



MEDICAL UNIVERSITY – PLEVEN
FACULTY OF MEDICINE
**DEPARTMENT OF INFECTIOUS DISEASES, EPIDEMIOLOGY,
PARASITOLOGY AND TROPICAL MEDICINE**

Lecture № 4

BACTERIAL INFECTIONS OF THE CENTRAL NERVOUS SYSTEM (CNS)

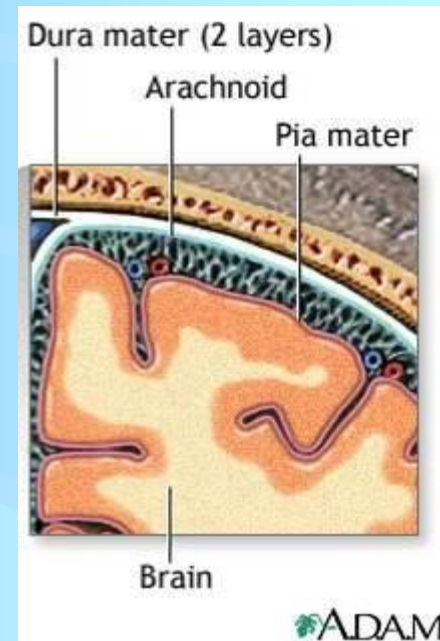
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INFECTIONS OF CNS – introduction

- Acute infections of the CNS – among the most important problems in medicine because are **life-threatening**.
- **Require**
 - ❖ early recognition,
 - ❖ efficient decision-making,
 - ❖ rapid institution of therapy.

INFECTIONS OF CNS – clinical syndromes

- **Meningitis** – inflammation of the meninges → subarachnoid space.
- **Encephalitis** → inflammatory involvement of brain tissue – encephalon (mainly viral).
- **Focal infections** – brain abscess, subdural empyema, infectious thrombophlebitis → focal involvement of brain tissue (bacterial, fungal, parasitic).



INFECTIONS OF CNS – classification

- Causative agents: bacteria, viruses, fungi, parasites.
- **Septic** (bacterial) meningitis – turbid CSF with polymorphonuclear pleocytosis↑, proteinorachia↑↑, glucosa↓↓, **bacteria**
- **Aseptic** meningitis – translucent CSF with mononuclear pleocytosis↑, proteinorachia↑, normal glucosa, **viruses**
Mycobacterium tuberculosis, Listeria monocytogenes

BACTERIAL MENINGITIS – etiology

- **Encapsulated bacteria – 80%**
 - ❖ *S. pneumoniae*
 - ❖ *N. meningitidis* (A, B, C, Y, W-135)
 - ❖ *H. Influenzae*
- **Rare bacteria**
 - ❖ *Listeria monocytogenes*
 - ❖ Gram (-) – *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*
 - ❖ *Staphylococcus epidermidis*, *Staphylococcus aureus*
 - ❖ *Streptococcus agalactiae*
 - ❖ *Mycobacterium tuberculosis* – increased number of immunosuppressed !!!

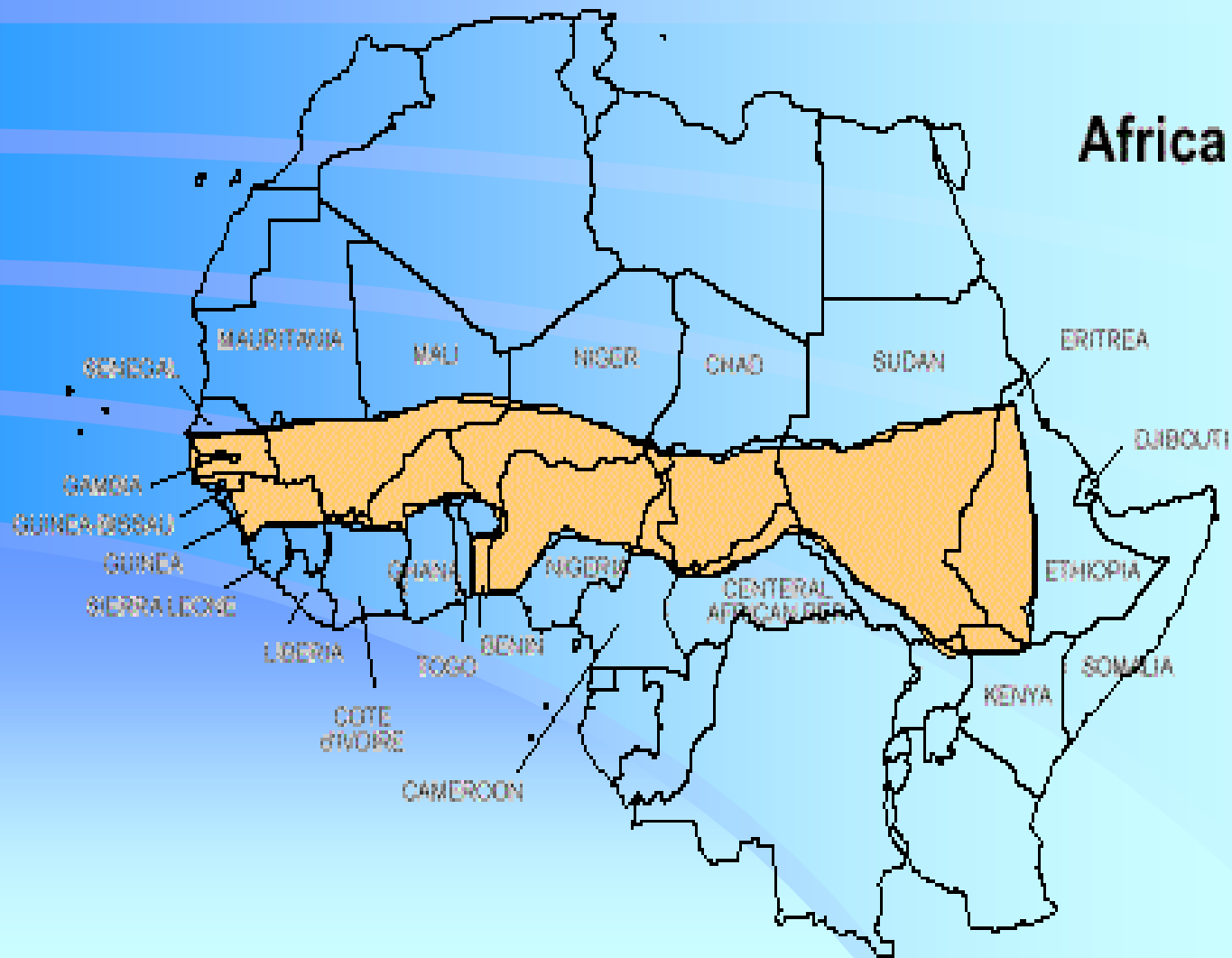
BACTERIAL MENINGITIS – *predisposing conditions*

