (HMSN = Charcot–Marie–Tooth disease – CMT)

Charcot–Marie–Tooth disease is characterized by slow and progressive atrophy and weakness of the distal muscles of the lower and upper limbs, usually accompanied by sensory disturbances. Skeletal defects such as pes cavus (hollow feet) and scoliosis can also be found in this group of patients. Most commonly detected is a duplication or deletion in the 17p11.2–p12 region with copy number analysis of the *PMP22* gene.

A demyelinating process occurs in CMT type 1 polyneuropathies and axonal damage in CMT type 2. Different mutations can occur within both types. There are also other types of motor–sensory polyneuropathies besides CMT1 and CMT2.

Additionally, we can distinguish hereditary neuropathy with liability to pressure palsy (HNPP, 17p11, *PMP22* deletion) – a hereditary disorder in which nerves become increasingly sensitive to pressure, injury, and use. Very rarely, other congenital polyneuropathies are recognized in which there is pure damage to motor, sensory, or autonomic fibers. Neuropathies can also be an important part of the clinical picture of other congenital conditions such as cerebellar ataxias, leukodystrophies, etc.

Acquired polyneuropathies

In most cases, acquired polyneuropathy is caused by chronic diseases, including diabetes mellitus, cancer, liver diseases (e.g., porphyria), and chronic kidney disease. Causes include chronic use of medications such as:

- proton pump inhibitors (PPIs);
 - metformin;
 - levodopa,
- which may contribute to reduced absorption of B vitamins in the gastrointestinal tract.

Other causes of neuropathy include:

- restrictive diets or inappropriate vegetarian or vegan diets;
- chronic alcohol abuse;
- toxin poisoning (e.g., lead, thallium);
- vitamin deficiencies;
- chemotherapy;
- infections (e.g., hepatitis B and C, Lyme disease);
- autoimmune reactions (e.g., chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy).

Guillain–Barré syndrome (GBS), as a type of polyneuropathy, is a disease manifested by progressive paresis and areflexia that develops over a period of less than 4 weeks. Most patients present with an antecedent illness, most commonly an upper respiratory tract infection, before the onset of progressive motor weakness.

Classically, 3 subtypes of GBS are distinguished:

- a) classic form with symptoms of flaccid para- or tetraparesis – GBS;
- b) form characterized by the triad of symptoms (ophthalmoplegia, ataxia and areflexia) – Miller–Fisher syndrome (MFS);
- c) form characterized by disturbances of consciousness – Bickerstaff brainstem encephalitis (BBE).

Every GBS patient requires hospitalization for monitoring of vital signs due to the potential risk of respiratory failure and the need for assisted ventilation. Additionally, severe autonomic symptoms, including cardiac rhythm disturbances, may be present.

Diagnosis consists of:

- taking a detailed medical history and performing a physical examination, because in the first few days of the disease the results of additional tests may fall within reference ranges;
- electrophysiological tests – demyelinating changes of peripheral nerves;
- cerebrospinal fluid analysis – high protein level, primarily albumin (albuminocytological dissociation). A cell count in cerebrospinal fluid greater than 10 suggests a diagnosis other than GBS;

– laboratory testing – in 25% of patients with the typical variant of GBS, antibodies against gangliosides are present. In Miller–Fisher syndrome, antibodies against GQ1b ganglioside are found in 95% of patients.

Two equivalent treatment options are used – plasma exchange (PE) or intravenous immunoglobulin (IVIg) therapy, administered at a dose of 0.4 g/kg/day for 5 consecutive days.

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a rare, heterogeneous, but treatable autoimmune-mediated peripheral neuropathy characterized by demyelination. In this disease, nerve roots and peripheral nerves are damaged. Autonomic involvement in classic CIDP is typically mild.

The clinical presentation is characterized by flaccid paralysis of the lower extremities, with weakness of proximal and distal muscle groups, progressively worsening over a period of more than 8 weeks.

The following variants of CIDP are distinguished:

- a) distal acquired demyelinating symmetric – DADS;
- b) multifocal acquired demyelinating sensory and motor neuropathy – MADSAM;
- c) focal CIDP;
- d) motor CIDP;
- e) sensory CIDP.

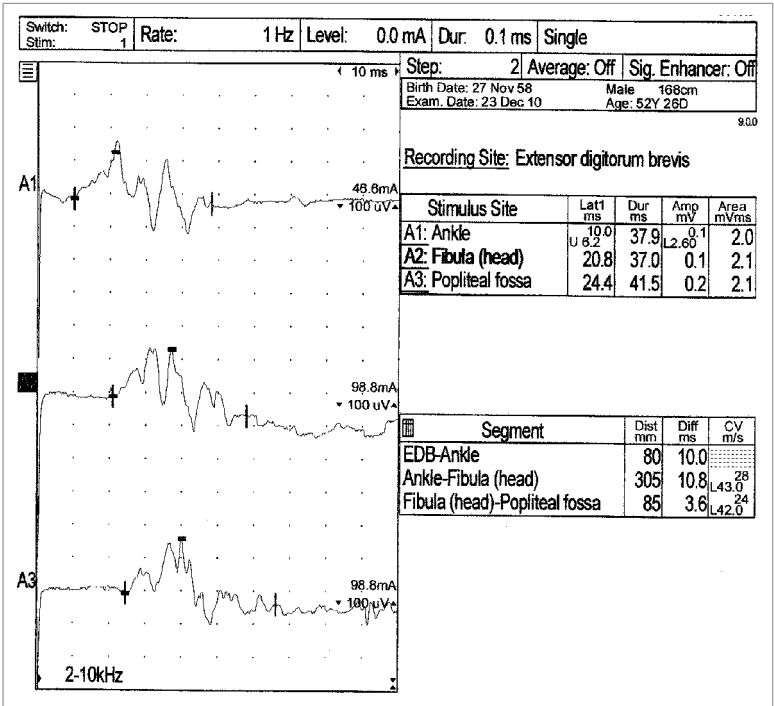


Fig. 11.6. 52-year-old patient with CIDP: demyelination – slow conduction velocity (24–28 m/s; normal value 45–50 m/s), polyphasic low-amplitude potentials, secondary axonal damage

Diagnosis consists of:

- electrophysiological testing – demyelinating signs;
- CSF analysis – elevated protein level;
- neuroimaging – ultrasound shows nerve enlargement, and MRI can show enlargement and/or increased signal intensity of nerve roots on T2-weighted sequences (DIXON/STIR, coronal and sagittal planes).

Treatment

Patients with CIDP typically respond well to treatment with immunomodulatory agents, including intravenous immunoglobulins (IVIg), plasma exchange, and corticosteroids.

Neuromuscular junction diseases

The neuromuscular junction is a site of chemical communication between a motor nerve fiber and a muscle cell. There are many types of channels at the neuromuscular junction that play indispensable roles in neuromuscular signal transmission, such as voltage-gated potassium channels and voltage-gated calcium channels on the presynaptic membrane, and acetylcholine receptors on the postsynaptic membrane.

In order to contract skeletal muscle, chemical neurotransmitters, such as acetylcholine (ACh), are released from the presynaptic membrane under the coordinated action of voltage-gated potassium channels (VGKCs) and voltage-gated calcium channels (VGCCs). Acetylcholine then binds to acetylcholine receptors (AChRs) on the postsynaptic membrane, whose clustering and maintenance depend on muscle-specific kinase (MuSK), lipoprotein-related protein 4 (LRP4), and agrin.

Neuromuscular junction channelopathies include a variety of disorders of autoimmune, genetic, or toxic origin. Regardless of the underlying cause, these disorders lead to impaired neuromuscular transmission.

Acquired autoimmune channelopathies at the neuromuscular junction include myasthenia gravis (MG), Lambert–Eaton myasthenic syndrome (LEMS), and Isaacs' syndrome.

Congenital myasthenic syndromes (CMS) are very rare and difficult to diagnose. They are genetically determined. The symptoms are caused by abnormalities in the structure and function of the neuromuscular junction, without an immunological basis. These syndromes can be classified as:

- presynaptic (with paroxysmal apnea);
- synaptic (with cholinesterase deficiency and acetylcholine quantum deficiency);
- postsynaptic (with abnormal activation of ion channels, among others).

Acquired neuromuscular junction diseases

Myasthenia gravis (MG) is an acquired autoimmune disease. Epidemiological studies indicate 2 peaks of incidence – between 20 and 30 years of age, predominantly in women, and after 60 years of age, mainly in men. The prevalence of new cases in women continues up to the age of 50. The pathology involves the postsynaptic part of the neuromuscular junction.

Myasthenia gravis is immunologically heterogeneous. Most patients produce IgG1 or IgG3 class antibodies against the nicotinic acetylcholine receptor (AChR). These AChR receptors are among the best-characterized neurotransmitter receptors. They are pentamers composed of homologous or identical subunits, symmetrically arranged to form a transmembrane cation channel.

Antibodies against AChR lead to a reduction in the number of acetylcholine receptors by activating complement and accelerating receptor endocytosis. In seronegative MG, antibodies to muscle-specific tyrosine kinase (MuSK) are present in a certain percentage of cases. This form, known as MuSK-positive MG, is characterized by certain clinical peculiarities and is generally less amenable to treatment.

The 3rd group, known as “double seronegative” myasthenia gravis, is characterized by the absence of both AChR-Abs and anti-MuSK antibodies. Clinically, it does not differ from seropositive myasthenia gravis. In some cases, AChR-Abs may be present in this group, but at very low titers and with low receptor affinity, making them undetectable by standard diagnostic methods.

Antibodies against muscle proteins are also important, including those against titin (a protein in the I band responsible for muscle elasticity), ryanodine receptor (RyR; protein in the sarcoplasmic reticulum that controls calcium release) and rapsyn (RAPSN protein inside cells), as well as low-density lipoprotein-related protein 4 (Lrp4).

Thyroid pathology is an important consideration in patients with myasthenia gravis. Thyroid follicular hyperplasia is found in about 60% of patients with seropositive MG and about 30% of those with double seronegative MG. Approximately 10% of patients with myasthenia gravis are diagnosed with thymic cancer. Thymus-associated thymoma (T-MG) is identified as a neoplasm originating from thymic epithelial cells, usually of the cortical subtype (World Health Organization type B).

The pathogenesis of T-MG suggests that epithelial tumor cells encircled by maturing T cells can express epitopes that cross-react with skeletal muscle proteins, such as the acetylcholine receptor (AChR). Thymoma is also associated with many autoimmune diseases, e.g., thyroiditis, systemic lupus erythematosus, and hypogammaglobulinemia.

Myasthenia gravis presents with many different clinical manifestations. The main clinical sign of MG is muscle weakness and fatigue, a progressive weakening of muscle strength with repeated activity, termed “apocamnosia” by Goldflam. The weakness and fatigue can affect:

- eye muscles (twitching, strabismus);
- eyelid muscles (ptosis);
- muscles of the face, jaw and neck (so-called transverse smile, weak eyelid closure, jaw drop with need to support it, head drop);
- limb muscles (hand weakness when brushing teeth, combing hair, shaving, difficulty raising the arms or climbing stairs).

Myasthenia gravis usually begins with ocular symptoms in the form of variable diplopia and drooping of one or both eyelids, usually asymmetrical. Some patients present with only ocular symptoms throughout their lives. When weakness and fatigue extend to the bulbar muscles, axial muscles (of the trunk and head), or limb muscles, we speak of generalized myasthenia gravis.

Variability of symptoms is very characteristic of myasthenia gravis. The paresis of individual muscle groups increases after exertion, while a transient improvement is observed after rest or after taking an acetylcholinesterase inhibitor. The course of the disease may include spontaneous remissions as well as significant deterioration. Periodic exacerbations are associated with infection, dose reduction of chronically administered immunosuppressive drugs, and with the menstrual period, pregnancy, or the postpartum phase.

Certain groups of drugs, such as aminoglycosides, macrolides, botulinum toxin, statins, beta-blockers, magnesium, corticosteroids (initially at high doses), live attenuated vaccines, and iodine contrast agents, may also worsen the course of myasthenia gravis. In some cases, the triggering factor cannot be determined.

Diagnosis consists of:

- clinical examination – apokamnosis and clinical improvement after administration of pyridostigmine;
- laboratory tests – determination of antibodies against AChR and MuSK. In both forms of myasthenia gravis, there is no correlation between the presence of antibodies and the severity of symptoms. Antibody levels can be low and symptoms severe, and vice versa. It is also not possible to predict the course of the disease using immunological tests;
- electrophysiological tests, such as:
 - a) Repetitive nerve stimulation (RNS) – myasthenic test – involves stimulation of a peripheral nerve with an electrical stimulus with recording of muscle response; in MG a decrease in amplitude during stimulation is observed, the so-called myasthenic decrement;
 - b) Single-fiber EMG (SFEMG) – electromyographic study of single muscle fibers.

Myasthenic crisis is a complication of myasthenia gravis characterized by worsening of muscle weakness resulting in respiratory failure that requires intubation and mechanical ventilation. Advances in critical care have reduced the associated mortality.

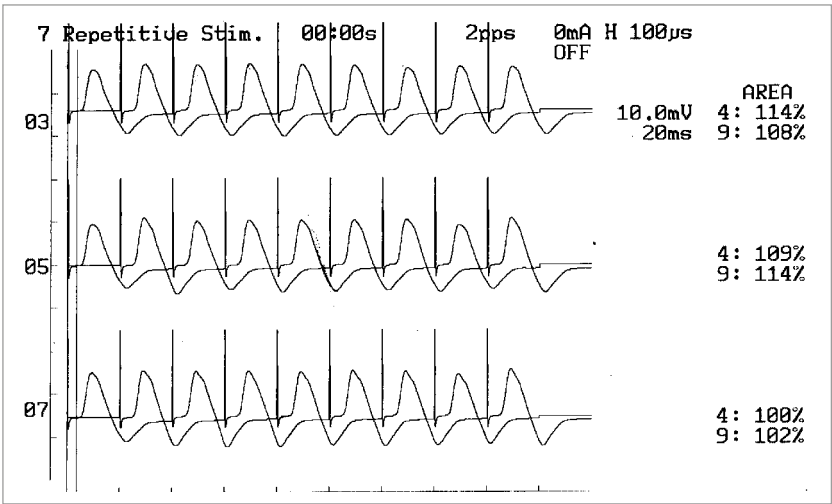


Fig. 11.7 A. Repetitive stimulation test in MG – normal

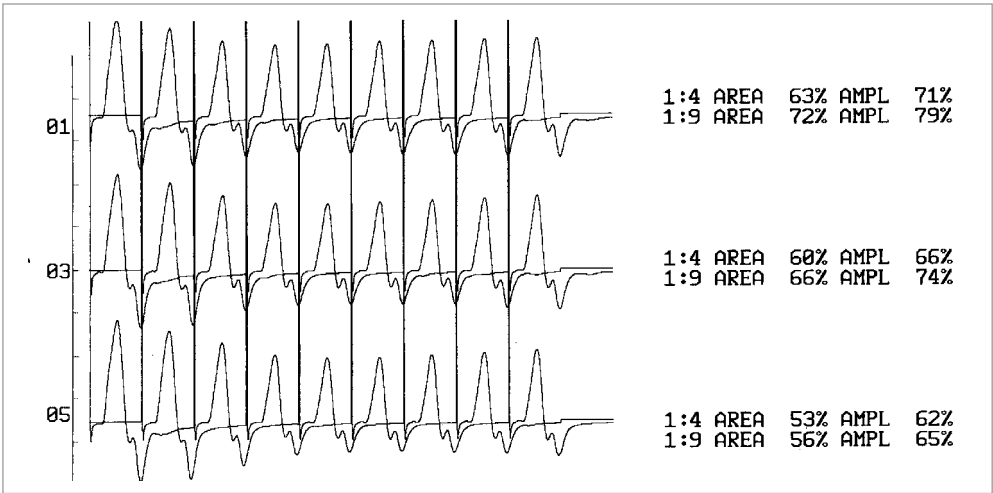


Fig. 11.7 B. Repetitive stimulation test in MG – abnormal: decreased amplitude and area of the potentials by more than 10%

In addition to generalized muscle weakness, including respiratory and bulbar muscles, myasthenic crisis is also characterized by autonomic symptoms such as:

- increased blood pressure;
- tachycardia;
- dilated pupils (mydriasis).

