Neuroinfections

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Introduction

- neurologic infections – purulent (suppurative) or aseptic (non-suppurative) infections

- purulent menininingitis – can be caused by any bacteria; most common world-wide in adults: *N. meningitidis*, *Haemophilus influenzae* type b, S. *pneumoniae;* in neonates: *S. agalactiae, E. coli,* in hospitals: enterobacteriae; *S. aureus* – associated with e.g. spondylodiscitis, endocarditis

- course of the infections - peracute, acute, subacute, chronic

- symptoms – meningeal syndrome – triad: 1. constant and severe headache, 2. vomitus or nausea, 3. positive meningeal signs (e.g.neck, back stifness) in children can absent (fever)

Purulent (suppurative, bacterial) meningitis

ETIOLOGY

- 5 months – 5 years and in adolescent: most common *N. meningitidis*
- 5 months – 5 years *H. ifluenzae* type b (before vaccination), most common in unvaccinated children
- adults: prevalent *S. pneumoniae* (prevalent also as posttraumatic meningitis), most frequent postoperative: gram-negative bacteria
- neonates: *S. agalactiae* (Streptococcus group B, GBS), *E.coli* (and other eneterobacteriae), rarely *L. monocytogenes*

Age	Etiology
0-2 months	**S. agalactiae** **E.coli and enterobacteria** **L.monocytogenes**
3 months-5 years	**H. influenzae** [a] **N. meningitidis** **S. pneumoniae**
5-60 years immunocompetent	**S. pneumoniae** **N. meningitidis** **Streptococci other than S. pneumoniae** **S. aureus** [b]
5-60 years immunocompromised	S. pneumoniae L. monocytogenes Gramnegative rods [c] S. aureus [b] Cryptococcus neoformans

Note: a - decreases the incidence of disease due to vaccination, b – mainly in postttraumatic meningitis or due to embolisation during septicemia, c – genera Pseudomonas, Escherichia, Klebsiella, Proteus, Acinetobacter etc.

Purulent (suppurative, bacterial) meningitis

VIRULENCE FACTORS

- Capsule – antiphagocytic properties (*N. meningitidis, H. influenzae type b, S. pneumoniae*)
- Lipoolygosaccharides (LOS) – analog to LPS in *N. meningitidis,* released during autolysis (could be enhanced by antibiotics) and responsible for toxic effects in disseminated meningococcal disease
- IgA protease (*N. meningitidis*) – cleaves IgA, helps pathogen to evade these immunoglobulins

Purulent (suppurative, bacterial) meningitis

PATHOGENESIS

- routes – blood stream, per continuatem
- primary or secondary (complication of other infections)
- children – often primary meningitis trough the blood stream, bacteremia occurs prior to developing meningitis
- secondary – when bacteria penetrate from the adjancet cavities (paranasal, otitis media, mastoitidis)

Purulent (suppurative, bacterial) meningitis

DIAGNOSIS

Microbiological examination of cerebrospinal fluid (CSF) is crucial to dg the infection:

- microscopy – Gram or another staining procedure
- culture – enriched and diagnostic culture media (liquid culture media to enhance the growth)
- cultivation free methods – e.g. PCR, agglutination of CSF with most prevalent bacterial agents
- hemoculture

Searching for focal infections or trauma (X ray of nasal cavity, CT of skll or brain…)

Purulent (suppurative, bacterial) meningitis

CAUSATIVE THERAPY

Should be prescribed immediately after CSF is collected

- cephalosporins of 3rd generation (ceftriaxon, cefotaxim) – penetrates in high concentration through hematoencephalic barier (ceftazidim for *P. aeruginosa, K. pneumoniae)*
- betalactam allergy – chloramphenicol
- resistant *P. aeruginosa, K. pneumoniae* – carbapenems (meropenem, imipenem)
- *L. monocytogenes* – to cephalosporins (primary resistant) should be added ampicillin

Purulent (suppurative, bacterial) meningitis

SUPPORTIVE THERAPY

- corticosteroids – help prevent hearing impairment
- antiedematous therapy – manitol
- nutrition, rehydratation, ions replacements

OUTCOME

- who recover within 72h – afebrile and mentally alert require no further evaluation of CSF, if not lumbar puncture and analysis is indicated

