PATHOPHYSIOLOGY OF THE NERVOUS SYSTEM 1

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

Introduction

The brain is the most organized structure. It is not completely known and understood.

Neurons - more than10^{11} (80% in the cerebellum, although it represents only 10% of the brain)

Glia - important structural and functional component of the nervous system, about 10 times more numerous than neurons.

- myelin, metabolism, nutrition, immunity (phagocytosis), cytokine production, synaptic transmission modulation, etc.

Functional and structural components of the nervous system, that are involved in its normal function and pathogenesis of diseases and disorders:

- neurons, glia
- neurogenesis
- brain development (critical periods)
- synapses, neuromediators, receptors
- brain vessels
- cerebrospinal fluid
- meninges
- skull, spine - protection and delimitation of space for the CNS

Glia

Astrocytes - support, neuron homeostasis (glucose, ions), part of the hematoencephalic barrier

Oligodendroglia – myelin in the CNS

Ependymal cells - CNS cavity lining

Microglia – specialized macrophages with immune functions (cytokines, phagocytosis)

Schwann‘s cells - myelin in the PNS

Pathophysiology of the nervous system

According to anatomical structures

- disorders of the peripheral nervous system
- disorders of the central nervous system (disorders of the spinal cord, individual parts of the brain stem, cerebellum, hypothalamus, basal ganglia, thalamus, individual parts of the brain cortex...)

According to affected functional systems

- disorders of motor functions, sensory systems, learning and memory, behavior, vegetative functions, biological rhythms, endocrine functions brain...

According to disease cause and pathogenesis

- developmental defects, injuries, vascular disorders, inflammations, neurodegenerative diseases...

Often combined approach

Lesions of the nervous system

1) extinction - suppression or elimination of the function of the affected structure
2) irritation - enhancement of the function of the affected structure

Specific features of nervous system diseases

- The nervous system is involved in control of function of other organs and in control of homeostasis (in cooperation with the endocrine and immune systems).
- The brain = vital organ, seat of memory, consciousness, self-awareness
- Brain death = death of the individual
- High sensitivity to harmful factors (e.g. hypoxia, hypoglycemia...)
- Low ability of regeneration, though neurogenesis in adulthood exists
- Plasticity can modify functions of the nervous system and sometimes compensate for quite significant damages. Plasticity decreases with age.

Methods of examination of the nervous system

Functional examinations

- **Reflexes** (according to the receptors: extero-, intero-, proprio-; according to the CNS level: spinal, bulbar, mesencephalic...)
  Possibilities: normal, areflexia, hyporeflexia, hyperreflexia, pathological reflexes

- **Examination of motor function** (assessment of motor activity on general and local level – movements, muscle tone)
  Possibilities: norm, hypokinesia, hyperkinesia; atonia, hypotonia, flaccidity, hypertonia, spasticity, rigidity, palsy, paresis, plegia, ataxia, astasia-abasia

- **Examination of sensory systems**

- **Examination of behavior, emotions, and psychic state**
  Methods of investigation of the highest nervous functions - appetitive, aversive
  Ethology
  Cognitive tests, psychological test...

Methods of examination of the nervous system

Electrophysiological methods

- also functional
- **stimulation** - stimulation of various CNS areas and detection of reactions
- **registration**

EEG, EMG, EP, LTP etc.

