NEUROINFECTIONS

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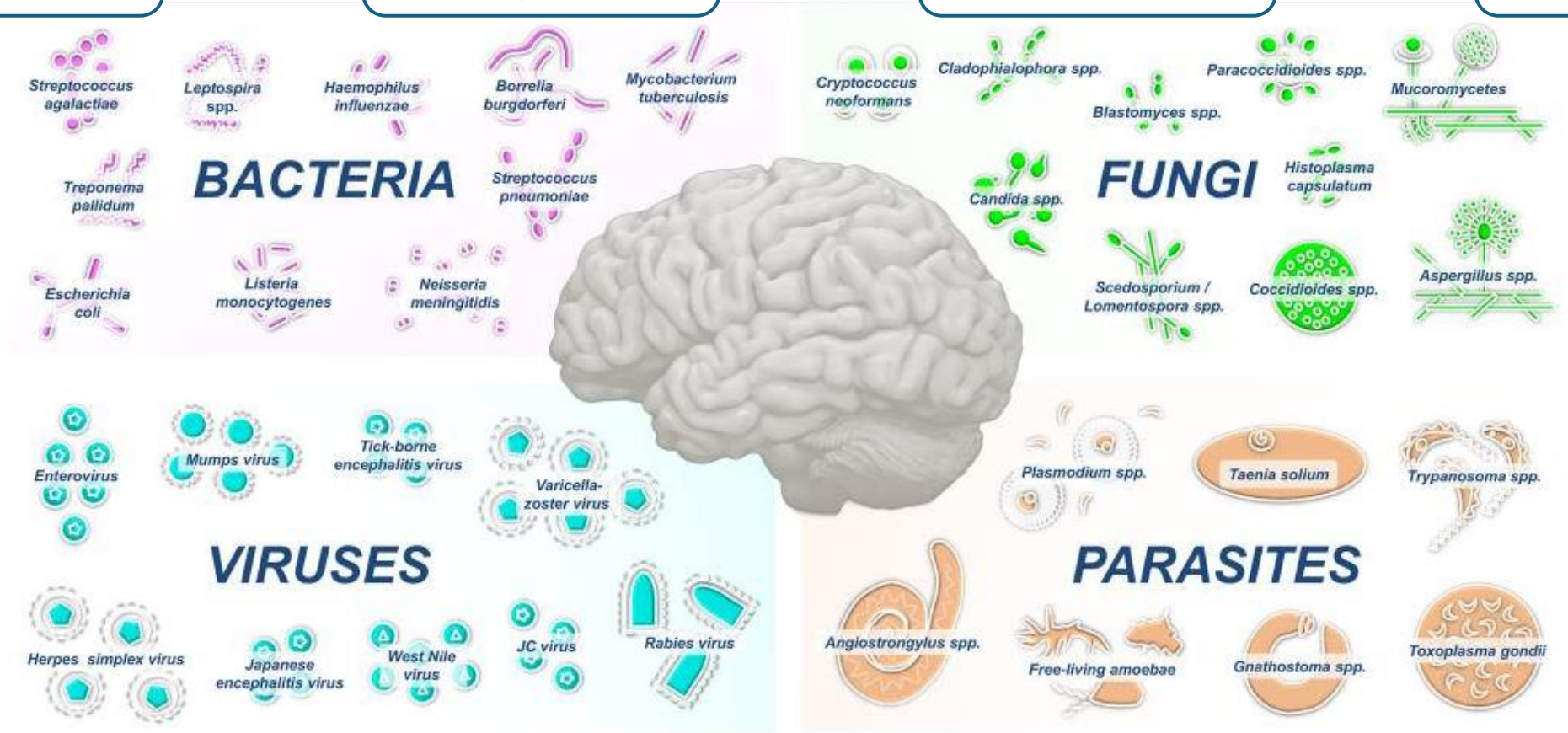
Microorganisms on Earth	Microorganisms in the human body	Pathogenic microorgansims for humans	Pathogenic microorganisms for the nervous system
Tens of nonilions (10^{30})	≈ 39 trillion (10^{12})	≈1400	150-200

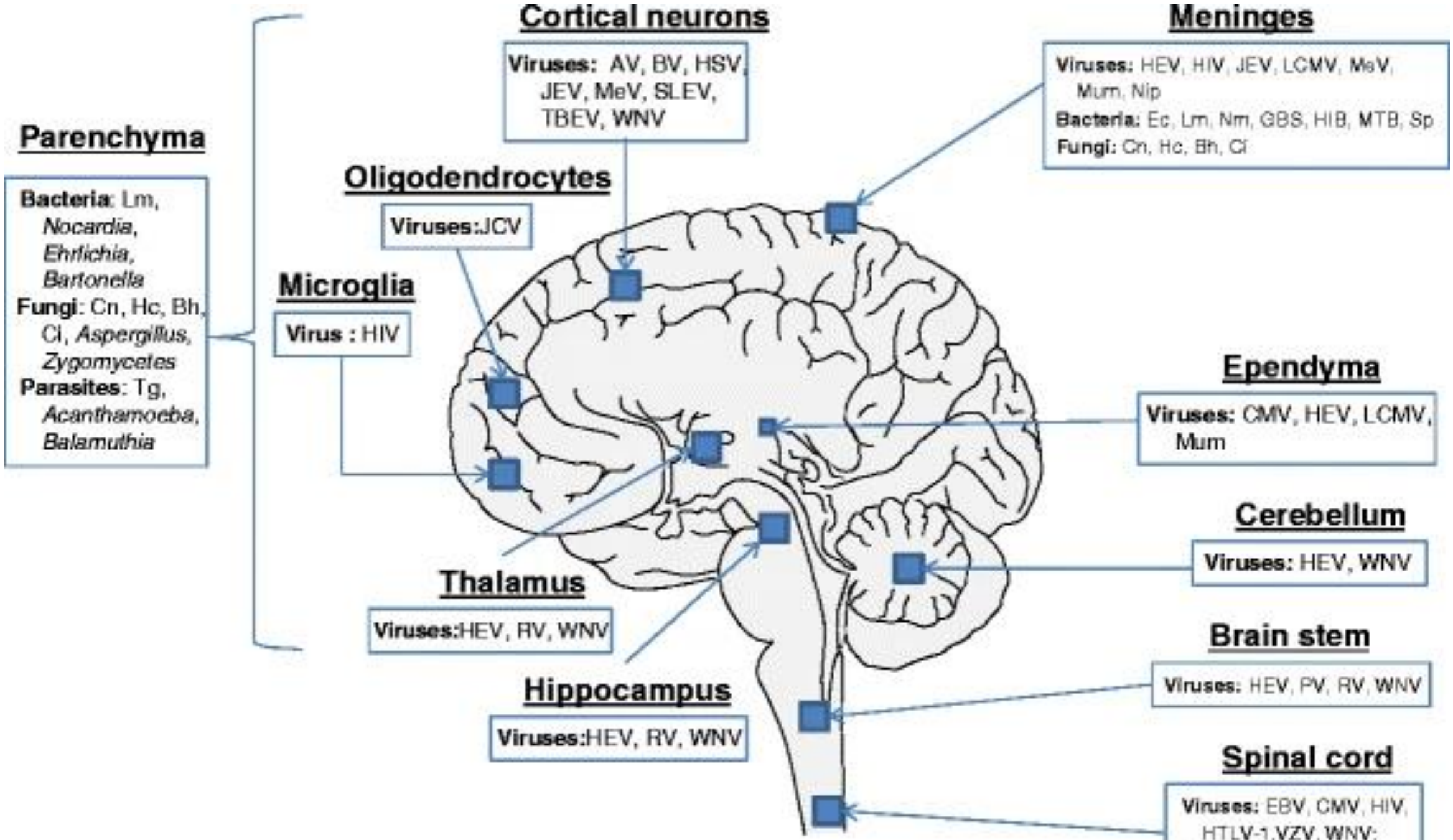


ROUTES OF TRANSMISSION OF PATHOGENS

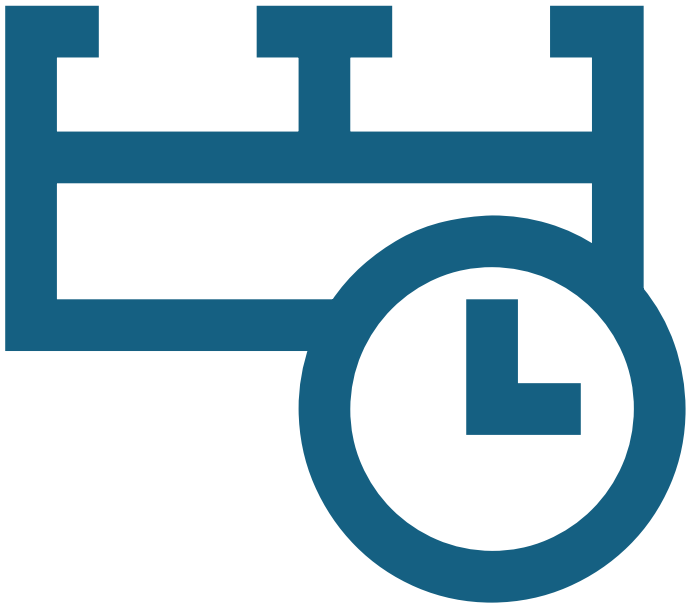
HUMANS	ANIMALS	BIRDS	INSECTS	SOIL	FOOD	WATER
N. Meningitidis	**Cat-***T.gondii*	**JCV**	**Mosquito -** West Nile virus, Malaria, Zika	**Fungi** (criptococcus, aspergilus, candida, mucormicosis, histoplasmosis)	***Toxopl. gondii***	***Naegleria flowery***
HSV	**Pork-**T.*Solium*	**Criptoccocus**	**Tick –** Lyme dis., tick-borne encephalite	***Clostridium tetani***	***Taenia Solium***	**Ameba**
Enteroviruses	**Mouse –** *Armstrong virus*	**Histoplasma**			***Echinoccocus***	
T. Pallidum	**Fox, dog, bat-** *Rabies virus*				***Brucella***	
E. coli					***Listeria monocitogenes***	
					Clostr.botulini	

“TROJAN HORSE” MECHANISM OF PATHOGENS

PATHOGEN	TYPE	"TRANSPORTER" CELL	CNS INVOLVMENT
HIV	Virus	Monocite, macrofage	Encephalopathy
JC virus	Virus	B limfocite	PML
CMV	Virus	Monocite	Encephalitis
Listeria monocytogenes	Bacteria	Monocite	Meningitis, abcess
M. tuberculosis	Bacteria	Macrofage	Meningitis
Toxoplasma gondii	Parasite	Monocite	Encephalitis
Trypanosoma brucei	Parasite	Leucocite	Encephalitis
Cryptococcus neoformans	Fungus	Monocite	Meningitis


Cortical neurons
Viruses: AV, BV, HSV, JEV, MeV, SLEV, TBEV, WNV
Meninges
Viruses: HEV, HIV, JEV, LCMV, MeV, Mum, Nip
Bacteria: Ec, Lm, Nm, GBS, HIB, MTB, Sp
Fungi: Cn, Hc, Bh, Ci
Parenchyma
Bacteria: Lm, Nocardia, Ehrlichia, Bartonella
Fungi: Cn, Hc, Bh, Ci, Aspergillus, Zygomycetes
Parasites: Tg, Acanthamoeba, Balamuthia
Oligodendrocytes
Viruses: JCV
Microglia
Virus : HIV
Ependyma
Viruses: CMV, HEV, LCMV, Mum
Cerebellum
Viruses: HEV, WNV
Thalamus
Viruses: HEV, RV, WNV
Brain stem
Viruses: HEV, PV, RV, WNV
Hippocampus
Viruses: HEV, RV, WNV
Spinal cord
Viruses: EBV, CMV, HIV, HTLV-1, VZV, WNV;
Bacteria: Tp