COMPLICATION, SEQUELAE

- sterile subdural effusion (usually spontaneously absorbed), hearing impairment, deafness, hydrocephalus…

PROGNOSIS, MORTALITY

- depends on age, agent, generally: 10% children, higher in adults (30%)

PREVENTION, PROPHYLAXIS

- early treatment of the other infections which can be focus for secondary meningitis (e.g.mastoitidis, sinusitis, otitis)
- protective chemotherapy – oral penicilin – close contacts with meningococcal infections, vaccination *H. inluenzae* b, pneumococci

Meningococcal infections

ETIOLOGY

- *Neisseria meningitidis* (meningococcus), gramnegative diplococcus, 13 serogroups most infection caused by A, B, C, Y and W135 serogroups CR prevalent serogroup B (75% cases) and C

EPIDEMIOLOGY

- world-wide (endemic in sub-Saharan Africa)
- primarily a disease of children and young adults
- CR – low incidence (100 cases annually)

CLINICAL SYMPTOMS

- 5 -15% asymtomatic carriers
- **superficial inf.** – pharyngitis, rhinitis, uretritis, conjunctivitis (untreated can result in invesive infection but may-be self limited)
- **invasive inf.** – invasion from mucosa to blood stream, **sepsis and/or meningitis** (obviously sepsis and meningitis)
- **sepsis –** is **peracute infection (hours),** consistent with **multiorgan dysfunction and failure** (severe DIC, petechiae, suffusion, septic shock)

Meningococcal infections

TREATMENT

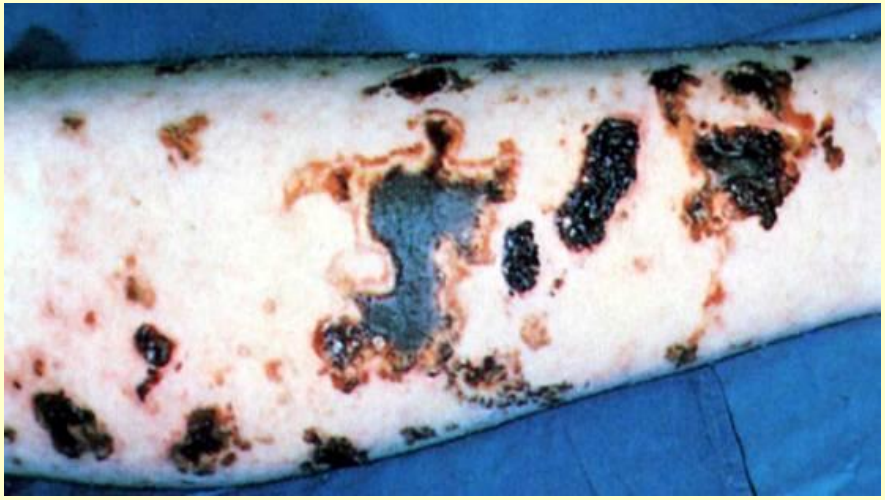
- penicillin, cephalosporins 3rd generation
- supportive multiorgan therapy – ventilation, circulation, renal function

OUTCOME, COMPLICATIONS

- Disseminated intravascular coagulation (DIC) - in severe sepsis can result in multiple necroses of peripheral part of extremites, the lost of which can follow (fig.below)
- mortality – meningitis up to 2%, sepsis about 30%

PREVENTION, PROPHYLAXIS

- only close contacts (kissing) oral penicillin 7 days
- vaccines serogroup A, C (bivalent) and A,C,Y,W135 (tetravalent)



Meningococcal infections

CLINICAL DIAGNOSIS

Initial therapy of meningococcal sepsis and sepsis/meningitis is entirely clinical (acute febrile disease & hemorragic exanthema) because of the urgency.

