CNS infections

Dita Smíšková

Meningeal syndrome

Causes of meningeal sy

- ↑ intracranial pressure
- Irritation of spinal roots
- Irritation of the cranial nerves
- Irritation of n.vagus

Diff.dg.meningeal sy

- meningismus (pneumonia, sepsis, pyelonephritis)- positivity of meningeal signs, but normal CSF results
- intracranial hemorrhagic processes
- intracranial expansive processes
- insolation
- trauma
- toxins, allergic reactions
- spondylogenic disorder (spondylodiscitis)

CNS infections

by affected structure

meningitis- encephalitis- myelitis

by time course

acute - subacute - chronic

By type of inflammation

purulent, purulent

non-purulent, serous, aseptic

By etiology

bacterial, viral, mycotic, parasitic

By the place of origin

Community

Nosocomial

CNS infections

Purulent

- CNS inflammation limited to the subarachnoid space
- **primary** (*N.menigitidis, Limax* amoebae)
- **secondary**

  otitis, mastoiditis (*Str. pneumoniae, H. influenzae*)

  post-traumatic (*S. aureus*)
- **secondary complication of sepsis**

  infective endocarditis, spondylodiscitis (*S. aureus*)

Non purulent

- **meningitis**
- **meningoencephalitis** - brain and meninges involvement
- **encephalitis** - brain involvement (e.g. cerebellitis, rhombencephalitis)
- **myelitis** - spinal cord involvement

Laboratory diagnostics of CNS infections

	Leuko/ mm ^{3}	Protein g/L *	Glucose mmol/L	Glyquor / G $_{sérum}$	Lactate mmol/L	pathogen
normal	0 - 5 lymphocytes	0,1 - 0,45 (0,6)	2,2 - 4,2	0,6-0,8	< 2,0	-
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mycotic or TB meningitis	tens to hundreds, lymphocytes	↑ ↑	↓	<0,5	↑	cryptococcus

- children aged 0-7 days - cell count 0-30/mm^3 , neutrophils may predominate, protein 0.2-1.4 g/l
- Children aged 7-30 days - cell count 0-20/mm^3 , neutrophils <20%, protein 0.15-1.0 g/l
- Examine the fluid immediately, at 22 ^{o} C up to 50% of the cells could be destroyed in 1 h

Bacterial (purulent) meningitis

- even with antibiotic treatment, the lethality rate is 10-30%
- TOP 10 infectious causes of death worldwide
- decrease in incidence
  - in countries where vaccinations are given
- change in the spectrum of causative agents
  - hemophilus ↓↓
  - pneumococci, meningococci ↓
  - listeria ↑↑
- shift of disease from childhood to adulthood

Etiology depending on age

0 - 6 weeks	***Streptococcus*** *agalactiae* ***E.coli*** + other Enterobacteriaceae *Listeria monocytogenes* *Enterococcus* sp.
6 weeks - 5 years children, adults	***Streptococcus pneumoniae*** ***Neisseria*** meningitidis *Haemophilus influenzae* b in areas without vaccination
> 50 years	***Streptococcus pneumoniae*** ***Listeria monocytogenes*** Enterobacteriaceae

Etiology depending on predisposing factors

mesotheitis, mastoiditis, sinusitis	*Streptococcus pneumoniae* *Haemophilus* influenzae
neurosurgery, penetrating craniotrauma, liquor shunt	*Staphylococcus aureus* *Staphylococcus epidermidis* *Pseudomonas aeruginosa* Enterobacteriaceae
fracture of the skull base, liquorrhea	*Streptococcus pneumoniae* bacteria colonizing the nasopharynx

Etiology depending on predisposing factors

cellular immunodeficiency, cytostatic therapy, chronic corticotherapy	*Listeria monocytogenes* Enterobacteriaceae fungi - *Cryptococcus*
antibody immunodeficiency, asplenia, neutropenia	*Streptococcus pneumoniae* *Haemophilus infulenzae* *Neisseria meningitidis*
infective endocarditis, spondylodiscitis	*Staphylococcus aureus*

Pathogenetic classification of suppurative meningitis

Primary:

- colonization of the nasopharyngeal mucosa
- spread by blood, crossing the blood-brain barrier

Secondary:

- primary focus of infection in the skull (otitis, sinusitis), in the spine (spondylodiscitis) → spread per continuitatem

  elsewhere in the body (pneumonia, endocarditis, pyelonephritis) → haematogenous spread
- craniotrauma, an invasive procedure breaching the dural barrier

Community vs. nosocomial meningitis

- community meningitis

- nosocomial meningitis, health-care associated

Difficult timing (>48 hrs after admission? <30 days after discharge?)

meningitis due to iatrogenic dural barrier disorder

- postsurgery (NCH, ENT)
- catheter - external drainage, internal drainage
- after spinal anesthesia, perimyelography, puncture

- due to nosocomial bacteraemia

Clinical signs

Fever + impaired consciousness with at least 2 of the 4 symptoms:

- headache
- nausea, vomiting
- positive meningeal symptoms
- seizures

- symptoms of severe intracranial hypertension and trunk oppression

  coma, hypertension, bradycardia, m. nn. paresis.