TIMELINE OF DISCOVERIES AND ADVANCES IN NEUROINFECTIONS



1685 – *Thomas Willis* (the father of neuroanatomy) described for the first time **inflammation of the meninges** in his medical works

1887 — *Neisseria meningitidis* identified (Anton Weichselbaum)

1928 — Discovery of penicillin (Alexander Fleming)

1944 — Introduction of antibiotic therapy

1952 — First description of herpetic encephalitis

1970 — First meningococcal vaccines

2000 — PCR in CSF diagnostics

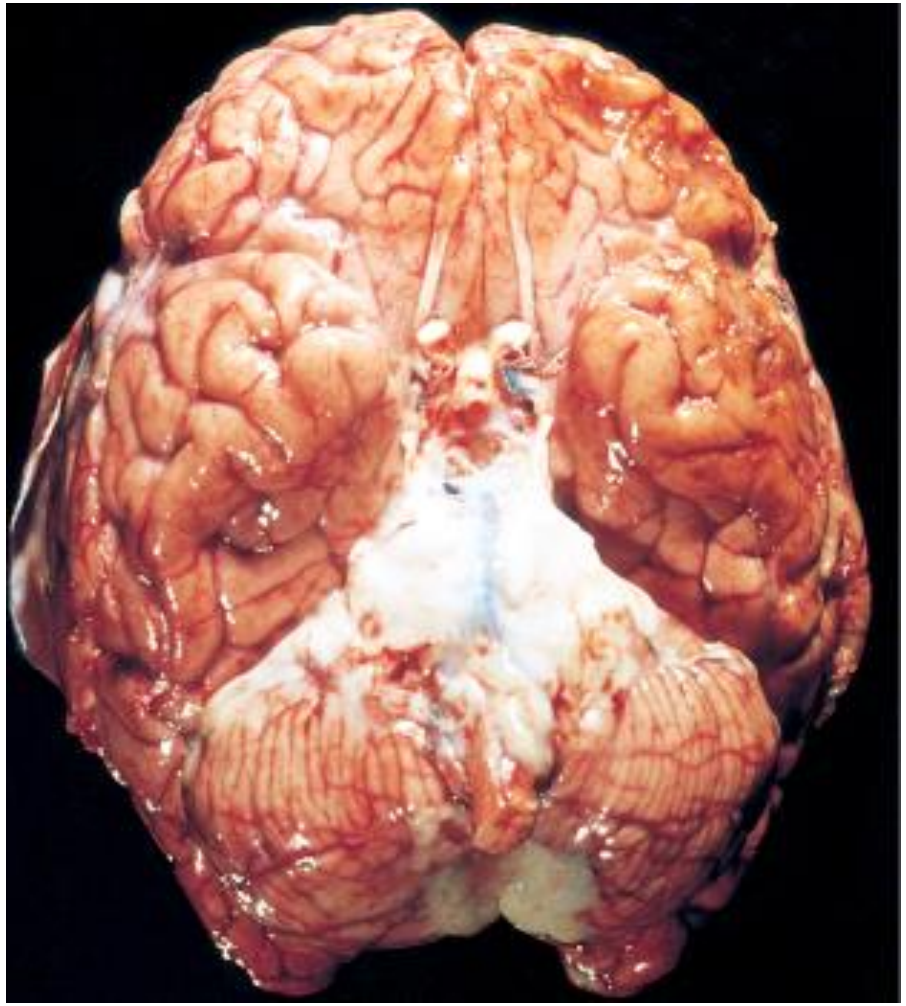
2010–2020 – Development of multiplex PCR panels, genomic sequencing, and advanced neuroimaging (MRI, DWI) for early diagnosis.

2020+ — Emerging neuroinfections (Zika, SARS-CoV-2)

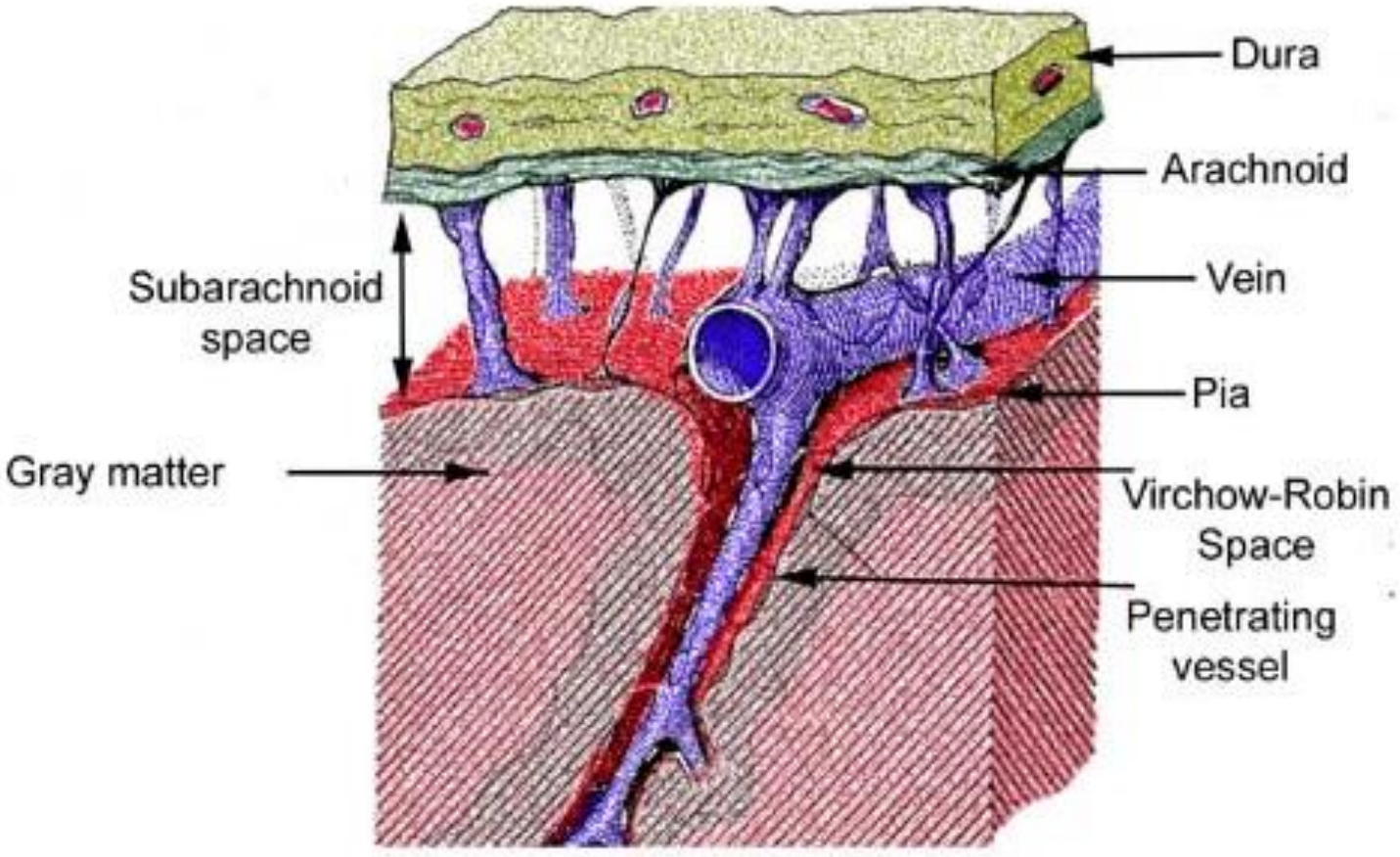
HISTORICAL OVERVIEW

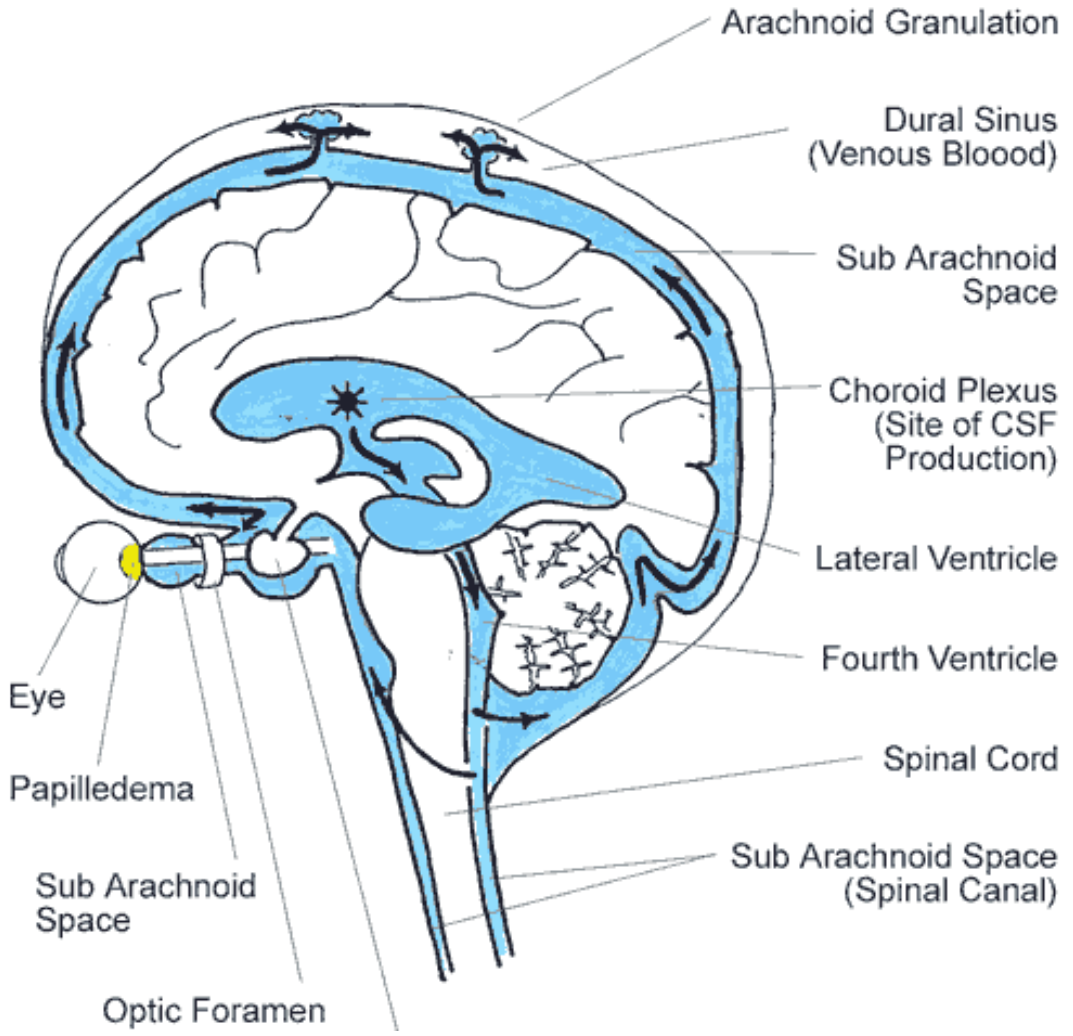
- Before antibiotics → meningitis = *fatal disease* (>90% mortality)
- With antibiotics → *treatable emergency*, yet >50% cases with sequelae
- **Conjugate vaccines** drastically reduced pediatric cases
- **Acyclovir** therapy decreased mortality in herpetic encephalitis from 70% → <20%
- **Globalization & climate change** → emerging neuroinfections (arboviruses, zoonoses)

MENINGITIS



ANATOMY


Dura
Arachnoid
Subarachnoid space
Vein
Pia
Gray matter
Virchow-Robin Space
Penetrating vessel


Arachnoid Granulation
Dural Sinus (Venous Bloood)
Sub Arachnoid Space
Choroid Plexus (Site of CSF Production)
Lateral Ventricle
Fourth Ventricle
Spinal Cord
Sub Arachnoid Space (Spinal Canal)
Eye
Papilledema
Sub Arachnoid Space
Optic Foramen

DEFINITIONS

MENINGITIS:

Inflammation of the **leptomeninges** (*arachnoid* & *pia mater*) with infection of **cerebrospinal fluid (CSF)** within the subarachnoid space of the brain, spinal cord, and ventricular system.