Macroelectrophysiological methods

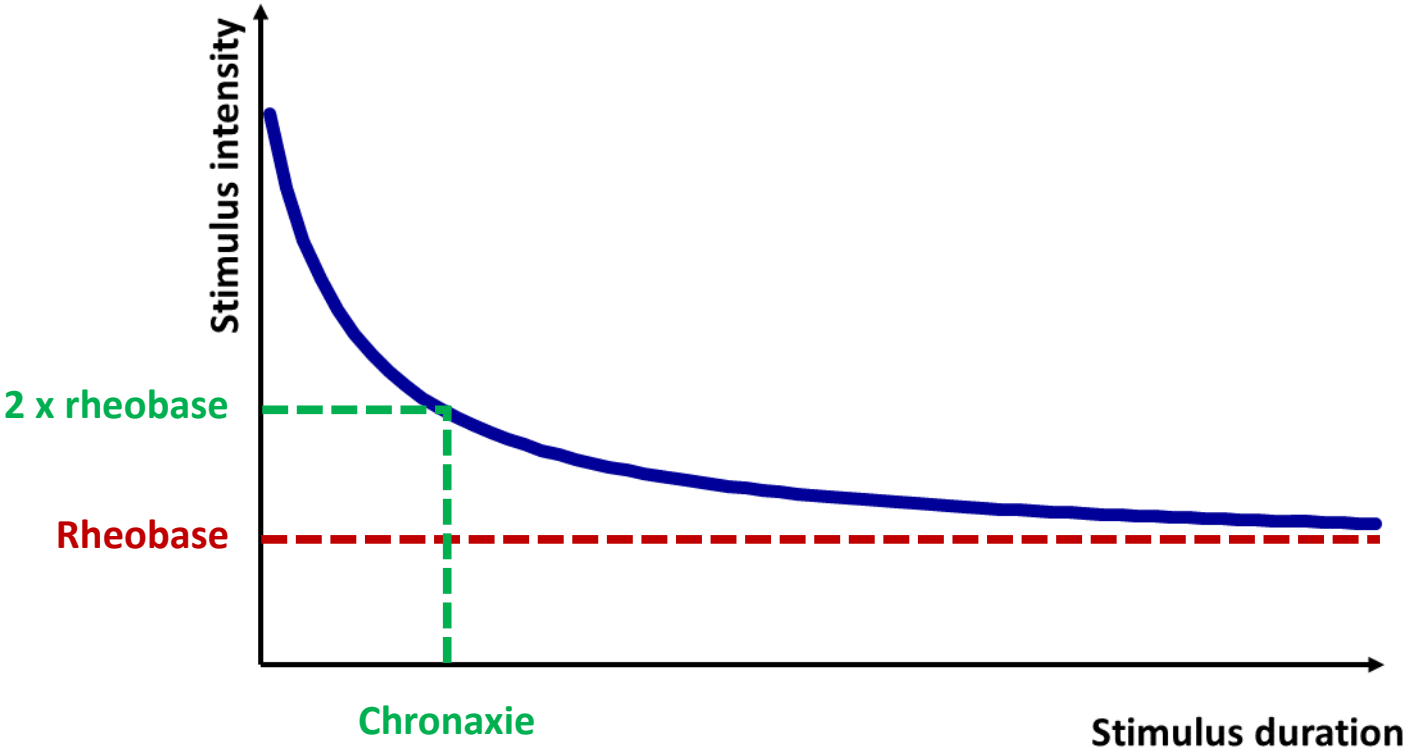
- EEG, ECoG, EMG

Microelectrophysiological methods

- unit electric activity, voltage clamp, patch clamp

Methods of examination of the nervous system

Rheobase = the lowest intensity of the stimulus that triggers AP (if it acts for a maximum time)
Chronaxie = duration of the stimulus having twice higher intensity that rheobase needed to induce AP



Methods of examination of the nervous system

Stereotaxis

= exact targeting of a structure deep in the brain based on a system of coordinates (stereotaxic atlas and frame)

Imaging methods

Thermography, sonography, RTG, computer tomography, nuclear magnetic resonance (NMR) + functional magnetic resonance, positron emission tomography (PET)

Morphological methods

anatomy, pathological anatomy, histology

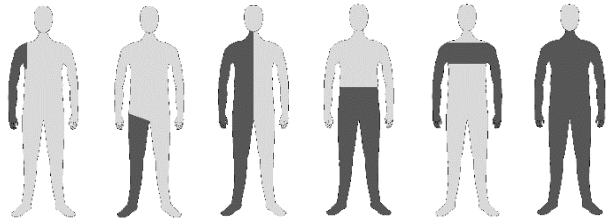
Overview of basic neuropathophysiological terms

Inhibitory (hypofunction, extinction) **and excitatory** (hyperfunction) **disorders** (lesions)

Inhibitory disorders of the motor system

- **Palsy** = complete inability of voluntary movement (**plegia**) or limitation of voluntary movement, i.e. reduction of muscle power (**paresis**)

Localization of the affection: mono- = 1 extremity, para- = 2 extremities of the same girdle (more often lower), hemi- = upper and lower limb on the same body side, quadri- = all 4 extremities



Classification of palsy:

1) **central palsy** (spastic)
   - affection of the central (upper) motoneuron
   - inability (limitation) of voluntary movement, hypertonia, hyperreflexia, pathological reflexes (Babinski...)

