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Headaches

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Introduction to neurology

Neurology is the branch of medicine concerned with the study and treatment of disorders of the nervous system.

Major neurological disorders include:

- Cerebrovascular disease, such as stroke
- Headache disorders
- Seizure disorders, such as epilepsy
- Autoimmune diseases of the central and peripheral nervous system, such as multiple sclerosis (demyelinating diseases), Guillain-Barre syndrome,...
- Infections of the brain, spinal cord and peripheral nervous system, such as meningitis, encephalitis, myelitis, radiculoneuritis
- Neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and syndromes, amyotrophic lateral sclerosis, etc.
- Neuromuscular disorders (myopathies, peripheral neuropathies, neuromuscular junction disorders).
- Degenerative spine diseases and their complications
- Traumatic lesions of the brain, spinal cord and peripheral nerves
- Sleep disorders
- Tumours

From an aetiological point of view, disorders of the nervous system can be divided into two basic groups: genetic (congenital) and acquired lesions. The latter group includes a wide range of causes: vascular disorders, infections, autoimmune diseases, traumatic lesions, compressive disorders or degenerative diseases.

In addition, lesions of the nervous system can be divided into two types: structural and functional. Structural lesions include trauma, stroke, tumour, inflammation, compression and many others. From a functional point of view, the nervous system can be affected by metabolic dysregulation, e.g. hypo-, hyperglycaemia; hypo-, hypernatremia; hypo-, hypercalcemia; hypo-, hypermagnesemia; hypoxia; hyperammonemia; ion and channel and synaptic abnormalities, ... Some diseases involve both of the above-mentioned components. If the cause of the disease is not known, this possibility is called idiopathic disease.

From another point of view, the nervous system can be damaged at a certain level to such an extent that some (or even all) of its function is lost (for example, paresis or loss of speech or language due to stroke). The second group of symptoms is called irritative. This term refers to a set of symptoms that are typically associated with increased neuronal excitability or abnormal electrical activity in the nervous system. These symptoms often arise from a part of the nervous system experiencing irritability or hyperexcitability (e.g. rhythmic motor activity during an epileptic seizure or neuropathic pain and paresthesia in painful mono- or polyneuropathies).

The clinical manifestation of the disease depends on whether the whole nervous system is affected or only part of it. In the latter case, only part of the nervous system is not functioning properly (For more details, see the section on focal and non-focal neurological deficits below.) In this situation, the first step is to determine whether the central or peripheral nervous system is affected (see below). In addition, by looking at the distribution of symptoms and signs, neurologists can usually identify the specific part of the nervous system that is affected in a particular patient. Knowledge of the basic anatomical principles

of the organization of the nervous system is therefore essential for making a correct diagnosis and for understanding neurology in general.

1. Nervous system

The nervous system is a highly complex and sophisticated system of the body that regulates and co-ordinates its actions and sensory information through the transmission of signals to and from different parts of the body. It has two main parts:

- The **central nervous system (CNS**): the brain and the spinal cord. The brain can be divided into the infratentorial area (brainstem and cerebellum) and the supratentorial area (cortex, thalamus, basal ganglia and white matter of the hemispheres).

- The **peripheral nervous system (PNS**) consists mainly of nerves, which are closed bundles of long fibres or axons that connect the CNS to every other part of the body. This system also includes neural elements called "sensory receptors" in the eyes, ears, skin, etc. The PNS is divided into two separate subsystems, the **somatic** (motor and somatosensory) and **autonomic (**sympathetic and parasympathetic). The autonomic nervous system is involuntary. Nerves that come from the brain are called **cranial nerves**, while those that come from the spinal cord are called **spinal nerves**. Several PNS levels can be distinguished: neuromuscular junction, peripheral nerve (motor-sensitive-mixed), plexus, spinal roots, peripheral (lower) motor neuron, pseudounipolar neuron.

At a cellular level, the nervous system is defined by the presence of a specific type of nerve cell called **a neuron**. Neurons have unique structures that allow them to send signals quickly and precisely to other cells. They send these signals in **electrochemical form along thin fibres** called axons, which cause chemicals called **neurotransmitter**s (glutamate, GABA, acetylcholine,...) to be released **at junctions called synapses**. A cell that receives a synaptic signal from a neuron can be excited, inhibited or otherwise modulated. The connections between neurons can form neural pathways, neural circuits and larger networks that generate an organism's perception of the external environment and determine its behaviour. In addition to neurons, the nervous system contains other specialised cells called **glial cells,** which provide structural and metabolic support.

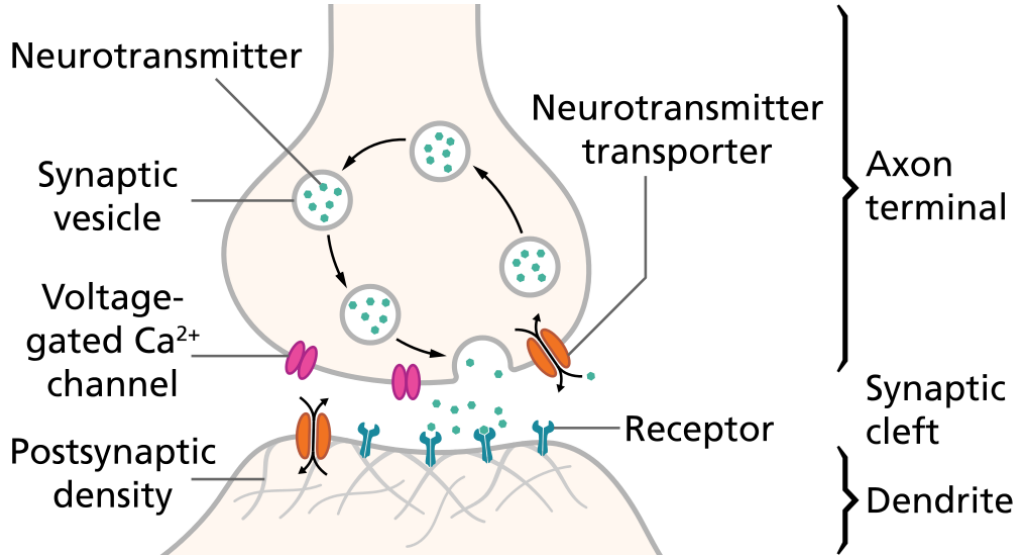


Fig. 1 Scheme of synaptic junction (nerve to nerve)

1.1 Signs and symptoms of nervous system disorders

In general, neurological deficits can be divided into focal and non-focal. **A focal neurological deficit** is caused by a lesion (ischemia, hemorrhage, tumor infiltration or compression, etc.) of a specific part of the peripheral or central nervous system, i.e. a specific area of the brain or spinal cord or a peripheral nerve The lesion therefore only affects the function of the relevant part of the nervous system. The clinical **manifestation depends on what specific functions are localized in the affected area** (i.e. what pathways pass through it or what centers are located there). The most common clinical manifestations are motor (paresis, repetitive focal movements during an epileptic seizure), sensory (hypoesthesia, paresthesia), or affect speech or language functions. Olfaction, vision, hearing and vestibular dysfunctions are also considered focal neurological deficits.

Typical examples of the focal neurological deficits are global aphasia and right-sided hemiparesis in left-sided middle cerebral artery ischaemia, or paresthesias of the fingers I-IV and the palm of the right hand in a patient with compression of the median nerve in the wrist, i.e. right-sided carpal tunnel syndrome.

The nature, distribution and severity of the clinical symptoms and signs may thus indicate which area of the brain or nervous system is affected.

Knowledge of at least the most important neural pathways and centres is therefore a key condition for the diagnosis of neurological diseases. Knowledge of at least the major nerve tracts and centres is therefore essential for the diagnosis of neurological diseases. The basic anatomical principles are reviewed below.

In contrast, **non-focal deficits** are **NOT specific to a particular area of the brain**. They can include confusion, headaches, cognitive impairment or emotional problems. It's usually not possible to identify the specific area of the brain or nervous system that is affected in patients with this type of clinical presentation.

The following **are the most common signs and symptoms of a nervous system disorders**. However, each person may experience the symptoms in a different way. In addition, each neurological condition presents with only some of these symptoms, often in typical and largely disease-specific combinations called '**syndromes'**.