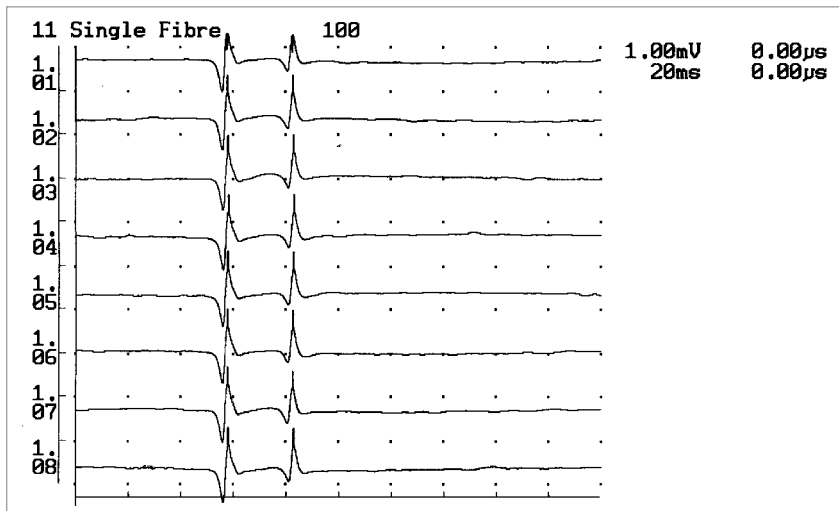


Fig. 11.8 A. SFEMG – normal

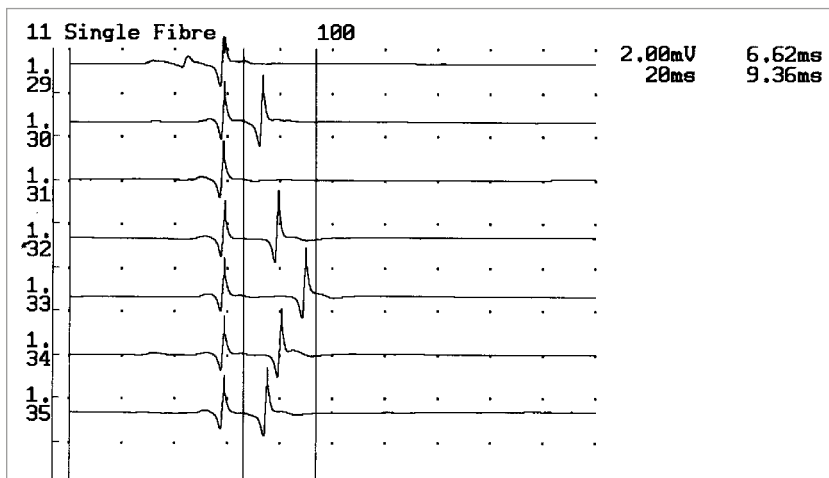


Fig. 11.8 B. SFEMG – long jitter, block of the second potential in line 1.31

The patient experiences increasing fatigue and needs to take higher doses of acetylcholinesterase inhibitors.

A cholinergic crisis is most often secondary to a myasthenic crisis and can occur in patients taking more than 12–16 pyridostigmine bromide tablets a day. It is characterized by:

- paradoxical bradycardia;
- constricted pupils (miosis);

- colicky abdominal pain;
- diarrhea.

Most crises in patients with myasthenia gravis are mixed in nature, resulting from both exacerbation and symptomatic overmedication. Current myasthenia gravis guidelines recommend intravenous immunoglobulin or plasmapheresis, along with discontinuation of pyridostigmine during a myasthenic crisis.

Treatment

Symptomatic oral drugs belonging to the acetylcholinesterase inhibitor group: the most common is pyridostigmine bromide or ambenonium. Failure to improve after symptomatic treatment with acetylcholinesterase inhibitors is an indication for immunosuppressive treatment.

Immunosuppressive treatment of MG:

This type of treatment is started when the symptoms do not improve satisfactorily with symptomatic medication. It is always given for at least 6 months and usually for 1–2 years. Immunosuppressive treatment is usually needed for 1–2 years, but may be needed for life in severe MG.

Corticosteroids are the first-line immunosuppressive treatment for myasthenia gravis. In more than half of patients with MG, administration of high doses of corticosteroids leads to a worsening of the clinical condition within the first few days, followed by subsequent improvement. The second-line immunosuppressive drug is azathioprine. If other immunosuppressive drugs are not effective, cyclophosphamide is used to treat severe MG.

Immunomodulatory therapy:

This treatment is used in patients with a life-threatening condition (myasthenic crisis) and as preoperative preparation for thymectomy in patients with severe bulbar symptoms. Another, less common indication is bridging therapy, applied when rapid stabilization of a patient's neurological condition is required before oral immunosuppressive drugs achieve their full therapeutic effect. Immunomodulatory treatment includes intravenous human immunoglobulin (IVIg) or plasma exchange.

Patients with myasthenia gravis who have antibodies to muscle-specific kinase (MuSK) often show poor tolerance to acetylcholinesterase inhibitors and may develop severe cholinergic symptoms even at low doses (2–4 tablets/day). In MuSK-positive MG, even in cases with severe generalized symptoms, low doses of acetylcholinesterase inhibitors are used, or these drugs are discontinued and only immunosuppressive treatment is continued.

Lambert–Eaton Myasthenic Syndrome (LEMS)

This is a rare autoimmune disease of the neuromuscular junction. Autoantibodies directed against voltage-gated calcium channels (VGCC) in the presynaptic membrane of the neuromuscular junction are responsible for the pathophysiology of LEMS. This myasthenic

syndrome is often a paraneoplastic syndrome, most commonly associated with small-cell lung carcinoma (SCLC), as these tumor cells also express functional VGCC.

The clinical picture is dominated by proximal muscle weakness, while ocular and bulbar symptoms are rare. Neurological examination typically reveals areflexia and autonomic dysfunction (such as dry eyes, orthostatic hypotension, and micturition difficulties). Typically, patients feel worse in the morning than in the evening.

Diagnosis:

- clinical examination;
- antibody testing;
- electrophysiological testing – repetitive nerve stimulation abnormalities:
 - a) low compound muscle action potential;
 - b) decrement >10% at low frequency (1–5 Hz);
 - c) increment >100% after maximum voluntary contraction or at high frequency (50 Hz).

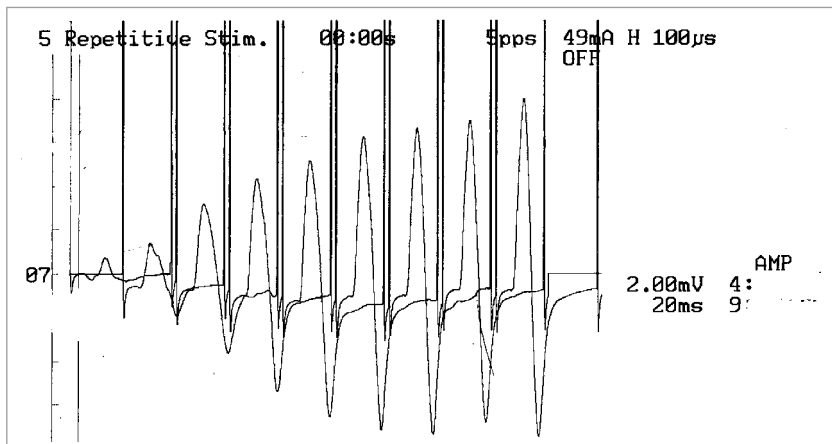


Fig. 11.9. Very high increment (facilitation) in LEMS in repetitive stimulation test

Treatment includes:

- 3,4-diaminopyridine and immunosuppressive treatment;
- Amifampridine (Firdapse) – blocks potassium channel efflux in nerve terminals, increasing action potential duration.

In case of co-occurrence of cancer, oncological treatment is implemented.

Myopathies

Hereditary myopathies

(“Dystrophies” – progressive hereditary myopathies, and others)

The spectrum of genetically determined muscle diseases is very wide, and ongoing advances in genetic research continue to expand and refine their classification. There is currently no universally accepted division of this group of diseases. However, we can distinguish:

- Muscular dystrophies (traditional name) – muscle diseases with a genetic basis, usually with progressive course and similar morphology. Within this group, there are many different conditions, including:
 - a) dystrophinopathies;
 - b) limb-girdle muscular dystrophies;
 - c) facioscapulohumeral muscular dystrophy;
 - d) Emery–Dreifuss muscular dystrophy.
- Congenital myopathies, myotonic syndromes, myofibrillar dystrophies, mitochondrial myopathies, and myopathies associated with metabolic disorders (such as glycogenoses and lipidoses) also have a genetic basis.
- Duchenne muscular dystrophy (DMD) is the most common and most severe form of muscular dystrophy. It is part of a spectrum of diseases known as dystrophinopathies, which also includes Becker muscular dystrophy and other, less common disorders.
- Duchenne muscular dystrophy is an X-linked recessive disorder caused by a mutation in the dystrophin gene at Xp21, with an incidence of 1 in 3,500 male births. Dystrophin is a cytoskeletal protein located in the muscle fiber membrane and is responsible for maintaining muscle fiber integrity. In DMD, dystrophin staining is completely absent.

Clinical symptoms include:

- onset at the age of around 3 years;
- delayed walking;
- Gowers’ sign (the boy must use his hands and arms to “climb” up his own thighs and hips from a squatting position to a standing position);
- boys never run normally;
- later they develop exaggerated lumbar lordosis, which helps to maintain balance;
- at ages 9 to 12 boys no longer walk and use a wheelchair.

Scoliosis leads to respiratory dysfunction. Congestive heart failure and arrhythmias can appear, and intellectual impairment is seen in about one-third of cases. Life expectancy is about 20–30 years.

Diagnosis consists of:

- laboratory testing – markedly elevated serum creatine kinase activity;
- neurophysiological testing: ENG – normal, EMG – myopathic pattern (Fig. 11.10);

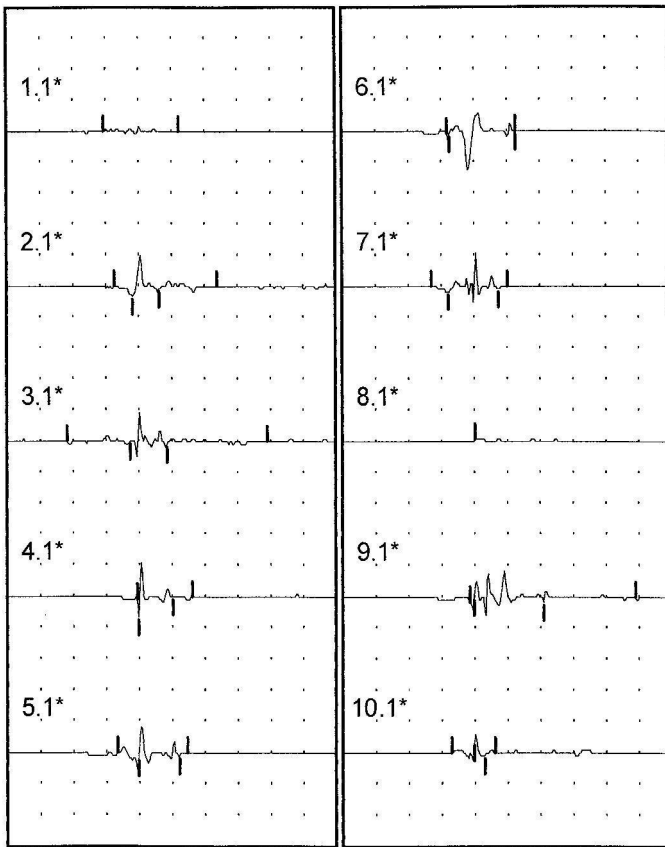


Fig. 11.10. EMG: myopathic, small-amplitude potentials

- genetic testing for mutations in the gene encoding dystrophin; newborn screening in some countries;
- additionally, cardiac monitoring (ECG, echocardiography) and pulmonary function tests.

Treatment

Currently, antisense oligonucleotides are used in the treatment of DMD, varying according to the type of mutation:

- Amondys 45 – for exon 45 skipping mutations;
- Vyondys 53 – for exon 53 skipping mutations;
- Exondys 51 – for exon 51 skipping mutations;
- Ataluren – for nonsense mutations.

Elevidys, approved in 2023, is a recombinant gene therapy, an adeno-associated virus vector-based gene therapy indicated for the treatment of ambulatory pediatric patients with DMD who have a confirmed mutation in the *DMD* gene.

Corticosteroids, such as prednisone and deflazacort (Emflaza), are used to improve muscle strength and delay disease progression.

Myotonic muscular dystrophy (MMD) is the most common form of muscular dystrophy that begins in adulthood. There are 2 different types of MMD:

- Myotonic dystrophy type 1 (DM1; Steinert disease) – caused by mutations in the DMPK gene on chromosome 19, inherited in an autosomal dominant (AD) manner. The mutation involves an expansion of CTG repeats, which are normally between 5 and 34. DM1 usually has a more severe clinical course.
- Myotonic dystrophy type 2 (DM2; proximal myotonic myopathy, PROMM or Ricker disease) – results from mutations in the CNBP gene on chromosome 3 (AD inheritance), a tetranucleotide CCTG repeat which should normally be fewer than 26.

Clinical symptoms include: onset at any age, more common between 20–30 years:

- muscular dystrophy (in type 1 – mainly distal muscles; in type 2 – mainly proximal muscles);
- myotonia (difficulties in muscle relaxation and prolonged muscle contraction);
- cardiomyopathy;
- arrhythmias;
- cataracts;
- endocrinopathy (diabetes mellitus, testicular atrophy, diminished fertility);
- cognitive impairment;
- behavioral disorders.

Diagnosis consists of:

- laboratory testing: serum creatine kinase activity, glucose level, hormone levels;
- genetic testing;
- neurophysiological testing: ENG – normal, EMG – myopathic pattern with myotonic discharges;
- additionally: cardiac monitoring (ECG, echocardiography) and ophthalmological evaluation.

Treatment

Multisystem treatment includes cardiological, endocrinological, ophthalmological and neurological care. Medications that reduce myotonia include sodium channel blockers such as mexiletine, as well as:

- tricyclic antidepressants;
- benzodiazepines;
- calcium channel blockers.

Physical and occupational therapy for muscle strengthening, therapy for speech and swallowing disorders, and psychiatric and psychological care are also important components of management.

Acquired myopathies

Acquired myopathies may be hormonal, associated with disorders of the thyroid gland, adrenal glands, or pituitary insufficiency. They can also be caused by different toxins and medications, such as:

- alcohol;
- heroin;
- chloroquine;
- emetine;
- colchicine;
- statins.

Inflammatory myopathies, including polymyositis, dermatomyositis, and inclusion body myositis (IBM), may occur in the course of rheumatological disorders, paraneoplastic syndromes, or various infections, mainly of viral origin.

Polymyositis (PM) and dermatomyositis (DM) are autoimmune myopathies characterized by inflammation and weakness of proximal muscles, often accompanied by extra-muscular manifestations. Polymyositis is an inflammatory myopathy mediated by cytotoxic T cells, while DM is a humoral process directed against the endothelium of capillaries and arterioles. Dermatomyositis is also strongly associated with malignancy.

Clinical symptoms include:

- muscle tenderness or pain;
- muscle weakness;
- difficulties in swallowing;
- sometimes fever;
- general fatigue;
- weight loss.

In DM, a skin rash accompanies or precedes the onset of subacute muscle weakness. Pathognomonic findings of DM include Gottron's papules and heliotrope rash. In both PM and DM, extra-muscular manifestations can be seen, involving the heart, lungs, kidneys, and blood vessels, with Raynaud's phenomenon being a common feature.

Diagnosis consists of:

- laboratory testing: muscle enzymes – creatine kinase (CK), aldolase, lactate dehydrogenase (LDH), aspartate aminotransferase (AST) and alanine aminotransferase (ALT), C-reactive protein (CRP), antinuclear antibodies (ANA), myositis-specific antibodies, and myositis-associated antibodies;
- neurophysiological testing: ENG – normal, EMG – myopathic pattern with acute denervation discharges (fibrillations, positive sharp waves) and complex repetitive discharges;
- imaging studies (MRI, CT, ultrasonography) – to locate an area of muscle damage and also to diagnose malignancy.

Treatment

The first-line treatment is systemic glucocorticoids in gradually decreasing doses, with or without other immunosuppressants such as azathioprine or methotrexate. Second-choice options include cyclophosphamide, rituximab, mycophenolate mofetil, or calcineurin inhibitors. Intravenous immunoglobulin (IVIg) should be considered for resistant cases.

Inclusion body myositis (IBM) is an autoimmune myopathy whose pathogenesis is not completely understood, but is probably inflammatory–neurodegenerative in nature. Inclusion body myositis occurs mainly in patients above 50 years old and predominates in men.

