Neuroinfections

- Diseases of the NS caused by:
  - Viruses
  - Bacterias
  - Candides
  - Parasites
- sometimes fulminant course of disease and fatal complications

Neuroinfections - etiological classification

- 1. Bacterial
- 2. Viral
- 3. Fungal
- 4. Specific (e.g. TBC)

Etiopatogenesis

- Spread of viruses to the CNS by the hematogeneous or neural route

A) Hematogeneous route: the viruses gain the CNS through perivascular spaces, entrance in the CSF is through the epithelial cells of the choroid plexus

B) Neural: (Herpes simplex virus - HSV, Varicella zoster virus - VZV)

C) Direct spreading from ear, nose, injury

Meningitis

- Meningitis is the inflammation of the meninges, (the membranes around the brain and spinal cord)
- Pachymeningitis, involves the outermost membrane
- is generally caused by trauma, such as a skull fracture, or by extension of an infection
- Leptomeningitis, involves the inner membranes, and may be caused by invading bacteria from other organisms

Meningitis

- The germs that cause bacterial meningitis are very common and live naturally in the back of the nose and throat
- People of any age can carry these germs without becoming ill

Meningitis:

- 1. Bacterial
- 2. Viral
- 3. Mycotic
Meningitis

- Etiological agents
  - Streptococcus pneumoniae
  - Neisseria meningitidis

- Enteroviruses: Echovirus, Coxackie
- Mumps (late winter and spring)
- Herpes simplex, typ 2, Epstein-Barr
- Lymfocytic choriomeningitis (winter)
- Adenovirus infections
- HIV

Pneumococcal meningitis

- Pathogenesis - bacterial, purulent meningitis
  - Bacteria from the place of primary infection → to blood → CSF through choroid plexus of the lateral ventricles, or other areas of altered BBB permeability
  - Germs multiply rapidly in the subarachnoid space
  - Recruitment of inflammatory cytokines (IL-1, TNF) and polymorphonuclear leukocytes
**Pathogenesis - bacterial, purulent meningitis**

- Result – purulent exudate in subarachnoid space, which is the basis of the neurological complications
- Obstruction of flow of CSF
- Adherence of leukocytes to the cerebral capillary endothelial surface increase the permeability of cerebral vessels → allowing for leakage of plasma proteins through open intercellular junctions → vasogenic brain edema

**Clinical features**

- Headache
- Fever ↑ (↓ - sepsis)
- Neck stiffness (not present in sepsis !)
- Photophobia
- Vomitus
- Intracranial hypertension
- Altered level of consciousness
- Seizures

**Meningeal syndrome**

- Kernig – flexion of passive extended LE

**Petechial rash in meningococcemia (Neisseria meningitidis) – develops in few hours**

(trunk, LE, mucous membranes, conjunctiva, palms, soles)

**Meningococcal meningitis**

**Clinical features – neonates !**

- Fever or hypothermia
- Lethargy
- Seizures
- Irritability
- Bulging fontanel
- Poor feeding
- Vomitus
- Respiratory distress
- Absence of meningeal syndrom – can be
**CSF**
- Increased CSF pressure
- Blood - ↑ Leu, FW, CRP
- **Viral meningitis**
  - Pleocytosis: ↑ lymphocytes, proteins +/-, sugar is normal
- **Bacterial meningitis**
  - Pleocytosis: ↑ polymorphonuclear leukocytes
  - ↑ proteins, ↓ sugar

**Brain CT**

**Therapy**
- The 3rd generation Cephalosporins
- Ampicillin
- Dexamethasone – inhibits the synthesis of inflammatory cytokines – IL-1, TNF
- Antiedematous treatment – Manitol
- Symptomatic therapy

**TBC, tuberculous meningitis**
- TBC – frequent in 20th century
- Chopin, Keats, Paganini, Modigliani, Thomas Wolf – died because of TBC
- 90-ties of 20th century – again increased number of TBC

**TBC meningitis**
- **Etiology** - Mycobacterium tuberculosis
- During dissemination from caverna - exudate, which is located predominantly in basilar cisterns, surrounds the cranial nerves and major blood vessels at the base of the brain
- Headache
- Meningeal syndrome
- Cranial nerves lesions - VI, III, IV, VII
- Changes in behaviour, confusion
- Hydrocephalus
- Brain edema
CSF

- Increased CSF pressure
- Pleocytosis – Ly
- ↓↓ sugar
- ↑ proteins
- positive cultivation
- Positive PCR test