2) **peripheral** (flaccid)
   - affection of the peripheral (lower) motoneuron
   - inability (limitation) of voluntary movement, hypotonia (atonia), areflexia, atrophy

Overview of basic neuropathophysiological terms

Inhibitory disorders of the motor system

- **ataxia** - disorder of movement coordination (spinal, cerebellar, vestibular)
- **abasia** - gait disorder
- **astasia** - posture disorder
- **akinesia (hypokinesia)** - inability (difficulty) to initialize movements

Excitatory disorders of the motor system

- **epilepsy** affecting motor structures
  - e.g. Jackson‘s motor epilepsy
- **tremor**
- **myoclonia**
- **hyperkinesia**

But: Some of these „plus“ symptoms can be a consequence of extinction lesion of certain structure that leads to imbalance in neural circuitries and relative predominance or hyperactivity of another structure (e.g. static tremor as a part of the Parkinson syndrome in substantia nigra damage).

Overview of basic neuropathophysiological terms

Inhibitory (extinction) disorders of afferent systems

- decrease or loss of sensitive and sensory functions
- anesthesia (hypesthesia), thermoanesthesia, dissociation of sensation, anacusis (hypoacusis), amaurosis, hemianopsia, scotomas, ageusia (hypogeusia), anosmia (hyposmia)...

Excitatory disorders of afferent systems

- Jackson‘s sensitive epilepsy, paresthesia, hyperesthesia, dysesthesia, causalgia, neuralgia, phantom pain, hyperalgesia, aura (in fact, pseudohalucinations - illusive perception of visual, olfactory or sensitive qualities), nystagmus or vertigo in the case of vestibular (can be also due to extinction lesion because it arises from imbalance of the left and right vestibulum)

The effect of stimulation on nervous system development

- Adequate stimulation is necessary for normal and successful brain development. The development of nerve functions is, in some point of view, a response to its stimulation and usage. I.e., brain function is determined by a combination of gene effects and appropriate external stimulation - adequate character, complexity, intensity and timing of stimulation is crucial (see critical developmental period).
- Insufficient stimulation (lack of complex stimuli from the external environment) delays or even disables normal brain development and leads to the state of **deprivation**.
- The consequences of long-term deprivation, especially in infancy and early preschool age, are permanent, and even subsequent stimulation (because it came late) can no longer correct the condition.
- On the other hand, if the level of stimulation (intensity, complexity, duration) exceeds the capacity of the developing brain (normal or pathologically damaged), it has a negative effect.

Plasticity and compensation in the nervous system

Brain plasticity (neural plasticity)

= the ability of the organism to respond adequately to external influences and to adapt its further functions to the needs of the organism.

- The mechanisms of plasticity are also part of the processes of memory, learning and behavior.
- The nervous system develops to some extent in response to stimuli and activity. It can modulate its functions and, within certain limits, change morphology (e.g. larger hippocampus in people with highly trained spatial memory).
- Plasticity has its limits and decreases with age.

Example: After the formation of nerve anastomoses (e.g. the treatment of the paralysis of one cranial nerve by connecting its fibers to part of the fibers of another functioning nerve; e.g. n. facialis - n. hypoglossus), signals are sent from cortical areas representing movement of certain muscles to muscles originally controlled from other areas. After a sufficiently long time and intensive rehabilitation, the somatotopic organization of the cortex will be reorganized and the relevant area of the cortex will adopt a representation of movement, which it now actually controls (remapping).

Plasticity and compensation in the nervous system

Mechanisms of neural plasticity are:

- **Synaptic plasticity**
  - changes of synapses - creation of new synapses, extinction, functional changes
- **Neurogenesis** (= new neurons) - plays a role in the development of nervous system function, learning and memory, it was found also in the adult human brain.

The capacity of plasticity and neurogenesis varies in different parts of the brain. Areas with high neurogenic potential include the hippocampus, in which neural stem cells have a relatively high tendency to differentiate in the neuronal lineage. In many areas, on the other hand, there is a strong tendency to differentiate in glia.

The neurogenic potential can also be influenced by pathological changes in nervous tissue, theoretically in both directions. Damage can, on the one hand, activate repair processes, on the other hand, it has been shown that, for example, inflammation and glia proliferation in response to damage reduce the neurogenic potential of the tissue.