Typically, IBM is characterized clinically by progressive asymmetric weakness, predominantly affecting the quadriceps and/or finger flexor muscles. Progressive dysphagia can occur, even as an isolated symptom. The progressive course of IBM slowly leads to severe disability, and respiratory complications can cause death.

Diagnosis consists of:

- clinical examination – distinctive clinical phenotype;
- laboratory testing: elevated creatine kinase (CK), antibodies to cytoplasmic 5'-nucleotidase (cN1A; NT5C1A);
- neurophysiological testing: ENG – slight polyneuropathy or mononeuropathy multiplex; EMG – acute denervation discharges (fibrillations, positive sharp waves) and myotonic discharges or complex repetitive discharges; EMG pattern is mixed, with myopathic together with neuropathic changes;
- muscle biopsy: so-called auto-aggressive inflammation; rimmed vacuoles; and protein aggregations (e.g., beta-amyloid, TDP-43) – “inclusion bodies”;
- muscle MRI: characteristic pattern with preferential, asymmetrical involvement of flexor digitorum profundus and quadriceps muscles.

Treatment

There is a lack of effective pharmacological treatment for inclusion body myositis (IBM). Intravenous immunoglobulin (IVIg) and other agents targeting the immune system are used, but there is no evidence that IVIg changes the disease course, and treatment with corticosteroids seems to be potentially harmful. Supportive and rehabilitative care remains the mainstay of management.

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12. Hydrocephalus and other high intracranial pressure syndromes

Krystian Obara

Intracranial hypertension

The cranial cavity has a fixed volume, which consists of:

- brain parenchyma (approx. 1,300 mL),
- cerebrospinal fluid (CSF) (approx. 65 mL),
- blood (approx. 110 mL).

According to the Monro–Kellie doctrine, if the above 3 components remain in balance, normal intracranial pressure (ICP) is maintained. If the volume of one of the above components increases, ICP rises. In adults, normal ICP values range between 10–15 mmHg (7.5–20 cm H₂O).

The causes of intracranial hypertension include:

- **Intracranial (primary):**
 - brain tumors: primary, metastatic;
 - infections: purulent, tuberculous meningitis, brain abscesses;
 - injuries: supra- and subdural hematomas, brain contusions;
 - non-traumatic intracerebral hemorrhage, subarachnoid hemorrhage (SAH);
 - ischemic stroke;
 - thrombosis of sinuses/cerebral veins;
 - communicating and non-communicating hydrocephalus;
 - spontaneous intracranial hypertension;
 - other: pneumothorax, cysts, congenital skull defects, such as craniostenosis.
- **Extracranial (secondary):**
 - airway obstruction;
 - hypoxia or hypercapnia (hypoventilation);
 - overpressure orifice;
 - situations involving the abdominal press: cough, pain, defecation;
 - head turns;
 - fever;
 - poisoning with drugs and other substances, e.g.: tetracycline, rofecoxib, sodium valproate, lead;
 - other: high altitude cerebral edema, liver failure, acute hyponatremia.

Clinical picture

- Headaches that worsen at night, after waking up, when coughing;
- nausea and vomiting after waking up;
- visual disturbances with swelling of the second nerve disc,
- VI nerve palsy;
- stiff neck;
- behavioral changes, disturbances of consciousness (from excessive drowsiness to coma);
- seizures.

Cushing's triad is a set of symptoms indicating a significant increase in ICP, which includes:

- bradycardia;
- increase in blood pressure;
- breathing disorders.

A heterogeneous increase in ICP leads to the creation of a pressure gradient in the central nervous system (CNS), which in turn leads to the movement of the brain between anatomical compartments (wedging). We distinguish the following types of wedging:

- Wedging of the cingulate gyrus under the falx cerebri, which occurs without characteristic clinical symptoms.
- Wedging of the hippocampal uncus into the tentorium notch of the cerebellum with the following symptoms:
 - dilatation of the ipsilateral pupil, abolition of its reaction to light;
 - contralateral paresis;
 - dilation of the contralateral pupil with divergent positioning of the eyeballs;
 - quadriparesis with bilateral pyramidal symptoms;
 - progressive disturbances of consciousness and breathing with pathological reflex phenomena – flexion or extension of limbs;
 - decerebrate posturing.
- Wedging in infratentorial lesions that move the cerebellar tonsils into the foramen magnum, manifesting as:
 - increasing symptoms of brainstem damage with impaired consciousness, quadriplegia, breathing, and circulatory disorders.

Diagnostic tests

- Physical examination, including the assessment of:
 - state of consciousness;
 - breath;
 - heart rate;

- blood pressure;
- fundus of the eye;
- function of oculomotor nerves (assessment of pupil width);
- motor functions (paresis, decorticate posturing, decerebrate posturing);
- assessment of the clinical condition based on the Glasgow Coma Scale.
- Neuroimaging tests (CT, MRI of the head with contrast, angio-CT, angio-MRI).
- Lumbar puncture (only in selected situations, after performing diagnostic imaging and excluding the risk of impaction), e.g., in spontaneous intracranial hypertension, SAH, normotensive hydrocephalus.
- Electroencephalography (EEG) in the differential diagnosis of consciousness disorders.
- Laboratory tests, such as:
 - blood count;
 - CRP;
 - glycemia;
 - electrolyte concentration;
 - kidney and liver parameters;
 - ammonia concentration in blood;
 - blood gas analysis.
- Invasive ICP monitoring:
 - intraventricular, interstitial, subarachnoid, epidural probes.



Fig. 12.1. Head CT: Diffuse bilateral blurring of the cortical–subcortical junction, with edema in the right hemisphere in a patient with sudden cardiac arrest

Treatment

- Raising the head of the bed to 30–45 degrees; keeping the patient’s head in a straight line.
- Avoiding hypotonic solutions (hypotonic salt, 5% glucose solution).

- Antipyretic, anti-convulsive, analgesic treatment; sedative treatment in case of an agitated patient.
- Avoiding activities involving the abdominal press.
- Avoiding both low and high blood pressure values to maintain proper cerebral perfusion.
- Insertion of a central line for the administration of hyperosmolar drugs.
- Osmotic and dehydration therapy:
 - 20% mannitol 0.25–0.5 g/kg body weight IV every 4–6 h;
 - hypertonic 23% saline solution in a dose of 30 mL, administered into the central line in 10–20 min, maintaining a dose of 1 mL/kg body weight/h of 3% saline until the serum concentration reaches 150–155 mmol/L – risk of pulmonary edema;
 - furosemide 40–60 mg/2 h IV in 3–4 doses, often administered after a mannitol infusion.
- Glucocorticosteroids (in vasogenic edema), e.g., dexamethasone IV 16–32 mg/24 h in 4 divided doses, methylprednisolone IV 1 g/24 h for 3–5 days, with subsequent gradual dose reduction.
- Short episodes of controlled hyperventilation are recommended in patients with a sudden increase in ICP.
- Consider a neurosurgical consultation to qualify for decompressive treatment or the installation of ventricular drainage.

Summary

Increased ICP remains a medical and surgical emergency that requires urgent diagnosis and intervention to avoid irreversible CNS damage.

Cerebral edema

Cerebral edema is an increase in the volume of brain tissues caused by the accumulation of water and elevated sodium concentration, in contrast to hydrocephalus, in which excess fluid accumulates in the ventricular system. Brain edema, by producing a mass effect, can lead to catastrophic consequences of intussusception with pressure on the brainstem centers responsible for circulation and respiration.

Cerebral edema is divided into:

- **Extracellular:**
 - Vasogenic:

It occurs because of damage to the blood–brain barrier and increased vascular permeability, which leads to the accumulation of fluid with a high protein content in the extracellular white matter of the brain.

Causes include: primary and metastatic brain tumors, brain abscess, cerebral perfusion syndrome following reperfusion procedures, high-altitude exposure, posterior reversible encephalopathy syndrome (PRES) during hypertensive encephalopathy, eclampsia, use of immunosuppressive drugs, and poisoning.

- **Parenchymal:**

It occurs because of CSF filtration from the ventricular lumen into the periventricular white matter. The cause is, for example, hydrocephalus.

- **Intracellular:**

- **Cytotoxic:**

It occurs because of hypoxic or toxic damage to nerve, glial, and endothelial cells, with a subsequent increase in their volume. Causes include ischemic stroke and hypoxic–ischemic encephalopathy.

- **Osmotic:**

Formed because of disturbed osmotic balance within the CNS, caused by conditions such as acute hyponatremia, ketoacidosis, or dialysis disequilibrium syndrome (DDS).

- **Mixed (vasogenic and cytotoxic):**

Causes include intracerebral hemorrhage, subarachnoid hemorrhage (SAH), dural venous sinus thrombosis, purulent meningitis, encephalitis, traumatic brain injury, and hepatic encephalopathy.

In most cases, individual types of edema overlap, although the sequence of events leading to edema varies depending on the primary cause.

Clinical picture

- Clinical symptoms are a consequence of increased ICP (see the section above).
- Slight swelling in non-eloquent areas may occur without clinical manifestations (e.g., in the frontal lobes).
- The time of progression of clinical symptoms depends on the primary cause of CNS damage, e.g., the course in malignant cerebral edema due to middle cerebral artery occlusion is much more rapid compared to the subacute progression of edema in CNS neoplastic processes.
- Symptoms characteristic of causes of cerebral edema:
 - in PRES, the dominant symptoms are headaches, disturbances of consciousness, epileptic seizures, characteristic visual disturbances, including cortical blindness due to the predilection of lesions to the posterior areas of the CNS;
 - pulsating headache is a disturbing symptom after reperfusion procedures on the carotid arteries – it indicates cerebral edema due to impaired autoregulation of intracranial vessels;

- in idiopathic intracranial hypertension (IIH) predominates: headaches, visual disturbances (in terms of sharpness, the vision behind the fog, up to blindness), which may occur paroxysmally, mainly during coughing and physical exertion; they may be accompanied by tinnitus and damage to the VI nerve;
- cognitive dysfunction, subacute behavior may suggest a growth lesion in the frontal lobes;
- disturbances of consciousness, headaches, and fever suggest CNS infection.

In every patient with a persistent headache that does not respond to treatment and is accompanied by visual disturbances, a fundus examination should be performed to look for swelling of the second nerve disc.

Diagnostic tests

The same diagnostic scheme applies as in cases of increased ICP, with particular attention paid to:

- state of consciousness;
- nerve II function;
- oculomotor nerves;
- neuroimaging tests (CT, MRI of the brain, possibly with an angio option);
- in selected cases: lumbar puncture, EEG, blood pressure measurement, laboratory tests, including toxicological ones (including ammonia concentration).

Characteristic abnormalities

Characteristic abnormalities in diagnostic tests in selected diseases associated with cerebral edema:

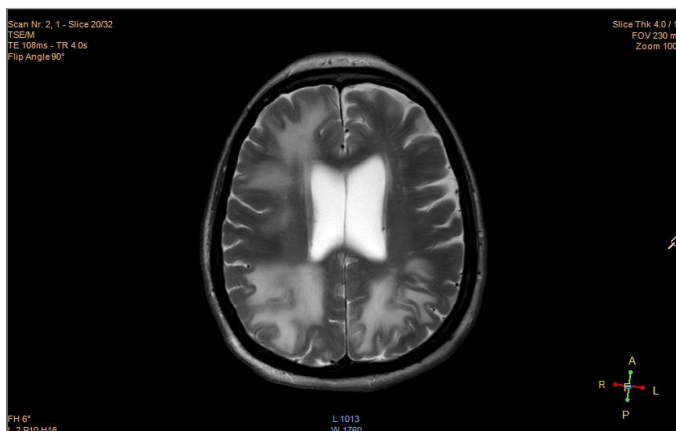


Fig. 12.2. Brain MRI: bilateral subcortical extensive hyperintense lesions in the white matter, sparing the gray matter, in a patient with PRES

- cytotoxic edema in acute ischemic stroke is visible a few minutes after the onset in the diffusion-weighted imaging (DWI) sequence as an enhanced signal with a simultaneously reduced signal in the apparent diffusion coefficient (ADC) sequence;
- extensive mass effect with coexisting ischemic and hemorrhagic foci may suggest acute cerebrovascular thrombosis;
- digital cerebral edema (along the white matter fibers), lesions extending continuously to the other hemisphere of the brain, suggesting a CNS tumor process;
- lesions in the medial part of the temporal lobes and/or at the base of the frontal lobes suggest herpes encephalitis;
- changes in the posterior areas of the CNS with scattered microhemorrhages with characteristic sparing of the cerebral cortex suggest PRES.

Treatment (see: ICP treatment)

Osmotic therapy:

- hypertonic saline is preferred in patients with cerebral edema resulting from intracerebral hemorrhage, including SAH;
- in traumatic brain injury, hypertonic saline boluses are preferred, anti-edematous treatment is not recommended in pre-hospital conditions;
- in ischemic stroke accompanied by edema, hypertonic saline solution should be considered if the response to mannitol is insufficient; there are no indications for preventive anti-edema treatment for stroke.

There is no basis for the use of glucocorticoids in patients with ischemic/hemorrhagic stroke accompanied by cerebral edema.

- In patients using mannitol/hypertonic saline, renal parameters should be regularly monitored (risk of acute kidney damage);
- Sodium concentration >155–160 mEq/L and chloride concentration >110–115 mEq/L should not be exceeded during therapy with hypertonic saline (regular assessment of sodium and chloride concentration in serum is recommended) – risk of acute kidney damage.

Cerebral edema in purulent/tuberculous meningitis:

- dexamethasone 10 mg IV every 6 h for 4 days; alternatively, 0.15 mg/kg body weight IV every 6 h for 4 days in patients with low body weight or with a high risk of side effects of glucocorticoids;
- it is recommended to administer dexamethasone before or with the first dose of antibiotic;
- in the case of tuberculous meningitis, glucocorticoids are used for 2 or more weeks;
- no evidence of the effectiveness of other anti-edematous drugs.
 - If possible, in brain tumors accompanied by edema, low doses of dexamethasone (4 mg) should be used to avoid side effects; in emergencies, higher doses of dexamethasone may be used (16 mg IV or more), sometimes together with osmotherapy (mannitol) with a slow reduction of the glucocorticoid dose.

Summary

Conditions leading to cerebral edema are usually a serious threat to health and life, and the coexistence of increased ICP significantly worsens the prognosis. This justifies the initiation of appropriate anti-edema treatment even before the correct diagnosis is made.

Hydrocephalus

Hydrocephalus is a condition characterized by dilation of the ventricular system due to an increased volume of cerebrospinal fluid. It can occur at any age but is most common in infants and people >60 years of age.

Hydrocephalus classification

Due to the place of blockage of CSF flow:

- **Non-communicating hydrocephalus** – the presence of an obstruction inside the ventricular system:
 - congenital defects, e.g., narrowing of the aqueduct of Sylvius;
 - consequences of intracerebral hemorrhage, ischemic stroke (mainly in the posterior cranial fossa);
 - brain tumors (mainly around the 3rd and 4th ventricles, the aqueduct of Sylvius);
 - intracranial cysts.
- **Communicating hydrocephalus** – obstruction outside the ventricular system:
 - SAH;
 - meningitis;
 - congenital absence of arachnoid granules;
 - increased protein levels in the CSF (>500 mg/dL), e.g., in chronic inflammatory polyradiculoneuropathy, spinal tumors.

Due to CSF pressure:

- **Hypertensive hydrocephalus:**
 - overproduction of CSF – choroid plexus papilloma;
 - CSF malabsorption disorders – consequences of SAH, meningitis (e.g., in tuberculosis, syphilis), meningeal carcinomatosis;
 - venous circulation disorders – a consequence of thrombosis of the cerebral venous sinuses.
- **Normotensive hydrocephalus.**

Due to etiology

- **Congenital hydrocephalus:**
 - Arnold–Chiari malformation;
 - Dandy–Walker syndrome;
 - myelomeningocele;
 - intrauterine infections;
 - intracranial bleeding because of perinatal trauma.
- **Acquired hydrocephalus:**
 - meningitis;
 - brain tumors;
 - intracranial injuries;
 - SAH.
- **Hydrocephalus from atrophy (ex vacuo)**, e.g., in Alzheimer’s disease.



Fig. 12.3. Brain MRI: Congenital hydrocephalus in a patient with aqueductal stenosis and Dandy–Walker malformation

Clinical picture

A dramatic course is observed in non-communicating hydrocephalus, in which a significant increase in ICP in a short time leads to a rapidly increasing neurological deficit, including disturbances of consciousness, locked-in syndrome.

