

# Neuroinfections



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# Introduction

- **neurologic infections** – **purulent** (suppurative) or **aseptic** (non-suppurative) infections
- **purulent meningitis** – can be caused by any bacteria; most common world-wide in
  - Community - adults: *N. meningitidis*, *Haemophilus influenzae* type b, *S. pneumoniae*; in neonates: *S. agalactiae*, *L. monocytogenes*, *E. coli*,
  - HAI (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 stiffness) in children can be absent (fever)

# Purulent (suppurative, bacterial) meningitis

## ETIOLOGY

- **5 months – 5 years** and in **adolescent**: most common *N. meningitidis*
- **5 months – 5 years** *H. influenzae* 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 enterobacteriae), rarely *L. monocytogenes*

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

**Note:** a - decreases the incidence of disease due to vaccination, b – mainly in posttraumatic 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 continuitatem
- **primary** or **secondary** (complication of other infections)
- **children** – often **primary meningitis** through the blood stream, bacteremia occurs prior to developing meningitis
- **secondary** – when bacteria penetrate from the adjacent cavities (paranasal, otitis media, mastoiditis)

# 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 skull 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 barrier
- betalactam allergy – chloramphenicol
- (ceftazidim for *P. aeruginosa*, *K. pneumoniae*) for resistant–carbapenems (meropenem, imipenem)
- *L. monocytogenes* – primary resistant to cephalosporins should be added ampicillin



# Purulent (suppurative, bacterial) meningitis

## SUPPORTIVE THERAPY

- corticosteroids – help prevent hearing impairment
- antiedematous therapy – mannitol
- nutrition, rehydration, 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. mastoiditis, sinusitis, otitis)
- protective chemotherapy – oral penicillin – close contacts with meningococcal infections, vaccination *H. influenzae* 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% asymptomatic carriers
- **superficial inf.** – pharyngitis, rhinitis, urethritis, conjunctivitis (untreated can result in invasive 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 extremities, 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 & hemorrhagic exanthema) because of the urgency.

## MICROBIOLOGICAL DIAGNOSIS

- **microscopy** – Gram staining procedure

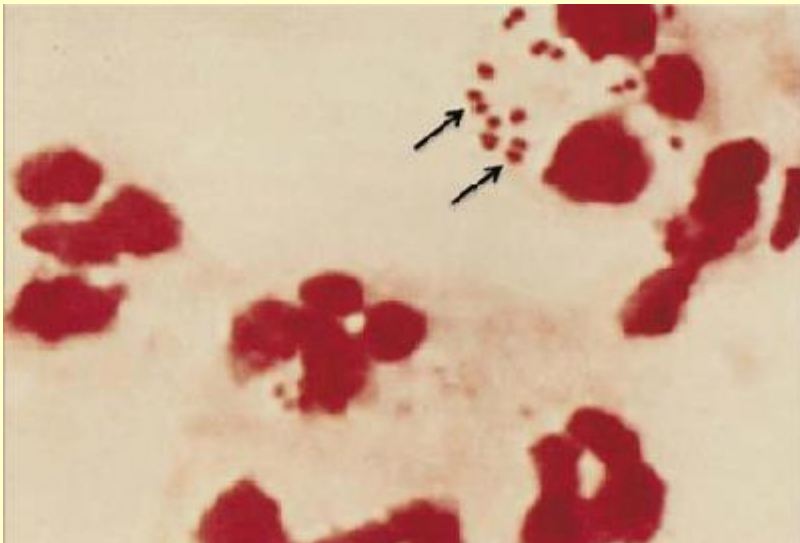


Figure 1. Gram stain of *N. meningitidis* in CSF with associated PMNs.