Plasticity and neurogenesis are greatly influenced by neural trophic factors (BDNF, GDNF, NGF...).

Plasticity and compensation in the nervous system

Compensation is a general term that means recovery or substitution (complete or partial) of functions lost or deteriarated for various reasons.

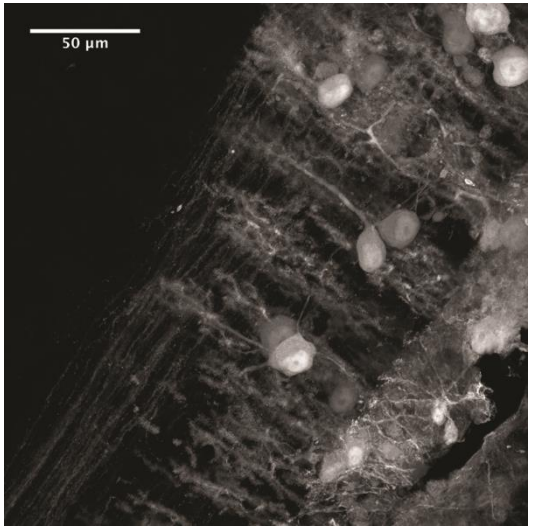
Components and mechanisms of compensation and plasticity

- **redundancy** – there are more neurons in the brain centers than needed, so partial extinction (even physiological) may not always be functionally noticeable
- **alternation** – the function of the damaged center (especially in youth) will be taken over by another structure
- **vicarious function** – extinct function is partially compensated by another function (e.g. vision loss is partially compensated by improvement of hearing, touch)
- **diaschisis** - temporary elimination of function of certain structure

Neurotransplantation

Specific features of the CNS

- Brain = vital organ, the seat of memory, consciousness, self-awareness
- Low regeneration capacity
  - low natural cell turnover - why?
- Neurogenesis in adulthood in mammals
- It is usually necessary to restore the structure of the tissue or at least connection of particular cells. Problematic recovery of distant connections.
- Grafting of mature neurons is impossible.
- Grafting of immature cells – more resistant, completion of their development after engraftment
- The Brain = a „privileged organ“, in experimental animals successful xenotransplantation



Disorders of mitochondrial function

4 fundamental functions of mitochondria

- ATP generation = universal source of energy for cellular processes
- mediating cell death by apoptosis
- heat generation
- genetic information in mitochondria (mitochondrial DNA)

Mitochondria are significantly involved in homeostasis and energy metabolism of the cell.

Mitochondrial disorders are caused by:

- spontaneous mutations of mtDNA or nDNA in genes encoding mitochondrial proteins and thereby properties and functions of mitochondria
- **extrinsic factors** - medicaments, drugs, toxins, infections

Due to the importance of mitochondria in tissues, mitochondrial disorders are mostly multisystem diseases with more pronounced manifestations in tissues and organs with high O_2 consumption (nervous system, heart, muscles, endocrine system and visual system).

Excitotoxicity

= excessive excitation of neurons leading to their damage

Glutamate, one of the most important excitatory neurotransmitters, is involved in excitotoxicity.

Excessive activation of glutamatergic receptors by increased level of glutamate in the extracellular space (norm. 0.6 µmol/l, excitotoxic damage from 2-5 µmol/l, in traumas sometimes up to 10 µmol/l).

Activation of ionotropic glutamatergic receptors leads to the influx of cations (Ca^{2+}, Na^{+}) into cells and thus to depolarization of the membrane. This brings the cell closer to the threshold for action potential. Excessive excitation represents overload of the cell (need to restore ion distribution, energy consumption) and can lead to the triggering of excitotoxic neuronal apoptosis.