Clinical symptoms in infants (before the skull sutures heal):

- widening the circumference of the head and fontanelles;
- widening of the veins on the surface of the skull;
- “the sound of a broken pot” when tapping the head;
- significant irritability of the child;
- disturbances of consciousness;
- seizures;
- symptoms of damage to the corticospinal tract;
- eyeballs pointing downwards (sunset symptom);

- apneas;
- bradycardia;
- increase in blood pressure.

Clinical symptoms in older children and adults:

- severe headache,
- nausea, vomiting,
- disturbances of consciousness,
- cognitive disorders,
- deterioration of motor coordination,
- deterioration of vision with swelling of the optic nerve discs,
- damage to the oculomotor nerves,
- Cushing’s triad as an expression of significantly increased ICP.

In normotensive hydrocephalus, there are particularly characteristic symptoms, the so-called Hakim’s triad:

- a) cognitive function disorders (including attention and executive functions),
- b) abnormal gait – “magnetic”, like that observed in extrapyramidal syndromes,
- c) urinary incontinence.

Diagnostic tests

- Transfontanellar ultrasound is helpful in infants in diagnosing and monitoring hydrocephalus.
- Neuroimaging tests – CT scan of the head, optimally MRI of the head – a test with greater sensitivity in diagnosing malformations in the posterior cranial fossa and small hyperplastic lesions; MRI also has greater sensitivity in assessing CSF leakage outside the ventricular system – hyperintense periventricular changes on T2-weighted and FLAIR (fluid-attenuated inversion recovery) images.
- Lumbar puncture (only in the case of communicating hydrocephalus) to assess CSF pressure, possibly diagnosis of other causes of hydrocephalus: inflammatory processes, SAH.
- Infusion test to assess CSF hydrodynamics.
- Fisher’s test – discharging 30–50 mL of fluid and then assessing any improvement in the neurological condition; a valuable test in predicting the appropriateness of using drainage of the ventricular system.

Treatment

- Symptomatic treatment as in increased ICP:
 - lifting the torso;
 - limiting fluid intake;

- anti-swelling and dehydration treatment;
- glucocorticosteroids in the case of brain tumors with vasogenic edema.
- Surgical treatment of lesions responsible for hydrocephalus:
 - a brain tumor;
 - colloid cyst.
- Decompressive treatment:
 - external drainage (temporary drainage of CSF from the lateral ventricles of the brain to the external system, e.g., Rickham's reservoir);
 - ventriculoperitoneal shunt, ventriculoatrial shunt;
 - ventriculostomy of the third ventricle – creating a connection between the third ventricle and the subarachnoid space.

Summary

The prognosis of hydrocephalus depends on the underlying cause, the severity of symptoms at the time of diagnosis, and the type of treatment used, which is sometimes associated with complications (e.g., infection, drainage valve damage).

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13. Paraneoplastic neurological syndromes

Maria Ejma

A common complication of internal organ cancers is damage to the nervous system. It usually occurs in an advanced stage of the disease and results from metastatic processes, direct compression, or infiltrative spread of cancer cells into neural structures. Damage to the nervous system may also be caused by:

- iatrogenic (related to surgery, chemotherapy, radiation);
- inflammatory (coexistence of opportunistic infections);
- vascular (stroke due to coagulation disorders);
- metabolic;
- deficiency (cachexia);
- hormonal (endocrine tumors);
- autoimmune (paraneoplastic syndromes).

Paraneoplastic neurological syndrome (PNS) is a long-term effect of the presence of a malignant tumor of internal organs, manifesting as damage to structures distant from the primary and metastatic tumor sites. The pathogenesis of PNS has not yet been fully explained, but immunological reactions initiated by the presence of the tumor probably play a fundamental role in their development. These syndromes constitute a diverse group of neurodegenerative diseases that may involve:

- central and/or peripheral nervous system;
- autonomic system;
- retina;
- skeletal muscles.

Paraneoplastic neurological syndromes are divided into 2 main categories – classic syndromes, which are usually associated with underlying oncological disease, and non-classic syndromes, which often occur without a malignant process.

Classic PNS:

- paraneoplastic encephalomyelitis (PEM);
- limbic encephalitis (LE);
- paraneoplastic cerebellar degeneration (PCD);
- paraneoplastic opsoclonus–myoclonus (POM);
- sensory neuropathy (SN);
- Lambert–Eaton myasthenic syndrome (LEMS);
- paraneoplastic chronic intestinal pseudo-obstruction (CIPO);
- dermatomyositis.

Paraneoplastic neurological syndromes are rare. They most often occur in:

- tumors expressing neuroendocrine proteins (small cell lung carcinoma, neuroblastoma);
- tumors of immunomodulatory organs (thymoma);
- cancerous growth of cells producing immunoglobulins (B-cell lymphomas, monoclonal gammopathies).

Paraneoplastic neurological syndromes are usually subacute and progressive, often leading to profound disability, and in approximately half of the cases – to death. Rarely, their course is mild, chronic, or with relapses, and in exceptional cases, it is rapidly progressive. Diagnosing the underlying cancer may be difficult because the PNS slows down and alleviates its course.

In some patients with PNS, onconeural antibodies are present in the blood serum and sometimes in the cerebrospinal fluid. These antibodies target antigens that are normally components of the nervous system and are aberrantly expressed by cancer cells in the disease process. For unknown reasons, some onconeural antigens may be recognized by the immune system as foreign and then become the target of the immune response.

In clinical practice, onconeural antibodies act as diagnostic markers of PNS, facilitating early detection of cancer. These antibodies do not directly identify a given cancer, although some are often associated with specific tumors and specific PNS types. For example, **anti-Hu** antibodies are often found in patients with SCLC, and **anti-Yo** antibodies in patients with breast and gynecologic cancers (Table 13.1).

The presence of onconeural antibodies is an indication for full oncological diagnostics. If no cancer is found, oncological diagnostics should be repeated every 3–6 months for at least 4 years. In some cases of PNS, onconeural antibodies may be absent, which does not exclude the coexistence of an underlying proliferative process.

Table 13. 1. Association of onconeural antibodies with paraneoplastic neurological syndromes and with the type of cancer

Onconeural antibodies	Paraneoplastic neurological syndromes	Cancer
Anty-Hu	– paraneoplastic encephalomyelitis, – limbic encephalitis, – sensory neuropathy, – paraneoplastic cerebellar degeneration, – autonomic neuropathy	– small cell lung carcinoma, – neuroblastoma, – prostate cancer
Anty-Yo	– paraneoplastic cerebellar degeneration,	– ovarian cancer, – breast cancer
Anty-Ri	– paraneoplastic opsoclonus-myoclonus, encephalitis (brainstem), – paraneoplastic cerebellar degeneration	– small cell lung carcinoma, – breast cancer, – tumors of the reproductive system

Currently, there are 3 types of autoantibodies:

- autoantibodies directed against intracellular, cytoplasmic, or nuclear epitopes (e.g., anti-Hu, anti-Yo, anti-Ri);
- autoantibodies directed against intracellular epitopes at synapses (e.g., against glutamic acid decarboxylase, glycine receptor, amphiphysin);
- autoantibodies directed against extracellular, membrane-bound epitopes (anti-VGCC, anti-NMDAR).

Paraneoplastic neurological syndrome diagnostics include the following tests:

- immunological (detection of onconeural antibodies);
- neurophysiological (neurography, EMG, assessment of the neuromuscular junction);
- histo-pathological (e.g., in dermatomyositis or polymyositis);
- radiological (e.g., MRI in limbic encephalitis);
- oncological (looking for cancer of internal organs).

An essential element of PNS therapy is quick and effective oncological treatment, which creates the best chance to improve or at least stabilize the patient's neurological condition and prevent further progression of neurological symptoms. Additionally, various forms of immunotherapy are used, which is supported by the involvement of immunological disorders in the PNS pathomechanism. Attempts have been made to use intravenous immunoglobulins, steroids, rituximab, cyclophosphamide, or plasmapheresis. Syndromes associated with antibodies to cell membrane antigens often respond well to such therapies. However, in PNS involving antibodies against intracellular antigens, when the disease mechanisms are dominated by the cellular response, treatment is usually ineffective.

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14. Back pain

Monika Służewska-Niedźwiedź

Back pain is defined as discomfort, a feeling of muscle tension, or stiffness in the back. It may affect the cervical (neck pain, ~15%), thoracic, or lumbar part of the spine (low back pain, ~80%) and may radiate along one or both upper limbs, the trunk, or along one or both lower limbs, respectively. It is a common cause of neurological consultation. Pain may arise from the nervous system or non-neural structures, which should be determined through neurological examination and further diagnostic tests.

Depending on its duration, back pain is divided into:

- acute (<4 weeks);
- subacute (from 4 weeks to 3 months);
- chronic (>3 months).

A relapse is defined as a new episode of pain after a period of remission lasting at least 6 months.

Non-specific pain occurs in 90% of cases. Its cause cannot be detected by imaging tests, although they may reveal degenerative changes typical of the natural aging process of the spine, for example:

- narrowing of the intervertebral space;
- dehydration of the intervertebral disc;
- bulging of the intervertebral disc;
- spondylolisthesis;
- osteophytes.

Specific pain is present in 10% of cases and may come from (Table 14.1):

- intervertebral discs – discogenic pain:
 - rupture and tear of the annulus fibrosus;
 - degeneration of the intervertebral disc;
- intervertebral and sacroiliac joints:
 - degenerative changes,
 - arthritis,
 - excessive mobility,
 - joint overload due to gait disorders,
 - asymmetry in the strength of the back muscles and pelvic girdle;
- compression of spinal nerves and their roots (Fig. 14.1):
 - hernia of the nucleus pulposus,
 - spinal stenosis;
 - the muscles and fascia of the back;
 - the ligamentous-fascial-capsular apparatus of the pelvis.

Table 14.1. The most important and frequent causes of specific back pain

The most important causes of specific spine pain
A. Serious (<1%) – urgent diagnostics and treatment required – cancer – most often metastases from breast, prostate or lung cancer; multiple myeloma, – spinal epidural abscess – risk factors include generalized or local (tissues near the spine) infection, recent spinal canal puncture, catheter in the epidural space, intravenous drug use, immunodeficiency, – osteomyelitis – risk factors include bacteremia, immunodeficiency, intravenous drug use
B. Other – compression of the roots and/or spinal nerves (most frequent sites: L5/S1, L4/L5, less often L3/L4 and L2/L3; C5/C6 and C6/C7) by prolapse of the intervertebral disc or degenerative changes in the intervertebral joints and vertebrae, – narrowing (stenosis) of the spinal canal caused by the degenerative changes in the intervertebral joints, ligaments and vertebrae or deformations (spondylolisthesis, scoliosis, hyperkyphosis) of the spine – vertebral compression fracture, usually due to osteoporosis (4% of spine pain cases), – spondyloarthropathies (e.g., ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis), – non-spinal causes: a) degeneration, overload or inflammation of the sacroiliac joints, piriformis muscle syndrome. b) shingles within the trunk; back pain as manifestation of pancreatitis, urolithiasis, pyelonephritis, aortic aneurysm; depression with somatization.

Clinical features of:

- **Non-specific pain:**
 - a) limited to the midline area in the neck or back, axial in nature;
 - b) no projected or radicular component (radiation to any other parts of the body);
 - c) usually disappears within a few days (most patients do not consult a doctor);
 - d) may be recurrent (relapses);
 - e) in 10–15% of cases, acute pain turns into chronic pain; risk factors include:
 - psychosocial problems (e.g., depressed mood/depression, problems with permanent employment/job);
 - previous history of back pain;
 - hard physical work.
- **Specific pain** may be exclusively axial in nature or may be accompanied by:
 - a) referred pain, especially radicular pain;
 - b) neurological deficits: sensory disorders, paralysis of the upper and/or lower limbs, dysfunction of the urethral and anal sphincters;
 - c) problems with walking (neurogenic claudication);
 - d) symptoms of spinal cord affection (myelopathy);
 - e) general symptoms of infection or systemic disease.

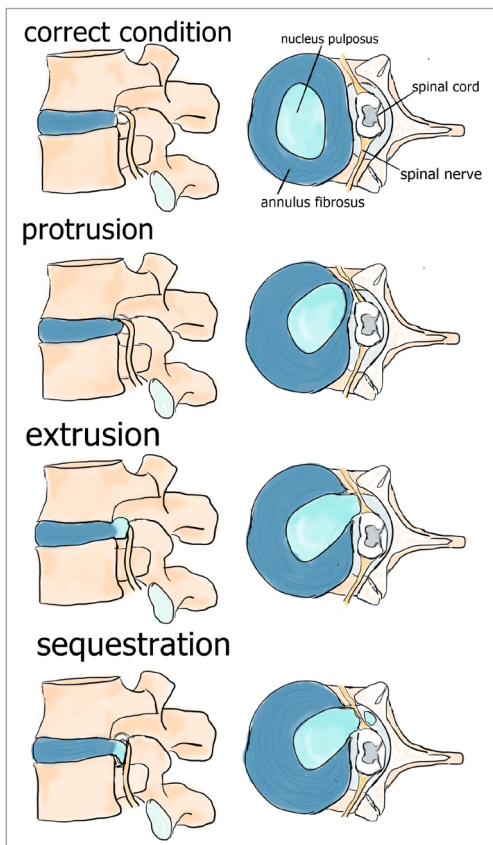


Fig. 14.1. Mechanism of root compression by hernia of the nucleus pulposus

Degenerative spine disease – pain is triggered or worsened by physical activity and is reduced or relieved at rest (no load on the spine).

Diagnostics

- **History** – onset, character, distribution of pain, associated motor symptoms, bladder or bowel control, predisposing factors.
- **Neurological examination** – signs of neurological deficit help to attribute the source of pain to the spinal cord, neural roots, or peripheral nerves:
 - motor signs (atrophy of muscles, fasciculations, weakness);
 - increased tendon reflexes indicate affection of the spinal cord, absent or decreased reflexes – affection of particular neural roots (e.g., C5 – biceps reflex, C6/C7 – triceps reflex, L3/L4 – knee reflex, S1 – Achilles reflex);
 - sensory signs (distribution of sensory loss or hyperesthesia within dermatomes);
 - radicular signs – exacerbation of pain by stretching affected roots/nerves – Spurling sign, Lasègue sign.

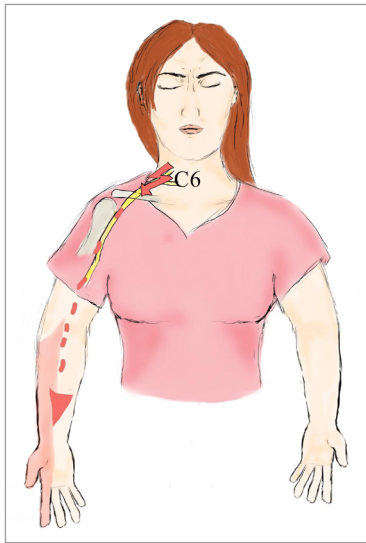


Fig. 14.2. Paralytic brachialgia

Weakening the strength and/or precision of hand movements, e.g. clumsy hand writing, difficulty in buttoning, or objects falling out of the hand

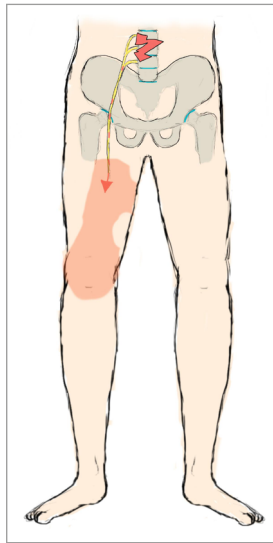


Fig. 14.3. Paralytic femoral pain

Inability to straighten the knee joint and difficulty in getting up

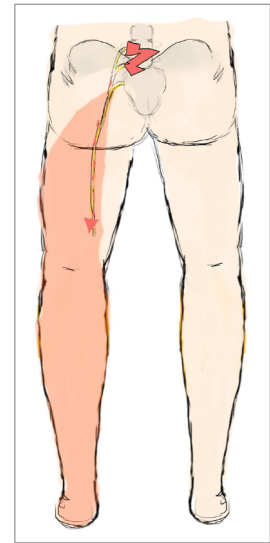


Fig. 14.4. Paralytic sciatica

Dropping of the foot while walking, tripping over obstacles on flat ground, inability to keep the body weight on the heel and walk on the heels



Fig. 14.5. Cauda equina syndrome

Muscle weakness in the lower limbs is usually more generalized, may lead to loss of the ability to walk and stand. Sensory disorders may affect not only the lower limbs, but also the anus and perineum area. The external sphincters of the urinary bladder and anus may become paralyzed

Table 14.2. Clinical features depending on specific back pain causes

Reason/source of pain	Clinical features
Intervertebral disc	– pain usually axial, along the midline, without radiation
Intervertebral joint	– pain usually located asymmetrically (lateral to the long axis of the spine), from the joints of the cervical spine – around the scapula or shoulder, from the joints of the lumbar spine – above the iliac crest or in the buttock
Radiculopathy	– referred pain may radiate along the dermatomes from the spine or only within the limb – pain often decreases during movement and worsens at rest in a certain position) – may be accompanied by: sensory impairment – hypoesthesia (numbness), paresthesias (tingling, burning, “pins and needles”) or/and weakness of innervated muscles and diminished tendon reflexes
Inflammation of the sacroiliac joint	– pain usually occurs in the buttock area, often axially in the groin and even in the lower limb – in systemic diseases usually chronic with exacerbations and remissions, otherwise often subsides spontaneously or after treatment
Myofascial pain	– pain may be local, almost point-like it may radiate, but not along the dermatomes; duration may differ from minutes to hours or many days
Osteoporotic fracture	– often initially painless; the sharp, axial pain usually appears after overloading the spine (tilting or turning the torso) or after a minor injury (falling from the height of one’s own body) – if nerve compression occurs, it may radiate alongside – pain may persist until the fracture is healed (up to several weeks)
Cancer	– pain is usually axial, constant, aggravated by movement, but does not subside with rest; often occurs at night – long-lasting, not responding to analgesics – pain and neurological deficits may develop gradually or rapidly as a result of a sudden pathological fracture of a vertebra
Spondylodiscitis	– the pain is constant and does not improve with rest. Initially, it is accompanied by general symptoms of inflammation (fever) – the pain is axial (unless there is compression of the spinal nerve roots or the spinal cord by an inflammatory tissue)

• **Nerve conduction study (NCS) and electromyography (EMG):**

- localization of affected roots/nerves;
- determination of the denervated muscles.