MENINGISMUS:

Symptoms and signs resulting from meningeal irritation caused by non-inflammatory conditions (subarachnoid hemorrhage, neoplasms, increased ICP …), in the absence of inflammatory changes in the cerebrospinal fluid.

MENINGITIS: CLINICAL SIGNIFICANCE

- **Medical emergency!** Delay in treatment can be fatal
- **Mortality rate:** ≈ 25% (bacterial meningitis)
- **High potential for CNS destruction**
- One of the most **treatable CNS diseases**
- **Diagnostic challenge:** onset may be fulminating or insidious; signs can be atypical
- **Incidence:** 2.5–6 cases per 100,000 population per year

MENINGITIS: CLASSIFICATION

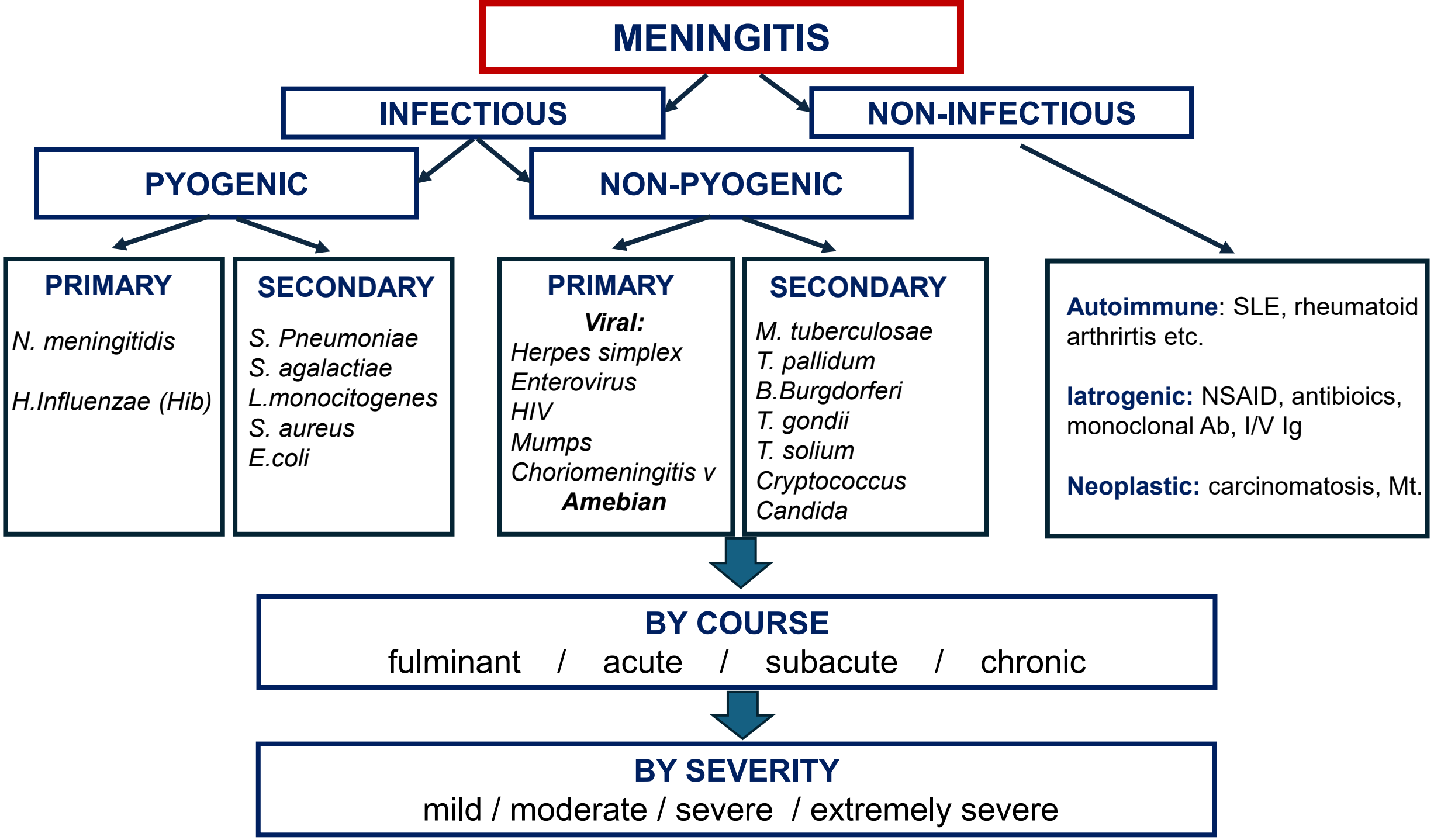
A. By type of inflammation: pyogenic, septic
non-pyogenic, aseptic

B. By pathogenesis: primary (meningococcal, amebic)
secondary

C. By etiology: bacterial, viral, fungal, protozoal, mycoplasmal, amebic

D. By course: fulminant, acute, subacute, chronic

E. By severity: mild, moderate, severe, extremely severe


MENINGITIS
INFECTIOUS
NON-INFECTIOUS
PYOGENIC
NON-PYOGENIC
PRIMARY
N. meningitidis
H.Influenzae (Hib)
SECONDARY
S. Pneumoniae
S. agalactiae
L.monocitogenes
S. aureus
E.coli
PRIMARY
Viral:
Herpes simplex
Enterovirus
HIV
Mumps
Choriomeningitis v
Amebian
SECONDARY
M. tuberculosae
T. pallidum
B.Burgdorferi
T. gondii
T. solium
Cryptococcus
Candida
Autoimmune: SLE, rheumatoid arthrirtis etc.
Iatrogenic: NSAID, antibioics, monoclonal Ab, I/V Ig
Neoplastic: carcinomatosis, Mt.
BY COURSE
fulminant / acute / subacute / chronic
BY SEVERITY
mild / moderate / severe / extremely severe

PYOGENIC MENINGITIS: ETIOLOGY

Risk and/or Predisposing Factor	Bacterial Pathogen
Neonate	Group B streptococci *E coli* *L monocytogenes*
Childhood–50 years	*S pneumoniae* *N meningitidis* *H influenzae* ⟶ Vaccine now exists
Age older than 50 years	*S pneumoniae* *N meningitidis* *L monocytogenes* Aerobic gram-negative bacilli
Immunocompromised state	*S pneumoniae* *N meningitidis* *L monocytogenes* Aerobic gram-negative bacilli
CSF shunts/neurosurgery	*Staphylococcus aureus* Coagulase-negative Staphylococci Aerobic gram-negative bacilli, including *Pseudomonas aeruginosa*
Skull fracture	*S pneumoniae* *H influenzae* Group A streptococci

PYOGENIC MENINGITIS :

the ways of spreading infection

1. **Hematogenous dissemination**

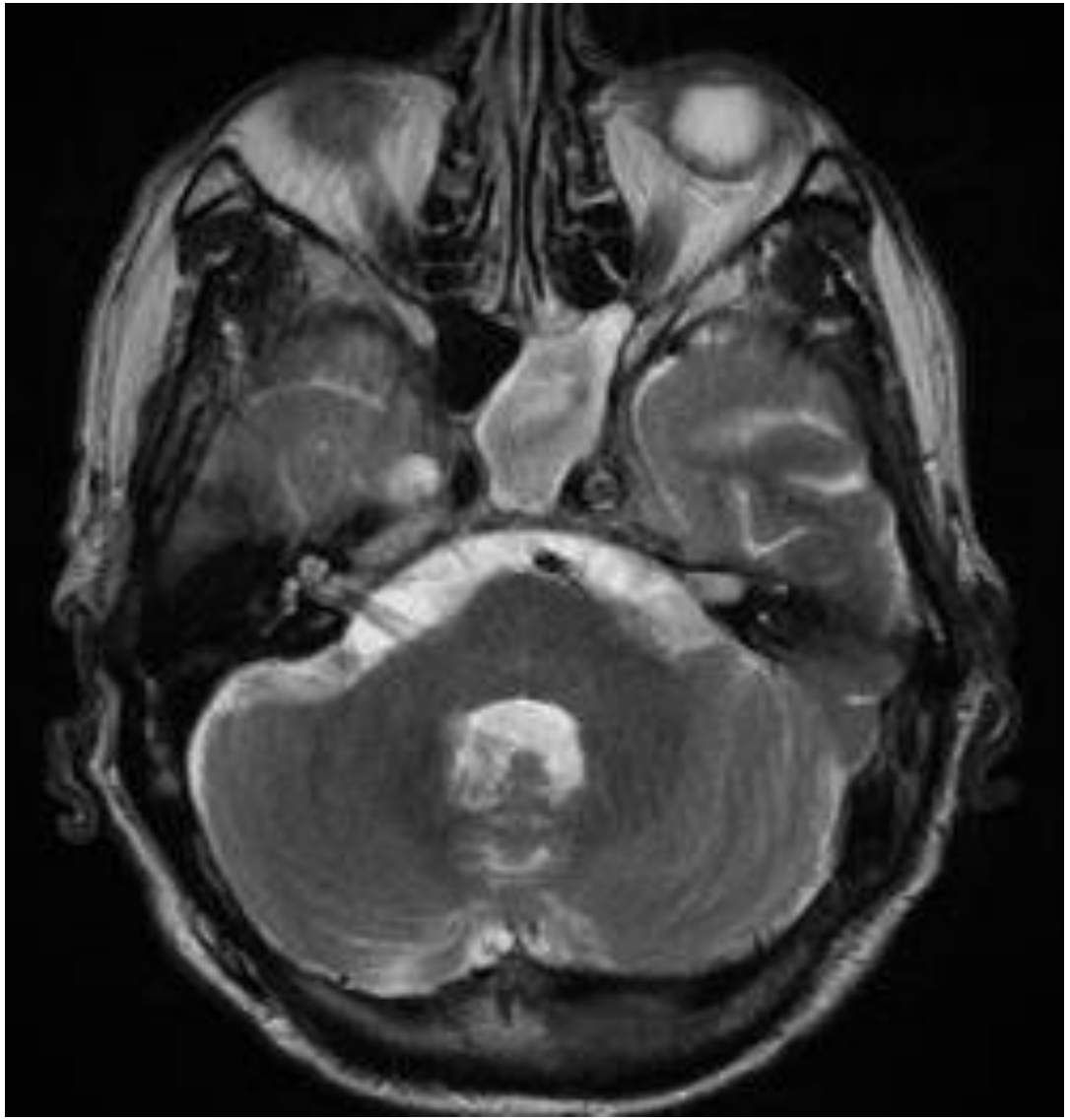
2. **Spread from adjacent foci:** paranasal sinuses, middle ear, mastoid

