# PATHOPHYSIOLOGY OF THE NERVOUS SYSTEM 2

Department of Pathophysiology, Faculty of Medicine in Pilsen, Charles University

# Secondary brain injury

Primary brain damage leads to the development of secondary injury.

Different types of primary injuries cause secondary injury of different dynamics and severity and involvement of various mechanisms can also differ.

**Mechanisms of secondary injury:**

- Intracranial hypertension
- Depolarization
- Biochemical cascade

# Secondary brain injury

**Intracranial hypertension**

**Depolarization**

→ excitotoxicity

- primary injury → disruption of energy metabolism of brain tissue → restriction of active transport → increase in intracellular concentration of $Na^+$, $Ca^{2+}$ → depolarization
- perfusion restriction → ↓ elimination of excitatory mediators → depolarization
- depolarization of presynaptic element → glutamate release → depolarization

# Secondary brain injury

**Biochemical cascade**

- $Ca^{2+}$ into the cells

  → protease activation → degradation of cell components

  → phospholipase A2 activation → cell membrane disintegration

  → NOS activation → NO - toxic at high concentrations

- reactive oxygen species - source: e.g. mitochondria at oxygen deficiency, activated leukocytes
- hypoxia → acidosis
- necrosis → cleaning reaction → inflammation → free radicals + restriction of microcirculation by adhering leukocytes (especially neutrophil) + neurotoxicity of some cytokines (IL-1, TNF-α)

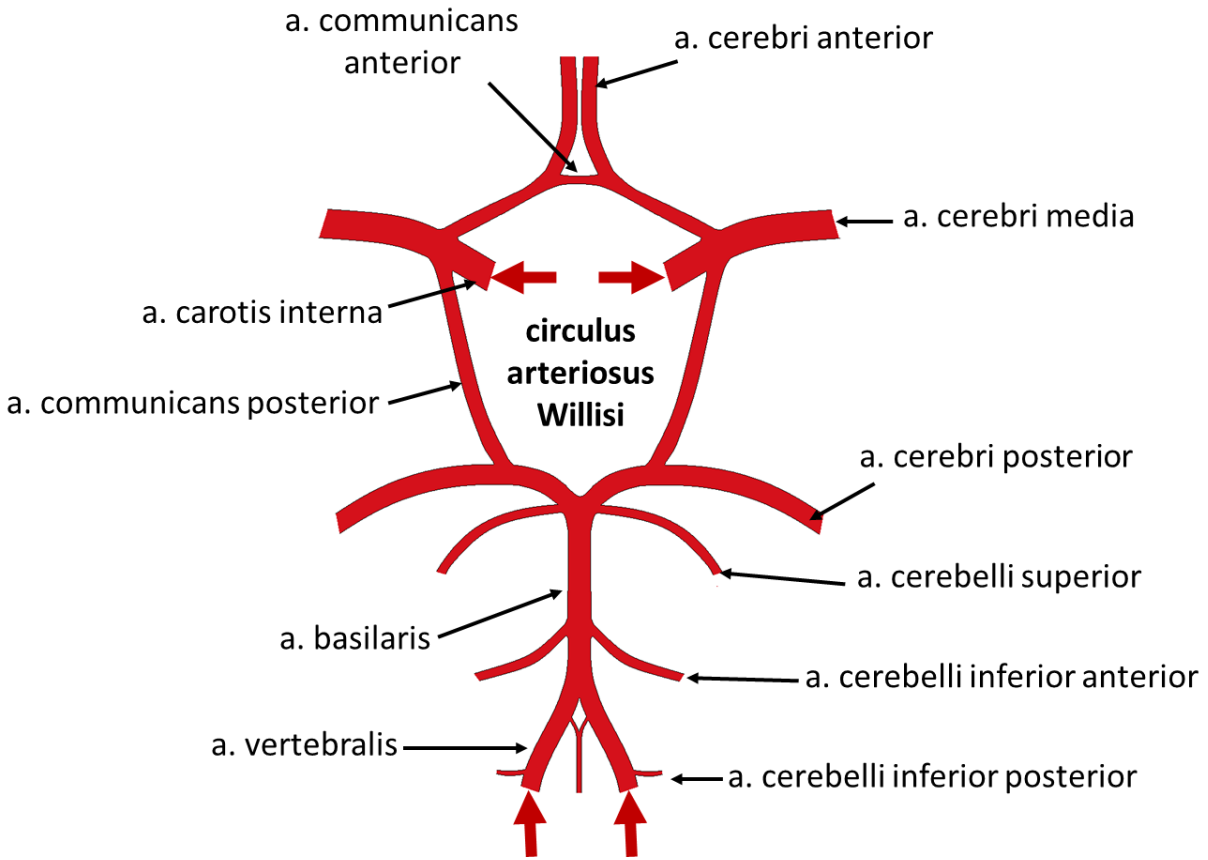
  → glutamate from disintegrated neurons