Table 14.3. Specific back pain syndromes with neurological deficits

Syndrome	Neurological deficits
Paralytic brachialgia	– diminished strength and/or precision of hand movements, e.g., clumsy handwriting, difficulty in buttoning, or objects falling out of the hand
Paralytic femoral pain	– inability to straighten the knee joint and difficulty in getting up
Paralytic sciatica	– may affect the extensors of the foot (dropping of the foot while walking, tripping over obstacles on flat ground, inability to stand and walk on the heels) or flexors of the foot (the patient cannot push off from the toes when walking, stand and/or walk on the toes)
Cauda equina syndrome (compression of the roots of many spinal nerves in the lumbar spinal canal)	– generalized muscle weakness in the lower limbs, impaired gait and posture – sensory impairment within lower limbs, but also the anus and perineum area – dysfunction of sphincters (urine and stool incontinence)
Cervical spinal stenosis	– may lead to weakness of the upper and lower limbs (tetraparesis) – gradual impairment of precise hand movements, followed by loss of strength and efficiency of the upper and lower limbs – paresis in the upper limbs is usually flaccid (low muscle tone, weak reflexes), in the lower limbs – spastic (increased muscle tone, exaggerated reflexes), when compression above C4 level – spastic paresis of four limbs
Lumbar spinal stenosis	– neurogenic claudication (problems with walking caused by weakness of the lower limbs, which increases with the distance) – sensory disturbances (paresthesias in the lower limbs) and a feeling of discomfort and heaviness in the lower back, which increase with a distance of walking but also while standing in a neutral position or lying on the back – symptoms may develop slowly and stay unnoticed at first

- **Imaging (X-ray, MRI, or CT) of the spine:**

- X-ray often reveals fractures or degenerative changes; it has low sensitivity in the diagnosis of tumors and infections;
- CT scan reveals vertebral/intervertebral disc abnormalities and fractures;
- MRI provides an exclusive image of the spinal cord (including the conus medullaris), spinal nerves and their roots, and shows intervertebral discs and joints more precisely; it is recommended if neoplasm or inflammation is suspected;
- laboratory diagnostic tests (e.g., inflammatory or neoplastic markers).

Table 14.4. Red flags indicating serious reasons of specific back pain

Cause	Red flags
Compression of nervous structures	– pain radiating along the dermatomes of the lower limb (sciatic or femoral) or upper limb (brachial) – sensory impairment, muscle weakness – specific neurological deficits (Table 13.2)
Vertebral fracture	– older age (age-related osteoporosis) – chronic treatment with corticosteroids (steroid-induced osteoporosis) – fall or injury (in elderly people can be a minor one)
Cancer	– age >50 or <20 years – history of cancer – night pain – pain that intensifies when standing upright and does not subside when lying on the back – weight loss – general malaise
Spondylodiscitis	– fever – local infection (e.g., palatine tonsil abscess, otitis media, odontogenic abscesses) – taking drugs intravenously – immunodeficiency (immunosuppressive treatment, HIV infection)

Treatment

If “red flags” are excluded – recognize non-specific back pain and begin symptomatic treatment (in charge of primary care physician). Signs of neurological deficit and other “red flags” – consultation with a neurologist or other relevant specialist is necessary.

Educating the patient

Reassure patients by informing them that most cases of back pain are not caused by any serious disease. Mild degenerative changes of the spine are due to the natural aging process, and there is no risk of permanent disability, even though back pain may recur.

Physical activity

Limited physical activity and bed rest should be recommended during the acute pain phase, for as short a time as possible. As soon as the pain is relieved, physical activity (including professional activity) should be restored, and regular physical exercise should be advised, according to the instructions of physiotherapists (including e.g. strengthening, flexion, extension, stretching of the spine and paraspinal muscles). It is important to maintain the correct position of the spine when lifting, bending, or sitting. Appropriate physical activity reduces the risk of chronic pain, as well as the risk of gait disorders and falls, especially in elderly persons.

Other physiotherapy methods

Warm compresses and relaxing massages may have a beneficial effect; manual therapy can be used with caution in some cases. No clear benefits have been demonstrated from the use of cold compresses, traction, corsets, or yoga.

Pharmacological treatment

In case of acute pain, use drugs for a short period of time (2–4 weeks):

- a) analgesics – start with non-steroidal anti-inflammatory drugs; in case of contraindications – paracetamol. Tramadol and other opioids can be used in patients with severe pain (or when other drugs are ineffective or contraindicated);
- b) myorelaxants (e.g., methocarbamol, baclofen, tizanidine).

If therapy is ineffective after 4 weeks – re-assess for “red flags” and consider further diagnostics.

If radicular pain is accompanied by sudden onset of neurological deficits – urgent consultation with a neurosurgeon is necessary to consider surgical decompression.

Summary

Back pain is a very common reason for patients to seek medical attention. It is important to distinguish between non-specific and specific back pain and to determine the presence or absence of neurological deficit. Based on the medical history (including “red flags”) and neurological examination, the physician may start symptomatic treatment or refer the patient to a specialist for further diagnostics and causative treatment.

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15. Neurological disorders in the course of diseases outside the nervous system

Maria Ejma

Damage to the central and/or peripheral nervous system is a common complication of internal diseases. The basis of neurological lesions are systemic metabolic disorders that lead to deficiencies in oxygen and energy substrates, as well as disturbances in water-electrolyte and acid-base balance.

Endogenous encephalopathy

Endogenous encephalopathy is a form of diffuse brain damage. In the acute form, it mainly presents with disturbances of consciousness. In the chronic form, intellectual degradation and focal neurological deficit gradually increase. The neuropathological picture of the brain is not characteristic, showing loss of nerve cells and secondary damage to glial cells, nerve fibers, and neurons. Some types of endogenous encephalopathies include:

- encephalopathy due to hypoxia or ischemia;
- hypertensive encephalopathy;
- hypercapnic encephalopathy;
- diabetic encephalopathy;
- hepatic encephalopathy;
- encephalopathy in renal failure;
- encephalopathy in electrolyte disorders;
- encephalopathies of deficiency syndromes.

Encephalopathy due to hypoxia or ischemia

Postanoxic encephalopathy is most often associated with cardiac arrest and successful resuscitation. Hypoxic-ischemic encephalopathy is one of the main forms of neonatal brain injury and can lead to neonatal disability or even death.

Both forms of encephalopathy result from an insufficient supply of oxygen to the brain and the inhibition of aerobic metabolic processes. In severe hypoxic encephalopathy, when brain death has not occurred, respiratory function and heart rate often stabilize.

The patient then remains in a deep coma, and decerebrate posturing, generalized convulsions, and isolated or grouped muscle twitches may occur. In cases of diffuse cortical damage with sparing of brainstem structures, the patient remains in the so-called persistent vegetative state. In cases of minor damage, after regaining consciousness, the following may occur:

- confusion;
- visual agnosia;
- extrapyramidal stiffness;
- myoclonus;
- choreoathetosis;
- Korsakoff's amnesic syndrome.

Sometimes, the so-called delayed post-hypoxic encephalopathy is observed when, after initial improvement, neurological symptoms recur (usually after 1–4 weeks). These symptoms may gradually worsen (apathy, disorientation, anxiety, gait disturbances, generalized stiffness, and coma) and, after about 1–2 weeks, may even lead to death. In these cases, neuropathological tests show demyelinating changes in the CNS.

Hypertensive encephalopathy

Hypertensive encephalopathy is a sudden condition that develops during a hypertensive crisis. When the mean arterial pressure increases above 180 mmHg, the autoregulation of cerebral blood flow is disturbed. As a result, the following occurs:

- dilatation of cerebral vessels;
- increasing cerebral blood flow;
- disruption of endothelial function and the blood–brain barrier;
- brain swelling.

The clinical picture includes:

- severe headache;
- nausea;
- vomiting;
- disturbances of consciousness;
- seizures;
- visual impairment;
- swelling of the optic nerve disc;
- symptoms of central neurological deficit.

Lowering blood pressure, which should be implemented as soon as possible, leads to the disappearance of disease symptoms. Hypertensive encephalopathy is associated with posterior reversible encephalopathy syndrome (PRES), in which the lesions mainly affect the structures of the posterior cranial fossa. In neuroimaging studies, PRES is usually characterized by bilateral reversible vasogenic edema of subcortical white matter in the parieto-occipital regions.

Hypercapnic encephalopathy

Hypercapnic encephalopathy occurs in the late stages of chronic respiratory failure. Symptoms of the disease result from excess CO_2 in the blood, hypoxia, and central nervous system acidosis, which result in increased intracranial pressure, cerebral edema, and impaired glucose utilization. The clinical picture is dominated by:

- persistent headaches;
- apathy;
- slowdown;
- memory and sleep disorders;
- swelling of the optic nerve discs;
- discreet symptoms of neurological deficit;
- fluttering hand tremors (asterixis);
- epileptic seizures;
- disturbances of consciousness.

In severe cases, delirium and coma may occur. The EEG recording is usually abnormal, with pathological theta-delta activity.

Diabetic encephalopathy

The causes of neurological complications in diabetes are:

- chronic disorders of carbohydrate, lipid, and amino acid metabolism;
- changes in small and large blood vessels (diabetic micro- and macroangiopathy);
- disturbances in the permeability of the blood–brain barrier;
- reducing effective neurogenesis;
- disturbances of intracellular free Ca^{2+} homeostasis;
- microglia activation;
- disturbances in signal transduction by insulin and some neurotrophic factors;
- malfunction of the lymphatic system, responsible for brain cleansing processes.

In addition to frequent vascular damage, neuroimaging studies in diabetic patients show generalized brain atrophy, changes in the thickness of the cerebral cortex, and microstructural changes in the gray and white matter.

Hypoglycemic encephalopathy

Hypoglycemic encephalopathy is a consequence of repeated episodes of hypoglycemia. Even a single reduction in blood glucose concentration below 20 mg/dL for longer than 2 h can cause irreversible damage to the CNS. A drop in glucose concentration below 30 mg/dL is manifested by:

- feeling of hunger;
- headache;
- heart palpitations;
- facial redness;
- sweating;
- shaking;
- anxiety and irritability;
- concentration disorders.

Sometimes, patients may perform automatic activities, which are present despite amnesia. If the state of hypoglycemia is prolonged, disorientation, drowsiness, sometimes excitement and agitation, and focal neurological symptoms gradually appear. There may be involuntary movements, muscle spasms, myoclonus, convulsions, and in the final stage – decerebrate posturing. A glucose concentration of approx. 10 mg/dL is manifested by:

- deep coma with muscle hypotonia;
- dilated pupils;
- pallor of the skin;
- slow heart rate;
- shortness of breath.

This stage is referred to as the core phase of hypoglycemia. If the patient is given glucose before this stage develops, neurological symptoms disappear completely within a few minutes. However, if the spinal phase persists longer, it takes several days or weeks to achieve neurological improvement, and some symptoms of the neurological deficit may become permanent.

Keto coma

Ketoacidosis develops as a result of insulin discontinuation (increase in glucagon concentration) or because of stress (indirect effect of adrenaline). Symptoms develop within at least 12 h. The clinical picture may include:

- anorexia;
- nausea and vomiting;
- polyuria;
- stomach pain;
- skin itching;
- psychomotor agitation or apathy;
- increasing disturbances of consciousness, which progress to coma.

The air exhaled by the patient smells of acetone. The face is pale, the skin and tongue are dry, the pupils are narrow and poorly responsive to light, the heart rate is accelerated, and blood pressure is low.

Nonketotic hyperosmolar coma

Nonketotic hyperosmolar coma results from dehydration due to persistent hyperglycemic diuresis. Clinically, increasing disturbances of consciousness, visual hallucinations, epileptic seizures, and sometimes symptoms of neurological deficit are observed. Extremely high glucose values (500–2,000 mg/dL) and plasma hyperosmolality (>350 mOsm/kg) are found in the blood. Infections and thrombosis are common complications. The condition is associated with high mortality.

Lactic acid coma

Lactic acid coma may occur in diabetic patients with poor general condition due to concomitant diseases. It may also be a consequence of the use of biguanidine derivatives in people with liver damage. The onset is sudden, with rapid loss of consciousness and respiratory disorders. Laboratory tests reveal severe acidosis, moderate hypoglycemia, and glycosuria.

Hepatic encephalopathy

Hepatic encephalopathy develops during advanced liver damage. Its pathogenesis is mainly related to abnormal nitrogen metabolism. Several clinical forms of hepatic encephalopathy are distinguished:

Acute:

It is a consequence of acute liver failure and develops over days or weeks. The course of the disease is often unfavorable, although once liver function improves, the symptoms of neurological deficit may disappear completely. Patients are diagnosed with:

- facial grimaces;
- deliberative, palmar grasp and sucking reflex symptoms;
- variable muscle stiffness;
- asterixis;
- excessive deep reflexes;
- Babinski sign;
- disorientation;
- delirious states.

As a result of rapidly progressing cerebral edema, disturbances of consciousness, convulsions, cerebral stiffness, and, in severe cases, coma occur.

Recurrent (reversible):

It concerns patients with liver damage when additional precipitating factors are present, for example after a high-protein meal, certain drugs (thiazide diuretics, sedatives), or infection. Neurological changes appear suddenly and are characterized by disturbances of consciousness, asterixis, and extrapyramidal signs. Symptoms of encephalopathy usually subside but may recur.

Chronic:

In this form, neurological symptoms develop gradually. Damage to the central nervous system is usually irreversible and progressive. It includes:

- cognitive impairment;
- personality changes;
- mood disorders;
- reversal of the sleep–wake rhythm;
- increasing disturbances of consciousness up to coma.

Sometimes asterixis, chorea, choreoathetosis, cerebellar ataxia with gait disturbances and dysarthria, facial grimaces, and psychotic symptoms are observed. In addition to cerebral symptoms, spinal disorders and polyneuropathy may also occur. A musty smell of urine and exhaled air (fedor hepaticus) is characteristic, which is probably related to the presence of mercaptans. The MRI examination shows brain atrophy and changes in the subcortical nuclei.

Latent (subclinical):

In this form, discrete cognitive impairments can be detected in psychometric tests, but physical examination shows no symptoms of neurological deficits or changes in mental status.

Uremic encephalopathy

Uremic encephalopathy follows renal failure occurring in both progressive chronic kidney disease and acute kidney injury. The syndrome is likely caused by retention of uremic solutes, alterations in hormonal metabolism, changes in electrolyte and acid-base homeostasis, as well as changes in vascular reactivity, blood–brain barrier transport, and inflammation. Patients experience:

- orientation disorders;
- changes in behavior;
- apathy;
- somnolence;
- fasciculations and muscle cramps;
- sometimes hiccups;
- chorea movements.