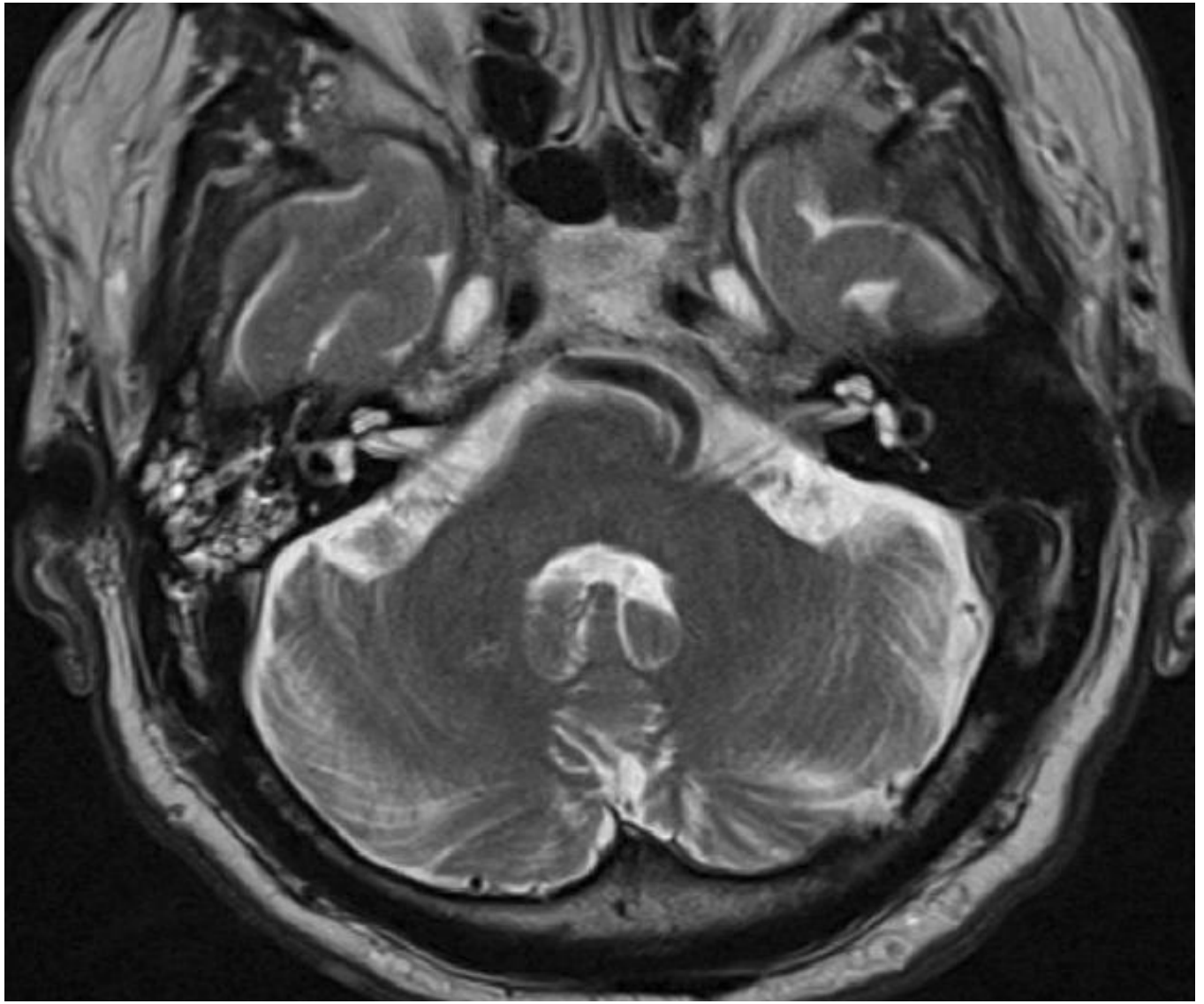
3. **Bone defects:**

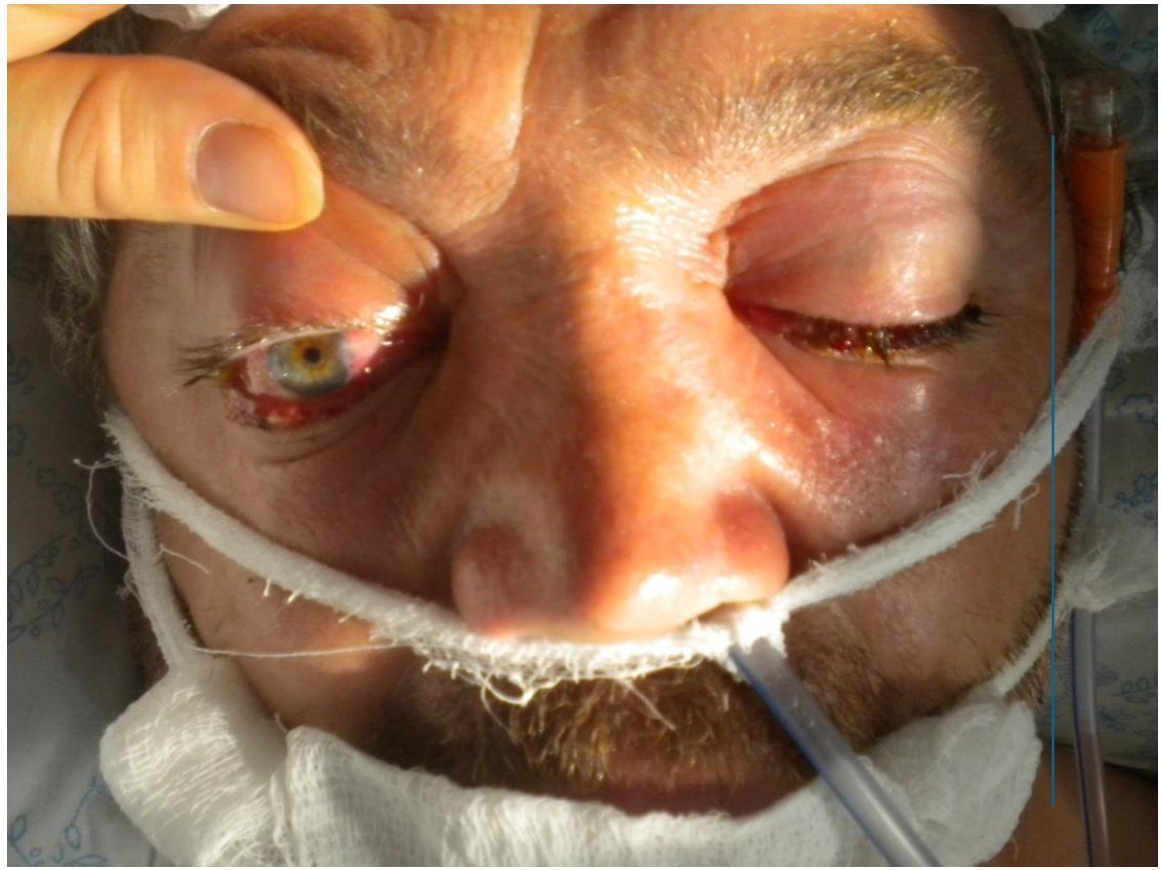
- ***congenital*** – neural tube closure defects (often cervical/lumbosacral)

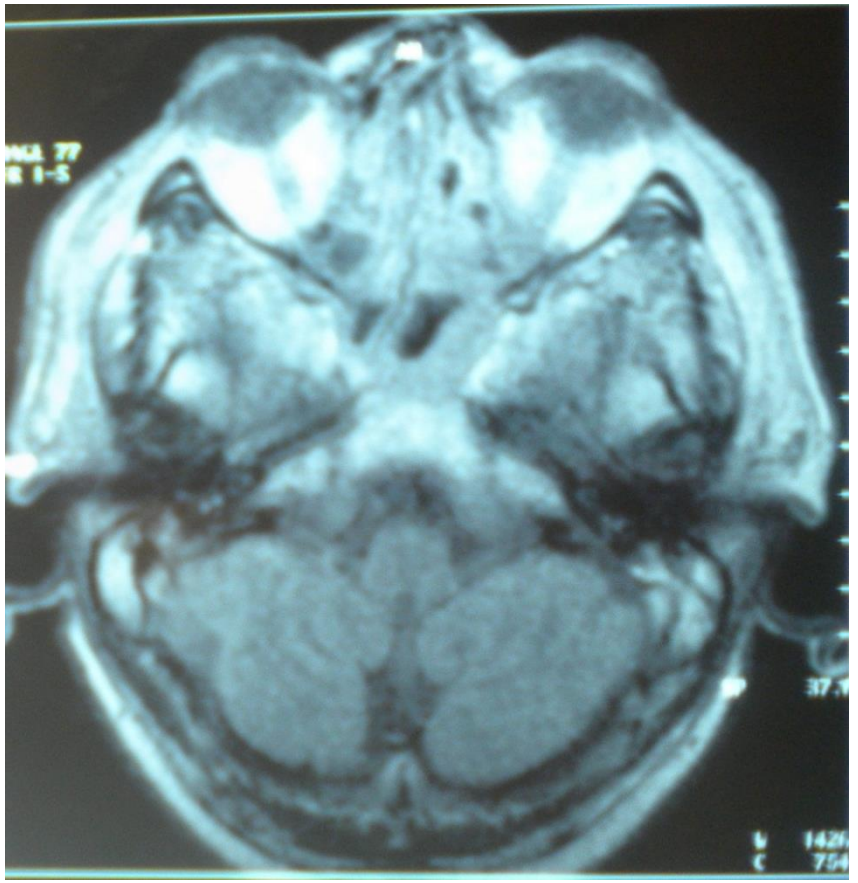
- ***acquired*** – skull base fractures, surgical procedures

PATHOGEN	WAY OF ENTRY
Neisseria meningitidis (meningococcus)	Nasopharynx
Streptococcus pneumoniae (streptococcus)	Nasopharynx or direct extension through skull fracture
Listeria monocytogenes	Gastrointestinal tract, placenta
Haemophilus influenzae	Nasopharynx
Staphylococcus aureus	Bacteremia, skin or foreign body
Staphylococcus epidermidis	Skin or foreign body