- apoptosis

Reperfusion - supplies substrates for autodestructive processes, allows delivery of leukocytes, enables development of vasogenic edema

# Cerebrovascular disorders

- **Ischemia**
- **Hemorrhage**




**Ischemia**

perfusion reduction in whole carotic bed

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occlusion of only a certain branch

# Cerebrovascular disorders

Cerebrovascular disorders are usually complications of atherosclerosis and hypertension.

**Ischemia, hemorrhage**

→ focal symptoms

→ pain

→ consciousness disorders

→ secondary affection - brain edema, intracranial hypertension with relevant consequences

**Stroke** (= ictus) = sudden or rapidly developing focal brain dysfunction that lasts for more than 24 hours or leads to death and that is due to a cerebral circulation disorder.

**Transitory ischemic attack** = sudden and transient loss of focal brain function, minutes to hours (< 24 h), without permanent consequences

# Cerebrovascular disorders - ischemia

Autoregulation of brain perfusion

**CMF = CPP/CVR**

**CPP = MAP - ICP**

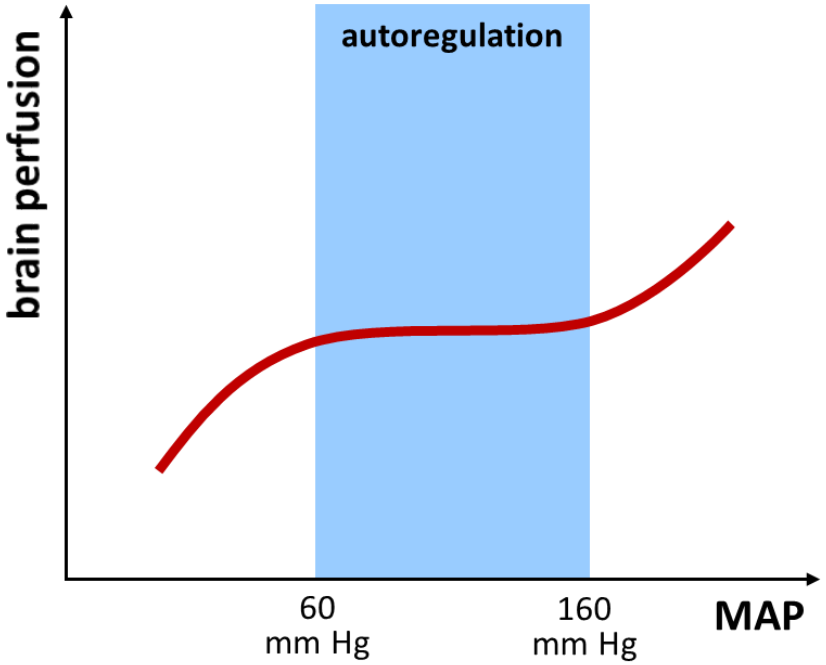
CMF...cerebral minute flow

CPP...cerebral perfusion pressure

CVR...cerebral vascular resistance

MAP...mean arterial pressure

ICP...intracranial (intracerebral) pressure




**Obstructive mechanism X non-obstructive mechanism**

- Atherosclerosis + thrombus
- Non-atherosclerotic artery affection (vasculitis, migraine infarction, vasospasms, mechanical vessel affection, compression...)
- Embolization
- ↓ MAP