Purulent meningitis clinical manifestations

Short history, sudden onset

Newborns,

- few specific symptoms
- behavioural change (apathy x irritability)
- seizures
- fever x hypothermia
- development or worsening of icterus

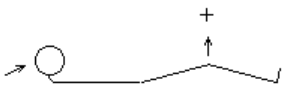
Infants

- vomiting
- fever
- deterioration of peripheral blood circulation
- bulged fontanella
- disorder of consciousness

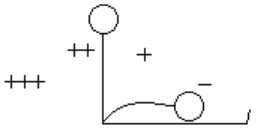
Children > 1 year and adults

- meningeal syndrome - cephalea, vomiting, impaired consciousness
- positivity of meningeal symptoms
- seizures
- photophobia
- petechiae

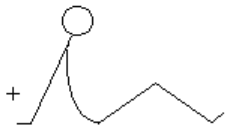
opozice šíje



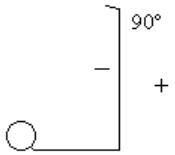
Brudziński



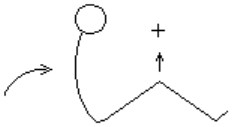
spine sign



Amoss (trojnožka)



Lasègue



Kernig

CAVE!
ATBs may mitigate clinical symptoms

Diagnostics of CNS infections

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purulent inflammation	thousands, neutrophils	↑ ↑ ↑	↓ ↓	<0,5	↑ ↑	Bacteria amoeba
mycotic meningitis	tens to hundreds, lymphocytes	↑ ↑	↓	<0,5	↑	cryptococcus

Microbiological diagnostics - detection of agents

Liquor

- **microscopy** - sensitivity 60-90%, depends on bacterial concentration, highest in pneumococci
- **culture** - sensitivity up to 70% without prior ATB treatment
- molecular genetic methods - **PCR**

Blood

- hemoculture
- (PCR)

Molecular genetic diagnostics - PCR

- multiplex real-time PCR

  pathogen-specific hybridization probes amplify genes encoding 16S rRNAs of typical bacterial pathogens:

  S. pneumoniae, N. meningitidis, L. monocytogenes, H.influenzae, Fusobacterium nucleatum

- universal detection of bacteria and fungi

  primers amplifying genes encoding 16S rDNA (bacterial) and 18S rDNA (fungal), subsequent direct sequencing of the product and comparison of the obtained sequence with the database

It cannot replace culture and ATB susceptibility testing !!!

Treatment

Start as soon as possible, ideally within 1 hour!

Objectives:

- sterilise the CSF - antibiotics
- reduce inflammation in the subarachnoid space - corticosteroids

  dexamethasone 0.15 mg/kg (8mg) á 6 h i.v., 4 days

  before the first dose of ATB or at the same time

- reduce brain edema

  corticosteroids, mannitol, resting mode, elevation 30^{o}
- maintain cerebral circulation and oxygenation

  circulatory and ventilatory stabilization, elimination of spasms
- sanitise the primary focus

  mastoidectomy, sinus rehabilitation

Empirical antibiotic treatment

Age, predisposition	1.choice	Alternative
0-4 (-8) weeks	AMP + cefotaxime	AMP + GEN
2 months - 50 years	CEFIII	CMP, MER
> 50 years, immunodeficiency	CEFIII + AMP	CMP instead of CEFIII, COT instead of AMP, MER
neurochir. surgery, penetr. craniotrauma, shunt	VAN + CTZ	VAN + MER

Targeted antibiotic treatment

Pathogen	Standard	Alternative
S. pneumoniae	PNC-G	AMP, CEFIII, CMP
N. meningitidis	PNC-G	CEFIII, CMP, MER
H. influenzae	CEFIII	CMP, MER
L. monocytogenes	AMP (+ GEN)	COT, MER
Enterobacteriacae	CEFIII (+ GEN)	MER
P. aeruginosa	CTZ	MER, CIP
S. aureus MSSA MRSA	OXA (+ RIF) VAN (+ RIF)	VAN, MER (+ RIFF) COT, LNZ (+ RIF)

Duration of ATB treatment

Recommended duration of antibiotic treatment [days]

N. meningitidis 7-10

S. pneumoniae 10-14

L. monocytogenes 21

S. agalactiae 10-14

Gram-negative rods 21-28

adjust according to clinical and laboratory response to treatment

Symptomatic treatment of meningitis

Antiedema treatment

Dexamethasone - mozkového edema, intracranial pressure, protects hearing (v.s.blockade of TNΦ–α release)

Mannitol 20% (?)

Hyperventilation (controlled hypocapnia)

Other supportive and symptomatic therapies

- i.v. fluids
- Antipyretics, anticonvulsants
- Treatment of DIC
- Oxygen therapy if necessary

Consequences

- encephalopathy - headaches, vertigo, sleep and memory disorders, difficulty concentrating and learning
- hearing impairment
- paresis
- epilepsy
- severe deficits - organic psychosyndrome, apalic state

If there is Staphylococcus aureus in the CNS...