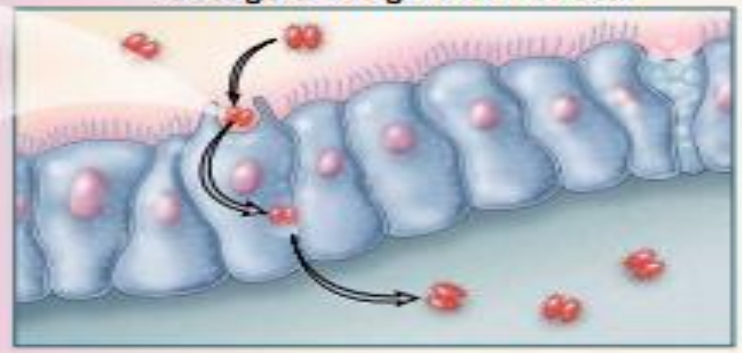
Nasopharyngeal mucosa

Blood

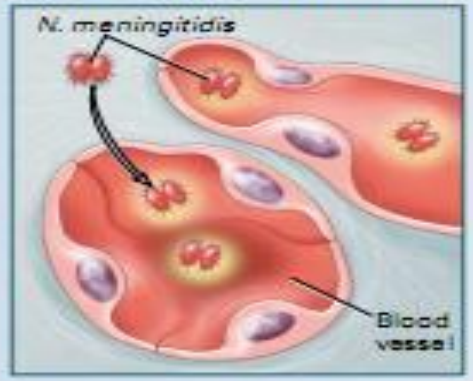
Cerebrospinal fluid

Attachment to and interaction with nasopharyngeal epithelium

Passage through the mucosa



Survival in the bloodstream



Factors affecting intravascular survival

- **Capsule:** protects against complement-mediated bacteriolysis and phagocytosis
- **Acquisition of iron from transferrin**

Endotoxin and other cell components

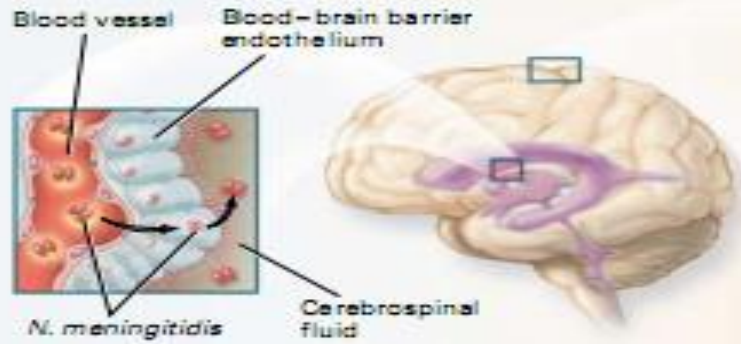
Host-cell cytokine production

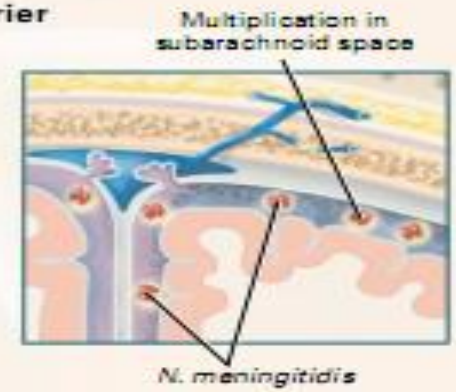
Alternative complement pathway

Inflammatory cytokines
tumor necrosis factor α, interleukin-1β, 6, 8)

Antiinflammatory cytokines
(interleukin-10)

Crossing of the blood–brain barrier





MENINGITIS: CLINICAL MANIFESTATIONS

MENINGEAL TRIAD

1) Fever

2) Neck stiffness

3) Altered mental status
(from confusion and irritability
to somnolence or coma)

1. General infection signs: fever, headache, photophobia, phonophobia, nausea, vomiting

2. Meningeal syndrome:

Neck stiffness

Kernig's sign

Brudzinski's signs (superior, middle, inferior)

3. CSF changes:

"Meningitic liquor syndrome":

- elevated cell count (pleocytosis)

- increased protein

MENINGEAL TRIAD: IMPORTANT CONSIDERATIONS

➢**Not always present:**
The triad is not consistently present, even in cases of bacterial meningitis, so a diagnosis cannot be ruled out if all three symptoms are absent.

➢**Atypical presentations:**
The classic triad may not be seen in very young, very old, or immunocompromised patients. Infants may present with different signs, such as a bulging fontanelle or unusual crying.

➢**A medical emergency:**
Meningitis is a serious condition that requires prompt medical evaluation, as it can be life-threatening.

SYMPTOMS	NON-PYOGENIC MENINGITIS	PYOGENIC MENINGITIS
Fever, headache, nausea, vomiting	++	+++
Altered consciousness	rare	frequent
Epileptic seizures	infrequent	++ (≈40%)
Cranial nerves palsies *(nn. VI, III, VII, VIII, II)*	TB, sifilis borreliosis, HIV	++
Hemiparesis, aphasia, high ICP	+	+++
Skin rash	HSV-1,2, VZV, enterovirus	meningococcus, staphylococccus, streptococcus

MENINGEAL SIGNS

NECK STIFFNESS

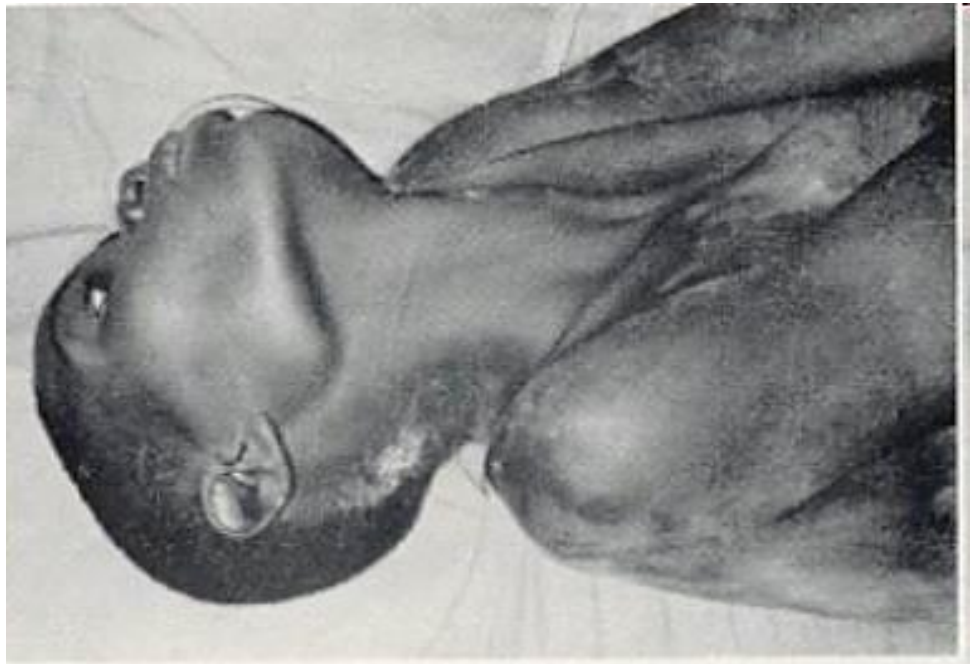
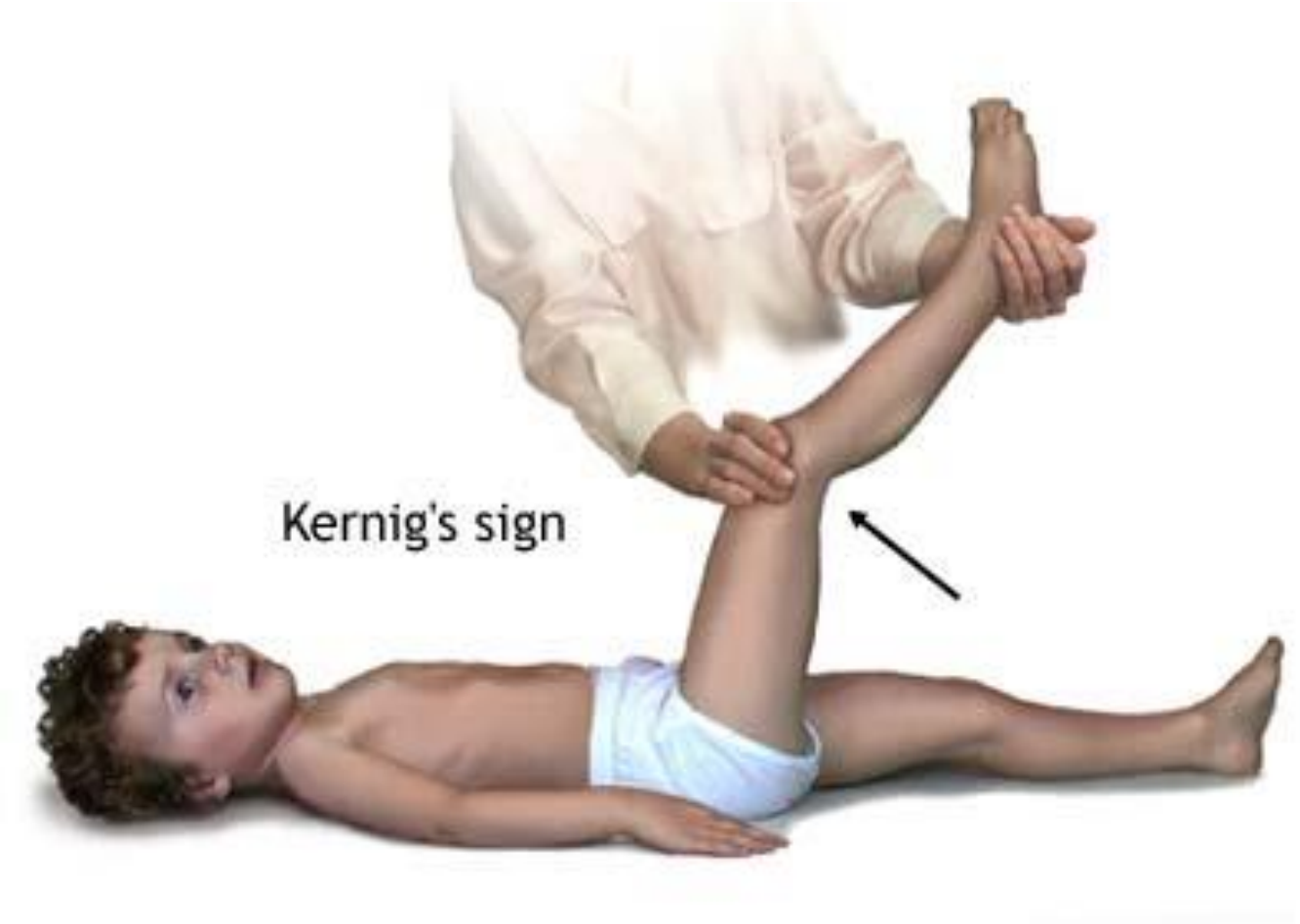
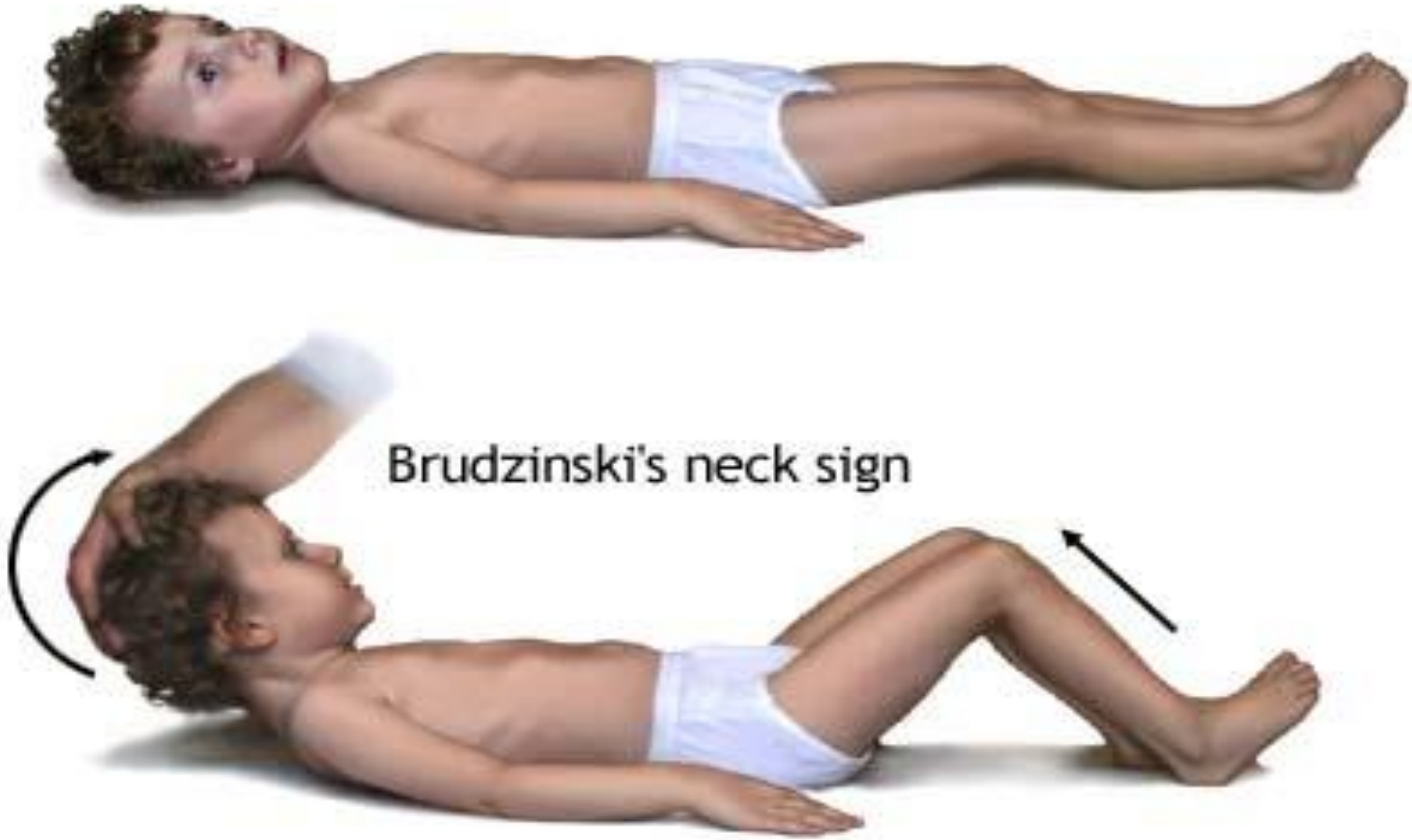