# Cerebrovascular disorders - ischemia

**Ischemia → hypoxia**

→ ATP deficit

→ excessive effect of excitatory neurotransmitters

→ changes of ion concentration (↑ intracellular $Ca^{2+}$)

→ oxidative injury, ischemic-reperfusion injury

**→ apoptosis, necrosis**

Necrosis of whole tissue → malacia → postmalatic pseudocyst

Partial damage → reactive gliosis, glial scar

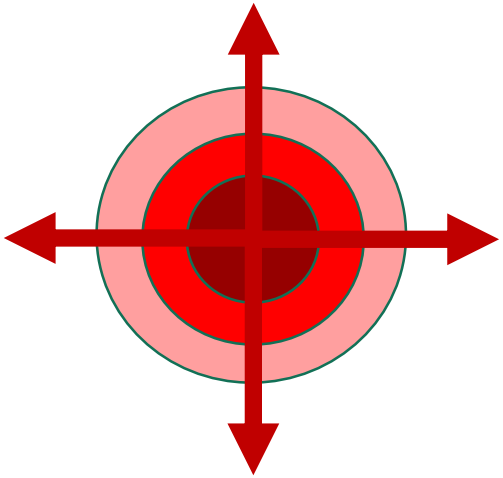
Sensitive areas: the brain cortex on the top of the gyri, hippocampus, basal ganglia

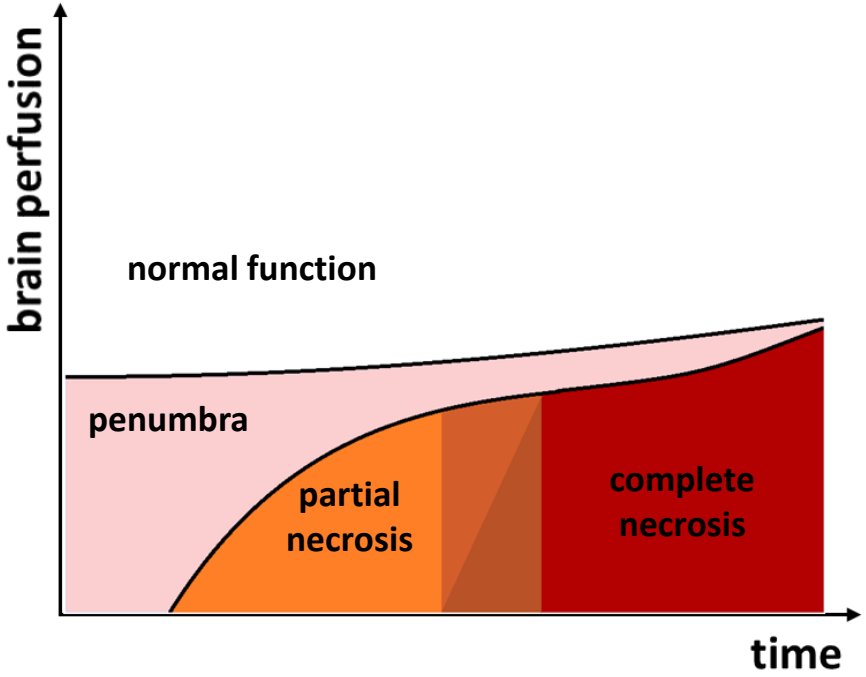
# Cerebrovascular disorders - ischemia

**Ischemic injury focus**

- irreparable damaged center
- partially reparable tissue
- reversible affection = penumbra

→ increase of zones of injury: severity of hypoxia, duration of hypoxia, tissue sensitivity, secondary brain injury (e.g. brain edema)





# Chronic cerebrovascular disorders

- reduction of total or regional blood perfusion of the brain

→ reduction of reserve and adaptation capability

- problems namely when demands are increased and when cardiac output and MAP are reduced
- small brain infarctions without marked manifestations but with a cumulative effect

→ mild cognitive deficit, vascular dementia (multi infarction dementia)

# Non-obstructive ischemic brain injuries

→ hypoxic-ischemic encephalopathy

= hypoxia due to extracerebral causes:

- systemic hypoperfusion
- respiration failure
- CO intoxication

→ Interterritorial infarctions

More severe affection of areas with a high metabolic activity:

- basal ggl., thalamus, hippocampus, gyrus parahippocampalis, cerebellar hemispheres, brainstem nuclei, white matter

Possible **combination of non-obstructive and obstructive mechanisms** of brain tissue hypoxia

→ focal damage more severe in regions supplied by the narrowed arteries

# Cerebrovascular disorders - hemorrhage

**Intracerebral bleeding** is often **due to hypertension**.

vessel rupture → hemorrhage

**Other causes:**

vascular malformations, hemorrhagic diatheses (including antikoagulant therapy), amyloid angiopathy in aged people

**Consequences:**

- destructive bleeding → destruction of the brain tissue
- intracranial hypertension
- hemocephalus = if hematoma breaks into the ventricular system → risk of liquor circulation obstruction → hydrocephalus

**Other types of intracranial hemorrhage** - see Intracranial hypertension

# Intracranial venous thrombosis

Septic - complication of inflammation in surrounding areas

Aseptic - trauma, thrombophilia, peroral contraceptives, dehydration...

**Consequences:**

headache, intracranial hypertension, venous bleeding, consciousness disorders...

Sometimes in only mild symptoms

# Vascular disorders of the spinal cord

- less frequent than cerebrovascular diseases

Spinal cord infarction

Spinal cord hemorrhage

Subdural hemorrhage

Subarachnoid hemorrhage

# Vascular disorders of the peripheral nerves

vasa nervorum damage → nerve ischemia

e.g. contribution of vasa nervorum angiopathy to diabetic neuropathy

# Injuries of the nervous system

- PNS injuries = damage of spinal roots, peripheral nerves

  - some possibility of partial regeneration

- CNS injuries = injury of the brain or spinal cord

  - very limited regeneration, a role of plasticity

**Extent and consequences of damage**

= primary injury directly from the injury + secondary changes in the CNS (brain edema, hemorrhage, vasospasm, disorders of brain perfusion autoregulation... - for basal mechanisms see before)

+ contribution of systemic changes caused by the injury (hypoxemia, hypercapnia, hypotension...)

# Craniocerebral injury

- Traffic accidents, professional accidents, falls, violence…

**Contact injury:**

Usually a very short force on the head (impact, blow), less frequently longer action of the force on the head (head compression → bone fractures)

Damage in the place of the impact, but also on the opposite side (= contre coup; the impact of the brain on the skull)

**Contactless injury:**

A consequence of acceleration or deceleration → impact of the brain on the skull or tension and compression inside the brain tissue

# Craniocerebral injury

**Primary injury** = structural damage of the brain tissue arising at the moment of the trauma

**Secondary injury** = brain edema, intracranial hypertension, biochemical processes, depolarization

**Focal lesion**

- Brain contusion
  - usually by contact mechanism
  - damage rather on the brain surface
  - often accompanied by bleeding
- Penetrating (perforating) injury - gunshot and stab wounds

**Diffusion lesions**

- Brain commotion - short-term reversible disorder, unconsciousness, amnesia
- Diffuse axonal injury -affection of axons and their subsequent degeneration

# Craniocerebral injury

**Extracerebral injury**

Skull fracture

- Calva fracture - linear or comminuted
  - Potential epidural hemorrhage
  - Open fractures → risk of intracranial infection
  - Comminuted fractures → bone fragments can compress or injure the brain tissue
  - If intracranial sinuses are affected → risk of thromboses, bleeding, air embolism
  - If dura mater is broken → liquorrhea
- Skull base fractures
  - Risk of the middle ear affection or paranasal cavities → risk of infection penetration into the skull cavity
  - Risk of affection of cranial nerves or vessels in the skull foramina

Intracranial hematomas

# Nervous system tumors

Compression of surrounding nervous tissue particularly in the limited space of the spinal channel or skull cavity (intracranial hypertension)

→ clinical malignity even in biologically benign tumors

Focal symptoms according to the size and localization of the tumor + intracranial hypertension