..... the source of meningitis is probably

infective endocarditis (embolization) - echocardiography, haemoculture repeatedly

or

spondylodiscitis - MRI of the spine

Subacute and chronic meningitis

1. Infectious
2. Autoimmune
3. Tumor

Infectious etiology

Cryptococcus species

Coccidioides immitis

Histoplasma capsulatum

Blastomyces dermatitidis

Aspergillus fumigatus

Mycobacterium tuberculosis

Treponema palidum

Etiological agents of importance in the Czech Republic

Cryptococcus species

Coccidioides immitis

Histoplasma capsulatum

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Cryptococcal meningitis

Cryptococcus neoformans

- ubiquitous agents, in soil, bird excreta, tree bark
- inhalation route of infection
- disseminated infection in patients with cellular immunodeficiency - lymphomas, AIDS, post-transplant, chronic corticotherapy and other immunosuppressive drugs, rarely immunocompetent
- the most common agent of meningitis in Africa, the 4th infectious cause of death

Cryptococcal meningitis

Clinical signs

- **Subacute development** 2-4 weeks
- headache, subfebrile to fever, nausea, vomiting, irritability, behavioural disturbances
- focal symptoms - cranial nerve paresis, diplopia
- meningeal symptoms often negative

Cryptococcal meningitis - diagnosis

- microscopic examination of the liquor after staining (sens. 75 %)
- cryptococcal polysaccharide antigen in the lysate (sensitivity up to 95%)
- culture of liquor (sensitivity 90%), blood, sputum, urine
- PCR detection of fungal DNA

CT - hydrocephalus, edema, MR - enhancement of leptomening

Cryptococcal meningitis - treatment

- Antifungal
  - induction: amphotericin B + fluconazole 800 mg 2 weeks
  - consolidation: fluconazole 400-800 mg for 8 weeks
  - suppressive: fluconazole 200-400 mg 6-12 months

- treatment of IC hypertension - repeated LP, lumbar drainage, VP shunt, mannitol and corticosteroids not recommended

Tuberculous meningitis

CNS forms of TB ... 0.5-1% of all TB cases

Difficult diagnosis

- ✓ symptomatology not very specific
- ✓ conventional bacteriological methods not very sensitive
- ✓ new laboratory methods a little better

Predisposition

Unvaccinated individual (immigrants), repeated and prolonged contact with TB infection, alcoholism, nutritional withdrawal, HIV infection, immunosuppressive and biological treatment

Pathogenesis

- pulmonary TB ⇨ haematogenous dissemination to the integuments and brain ⇨ tubercles
- rupture of the cerebral tubercle ⇨ meningitis

Tuberculous meningitis

Pathological anatomy

thick to gelatinous exudate with a peak at the base of the brain ("basilar meningitis")

➔ 3 main pathological processes:

- basal cistern obstruction → obstructive hydrocephalus
- obliterating vasculitis of arteries and veins at the base of the brain → thrombosis, aneurysm → ischemia, hemorrhage
  - formation of fibrous adhesions in the vicinity of the cerebral nerves → cerebral nerve disorders VI, III, IV, VII

➔ the severity of these disabilities determines the outcome

Clinical picture of TBM

- gradual, subacute development of difficulties and symptoms
- prodromes - fatigue, intermittent headache, subfebrile
- persistent headache, vomiting, fever, photophobia, focal symptoms - paresis, dysarthria, ataxia

  impaired consciousness, meningeal symptoms

  rarer: abnormal movements, symptoms of a vascular event
- fever and meningeal symptoms may be absent for a long time
- symptoms of TB infection outside the CNS

Aseptic inflammation of the CNS

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Aseptic CNS infections

- **meningitis**
- **meningoencephalitis**
- **encephalitis** - brain involvement (e.g. cerebellitis, rhombencephalitis)
- **myelitis** - involvement of the spinal cord

The most common agents

Viruses

- **TBE**
- **enteroviruses**
- **herpes viruses (HSV1,2, VZV)**
- **mumps virus**
- respiratory viruses
- viruses of exanthem. diseases
- **HIV**

Bacteria

- spirochets (**borrelia**, treponema, leptospira)
- Ehrlichie
- Mycoplasmas
- Chlamydia

Parasitic agents
Amoeba (?)
Trypanosoma

Mycotic agents
histoplasmosis

Diagnostics

History

- tick bite
- stay in nature, contact with rodents
- travel
- similar manifestations in the family or collective

Clinical symptoms

- fever
- positivity of meningeal signs
- photophobia, phonophobia,
- ataxia
- unsteady walking, vertigo
- eyelid or fingertip tremor,
- confusion, drowsiness, behavioural changes, sleep disturbances
- dysarthria
- paresis

Laboratory tests - blood

- Blood count, diferential count of WBC
- CRP, basic biochemical examination
  - MEK :↑ AST, ALT
  - Leptospirosis : ↑ bili, AST, ALT, CK, urea, creat
  - Parotitis : ↑ amylase, lipase
- serology TBE, LB , mumps

unnecessary: serology of herpes viruses

Herpetic neuroinfections

- HSV 1
- HSV 2
- VZV
- EBV
- CMV
- HHV 6
- HHV 7

Monkey herpes B-virus - infects macaques. Transmission to humans by bite or scratch- vesicles around wound. Fatal in untreated persons (acute ascending encephalomyelitis)