- age>60;
- pneumonia;
- coexisting chronic or acute sinusitis;
- otitis media;
- diabetes;
- splenectomy;
- alcoholism;
- cranial fracture and CSF rhinorhea (pneumococcal meningitis, relapsing),
- congenital defect (spina bifida);
- crowding (e.g. military recruits and college camp residents) – increases risk of outbreaks of meningococcal meningitis.

BACTERIAL MENINGITIS – epidemiology

- N. meningitis – sporadic, **epidemic**
- ❖ African meningitis belt – sub-Saharan Africa (December-June),
- ❖ Saudi Arabia – religious pilgrim for Hajj, Umrah;
- Increased incidence of nosocomial meningitis.

African meningitis belt

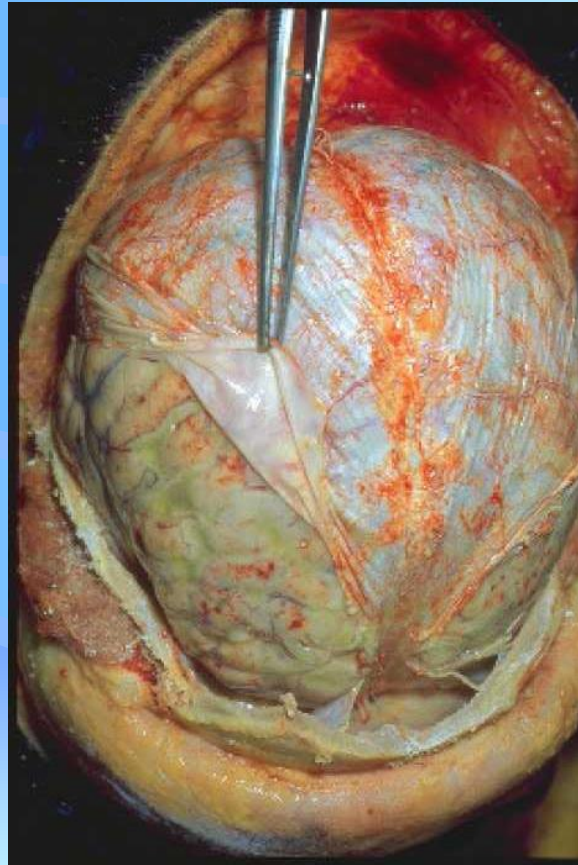


BACTERIAL MENINGITIS – patophysiology

Bacteria reach the intracranial structures by:

- **hematogenous spread**
- **direct invasion:**
 - ❖ *from infective focus of infection* (sinusitis, mastoiditis, skull and vertebral osteomyelitis),
 - ❖ *loss of CSF integrity*: congenital (meningomyelocelle), traumatic or surgical (basal skull fracture, CSF shunt),
 - ❖ occasionally a brain abscess may rupture into the subarachnoid space or ventricles, infecting the meninges.

Bacterial (purulent) meningitis



BACTERIAL MENINGITIS – clinical presentation

- Onset:
 - ❖ acute (<24 h) – 25%; fulminant onset
 - ❖ subacute (1-7 days)
- **Classic triad:** fever, headache and vomiting.
- Photophobia, hyperacusis, hyperesthesia.
- Myalgia, adynamia.

BACTERIAL MENINGITIS – clinical presentation

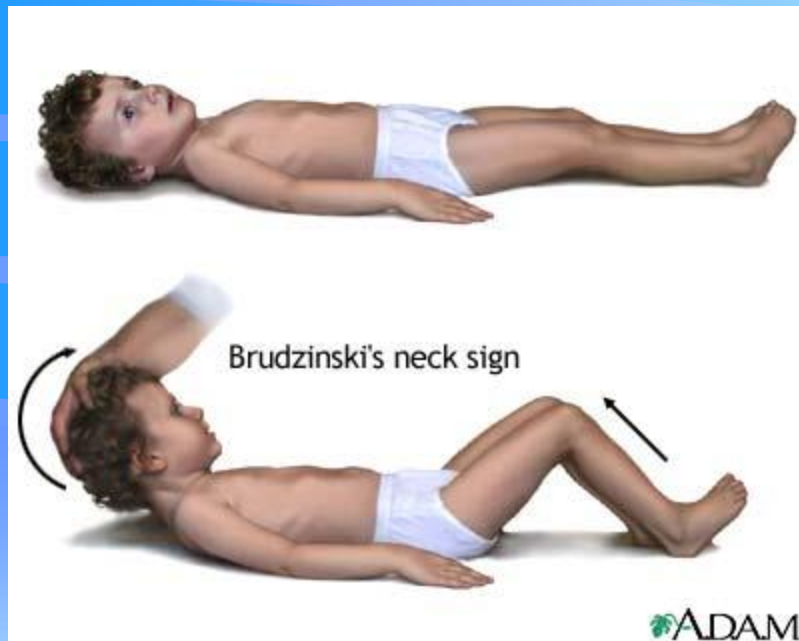
- **Mental status** – alteration: lethargy to coma or confusion
- **Signs of meningeal irritation:** nuchal rigidity, Kernig's, Brudzinski's signs
 - ❖ **absent or reduced in:** infants (looking for symptom of Lesage), elderly, immunocompromised, severely depressed.
- **Focal neurologic signs** (10-20% of cases):
 - ❖ Seizures – focal or generalized (generalized are more common at H. influenzae);
 - ❖ Isolated cranial nerve abnormalities (principally III, IV, VI, VII) – 10-20% of patients.