Over time, deeper disturbances of consciousness, epileptic seizures, and coma appear. Characteristic symptoms include asterixis, myoclonus, and uremic twitch-convulsive syndrome. Sometimes, meningeal syndrome (aseptic meningitis) is diagnosed. In such instances, CSF pressure is increased, and the protein concentration is slightly higher, but the cell number is normal.

Dialysis encephalopathy (dialysis dementia)

Dialysis encephalopathy is a progressive disease with a high mortality rate. It is probably related to aluminum poisoning. The clinical picture includes:

- personality disorders;
- progressive decline in intellectual ability;
- speech disorders (dysarthria, aphasia);
- myoclonus;
- seizures;
- sometimes psychotic incidents.

Initially, the symptoms are transient and last a few hours, occurring during dialysis or shortly after its completion. As they continue, they persist longer and longer, become permanent, and deepen.

Hypercalcemic encephalopathy

Hypercalcemic encephalopathy occurs with extremely high serum calcium concentrations (>15 mg/dL). It presents initially with concentration disorders and, as it progresses, may lead to confusion, drowsiness, and coma.

Hyponatremic encephalopathy

Hyponatremic encephalopathy is an emergency condition caused by cerebral edema in the setting of low osmolarity. Quick diagnosis and early treatment are crucial for successful treatment outcomes. The absolute change in serum sodium concentration alone is a poor predictor of clinical symptoms.

Risk factors for developing encephalopathy, even with low levels of hyponatremia, include hypoxia or previous CNS damage, female gender, and childhood age. Early symptoms include headache, nausea, and vomiting. Hyponatremia <110 mmol/L usually results in confusion, drowsiness, decreased muscle tone, loss of tendon reflexes, Babinski's sign, convulsions, and coma. Irreversible brain damage may occur. A rare complication of overly rapid correction of hyponatremia is CNS demyelination.

Encephalopathy caused by thiamine deficiency

Wernicke's encephalopathy is a serious neurological condition resulting from thiamine deficiency. Most cases involve alcoholism; however, non-alcohol-associated forms of encephalopathy also occur and are often under-recognized.

Wernicke's encephalopathy often co-occurs with Korsakoff's amnesic syndrome. It typically begins with a short-term period of non-specific prodromal symptoms, which include

malaise, sleep disturbances, and vomiting. Then, symptoms of neurological deficit appear, including impaired memory and confabulations.

The clinical picture is dominated by oculomotor disorders but also includes dysarthria, involuntary movements, intention tremor, ataxia, vegetative symptoms, disturbances of consciousness, and even coma. Anxiety and productive symptoms may also occur.

The disease progresses rapidly and frequently (usually after approx. 2 weeks) leads to death caused by paralysis of the respiratory and circulatory centers. In patients who survive, the symptoms of neurological deficit and memory disorders typically do not regress.

Damage to the peripheral nervous system in diabetes

The most common complication of diabetes is neuropathy, which occurs in 50–90% of patients. The frequency of peripheral nervous system involvement in diabetes increases with the duration of the disease and also depends on other coexisting risk factors (degree of hyperglycemia, insulin resistance, lipid disorders, obesity, age, hypertension, inflammatory processes, cigarette smoking, alcohol consumption, and genetic predispositions).

The patho-mechanism of diabetic neuropathy is not fully known. It is believed that ischemia of nerve endings, caused by damage to small blood vessels supplying the nerves (vasa nervorum), and excess glucose in the blood, which cannot be efficiently metabolized within the peripheral nerves, play important roles.

Neuropathies caused by hypoglycemia are rare because the peripheral nervous system is quite resistant to decreases in glucose concentration. Chronic inflammatory demyelinating neuropathy occurs approx. 11 times more often in people with diabetes than in the general population. The main clinical forms of diabetic neuropathy include:

- symmetrical sensory-motor polyneuropathy;
- asymmetric polyneuropathy;
- unifocal and multifocal neuropathies;
- autonomic neuropathy;
- treatment-induced diabetic neuropathy.

Some diseases of the digestive tract

More than 50% of patients with chronic hepatitis C (HCV) may develop neurological and/or psychiatric disorders of varying severity. Reported complaints are often non-specific and mild (fatigue, attention disorders, forgetfulness, depressed mood). However, in some patients, the course of the disease is severe, and the symptoms develop rapidly (encephalitis and meningitis, spinal cord damage, or encephalopathy).

The most common neurological syndromes in HCV include peripheral neuropathy, cognitive disorders, and cerebrovascular accidents, and among psychiatric disorders – depressive syndrome.

Gastric resection

Previous gastric resection leads to deficiency syndromes, manifested by:

- polyneuropathy;
- myelosis funicularis;
- tetany;
- headaches;
- memory disorders.

Celiac disease

About 10% of cases of celiac disease develop:

- neuropathy;
- ataxia;
- epilepsy (with calcifications in the brain);
- stupor;
- depression;
- headaches.

These symptoms usually persist despite the introduction of a gluten-free diet.

Kidney failure

Neurological symptoms during renal failure occur frequently and affect both the peripheral and central nervous systems. Neurological symptoms in chronic renal failure include:

- polyneuropathy;
- mononeuropathy;
- restless legs syndrome (Willis–Ekbom syndrome);
- muscle symptoms: spasms, uremic myopathy, rarely myasthenic syndrome;
- syndrome of symptoms of hyperexcitability of the nervous system: fibril tremors, myoclonus, asterixis, convulsions;
- uremic encephalopathy;
- neurological symptoms related to dialysis therapy: sleep disorders, post-dialysis syndrome, dialysis encephalopathy.

Diseases of the endocrine glands (endocrinopathy)

Hyperthyroidism

Excess thyroid hormones cause increased metabolism and increased tension of the sympathetic nervous system. Neurological symptoms of hyperthyroidism include:

Autonomic disorders:

- tachycardia;
- heart arrhythmia;
- excessive sweating;
- increased thirst and diuresis;
- excessive digestive tract kinetics.

Eye symptoms:

- apparent proptosis;
- infrequent blinking;
- eyelid tremors;
- thyroid orbitopathy;
- eyeball pain;
- ocular muscle paralysis;
- diplopia;
- sometimes swelling of the optic nerve disc.

Myopathy:

- thyrotoxic myopathy;
- myasthenic syndrome;
- thyrotoxic periodic paralysis.

Tremor – intensification of physiological tremor.

Mental disorders:

- emotional lability;
- excessive irritability;
- mood swings;
- feeling of anxiety;
- concentration disorders;
- insomnia;
- rarely: depressive states or psychotic symptoms;
- in thyroid storm, the possibility of delirium and coma.

Cerebral ischemia resulting from cardiovascular disorders.

Hypothyroidism

Neurological symptoms depend on the age at which hypothyroidism develops. Congenital hypothyroidism causes mental retardation (cretinism). Thyroid hormone deficiency later in life manifests as myxedema. In adolescence, physical and mental impairment of varying severity, signs of premature puberty, and prolactinoma are observed.

Characteristic features of adults include:

- general weakness;
- psychomotor retardation;
- headaches and dizziness;
- tinnitus;
- apathy and drowsiness.

Disorders of intellect, memory, concentration, and association may vary in severity – from mild impairment to severe dementia. Delirium, depression, and psychotic syndrome may develop. Cerebellar symptoms can sometimes occur. Muscles and peripheral nerves are often affected. Myopathy is accompanied by muscle pain and stiffness.

Myasthenic syndrome occurs less frequently than in hyperthyroidism, and recurrent episodes of muscle paralysis manifest similarly to the familial form of hypokalemic periodic paralysis. Symptoms of neuropathy are related to carpal tunnel syndrome, while sensory polyneuropathy, mild polyneuritis, or cranial nerve damage occur less commonly.

Hyperparathyroidism

Hyperparathyroidism results in high levels of calcium in the blood. Neurological complications affect peripheral nerves and muscles, while central symptoms and psychiatric disorders occur less frequently. Neurological symptoms in hyperparathyroidism include:

Neuromuscular symptoms:

- paresthesia;
- muscle cramps;
- fatigue;
- symmetrical weakness and atrophy of the extremity muscles.

Central symptoms and psychiatric disorders:

- hypercalcemic encephalopathy;
- headaches;
- apathy;
- concentration and memory disorders;
- irritability;
- sleep disorders;
- depression.

Hypoparathyroidism

Among the neurological symptoms occurring during hypoparathyroidism, the most common is tetany, which may be latent or manifest as numbness of the limbs and mouth area, painful, paroxysmal, tonic spasms of the hand muscles (Trousseau sign), feet (club-foot position), and, extremely rarely, the hamstring, axial, or laryngeal muscles (stridor). Generalized seizures that do not respond to antiepileptic drugs may also occur. Physical examination reveals signs of increased neurovegetative excitability:

- eyelid tremors;
- excessive sweating of hands and feet;
- increased dermatographism;
- very lively deep reflexes;
- extremely positive Chvostek's sign;
- Trousseau's sign.

Neurological symptoms of hypoparathyroidism include:

- tetany;
- convulsions;
- myopathy;
- extrapyramidal syndromes;
- syndrome of increased intracranial pressure with edema of nerve discs II (rare);
- intracerebral calcifications.

Adrenal hyperfunction

In hyperadrenalism, neurological symptoms are associated with excessive levels of corticosteroids, aldosterone, or catecholamines.

Neurological symptoms associated with hypercortisolemia include:

Mental disorders:

- insomnia;
- anxiety;
- stimulation;
- cloudiness;
- rarely psychotic states.

Muscle disorders:

- myopathy: acute form (after large intravenous doses of steroids), subacute, chronic;
- increased intracranial pressure (symptoms in case of sudden withdrawal of steroids).

Patients with high aldosterone levels experience electrolyte disturbances (hypokalemia, hyponatremia), acid-base disturbances (alkalosis), excessive urine output, and arterial hypertension. Neurological symptoms in primary hyperaldosteronism include seizures mimicking periodic paralysis and tetany. Intracranial aneurysms are common in familial hyperaldosteronism.

In pheochromocytoma, the symptoms result from increased catecholamine secretion.

Neurological symptoms in pheochromocytoma:

- hypertension (moderate or severe, paroxysmal, or persistent);
- palpitations;
- excessive sweating;
- nausea;
- vomiting;
- diarrhea;
- headaches;
- anxiety attacks.

Adrenal insufficiency

The general symptoms of adrenal insufficiency include:

- increased skin pigmentation;
- weight loss;
- weakness;
- hypoglycemia;
- low blood pressure.

Neurological symptoms include behavioral disorders, cognitive function deficits, and extremely rare psychotic reactions. In some cases, increased intracranial pressure syndrome may develop.

Hyperpituitarism

Excessive secretion of growth hormone manifests in gigantism or acromegaly. Neurological symptoms may include headaches, fatigue, paresthesia, and visual disturbances. Sometimes, carpal tunnel syndrome may occur.

Hypersecretion of adrenocorticotrophic hormone, which is responsible for the symptoms of Cushing's disease, causes mental disorders and myopathy. Due to concomitant hypertension, secondary vascular damage to the nervous system may also occur.

Excessive secretion of antidiuretic hormone causes decreased serum sodium concentration, increased water retention, and excessive sodium excretion in the urine. Neurological symptoms include headaches, disturbances of consciousness, seizures, and transient symptoms of neurological deficit.

Hypopituitarism

Hypopituitarism may occur because of developmental disorders, trauma, inflammatory diseases, vascular diseases, and cancer. Clinical symptoms of hypopituitarism vary depending on the etiology of the disease (Table 15.1).

Table 15.1. Clinical symptoms of hypopituitarism depending on the etiology of the disease

Disease	Symptoms of hypopituitarism associated with the disease
Pituitary tumor	– headaches – blurred vision – damage to the structures of the cavernous sinus (tumor growth to the sides) – hydrocephalus (tumor growth upwards) – hormonal disorders
Pituitary hemorrhage	– headaches – meningeal symptoms – vision loss – oculomotor disorders – disturbances of consciousness
Postpartum pituitary necrosis (Sheehan's syndrome)	– disturbances of consciousness (acute phase) – low blood pressure – tachycardia – hypoglycemia – lack of menstruation and lactation – diabetes insipidus (rare) – dizziness – disturbances of libido

Nutritional deficiencies

Chronic malnutrition and starvation

Symptoms of chronic malnutrition and starvation depend on their severity and duration and include:

- headaches;
- fatigue;
- irritability;
- behavioral disorders;
- apathy;
- somnolence;
- concentration and memory disorders;
- starvation polyneuropathy (sensorimotor), with involvement of the nerves of the limbs, sometimes also the cranial nerves (retrobulbar inflammation of the II nerve, hearing disorders);
- delirium syndrome;
- coma (extreme exhaustion).

Malabsorption syndromes

Malabsorption syndromes are mainly associated with diseases of the small intestine, pancreas, liver, bile ducts, and stomach. They may include:

Primary:

- celiac disease.

Secondary:

- condition after stomach resection;
- parasitic and cancerous diseases of the digestive system;
- amyloidosis.

Absorption disorders lead to emaciation and reduced body defenses, dehydration, electrolyte disorders, and symptoms related to vitamin and microelement deficiency (Table 15.2).

Table 15.2. Neurological symptoms in deficiency syndromes

Deficiency	Symptoms
Iron deficiency	disorders of the vegetative system, general weakness, fatigue, excessive irritability, sleep disorders, lack of appetite, headaches and dizziness
Vitamin B1 (thiamine) deficiency beriberi disease	peripheral neuropathy (acute or chronic), sometimes involvement of cranial nerves, Wernicke's encephalopathy, Korsakoff's amnesic syndrome
Vitamin PP deficiency (niacin, nicotinic acid)	Pellagra; pseudo-neurotic syndrome, anxiety states, sometimes Korsakoff's syndrome, dementia, Parkinson's syndrome, spinal cord degeneration, sensory polyneuropathy with unpleasant paresthesia.
Vitamin B6 (pyridoxine) deficiency	Usually coexists with a deficiency of other vitamins; may cause seizures, hyperarousal, psychotic episodes, and polyneuropathy.
Vitamin B12 deficiency	Neurological disorders are not specific, they appear later in the disease; despite substitution treatment – they withdraw slowly, often incompletely. They include symptoms of spinal cord degeneration, vision disturbances, encephalopathy with subcortical dementia, and psychotic syndrome (paranoid or depressive).
Folic acid deficiency	subacute polyneuropathy, myelopathy, cerebellar syndrome; in the fetal period – neural tube defects, i.e., spinal dysraphism
Vitamin A deficiency	night blindness, drying of the cornea, skin lesions, decreased immunity; compression syndromes associated with swelling of the nerves where they pass through the bone holes
Vitamin D deficiency	rickets, tetany, and myopathy characterized by muscle weakness.
Vitamin E deficiency	spinocerebellar ataxia, polyneuropathy, and sometimes retinitis pigmentosa

Hypervitaminosis

An excess of certain vitamins (hypervitaminosis) may cause unfavorable neurological symptoms. This applies primarily to fat-soluble vitamins that accumulate in the body. An overdose of vitamin A results in symptoms of mild intracranial hypertension, such as headache, dizziness, nausea, vomiting, and swelling of the optic nerve discs. Excess vitamin E can also cause headaches. Water-soluble vitamins are quickly excreted in the urine, which is why they rarely cause toxic symptoms; however, chronic intake of, e.g., several grams of pyridoxine a day may cause disturbances in deep sensation.

Systemic diseases of connective tissue

Systemic connective tissue diseases are autoimmune diseases that cause damage to the joints, internal organs, skin, nervous system, and muscles. The main cause of neurological symptoms is vascular involvement.

Neurological symptoms in systemic lupus erythematosus:

- mild cognitive impairment;
- headaches (migraine-like or non-specific);
- encephalopathy;
- chorea;
- epileptic seizures;
- stroke of the brain or spinal cord;
- aseptic meningitis;
- peripheral neuropathy (also damage to cranial nerves);
- polymyositis;
- opportunistic infections involving the nervous system.

Neurological symptoms of giant cell arteritis:

- headaches, often in the temporal area, unresponsive to standard analgesics, disappearing after administration of steroids (e.g., dexamethasone);
- nodular thickening and painful swelling (sometimes with loss of pulse) of the superficial temporal artery and/or occipital arteries;
- temporary visual impairment or blindness (ischemic neuropathy of nerve II, occlusion of the central retinal artery);
- pallor of the optic disc or its swelling with hemorrhages in the retina (the disc may be normal);
- damage to the oculomotor nerves with double vision;
- transient ischemic attack (TIA) or stroke (usually in the posterior circulation);
- reversible dementia, psychosis, depression, personality disorders;
- peripheral neuropathy, mononeuropathy;
- pain and stiffness in the muscles, mainly in the neck, arms, buttocks, and thighs.