Cave!
Hemorrhagic necrotizing encephalitis

- primoinfection or reactivation of Herpes simplex 1 infection
- life-threatening infections - formation of necrotic hemorrhagic foci in the CNS
- early initiation of causal therapy is necessary

HSV encephalitis

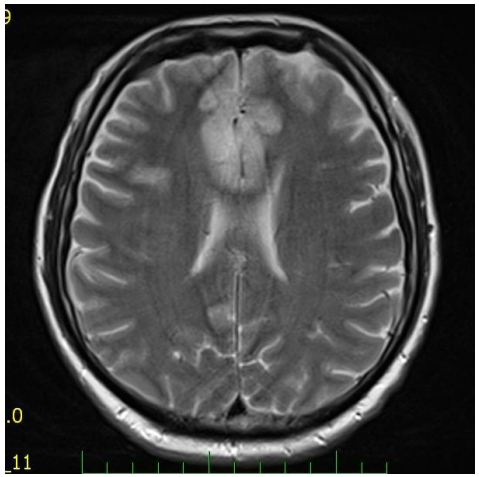
- HSV 1 90%, HSV 2 10%
- primoinfection and reactivation

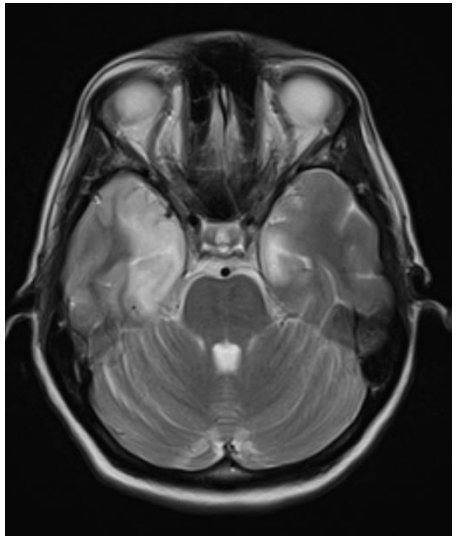
Clinical manifestations

- fever, subfebrile
- cephalea
- nausea, vomiting
- confusion
- **speech disorder**
- **behavioural changes** (cave alcoholics, drug addicts...)
- Cramps
- somnolence
- coma

HSV encephalitis - diagnosis

- **aseptic liquor finding + PCR positivity in liquor**
- PCR negativity in the first LP does not exclude disease, repeat after 2-4 days
- synthesis of antibodies in the liquor starts on day 10-12 of the disease





HSV encephalitis - therapy

Initiate prior to confirmation of the agent

- **acyclovir i.v.** 10mg/kg every 8 hours for 14-21 days
- immunosuppressed patient always 21 days
- dose adjustment according to renal function, especially in old patients

Side effects :

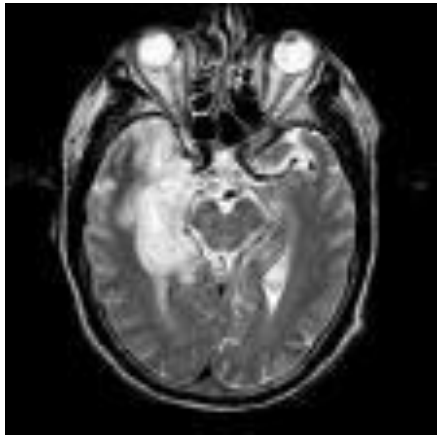
- **Psychiatric symptoms**
  agitation, confusion, hallucinations, psychotic symptoms.
- **Nervous system disorders**
  headache, dizziness, tremor, ataxia, dysarthria, convulsions, somnolence, encephalopathy and coma.

Hemorrhagic necrotizing encephalitis

Diagnostics

Imaging methods

- MRI - changes mostly in temporal and frontal region, appear on day 3
- CT scan in the first days of the disease normal
- EEG



Tick-borne meningoencephalitis

transmission from a tick within 10 minutes of bite

2-phase course: flu-like symptoms, then 2-7 days of asymptomatic phase, followed by neurological symptoms

- meningitis
- meningoencephalitis
- encephalomyelitis

Paretic complications
in about 5-10% of patients, in elderly people paresis is more severe and long-lasting

- cranial nerves (n.VII, III, VI)- usually at the beginning of the disease
- plexus brachialis
- quadruparesis
- bulbar syndrome

No specific antiviral drug
Vaccine available

Neuroborreliosis

Clinical manifestations

- aseptic meningitis
- aseptic meningitis + cranial nerve paresis
- meningopolyradiculoneuritis (Bannwarth's syndrome)