In older children and adults, the severity of symptoms varies.

Nearly all patients have fever, headache, and nuchal rigidity.

The most common finding is a stiff neck characterized by pain and resistance on flexion.

Neurological findings include Brudzinski's sign, and Kernig's sign



Tripod sign of spinal rigidity



BACTERIAL MENINGITIS – clinical presentation

- **Pappilar edema uncommon (<5%):**
 - ❖ if presents suggests abscess, suddbdural empyema, occlusion of dural venous sinus;
 - ❖ its absence does not exclude increased intracranial pressure!
- **Systemic findings:**
 - ❖ Extracranial infection (e.g. sinusitis, otitis media, mastoiditis, pneumonia, urinary tract infection) may be noted.
 - ❖ Arthritis is seen with *N. meningitidis*, less commonly with other bacteria.
 - ❖ Petechial rash – 50% *N.meningitidis*, rare Echovirus 9, *Staph.aureus*.

BACTERIAL MENINGITIS – clinical presentation

- *Symptoms in infants:*

- ❖ fever – temperature instability;
 - ❖ lethargy and/or change in level of alertness;
 - ❖ poor feeding and/or vomiting;
 - ❖ screaming cry;
 - ❖ respiratory distress, apnea, cyanosis;
 - ❖ neurological examination – may be false negative (looking for symptom of Lesage);
 - ❖ bulging fontanel late;
 - ❖ Paradoxical irritability (i.e., quiet when is stationary, cries when held).
- **Key to early diagnosis** → high index of suspicion – lumbar puncture (LP)!!!

CLINICAL MANIFESTATIONS:
vary considerably depending on the
virulence of the organism and the
age of patient.

In neonates the signs of meningeal
irritations (nuchal rigidity, Brudzinski's
sign, and Kernig's sign) are
infrequent and are often minimal when
found. Early signs include:

temperature instability

irritability

poor feeding

vomiting.

In children 1-18 months of age

signs and symptoms are often
non specific:

fever

irritability

drowsiness

vomiting

poor feeding

crying when handled

bulging fontanels (due to increased
intravascular pressure)

seizures.



BACTERIAL MENINGITIS – clinical presentation

- *Symptoms in elder patients:*

- ❖ insidiously, with lethargy, no fever, variable signs of meningeal irritation.
- ❖ Altered mental status should not be explained with other causes until bacterial meningitis has been excluded by CSF examination!!!
- ❖ Patient with neurosurgery or undergone cranial trauma – **unique clinical situation** – they already have many of the symptoms and signs of meningitis from their underlying disease process!!!

BACTERIAL MENINGITIS – laboratory investigations

- Blood cells – leucocytosis with neutrophilia and left shift; lymphopenia.
- Increased erythrocytes sedimentation rate (ESR), increased c-reactive protein and fibrinogen levels.
- CSF – turbid CSF with polymorphonuclear pleocytosis↑, proteinorachia↑↑, glucosa↓↓, *bacteria*.

CSF findings in meningitis with different etiology

Type of meningitis	Leucocytes x 10 ⁶ /l (range)	Predominant cell type	Glucose level (mmol/l)	Protein level (g/l)	Micro biological tests
Bacterial	0 – 60 000	Neutrophils	Low (0.5 – 2.0)	Elevated	Positive*
Viral	0 – 1 000	Mononuclear cells**	Normal (2.2 – 4.4)	Normal to slightly elevated	Negative
Tuberculous	25 – 500	Mononuclear cells	Very low (0.2 – 0.4)	Elevated	Negative
Fungal	0 – 1 000	Mononuclear cells	Low	Elevated	Negative

Lumbar puncture



BACTERIAL MENINGITIS – management and treatment

- **Start empirical antimicrobial therapy:**
 - on **Gram stain** result: rare
 - **Gram stain (-):** based on patient age and underlying disease status.

AB characteristics:

- penetration of the antimicrobial agents into CSF:
- high lipid solubility
- low molecular weight
- low degree of protein binding in serum
- bactericidal within purulent CSF
- empirical antimicrobial therapy – 3rd generation cephalosporins - (ceftriaxone, cefotaxime, ceftazidime) – first choice
- i.v. high doses, duration

BACTERIAL MENINGITIS – supportive treatment

- Corticoids: **dexamethazone** – 0,15 mg/kg every 6 hours 2-4 days. Before or with initiation of antibiotic therapy – inhibits the inflammation in subarachnoid space better
- Dehydration:
 - ❖ mannitol 10% 1-2 g/kg/24 h i.v. for 30 min – 2x daily – 3-5 days
 - ❖ furosemid 1mg/kg
- Sedation – sedative, analgesics
- controlling aggravating factors
 - ❖ fever, seizures- anticonvulsant
- Fluids – restrict only in SAH ($\text{Na} < 130$)

BACTERIAL MENINGITIS – prevention

- Patient – in separate room,
- Staff – with mask!
- **Antimicrobial prophylaxis** – after contact with meningococcal meningitis or H. influenzae-meningitis:
 - ❖ close contact – onset of with 24 hours
 - ❖ live in the same household, day-care center contacts
 - ❖ **Tubocin**, ciprofloxacin – 5 days
- **Vaccines (A,C,Y,W) – for travelers, UK**

