Neuroinfections

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By the affected site

- meningitis
- encephalitis
- myelitis

- meningoencephalitis (ME)
- meningoencephalomyelitis
- meningo-myelo-radiculo-neuritis

By the affected site

- focal processes
  - brain abscess
  - epidural abscess, subdural empyema
  - septic trombophlebitis of veins and sinuses
  - epidural and subdural abscesses in the vertebral canal

By the inflammation type

- purulent
- non-purulent (serous, aseptic)

By the cause

- purulent
  - bacteria – meningococcus, pneumococcus, gram-negative bacilli, mycobacteria, …
  - fungi – *Cryptococcus neoformans*, candida, aspergillus
  - parasites – amoebas (*Naegleria fowleri)*
- non-purulent (serous, aseptic)
  - bacteria – borrelia, leptospira, treponema
  - viruses – herpetic, enteroviruses, parotitis, rabies, …
  - parasites – *Toxoplasma gondii*

Patogenesis of the microbial invasion

- along the nerve fibres
  - rabies virus, HSV, VZV, *Naegleria fowleri*
- direct invasion
  - bruise, developmental defects, purulent affection
- hematogenous spread
  - across the blood-brain barrier

Clinical symptoms of neuroinfections

- headache, fever, nausea, vomitting, vertigo
- progressive quantitative or qualitative impairment of consciousness

  (agitation, hallucination, confusion, somnolence to coma)
- meningeal symptoms
- focal neurological symptomatology
- first manifestation is epileptic seizure (type grand mal)

Conditions resembling neuroinfections

- toxic infectious encephalopathy
  - CNS dysfunction associated with infectious diseases
  - cerebral oedema – toxins, cytokines, impaired circulation
  - qualitative/quantitative impairment of concsiousness
  - normal findings in the CSF
  - associated with sepsis, typhoid
- subarachnoid haemorrhage
  - medical history, spectrophotometry, CT, CT angio
- sunstroke

Meningeal symptoms

- **upper**
  - **neck stiffness** (patient cannot place their head on the sternum – unable of head anteflexion)
  - **spine sign** (patient unable to touch their knees with their forehead)
  - **Amoss‘ sign** (patient leaning on their arm when sitting, supporting the body with 3 limbs)
  - **Brudzinski‘s sign** (patient bends their knees on passive head flexion when lying down)

Meningeal symptoms

- **lower**
  - **Lasègue‘s** (limited ventral flexion with extended limbs)
  - **Kernig‘s** (trying to extend the lower leg with the patient lying on the back, with flexed hips)

Lumbar puncture

- appropriate premedication (modified coagulation, patient sedation)
- atraumatic / traumatic needle
- taking around 2-3ml (as needed for the tests to be performed) CSF into multiple test tubes
- CSF tests:
  - cytology
  - biochemistry, blood-CSF barrier
  - cultures, microscopy
  - serology, intrathecal synthesis
  - PCR, universal detection of microbial pathogens
  - flow cytometry, cytology
  - fungal antigens
  - limbic encephalitis
  - spectrophotometry

Contraindications (LP)

- skin or subcutaneous infection
- increased intracranial pressure
- severely impaired haemocoagulation
- severe lumbar spine deformities

- risk of occipital lobe herniation

CSF findings

	Appearance	Cells	Protein	Glucose	Lactate	Chloride
Normal findings	transparent, colourless	max 5/mm^3, lymphocytes	0.2-0.4 g/l	2.2-4.2 mmol/l	1.1-2.2 mmol/l	116-130 mmol/l
Aseptic ME	transparent to translucent	tens to thousands, lymphocytes	slightly elevated	normal	normal	normal
Purulent ME	cloudy to purulent	thousands, tens of thousands, PMN	significantly elevated	decreased	elevated	normal
TB-induced ME	transparent to cloudy	tens to hundreds, lymphocytes > PMN	significantly elevated	decreased or normal	elevated or normal	decreased or normal
Brain abscess, spondylodiscitis	transparent to translucent	tens to hundreds, PMN and lymphocytes	elevated	normal or decreased	normal or elevated	normal
Subarachnoid haemorrhage	pink to crimson	RBCs	elevated	normal	normal	normal
Guillaune-Barré syndrome	transparent	normal findings	significantly elevated	normal	normal	normal

Purulent meningitis

Definition

- bacterial meningitis = purulent infection of the meninges
- CSF findings
  - macroscopically cloudy to purulent
  - microscopically usually thousands of polymorphs, elevated protein, reduced glucose, elevated lactate
- Still one of the most severe infectious diseases with a high mortality rate!

Etiology

- different for different age groups
  - **0-2mo** : *Streptococcus agalactiae, E.coli, Listeria monocytogenes*
  - **3mo-5yrs**: *Hemophillus influenzae*, *Neisseria meningitidis*, *Streptococcus pneumoniae*
  - **5-60yrs (immunocompetent):** *S. pneumoniae*, *N. meningitidis*, stretokoky, *S. aureus*
  - **Over 60yrs**: *S. pneumoniae*, *L. monocytogenes*, *S. aureus*
  - **Immunocompromised**: *Cryptococcus neoformans*, gram negative bacilli (pseudomonas, escherichia, klebsiella…)

Classification of bacterial meningitis

1. by origin
   - *primary* – haematogenous → primary manifestation ME
   - *secondary* → complications of another purulent disease
     - per continuatem (infection in close proximity of the CNS – otitis media, sinusitis, osteomyelitis)
     - hematogenous from a site outside of the CNS
     - inborn or acquired extra-intradural communication (trauma, fistule, shunt, CSF leak)

2. by the time course

- peracute (impaired consciousness manifest within several hours)
- acute
- subacute
- chronic (rare, TB etiology)
- recurrent – persisting cause (CSF leak, infected shunt, chronic vertebral osteomyelitis…)

Diagnostics

- clinical progression and medical history (premorbid otitis media, toothache, inserted ventriculoperitoneal shunt etc.)
- objective findings
- laboratory tests
  - ↑ leu, ↑ CRP, and/or procalcitonin (sepsis marker)
  - taking blood cultures !!!! (always before starting an ATB therapy)
  - CSF tests:
    - cytology and biochemistry
    - microbiology – microscopy+culture !!!!, latex, PCR diagnostics
- radiological tests – brain CT or MRI, if necessary to identify the source of infection (sinusitis, mastoiditis) or complications (oedema, abscess)

Therapy

1. *causal*
   - i.v. bactericidal ATB at high doses
     - **third-generation cephalosporins + ampicillin** (in patients 50 years of age and older or immunocompromised patients – risk of listeria etiology)
     - other ATBs penetrating the CNS – benzylpenicillin, fourth-generation cephalosporins, chloramphenicol, meropenem, trimethoprim/sulfamethoxazole (more as an alternative ATB or for specific indications)
2. *symptomatic*
   - anti-oedema therapy
   - analgosedation
   - antispasmodics
   - oxygen therapy, artificial ventilation, rehydration, nutrition, …..

Complications and consequences

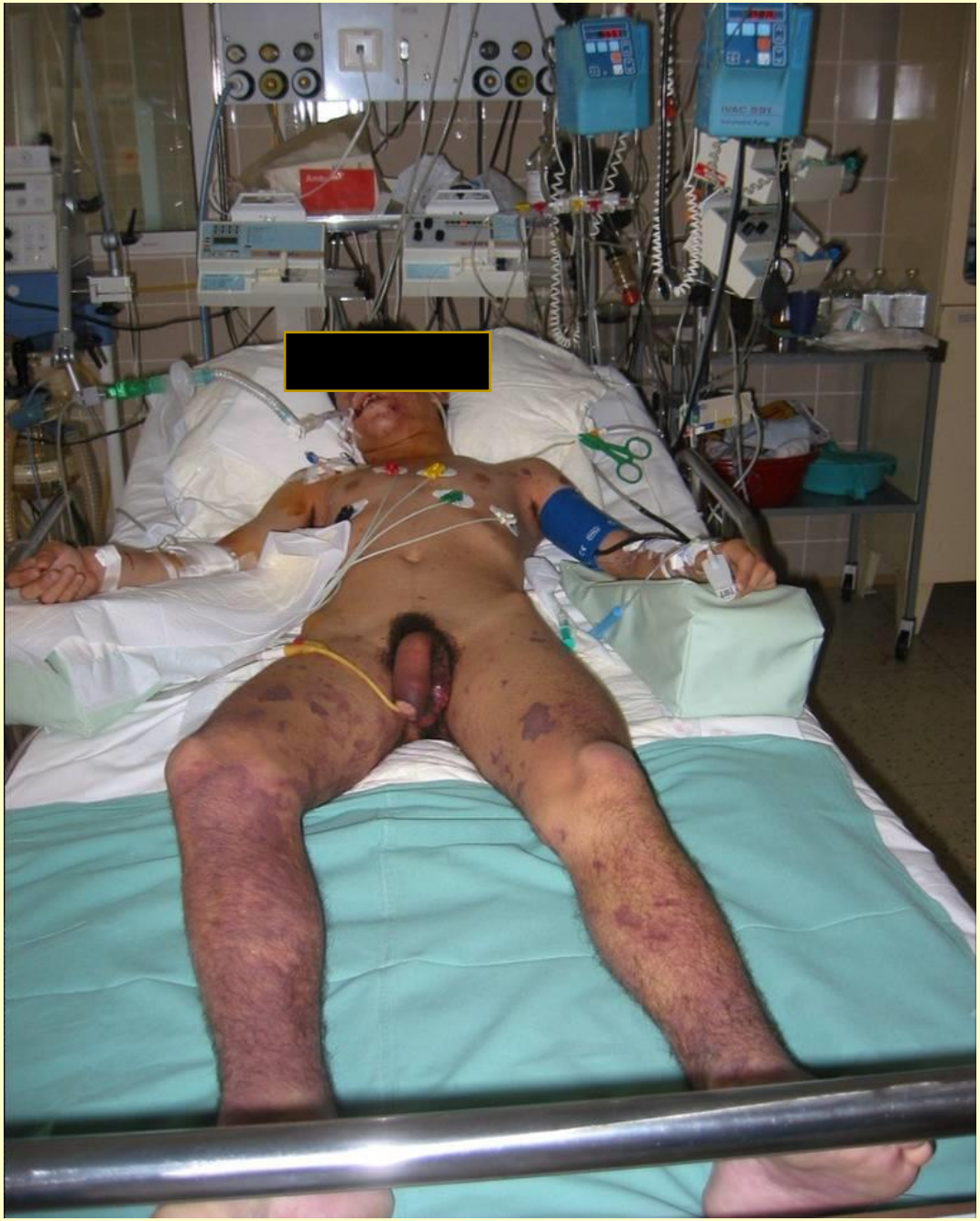
- **impaired hearing**
- developing an **abscess**, subdural effusion (sterile fluid accummulation, resulting from intermening. adhesions, more frequently in children)
- **vascular complications** (haemorrhage, sinus thromboses, cerebral artery occlusions)
- **post-inflammatory epilepsy**
- **impaired ion and water homeostasis** (syndrome of inappropriate antidiuretic hormone secretion (SIADH), cerebral salt-wasting syndrome (CSWS))
- **PNS impairment** (cranial nerve paresis, limb paresis, diffuse peripheral polyneuropathy)
- **hydrocephalus**
  - obstructive x CSF hypersecretion
  - clinically fast progression of consciousness impairment