+

Lymphocytic pleocytosis

+

Intrathecal synthesis of antibodies

Early Lyme borreliosis	**Early localised stage** (days to weeks after infection)	**Erythema migrans** - sometimes with general flu-like symptoms
	Early disseminated stage (weeks to months after infection)	**Multiple migratory erythema** **Borrelial lymphocytoma** **Acute neuroborreliosis** - Cranial neuritis: paresis of n. VII and other cranial nerves - aseptic meningitis, encephalitis - Garin-Bujadoux-Bannwarth syndrome **Lyme arthritis** - arthralgia, migratory arthritis **Lyme carditis** - dysrhythmias, myocarditis, pericarditis **Affection of the eye** - conjunctivitis, keratitis, uveitis, paresis of the eye muscles
Late Lyme borreliosis	**Late disseminated stage** (months to years after infection)	**Acrodermatitis chronica atrophicans** - sometimes with general flu-like symptoms **Late neuroborreliosis** - chronic progressive encephalitis, encephalomyelitis - chronic polyneuritis **Late Lyme arthritis**

Bannwarth syndrome (meningopolyradiculoneuritis)

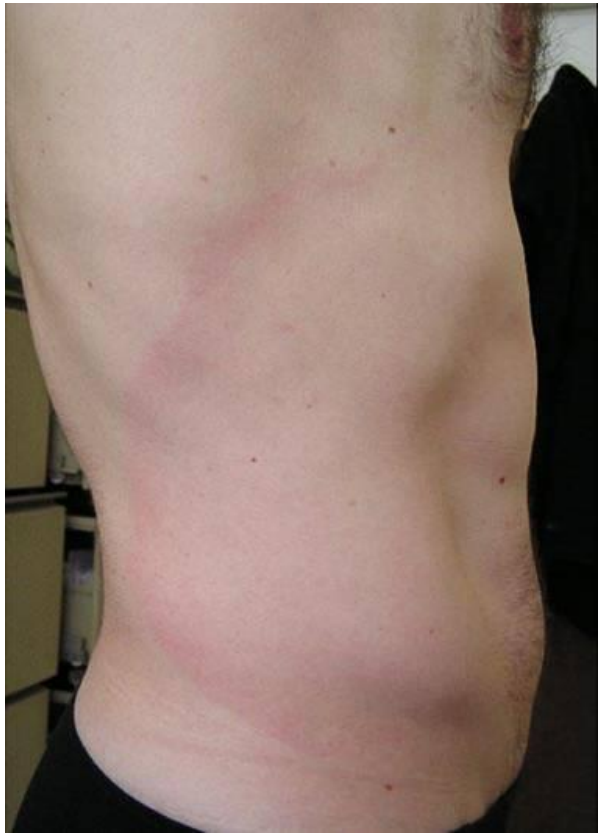
- **aseptic liquor finding**
- **radicular pain caused by inflammation of the spinal roots**
  - usually with impaired hearing and muscle weakness to paresis of the affected limbs
  - the lumbosacral nerves are most commonly affected
- almost half of the cases also have **cranial neuritis -** paresis of n.VII, less often paresis of the oculomotor nerves

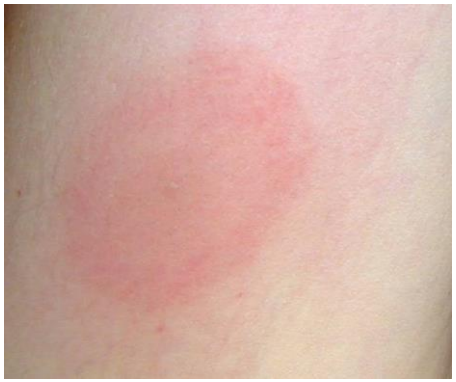
Complications and sequelae of aseptic CNS inflammation

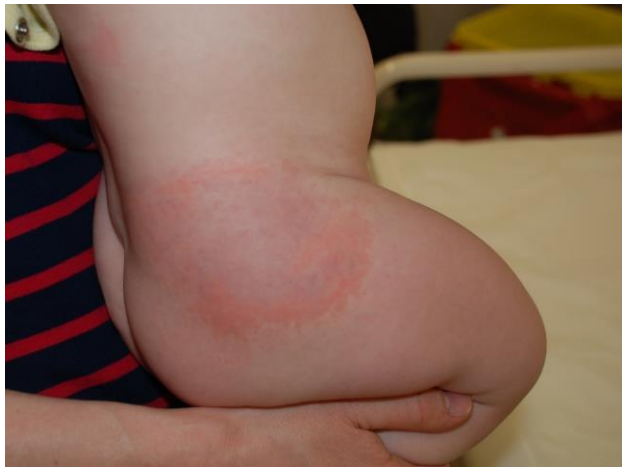
- paresis
  - most often neuroborreliosis, MEK
- postencephalitic syndrome
  - headaches
  - disturbances in concentration, memory, sleep
  - neurovegetative imbalance