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16. Selected aspects of pediatric neurology

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The child's neurological examination should be performed in conditions that ensure safety and take into account the child's natural daily activity rhythm. It is particularly important to observe the child's behavior and establish good rapport. The examiner should assess:

- general appearance and body proportions;
- dysmorphic features;
- spontaneous movements;
- facial expressions;
- body symmetry at rest and during activity.

It is important to assess, relative to the child's age:

- dynamics of head circumference growth;
- development of locomotion;
- attitude development;
- social contact;
- speech.

In the early developmental period, several automatisms are observed, the most important of which are the sucking, searching, and embracing (Moro) reflexes. The embrace reflex should be symmetrical and typically disappears by 6 months of age. In addition, other reflexes are assessed early in life, including:

- crawling;
- walking;
- oculo-palpebral and auriculo-palpebral (tightening of the eyelids in response to a strong light or auditory stimulus);
- grasping reflexes (light pressure on the palmar side of the fingers causes them to clench and adduct the thumb, and a similar stimulus in the foot causes plantar flexion of the fingers).

Grasping reflexes disappear in the upper limbs after 4 months and in the lower limbs after 12 months of life. During the first 6 months, postural reflexes are important for the proper development of the child, such as:

- tonic labyrinthine (increased tension of the flexor muscles in the prone position and extensor muscles in the supine position);
- Galant's (bending the torso on the side of the irritation);
- crossed extension (irritation of the medial part of the lower leg of one limb causes adduction and extension of the other lower limb; disappears by 3 months of age);

- asymmetric tonic neck reflex (turning the head to the side causes straightening of the limbs on the side of the head, and flexion – on the opposite side, disappears by 6 months of age);
- symmetrical tonic neck reflex (bending the head forward causes flexion of the upper limbs and straightening of the lower limbs while tilting the head backward – the opposite reaction, disappears by 6 months of age).

In the second half of life, postural reflexes are replaced by straightening reflexes, which involve visual and vestibular (labyrinthine) input. These include:

- helical straightening reflex (>7 months of age, shoulders, upper limbs, pelvis, and lower limbs follow the turning of the head);
- head straightening reflex (>6 months of age, minimally persists until the end of life, determines the correct positioning of the head when tilting the child, the line of the mouth remains parallel to the ground);
- the reaction of readiness to jump and parachute reaction (rapid lowering of the child's body causes the head to be raised and the limbs to be supported).

By the 9th month of life, the straightening reaction is joined by balance reactions, which enable the adoption of a standing posture and are fully developed in the 1st–2nd year of life. If a child's development differs significantly from the average for their age, considering the family history of early development, neurodevelopmental disorders should be suspected.

Developmental disorders of the nervous system

Developmental defects of the brain and spinal cord are the result of genetic defects, metabolic disorders, exposure to various exogenous factors, or developmental defects of the skeletal system. Nervous system defects are one of the main causes of miscarriages or deaths in the first years of life and an important cause of pathologies appearing in the neonatal period, infancy, and early childhood, as well as in adolescents and even adults (e.g., cortical dysplasias as a cause of epileptic seizures).

The development of the nervous system begins between the 18th and 19th days after fertilization, when thickening of the ectoderm produces the neural plate, which then forms the neural groove. Six days later, the neural groove transforms into the neural tube and the neural crest, made of neuroblasts, i.e., stem cells that give rise to nerve cells. The process of neural tube closure is called neurulation. The inside of the neural tube forms the ventricles of the brain and the spinal canal. Before the 4th week after fertilization, 3 follicles form:

- the forebrain;
- the midbrain;
- the hindbrain.

Then the forebrain divides into the telencephalon and the diencephalon, and the optic chiasm plate, choroid plexus, buds of the hemispherical vesicles, the 4th ventricle, and anterior horns of the spinal cord appear. By the 6th week, the cerebral hemispheres grow, and the migration of neuroblasts to the developing cerebral cortex begins. Two weeks later, the hemispheres cover the diencephalon, the choroid plexus is formed in the lateral ventricles of the brain, and the nuclei of the cranial nerves are formed in the brainstem. By the 11th week, cerebral sulci are visible, and the development of the corpus callosum begins.

In the 4th month, the lamina quadrigemina, cerebellar tentorium, and simple sinus are formed, and a very intensive process of neuroblast migration takes place, lasting until the 20th week. From weeks 8 to 18, neuronal proliferation is observed. In the 6th month, the processes of myelination and synaptogenesis begin. In the 7th month, pyramidal cells are found in the cerebral cortex. In the 1st year of life, the development of the nervous system structures is still intensive, and the process of shaping cerebral gyri and cortical layers is completed. The process of myelin maturation can last up to the age of 20.

Dysraphism – these defects occur between the 4th and 10th week of embryogenesis because of incorrect closure and formation of the neural tube. Dysraphic syndromes of the spinal cord and spine include:

- spina bifida;
- meningocele and myelomeningocele;
- hydromyelia;
- diastematomyelia, diplomyelia;
- syringomyelia: the presence of cavities in the spinal cord, usually located dorsal to the central canal, occupying the posterior horns and cords, lined with fibrous glia, abnormal vessels, sometimes connective tissue and cancer cells, causing damage to the spinothalamic tracts transmitting pain and temperature sensations, which results in split sensory disorders (abolition of pain and temperature sensation with preserved sense of touch and deep sense of position and vibration), may also cause peripheral paresis and atrophy of limb muscles;
- neuroenterogenic cysts;
- lack of spine (amyelia).

Dysraphic syndromes of the brain and skull include:

- meningocele;
- Arnold–Chiari syndrome (displacement of the structures of the posterior cranial fossa into the spinal canal);
- anencephaly.

The risk of dystrophic defects can be reduced by taking folic acid prophylactically before conception and in the first 3 months of pregnancy.

Other developmental disorders:

- single-chamber forebrain (holoprosencephaly);

- defects of the commissural system – absence or underdevelopment of the corpus callosum;
- septo-optic dysplasia;
- septum pellucidum cyst;
- Dandy–Walker syndrome (disturbance of the development of the cerebellar vermis, dilatation of the fourth ventricle, cyst of the posterior cranial cavity and high tentorium of the cerebellum);
- cerebellar hypoplasia;
- agyria;
- lissencephaly;
- pachygyria;
- polymicrogyria;
- gray matter heterotopias;
- cortical dysplasias;
- congenital hydrocephalus;
- microcephaly;
- macrocephaly;
- porencephaly;
- craniosynostosis (premature closure of cranial sutures causing skull deformation, increased intracranial pressure, and impaired brain function);
- dent in the base of the skull (impressio basilaris).

Perinatal damage may be caused by mechanical, biochemical (hypoxia, poisoning), physical (intrauterine pressure fluctuations), infectious factors, or hematological abnormalities. Their frequency has decreased with improvements in maternity care. In full-term newborns, the most common problem is hypoxic-ischemic encephalopathy, while in premature infants, intraventricular hemorrhages and periventricular leukomalacia are most frequent. Mechanical injuries occur more often in newborns weighing more than 4,500 g.

Lesion to the peripheral nervous system

Duchenne–Erb’s type brachial plexus injury (upper) is caused by a lesion to the C5 and C6 cervical spinal roots during prolonged vaginal delivery of a large fetus or as a result of manual assistance or forceps. It is the most common type of brachial plexus injury. The symptoms include:

- positioning the inwardly rotated upper limb along the newborn’s body; forearm straight and pronated;
- paresis or paralysis of the shoulder and biceps muscles;
- weakened or absent biceps and radial reflexes;
- preserved grasping reflex;

- asymmetric Moro reflex;
- preserved movements of the fingers and wrist;
- upper limb muscle atrophy;
- surface sensation disorders in the upper limb;
- phrenic nerve palsy in case of C4 root lesion.

Klumpke-type brachial plexus injury (lower) results from lesion to the spinal roots of C7, C8, and T1. The symptoms are:

- paresis of the muscles of the hand, fingers, and forearm, preserved arm movements, fingers of the hand arranged in the Trousseau form, thumb positioned in adduction;
- weakened or absent triceps reflex;
- disturbances of surface sensation in the hand and forearm;
- Horner's syndrome in case of lesion to the ciliospinal center.

Complete damage to the brachial plexus is the result of a lesion to the C5, C6, C7, C8, and T1 roots. This is the most severe and 2nd most common injury to the brachial plexus. It occurs in up to 23% of breech deliveries. Diagnosis is based on the clinical picture, while the exact location of the lesion can be determined using electromyography (EMG) and magnetic resonance imaging (MRI). Treatment consists of rehabilitation. If elbow flexion and shoulder abduction are not achieved by the age of 6 months, surgical treatment with sural nerve autograft should be considered.

Lesion to the phrenic nerve is usually unilateral and results in an immobile diaphragm with upward elevation, leading to breathing disorders. The diagnosis is confirmed by chest X-ray. Clinical symptoms disappear spontaneously after a few months, but in some cases, it is necessary to use respiratory support. If symptoms do not subside after 3 months, surgical treatment is necessary.

Lesion to the central nervous system

Hypoxic-ischemic encephalopathy develops because of factors affecting the mother (infections, heart failure, cardiac defects, bronchial asthma) or the placenta (premature abruption). It is caused by perinatal biochemical trauma, oxidative stress, free radicals, and energy deficits, leading to neuronal damage. Diagnostic criteria include:

- pH of umbilical cord blood <7.1 ;
- sum of Apgar points in the fifth minute of life from 0 to 3;
- presence of meconium in the amniotic fluid;
- abnormal cardiotocography (CTG) recording;
- the need to resuscitate the newborn after birth.

Symptoms

- disturbances of consciousness – hyperactivity, lethargy, or coma;
- excessive deep reflexes;

- seizures;
- respiratory and circulatory failure.

Brain lesions resulting from hypoxic-ischemic encephalopathy are visible on ultrasound and MRI examinations, particularly in the thalamus, subcortical nuclei, brainstem, and cerebral cortex. Over time, various degrees of cortical-subcortical brain atrophy are observed. Treatment involves proper respiratory ventilation, correction of acid-base and water-electrolyte disorders, and treatment of seizures and multi-organ failure. The mortality rate is between 15 and 20%.

Intracranial bleeding is a typical lesion of the central nervous system, occurring in 20–50% of newborns born before the 35th week of pregnancy. The causes of periventricular or intraventricular bleeding are intravascular, vascular, and extravascular factors, including:

- excessive fibrinolytic activity;
- platelet aggregation disorders;
- fluctuations in cerebral blood flow;
- decreased blood pressure due to hypovolemia.

Subarachnoid hemorrhage in premature newborns is caused by lesion to capillaries and small veins during hypoxic-ischemic encephalopathy. Clinical symptoms are usually mild and may include convulsions, decreased muscle tone, and incorrect positioning of the eyeballs; however, in 50% of cases, symptoms do not occur. In severe bleeding, a catastrophic syndrome occurs, lasting from several minutes to several hours, with the following symptoms:

- disturbances of consciousness (stupor or coma);
- no reaction of pupils to light;
- decerebrate posturing;
- breathing disorders;
- bradycardia;
- thermoregulation disorders;
- low blood pressure.

Intracranial bleeding requires differentiation from sepsis, hypoglycemia, and electrolyte deficiencies. Diagnosis is based on neuroimaging tests, primarily transfontanelle ultrasonography. Treatment involves the treatment of seizures, correction of fluid and electrolyte disorders, treatment of coagulation disorders and post-hemorrhagic anemia, as well as supportive care.

Post-hemorrhagic hydrocephalus is the most serious complication of severe intraventricular bleeding. Treatment involves decompressive punctures, external drainage, implantation of a Rickham reservoir and valve system, as well as the DRIFT method (drainage, irrigation, and fibrinolytic therapy).

Leukomalacia is characterized by the presence of malacia cavities in the white matter of the cerebral hemispheres, located in the periventricular and subcortical areas. It occurs

in 4–26% of premature newborns. The cause is the incomplete development of the arterial vasculature of the periventricular white matter and immature regulation of cerebral blood flow, favoring ischemia and focal necrosis. Premature infants with malacia changes initially show flaccid muscle tone, which later progresses to increased tone, severe tremors, hyperactivity, a flexed position of the upper limbs with extension of the lower limbs, as well as a tendency toward flexion. A routine diagnostic test is transfontanelle ultrasonography, which shows hyperechogenicity of malar cavities up to 3 mm in size. Magnetic resonance imaging with the FLAIR sequence is more sensitive and specific. It should be differentiated from bleeding. There is no effective treatment. The prognosis depends on the extent of the lesions – 20–60% of affected infants develop cerebral palsy and epilepsy.

Perinatal strokes are arterial ischemic strokes resulting from a clot in a cerebral vessel or an embolism originating from the heart, placenta, or umbilical vein. They are associated with hypoxic-ischemic encephalopathy, congenital heart defects, coagulation disorders, infections, dehydration, forceps or vacuum extraction, cesarean section, and the use of ECMO. They occur 17 times more often in newborns than in older children, with an estimated frequency of 1 in 2,300 full-term newborns, and they occur extremely rarely in premature newborns. Symptoms are very non-specific and include seizures, hypotension, and apnea. Ultrasound and MRI are helpful in diagnosis. The most common complication of perinatal stroke is cerebral palsy presenting as hemiparesis.

Kernicterus is a chronic and permanent consequence of the toxic effects of bilirubin. Most often, it is the result of a serological conflict. Symptoms include:

- disturbances of consciousness;
- hypotension;
- impaired sucking and swallowing reflexes;
- stupor;
- hypertonia;
- brow presentation;
- irritability;
- convulsions;
- fever;
- athetosis;
- dystonia;
- deafness;
- oculomotor disorders;
- changes in the color of tooth enamel.

Brain lesion, especially in the globus pallidus, is visible in MRI. Treatment of hyperbilirubinemia involves intensive phototherapy and exchange transfusion.

Perinatal spinal cord injury occurs rarely and may be caused by bleeding or mechanical trauma, usually during breech delivery or when manual assistance is used. The initial symptoms include impaired sensation, sweating, and flaccid paralysis below the level

of the lesion. Spasticity appears within the first days or weeks of life. When the spinal lesion is complete, paralysis of the intercostal muscles, abdominal muscles, and sphincter dysfunctions occurs.

The differential diagnosis should include congenital spinal cord tumors, spinal cord hemangiomas, myelodysplasia, spinal muscular atrophy, and hypoxic-ischemic encephalopathy. Treatment consists of skin care, prevention of trophic ulceration, and treatment of respiratory and urinary tract infections.

Cranial nerve injuries – the VII nerve is most often lesioned due to the use of forceps, vacuum extraction, or during facial delivery, while the IX, X, XI, and XII nerves may be affected following selective necrosis of their brainstem nuclei. Facial asymmetry and difficulties with sucking and swallowing are observed.

Cerebral palsy

Cerebral palsy is a group of permanent, non-progressive movement and posture disorders resulting from abnormalities in brain development that occur during the fetal and neonatal periods. It is not a single disease entity but a complex of numerous disease symptoms with various etiologies:

- prematurity (40–50%);
- hypoxic-ischemic encephalopathy (25–30%);
- mechanical perinatal trauma (5–10%);
- congenital infections (5–10%);
- hypoglycemia;
- kernicterus;
- meningitis;
- injuries;
- thyroid disease in the mother.

Clinical forms:

- hemiplegia spastica – paresis of the upper and lower limbs, paresthesia and choreo-athetosis of the same half of the body;
- diplegia – paresis of the lower limbs predominates;
- hemiplegia bilateralis – paresis of the upper limbs predominates;
- cerebellar form – in this form, muscle tension may be reduced;
- extrapyramidal form – characterized by athetosis, chorea, and dystonia;
- mixed form.

Neuroimaging tests, especially MRI, play an important role in diagnosis. It requires differentiation from progressive neurological diseases. Treatment mainly involves comprehensive rehabilitation. Some patients require treatment of spastic muscle tension with botulinum toxin or, due to epilepsy, the use of antiepileptic drugs.

Metabolic and genetic diseases

Lysosomal storage diseases are genetically determined disturbances in the activity of lysosomal enzymes, leading to the deposition of partially degraded substrates within lysosomes and damage to the structure and functions of the affected cellular systems. Characteristic features include enlargement of cells and entire organs, a progressive course, different rates of progression, and variable severity of symptoms. Diagnosis is based on testing the activity of lysosomal enzymes, demonstrating undegraded substrates, and microscopic examination. Treatment involves rehabilitation, symptomatic treatment, and, in some diseases, enzyme replacement therapy.