MICROBIOLOGICAL DIAGNOSIS

- microscopy – Gram staining procedure

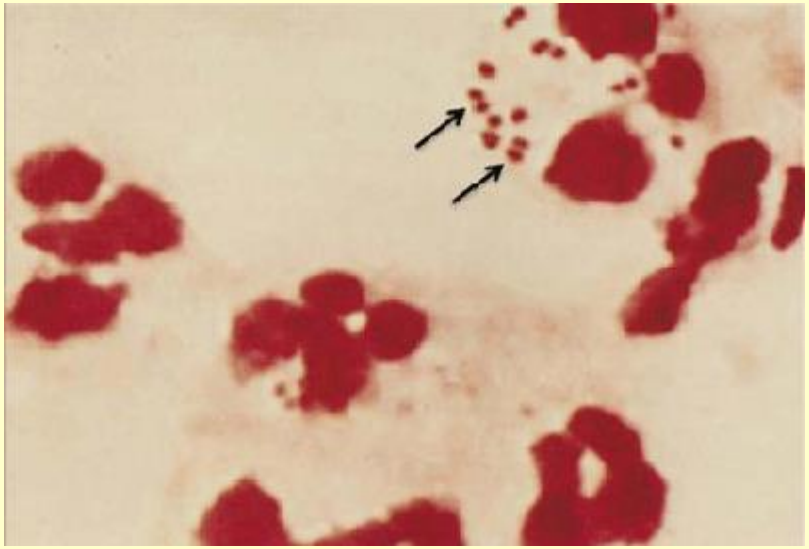


Figure 1. Gram stain of *N. meningitidis* in CSF with associated PMNs.

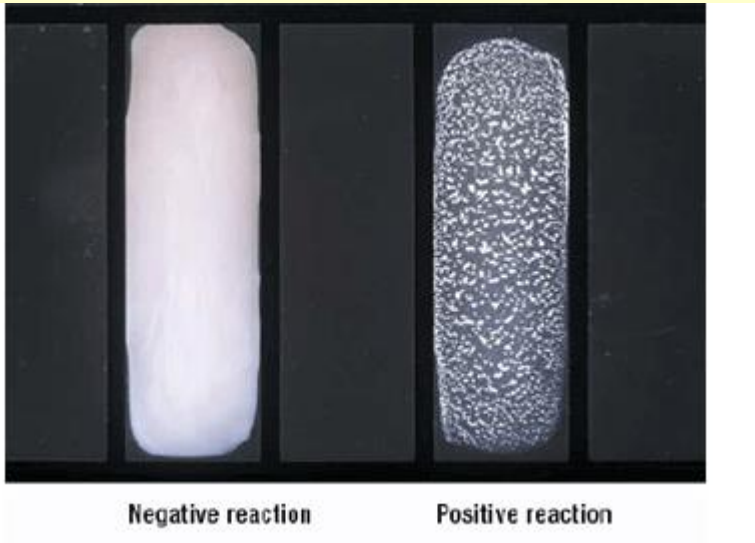
Diagnosis - http://www.cdc.gov/meningitis/lab-manual/chpt06-culture-id.html

Meningococcal infections

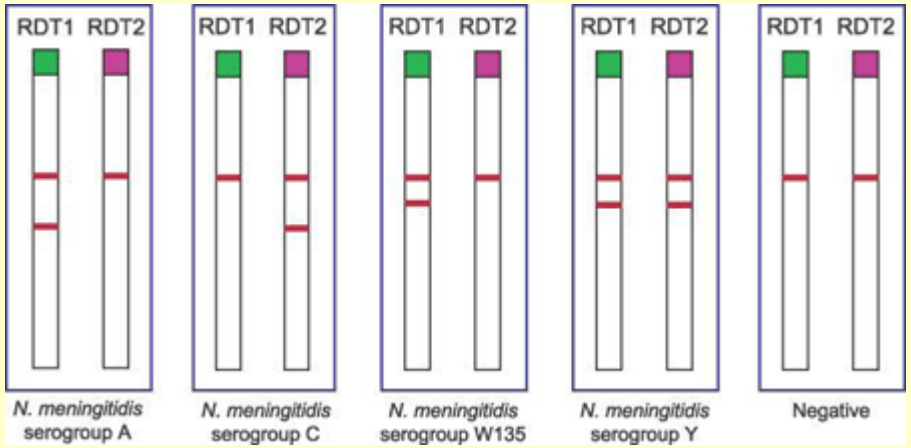
MICROBIOLOGICAL DIAGNOSIS

cultivation free methods – e.g. PCR, agglutination immunochromatography of CSF

agglutination



immunochromatography



RDT results for N. meningitidis serogroups A, C, W135, and Y, as well as a negative control

RDTs have been developed for direct testing of CSF specimens without prior heat or centrifugation (2). The test is based on the principle of vertical flow immunochromatography in which gold particles and nitrocellulose membranes are coated with monoclonal antibodies to capture soluble serogroup-specific polysaccharide antigens in the CSF. The test consists of 2 duplex paper sticks (also called dipsticks), which together enable identification of four serogroups of *N. meningitidis* (A, C, W135, and Y). RDT1 tests for serogroups A and W135/Y and RDT2 tests for serogroups C and Y.