Symptoms may include:

- Weakness or loss of muscle strength
- Muscle wasting
- Loss of sensation (numbness) or tingling
- Headaches
- Visual field loss
- Double vision
- Language impairment (expression or comprehension)
- Slurred speech
- Altered consciousness or awareness
- Memory loss, confusion
- Impaired mental ability
- Lack of coordination
- Dizziness or loss of balance
- Muscle rigidity, hypokinesia, and bradykinesia
- Tremors, hyperkinesias
- Seizures

— Back pain that radiates into the leg or the arm

1.2 Upper and lower motor neuron

Voluntary movement is controlled by a motor nervous system. The body of the **first (upper) motoneuron is located in the cerebral cortex**. Nerve cell impulses (or action potentials) leave the motor cortex via the axons of the upper motoneurons, which cross (decussate) at the junction of the medulla oblongata and the spinal cord. The axons then enter the spinal cord as part of the **corticospinal tracts**. The corticobulbar pathway then carries impulses from the motor cortex to the nuclei of the cranial nerves in the brainstem. In this case, the pathway crosses just short of the nucleus. **Second (lower) motor neurons** then carry impulses from **the ventral horns of the spinal cord or the nuclei of the cranial nerves** to the skeletal muscles. If a lesion occurs in the upper motor neuron (and it does not matter whether it is the body or the axon), we are talking about a **central lesion**. The manifestation of the affected function will be **contralateral** to the lesion. Similarly, a lesion of the lower motor neurons is called a **peripheral lesion**. The manifestation of the affected function is **ipsilateral** to the lesion. The manifestation of a motor neuron lesion is paresis (some movement is possible) **or plegia** (no movement).

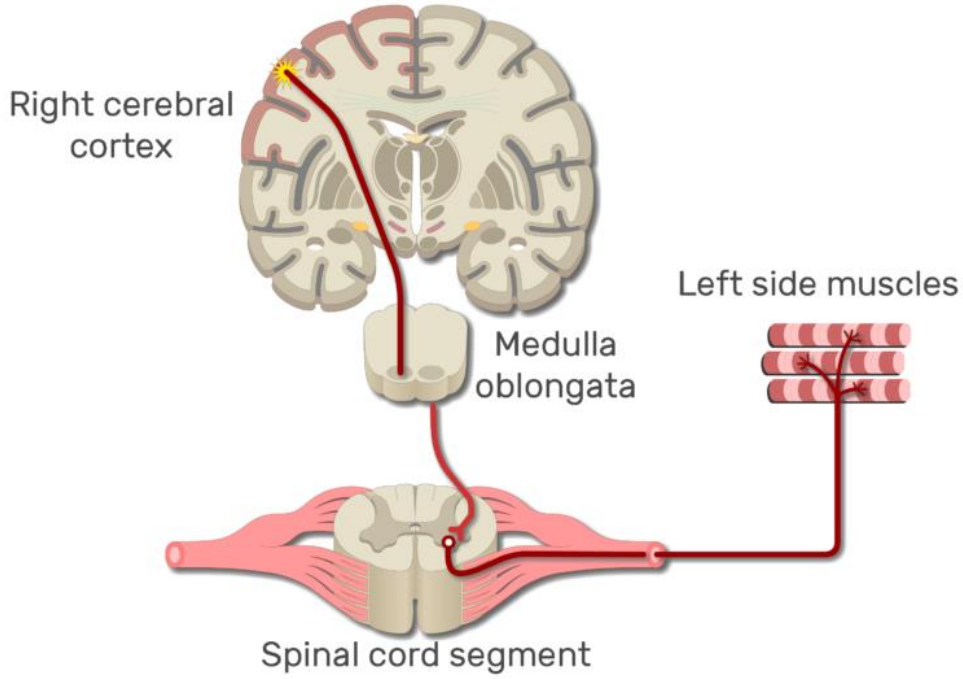


Fig.2 Upper and lower motor neuron

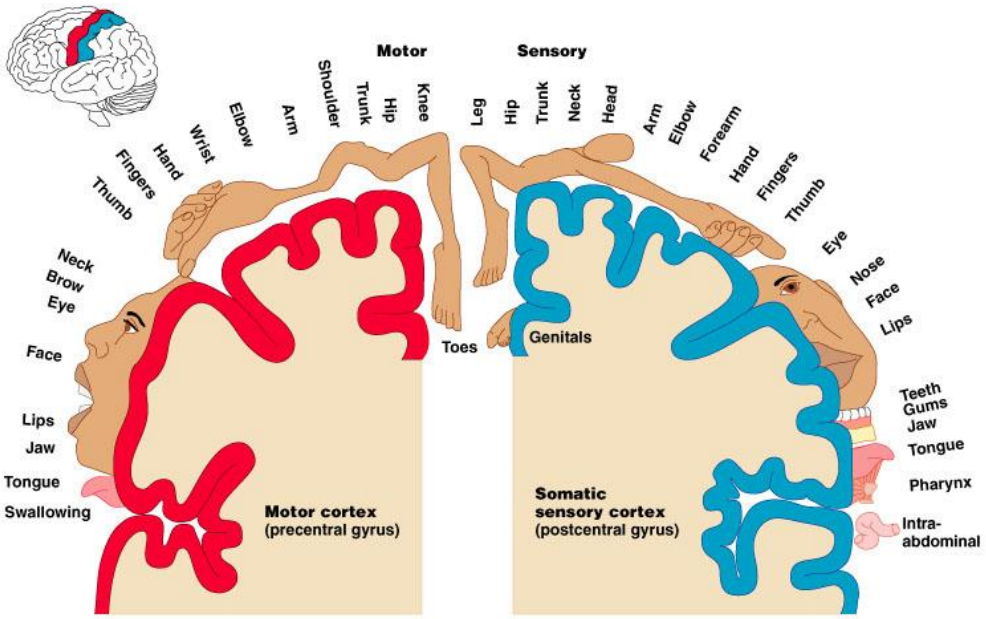


Fig. 3 The topographical representation of the homunculus - sensory and motor cortex

1.3 Somatosensory system

The somatosensory system is a complex system of sensory neurons and pathways that respond to changes at the surface or inside of the body. The axons (as afferent nerve fibres) of sensory neurons connect to or respond to different **receptor** cells (mechanoreceptors, thermoreceptors, chemoreceptors and nociceptors,...). Sensory receptors are found throughout the body, including the skin, epithelial tissues, muscles, bones and joints, internal organs and the cardiovascular system. **The first-order neurons** are the pseudounipolar cells whose cell bodies are located in the **dorsal root ganglion** of the spinal nerve, or in the trigeminal ganglion, or in the ganglia of other sensory cranial nerves. These neurons are connected to the receptor and transmit the signal to the spinal cord. The somatosensory system consists of **two basic neural pathways.**

1. Neurons that carry information about **deep sensations (vibration and proprioception**, i.e. the sensation of position, direction and changes in speed of movement). When these neurons enter the spinal cord, they rise in the ipsilateral spinal column in the medulla oblongata of the brainstem, where they switch to second-order neurons and cross over. They then continue to the thalamus and primary somatosensory cortex. This pathway is called the **spino-bulbo-thalamo-cortical pathway** (dorsal column, spinobulbar pathway).