Pompe disease is caused by a deficiency of the enzyme alpha-glucosidase and is inherited in an autosomal recessive manner. It involves the accumulation of glycogen in the liver, muscles, heart, glial cells, motor nuclei of the brainstem, and the anterior horns of the spinal cord. The condition results in decreased muscle strength and tone, cardiomegaly, heart failure, respiratory failure, and enlargement of the tongue and liver. It can appear in childhood, adolescence, and adulthood. It involves elevated activity of creatine phosphokinase (CPK) and liver enzymes. EMG, cardiac ultrasound, and abdominal ultrasound are helpful diagnostic tools. The diagnosis is confirmed by an enzyme test showing reduced alpha-glucosidase activity using the dried blood spot method and by genetic testing showing mutations in both copies of the alpha-glucosidase gene. Treatment involves enzyme replacement therapy with acid alglucosidase alfa, which enables glycogen processing.

Fabry disease is caused by alpha-galactosidase deficiency, inherited recessively, and linked to the X chromosome. It leads to the accumulation of globotriaosylceramide in the skin, kidneys, blood vessels, and the peripheral and autonomic nervous systems. The dominant symptoms are:

- pain and paresthesia of limbs;
- angiokeratoma-type lesions;
- angiectasia;
- impaired sweat excretion;
- hypertrophic cardiomyopathy;
- kidney failure;
- strokes;
- fever of unknown origin;
- macular and maculopapular skin lesions with hyperkeratosis, around the groin, navel, and buttocks;
- proteinuria and renal failure;
- hypertension;
- corneal opacity.

The disease usually begins in adolescence. Diagnosis is confirmed by demonstrating reduced alpha-galactosidase A activity in plasma, leukocytes, or fibroblasts using a dry

blood test, and by genetic testing revealing mutations in the alpha-galactosidase gene. Treatment involves enzyme replacement therapy with agalsidase.

Metal metabolism disorders

Wilson's disease is inherited in an autosomal recessive manner and is associated with a mutation in the gene located on chromosome 13 (13q14.3-q21.1) encoding the ATP7B protein. This protein mediates the binding of copper to apoceruloplasmin and its excretion into the blood in the form bound to ceruloplasmin. The disease involves abnormal copper metabolism, leading to its deposition in many organs, mainly the liver, brain, kidneys, and cornea, with secondary damage to these organs.

Symptoms of the disease can occur at any age, but most commonly begin between the ages of 5 and 35. The clinical course is characterized by considerable diversity. It may involve liver damage only with biochemical abnormalities and no clinical symptoms, as acute hepatitis (with jaundice, abdominal pain), as fulminant liver failure (high mortality), or as chronic hepatitis (most common). Neurological symptoms usually appear at the age of 20 and mainly concern the extrapyramidal system:

- resting tremor;
- muscle stiffness;
- dystonia;
- dysarthria;
- dysphagia;
- chorea;
- tics;
- ballism.

Symptoms may also include:

- cerebellar;
- dysautonomia;
- gait disturbances;
- headaches;
- rarely pyramidal symptoms and sensory disturbances.

More than half of patients also experience psychiatric symptoms:

- mood disorders;
- personality disorder;
- antisocial behavior;
- psychotic symptoms and cognitive impairment.

Ophthalmological examination reveals a Kayser–Fleischer ring in the cornea and a sunflower cataract in the lens. The diagnosis is based on the demonstration of a decrease

in serum ceruloplasmin concentration, an increase in the concentration of free copper (not bound to ceruloplasmin) in serum, and an increase in daily urinary copper excretion.

In children, the examination of copper excretion in urine after penicillamine load is used – an increase in copper excretion is considered a positive result. Genetic diagnostics involves detecting mutations in the gene for the ATP7B protein. Histopathological examination of the liver showing increased copper concentration in the liver is useful.

In neurological forms, an MRI of the brain shows abnormalities in almost 100% – in the basal ganglia, thalamus, midbrain, and pons, showing neurodegenerative, pathogenomic changes – an image of a large panda in the midbrain and an image of a small panda in the brainstem. The treatment involves penicillamine, zinc salts, and in advanced cases – liver transplantation.

Skin and nerve diseases (phakomatoses)

Tuberous sclerosis is inherited in an autosomal dominant manner and is associated with mutations of the TSC1 gene on chromosome 9 and TSC2 on chromosome 16. These mutations form a complex that inhibits the mTOR pathway, which is responsible for cell maturation and differentiation. Improper functioning of this pathway is responsible for the development of benign tumors in many organs, such as the brain (subependymal periventricular tumors, cortical-subcortical nodules, subependymal giant cell astrocytomas), kidneys, heart, liver, lungs, retina, and skin. Characteristic skin lesions include colorless nevi, angiofibroma nodules, fibromas, and scarring lesions. The most common neurological symptoms include epileptic seizures, inhibition of psychomotor development, and delayed mental development. The diagnosis is based on the statement of Vogt's triad, which consists of:

- epilepsy;
- delays in mental development;
- angiofibroma changes on the face.

Treatment involves controlling epileptic seizures, with vigabatrin as the first-line drug. Everolimus, an mTOR kinase inhibitor, is effective in inhibiting the growth of organ lesions. In selected cases, surgical treatment is used.

Neurofibromatosis type I (also known as Recklinghausen's disease) is the most common neurocutaneous disease. It is inherited in an autosomal dominant manner and associated with a gene mutation in the 17q11.2 region. It has a slow and progressive course and is characterized by skin discoloration in the form of café au lait spots (the color of coffee with milk), neurofibromas and plexiform neurofibromas (may become malignant), Lisch nodules, and tumors of the central nervous system – most often optic nerve gliomas, and less frequently, meningiomas.

Neurofibromatosis type II occurs much less frequently, is inherited in an autosomal dominant manner, and is associated with a gene mutation in the 22q11.21-q13.1 region. The basic symptom is the presence of acoustic neuromas, which manifest as progressive hearing loss, balance disorders, and bilateral facial nerve palsy leading to facial muscle weakness. Other symptoms may include headaches, less commonly, café au lait skin spots or neurofibromas (may not be present at all), subcapsular lens opacity, brain and spinal cord tumors such as glial tumors, neuromas, and meningiomas. Diagnosis is based on genetic testing, neuroimaging, audiological tests, and auditory evoked potentials. Management of both types of neurofibromatosis involves genetic counseling and surgical reduction or removal of tumors.

Porphyrias

Porphyrias are a group of heterogeneous diseases caused by reduced activity of heme synthesis enzymes, which results in excessive accumulation of porphyrins and their precursors in the body. The symptoms of porphyria are highly non-specific and can affect all functions of the nervous system at the autonomic, peripheral, and central levels, including:

- stomachache;
- vomiting;
- constipation;
- tachycardia;
- hypertension;
- electrolyte disorders;
- skin changes;
- muscle weakness;
- sensory disturbances;
- behavioral disorders;
- irritability;
- disorientation;
- sleep disorders;
- convulsions;
- psychosis;
- depression.

The 2 most common types of porphyria with neurological symptoms are:

Acute intermittent porphyria (AIP)

Acute intermittent porphyria is inherited in an autosomal dominant manner and caused by a deficiency of hydroxymethylbilane synthase (HMBS) activity due to gene mutations

in the 11q24.1-11q24.2 region. Neurological symptoms result from neurotoxicity of porphyrin precursors and heme deficiency. Clinical symptoms develop between the ages of 15 and 45, occurring in 80% of cases in women. They present with periodic exacerbations (acute attacks) and periods of remission, the frequency of which varies widely (from once in a lifetime to weekly). There are several factors that trigger a seizure, such as:

- medicines;
- chemicals (paints, varnishes, solvents);
- hormonal changes (menstruation, pregnancy);
- stimulants (alcohol, smoking, drugs);
- infections;
- starvation;
- caloric deficiencies;
- intense effort;
- severe stress.

Visceral symptoms precede mental symptoms, but a painless course limited to only mental or neurological manifestations is also possible. Most patients experience darkening of the urine after 10–30 min of exposure to light. If left untreated, an attack can lead to death. The diagnostic criteria are increased urinary excretion of porphyrin precursors PBG (porphobilinogen) and ALA (delta-aminolevulinic acid), decreased HBMS (hydroxymethylbilane synthase) activity, and detection of HBMS gene mutations. Treatment involves removing the triggering factors and administering drugs to stop the attack, including large amounts of glucose (300–400 mg per day) given orally or intravenously, as well as hemin.

Mixed porphyria

Mixed porphyria (VP – variegate porphyria) is inherited in an autosomal dominant manner and is caused by deficiency of protoporphyrinogen oxidase activity (PPOX) because of gene mutation in the 3q19 region. In addition to the symptoms typical of acute intermittent porphyria, the accumulation of uroporphyrins and coproporphyrins in tissues results in skin hypersensitivity to UV radiation. The skin becomes susceptible to injuries, blistering, hyperpigmentation, or hair loss. Its course is milder than that of acute intermittent porphyria, and the diagnosis is the same.

Diseases caused by disorders of amino acid metabolism

Phenylketonuria is a congenital disorder of phenylalanine metabolism, inherited in an autosomal recessive manner and caused by a mutation in the gene encoding phenylalanine hydroxylase. Consequently, the synthesis of neurotransmitters (especially

dopamine and serotonin) and the process of myelination are impaired. The main symptom in untreated patients is developmental delay and, later in life, intellectual disability. Characteristic features include fair skin and light hair, as well as a specific, mousy odor of urine. Symptoms include:

- involuntary movement;
- irritability;
- epileptic seizures;
- cataract;
- microcephaly;
- atopic dermatitis;
- baldness.

Diagnosis is based on a positive screening result (colorimetric test or Guthrie test) and the detection of increased levels of phenylalanine in the blood. Treatment involves a low-phenylalanine diet and vitamin supplementation.

Maple syrup disease is an inborn error of metabolism of the branched-chain amino acids – leucine, isoleucine, and valine. It is inherited in an autosomal recessive manner and caused by a deficiency of the mitochondrial branched-chain alpha-keto acid dehydrogenase complex. The effect is an increase in the concentration of leucine, isoleucine, and valine in body fluids, leading to a toxic effect on the central nervous system. Usually, after 5–7 days of life, severe encephalopathy develops, manifested by:

- feeding difficulties;
- alternating increase and decrease in muscle tension;
- involuntary movements;
- epileptic seizures;
- opisthotonus.

A characteristic feature of the disease is the urine odor, reminiscent of maple syrup. Approximately 50% of patients develop severe hypoglycemia, and coma may occur rapidly. The diagnosis is based on screening tests and the detection of high levels of leucine, isoleucine, and valine in the serum, as well as organic acids in the serum and urine. Treatment is primarily dietary. In the acute period of the disease, high-energy and protein-free intravenous nutrition is administered.

Homocystinuria is a heterogeneous group of disorders of sulfur amino acid metabolism (methionine), inherited in an autosomal recessive manner and caused by a mutation in the cystathionine synthase gene located at 21q22.3. The result is an increase in homocysteine concentration in serum and urine, which favors the development of atherosclerosis and embolism. Around 5–9 months of age, seizures and multiple strokes appear, and developmental delay is noticeable. Other symptoms include venous sinus thrombosis, cataracts, glaucoma, skeletal and skin lesions, myocardial infarction, and involvement of the kidneys, liver, and lungs. Diagnosis is based on increased urinary excretion of homocysteine, increased serum levels of methionine and homocysteine,

and a positive nitroprusside test. Treatment involves dietary management and folic acid supplementation.

Lowe's syndrome (oculocerebrorenal syndrome) is inherited in a sex-linked recessive manner and is associated with a mutation in the OCRL gene located on the X chromosome in the Xq26 region, encoding the OCRL1 protein involved in transmembrane transport in the Golgi apparatus. It manifests as:

- congenital cataracts (less commonly, glaucoma);
- severe muscle hypotonia of the newborn;
- progressive and severe impairment of psychomotor development with impaired kidney function.

Diagnosis is based on a triad of clinical symptoms – cataracts, delayed psychomotor development, and renal dysfunction. Treatment includes correction of water and electrolyte imbalances, carnitine supplementation, and surgical treatment of cataracts and, when necessary, glaucoma.

Hartnup disease is an autosomal recessive syndrome associated with a mutation of the SLC6A19 gene located at 5p15.33, encoding a sodium-dependent and chloride-independent neutral amino acid transporter in the intestine and kidneys. The result is a deficiency of amino acids, especially tryptophan, compensated by increased protein metabolism. It manifests as:

- ataxia (sometimes with periods of remission);
- behavioral disorders;
- delayed psychomotor development;
- headaches;
- double vision;
- skin lesions resembling pellagra;
- body weight deficiency;
- increased excretion of amino acids in urine.

The course is usually mild. Diagnosis is based on clinical symptoms, the presence of neutral amino acids, as well as indole compounds in urine, and normal concentrations of neutral amino acids in the blood. Treatment includes a high-protein diet, tryptophan ester supplementation, and avoidance of sunlight and photosensitizing medications.

Disorders of chromosome structure and number

Down syndrome is trisomy of the 21st chromosome pair. An additional copy of the superoxide dismutase gene on the long arm of chromosome 21 is responsible for the clinical picture. From the first months of life, decreased muscle tone and facial dysmorphic features are observed, such as oblique palpebral fissures, wide nasal bridge, epicanthic wrinkles, and small dysplastic ears. The mouth is open, the tongue is protruding and furrowed,

and the corners of the mouth are turned downwards. It is also noteworthy that the head is small and round, flattened in the anterior-posterior dimension, with a short and wide neck, short stature, obesity, dry scaly skin, thin and soft hair, heart defects, and, less commonly, cataracts, hypothyroidism, intestinal obstruction, and dental hypoplasia. Epileptic seizures occur in 5–6% of patients, and most of them show delayed mental development.

Edwards syndrome is trisomy of the 18th chromosome pair. The symptoms include:

- low birth weight;
- underdevelopment of adipose tissue and skeletal muscles;
- decreased muscle tension;
- sucking disorders;
- poor motor activity;
- weakened response to auditory stimuli;
 - dysmorphic features: bitemporally flattened head; low-set and distorted auricles; small lips; receding jaw; high palate; the characteristic arrangement of the fingers is the index finger on the middle finger and the fifth finger on the fourth finger;
 - clitoral hypertrophy;
 - cryptorchidism;
- heart defects;
- inguinal and umbilical hernias;
- eye defects;
- hypertelorism;
- cleft lip and palate;
- hypoplastic nails;
- brain structure defects: hypoplasia of the corpus callosum; cerebellar hypoplasia; cortical dysplasias.

Patau syndrome is trisomy of the 13th chromosome pair. The classic triad of symptoms includes:

- cleft lip and palate;
- microphthalmia;
- polydactyly (extra fingers).

Additional clinical manifestations may include:

- microcephaly;
- low-set and distorted auricles;
- skin defects around the posterior fontanelle;
- widening of the fontanelles and cranial sutures;
- flat hemangiomas around the forehead;
- profound developmental delay;
- lack of response to visual and auditory stimuli, overlap of the fifth finger with the fourth finger;
- heart defects;

- inguinal and umbilical hernias;
- uterine defects;
- cryptorchidism;
- epileptic seizures;
- holoprosencephaly and arhinencephaly.

Klinefelter syndrome occurs in boys and is caused by the presence of at least 2 X chromosomes and at least 1 Y chromosome. The main symptoms involve development of sexual characteristics, which is why it is rarely diagnosed before puberty. Characteristic features include:

- a slim, eunuchoid body habitus;
- gynecomastia;
- long limbs;
- underdevelopment of the testicles and penis.

Spinal curvature, osteoporosis, and pulmonary emphysema are less common. Mental development is delayed in 15–20% of patients.

Fragile X syndrome type A (FRAXA) is caused by a dynamic mutation at Xq27.3, involving the amplification of the CGG sequence. It is the most common cause of intellectual disability in boys after Down syndrome. Characteristic symptoms include psychomotor agitation, difficulty concentrating, and stereotyped hand movements. The other symptoms are:

- facial dysmorphism;
- macrocephaly (enlargement of head dimensions);
- large ears;
- hypotonia (decreased muscle tension);
- macroorchidism (enlarged testicles after puberty).

The diagnosis of chromosomal structure and numerical abnormalities is established through genetic tests. Currently, the treatment is only symptomatic.

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ISBN 978-83-7055-707-2



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