Meningococcal infections

MICROBIOLOGICAL DIAGNOSIS

cultivation – enriched and diagnostic culture media (liquid culture media to enhance the growth)

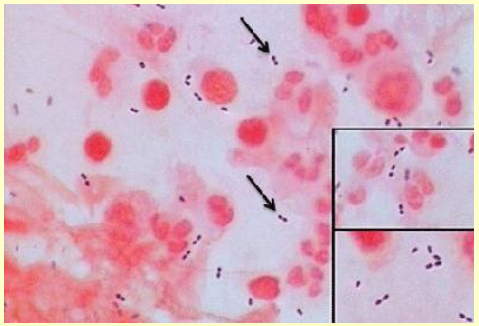
A B C

Neisseria meningitidis cultured on the selective Thayer Martin medium (A) (when commensal flora contaminated the specimen), culture on chocolate agar (B) and blood agar (C). Carbon dioxide enhances growth, but is not required. *N.meningitidis* is oxidase positive. Identification – phenotypical (biochemical, mass spectrometry) or genotypical identification.

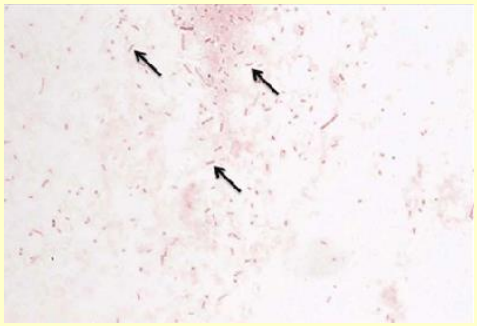
Other bacterial meningitis

MICROBIOLOGICAL DIAGNOSIS

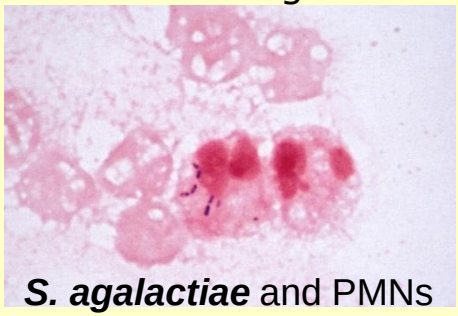
- microscopy – Gram staining procedure (bacteria in CSF)



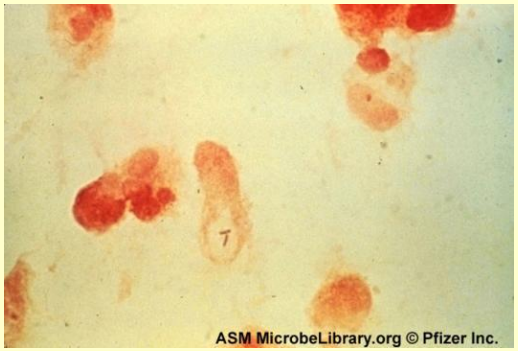
S. pneumoniae may occur intracellularly or extracellularly and will appear as **gram-positive, lanceolate diplococc**i, sometimes occurring in short chains.



H. influenzae are small, **pleomorphic gram-negative rods or coccobacilli** with random arrangements.



S. agalactiae and PMNs



This cerebrospinal fluid contains a few neutrophils and two slender gram-positive bacilli – ***L. monocytogenes***. Although Gram stains of cerebrospinal fluid are positive in specimens from about 80% of all patients with bacterial meningitis, organisms are detected in the cerebrospinal fluid of only about 40% of patients with *Listeria* meningitis. Even when specimens reveal bacteria, only a small number may be visible.