2. Neurons that carry information about **superficial sensations - temperature and pain -** cross in the spinal cord near their entry point and the rest of the pathway goes along the contralateral part of the spinal cord and the brainstem in the thalamus and later on to the primary somatosensory cortex. This pathway is called the **spinothalamic (or spino-thalamo-cortical) pathway.**

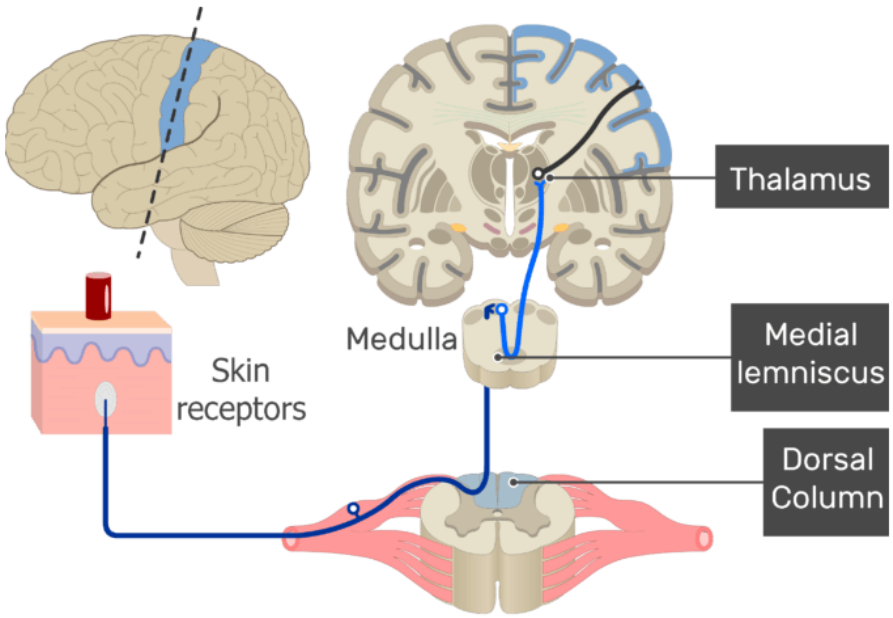


Fig.4 The somatosensory system – spinobulbar pathway

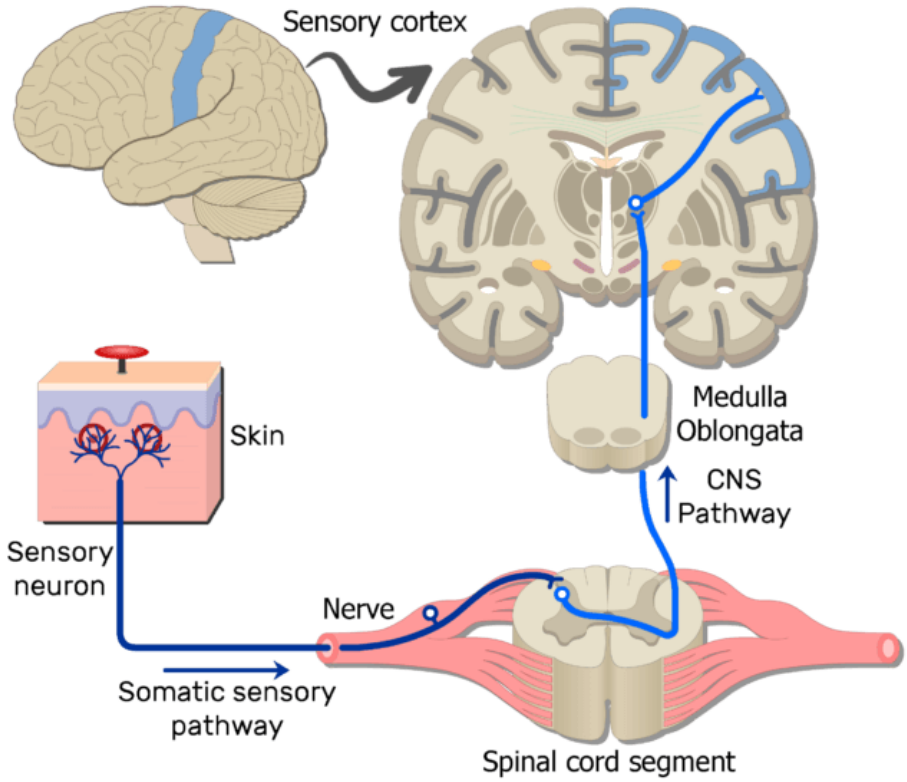


Fig.5 The somatosensory system – spinothalamic pathway

The superficial **tactile sensation (touch)** is transmitted in both pathways.

As can be seen from the pictures information, the two tracts cross each other in their course. Therefore, lesions localized above the crossing point lead to **contralateral** clinical manifestations (i.e., contralateral hemihypoesthesia for the corresponding modalities). **Second-order neurons** have their cell bodies either in the spinal cord (spinothalamic pathway) or in the brainstem (spinobulbar pathway). **Third-order** neurons are located in the **thalamus and terminate in the postcentral gyrus** of the parietal cortex, specifically in the primary somatosensory cortex or related areas. The most common clinical symptoms caused by lesions of the somatosensory system are **hypoesthesia or anesthesia** (for some or even all modalities) (so-called negative symptoms) or **paresthesia and neuropathic pain** (positive symptoms). Some patients experience a combination of these two types of symptoms**.**

1.4 Cranial nerves

The olfactory nerves (I) and the optic nerves (II) arise from the **cerebrum**, while the remaining ten pairs of cranial nerves arise from **the brainstem**, the lower part of the brain. The cranial nerves provide **motor, sensory and autonomic s**upply mainly to the structures within the head and neck. The sensory supply includes both 'general' sensations such as temperature and touch, and 'special' senses such as taste, visual perception, smell, balance and hearing.

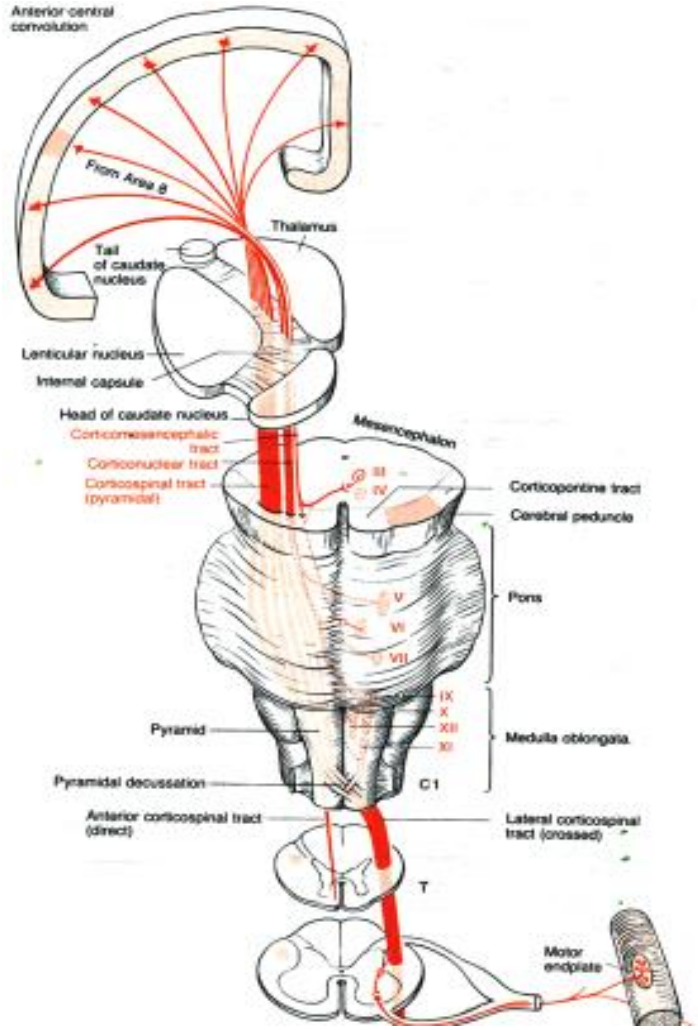


Fig.6 The cortico-bulbar motor pathway, the position of motor nuclei of cranial nerves