Hydrocephalus when closing cerebrospinal fluid circulation

# Immune mediated diseases of the nervous system

Former point of view: the brain = privileged organ - blood-brain barrier, MHC expression features

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Microglia, autoimmune CNS diseases

- Autoimmune inflammation of the nervous system
- Autoimmune demyelinating processes (multiple sclerosis)
- Myasthenia gravis
- Nervous system affection accompanying systemic autoimmune diseases, e.g.:
  - Arteritis - e.g. polyarteritis nodosa - in 50% affection of peripheral nerves (neuropathies), in 25% brain ischemia (thrombosis of intracranial arteries, more often rupture of the artery)
  - Lupus erythematosus - affection of conjunctive tissue, in 85% also affection of the NS (organic psychosyndrome, epileptic seizures, stroke, dementia...)

# Multiple sclerosis

- Chronic demyelinating diseases of the CNS, attacks
- Prevalence in the Czech Republic = 1/1000
- Begins usually at the age of 20 - 40 years.
- Unclear etiology

**Risk factors:**

- minimum occurrence near the equator and increase towards the poles - relation to vit. D?
- heredity
- more frequent in women
- role of infections as factors influencing the immune system and as a autoimmune process triggering factor
- smoking

**Factors triggering attacks:**

- activation of immune system - infections, vaccination
- stress
- hormonal changes

# Multiple sclerosis

- Autoimmune process attacking components of central myelin
- Inflammatory infiltrates in the white matter (plaques)
- Deteriorated blood-brain barrier in acute inflammatory focuses
- Disintegration of myelin and some of the oligodendrocytes
- After the inflammation subsides, the remaining and newly formed oligodendrocytes can form new myelin in the plaque.
- Extinction of axons - probably more mechanisms (attack of demyelinated fiber by Tc-lymphocytes, high energy consumption due to conduction of action potential by demyelinated fiber, excitotoxicity of glutamate not eliminated by oligodendrocytes)

→ disturbance of conduction of action potential by demyelinated fibers + extinction of axons

→ manifestations, course in attacks with partial recovery of disturbed functions, accumulation of functional deficits after repeated attacks

# Multiple sclerosis

**Manifestations:**

- according to localisation of foccusses of demaelination
- retrobulbar neuritis → visual impairment
- sensitivity disorders (hypesthesia, paresthesia) without typical peripheral distribution acording to the innervation areas
- spastic palsy
- cerebellar syndrome
- sphincter disorders
- autonomic dysfunction
- trigeminal neuralgia due to affection of the initial segments of the n. V by inflammatory infiltrate
- epileptic seizures
- neuropsychiatric manifestations - depression, anxiety, emotional incontinency
- cognitive deficits
- fatique

# Myasthenia gravis

- the most common neuromuscular plate disease
- association with thymus
- antibodies against α-subunit of the cholinergic receptor of the neuromuscular plate
- muscle weakness worsening after repeated movements, after rest improvement, diplopia, swallowing difficulties , vertebrogenic problems from neck muscle weakness
- myasthenic crisis - severe muscle weakness with respiratory insufficiency

# Neurodegenerative diseases

= progressive extinction of certain neuronal populations, gradual development of clinical manifestations, irreversible affection

**Etiology:**

- Heredity
  - genetic predisposition in multifactorial neurodegenerations
  - Huntington disease, cerebellar degenerations, 10% of Alzheimer disease cases
- Idiopathic
- Hypothetically - prions, viruses, intoxications, contribution of inflammation...

Increasing incidence in the population, frequent in older people but not only in them (hereditary diseases starting in middle age and in childhood)

# Neurodegenerative diseases

**Pathogenesis:**

- Often unclear
- Accumulation of pathologic protein interfering with function of neurons and/or causing their death (amyloidopathies, polaglutaminopathies, tauopathies...)
- Clinical manifestation depend mainly on localization of pathologic changes.

**Clinical classification:**

- dementia
- extrapyramidal hypokinetic and hyperkinetic syndromes
- spinocerebellar degenerations

Nosologic units can actually include several diseases with different etiology and pathogenesis. Their differentiation is problematic.