Therapy

- INH + Rifampicin + Pyrazinamid
- Corticosteroids
- Manitol
- Symptomatic therapy

Spirochetal infections

- Borreliosis (Lyme disease)
  Etiology: Borrelia Burgdorferi
- Syphilis (Lues)
  Etiology: Treponema pallidum

Borrelia burgdorferi

Lyme disease

- After tick bite
- Skin lesion

Lyme disease
**Lyme disease - pathogenesis**

- **Spreading** – by spirochtemia, spreading in all the body
- CNS and PNS clinical feature

- **Early symptoms**: meningitis, facial nerve palsy (less other cranial nerves), radiculoneuritis
- **Late symptoms**: encephalopathy senzorimotor polyradiculoneuropathy

**Lyme disease - meningitis**

- Within 12 weeks of infection
- **Headache, fatigue, myalgia, arthralgia**

- **CSF**:
  - pleocytosis – Ly
  - ↑ proteins
  - sugar – normal
  - intrathecal production of BB antibodies -IgG, IgA
- **PCR**

**Lyme disease – facial palsy**

- In 4 weeks from erythema migrans
- Unilateral or bilateral facial palsy
- Other cranial nerves - rarely

- **Dg**: ELISA test (antibodies)
- **CSF**: pleocytosis – Ly, intrathecal production of antibodies (about 10 %)
- **Treatment**:
  - CSF negat.- Doxycycline (2x100 mg/D, 2W) i.v.
  - CSF pozit.- Ceftriaxone

**Lyme disease - radiculoneuritis**

- Severe, sharp, jobbing or deep and boring pain, in a radicular nerve distribution
- Within days, weeks: sensory loss, weakness, hyporeflexia, if there is myelitis – sphincter dysfunction, + Babinski

- **CSF**: Ly, ↑ proteins, intrathecal production of antibodies
- **EMG**: axonal lesion

**Lyme disease - encephalopathy**

- In patients with systemic manifestation and arthritis
- Confusional state, memory and cognitive slowing

- **CSF** – only in 5 % pozit. Ly less than in 50 % pozit. antibodies

**Lyme disease– senszorimotoric polyradiculoneuropathy**

- Chronic radiculoneuropathy – sensory symptoms, particularly distal paresthesias in a stocking and glove distribution, less severe than in acute polyradiculoneuritis Guillain Barre syndrome
- **EMG** – axonal lesion
- **CSF** – frequently negat.
Syphilis (Lues)

- 1/3 nontreated patients – neurovascular complications of syphilis
- Etiology: spirochetal inf. Treponema pallidum

Neurosyphilis

- Pathogenesis
- Perivascular infiltration of the meninges
- focal meningeal inflammation – hypertrophic meninges or gumma
- Inflammatory cells invade blood vessel wall – arteritis (luminal occlusion, stroke like episodes)
- Parenchymal involvement – gliosis in late stages
- Lymphocytic infiltration of preganglionic portion of dorsal roots and posterior columns atrophy of posterior columns

Neurosyphilis – meningitis

- CSF Ly, ↓ Glu, ↑ proteins
- Pozit. VDRL test

Neurosyphilis – meningovascular

- Endarteritis – small and medium vessels (MCA) – can be stroke etiology in young people !!!
- Focal signs
- AG: narrowing of arteries
- MRI: multiple infarcts
- Spinal artery – transversal myelitis

Dementia paralytica

- Progressive paralysis

- Decreased cognitive functions
- memory problems
- pupillary abnormality- Argyll-Roberts pupils
**Tabes dorsalis**

- Paresthesias in root distribution
- Decreased proprioception
- Spinal ataxia
- Argyll-Roberts pupils

**Brain abscess**

A rare complication in immunocompetent individuals:
- AIDS
- Chronic corticosteroid therapy
- Immunosuppression after bone marrow transplantation

**Clinical feature**

- Headache
- Fever
- Vomitus
- Focal neurological deficit
- Focal or generalized seizures
- Syndrome ICH – letargy, confusion, coma
- Papilledema
- Palsy of cranial nerves III, VI, or both
Brain abscess - CT

- Brain abscess in a 2-year-old child
- Ptosis, fever, papilloedema
- 60 ml of pus Gram + and Gram – bacteria

Diagnosis and therapy

- Brain CT (enhancing lesion)
- CSF – lumbar puncture – contraindicated!! in brain abscess

- Therapy: aspiration or extirpation abscess + antibiotics

Encephalitis

- Inflammation of brain tissue
- Frequently with meningitis (meningo-encephalitis)