Excitotoxicity is involved in the pathogenesis of many pathological conditions:

- **acute states** - injury, ischemia, infection, inflammation, hypoglycemia, epilepsy
- **chronic states** - neurodegenerative diseases (Alzheimer, Parkinson, Huntington), probably also the multiple sclerosis

Causes and mechanisms of diseases and disturbances of the nervous system

- heredity
- developmental defects (effect of heredity, teratogenic factors)
- perinatal complications (hypoxia, mechanic injuries during parturition)
- injuries
- chemical substances - toxins, drugs, side effects of medicaments
- infections
- autoimmune processes
- tumors, paraneoplastic syndromes
- vascular causes - ischemia, hemorrhage
- metabolic disorders and endocrinopaties
- malnutrition - essential substances deficiency
- hypoxia - various types from various causes
- neurodegenerative diseases of various or unknown etiology
- psychogenic factors, inadequate stimulation (excessive stimulation or deprivation)

Developmental defects of the nervous system

- Inborn developmental defects arising prenatally and manifesting from the birth
- Developmental defects arising postnatally

- Formation of the basis of the nervous system during the 3rd week of intrauterine development
- The 4th - 6th week - formation of brain vesicles
- Neuronal proliferation and migration from the 2. month of intrauterine development, maturation in neuronal cells
- The 6th postnatal month - beginning of glia migration, proliferation and migration of glia continues also postnatally
- Intensive synaptogenesis prenatal week 20-30
- Myelination from the 2nd trimester till adolescence
- brain growth spurt - the last trimester of gravidity - 18 postnatal months

Causes of nervous system developmental defects

Genetic factors; chromosomal aberrations are important

Up to 10% of embryos carry chromosomal aberrations. Most are incompatible with further development and the embryo is aborted. Chromosomal aberrations occur in about 0.5% of live births.

Genetic influences are also exerted through, for example, hereditary metabolic diseases (phenylketonuria, galactosemia, storage diseases...)

Chemical factors

- Alcoholic fetal syndrome
  - low birth weight, microcephaly, disorder of proliferation, migration (→ neuronal heterotopy) of cells, disorder of synaptogenesis, white matter dysplasia
  - severe mental retardation, often epilepsy
  - growth retardation, often heart defects, facial dysmorphia
- Drugs, medicaments, heavy metals, toluene...

Causes of nervous system developmental defects

Nutrition

- iodine deficiency
- protein malnutrition

Metabolic diseases

phenylketonuria, galactosemia, storage diseases...

Endokrine disorders

- hypothyroidism

Causes of nervous system developmental defects

Radiation

- including RTG

Infections - TORCH

- Toxoplasma - only in acute infection of the mother during pregnancy, brain calcifications, hydrocephalus, psychomotor retardation
- Rubella - vaccination
  - structural changes in the brain, mental retardation, hydrocephalus
- Cytomegalovirus - in adult people often without any symptoms
  - microcephaly (or head enlargement in hydrocephalus), mental retardation, epilepsy

Inborn developmental defects of the nervous system

Anencephaly = missing brain hemispheres

Microcephaly = small head

Encephalocoela = herniation of the brain tissue and meninges through a defect in the skull

Myelocoela = herniation of the spinal cord tissue due to defective spinal closure (spina bifida)

Meningocoela = herniation of only meninges

Inborn hydrocephalus

Arnold-Chiari malformation

Dandy-Walker cyst = cystic 4th ventricle

etc.

Perinatal complications

Mechanic injuries

Hypoxic-ischemic encephalopathy

- necrosis of neurons in various areas → variable symptomatology, various forms of cerebral palsy, extrapyramidal disorders, mental retardation, epilepsy....

Periventricular, intraventricular hemorrhage

- namely premature infants
- risk of hydrocephalus and spastic forms of cerebral palsy

Fetal erythroblastosis - kernicterus

Developmental defects of the nervous system in childhood

Mild brain dysfunction

- motor clumsiness, but without clear morphological changes in the brain
- mild neurological disorders of various types (spastic phenomena, extrapyramidal disorders, cerebellar disorders...), dyspraxia, dysgnosia, space orientation disorders
- disorders of learning and behavior
- perinatal complications often in the case history

Developmental defects of the nervous system in childhood

Developmental disorders of behavior

- Attention Deficit/Hyperactivity Disorder syndrome = ADHD
  - in 3-5 % preschool children
  - considered as a part of the mild brain dysfunction
  - inattention, hyperactivity, sleep disorders, impulsive behavior, aggression or anxiety, risk of addiction and social behavior disorders
  - often combined with other disorders
- Autism spectrum disorders (autism, Asperger syndrome...)
  - probably genetic predisposition + perinatal complications in the case history
  - more frequent in boys
  - larger total brain size + changes in some brain regions
  - manifestation from the 1st-3rd year of age
  - disorder of social communication and interaction, problematic contact with other people, stereotype behavior, perseveration

Developmental defects of the nervous system in childhood

Developmental disorder of speech and phatic functions

- dyslexia, dysgraphia, disorders of understanding, disorders of sound differentiation in normal intellect capacity
- sometimes also signs of mild brain dysfunction
- genetic predisposition + perinatal complications

Other disorders

- dyscalculia...