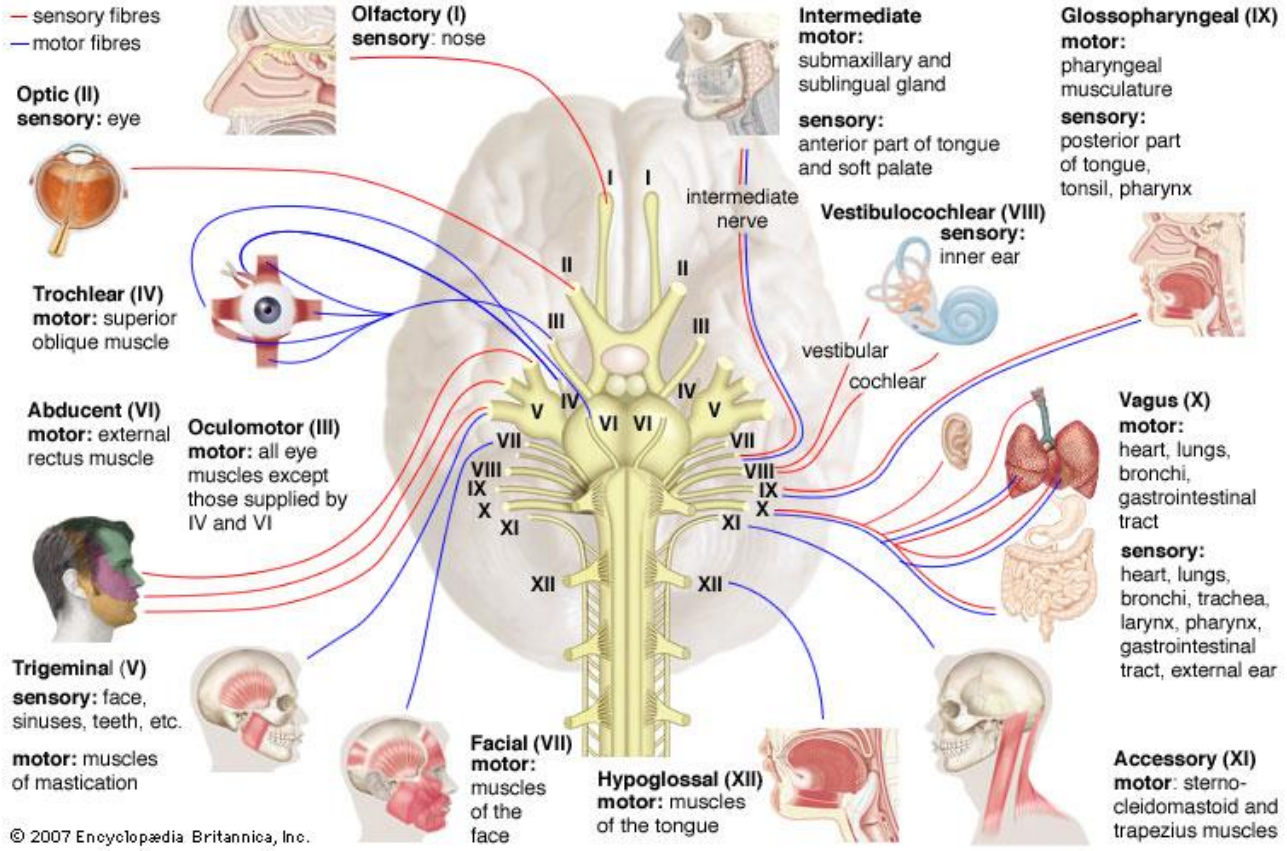


Fig.7 Examples of cranial nerve functions

1.5 Functions of individual brain lobes/neocortex

The functional specialisation of individual parts of the neocortex has been taught in detail in neuroanatomy. The most important information is summarised in the following tables and figures.

Frontal Lobe

- Frontal Lobe
- Body Movement
- Personality
- Reasoning, concentration, judgement
- Executive function (planning, organising, problem solving)
- Emotional control centre and reactions, impulse control
- Social interactions
- Memory (mainly short-term)
- Language - Expression (dominant hemisphere)
- Smell

Parietal Lobe

- Receives and processes sensory input from the body and skin (somatosensory information)
- Integrates sensory information between different modalities
- Body awareness

Temporal Lobe

- Hearing
- Language - understanding (dominant hemisphere)
- Recognising faces
- Meaning and emotion
- Memory (mainly long term)
- Smell

Occipital Lobe

- Visual perception

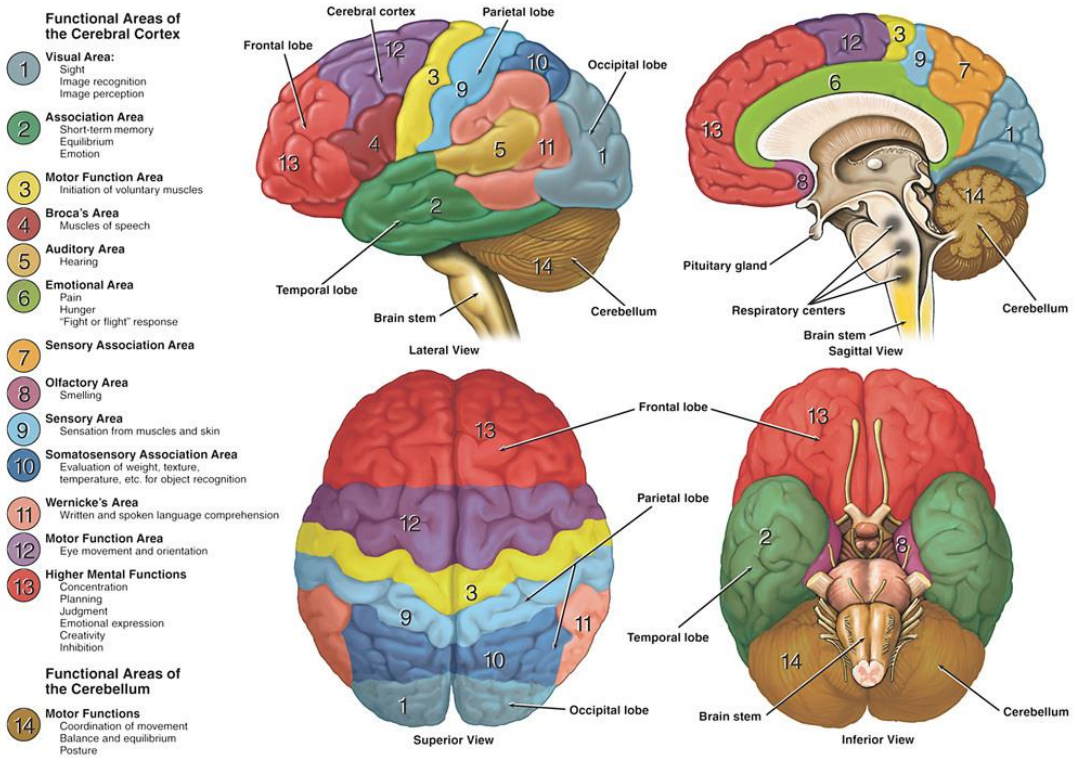


Fig.8 Functional Areas of the Cerebral Cortex

1.6 Basal ganglia

The term "basal ganglia" (BG) refers to a group of subcortical nuclei that are primarily responsible for **motor control**. Disruption of the basal ganglia network is the basis of several movement disorders. Important functions of the BG are posture, regulation of muscle tone and coordination of voluntary and automatic movements. The basal ganglia are involved in the generation of movement programmes, the initiation and timing of movements, the adaptation of movements to external conditions, as well as other functions such as motor learning, executive functions and behaviour, emotionality and mental integration. Manifestations of basal ganglia damage include rigidity, hypo- and bradykinesia, tremor, dystonia, chorea, etc.

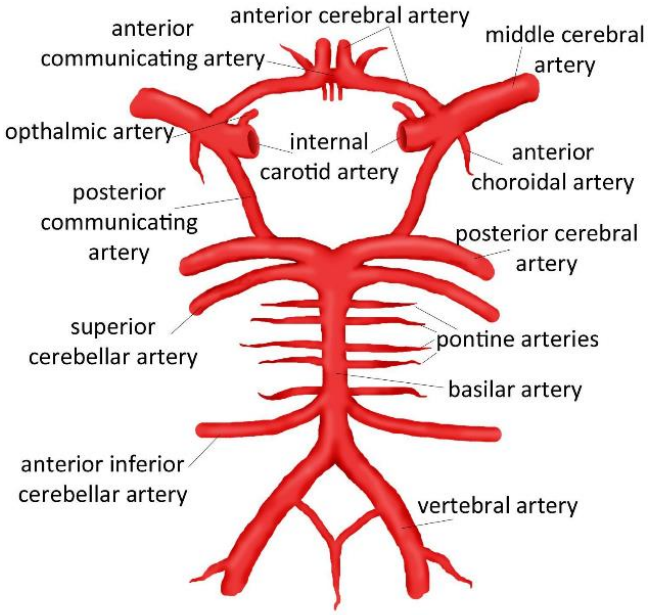
1.7 Cerebellum

The physiological functions of the cerebellum are the regulation of muscle tone, balance and movement co-ordination (course and goal of movement, positioning of body segments, recruitment of muscle groups during movement). Clinical manifestation **is ipsilateral**, i.e. the affected part of the body is on the same side as the affected hemisphere of the cerebellum.