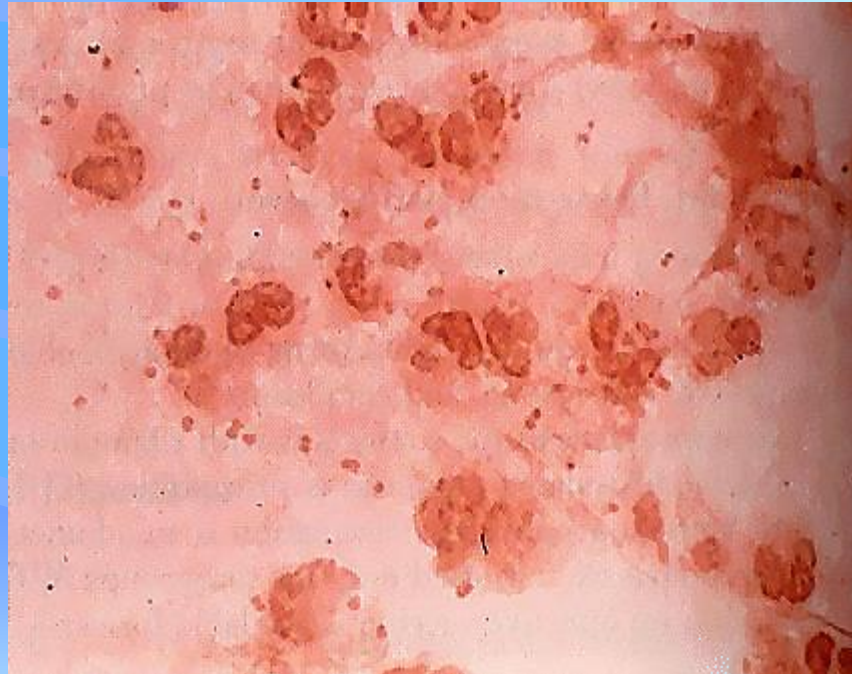
Meningococcal disease – definition

- **Acute infectious bacterial disease, manifested by:**
- **intoxication,**
- **meningitis,**
- **encephalitis,**
- **specific rash and**
- **changes in cerebrospinal fluid (CSF).**

Meningococcal disease – etiology

- Neisseria meningitidis – Gram (-) diplococci.
- 13 serological group. Most important – groups A, B, C and W135.
- Low resistance in the environmental.