Disease course and symptoms:
- Impairment of consciousness – confusion, stupor, coma, seizures, aphasia, hemiparesis, involuntary movements, cerebellar ataxia, polymyoclonus, cranial nerves lesions
- Except herpetic - seasonal, epidemic form

VIRAL:
- Herpetic
- Epstein-Barr virus
- Tick-borne
- CMV
- Varicella zoster
**Herpes simplex encephalitis**

- Herpes simplex virus 1
- Incidence – 4/1 million people/year
- Most severe, most frequent
- Without therapy – mortality 70%

**Herpes simplex encephalitis**

- After primoinfection – most often oropharyngeal – virus is transported to ganglion Gassen
- Virus survives latent for all life
- In the case of reactivation - there is retrograde transport of the virus by rought of n.V.

**Herpes simplex encephalitis**

- Clinical feature
  - High fever
  - Headache
  - Vomitus
  - Dezorientation, confusion, memory problems
  - Focal neurological symptoms
  - Seizures

**Herpes simplex encephalitis**

- Signs from temporal lobe – changes in personality and behaviour, aphasia, seizures
- Brain edema – can lead to temporal herniation
- Inflammation, bleeding and pan necrosis of nearly all tissue elements
Herpes simplex encephalitis - diagnosis

- CSF – ↑ Ly, ↑ proteins
- CT, MRI
- EEG – high, periodical waves in temporal region and complex of slow waves in interval 2-3 sec.
- ½ of patients do not survive
- Th: Acyclovir 30 mg/kg/D 14 days – the better prognosis after earlier beginning

Tick-born encephalitis

- TBE is caused by tick-borne encephalitis virus (TBEV), a member of the family Flaviviridae
- Transmitted by Ixodes ricinus
- Initially isolated in 1937
- Clinical course – non-specific with symptoms that may include fever, malaise, anorexia, muscle aches, headache, nausea, and/or vomiting
- The CNS symptoms of meningitis (e.g., fever, headache, and a stiff neck) or encephalitis (e.g., drowsiness, confusion, sensory disturbances, and/or motor abnormalities such as paralysis) or meningoencephalitis
- Myelitis
- Consequences – 10% patients
**Tick-born encephalitis**

- CSF - an increase in the number of white blood cells
- Low white blood cell count (leukopenia) and a low platelet count (thrombocytopenia)
- There is no specific drug therapy for TBE
- Anti-inflammatory drugs, such as corticosteroids, may be considered

**Encephalitis**

- **Varicella zoster encephalitis (VZV)**
- through n.V.
- **Epstein-Barr virus (EBV)**
- EBV in 90% people
- Manifestation – mononukleosis, with meningitis, encephalitis
- **CMV encephalitis**
- Immunodeficient people - AIDS

**Encephalitis CMV**

- **Encephalitis cytomegaloviral (CMV)**
- After reactivation CMV in immunodeficient persons, AIDS
- Slow disease course (weeks)
- Therapy: antiviriotics

**Herpes zoster (shingles)**

- Varicella zoster virus
- Incidence 3-5/1000/year
- Old people, with malignancies, mainly lymphoma and M. Hodgkin
- Reactivation of varicella virus – latent in senzoric ganglia after the primary infection with chicken pox

**Herpes zoster**

- Radicular pain – sometimes before erruption
- Vesicular cutaneous eruptions spread over two or three dermatomes on one side
- Most often - **thoracic part**
- Cranial ganglia – oftalmic paresis
  - Ramsay Hunt - n. VII, palsy, vertigo, deafness

**Herpes zoster**

- Image: [Credit: NIAID]
Herpes zoster

- CSF – ↑ Ly and proteins
- Pain 1 – 4 weeks
- Later complication = postherpetic neuralgia
- Treatment: Acyclovir 800 mg 5x/day, 7 days
  reality → 5 x 200 mg

Herpes zoster

- Postherpetic neuralgia
- Pain in territory of herpes zoster, lasting minimally 3 months after skin eruptions
- 10 -15% patients
- Treatment – Gabapentin 3 x 300 mg –
  3 x 1200 mg, pregabalin
  Common analgetics are not effective!