1.8 Blood supply to the brain

The **brain** receives **blood** from two sources: the internal carotid arteries, which arise from the common carotid arteries, and the vertebral arteries. The internal carotid arteries branch to form two major cerebral arteries, the anterior cerebral artery, and the middle cerebral artery. These two arteries together supply the major part of the anterior and middle cerebral hemispheres.

The two vertebral arteries join together at the base of the skull to form the basilar artery, which supplies the brainstem. At the level of the midbrain, the basilar artery bifurcates to form the two posterior cerebral arteries, which supply the posterior cerebral hemispheres.



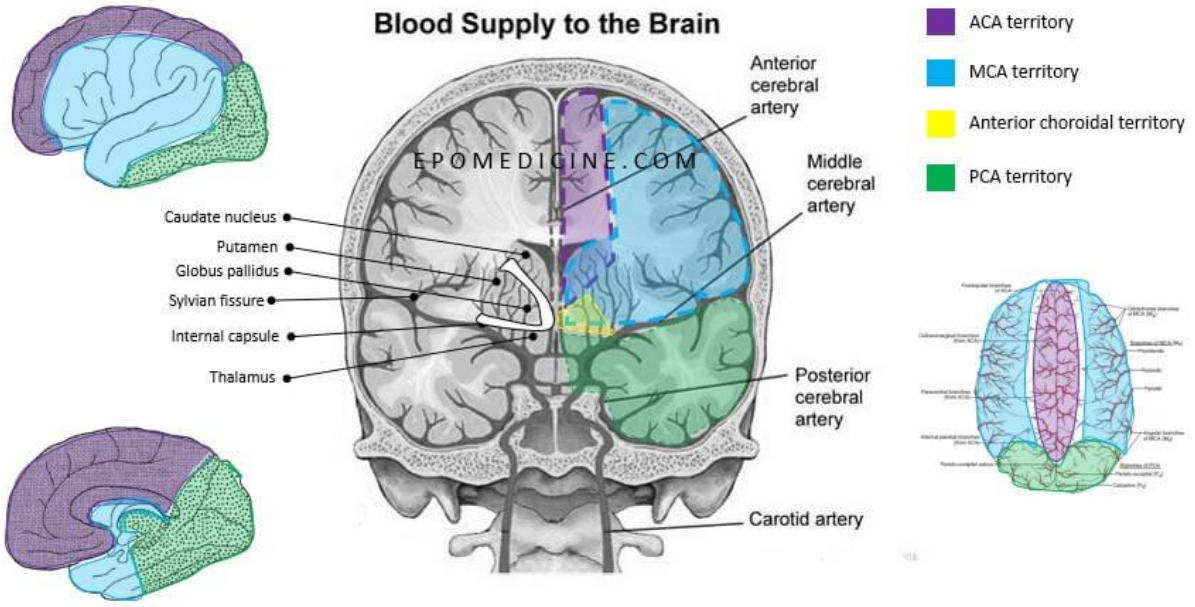


Fig.9 Blood supply to the brain – territories

2 Headache

2.1 Basic terms

Headache: Pain located in the head, above the orbitomeatal line and/or nuchal ridge.

Facial pain: Pain below the orbitomeatal line, anterior to the auricles, and above the neck.

Cervical pain: Pain in the nuchal region (dorsal aspect of the upper neck, including the region of insertion of neck muscles on the cranium).

Attack of headache: Headache that builds up, remains (at a certain level for minutes, hours or days), then wanes until it has resolved completely.

Duration of attack: Time from onset until termination of an attack of pain.

Frequency of attacks: The rate of occurrence of attacks of headache per time period (commonly one month).

New headache: Any phenotype of headache from which the patient was not previously suffering.

Headache diagnosis: Diagnostic criteria for the particular type of headache must be met in an individual patient to obtain a specific headache diagnosis. The basic classification of headaches is based on pathophysiology, as primary or secondary (with different types, subtypes or subforms). Patients with different headache phenotypes should receive more than one diagnosis (remember that patients with migraine or tension-type headache may have any type of secondary headache, which should be considered especially if the clinical presentation of the headache is different from previous episodes experienced by the patient).

Primary headache: Headache or headache disorder that is not caused by or attributed to another disorder. The potentially causative disorder must be excluded, the headache phenotype must fulfil the requirements described in the criteria for this diagnosis and a minimum number of attacks (usually five) must be experienced.

Secondary headache: Headache or headache disorder caused by another underlying disorder. A secondary headache is attributed to the causative disorder, although it may have clinical characteristics similar to some types of primary headache.

In general, the most important tools for distinguishing between headache types are the **patient's history and the clinical neurological examination**. The former provides information about the quality and intensity of the headache, the mode of onset, the time course (including the presence of exacerbations/remissions or continuous increase in pain intensity), the presence of associated symptoms like nausea and vomiting, photophobia (intolerance of bright light), phonophobia (intolerance of intense sounds), and factors that relieve or aggravate the pain. The latter focuses on identifying the presence of any focal neurological deficits.

2.2 Headache classification (examples of types or subtypes are provided in brackets)

2.2.1 Primary headaches

1. **Migraine** (e.g. migraine with aura, migraine without aura)

2. **Tension-type** headache

3. **Trigeminal autonomic** cephalalgias (e.g. cluster headache)

4. **Other** primary headache disorders (e.g. primary exercise headache, primary headache associated with sexual activity)

2.2.2 Secondary headaches

(It is not necessary to know this classification in detail - rather, it is here to give an idea of the basic spectrum of causes for the development of secondary headaches)

5. Headache attributed to **trauma or injury** to the head and/or neck (e.g. acute headache attributed to traumatic injury to the head or whiplash, persistent post-traumatic headache)

6. Headache attributed to cranial and/or cervical **vascular disorder** (e.g. acute headache attributed to non-traumatic subarachnoid haemorrhage, headache or facial or neck pain attributed to cervical carotid or vertebral artery dissection, headache attributed to cerebral venous thrombosis, headache attributed to reversible cerebral vasoconstriction syndrome, headache attributed to giant cell arteritis)

7. Headache attributed to **non-vascular intracranial disorder** (e.g. headache attributed to intracranial neoplasia, headache attributed to idiopathic intracranial hypertension)

8. Headache attributed to a **substance or its withdrawal** (e.g. medication-overuse headache, alcohol-induced headache)

9. Headache attributed **to infection** (e.g. headache attributed to intracranial infection, headache attributed to systemic viral infection)

10. Headache attributed to **disorder of homoeostasis** (e.g. headache attributed to arterial hypertension [systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥120 mmHg is required; headache remits after normalization of blood pressure])

11. Headache or facial pain attributed to disorder of the **cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cervical** structure

12. Headache attributed to **psychiatric** disorder

2.3 Red flags for severe secondary headaches

In the case of a new or unexpected headache, the differential diagnosis includes a number of serious secondary headaches that are important to recognize and require urgent investigations, including CT and CT angiography (both arterial and venous phases) of the head and/or CSF examination.

The following red flags in the history or on examination may suggest secondary headache:

- Headache that is **new in an individual patient** (especially in a patient older than 50 years or in a prepubertal child, in a patient with a history of cancer, HIV infection, immunodeficiency, or recent head trauma) (may indicate meningitis, space-occupying lesions, stroke and many others).
- **Thunderclap** headache (severe headache with abrupt or 'explosive' onset) (may indicate subarachnoid hemorrhage).
- **Progressive** headache that worsens over weeks or longer, usually worse when lying down (may indicate intracranial space-occupying lesion).
- Headache associated with **focal neurological signs**, including headache with "atypical aura" (no history of migraine with aura, lasting >1 hour, or including motor weakness) (may be symptoms of transient ischemic attack or stroke).
- Otherwise unexplained **fever** associated with headache (may indicate meningitis).