# Meningococcal infections

## MICROBIOLOGICAL DIAGNOSIS

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

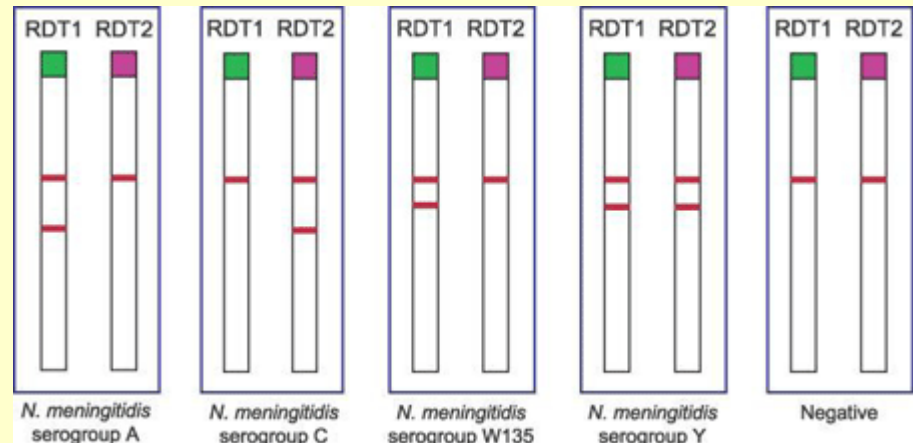
### agglutination



Negative reaction

Positive reaction

### 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

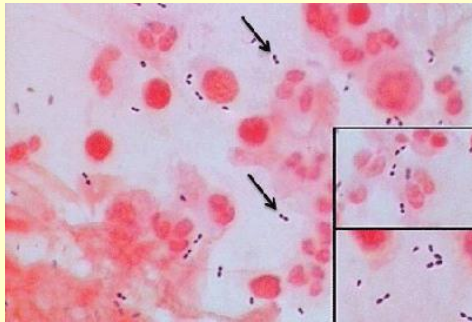
*Neisseria meningitidis* cultured on the selective Thayer Martin medium (A) (when commensal flora contaminated the specimen), culture on chocolate agar (B) and blood agar (C). Carbon dioxide enhances growth, but is not required. *N.meningitidis* is oxidase positive. Identification – phenotypical (biochemical,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



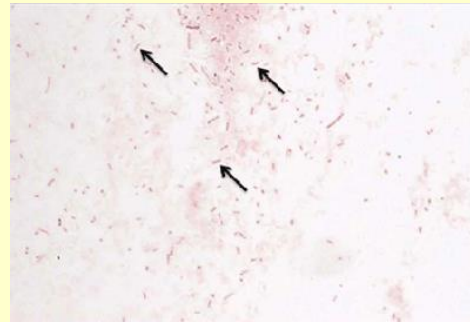
# Other bacterial meningitis

## MICROBIOLOGICAL DIAGNOSIS

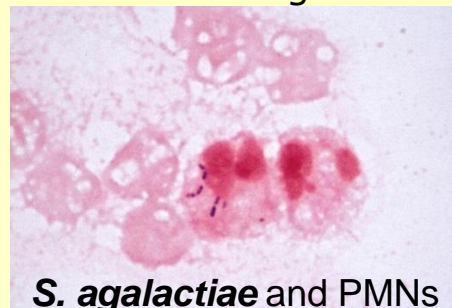
- **microscopy** – Gram staining procedure (bacteria in CSF)



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



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



***S. agalactiae*** and PMNs



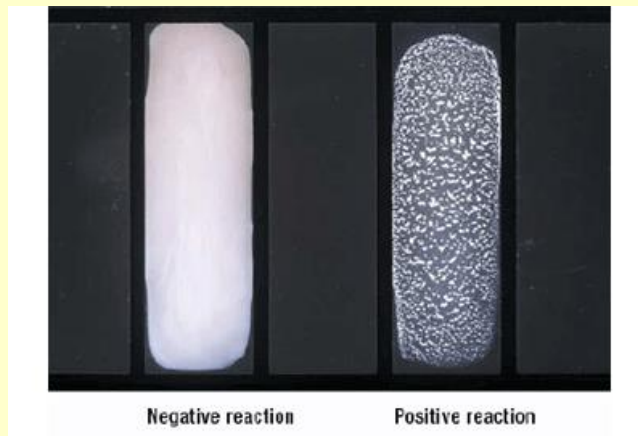
This cerebrospinal fluid contains a few neutrophils and two slender gram-positive bacilli – ***L. monocytogenes***. Although Gram stains of cerebrospinal fluid are positive in specimens from about 80% of all patients with bacterial meningitis, organisms are detected in the cerebrospinal fluid of only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