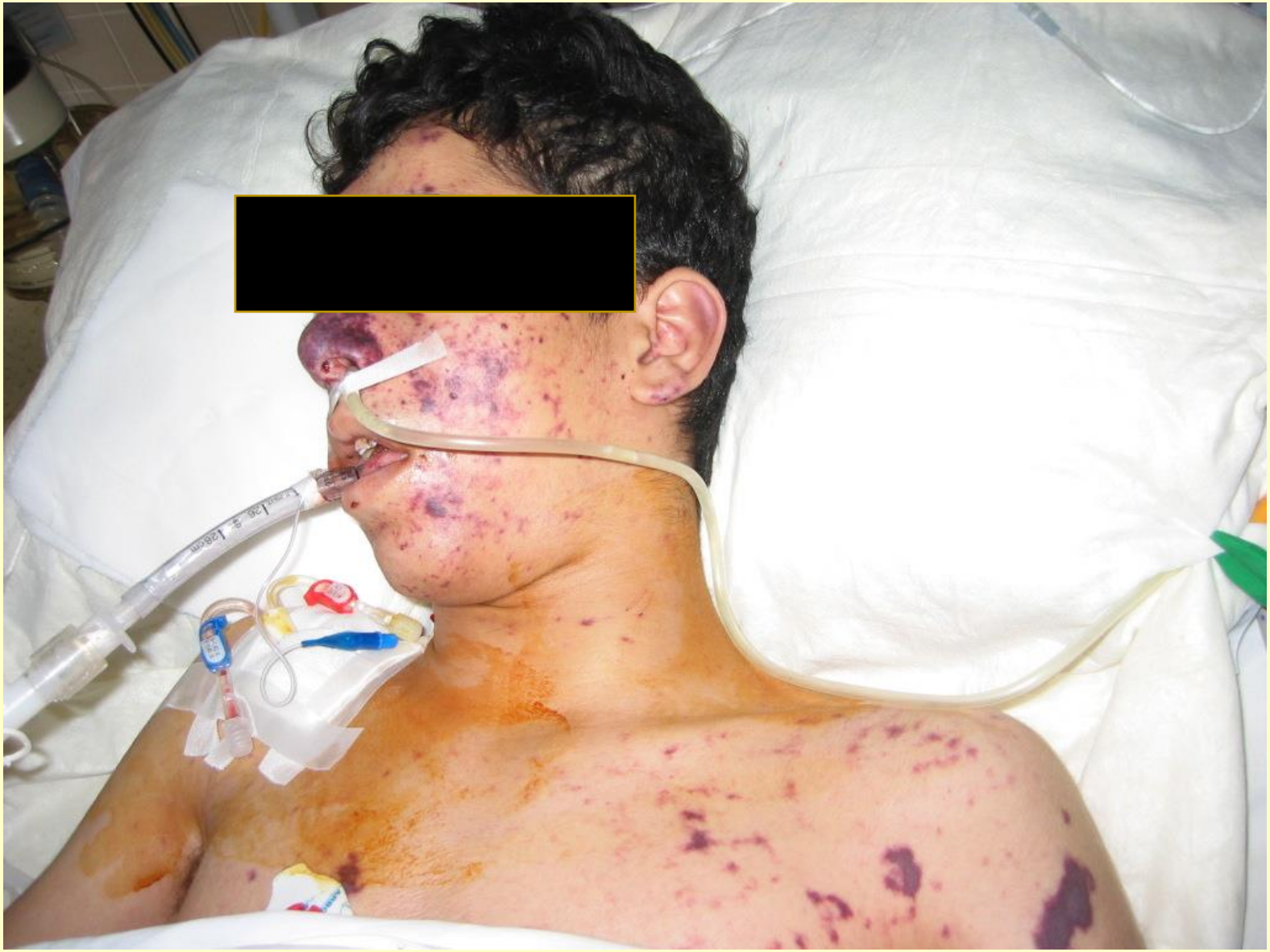
Meningococcal meningitis

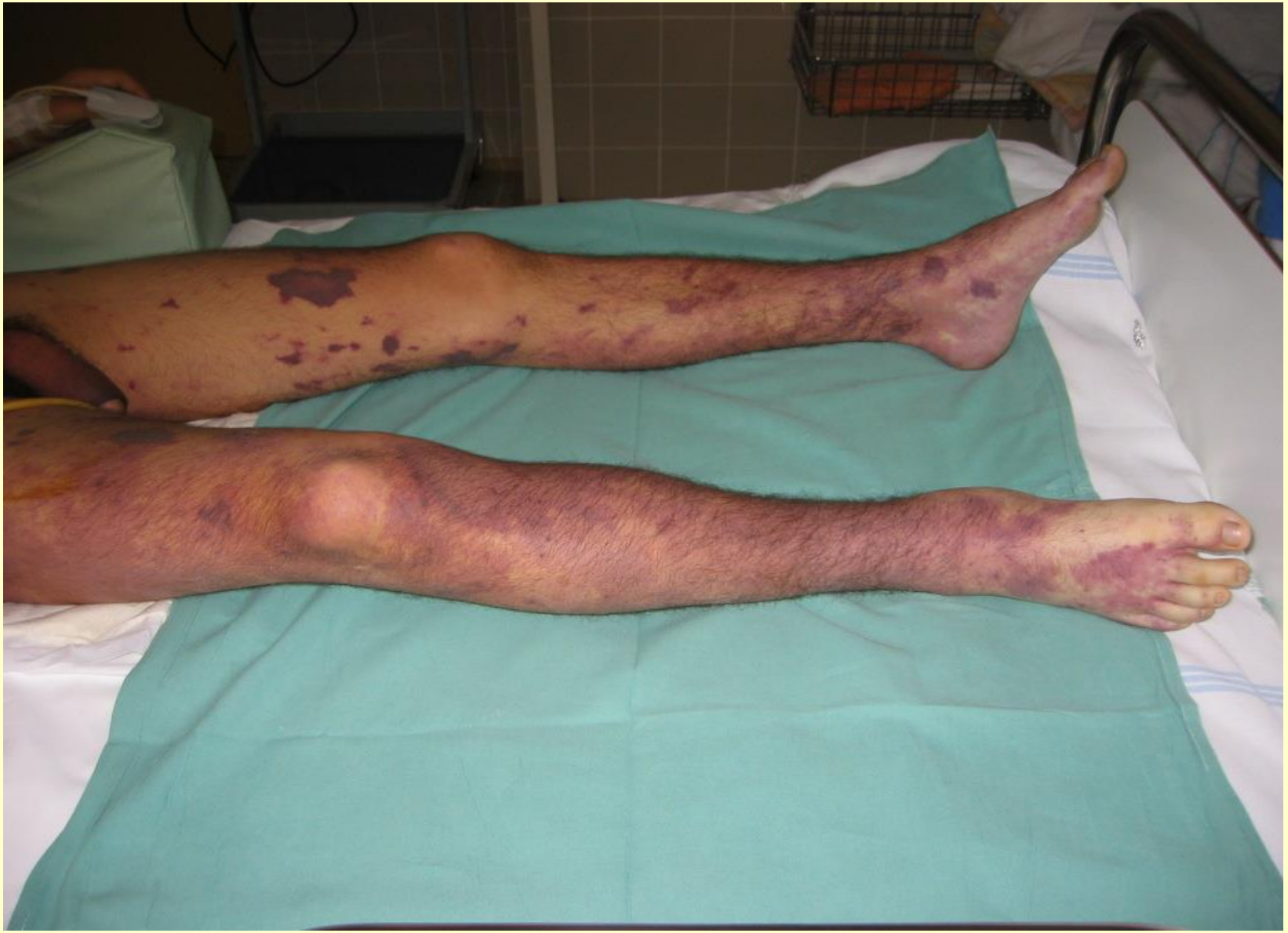
- IMD (invasive meningococcal disease)
  - meningitis – symptoms of influenza and meningitis, spasticity, focal symptoms, impaired consciousness
  - sepsis – hypotension, haemorrhage, MODS
  - mixed – most common
- pre-school children, adolescents
- dgs – clinical suspicion
- immediate therapeutic triad:
  - 1. circulation stabilisation
  - 2. oxygenation
  - 3. ATB administration (taking blood culture, cefotaxime 3g)