Diagnosis - http://www.cdc.gov/meningitis/lab-manual/chpt06-culture-id.html

Meningococcal infections

MICROBIOLOGICAL DIAGNOSIS

cultivation free methods – e.g. PCR, agglutination of CSF

agglutination

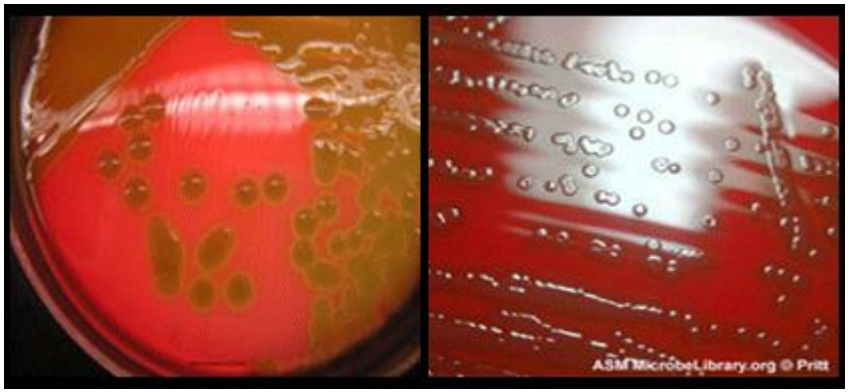
Latex agglutination procedure for CSF

Follow the manufacturer's instructions on the package insert for the specific latex kit being used. General instructions are listed below:

1. Centrifuge the CSF for 10-15 minutes at 1000 x g and collect the supernatant.
    1. The sediment should be used for Gram stain and primary culture.
2. Heat the CSF supernatant to be used for the test at 100°C for 3 minutes.
3. Shake the latex reagents gently until homogenous.
4. Place one drop of each latex reagent on a disposable card provided in the kit or a ringed glass slide.
5. Add 30-50 µl of the supernatant of the CSF to each latex reagent.
6. Rotate by hand for 2-10 minutes. If available, mechanical rotation at 100 rpm is recommended.
    1. Avoid cross-contamination when mixing and dispensing reagents.
7. Examine the agglutination reactions under a bright light without magnification.

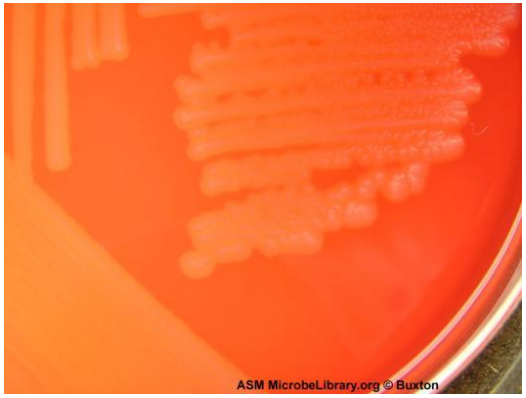
Other neuroinfections

MICROBIOLOGICAL DIAGNOSIS
cultivation – enriched and diagnostic culture media (liquid culture media to enhance the growth)