Prion diseases

- Normal prion protein PrP^c – encoded by the prion gene (PRNP) on human chromosome 20
- The function of PrP^c: role in anti-oxidant systems cellular copper metabolism
- PrP^Sc – insoluble and protease resistant protein → accumulates in tissues forming amyloid structures

Prion diseases or transmissible spongiform encephalopathies (TSEs)

- rare progressive neurodegenerative disorders that affect both humans and animals
- They are distinguished by long incubation periods, characteristic spongiform changes associated with neuronal spongiform changes, and a failure to induce inflammatory response.
Prion diseases

- PrP\textsuperscript{sc} deposition
- Neuronal loss, astrocytic gliosis, spongiform change

Prion diseases

- In human prion diseases – common polymorphism at codon 129 → important effects on susceptibility to disease
- At codon 129 of PRNP an individual may encode for methionin or valin
- 80% of UK sporadic JCD – MM

Prion diseases

- Creutzfeldt - Jakob Disease (CJD)
- Variant Creutzfeldt-Jakob Disease (vCJD)
- Gerstmann-Straussler-Scheinker Syndrome
- Fatal Familial Insomnia

Creutzfeldt – Jakob sporadic form

- 90%
- Annual frequency – 1/million/ per year
- Middle age (55-70 years)

Creutzfeldt – Jakob sporadic form

- Mental deterioration
- Speech disorders
- Memory loss
- Cerebellar signs
- Visual –
- Pyramidal , extrapyramidal signs
- Involuntary movements (myoklonus)
- Mutism, global dementia – death (6M-2R)
- Lost ability to walk

The typical periodic EEG seen in many cases of sporadic CJD.
Creutzfeldt – Jakob disease

- CSF – protein 14-3-3
- Normal protein being released to CSF following neuronal damage
- Not specific for JCD
- Sensitivity – 94%
- Genetic testing – most common mutation – E200K

Gerstmann-Sträussler-Scheinker sy (GSS)

- Begins between the ages of 45 and 50
- Slowly evolving ataxia
- Mental deterioration
- Dementia, myoclonus, duration 5-10 years
- Point mutation at codon 102, 105 (spastic paraparesis), 117 (pseudobulbar signs), 145, 196, 217 (GSS + AD)

Fatal familial insomnia (FFI)

- Autonomic and endocrine dysfunction
- Insomnia (during day - somnolence)
- Unexplained disorders of temperature, cardiovascular and respiratory regulation
- Later – pyramidal, extrapyramidal signs, cerebellar ataxia, myoclonus
- Duration: 1 –2 years
- Mutation at codon 178

Creutzfeldt – Jakob iatrogenic – accidentally transmitted

- Accidentally introduced into the body
- Length of incubation – 2 years in cases when infection introduced directly into the brain, 15 years – after s.c. inoculation
- Now - rare
- Corneal graft, stereotactic EEG
Creutzfeldt – Jakob new variant (vCJD)

- Due to consumption of beef contaminated by the agent of bovine spongiform encephalopathy (BSE)
- Young age at onset of illness (27-50)
- Psychiatric or sensory disturbance
- Long duration of illness (14 months)
- Clinical feature – like sporadic form (dementia, myoclonus, multisystem neurological deficits)

Creutzfeldt – Jacob variant (vCJD)

- There are no changes on EEG
- There is no protein 14-3-3 in CSF
- MRI – abnormally high symmetrical signal in pulvinar talami – strong diagnostic clue
- Neuropathological examination – diffuse spongiform changes, especially in BG, posterior thalamus and cerebellum

Acquired immunodeficiency syndrome (AIDS)
Human immunodeficiency virus (HIV)

- Neurological complications
- Aseptic meningitis
- Cognitive disturbances – adults
- Progressive encephalopathy – children
- Myelopathy
- Neuropathy (inflammatory demyelinizing polyneuropathy, brachial plexopathy, mononeuritis)
- Myopathies – myopathy, myositis

AIDS

- tumors
- Primary lymfoma of CNS (PCNSL) most frequent, children, adult – 5% clinical feature – headache, confusion, impaired memory, seizures, cran. nn. )
- Dg.: MRI
- MTS non-Hodgkin lymfoma into CNS
- Kaposi sarcoma
AIDS

- Oportune infections
- **Bacterial** — (Mycobacterium tuberculosis, Treponema pallidum, Nocardia, ...)
- **Viral** — (Cytomegalovirus, Herpes simplex, Varicella zoster, JC, ...)
- **Fungal** — (Cryptococcus neoformans, candida, ...)
- **Protozoal** — (Toxoplasma gondii, ...)

AIDS dementia complex (ADC)

- **T2- MRI:**
  - Enlargement of ventricles,
  - Hyperintensity in subcortical white matter of both frontal lobes

brain atrophy, wide ventricles and subarachnoid space