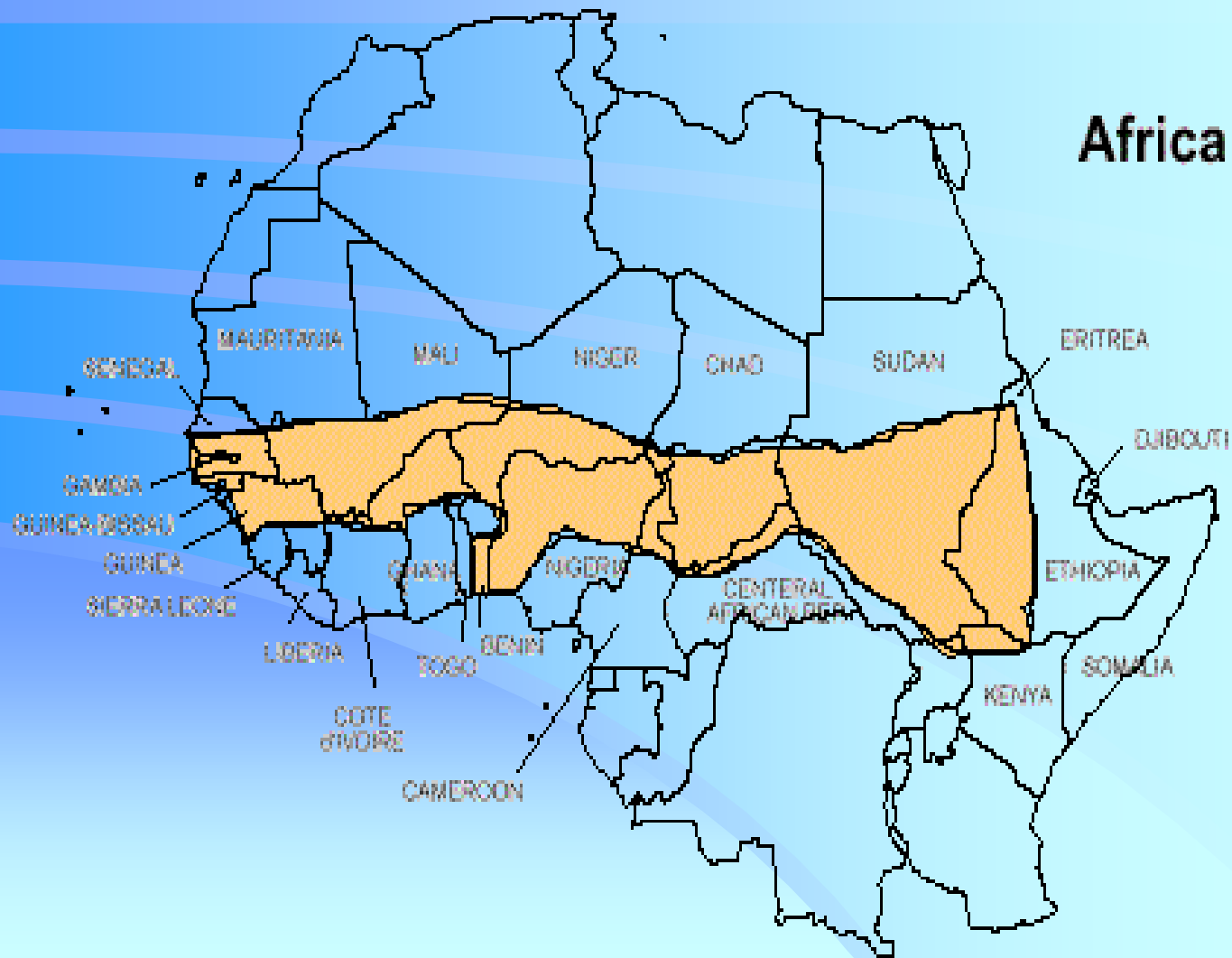
Neisseria meningitidis



Meningococcal disease – epidemiology

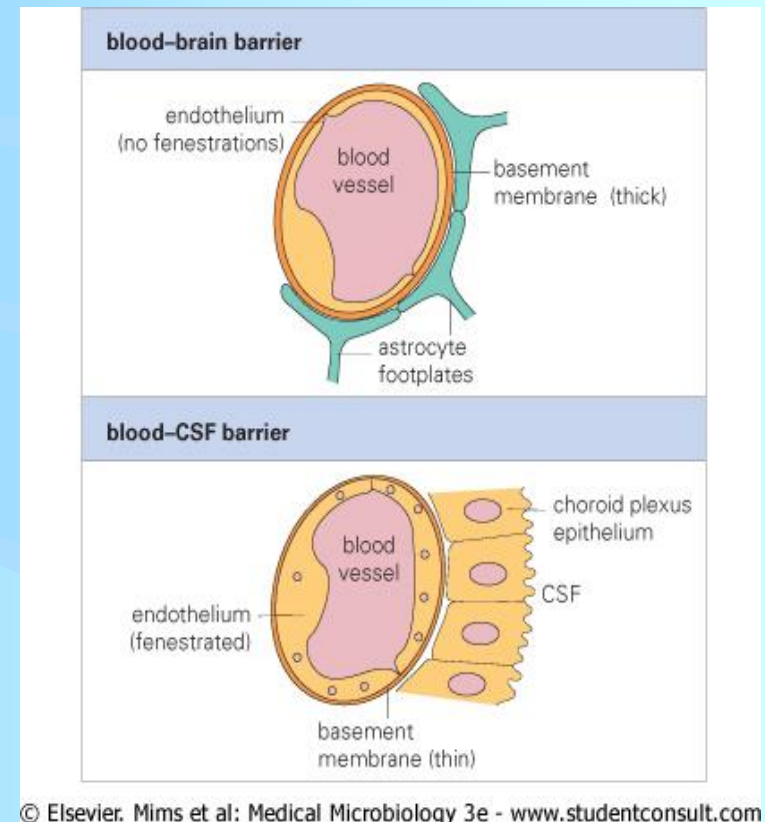
- **Source of infection** – man – patient or carrier.
- **Route of transmission** – respiratory, less common by direct contact.
- **Great significance** – health carriers and patients with meningococcal meningitis.
- Worldwide distribution.
- **Winter and spring.**

African meningitis belt



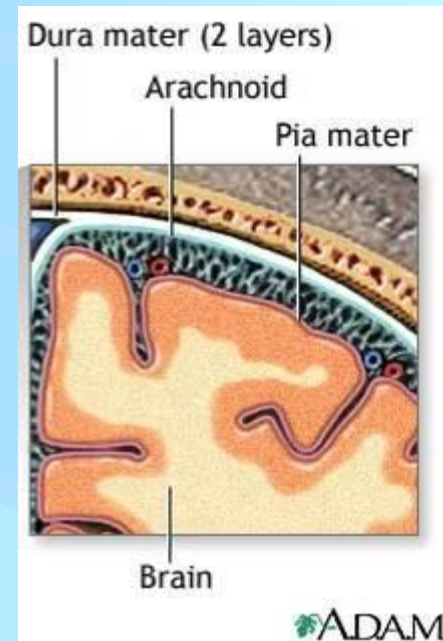
Meningococcal disease – pathophysiology

- **Portal of entry – nasopharynx.** The pathogen multiplies in mucosa and catarrhal inflammation appears →
- **regional lymph nodes** →
- **blood – bacteremia** → 1, 2, 3
- **1 – skin** – specific hemorrhagic-necrotic rash
- **2** – penetrates through blood-CSF barrier and reach to the **CSF space** → **invades the meninges (pia mater) and purulent meningitis appears**
- **3** – later invasion of brain tissue (encephalon) is possible and **purulent meningoencephalitis** appears.
- Some bacteria are destroying and **endotoxin** releases.
- **The complement** activates, **interleukins** (mediators of inflammatory process) are producing.



Meningococcal disease – pathophysiology

- 1) Endotoxin stimulates the sympathetic → **spasm of the vessels and increased permeability of the cells' membranes.**
- 2) Endotoxin stimulates plexus chorioideus → **increased production of cerebrospinal fluid.**
- In result of 1) and 2) disorders in circulation of CSF appear followed by intra- and extracellular brain edema.



Meningococcal disease – clinical forms

- Asymptomatic carriage – 1%
- Meningococcal nasopharyngitis
- Meningococcal meningitis / meningoencephalitis
- Meningococemia (meningococcal sepsis)
- Fulminant meningococcal sepsis (syndrome of Waterhouse-Friderixen) – the most severe form – septic shock.

Meningococcal disease – clinical manifestations

- Incubation period – 1-4 days (2-10) days
- Strong headache
- Sudden vomiting without relief
- Photophobia
- Hyperacusis
- Hyperesthesia
- Excitation
- Seizures
- Bulging fontanel
- Symptom of Lesage
- **Sindrome of meningeal irritation.**