FIG. 33

Typhoid Meningitis.




Brudzinski's neck sign

MENINGITIS: DIAGNOSIS

Lumbar puncture & CSF analysis – crucial!

- Confirms diagnosis
- Identifies causative agent
- Allows antibiotic sensitivity testing
- Enables targeted therapy

MAJOR INDICATIONS FOR LP AND CSF ANALYSIS

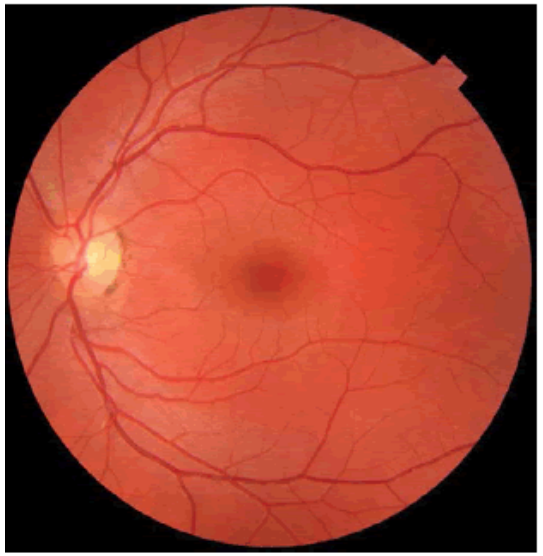
Urgent	Non-urgent	
For diagnostic purposes:	***For diagnostic purposes***:	***For therapeutic purposes:***
• Suspected **infectious meningitis or encephalitis**	• Multiple sclerosis • Guillain-Barré syndrome • Chronic inflammatory demyelinating polyneuropathy • Paraneoplastic syndromes • Neurosarcoidosis • Autoimmune encephalitis • Idiopathic intracranial hypertension • Carcinomatous meningitis • Normal pressure hydrocephalus • CNS syphilis • Leptomeningeal CNS lymphoma	• Spinal anesthesia • Intrathecal administration of chemotherapy • Intrathecal administration of antibiotics • Injection of contrast media for myelography or for cisternography • Therapeutic drainage of CSF
• Suspected **subarachnoid hemorrhage** in a patient with a negative CT scan		

CONTRAINDICATIONS FOR LP

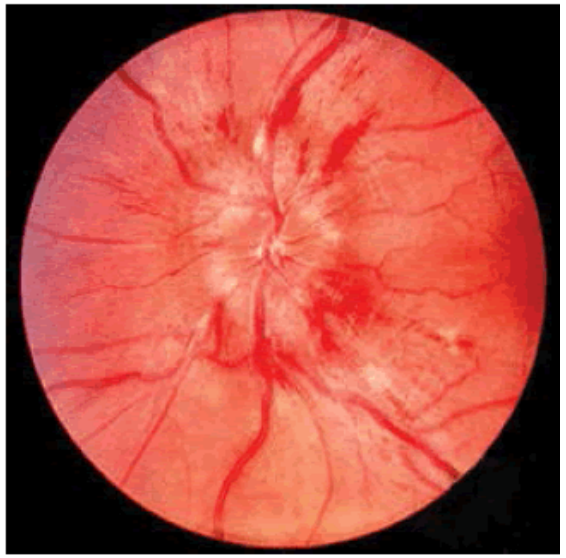
1. Suspected **raised intracranial pressure** (ICP) with risk for cerebral herniation due to obstructive hydrocephalus, cerebral edema, or other space-occupying lesion

2. **Thrombocytopenia** or other bleeding diatheses, including ongoing **anticoagulant therapy**

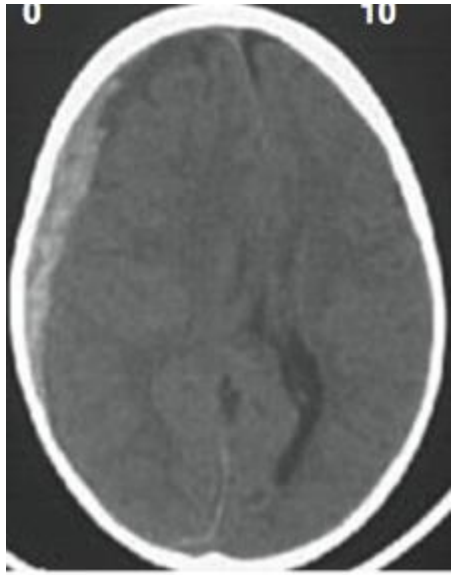
3. Suspected spinal epidural abscess or **skin/soft tissue infection** overlying the LP site

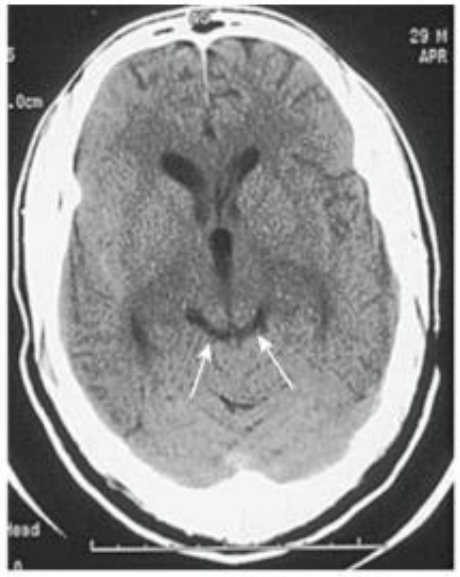


Normal optic disc

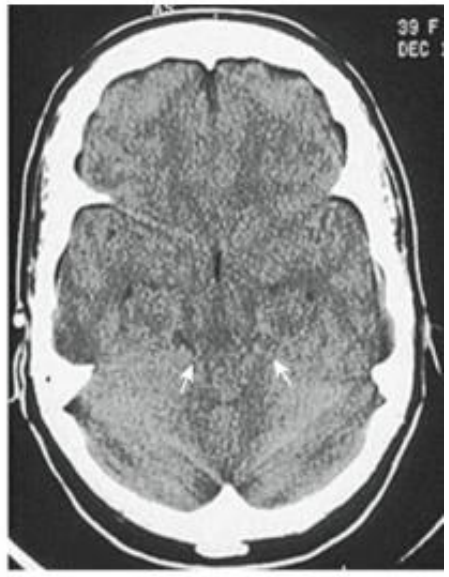


Papilledema





A

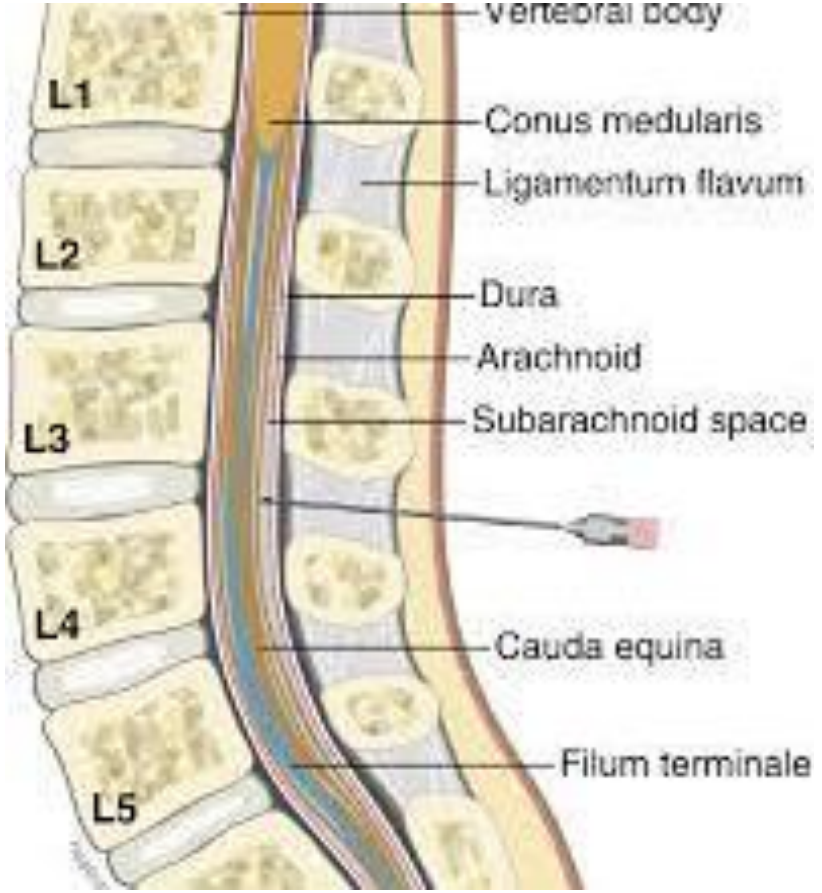


B

INDICATIONS FOR BRAIN CT BEFORE LUMBAR PUNCTURE

1. Glasgow Coma Score below 10
2. Focal neurological signs
3. Cranial nerve deficits
4. Papilloedema
5. New-onset seizures (in adults)
6. Severe immunocompromised state