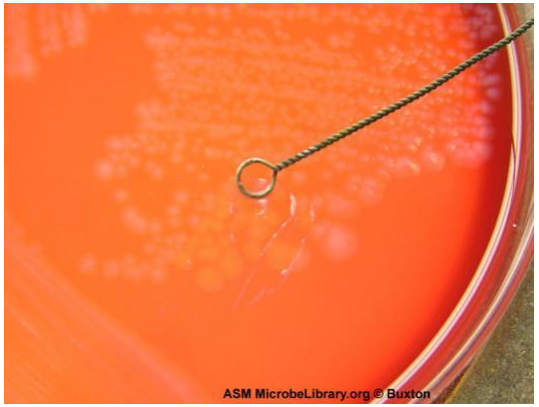


A B

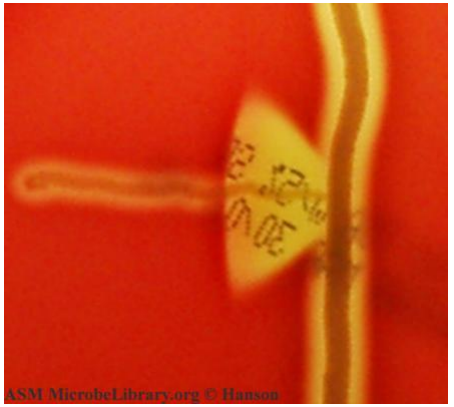
C



D



E



F

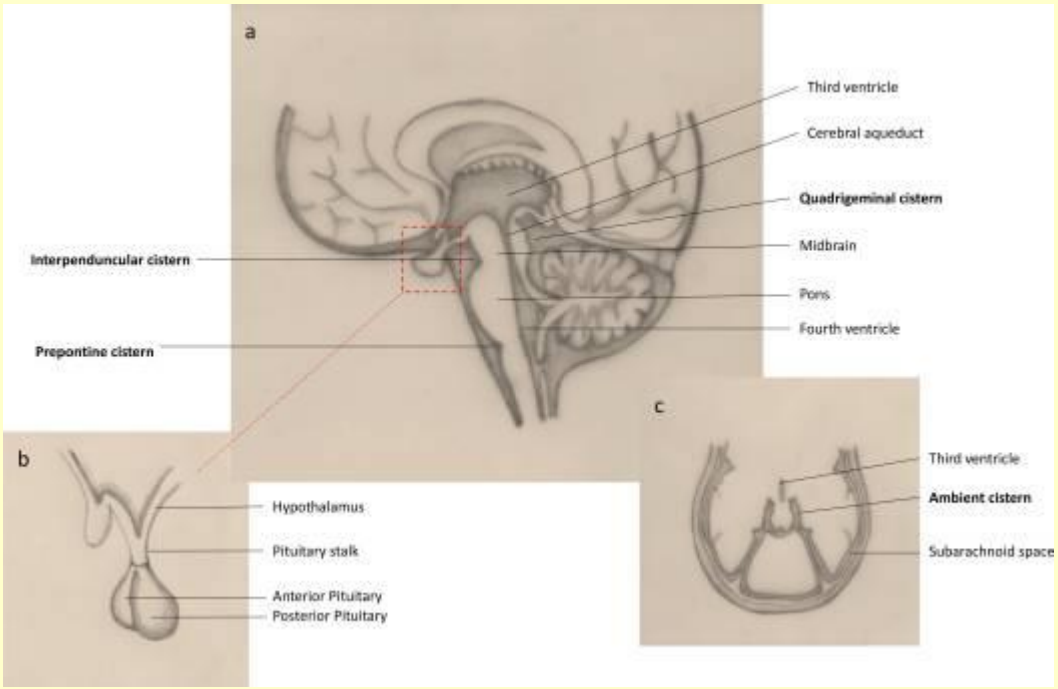
Blood agar: S.pneumoniae (A, B – detail), Haemophilus influenzae – satelite growth in vicinity of S. aureus (C), S. agalactiae (D), Listeria monocytogenes (E), both the latter are CAMP psoitive (F)

Other neuroinfections – M. tuberculosis (basilary/basal meningitis)

Tuberculosis (TB) remains a leading cause of death globally. Dissemination of tuberculosis to the brain results in the most severe form of extra-pulmonary TB, tuberculous meningitis (TBM), which represents a medical emergency associated with high rates of mortality and disability. Via various mechanisms the *Mycobacterium tuberculosis* (*M.tb*) bacillus disseminates from the primary site of infection and overcomes protective barriers to enter the central nervous system. There it induces an inflammatory response involving both the peripheral and resident immune cells, which initiates a cascade of pathological mechanisms that may either contain the disease or result in significant brain injury.

- Longer incubation period – e.g. 2 week
- Dg – material – CSF, Zn staining, PCR, culture

Other neuroinfections – M. tuberculosis (basilary/basal meningitis)



A: Basal cisterns affected in TBM are represented here in a sagittal view of the brain. Note the quadrigeminal cistern which extends laterally to become a thin sheet like cistern surrounding the midbrain and posterior thalamus, named the ambient cistern shown in **C**. **B**: Anatomy of the pituitary gland and surrounding structures.