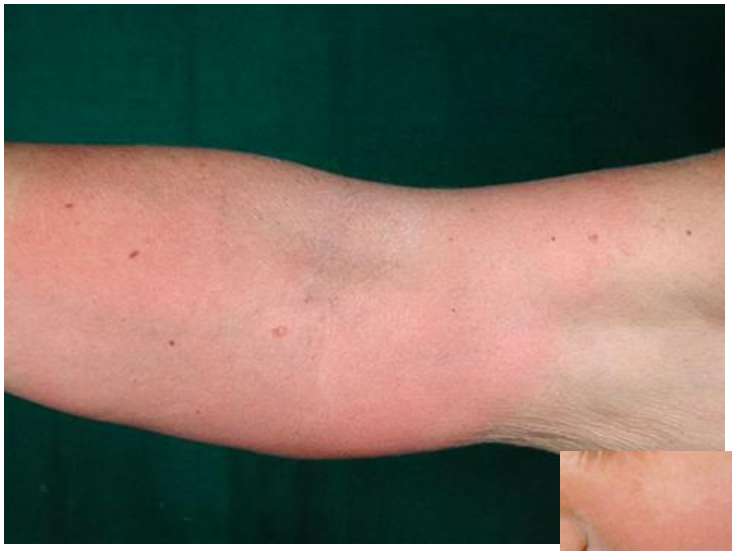
Regimen after uncomplicated aseptic inflammation of the CNS

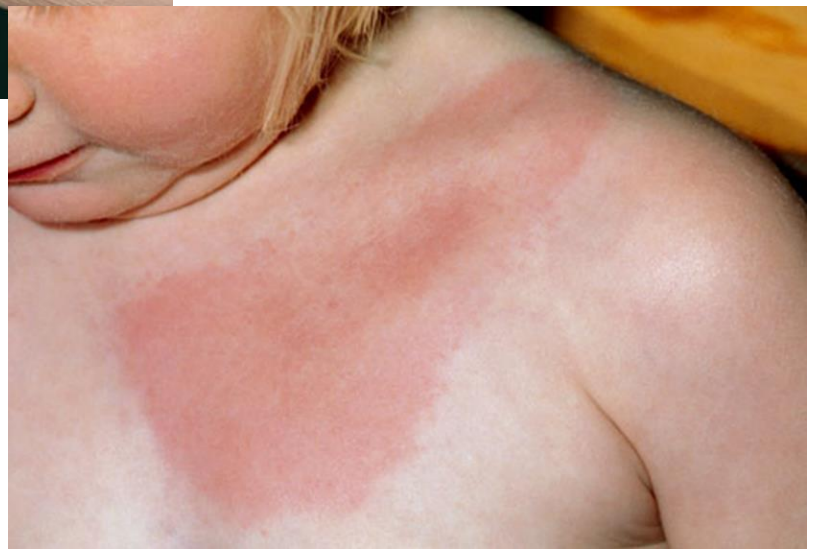
- first outpatient follow-up in 2-3 weeks after discharge, possibly follow-up EEG, total follow-up 6-12 months
- limitation of physical and mental exertion for 3-8 weeks
- do not watch TV, PC, limit reading (2 - 4 weeks)
- prohibition of alcohol
- no sun exposure
- no vaccination for 6 months with a non-live vaccine and 1 year with a live vaccine