TECHNIQUE FOR PERFORMING LUMBAR PUNCTURE



COMPLICATIONS OF LUMBAR PUNCTURE

- Post-LP headache
- Radicular or back pain
- Intracranial hypotension
- Infection
- Bleeding
- Cerebral herniation
- Cerebral vasoconstriction and encephalopathy syndromes
- Pneumocephalus

CSF VARIABLES	NORMAL VALUES	VIRAL (ASEPTIC) MENINGITIS	BACTERIAL (PYOGENIC) MENINGITIS
Color	**colorless**	**colorless**	**yellow-green**
Transparency	**clear**	**clear**	**cloudy**
Pressure (mm H2O)	**50-190**	**50-200**	**>200**
Proteins (g/l)	**0,15 – 0,33**	**0,66 - 1,0**	**1,0 - 5,0**
Cells /1 mcl	**5-7**	**300 – 900**	**1000–25 000**
-*lymphocytes*	**5**	**80%**	**15%**
-*neutrofils*	**2**	**20%**	**85%**
Glucose(mmol/l)	**2,4-4,4** (50-60% plasma glucose)	**normal**	**<50% plasma glucose**
Clorides (g/l)	**7,0-7,5**	**7,0**	**7,0**
Lactat (mmol/l)	**1,2-2,8**	**normal**	**>4**

MENINGITIS: TREATMENT

I. ANTIBACTERIAL THERAPY

Empirical therapy (adapted to local resistance patterns):

- 3rd-generation cephalosporins (Ceftriaxone/Cefotaxime)
- ± Vancomycin (resistant *S. pneumoniae*)
- ± Ampicillin (if *Listeria* suspected)
- Tailor therapy once culture/sensitivity available

II. MANAGEMENT OF CEREBRAL EDEMA

- **Corticosteroids (bacterial meningitis):**
  Dexamethasone 10 mg IV 20 min before or with first antibiotic dose, every 6 h for 4 days
- **Osmotic diuretics** (e.g., mannitol)
- **Controlled hyperventilation**
- **Head elevation**

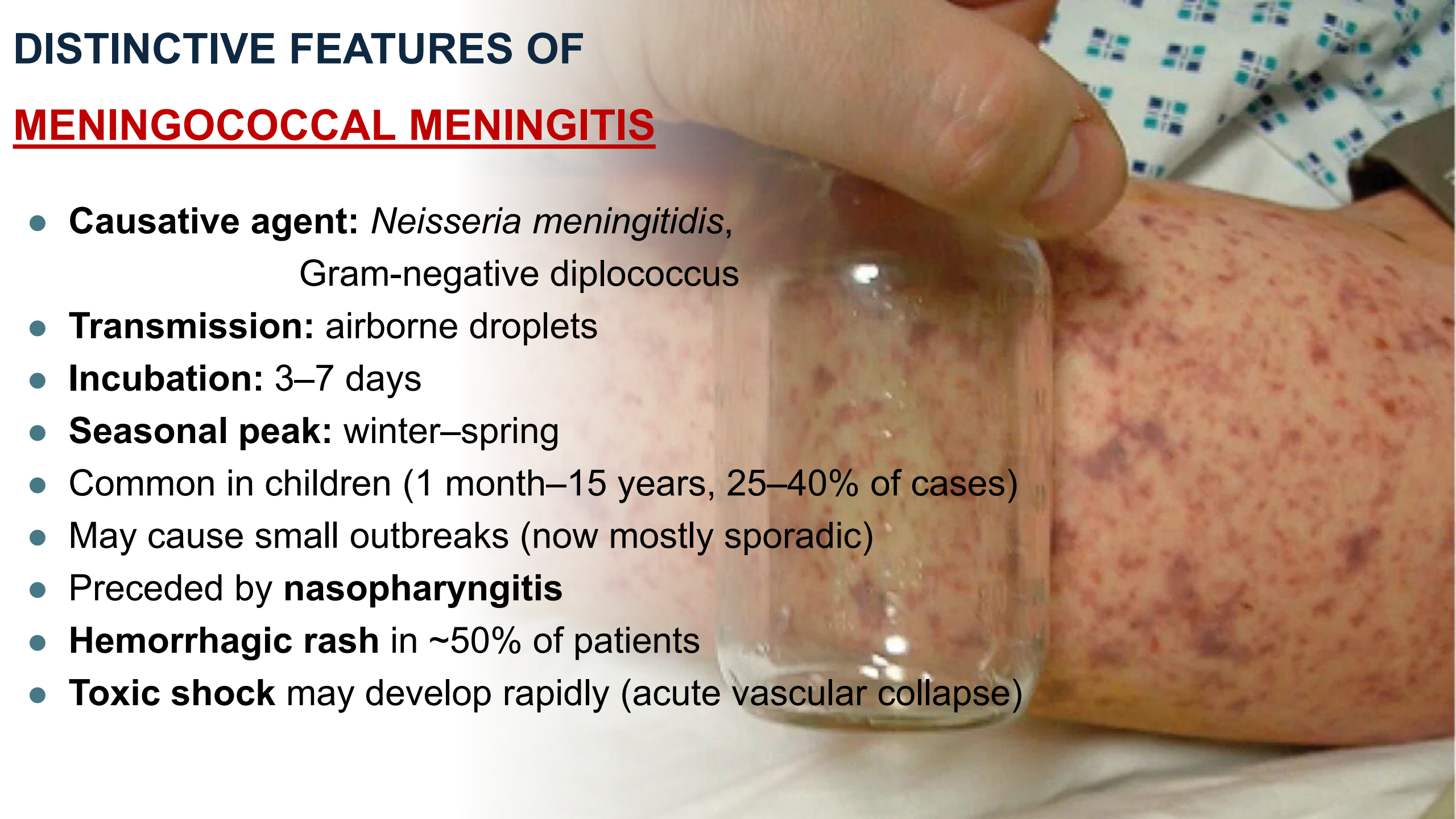
III. ADDITIONAL MANAGEMENT

- **Treatment of local infection:** abscess, empyema

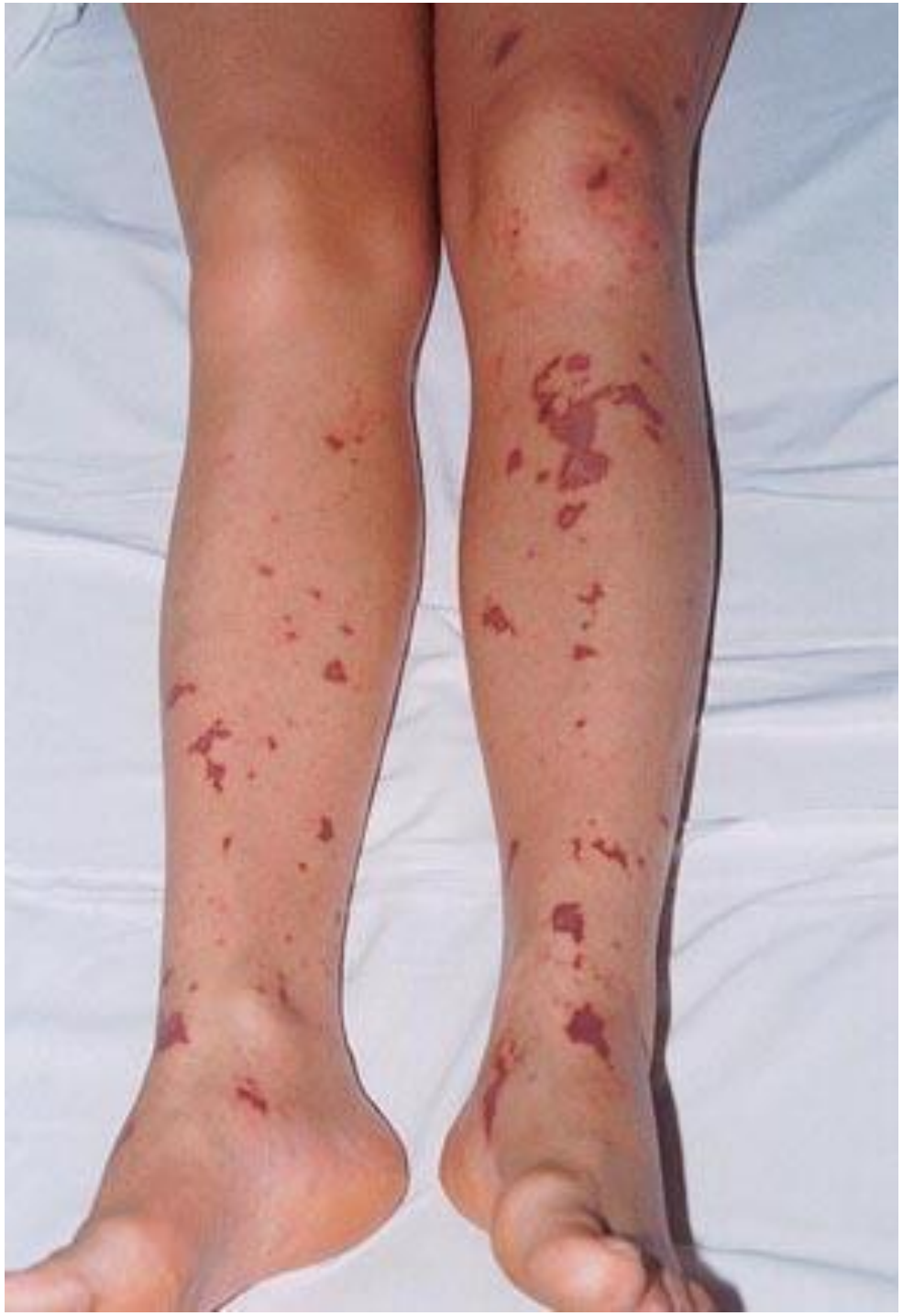
- **Correction of metabolic complications:**
  - septic shock, DIC, electrolyte disturbances (hypo-/hypernatremia)