# Meningococcal infections

## MICROBIOLOGICAL DIAGNOSIS

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

agglutination



### **Latex agglutination procedure for CSF**

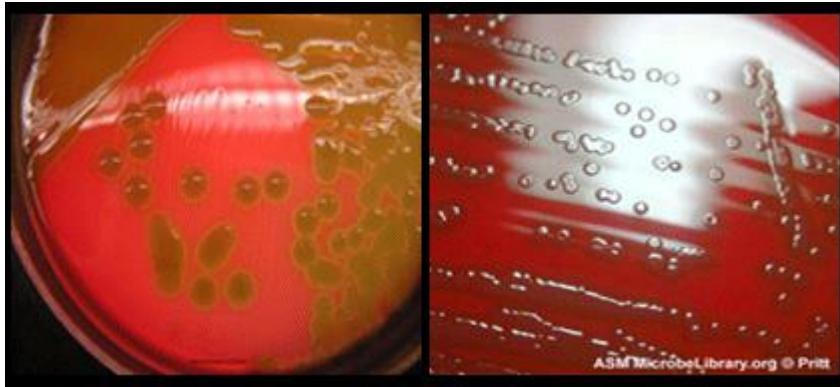
Follow the manufacturer's instructions on the package insert for the specific latex kit being used. General instructions are listed below:

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.



# MICROBIOLOGICAL DIAGNOSIS

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

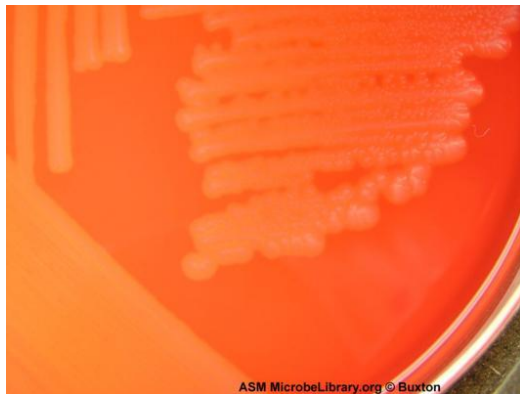


A

B



C



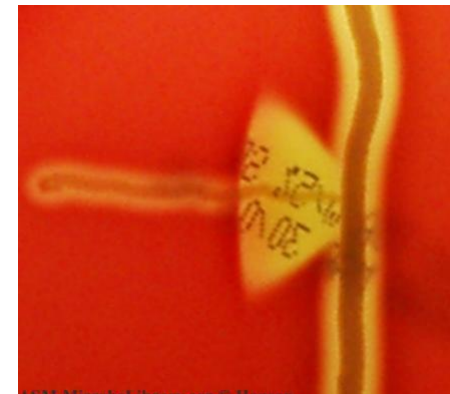
ASM MicrobeLibrary.org © Buxton

D



ASM MicrobeLibrary.org © Buxton

E



ASM MicrobeLibrary.org © Hanson

F

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

# Tuberculous meningitis

Currently, more than 2 billion people (i.e., one third of the world's population) are infected with tuberculosis (TB), 10% of whom develop clinical disease, and 1.4 million of whom die of the disease annually. Tuberculous meningitis (TBM) is a manifestation of extrapulmonary TB, developing in 1%–5% of the approximately 10 million cases of TB worldwide. Although rare in the United States and Europe, TB is a common cause of meningitis (and the most common cause of chronic meningitis) in endemic areas worldwide, particularly among patients co-infected with HIV.

*Mycobacterium tuberculosis* bacilli enter the host by droplet inhalation, after which the localized infection escalates within the lungs and then disseminates to the regional lymph nodes. The bacilli may then seed to the central nervous system (CNS) and result in three forms of CNS TB: tuberculous meningitis, intracranial tuberculoma, and spinal tuberculous arachnoiditis

*Ref: <https://emedicine.medscape.com/article/1166190-overview>*

***Basillary meningitis*** at the base of the brain, due usually to tuberculosis, syphilis, or any low-grade chronic granulomatous process; may result in an internal hydrocephalus.