# Neurodegenerative diseases

## Amyloidopathies

- amyloid accumulation

**Alzheimer disease**

- amyloid precursor protein pathologically split by β- and γ-secretase into insoluble fragments of 42 or 43 aminoacids → amyloid plaques, glial activation, inflammatory response, reactive oxygen species, excitatory aminoacids → neuronal death

**Dementia with Lewy bodies**

- deposition of amyloid in some forms of the disease

**Cerebral amyloid angiopathy** - deposition of amyloid in brain vessels

# Neurodegenerative diseases

## Tauopathies

- accumulation of tau protein - several variants with different length, binding on microtubules - importance in axonal transport

**Alzheimer disease**

**Frontotemporal dementia**

- familial and sporadic forms
- onset in late adulthood
- affection of the frontal and temporal lobes - brain cortex and subcortical white matter atrophy (X Alzheimer)

  → prefrontal syndrome, phatic disorders

# Neurodegenerative diseases

## Tauopathies

**Corticobasal degeneration**

- a sporadic disease with onset in higher age
- diffuse deposits of hyperphosphorylated tau protein + degeneration of neurons in the substantia nigra and frontoparietal cortex
- asymmetric parkinsonian syndrome, disorders of cortical functions (apraxia, agnosia, cognitive deficit)
- death within 8 years

# Neurodegenerative diseases

## Tauopathies

**Progressive supranuclear palsy** (Steel-Richardson-Olszewski disease)

- a sporadic disease with onset in higher age
- parkinsonian syndrome, cognitive deficit, supranuclear oculomotor disorder (vertical movement more affected), dysarthria, dysphagia
- death in average within 7 years after disease onset
- abnormal aggregation of hyperphosphorylated 4R-tau protein
- neurofibrillary tangles, degeneration of neurons (substantia nigra, nc. subthalamicus, mesencephalon)

# Neurodegenerative diseases

## Synucleinopathies

- accumulation of α-synuclein (normally plays a role in synaptic plasticity)

**Familial Parkinson's disease**

- a defective protein with tendency to oxidative injury and aggregation

**Multiple system atrophy (MSA)**

- a sporadic disease with onset in adulthood, death within 6-9 years
- parkinsonian syndrome, cerebellar syndrome, autonomic dysfunction
- glial cytoplasmatic inclusions of α-synuclein namely in the basal ggl., cerebellum, motor cortex, brainstem, autonomic ggl.

**Dementia with Lewy bodies**

- a sporadic disease
- parkinsonian syndrome + dementia with fluctuating cognitive deficit and psychotic manifestations

# Neurodegenerative diseases

## Polyglutaminopathies

- expansion of CAG trinucleotide in a gene → polyglutamine tract in a protein → tendency to aggregation, resistance to proteases, formation of intranuclear inclusions, impact on gene expression

**Huntington‘s disease**

**Some spinocerebellar ataxias**

# Parkinson‘s disease

- a neurodegenerative disease
- probably diverse and complex pathogenesis: intracellular inclusions typical for synucleinopathies (deposition of α-synuclein fibrils in Lewy bodies), tau protein and also signs of cerebrovascular affection
- degeneration of the substantia nigra with extinction of dopaminergic neurons, but also changes of brainstem nuclei and brain cortex

  → extrapyramidal disorders + vegetative, sensory and cognitive disorders

**Etiology:**

- an idiopathic disease, potential role of:

- Genetic predisposition
- Oxidative injury contributes to substantia nigra degeneration. Free radicals are formed during dopamine inactivation by MAO-B → predisposition of dopaminergic neurons to degeneration
- Toxic factors? - MPTP (methylphenyltetrahydropyrimidine) - after conversion catalyzed by MAO-B, it has a selective toxic effect on dopaminergic neurons

# Parkinson‘s disease

- degeneration of the pars compacta substantiae nigrae → reduction of dopamine in the striatum
- also changes of other neurotransmitters in various regions → complex symptomatology

Lack of dopamine in basal ggl. circuits

→ hypertonic-hypokinetic syndrome - see pathophysiology of motor functions

# Amyotrophic lateral sclerosis (ALS)

- degeneration of brain and spinal motoneurons with preservation of oculomotor muscle and sphincter innervation

**Forms:**

- Classic ALS - degeneration of both central as well as peripheral motoneuron
- Progressive bulbar paralysis
- Progressive spinal muscle atrophy - affection of peripheral motoneuron only
- Primary lateral sclerosis - affection of central motoneuron only

**Etiology:**

- sporadic cases
- 5-10% of cases are familial - in 20% of which the mutation is in the gene for SOD1.