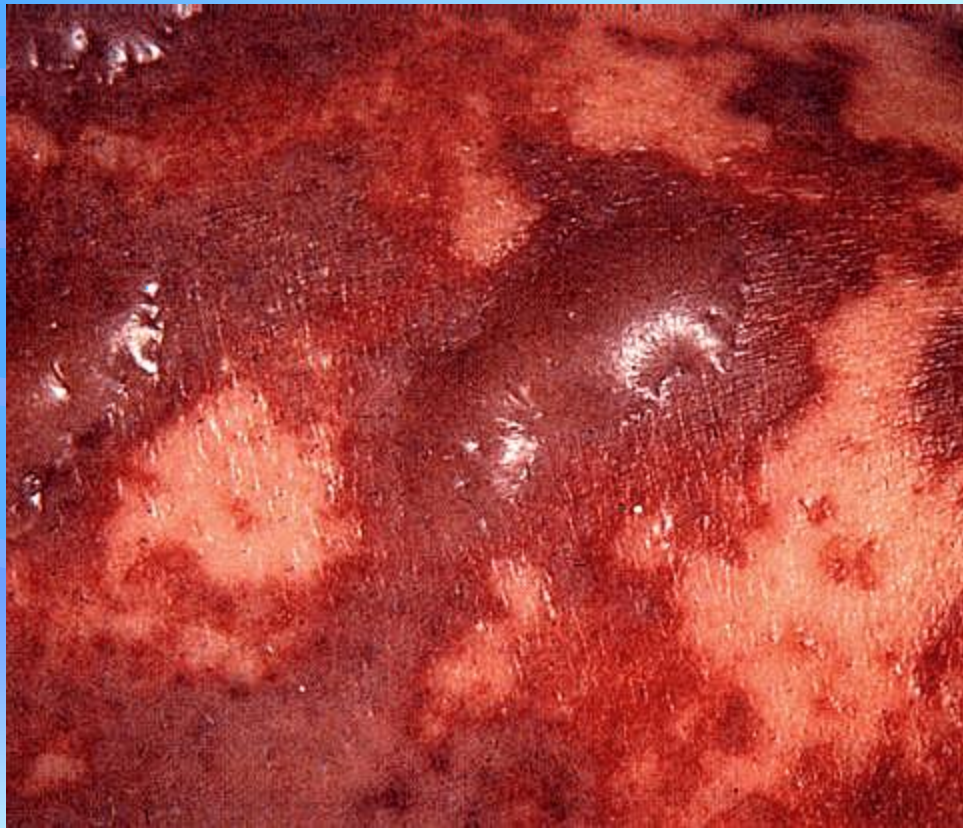
Meningococemia



Meningococemia



Meningococemia



Meningococemia



Meningococcal disease – laboratory investigations

- Blood cells – leucocytosis with neutrophilia and left shift; lymphopenia.
- Increased erythrocytes sedimentation rate (ESR), increased c-reactive protein and fibrinogen levels.
- CSF – turbid CSF with polymorphonuclear pleocytosis↑, proteinorachia↑↑, glucosa↓↓, *bacteria*.

Meningococcal disease – diagnosis

- Clinico-epidemiological.
- Microbiological – **culture** – isolation of agent in CSF and blood.

Meningococcal disease – management and treatment

- **Etiologic treatment** – cephalosporins 3rd generation (ceftriaxon).
- **Supportive treatment** – diuretics (Mannitol 10% i.v. – 1,0-1,5-2,0 g/kg/24 h 3 to 5 days, furosemide 2-3 mg/kg/24 h), corticoids (dexamethazone – 0,2-0,5 mg/kg/24 h, methylprednisolon – 1-2 mg/kg/24 h), Human albumin 20%.
- **Blood products** – plasma, immunovenin.
- **Anticonvulsive** – diazepam, phenobarbital
- **Antipyretics**
- **Vitamins (B2, B6, C).**
- **Oxygenation.**
- **Intensive monitoring of vital functions.**
- **Care.**

Meningococcal disease – prophylaxis

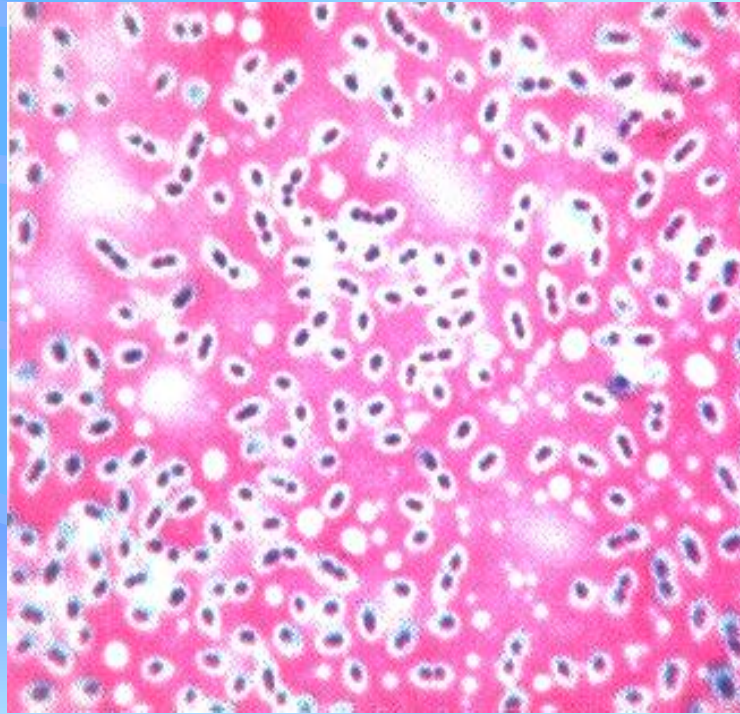
- At epidemic risk and for travelers – immunization by **combined vaccine** (A, B and W-strains).
- Isolation.
- Contact person – culture of nasopharyngeal smear.
- **Antimicrobial chemotherapy:**
 - ❖ At close contact with patient in the same household, day-care center contacts – initiation within 24 hours!!!
 - ❖ **Tubocin**, macrolides, ciprofloxacin – 5 days.

Other bacterial meningitis and meningoencephalitis

1. Pneumococcal meningitis and meningoencephalitis – acute bacterial infection of CNS with severe intoxication and meningeal syndrome, disturbed consciousness and pathologic changes in CSF.

- Etiology – *Streptococcus pneumoniae*.

Streptococcus pneumoniae



Other bacterial meningitis and meningoencephalitis

- Epidemiology:
- Source of infection – patient or carrier.
- Respiratory route of transmission.
- Predisposing factors – common-cold, head-trauma, immunosuppression, alcohol abuse, diabetes mellitus, chronic obstructive pulmonary disease, breast-feeding- and elder ages.
- Seasonal peak – autumn-winter.