# Aseptic (non-suppurative) neuroinfections

## INTRODUCTION

- **most viruses** can affect meninges and brain parenchyma
- manifestation depends: virus tropism and immune reactivity
- symptomatology: from subclinical to lethal
- viral meningoencephalitis: **obviously two-phase clinical course** (1st common viral inf. – flu like symptoms 3-7 days, 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 cytopathological effect result in tissue damage (e.g. rabies), after the tissue damage host immune response starts clinical symptoms

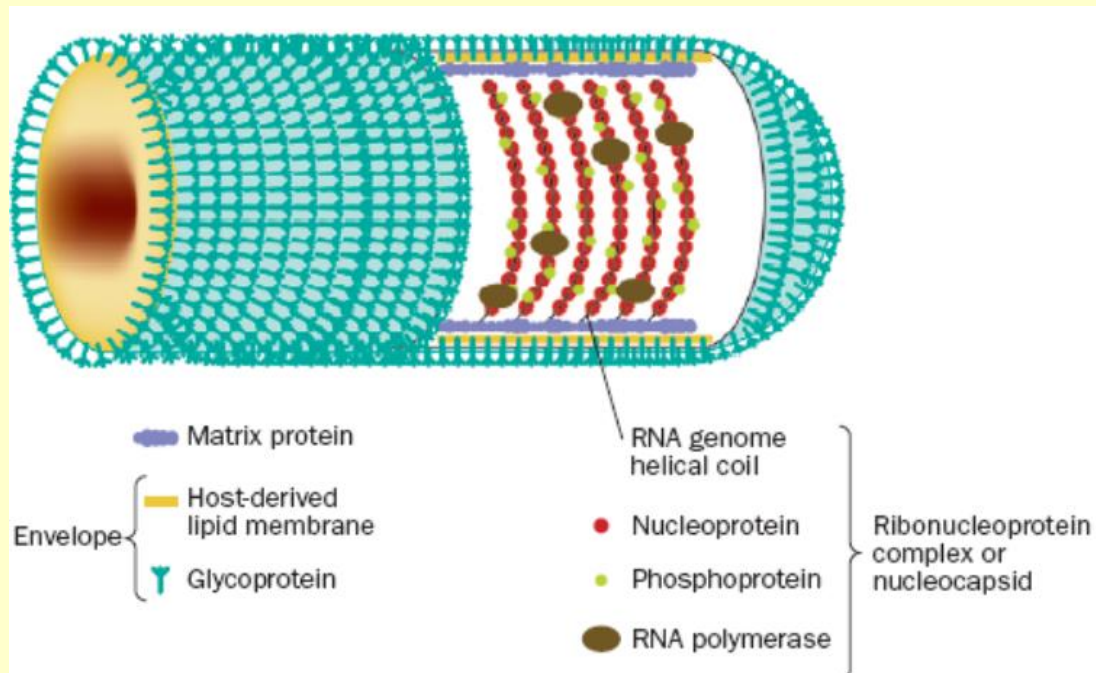
# Aseptic (non-suppurative) neuroinfections

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), rabies
Spirochaete*	<i>L. interrogans</i> , <i>B. burgdorferi</i> , <i>T. pallidum</i>
Intracellular bacteria*	<i>Chlamydia</i> , <i>Rickettsia</i> , <i>Ehrlichia</i> , <i>Coxiella</i> , <i>Legionella</i>
Other bacteria*	<i>Mycoplasma pneumoniae</i>