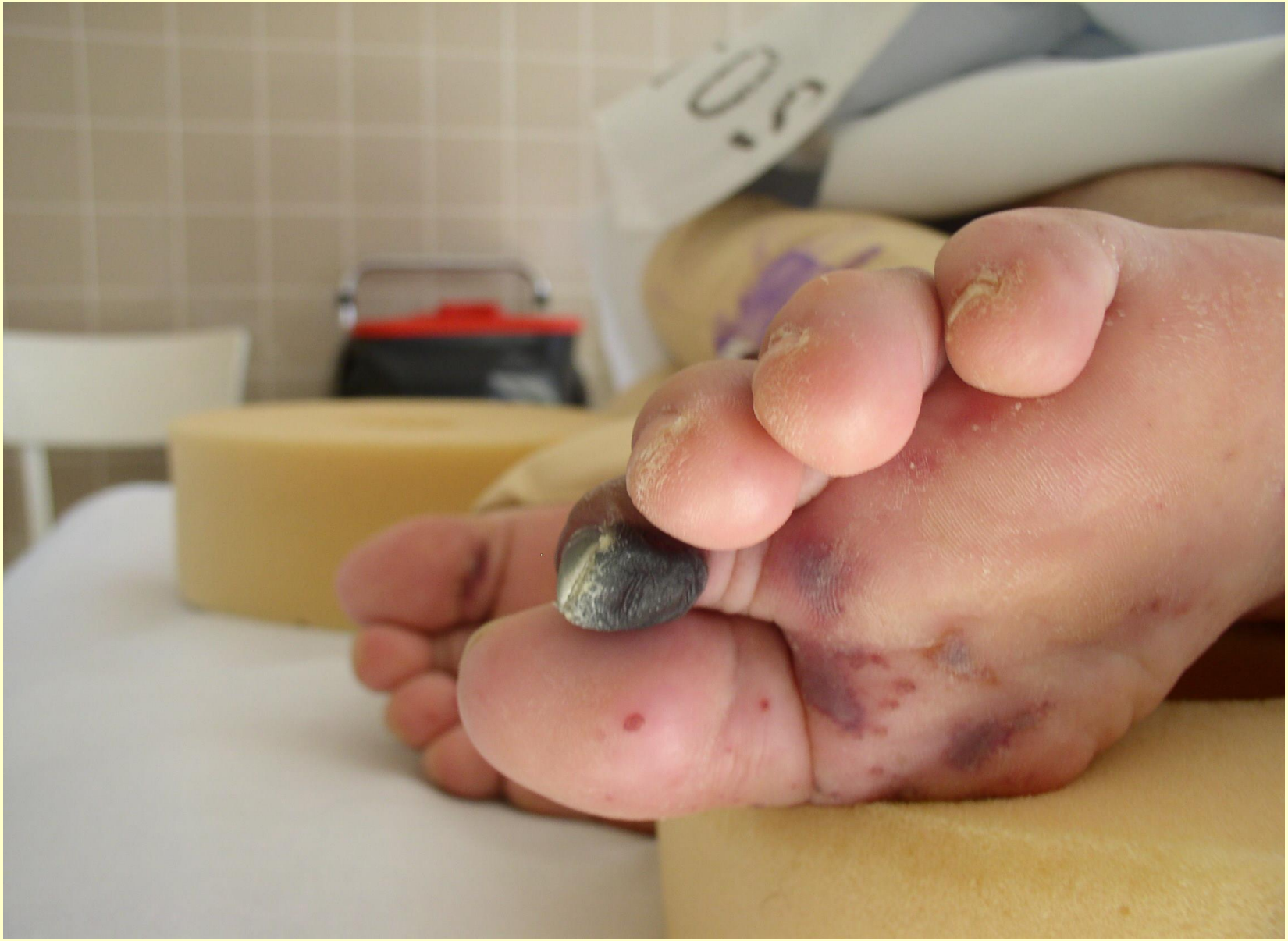
Meningococcal meningitis

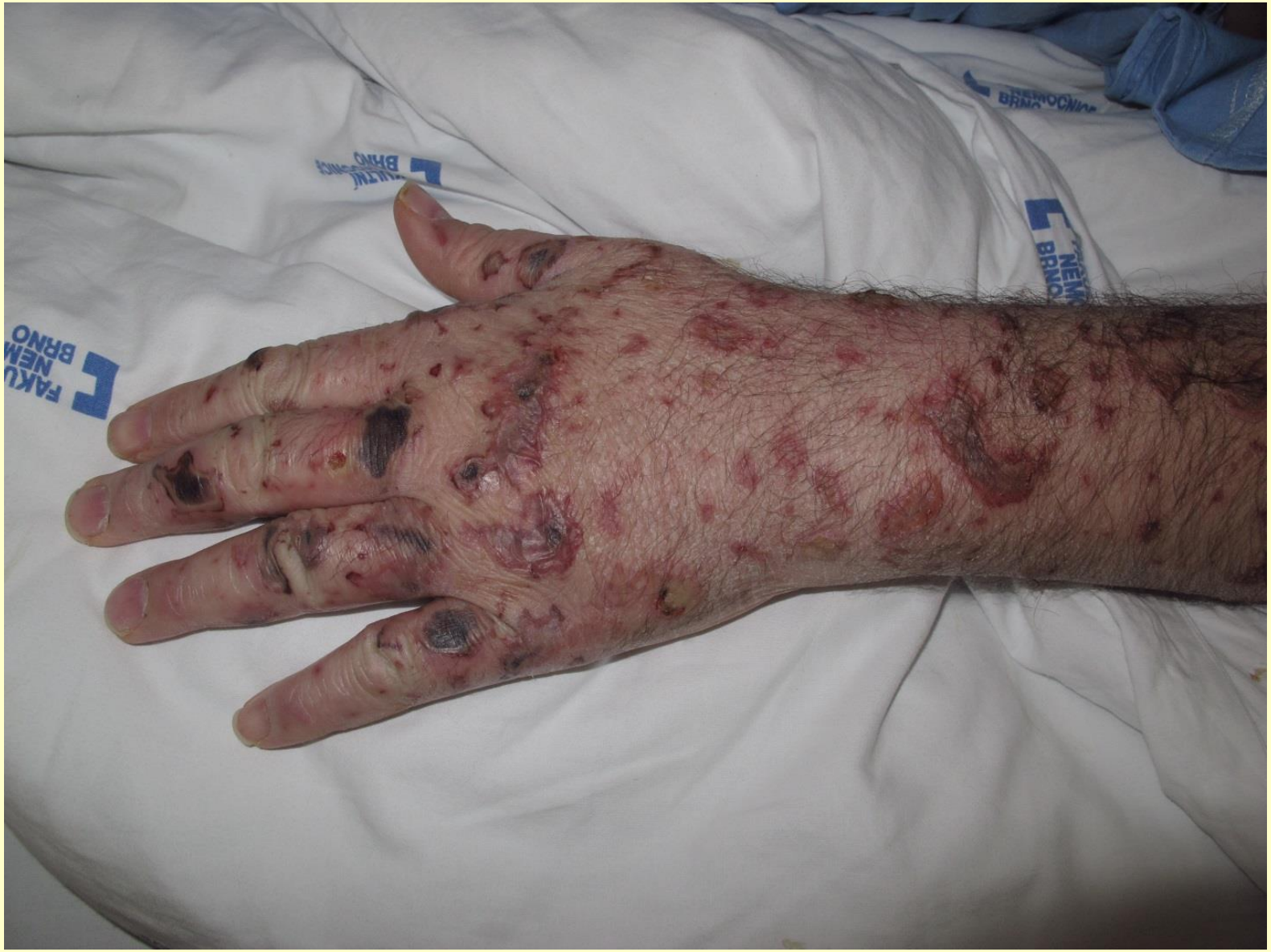
- CSF – microscopy, culture, PCR
- blood culture, from the haemorrhage sites
- laryngeal swab – culture
- therapy – cefotaxime, benzylpenicillin, chloramphenicol 7-10 days
- complex MODS treatment
- complications – amputation, cranial nerve impairment, deafness, hydrocephalus
- contacts – ATB prophylaxis – phenoxymethylpenicillin
- prevention – tetravalent vaccine (ACYW135) + against group B (since 2014)