In its **pathogenesis**, excitotoxicity (glutamate), mitochondrial dysfunction, oxidative stress, pro-inflammatory cytokines, calcium metabolism disorder, dysfunction of neurofilaments, lack of trophic factors of motoneurons (BDNF, GDNF, IGF-1, 2, NT3, 4, 5 ...), immune mechanisms

# Amyotrophic lateral sclerosis (ALS)

**Manifestations:**

- Development of motor deficit first distally on the limbs, clumsiness
- Later fasciculations
- Fatigue
- Progression of motor deficit
- Muscle atrophy
- Respiratory insufficiency

# Demyelinating diseases

= affection of myelin sheets of nervous fibers dominates over other lesions

Central X peripheral myelin

- Destruction of normally formed myelin = **demyelination**
- Disturbance of myelin formation = **dysmyelination**

**Missing myelin**

→ reduced speed of impulse conduction

→ loss of fiber synchronization (different degree of myelin damage → different speed)

→ axon extinction

# Demyelinating diseases

**Causes:**

- autoimmune process - multiple sclerosis
- viral infections
- vit. B12 deficiency
- disorders of water and mineral metabolism - e.g. myelinolysis after rapid correction of hyponatremia
- hypoxia
- irradiation

# Demyelinating diseases

**Demyelinating diseases**

- Multiple sclerosis
- Neuromyelitis optica - bilateral inflammation of the optic nerve
- Central pontine myelinolysis - alcoholism, ion disbalances
  → quadriplegia
- Acute disseminated encephalomyelitis - after viral infection
- Acute necrotizing hemorrhagic encephalitis - after viral infections
- Guillain-Barré syndrome - its most common form = acute inflammatory demyelinating polyneuropathy

**Dysmyelinating diseases = leukodystrophies**

- Metachromatic leukodystrophy - AR heredity, both central and peripheral dysmyelination due to accumulation of sulfatides in oligodendrocytes and Schwann‘s cells
- Adrenoleukodystrophy - X-linked, both central and peripheral dysmyelination due to accumulation of fatty acids in oligodendrocytes a Schwann‘s cells
- Krabbe disease - AR heredity, accumulation of galactocerebroside

# Toxic damage of the nervous system

- Partial protection of the CNS by the blood-brain barrier
- Toxins acting specifically on the NS, toxins acting non-specifically, secondary damage of the NS as a consequence of toxic injury of other organs
- Medicaments, drugs (including alcohol), industrial toxins

**Opioids**

- dependency, tolerance
- acute intoxication→ respiratory center inhibition

**Barbiturates**

- overdosing → coma, hypotension, hypothermia, respiration suppression

**Metals**

**Organophosphates**

- acetylcholinesterase inhibition

**Alcohol**

- toxic effect of alcohol, acute intoxication, deficiency sy, alcohol fetal sy

# Wernicke-Korsakoff syndrome

- neurologic disease due to lack of thiamin
- often as deficiency syndrome due to chronic alcoholism

**Clinical manifestation:**

- Wernicke encephalopathy
  - confusion + ophthalmoplegia + ataxia

    Qualitative disorder of consciousness with disorientation, memory disorders and inhibition predominance, sopor to coma
- Korsakoff syndrome
  - usually after fading of Wernicke encephalopathy manifestations
  - pure retrograde as well as anterograde amnesia with random loss of fresh information, that the patient replaces with confabulations

# Infectious diseases of the nervous system

- bacterial, mycotic, parasite, viral, prion infections

  + toxins produced by microorganisms (tetanus, botulism)

- infections with a specific affinity to the NS
- infections attacking, among other tissues, also the NS
- neurotoxic effects of microbial toxins
- NS damage  as a secondary consequence or complication of severe infections diseases, effect of inflammatory mediators (e.g. sepsis, hypoxia in severe pneumonia...)