Note: \* even if aseptic the neuroinfections are caused by bacterial agents

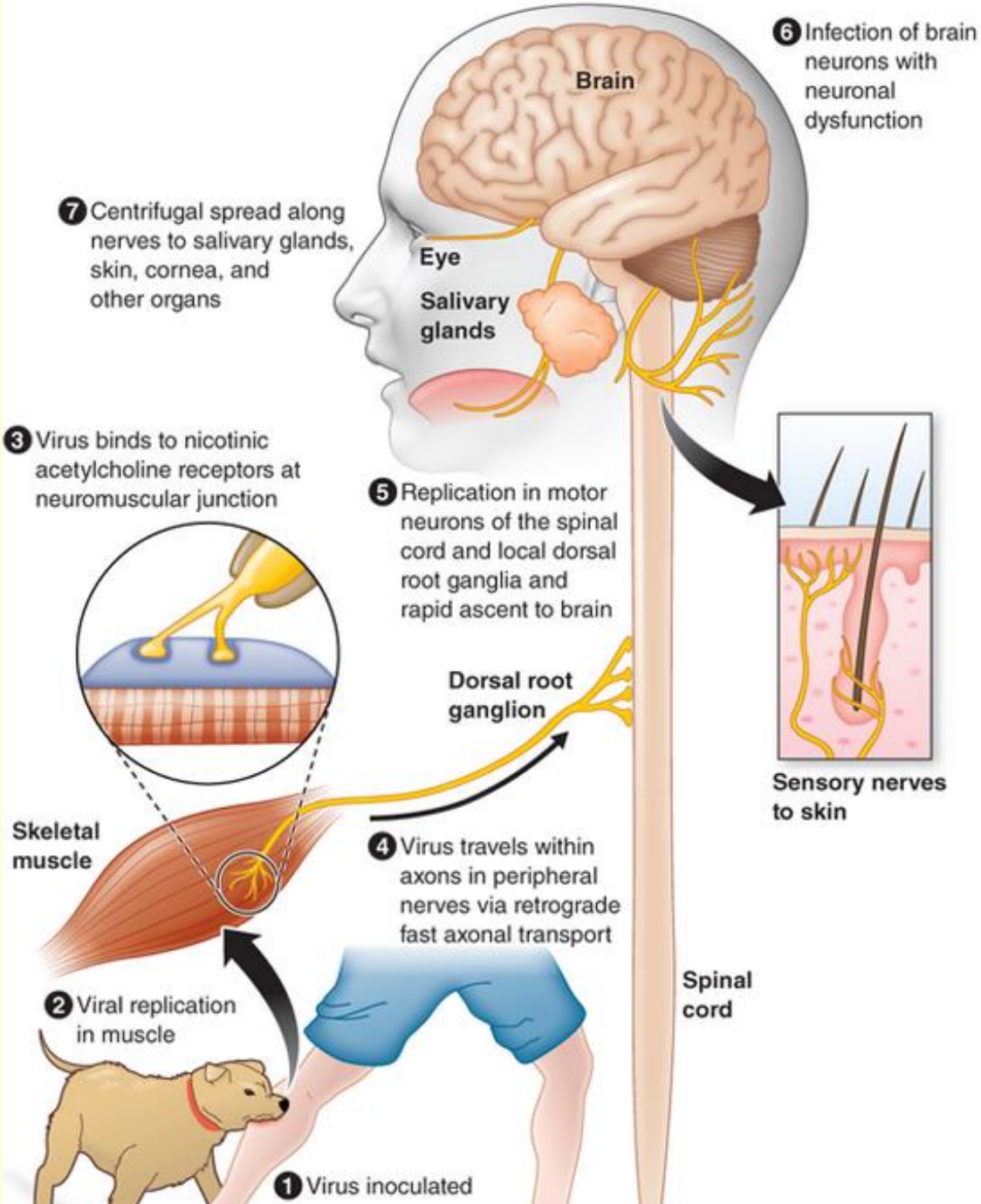
# Rabies

- Rabies is a preventable viral disease most often transmitted through the bite of a rabid animal. The rabies virus infects the central nervous system of mammals, ultimately causing disease in the brain and death.
- The lyssavirus is enveloped, rod shaped particles measuring  $75 \times 180$  nm.
- Mature virion appears either as bullet shaped particles with one rounded and one flattened end or as bacilliform particles.
- The particles are surrounded by a membranous lipid envelope.
- Inside the envelope is a ribonucleocapsid which encloses single-stranded, negative-sense RNA genome (12 kb;





# Pathogenesis



# 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 threatening, nonspecific symptoms as part of generalized inf (e.g. herpes virus), should be excluded of the bacterial infections
- older children – high temperature, headache, nausea, vomiting, 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 – postencephalitic 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 – after more severe CNS infections

## THERAPY

- **majority self-limited** – symptomatic treatment (e.g. brain edema – corticoids, convulsion – benzodiazepines)
- **intensive care – in complicated cases** (lethal 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 encephalitis (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