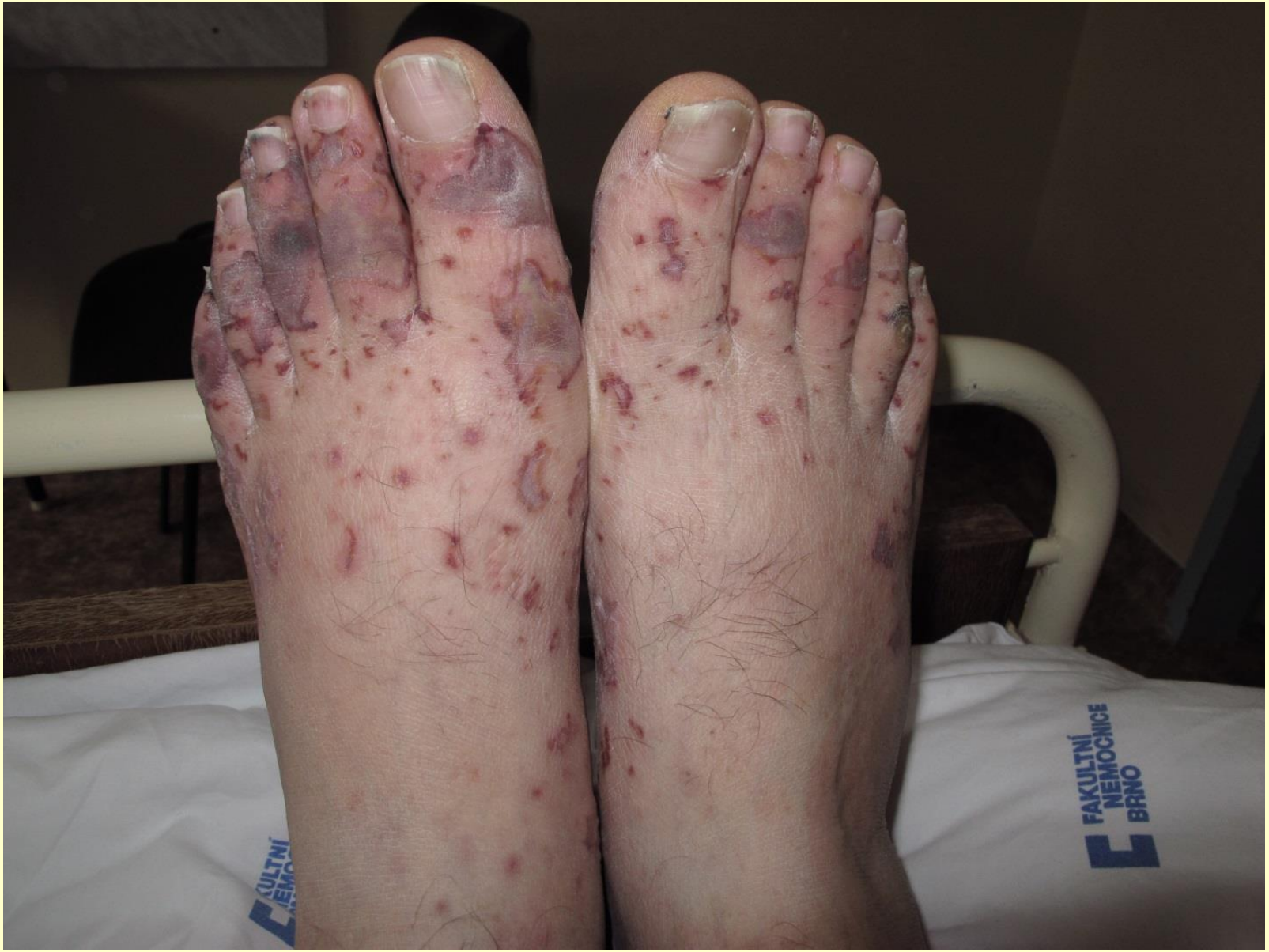








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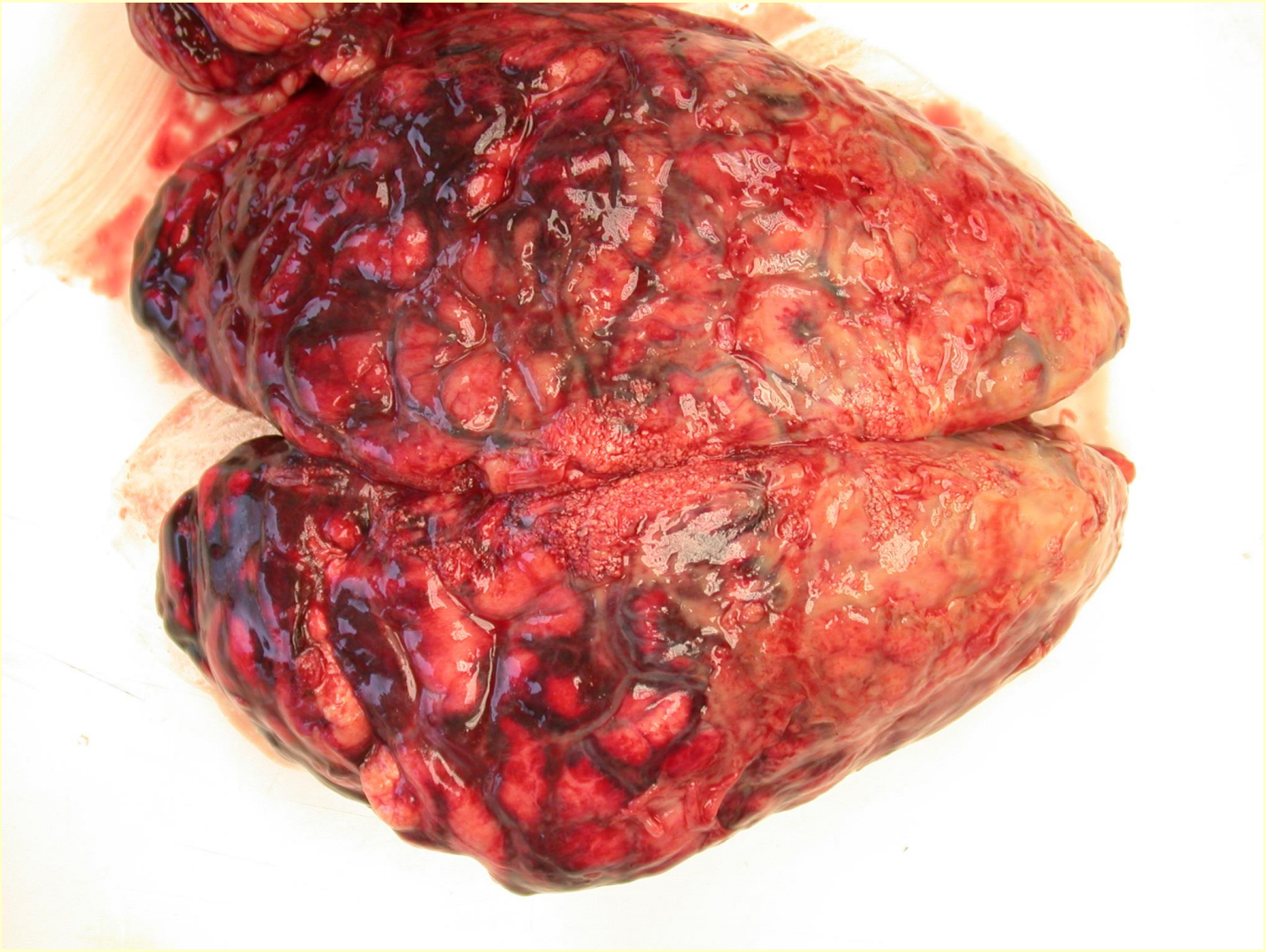
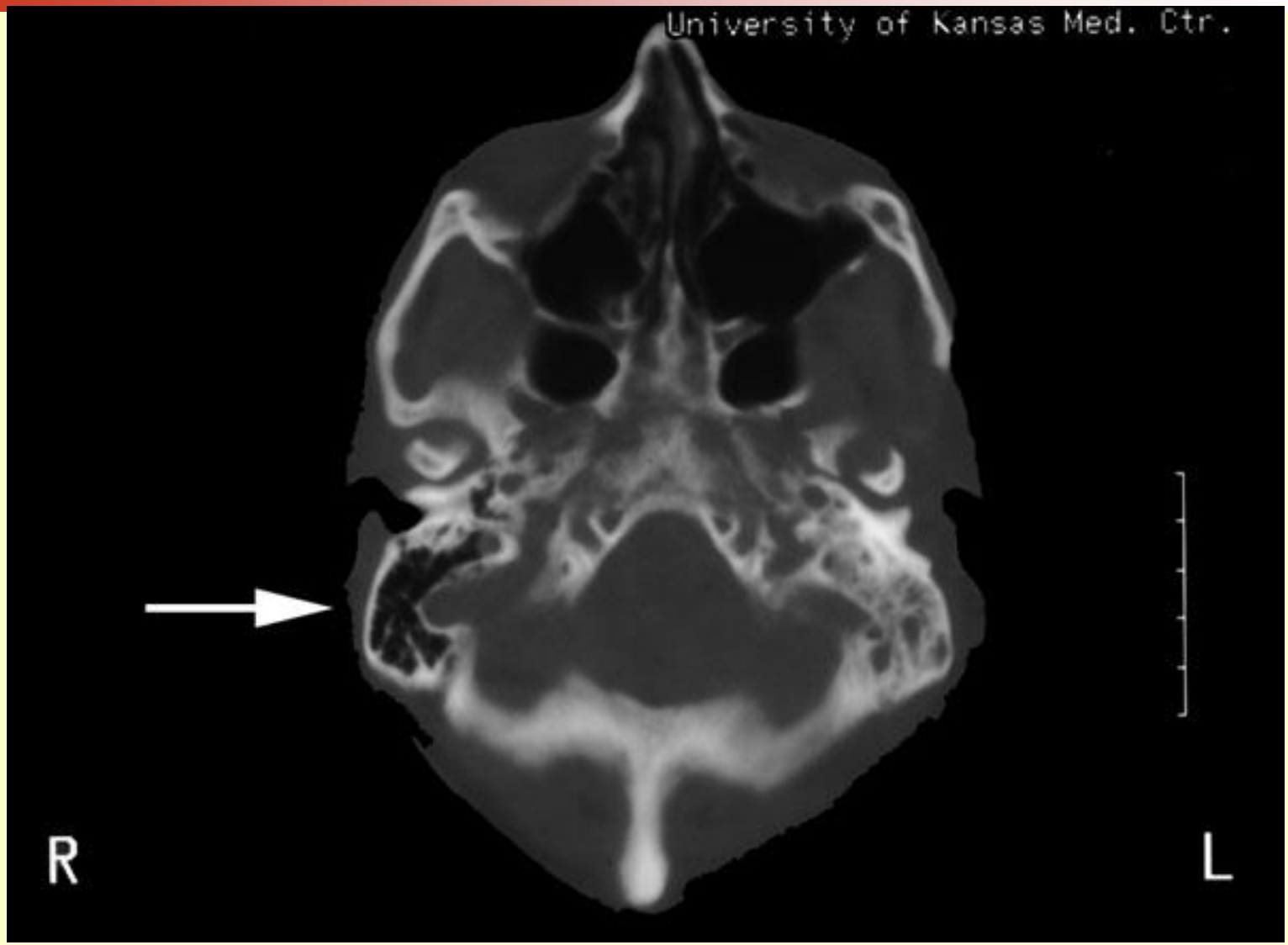
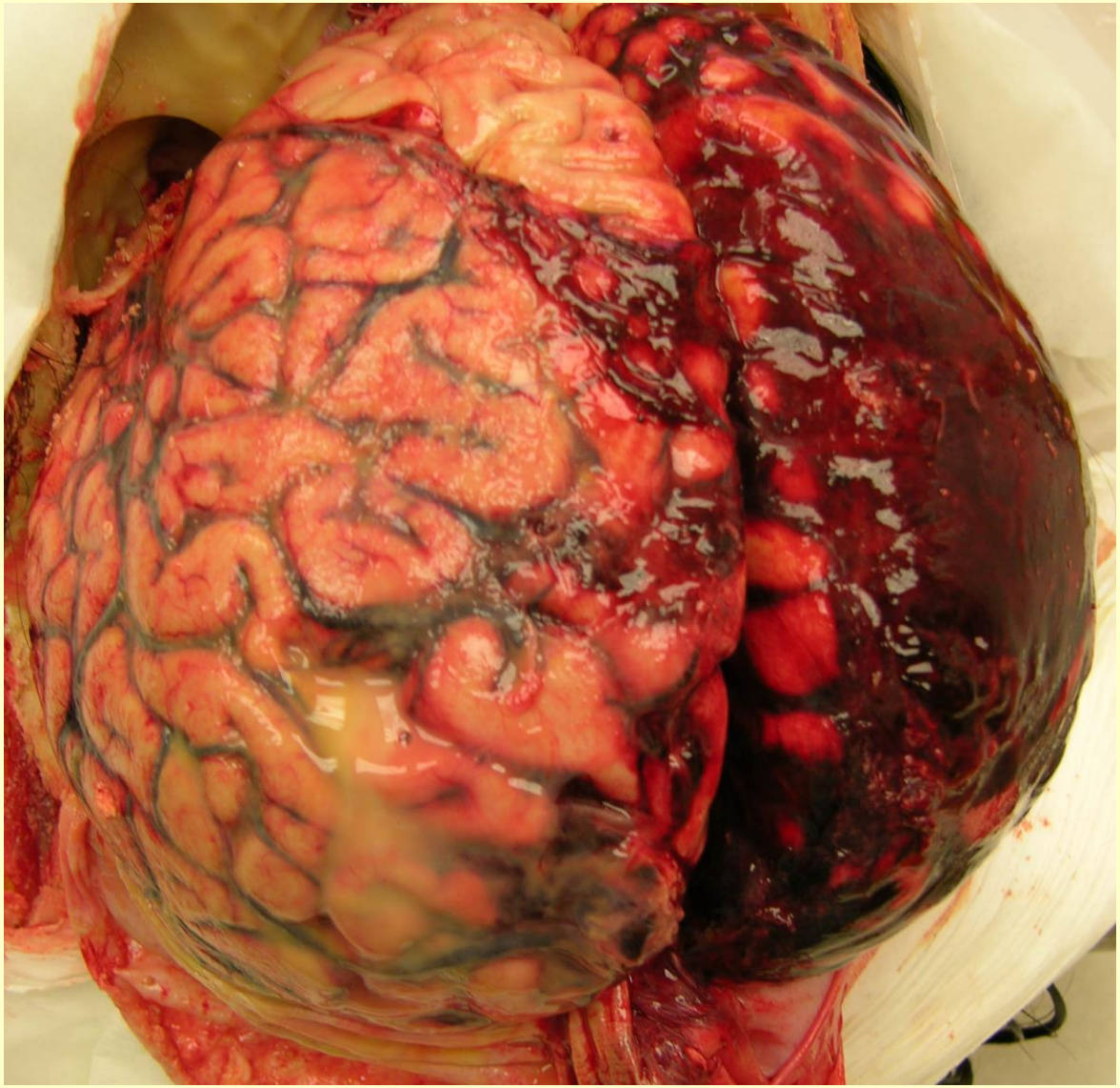


Pneumococcal meningitis

- the most common cause of purulent ME
- secondary – medium otitis, mastoiditis, sinusitis, pneumonia
- primary – in immunodeficiencies, after splenectomy
- dgs – respiratory disease history
- CSF – microscopy, culture, antigens, PCR
- blood cultur, urine antigens, secretions culture
- CT scan of the paranasal sinuses, temporal bone
- therapy – cefotaxime, benzylpenicillin
- treatment of the primary site! – FESS, mastoidectomy
- preventions – vaccination in risk groups, after pneumococcal ME



Pneumococcal meningitis with mastoiditis



Haemophilus meningitis

- in children of 5 months – 5 years of age
- minimum incidence in the Czech Republic after implementing the state-wide vaccination in 2001
- primary and secondary
- follows respiratory diseases
- haemorrhage into skin

Listeria meningitis

- newborns, patients of 60 years of age and older, immunocompromised
- adults (slow development of complications, initial gastroenteritis, less pronounced meningeal symptoms)
- newborns (up to 20% of ME)
  - perinatal (short before or during parturition) infection→ sepsis with ME
  - prenatal infection → general disease of the foetus affecting majority of organs – *granulomatosa infantiseptica*
  - progress more gradual than in other ME types
  - CSF biochemistry like in purulent meningitis, cytology shows a high proportion of polymorphs
- therapy – ampicillin 12-16g, meropenem

Staphylococcal meningitis

- usually in these cases:
  - extra-intradural communication (trauma, neurosurgery)
  - presence of a shunt
  - haematogenous in sepsis, infective endocarditis
- treatment must involve searching for the source of infection
- possibility of induced inflammation associated with a staphylococcal abscess or spondylodiscitis – not a classical ME, discrepancy between the CSF findings and the relatively good patient condition, practically also hard-to-distinguish forms