2.4 Basic principles of primary headaches treatment

Every headache requires an **appropriate initial evaluation**, i.e. assessment of the headache phenotype by history and clinical neurological examination, combined with neuroimaging in appropriate cases. Primary headache is usually a lifelong condition (at least in adult patients) and many patients with primary headache need only **acute (symptomatic) treatment**. Simple, common analgesics (paracetamol, non-steroidal anti-inflammatory drugs) should be taken in adequate doses early in the attack, combined with antiemetics in patients with nausea or vomiting. Opioids should be avoided. Specific symptomatic therapies are available for certain types of primary pain (e.g. triptans for migraine). Any patient with frequent or prolonged primary headache should be offered **prophylaxis** in addition to acute medication. Prophylactic treatment for 3-6 months in migraine and tension-type headache requires slow titration (starting with a low dose and increasing every 1-2 weeks) to reduce the risk of intolerance. It is better to avoid prophylaxis during pregnancy and lactation, as several drugs are contraindicated. If prophylactic treatment fails or is contraindicated, **biological therapies based on anti-CGRP drugs** should be considered in migraine patients.

2.5 The most important types of primary headache

2.5.1 Migraine

Migraine is the most disabling headache disorder, having a large negative socioeconomic impact due to temporary disability and loss of productivity during migraine attacks. The prevalence of migraine in the general population is 12% to 16%. In prepubertal children, the prevalence is around 3-7%, with no difference between girls and boys. From puberty onwards, the prevalence of migraine increases, and females are more affected than males by a ratio of 3:1. The pathophysiology of migraine attacks involves the vasoactive neuropeptide CGRP (calcitonin gene-related peptide). There are two main types of migraine: migraine without aura and migraine with aura.

Migraine without aura is a clinical syndrome characterized by attacks lasting 4-72 hours. Typical characteristics of the headache include:

- Unilateral location
- Pulsating quality
- Moderate or severe intensity
- Association with nausea, photophobia, and phonophobia
- Aggravation by routine physical activity

A minority of migraineurs (about 20%) experience migraine aura, which may present as:

- Visual disturbances (scotoma, colored or black-and-white zigzag lines)
- Sensory disturbances (usually unilateral arm and/or face paresthesias)
- Speech or language disturbances
- Motor symptoms (weakness)

The temporal course of the aura is characterized by the gradual development of symptoms (over more than 5 minutes), with each symptom's duration not exceeding 60 minutes. Aura symptoms are completely and spontaneously reversible and are usually, but not always, accompanied or followed by headache (with or without migraine characteristics). The following table summarizes treatment options for patients with migraine:

Acute treatment (NSAID or common analgesics and antimemetics)
Oral: ibuprofen, diclofenac, metamizol
Rectal administration of indomethacin
Intravenous infusion therapy containing sodium salicyliate + metoclopramide + Mg_2SO_4 in normal saline solution (many alternatives are available)
Acute treatment (triptans) (contraindicated in pregnancy; should be avoided in people with: uncontrolled hypertension; coronary heart disease, cerebrovascular disease or peripheral vascular disease; multiple risk factors for coronary or cerebrovascular disease)
sumatriptan (oral or nasal spray or subcutaneous injection), eletriptan or zolmitriptan
Prophylactic treatment (conventional drugs for daily oral medication)
topiramate (contraindicated in pregnancy)
amitriptyline
metoprolol or bisoprolol (ECG monitoring recommended)
cinarizine
sodium valproate (avoid in women of childbearing potential, contraindicated in pregnancy)
Prophylactic treatment – Biologic therapies (anti-CGRP monoclonal antibodies, subcutaneous administration monthly or quarterly)
erenumab

fremanezumab
galcanezumab

2.5.2 Tension-type Headache (TTH)

Tension-type headache is the most common type of headache, with a lifetime prevalence in the general population ranging from 30% to 78% (depending on the study). It is usually characterized by:

- Infrequent episodes of headache
- Typically bilateral headache
- A pressing or tightening quality
- Mild to moderate intensity
- Headache episodes lasting from minutes to days
- Pain not aggravated by routine physical activity
- Not associated with nausea
- Mostly without photophobia or phonophobia (although mild photophobia or phonophobia may be present).

The following table summarizes treatment options for patients with tension-type headache:

Acute treatment (NSAID or common analgesics, over-the-counter drugs)
Oral: ibuprofen, diclofenac, metamizol, paracetamol
Rectal administration of indomethacin
Prophylactic treatment
amitriptyline
mirtazapine
venlafaxine

2.5.3 Cluster Headache (CH)

Cluster headache is characterized by brief attacks of very severe unilateral orbital and/or supraorbital pain associated with ipsilateral cranial autonomic symptoms, including:

- Conjunctival injection
- Lacrimation
- Nasal congestion
- Rhinorrhea
- Forehead and facial sweating
- Miosis
- Ptosis
- Eyelid edema

These headache attacks usually last between 15 and 180 minutes and occur from once every other day to eight times a day, often at night. The attacks are somehow clustered into so-called cluster periods, which usually last several weeks with monthly or yearly breaks. The following table summarizes treatment options for patients with cluster headaches:

Acute treatment
sumatriptan
oxygen inhalation
Prophylactic treatment
verapamil
topiramate
lithium carbonate

2.6 The most important types of secondary headaches

As mentioned above (in Section 2.2), there is a wide range of diseases or conditions that may present with secondary headache. The most important clinical entities (which may even be life-threatening or cause significant and long-lasting disability) are the following:

2.6.1 Acute cerebrovascular diseases (Stroke)

Acute cerebrovascular diseases, commonly known as strokes, rank among the **leading causes of hospital admissions**. The incidence of these conditions varies across regions, with the Czech Republic reporting an annual incidence of approximately 241 per 100,000 people and a prevalence of 700 per 100,000, where nearly one-third of affected individuals face severe disability.

Strokes are categorized into three primary types based on their origin and characteristics:

- **acute ischemic stroke** (80-87%): This prevalent type occurs due to the sudden blockage or narrowing of a blood vessel in the brain, leading to a significant reduction or complete cessation of blood flow to specific brain regions. Common causes include large artery atherosclerosis (embolus or thrombosis), small vessel occlusion, cardioembolism (often linked to atrial fibrillation), and hypercoagulability conditions like antiphospholipid antibody syndrome or polycythemia vera.
- **acute intracerebral hemorrhage** (10-15%): This type arises from the localized accumulation of blood within the brain parenchyma or ventricular system, not associated with trauma. It typically results from the rupture of a blood vessel within the brain.
- **acute subarachnoid hemorrhage** (3-5%): In this less common form of stroke, bleeding occurs into the subarachnoid space, predominantly due to the rupture of an aneurysm. See the separate section below for more details on this type of stroke.

All of these conditions share a **common prominent clinical feature—an abrupt onset** of symptoms and signs that develop within seconds or a few minutes.

- In the case of acute ischemic stroke and acute intracerebral hemorrhage**, focal neurological deficits** are the major clinical symptoms, such as hemiparesis, hemihypesthesia, aphasia or dysarthria, hemianopia, and occasionally others. These deficits arise due to impaired function in specific brain regions caused by hypoperfusion or blood extravasation. While headaches may occur, they are usually not the primary clinical presentation.
- On the other hand, acute subarachnoid hemorrhage is characterized by a prominent **headache**, which may be accompanied by focal neurological deficits in some cases.

Additionally, the term transient ischemic attack (TIA) refers to a specific type of acute ischemic stroke characterized by a transient episode of neurological dysfunction resulting from focal brain, spinal cord, or retinal ischemia. Importantly, neuroimaging does not show evidence of acute infarction in TIA cases.

Major **risk factors for ischemic stroke**:

- Cardiovascular diseases, including arterial hypertension, myocardial infarction, atrial fibrillation, and left atrial enlargement.
- Metabolic factors, such as high cholesterol, diabetes, and obesity.
- Lifestyle factors, like smoking, heavy alcohol use, and drug abuse.
- Carotid artery stenosis.
- History of transient ischemic attack (TIA).
- Dietary factors, including increased sodium intake and consumption of processed foods, with lower intake of fruits, vegetables, fish, and whole grains.
- Poor physical function.
- Demographic factors, such as age, sex, race, and lower income.
- Genetic factors.
- Sleep apnea.
- Hormone replacement therapy and oral contraceptives (ethinylestradiol).

Major **risk factors for intracerebral hemorrhage**:

- Arterial hypertension.
- Bleeding disorders.
- Use of anticoagulant treatment.
- Presence of abnormal vascular structures, such as aneurysms, arteriovenous malformations, and abnormal vascularization in tumors.
- Demographic factors, smoking, and alcohol or drug abuse also contribute to the risk of hemorrhagic stroke.