Mental retardation X dementia

Genetically determined diseases of the nervous system

- Various types of mutations
- Various types of heredity (including polygenic disposition acting in combination with extrinsic factors = participation of heredity in multifactorial diseases)

- Diseases with predominant affection of the nervous system
- Diseases, in which nervous system affection is only a part of complex pathological phenotype, or affection of the nervous system is a secondary consequence or complication of the disease

Genetic diseases of the NS - chromosomal aberrations

Down syndrome = chromosome 21 trisomy

- mental retardation of various severity

Edwards syndrome = chromosome 18 trisomy

- microcephaly, psychomotor retardation

Patau syndrome = chromosome 13 trisomy

- brain malformations, mental retardation, deafness)

Turner syndrome = 45 X0, female

- growth retardation, infertility, potentially mild mental retardation

Klinefelter syndrome = 47 XXY, male

- gynecomastia, hypogonadism, potentially mild intelligence decline

„Supermale“ syndrome = 47 XYY, male

- tall, often asocial behavior, mild mental retardation, tendency to aggressiveness

„Superfemale“ syndrome = 47 XXX, female

- mild intellect deficit

Genetic diseases of the NS - chromosomal aberrations

Cry du chat syndrome = chromosome 5 short arm deletion

- microcephaly, psychomotor retardation, lower intellect

Prader-Willi syndrome = deletion (or other affection) of the long arm of the paternal chromosome 15

- mental retardation, obesity, sleep disorders

Angelman syndrome = deletion of the maternal chromosome 15 long arm

- microcephaly, psychomotor retardation, epilepsy, „happy puppet child“

Genetically determined diseases of the NS

Fragile X syndrome

- a frequent cause of mental retardation in boys (1:1500)
- expansion of the CGG triplet sequence in FMR1 promotor sequence on the long arm of the X chromosome
  - normally 6-50, so called pre-mutation = 50-200, amplification over 200 → methylation → expression arrest → clinical manifestation
- mental retardation, elongated face, neurologic disturbances
- pathology related to FMR1:
  - fragile-X associated tremor/ataxia syndrome (FXTAS)
  - fragile X-associated primary ovarian insufficiency (FXPOI)
  - fragile X-associated neuropsychiatric disorders (FXAND)

Genetically determined diseases of the NS

Huntington disease

- autosomal dominant
- extended CAG repeat in the huntingtin encoding gene → extension of polyglutamine tract in the huntingtin protein
- manifestation in adulthood (juvenile form before the age of 20)
- degeneration of the basal ganglia (striatum) and brain cortex
- choreatic movement, hypotonic-hyperkinetic syndrome, behavioral abnormalities, dementia

Degenerative diseases of the cerebellum

- AR: Friedreich ataxia (2:100 000), ataxia telangiectasia...
- AD: spinocerebellar ataxias (SCA1-....), episodic ataxias
- X-linked: fragile X syndrome
- mitochondrial

Genetically determined diseases of the NS

Hepatolenticular degeneration = Wilson disease

- autosomal recessive, defect of cooper transport
- defect of cooper elimination via the liver → liver damage, cooper depositions in the brain (→ atrophy of the brain cortex, basal ggl., cerebellum) and other organs
- hepatic insufficiency, neurologic manifestations, Kayser-Fleisher ring, endocrine disorders, affection of the heart, kidneys
- lethal without the treatment

Spinal muscular atrophy

- a group of heterogeneous AR hereditary diseases
- degeneration of spinal ventral horn and brainstem motoneurons

  → muscle hypotonia, hyporeflexia, muscle atrophy, fasciculations
- severe forms lead to death during infancy (bulbar syndrome, respiratory insufficiency), mild forms start in adulthood

Genetically determined diseases of the NS

Hereditary motor and sensitive neuropathy = Charcot-Marie-Tooth

- various mutations leading to defect of myelin in the peripheral nervous system
- symptoms appear during childhood or early adulthood
- paresis and muscle atrophy, les pronounced sensitive deficit, characteristic foot deformity