Shunt-associated meningitis

- around 20% shunts become infected and cause ME
- etiol. – staphylococci (*S. epidermidis, S. aureus*), gram negative bacteria, enterococci
- clinical – progress usually gradual
  - sub febrile temperature, headache, apathy, slepiness, vomitting
- dgs. – brain CT – distinguish shunt malfunction
- CSF – microscopy, culture, PCR
- therapy – meropenem, chloramphenicol, vancomycin + cefepime
- it is necessary to remove the infected shunt
- temporary external ventricular drain
- shunt re-insertion surgery after the treatment of the CSF

Meningitis caused by gram negative bacteria

- ***E.coli, Kl.pnemonie, Ps.aeruginosa*** – infants, old and immunocompromised patients
- prognosis always very bad
- therapy: according to sensitivity –third- and fourth-generation cephalosporins, Meronem

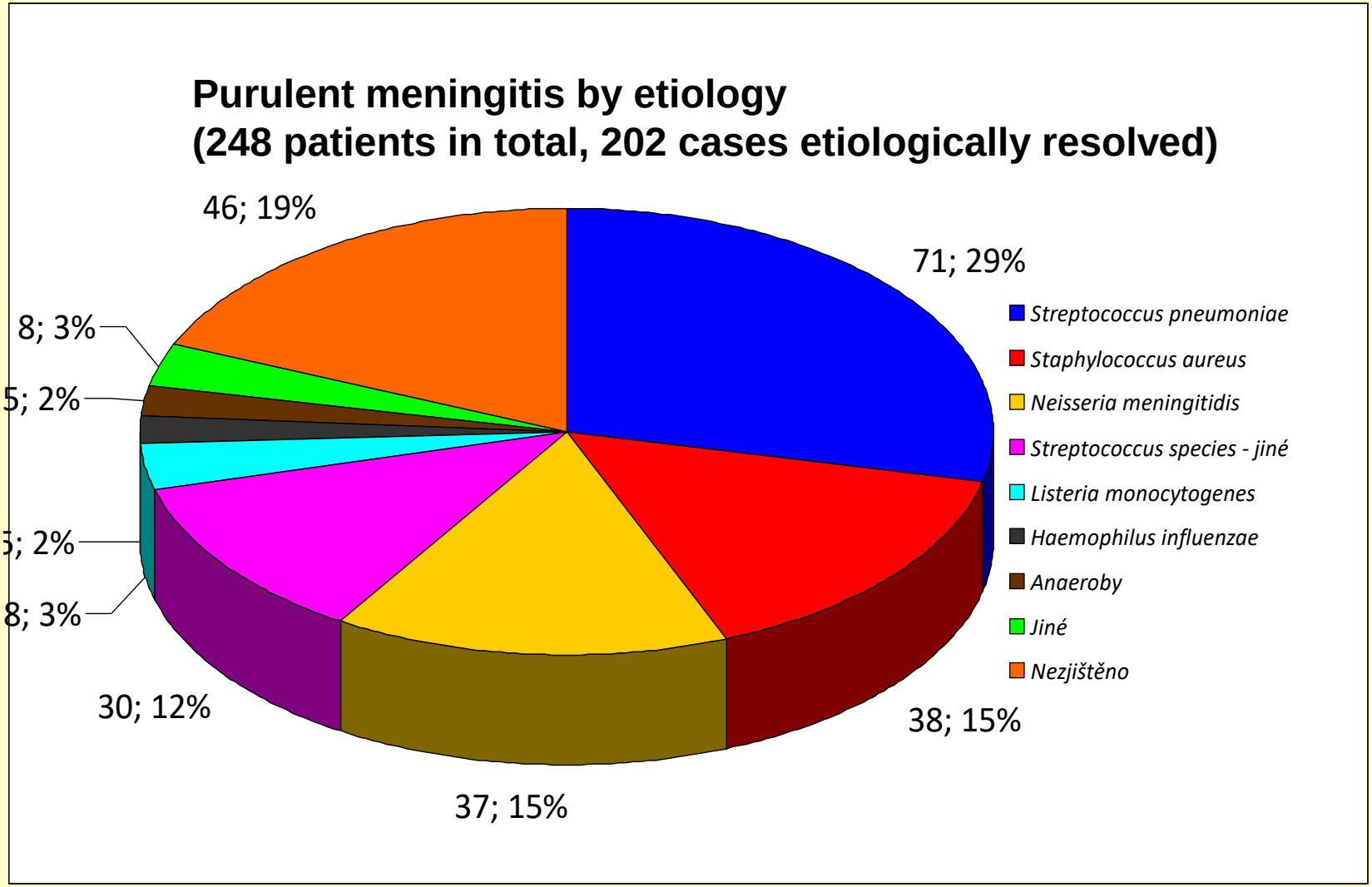
Basilar meningitis

- etiology *Mycobacterium tuberculosis*
- incidence 0,5% TB patients
- frequently occurs alongside subclinical pulmonary TB→ME signs often the only symptom
- gradual progression of clinical symptoms
- differences in the CSF
  - hundreds of cell, predominantly monocytes
  - ↑↑↑ **protein**, ↓ glucose, ↑ lactate, ↓ chloride

- diagnostics
  - PCR
  - microscopy and culture (low sensitivity to low concentration of mycobacteria in the CSF)
  - Evidence of miliary pulmonary TB (lung X ray, CT)
  - indirect diagnostics
    - Mantoux II
    - Quantiferon

Purulent ME of non-bacterial etiology

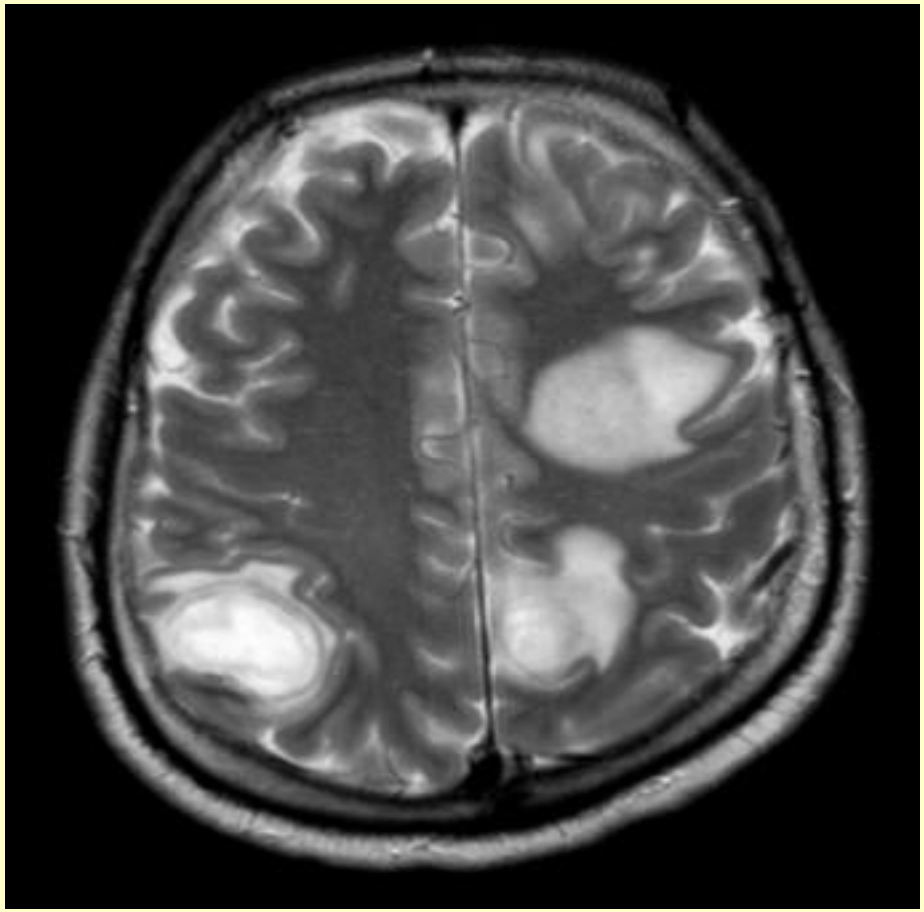
- mainly in patients with severe immunodeficiencies – tumours, after transplants, HIV patients
- subacute
- opportunistic pathogens
  - fungal
    - *Cryptococcus neoformans, aspergilus*, yeast
  - protozoa
    - *Naigleria fowleri*



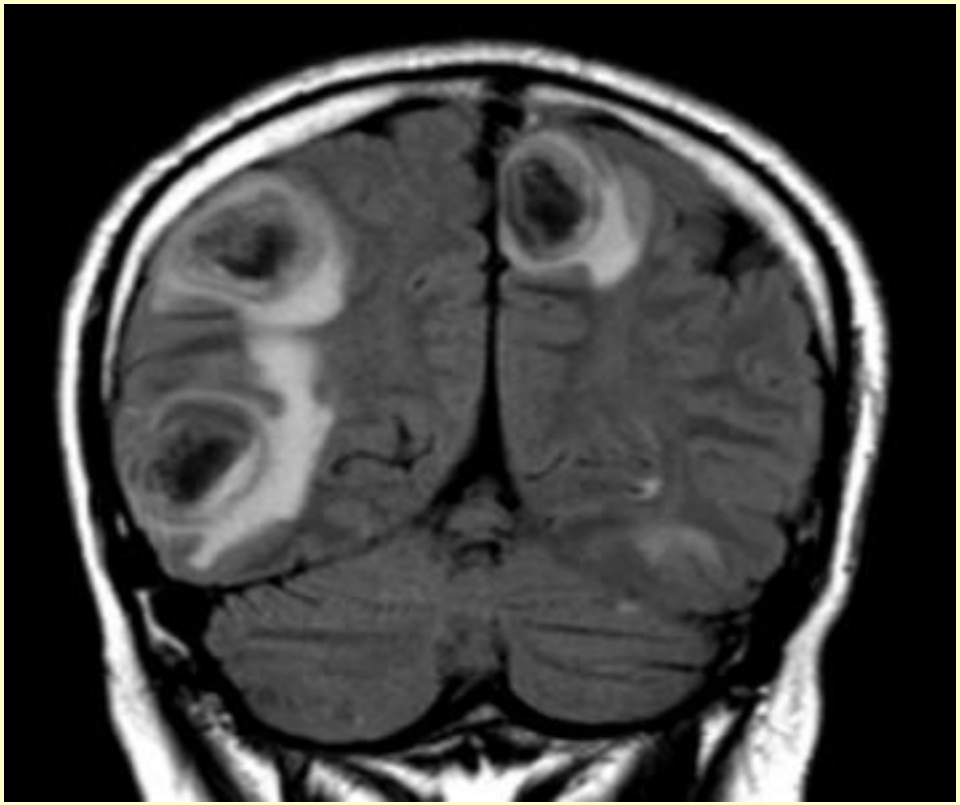
Purulent ME (primary+secondary) at KICH during years 2004-2011