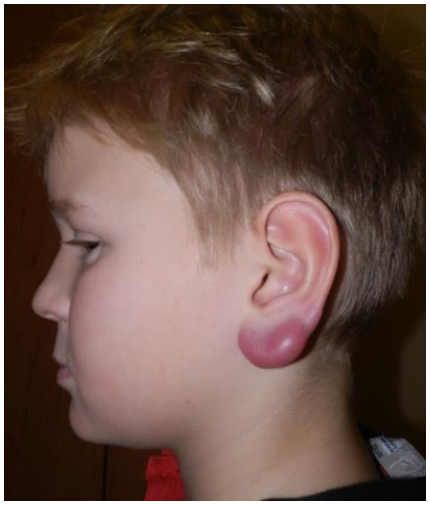


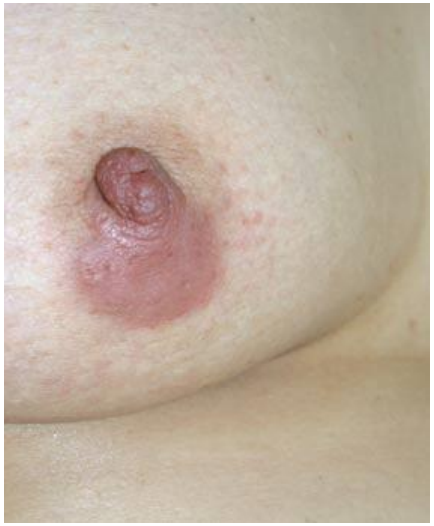


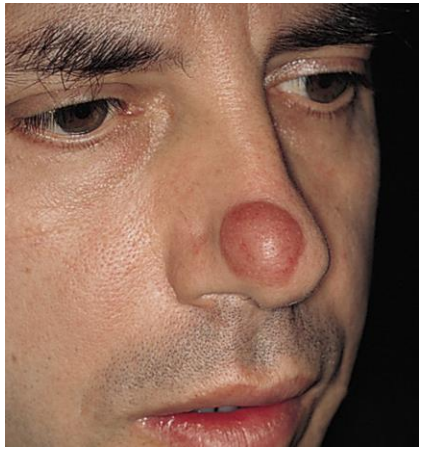


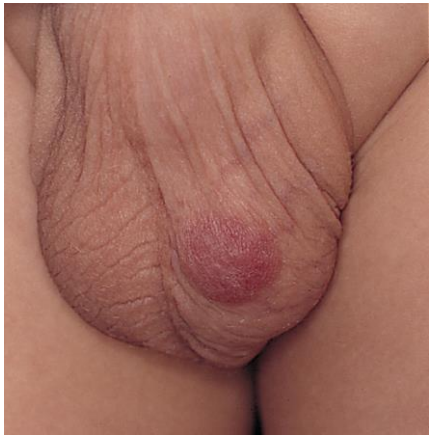












Lyme borreliosis - neurological manifestations

Neuroborreliosis

Clinical manifestations

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- meningopolyradiculoneuritis (Bannwarth's syndrome)

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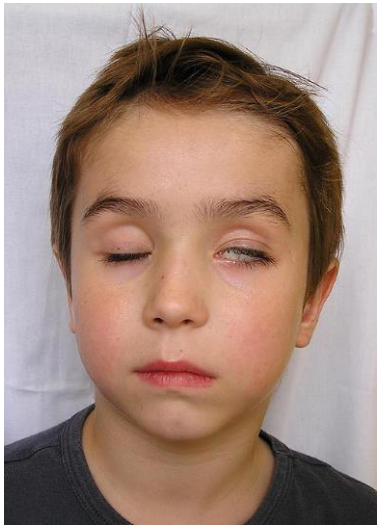
Lymphocytic pleocytosis

+

Intrathecal synthesis of antibodies
(controversial cases - CXCL13)

Cave!

Especially in children, isolated neuritis VII without liquor findings is possible



LB - therapy

ECM + early disseminated phase

- **doxycycline** p.o. 200 mg/day in one or two doses, children over 8 years of age 4mg/kg/day)
- **amoxycillin** p.o. 3 x 500-1000mg, children 50 mg/kg/day
- **cefuroxime axetil** p.o. 2 x 500 mg p.o. , children 30mg/kg/day
- V-penicillin p.o. 3 x 1-1.5 MIU, children 100 000j/kg/day
- **azithromycin** 1 x 500 mg p.o., children 10mg/kg/day, double dose on the first day
- **clarithromycin** 2 x 500mg p.o., children 7.5 mg/kg/day

Neuroborreliosis

- **ceftriaxone** i.v., i.m., 1 x 2g, children 50-75 mg/kg/day
- **cefotaxime** 3 x 2 g i.v., children 150-200 mg/kg per day
- **penicillin G** 4 x 5 million i.i.v. children 200,000-400,000 i/kg per day

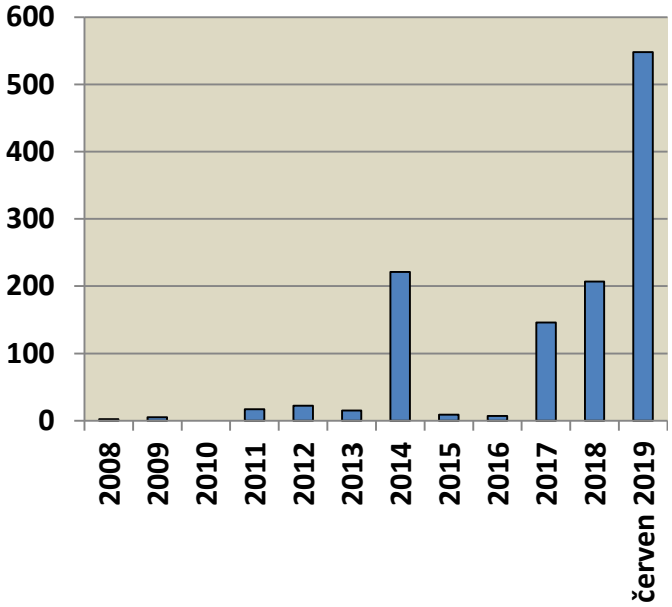
- in case of allergy to betalactam ATBs or paresis n.VII without liquor findings :
- **Doxycycline** 200-400 mg/day p.o., children over 8 years 4 -8 mg/kg/day

Isolated IgM positivity - can only be in the first weeks after the tick attachment → repeat sampling in 6-8 weeks, if no IgG is formed - **DO NOT treat!**

- false positive (not confirmed by WB)
- a consequence of polyclonal activation of the immune system