# Infectious diseases of the nervous system

## Neurotoxic infections

### Tetanus

- toxin (= tetanospasmin) produced by *Clostridium tetani*
- spores of *C. tetani* in the soil contaminated with animal excrements → wound contamination → activation of bacteria → production of toxin
- generalized convulsions of skeletal muscles + vegetative disorders
- death due to suffocation due to respiratory muscle convulsions and laryngospasm or due to increased sympathetic vegetative system activity

### Botulism

- intoxication with botulotoxin produced by *Clostridium botulinum*
- toxin usually already in food, rarely toxin production by bacteria directly in the organism
- blockade of acetylcholine release from nerve terminals
- peripheral palsy, dry mouth, diplopia, accommodation disturbances, autonomic dysfunction
- breathing disorders!

# Infectious diseases of the nervous system

## Bacterial infection

**Purulent meningitis**

- severe diseases with a rapid course, often lethal
- primary meningitis: hematogenic (Meningococcus, Pneumococcus, Hemophilus)
- secondary meningitis: complication of otitis media, sinusitis, head trauma

**Brain abscess**

**Tuberculous meningitis**

**Lyme borreliosis**

- multisystem disease
- Borrelia burgdorferi, vector = tick

**Neurolues**

- several forms or components of NS affection
- tabes dorsalis
- progressive paralysis

# Infectious diseases of the nervous system

## Mycotic infections

- rare but often serious diseases

**Cryptococcus infection** (C. neoformans)

## Parasitic infections

**Naegleria fowleri** - meningoencephalitis

**Toxoplasmosis** - Toxoplasma gondii

- inborn developmental defects, severe CNS affection in immunodeficient individuals
- prolongation of reaction time, risky behavior

**Alveococcus, Echinococcus** - hydatids in various localizations in the body, potentially also in the brain

# Infectious diseases of the nervous system

## Viral infections

- many neurotropic viruses

**Postinfectious encephalomyelitis**

- immunopathologic mechanism, affection of the white matter

**Middle European encephalitis**

**Poliomyelitis**

- In the Czech Rep., it did not occur since 1960 thanks to vaccination.
- fecal-oral infection transmission
- the 1st phase of unspecific signs similar to flue
- the 2nd phase - extinction of motoneurons → peripheral flaccid paresis with predominance of proximal muscle affection, various degrees of affection, even death due to respiratory insufficiency
- sometimes only without any symptoms or only the 1st phase

**Postpoliomyelitic syndrome**

- in individuals who hav experienced poliomyelitis
- late degeneration of motoneurons (exhaustion of motoneurons that survived the primary disease?)

# Infectious diseases of the nervous system

## Viral infections

**Rabies**

- Rhabdovirus
- If the signs occur the disease is lethal in 100%.
- Infection of tissue  with the saliva of an infected animal during a bite
- centripetal spreading of the virus via axons
- multiplication of the virus in the CNS → development of symptoms - long incubation period
- prodromal stage: fever, headache
- alternating agitation with normal behavior or apathy, palsy, hydrophobia

# Infectious diseases of the nervous system

## Prion infections

- protein infectious particles without nucleic acids
- affect the nervous system

**Kuru**

**Creutzfeldt-Jakob disease**

**Variant Creutzfeldt-Jakob disease**

**Fatal familial insomnia**

- hereditary

**Sporadic fatal insomnia**

# Radiation injury of the nervous system

Mature neurons are quite resistant to radiation. However, embryonic neural tissue is very sensitive (a teratogenic factor).

**Acute effects of radiation on the nervous system**

- disorientation
- excitatory forma - hyperreflexia, hyperexcitability
- inhibition form - somnolence to coma

**Chronic effects of radiation on the nervous system**

- post-irradiation demyelination

# THE END