Cerebral abscess

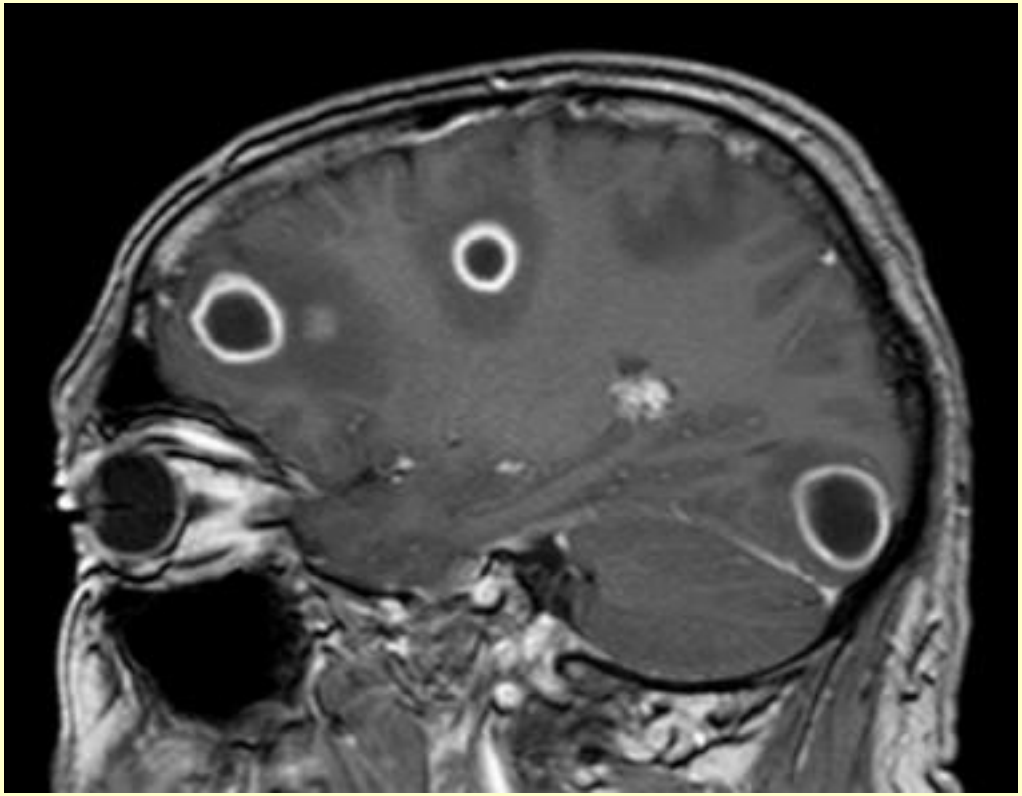
- origin per continuitatem, haematogenous, after trauma,
  20% cryptogenic
- etiol. - streptococci, anaerobes, enterobacteria, staphylococci, fungi
- clinical – subfebrile temperature, focal symptomatology, epileptic seizures, sometimes headache only
- dgs. brain CT / MRI
- CSF – culture and PCR – little benefit
- stereotactic aspiration of the affected site – culture, PCR universal detection of microbial agents
- therapy – cefotaxime + metronidazol + vancomycin, cefepime, meropenem, chloramphenicol
- peroral following treatment – rifampicin + trimethoprim/sulfamethoxazole
- surgical evacuation of the affected site

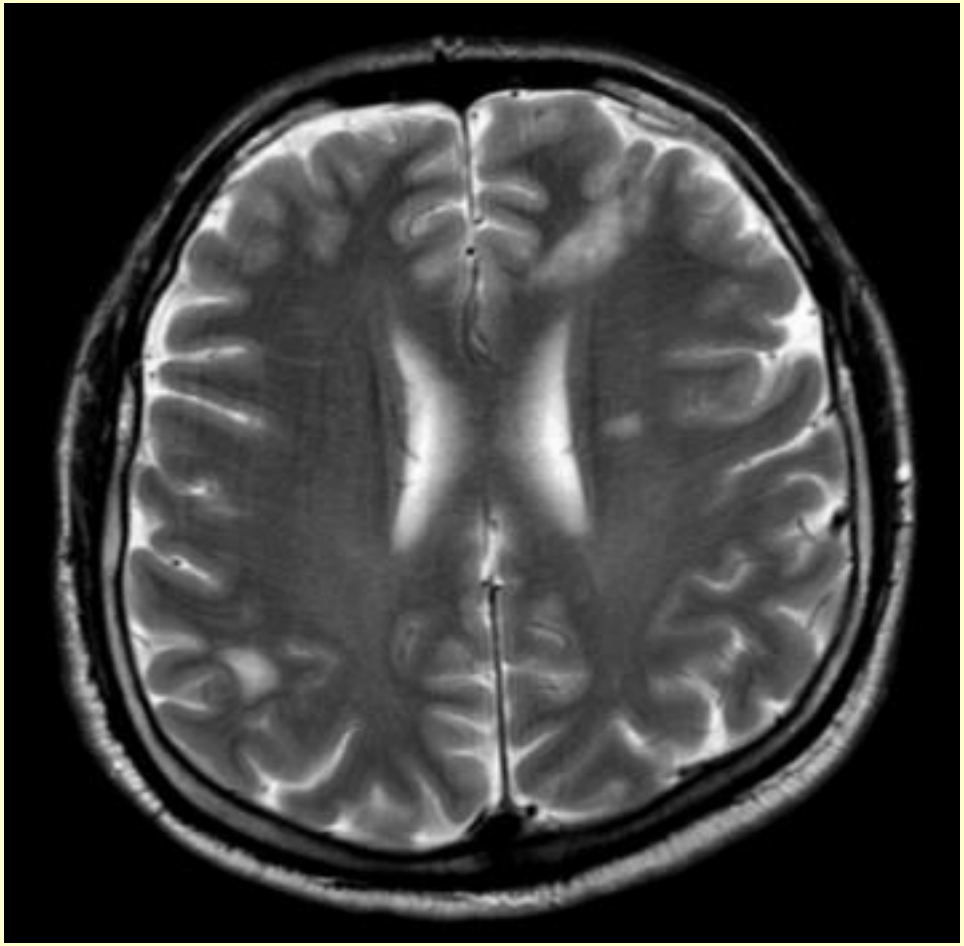


T2 weighted image, transverse – multiple hyperintense regions surrounded by oedema

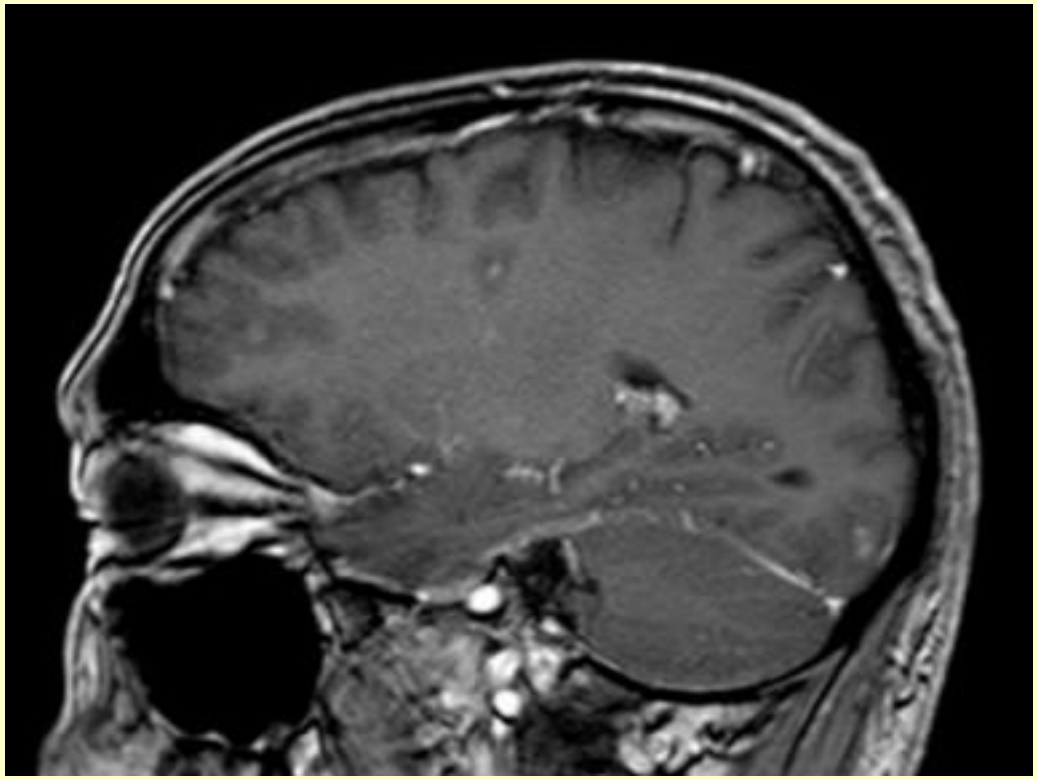


Coronal FLAIR – relatively thick walls of the affected site, content partly fluid (low-intensity signal), surrounding regions with high-intensity signal due to oedema





T2 transverse – several residual hyperintensities, significant regression of the findings



Other focal purulent infections of the CNS

epidural abscess

- spread of the purulent infection from surrounding tissues (pulpitis, sinusitis, mastoiditis, spondylodiscitis)

subdural empyema

- infection of a subdural haematoma in a transient bacteremia

subdural, epidural vertebral canal abscess

- free spread of the infection, across several vertebrae
- most frequently *S. aureus* haematogenous in sepsis

Aseptic meningitis

(the most common origin in the Czech Republic)

Tick-borne ME

- 2 stages

1. stage – fever, headache, weakness, influenza signs – lasts 3-7 days, then symptom regression