Measles

- Czech Republic 2019 583 measles cases



Neurological complications

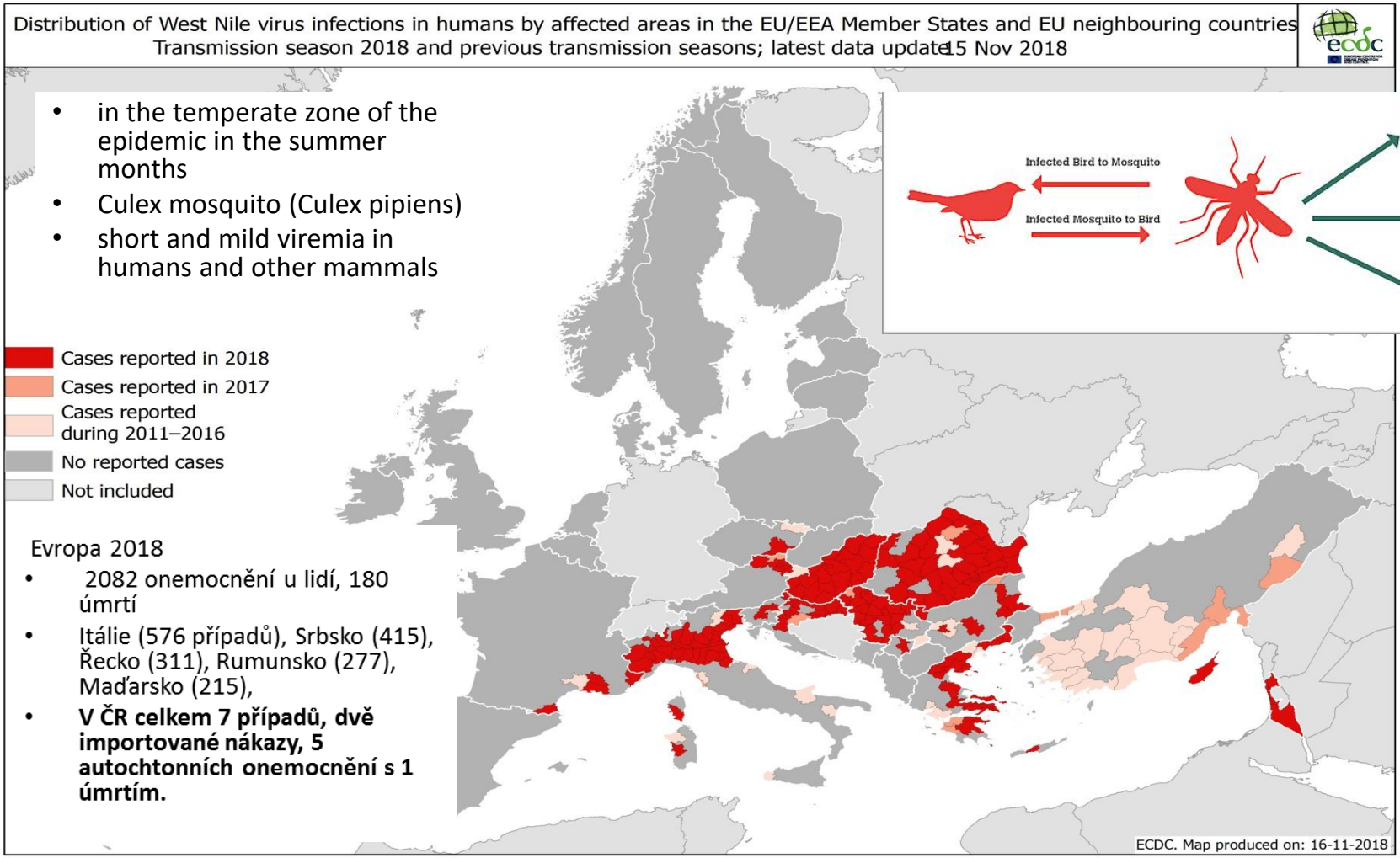
acute encephalitis - rather immunopathological reaction within two weeks after sowing

recurrence of fever, cephalea, cerebellar symptoms, cranial nerve paresis, convulsions, impaired consciousness. Lethality 3-5%.

measles inclusion encephalitis - several months after infection in immunodeficient individuals Prognosis unfavourable

Subacute sclerosing panencephalitis - a rare but lethal complication, reactivation of virus persisting in the CNS. Years after acute illness, behavioural disturbances, convulsions, hypertonia to spastic paresis with subsequent death.

West Nile Virus



- in the temperate zone of the epidemic in the summer months
- Culex mosquito (Culex pipiens)
- short and mild viremia in humans and other mammals

Evropa 2018

- 2082 onemocnění u lidí, 180 úmrtí
- Itálie (576 případů), Srbsko (415), Řecko (311), Rumunsko (277), Maďarsko (215),
- **V ČR celkem 7 případů, dvě importované nákazy, 5 autochtonních onemocnění s 1 úmrtím.**

WNF - clinical picture

- 80% of infections are inapparent
- 20-25% of patients - febrile influenza-like illness ('**West Nile fever**'), transiently including exanthema, resolves within four to seven days

Neuroinvasive form (1 in 150-250 patients) - elderly or immunosuppressed patients

- serous meningitis (25-35%)
- meningoencephalitis (65-75%)- mortality up to 10%
- manifestation also as acute flaccid paresis - myelitis with involvement of the anterior spinal cord horns

Other agents in travellers

- Toscana virus
- Japanese encephalitis
- cerebral form of malaria

The technique for needle lumbar puncture was introduced by the German physician Heinrich Quincke, he first reported his experiences at a conference in Wiesbaden, Germany, 1891.