In the management of acute stroke, **time plays a critical role**, and treatment must be administered as swiftly as possible. Precisely determining **the time of symptom onset** is essential when assessing eligibility for thrombolytic therapy, endovascular therapy, or other emergency interventions. This is typically defined as the moment the patient was last asymptomatic and at their neurological baseline or when they were "last known well."

The primary **diagnostic tool** used in acute stroke patients (besides history and clinical neurological examination) is a **noncontrast CT scan.** It serves multiple purposes, including diagnosing stroke, ruling out intracranial hemorrhage (which is an absolute contraindication to thrombolytic therapy), and is the preferred method for diagnosing subarachnoid hemorrhage. For potential candidates for mechanical thrombectomy for ischemic stroke, additional imaging techniques like **CT angiography, CT perfusion**, diffusion-weighted MRI, or MRI perfusion may be used to determine eligibility.

Furthermore, **certain blood tests** (such as blood glucose, serum electrolytes, renal function tests, blood count, and coagulation profile) and an electrocardiogram (**ECG**), along with other relevant tests when necessary, are highly relevant in the evaluation process.

Prompt evaluation and initial management of stroke patients are crucial to enable timely intervention, which can help preserve neurological function and reduce mortality. Patients should be **admitted to the stroke unit** or intensive care unit. **Thrombolytic therapy** (using a fibrinolytic agent called **alteplase**, also known as tissue plasminogen activator (tPA)) is recommended for patients with ischaemic stroke and a measurable neurological deficit within 4.5 hours of stroke onset (this interval may be extended based on CT perfusion scan according to specific criteria), provided there are no contraindications. Endovascular therapy, particularly **mechanical thrombectomy** with a stent retriever, is also an option for achieving reperfusion in adults with functionally disabling acute ischemic stroke within 6-24 hours after stroke onset, depending on imaging studies.

Moreover, several measures should be taken to **optimize the patient's internal environment**, including blood pressure control, blood glucose management, fluid and electrolyte balance, fever reduction, and treatment of any infectious complications. Early **physical therapy** is also essential.

In addition, the implementation of strategies to address underlying risk factors and prevent future strokes, such as lifestyle changes, elimination (or reduction) of cerebrovascular risk factors (if applicable) and medication management (e.g. **acetylsalicylic acid**, possibly in combination with clopidogrel, or oral anticoagulants in specific cases) is referred to as **secondary stroke prevention**.

For **hemorrhagic stroke**, managing high **blood pressure and discontinuing anticoagulant/antithrombotic therapy** are critical. In specific cases, surgical evacuation of the hematoma may be considered. Similar to ischemic stroke patients, optimizing the internal environment and early physical therapy are important steps in the management process.

2.6.1.1 Subarachnoid Hemorrhage (SAH)

Subarachnoid hemorrhage (SAH) is a serious type of stroke that occurs in approximately 8-10 patients per 100,000 per year. It is most frequently caused by the **rupture of aneurysms** of the vessels lying in the subarachnoid space (70-75%). Other causes, such as rupture of arteriovenous malformation (AVM) or so-called perimesencephalic SAH (presumed to be caused by the rupture of small intracranial veins), are much less frequent (the former representing up to 5% of SAH, and the latter about 20%).

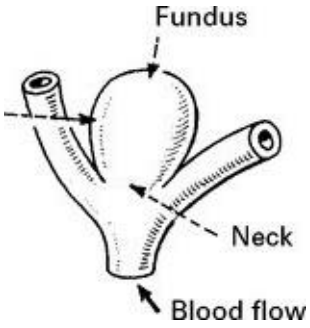
The most prominent clinical symptom is a **severe headache**. Its **onset is usually instantaneous** (often described as a 'blow to the head'), and patients often describe it as 'the worst they have ever experienced.' Nausea, vomiting, photophobia, and phonophobia commonly occur, and objective signs of **meningeal irritation** (neck stiffness, Kernig's sign) develop after 3–12 hours.

Other clinical symptoms depend on the extent of the bleed. In major SAH, a transient or prolonged loss of **consciousness or epileptic seizure** may immediately follow. If the ruptured aneurysm or AVM is located on the small vessel embedded within the brain tissue, a focal hematoma develops and leads to **focal signs** depending on the location of the hematoma, e.g., limb weakness or aphasia. Similar focal symptoms and signs may develop due to focal ischemia, which may occur in the territory supplied by the ruptured vessel, but this occurrence is less common among SAH patients.

The **CT scan** is the investigation of choice and should be performed as soon as possible after the headache onset. It confirms the diagnosis of SAH in 95% of patients (if within 48 hours of the bleed). In patients with a negative CT scan despite a highly suspicious medical history, **cerebrospinal fluid** (CSF) examination from the lumbar puncture should be performed more than 6-12 hours from onset. SAH could be confirmed by the presence of so-called hemoglobin degradation products (bilirubin, oxyhemoglobin, methemoglobin) detected on **spectrophotometry**. These products indicate an 'older

bleed,' i.e., more than 6 hours. Fresh blood is not significant since it may be artificial from the puncture procedure. In patients with confirmed SAH (either by CT or by spectrophotometry), **acute angiography** is a very important next diagnostic step (mostly CTAG, alternatively digital subtraction angiography or MRAG could be used), which shows the aneurysms or AVM.

Intracranial aneurysms are found in about 2% of the population (autopsy-based data). In patients below 40 years, they are more frequent in men, while in older age, more prevalent in female patients.



They are usually saccular.

Their size varies from a few millimeters to several centimeters and is mostly located in the vessel bifurcation of the circle of Willis.

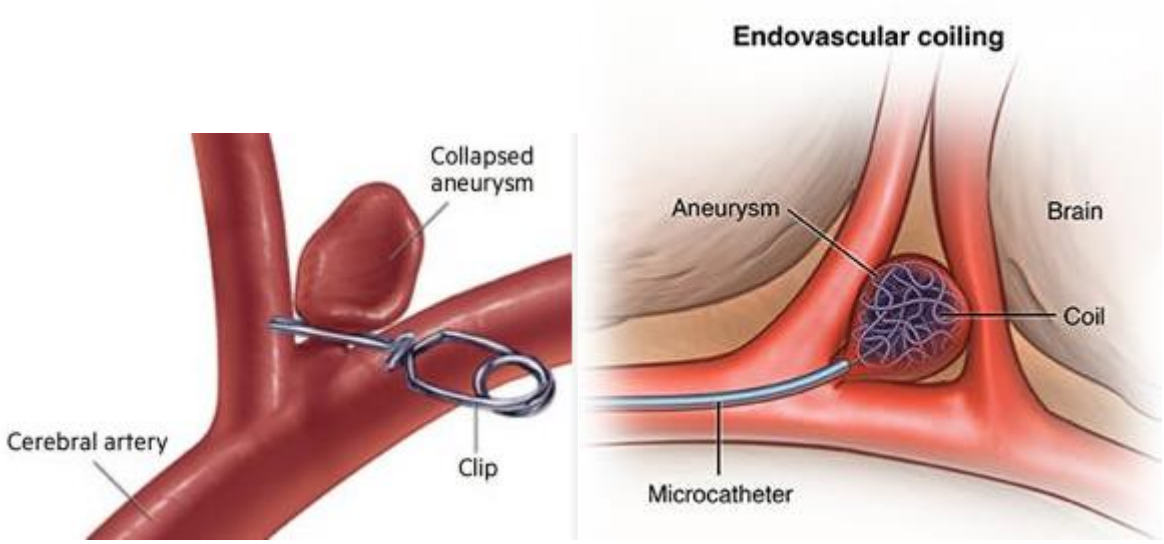
SAH from a ruptured aneurysm carries a high initial mortality risk, which gradually declines with time. Of those who survive the initial bleed, rebleeding and cerebral infarction are the major causes of death.