Interval usually 2-7 days

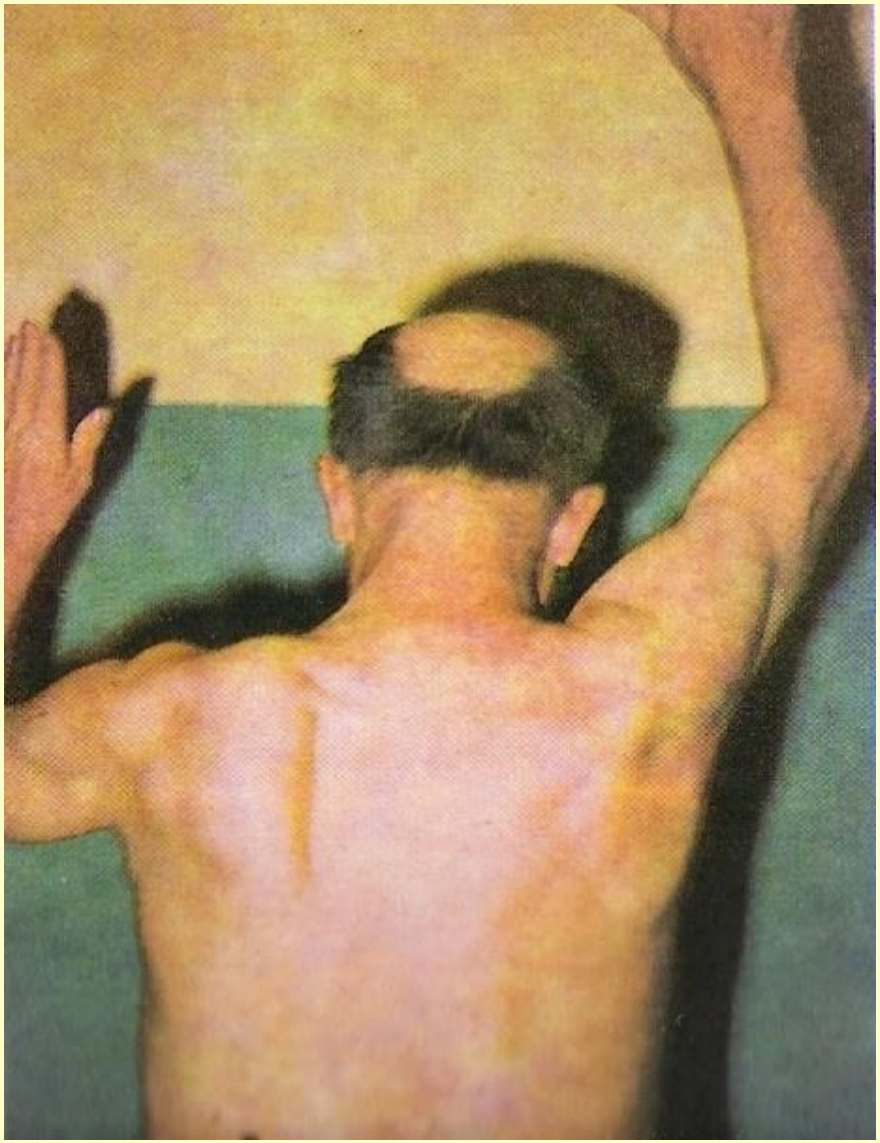
2. stage – neuroinfection

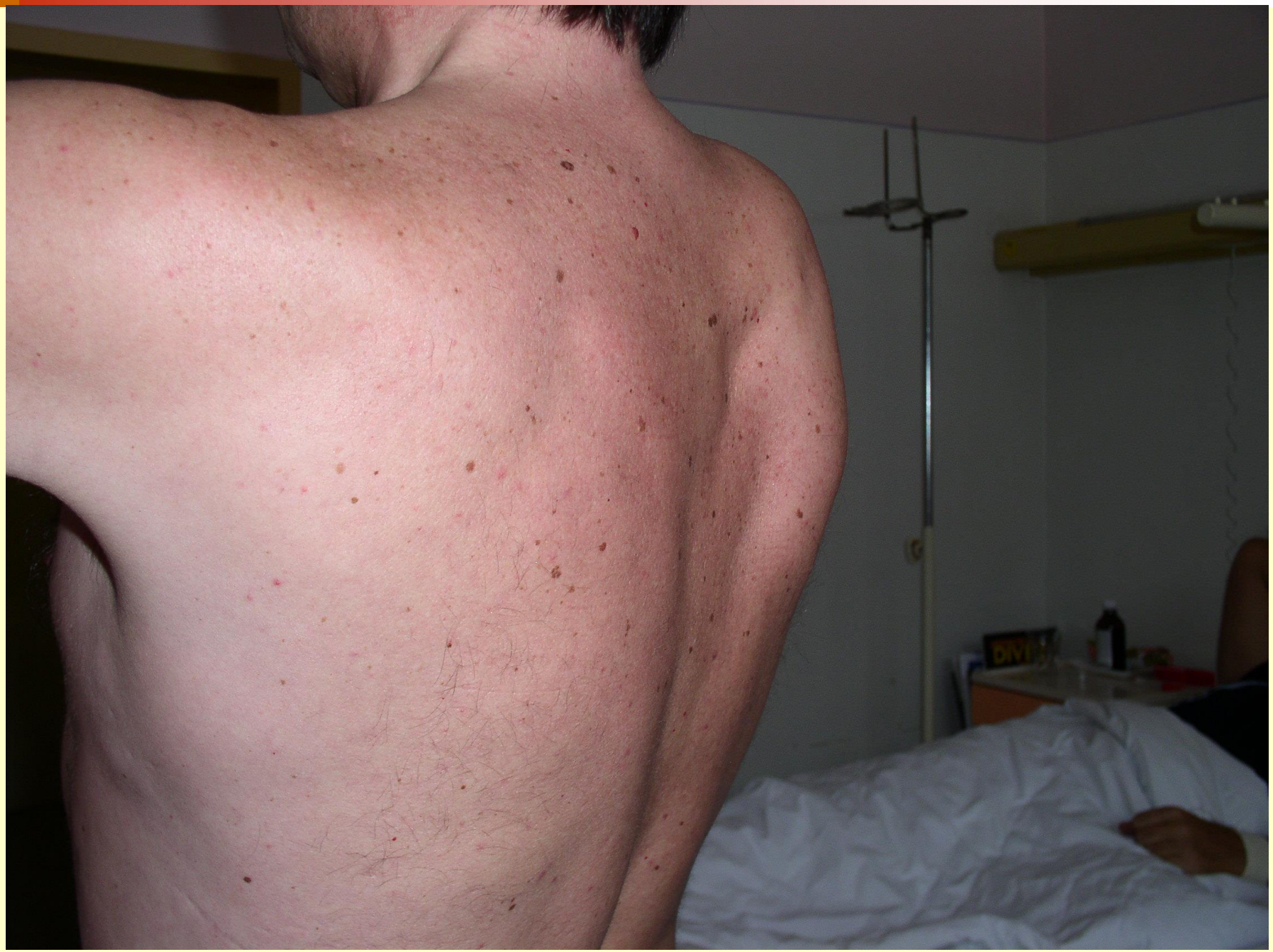
- fever, strong headache peaking behind the eyes, vertigo, nausea, vomitting, photophobia, noise intolerance, impaired concentration, blurry vision, sleep disorders (somnolenceXinsomnia, sleep inversion), qualitative and quantitative impairment of consciousness, delirious states, epilept. seizures, pareses

- form
  - inapparent, abortive
  - meningitic – typical development
  - encephalitic – eyelid twitching and upper limb tremor
  - encephalomyelitic – weak paresis of the brachial plexus
  - brainstem meningitis – bulbar symptomps, impaired respiration and cardiac rhythm
- severe in patients of 60 years of age and over

Tick-borne ME

- CBC – neutrophilia, CRP slightly elevated
- CSF – serous appearance, hundreds to thousands of cells (polymorphs might prevail initially)
- serology – serum, CSF, specific IgM
- treatment – symptomatic
- prevention – vaccination





Herpetic ME – HSV 1

- influenza symptoms, speech impairment, focal symptoms, impaired consciousness, spasticity
- CSF – tens of polymorphs only, elevated protein
- PCR HSV from the CSF
- CT – hypodense regions in the temporal lobe
- aciclovir immediately in case of clinical suspicion

Herpetic ME – HSV 2

- the most common cause of relapsing serous ME, patients tend to have relapsing eruptions of genital or perineal herpes
- milder symptoms, no necroses in the brain
- diagnostics: serous CSF inflammation, PCR evidence of HVS 2 DNA
- treatment: aciclovir, dexamethasone, mannitol 20%

Herpetic ME - VZV

1. varicella: cerebellitis occurs in 0,1% patients on 5th to 10th day of exanthema
2. herpes zoster: VZV persists in neural ganglia after varicella – reactivation – centrifugal movement into the skin and centripetal movement into the CNS – serous CSF inflammation with signs of affected CNS + peripheral neuralgia (administration of aciclovir within 72h reduces the incidence of postherpetic neuralgias)

Other viral infections of the CNS

- **enteroviruses** (ECHO, coxsackievirus) – cause summer „influenzas“, may cause CNS inflammations, no causal treatment, only symptomatic
- **parotitis** – 50% patients also develop meningitis or encephalitis – benign
- **measles and rubella viruses**
  - nn early stages of diseases like ADEM (acute disseminated encephalomyelitis) – severe with mortality rate of 3-5%
  - in immunocompromised patients within several weeks or months measles inclusion body encephalitis or subacute sclerosing panencephalitis

Leptospirosis

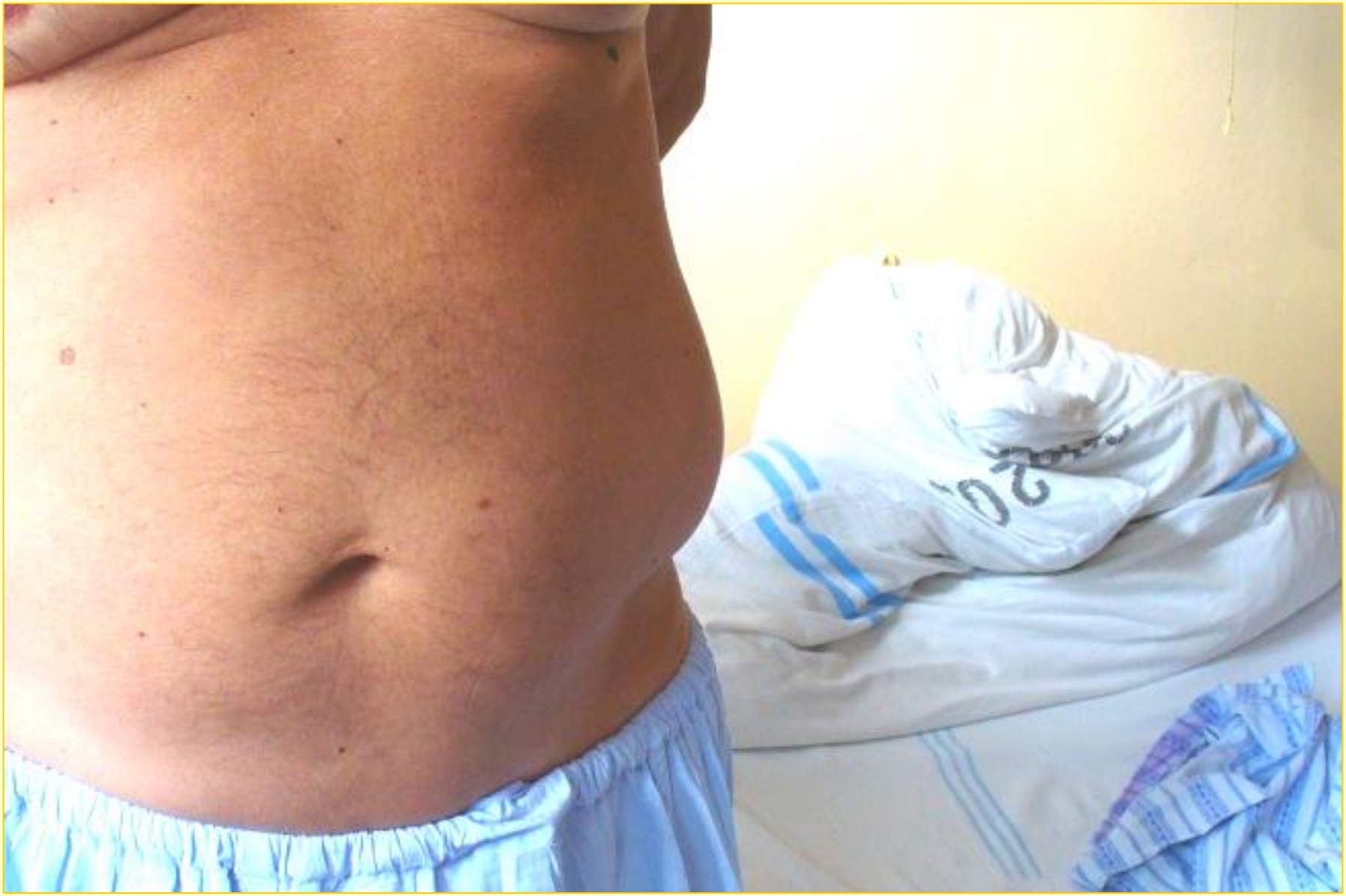
- history – stay in the nature, animal contact, drinking water
- in summer, 2 stages
- Weil‘s disease – signs of meningitis, sepsis, renal failure, hepatitis with icterus, haemorrhage
- leucocytosis, thrombocytopenia, coagulopathy
- hepatopathy, renal failure, haematuria
- CSF – hundreds of polymorphs (up to 1000/μl)
- CSF and serum PCR, culture difficult
- serology – antibodies not positive until 3rd to 4th week
- ATB empirical – benzylpenicillin, ceftriaxone, ampicillin