Other bacterial meningitis and meningoencephalitis

- Pathophysiology:
 - ❖ Portal of entry: in primary pneumococcal meningitis – upper respiratory tract; in secondary – purulent inflammatory foci (otitis media), mastoiditis, sinusitis, bronchiectasia etc. On the portal of entry pneumococci multiply →
 - ❖ Enter into the circulation – bacteremia appear →
 - ❖ Reach to arachnoids' space and meninges →
 - ❖ Inflammation appears – meningitis. If pneumococci penetrate into encephalon – meningoencephalitis appears.
 - ❖ Clinical symptoms – due to brain edema.

Other bacterial meningitis and meningoencephalitis

- Clinical manifestations:
 - ❖ Acute or sudden onset by fever, strong headache, vomiting.
 - Syndrome of meningeal irritation, excitation, seizures.
 - Stupor to coma.
 - Cranial palsies, rare peripheral paralysis.
 - Breathing arrhythmias, cardiocirculatory disorders – tachycardia or **bradycardia !!! Suggests cerebellar herniation!!! Due to life-threatening brain edema**); hypotension.

Other bacterial meningitis and meningoencephalitis

- Laboratory investigations:
- Blood cells – leucocytosis with neutrophilia and left shift; lymphopenia.
- Increased erythrocytes sedimentation rate (ESR), increased c-reactive protein and fibrinogen levels.
- CSF – turbid CSF with polymorphonuclear pleocytosis↑↑, proteinorachia↑↑, glucose↓↓ to 0 mmol/L, *bacteria*.
- Diagnosis – direct microscopy, latex-agglutination, culture of CSF.

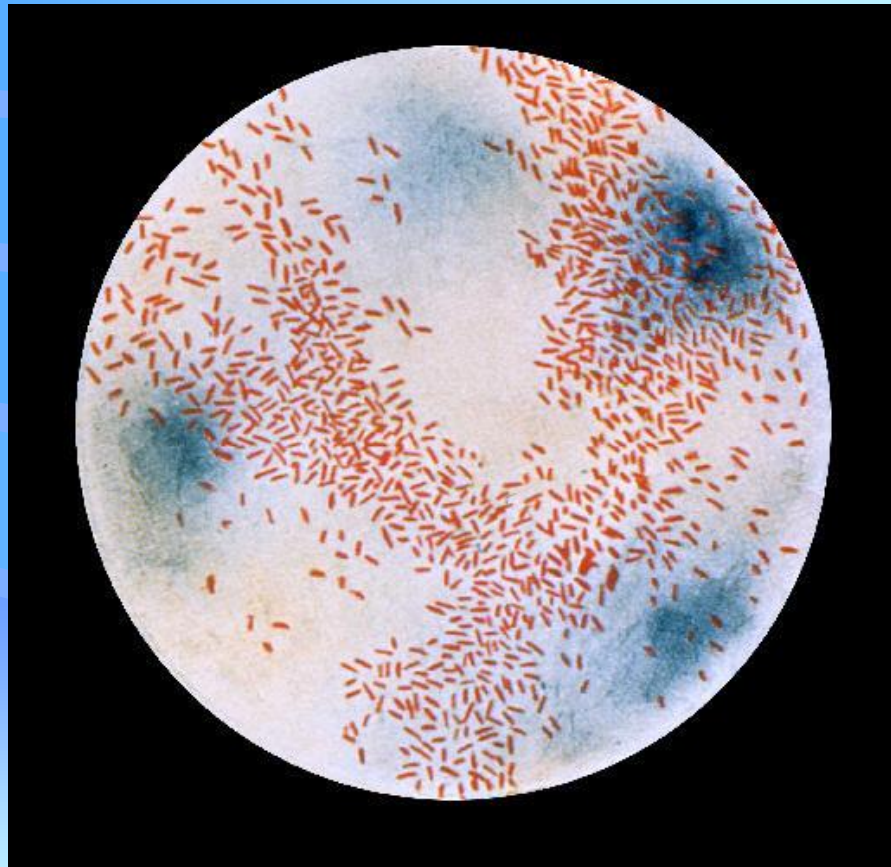
Other bacterial meningitis and meningoencephalitis

- Management and treatment:
- Antimicrobial therapy – cephalosporins 3rd generation (Ceftazidime); at resistance – vancomycin.
- Supportive – see treatment of meningococcal meningitis.

Other bacterial meningitis and meningoencephalitis

- 2. Haemophilus influenzae-meningitis and meningoencephalitis** – acute bacterial (rather primary) bacterial infection of CNS with severe intoxication and meningeal syndrome, deteriorated consciousness and changes in CSF.
- Etiology – Haemophilus influenzae.

Haemophilus influenzae



Other bacterial meningitis and meningoencephalitis

- Epidemiology:
 - ❖ Source of infection – patient or carrier.
 - ❖ Respiratory route of transmission.
 - ❖ More often – primary meningitis (or meningoencephalitis); secondary – in the course of respiratory infection.
 - ❖ Highest risk – in children under 5 years age.
 - ❖ Uncommon in adults – with diabetes mellitus, neoplasm, leukemia, lymphoma, alcoholism etc.

Other bacterial meningitis and meningoencephalitis

- Patophysiology:
 - ❖ In primary meningitis/meningoencephalitis: portal of entry (upper respiratory tract) → regional lymph nodes – multiplying → destroying by neutrophils – releasing of endotoxin → endothelial damage – penetration through the blood-CSF and blood-brain barrier → meningitis/meningoencephalitis.
 - ❖ In secondary meningitis/meningoencephalitis – spreading of the causative agent from inflammatory foci (otitis, sinusitis, cranial trauma) to CNS by blood/lymph circulation or direct penetration.

Other bacterial meningitis and meningoencephalitis

- Clinical manifestations:
 - ❖ Acute or sudden onset by fever, strong headache, vomiting, photophobia.
 - Syndrome of meningeal irritation, excitation, seizures.
 - Disturbed consciousness to coma.
 - Cranial palsies, rare peripheral paralysis.
 - Breathing arrhythmias, cardiocirculatory disorders – tachycardia or **bradycardia (!!! Suggests cerebellar herniation!!! Due to life-threatening brain edema)**; hypotension.
 - Uncommon sepsis-syndrome – hepatosplenomegaly, pneumonia, hemorrhagic diathesis, endotoxic shock.