The most important complications of SAH are mainly intracranial and include:

- **Rebleeding**: In untreated aneurysms, approximately 30% of patients would rebleed within the first 28 days; of these, 70% die. The clinical picture of rebleeding is that of SAH, but the effects are usually more severe than the initial bleed. Repeated CT scans help to disclose rebleeding.
- **Cerebral ischemia/infarction**: Cerebral ischemia/infarction may occur as an immediate and direct result of the hemorrhage, but more often develops 4–12 days after the onset due to **vasospasms**, i.e., arterial narrowings on angiography, which occur in up to 60% of patients after SAH and can be either focal or diffuse. Approximately 25% of patients develop clinical evidence of delayed ischemia/infarction. Vasospasms are caused by various vasoconstrictive substances released from the vessel wall or from the blood clot, appearing in the CSF after SAH, e.g., serotonin, prostaglandin, oxyhemoglobin, endothelin-1. Furthermore, endothelial dysfunction and the increased influx of calcium ions into the smooth muscle cells of the blood vessel walls contribute to their development. Vasospasms, together with hypovolemia and low blood pressure, contribute to the development of hypoperfusion in particular parts of the brain (or even diffuse brain hypoperfusion) and can lead to focal brain deficits (hemiparesis, aphasia, etc.) as well as non-focal deficits (increase in headache, decreased level of consciousness, etc.). All SAH patients are provided with nimodipine (calcium-channel blocker) for the prevention of vasospasms, and prevention of hypovolemia and blood pressure management are applied. Regular monitoring of vasospasms with transcranial ultrasound examination should be performed, and CT + CT angiography should be used in symptomatic patients to confirm vasospasms and reveal the extent of ischemic changes. Endovascular treatments using vasodilator substances are used in patients with symptomatic ischemia due to vasospasms.
- **Hydrocephalus**: Affects about 20% of SAH patients, usually in the first few days after SAH, due to the impairment of cerebrospinal fluid drainage. This might be caused either by blood clot within the ventricular system (which causes obstructive hydrocephalus) or by the clot within the basal cisterns and obstruction of the arachnoid villi, which may cause communicating hydrocephalus. Headache and impaired consciousness level represent the most prominent symptoms, followed by gait impairment, incontinence, and/or cognitive decline. The diagnosis is confirmed by CT, and treatment is neurosurgical.
- **Epileptic seizures.**

Furthermore, many **extracranial complications** may develop in SAH patients, e.g., myocardial infarction, cardiac arrhythmias, pulmonary edema, or gastric hemorrhage (stress ulcers).

The SAH treatment is based on **strict bed rest** with mild elevation of the upper part of the body, **analgesics**, and antiemetics, and prevention or treatment of complications. As a prevention of rebleeding, both **surgical (clipping of the aneurysm neck) and endovascular (coil embolization of the aneurysm sac**) techniques are used for aneurysm repair and should be performed within 48 hours of the bleed. Prevention and management of vasospasms/cerebral ischemia and hydrocephalus are mentioned above.



2.6.2 Neuroinfections

Neuroinfections refer to infections that involve the central nervous system (CNS), including the brain and spinal cord, and their coverings (meninges). Considering the anatomical structures affected, they can be divided into:

- meningitis (i.e., affecting meninges and sometimes cranial or spinal nerves that emerge from the central nervous system through meninges as its coverings),
- encephalitis (affecting the brain tissue and causing focal neurological deficits),
- myelitis (spinal cord infections),
- meningoencephalitis or meningoencephalomyelitis (combining more options).

They can be caused by various pathogens, such as:

- bacteria (e.g., Haemophilus influenzae, Streptococcus pneumoniae, Neisseria meningitidis, Borrelia burgdorferi),
- viruses (e.g., herpesviruses, tick-borne encephalitis virus),
- fungi,
- and parasites.

The agents may invade the subarachnoid space or nervous tissue directly by **spreading from contiguous structure**s, e.g., inner ears, sinuses, and fractures, or by **intravascular invasion** (bacteremia).

The clinical presentation of neuro-infections varies widely, making them challenging to diagnose and treat. Common symptoms include **fever, headache**, neck stiffness, nausea, vomiting, photophobia, and phonophobia as signs and symptoms of **meningeal syndrome**. Patients with encephalitis, myelitis, or

impairment of cranial or spinal nerves also develop focal neurological deficits. Altered mental status, or seizures are also frequent.

To diagnose neuroinfections, a thorough patient history, physical examination, and neurological assessment are important. **Lumbar puncture** (spinal tap) is a crucial diagnostic procedure to analyze **cerebrospinal fluid (CSF**) for signs of infection, such as increased white blood cells, elevated protein levels, and decreased glucose concentration. Blood tests (C-reactive protein, procalcitonin, leukocytosis), imaging studies like CT scans and MRI, and specific pathogen tests (e.g., antibodies, PCR) aid in identifying the causative agent.

Treatment of neuroinfections depends on the underlying pathogen. Bacterial infections usually require prompt and aggressive **antibiotic therapy**. The same applies to some viral infections (e.g., herpetic ones), where **antivirals** are provided for treatment, while other viral infections are managed symptomatically since no specific antiviral medication is available. In most cases, supportive care, such as **antipyretics, anticonvulsants, and corticosteroids**, is necessary to manage symptoms and reduce inflammation. Empirical treatment is often initiated while awaiting specific test results, and adjustments are made once the causative agent is identified.

Prompt recognition and management of neuroinfections are vital to prevent serious complications like brain damage, neurological deficits, or even death since the clinical course of some neuroinfections is **extremely rapid** (fulminant).

2.6.3 Intracranial Mass Lesions presenting with Intracranial Hypertension

Intracranial mass lesions, such as tumors, constitute a significant category of neurological disorders that can present with headaches due to **intracranial hypertension**. These conditions involve **abnormal tissue growth within the confined space of the skull,** resulting in increased pressure inside the cranial cavity. Intracranial hypertension is a critical medical condition characterized by elevated pressure exerted on the brain and its surrounding structures, which can lead to potentially life-threatening consequences if left untreated.

The most common types of intracranial mass lesions include **primary brain tumors** arising from the brain tissue itself (gliomas, glioblastomas) or its coverings (meningiomas) and secondary tumors that have spread from other parts of the body (**metastatic tumors**). Additionally, several **other clinical conditions**, such as obstructive hydrocephalus or chronic subdural hemorrhages, represent a growing mass in the intracranial space and may present with similar clinical pictures. Clinical manifestations of intracranial hypertension often include:

- severe **headaches** that gradually increase within days, weeks or even months, and worsen when lying down and decrease in the standing position,
- **nausea, vomiting**,
- altered mental status,
- **focal neurological deficits**, and seizures, depending on the lesion's location and size.

Furthermore, patients usually exhibit bradycardia (low heart rate), irregular respirations, and arterial hypertension with a significant difference between systolic and diastolic blood pressure, collectively known as **Cushing's triad**.

Diagnosing intracranial mass lesions and associated intracranial hypertension requires a comprehensive approach, including a detailed patient history, thorough physical examination**,** **fundoscopy** (ophthalmoscopy, where the prominence of optic papillae correlates with increased intracranial pressure), and **imaging techniques,** such as magnetic resonance imaging (MRI) and

computed tomography (CT) scans. Early recognition of these conditions is crucial, as prompt intervention can help prevent severe complications and improve patient outcomes.

Treatment strategies for intracranial mass lesions vary depending on the type, location, and extent of the lesion. They may involve surgical resection, radiation therapy or chemotherapy in certain types of tumors, or a combination of these approaches. Additionally, managing intracranial hypertension often involves approaches to **reduce brain swelling** and control elevated intracranial pressure, which can include medications (corticoids, mannitol), and sometimes drainage of cerebrospinal fluid.

2.6.4 Intracranial hypotension

Intracranial hypotension, also known **as low intracranial pressure (ICP),** is a medical condition characterized by abnormally low pressure within the cranial cavity. This condition typically occurs when **cerebrospinal fluid (CSF) leaks from the subarachnoid space**, often as a **complication of a spinal tap** (lumbar puncture) or, rarely, after traumatic events.

Common symptoms of intracranial hypotension include:

- **positional headaches** (worsening when upright and improving when lying down: Please note that this is opposite to intracranial hypertension!)
- **nausea, vomiting,**
- possibly **dizziness**.

Diagnosing intracranial hypotension involves a combination of patient **history and physical examination**, sometimes complemented by imaging studies such as magnetic resonance imaging (MRI) or computed tomography (CT) scans. Treatment approaches may include conservative management with **bed rest, hydration, and pain relief,** or, in some cases, specific surgical or local interventions to repair the CSF leak.

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