Neurofibromatosis - AD heredity, multiple tumors of the nervous system

- **type I** = m. von Recklinghausen
  - pigment spots on the skin
  - in early adulthood multiple (even several thousands) neurofibromas (tumors originating from Schwann cells and fibroblasts) in the subcutaneous tissue, bone deformities in the proximity of the tumors, neurologic symptoms in about 1/3 of patients (spinal cord compression by the tumors growing from the spinal roots, mental retardation, acoustic nerve neurinoma, optic nerve glioma, epilepsy)
- **type II** = bilateral acoustic nerve neurinoma

Hereditary metabolic diseases with an impact on the NS

Saccharide metabolism disorders

Galactosemia - AR, galactose metabolism defect

Glycogenoses - a group of diseases, mostly AR

- disorder of glycogen synthesis or breakdown → according to the type: disorder of the liver, muscles, myocardium, hypoglycemia, growth retardation, mental retardation

Mucopolysaccharidoses

- hereditary disorders of lysosomal enzymes → accumulation of mucopolysaccharides in cells → affection of the CNS (psychomotor development retardation), bones (disproportional growth disorders, skeleton deformities, facial dysmorphism), organs (hepatosplenomegaly, cardiomyopathy)
- Type I = Hurler syndrome = gargoylismus
  - More severe forms are lethal during childhood.

Hereditary metabolic diseases with an impact on the NS

Aminoacid metabolism disorders

Phenylketonuria

- AR, defect of hydroxylation of phenylalanine to tyrosine
- myelination disorder, mental retardation
- influence of pathologic metabolites (phenylpyruvate, phenylacetate), phenylalanine, interference with tryptophan and tyrosine transport across the blood-brain barrier, lack of tyrosine

Hartnup disease

- disorder of neutral aminoacid transport (tryptophan, phenylalanine, methionine)
- defective conversion of tryptophan to niacinamid (vit. B)
- skin photosensitivity, neurologic disorders (cerebellar ataxia, psychic disorders)

Also other disorders of aminoacid metabolism are related to neurologic disorders and mental retardation.

Hereditary metabolic diseases with an impact on the NS

Lipidoses

- AR, usually enzymopathies, accumulation of lipids in tissues (storage diseases)

Niemann-Pick disease (sphingomyelinose)

- accumulation of sphingomyelin in RES macrophages
- type A: neurovisceral affection, death in childhood
- type B: chronic disease beginning later during childhood or adulthood, affection of the liver, spleen, lungs, but not the NS
- type C (transport disorder): various manifestations - organ affections, ataxia, epilepsy, mental retardation, hypotonia or spasticity, dysarthria

Gaucher disease (cerebrosidosis)

- accumulation of cerebrosides in the RES
- infantile, juvenile and adult forms
- splenomegaly, hepatomegaly, lymphatic node and bone marrow affection
- neurologic disturbances mainly in the infantile form

Hereditary metabolic diseases with an impact on the NS

Lipidoses

Krabbe disease

- AR, defect of lysosomal galactosidase (galactocerebroside hydrolysis)
- leukodystrophy, myelin degeneration
- manifestation starts several weeks after birth, death within 2 years

Amaurotic familial idiocy (Tay-Sachs disease)

- accumulation of ganglioside
- mental retardation, blindness, deafness, dysphagia, movement disorders, death during childhood (rare less sever form - juvenile and late-onset)

Hereditary endocrine disorders with NS affection

Laurence-Moon-Bardet-Biedl syndrome

- AR
- hypogonadism, hypothalamic obesity, retinitis, central diabetes insipidus, mental retardation

Prader-Willi syndrome

- see before

Kallmann syndrome

- various types of heredity
- hypogonadotropic hypogonadism + olfaction disorder + growth and skeletal disorders

Other nervous system diseases with genetic factors

Genetic predisposition plays a role in many diseases of the nervous system.

E.g. 10% of Alzheimer disease cases are hereditary. In the other 90%, genetic predisposition may play a role.

Metabolic and endocrine diseases with an impact on the NS

- Hereditary metabolic diseases (see before)
- Hepatic encephalopathy
- Uremia, uremic coma
- Hypothyroidism, hyperthyroidism
- Steroid encephalopathy
- Hypoglycemia, hyperglycemia, diabetes mellitus
- Ion imbalances
- Malnutrition
- etc.

THE END