Other bacterial meningitis and meningoencephalitis

- Laboratory investigations:
- Blood cells – leucocytosis with neutrophilia and left shift; lymphopenia.
- Increased erythrocytes sedimentation rate (ESR), increased c-reactive protein and fibrinogen levels.
- CSF – turbid CSF with polymorphonuclear (>80%) pleocytosis↑↑, proteinorachia↑↑, glucose↓↓ to 0 mmol/L, *bacteria*. Longer duration of changes in CSF.
- Diagnosis – direct microscopy, latex-agglutination, culture of CSF.

Other bacterial meningitis and meningoencephalitis

- Management and treatment:
- Antimicrobial therapy – cephalosporins 3rd generation (Ceftazidime), alternative – Ampicillin.
- Supportive – dehydration (Mannitol, Furosemide), corticoids (Dexamethazone), Humman albumin 20%.
- Sedative (diazepam, phenobarbital), antipiretics.
- Vitamins.
- Oxygenation.
- Intensive monitoring, care.

Other bacterial meningitis and meningoencephalitis

- 3. Streptococcal meningitis/meningoencephalitis** – more often secondary; in newborns – primary (contamination is from vaginal secretions during delivery). Common sequels. Antimicrobial therapy – cephalosporins 3rd generation.
- 4. Staphylococcal meningitis/meningoencephalitis** – one of clinical forms of staphylococcal disease and in the course of staphylococcal pyoderma in newborns. Antimicrobial therapy – cephalosporins 3rd and 4th generations, imipenems, rifampicin, quinolones.
- 5. Enterobacterial meningitis/meningoencephalitis.** Causative agents – Enterobacteriaceae (E. coli, Klebsiella, Salmonella, Proteus) in the course of severe intestinal infections or sepsis. Severe diseases with lifelong sequels. Antimicrobial therapy – cephalosporins 3rd and 4th generations combined with amikacin, quinolones.

Nonviral aseptic meningitis and meningoencephalitis

1. Leptospirosis meningitis and meningoencephalitis.

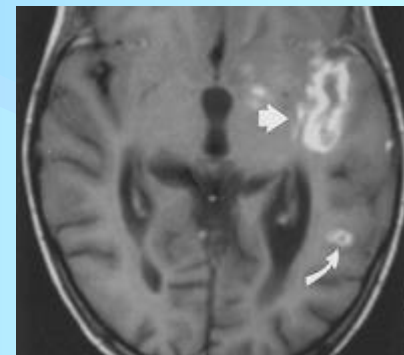
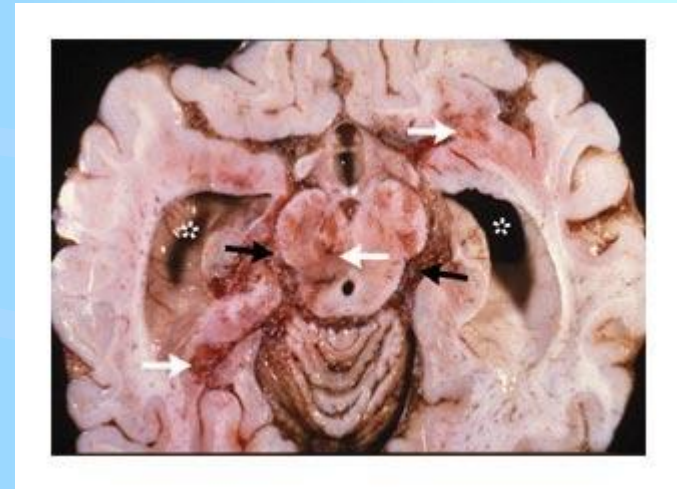
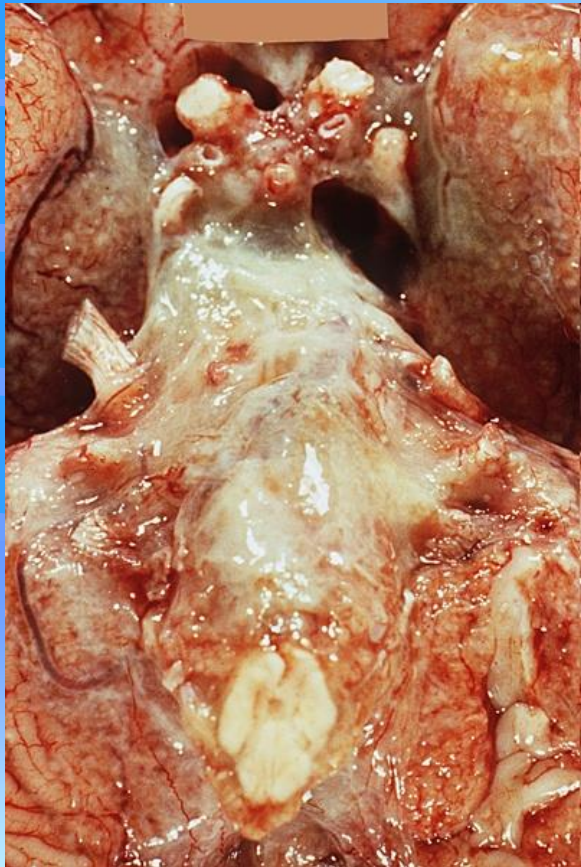
2. Tuberculous meningitis and meningoencephalitis.

CSF – protein is increased in rate more than is increased number of leucocytes – **protein-cells dissociation**; pleocytosis – tens to hundreds leucocytes (nearly 50:50% polymorphonuclear and mononuclear cells); low glucose level.

3. Listeria monocytogenes-meningitis and meningoencephalitis.

4. Infectious polyneuritis and polyradiculoneuritis.

Tuberculous meningitis



**THANK YOU
FOR YOUR ATTENTION !**