- Longer incubation period – e.g. 2 week
- Dg – material – CSF, Zn staining, PCR, culture

Aseptic (non-suppurative) neuroinfections

INTRODUCTION

- most viruses can affect meninges and brain parenchyma
- manifestation depends: virus tropism and immune reactivity
- symtomatology: from subclinical to lethal
- viral meningoencephalitis: obviously two-phase clinical course (1st common viral inf. –flu like symptoms 3-7days, latency – 3-7 days, 2nd symptoms of nervous system inflammation

ETIOLOGY AND EPIDEMIOLOGY

- Czech Republic - majority are air or arthropod borne
  - most frequent in the CR – arboviruses, enteroviruses
  - incidence – 1000-2000 annually

PATHOGENESIS

- 3 main routes: blood, CSF, nerve cells
- pathogenesis – viruses which provoke cytopatological effect result in tissue damage (e.g. rabies), after the tissue damage host immune response starts clinical symptoms

Aseptic (non-suppurative) neuroinfections

Group	Agens
Enteroviruses	**Coxsackie and ECHO, polioviruses**
Respiratory and related viruses	**Influenza and parainfluenza viruses, RSV, mumps, rubella and measles viruses**
Arbo viruses	**TBE virus, West Nile virus, Dengue virus, Japanese encephalitis (JE) virus, Eastern equine encephalitis virus (EEEV) etc.**
Herpetic viruses	**HSV1 and 2, VZV, CMV, EBV, HHV6**
Other viruses	**HIV, adenoviruses, lymphocytic choriomeningitis virus (LCMV)**
Spirochaete	L. interrogans, B. burgdorferi, T. pallidum
Intracellular bacteria	Chlamydia, Rickettsia, Ehrlichia, Coxiella, Legionella
Other bacteria	Mycoplasma pneumoniae

Aseptic (non-suppurative) neuroinfections

DIAGNOSIS

- crucial role – **CSF analysis**, aseptic means – elevated numbers of mononuclear cells (lymphocytes and macrophages)
- **virus isolation** - detection most specific, expensive, low sensitivity
(does not overlap the peak of symptoms)
- **direct detection of specific viral DNA (RNA)** – sensitive, specific
- **indirect detection of specific antibodies** – antibodies can be sign of a previous contact, only 4-fold rise of specific titres or seroconversion can mean confirm infection (can be detected also in CSF – important in laboratory diagnosis of neuroborreliosis, syphilis and other rare infections)

Aseptic (non-suppurative) neuroinfections

CLINICAL SYMPTOMS

Aseptic meningitis

- neonates (up to 4 weeks): rare, life threating, nonspecific symptoms as part of generalized inf (e.g.herpes virus), shoud be excluded of the bacterial infections
- older children – high temperature, headache, nausea, voomiting, biphasic, after 1-2 weeks fade away

Viral encephalitis

- most symptoms identical with meningitis, including 2 phase course
- clinical signs of the CNS damage in the 2nd phase, most common: central pareses, cerebellar ataxia, disturbances of consciousness, quick tremor of eyelids and fingers in the acute phase, general spasm rarely – if appears – in acute phase during brain edema

Myelitis

- inflammation of spinal cord – less frequent, serious sequelae, focal lesions – paresis, lost of sensitivity, pain

Aseptic (non-suppurative) neuroinfections

NEUROLOGICAL SEQUELAE

- viral meningitis is obviously self-limited – patients recover after several days without complications
- most common sequelae – postencepalitic or pseudoneurasthenic syndrome – headaches, disturbances of psychic and sleeping concentration, mood, memory and personality changes (persist for weeks, months, rarely longer)
- paresis, vertigo, sensoric pathology – aftre more severe CNS infections

THERAPY

- majority self-limited – symptomatic treatment (e.g. brain edema – corticoids, convulsion – benzodiazepines)
- intensive care – in complicated cases (letal rarely)
- long convalescence – 3 months substantial and the next 3 moderate reduction of activities

Aseptic (non-suppurative) neuroinfections

AGENTS

- herpes-simplex type 1
- herpes-simplex type 2
- cytomegalovirus
- Epstein-Barr virus
- human herpes viruses 6 and 7
- virus varicella zoster (VZV)
- enteroviruses
- polioviruses
- arthropod borne encephalitides

- tick-borne enecephalitis (TBE)
- the Russian spring-summer encephalitis
- Japanese encephalitis
- eastern (EEE) and western equine encephalitis (WEE)19

Lyme disease – multisystemic infection

3rd stadium – chronic meningoencephalitis or chronic polyradiculopathy or neuropathy

main source references: Inf. Diseases, Karolinum, 2012, J.Hobstová