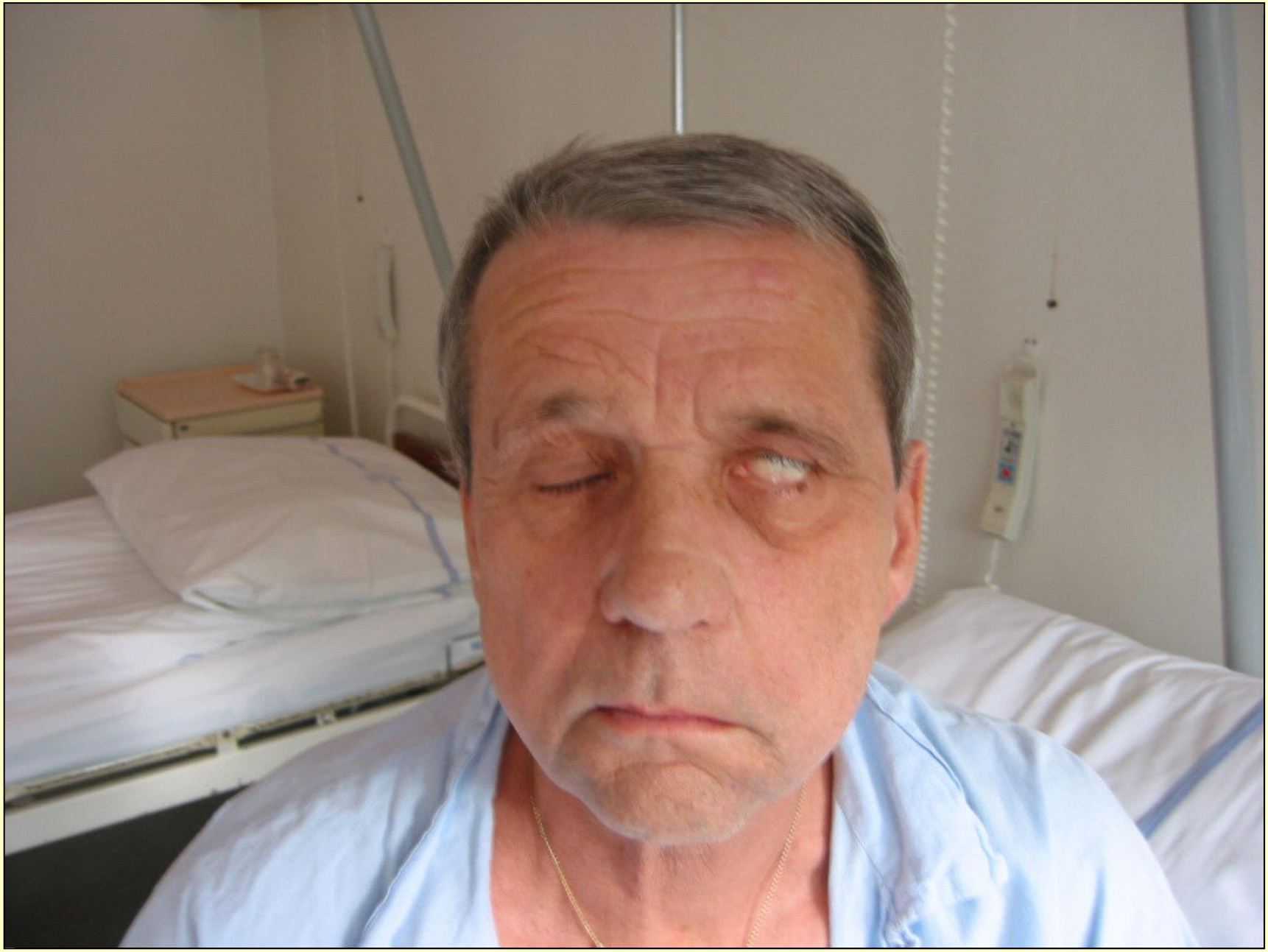
Lyme disease

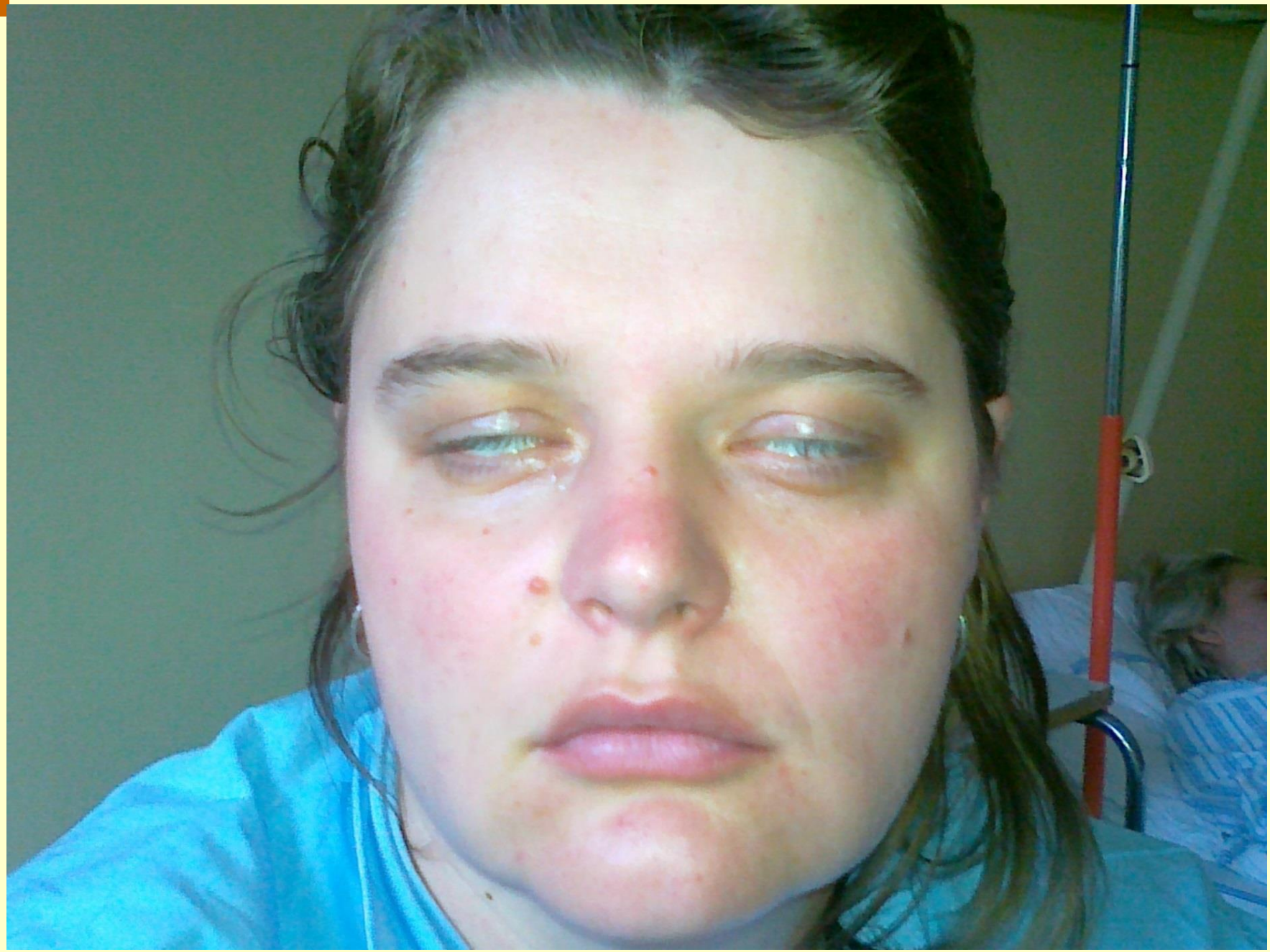
- disease with multiple organ failure, nervous system may be affected in both the early disseminated infection and the chronic stage, not lethal
- cause: *Borrelia burgdorferi sensu lato,* several genospecies, *B.garini, B.afzelii, B.bavariensis, B.burgdorferi sensu stricto*, *B.spielmanni* in the Czech Republic
- vector: tick, Ixodes ricinus in the Czech Republic, other transfer unconfirmed, borrelias may be carried by ticks of all 3 stages

- nervous system affected in early infection generalisation
  - **meningitis alone or with peripheral paresis of CN VII**, less commonly other cranial nerves (e.g. oculomotor)
  - **meningoradiculoneuritis = Garin-Bujadoux-Bannwarth syndrome (most common)** – excruciating radicular pain especially at night, impaired skin sensitivity, limb, thoracic muscle, cranial nerve paresis
- chronic disseminated infection
  - (meningo)encephalitis, myelitis, – headache, sleep disorders, paresthesia, pareses, fatigue, emotional unstability, impaired memory, chron. radicular night pains
  - **affects the peripheral nervous system** (associated with acrodermatitis)

- CSF tests always necessary – three conditions must be met to diagnose an acute neuroborreliosis – serous inflammation in the CSF + intrathecal synthesis of specific antibodies + clinical symptoms
- treatment: ceftriaxone i.v. 14-21 days, doxycycline if allergic, or corticosteroids in paretic patients, rehabilitation







Neuroinfection in syphilis

- growing incidence of STDs over the past few years – CNS impairment must be taken into consideration
- may be acute or chronic, associated with 10% of latent forms of syphilis, disappears spontaneously in 70% cases
- diagnostics: evidence of antibodies in the CSF – intrathecal synthesis
- ATB ceftriaxone

- *early syphilitic meningitis or ME –* during the 2nd stage – headache, nausea, vomitting, confusion, potential spasticity, cranial nerve pareses, including impaired hearing, rarely hydrocephalus
- *Subacute and chronic ME* used to occur before the ATB era, progression gradual, patients develop tabes dorsalis with typical gait and impaired proprioception, gradual development of dementia and immobility – progressive paralysis
- *Meningovascular syphilis* within 3-9 years after the infection – character of a cerebral infarction
- *Gummatous neurosyphilis –* gummata arise from the pia and gradually pass to the brain and the spinal cord, CT scans may simulate tumour scatter

Aseptic meningitis consequences

- frequent headaches
- lack of concentration, productivity; fatigue, sleep and memory disorders – postencephalitic syndrome
- residual pareses of cranial nerves and limbs
- epilepsy
- organic psychosyndrome
- dementia in older patients
- psychomotor retardation in children

Thank you for your attention.