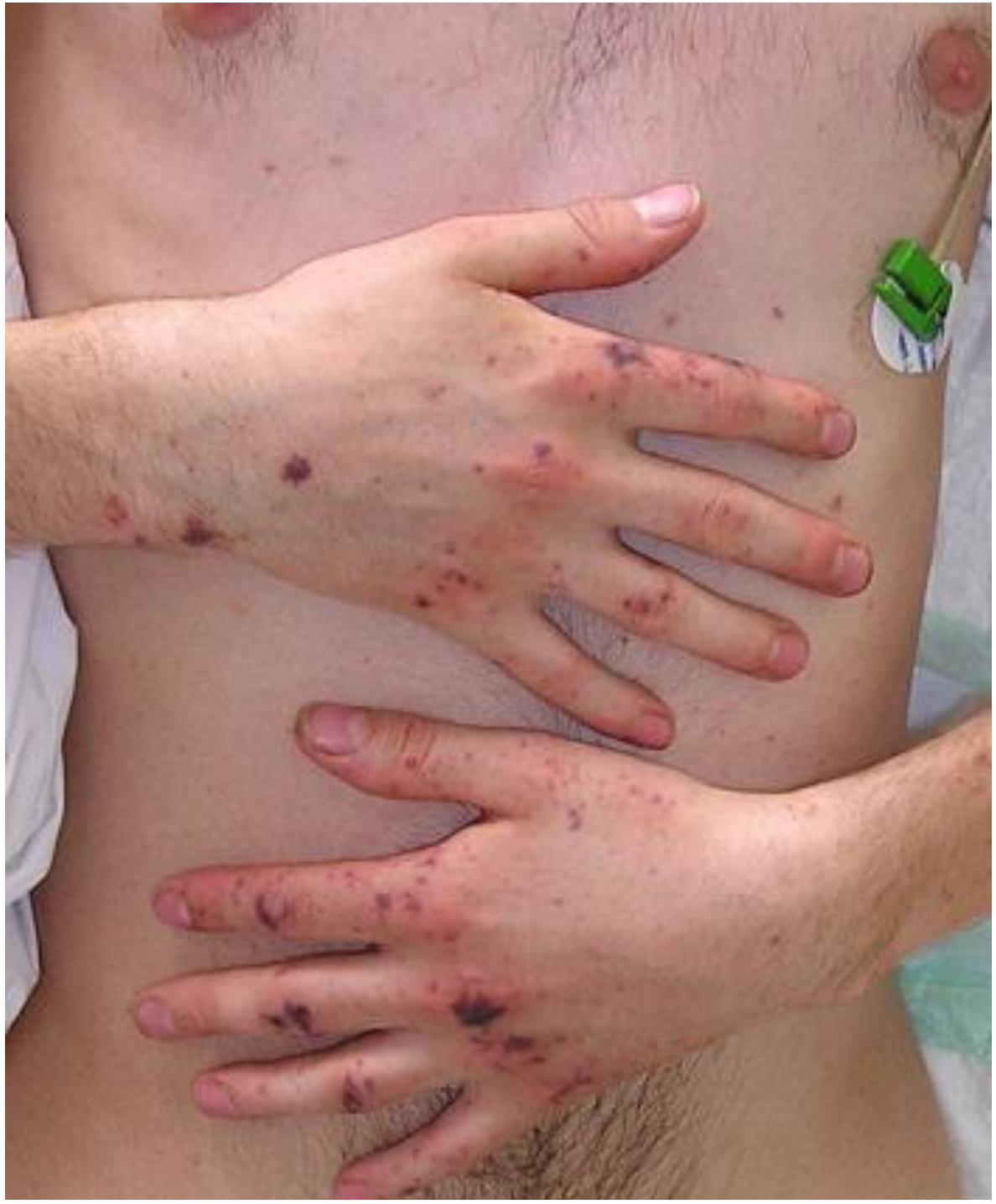
- **Symptomatic:** fever, headache, nausea, seizures

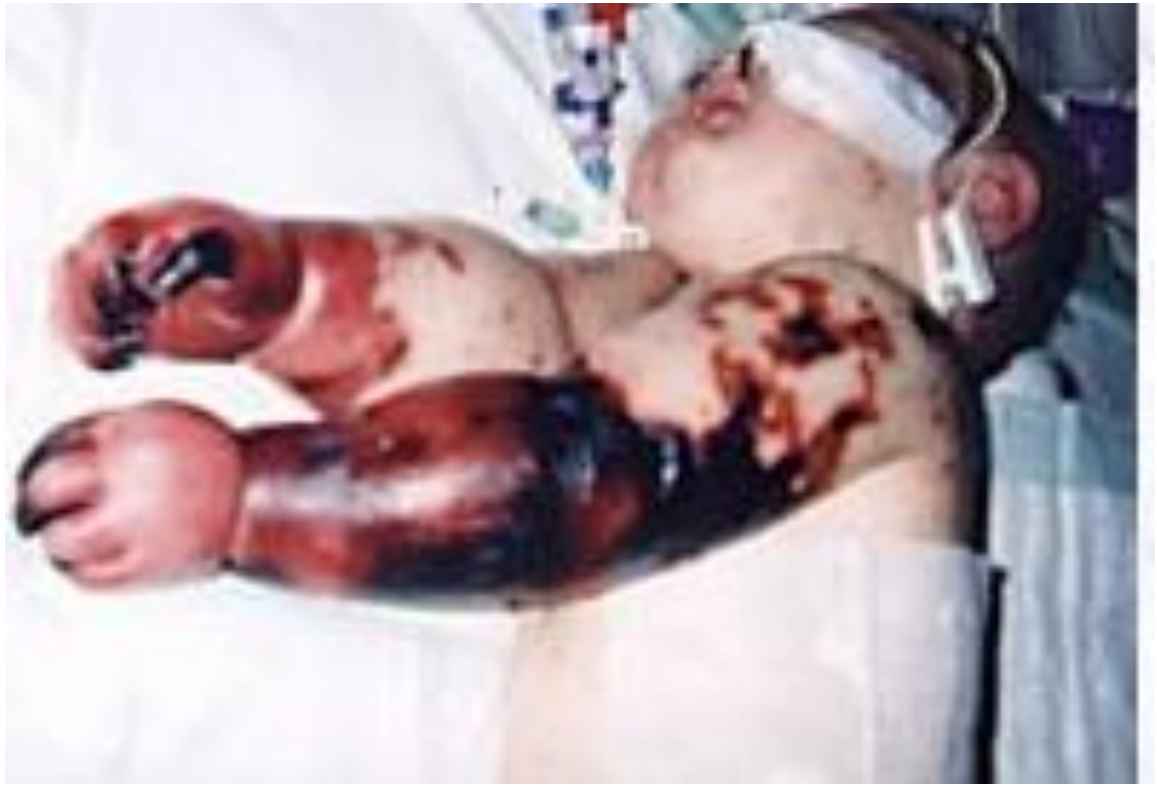
DISTINCTIVE FEATURES OF MENINGOCOCCAL MENINGITIS



- **Causative agent:** *Neisseria meningitidis*, Gram-negative diplococcus
- **Transmission:** airborne droplets
- **Incubation:** 3–7 days
- **Seasonal peak:** winter–spring
- Common in children (1 month–15 years, 25–40% of cases)
- May cause small outbreaks (now mostly sporadic)
- Preceded by **nasopharyngitis**
- **Hemorrhagic rash** in ~50% of patients
- **Toxic shock** may develop rapidly (acute vascular collapse)







Charlotte Cleverley-Bisman, child who survived amputations of all 4 limbs, and became "the face of" New Zealand's meningococcal meningitis vaccination campaign.

MENINGOCOCCAL MENINGITIS: CSF FINDINGS

Color: yellow-gray

Pressure: ↑ (≈ 300 mmH_2O)

Protein: ↑ (~6 g/L)

Cell count: 2,000–15,000 cells/ml (90% neutrophils)

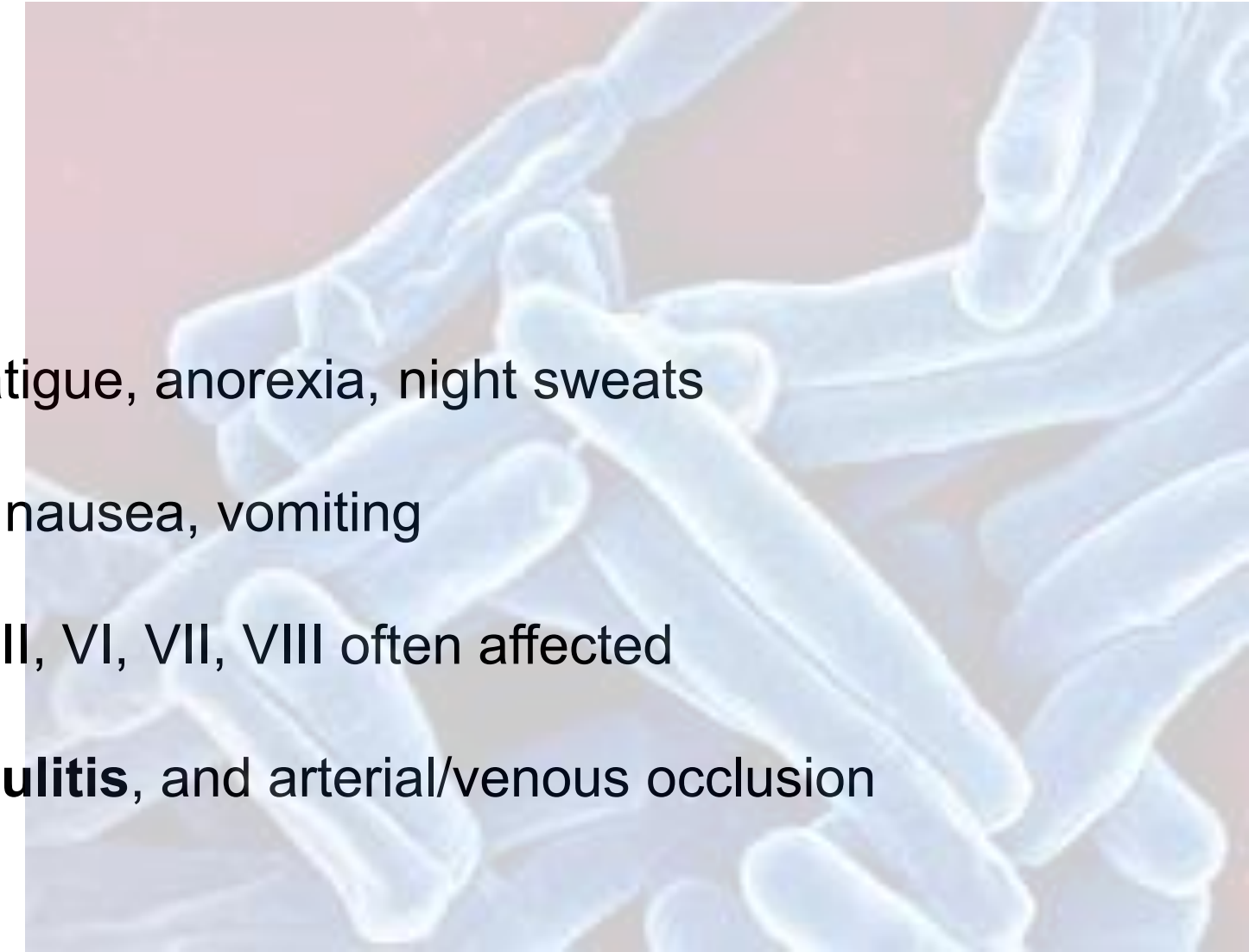
Glucose: ↓ (0.8–1.7 mmol/L)

Microscopy: intra- & extracellular diplococci

Culture positive in 70–80% cases

DISTINCTIVE FEATURES OF TUBERCULOUS MENINGITIS

- ✓**Prototype of chronic meningitis**
- ✓**Insidious onset**, slow progression
- ✓Early symptoms: low-grade fever, fatigue, anorexia, night sweats
- ✓Gradual development of headache, nausea, vomiting
- ✓**Basal meningitis** – cranial nerves III, VI, VII, VIII often affected
- ✓May develop **hydrocephalus**, **vasculitis**, and arterial/venous occlusion

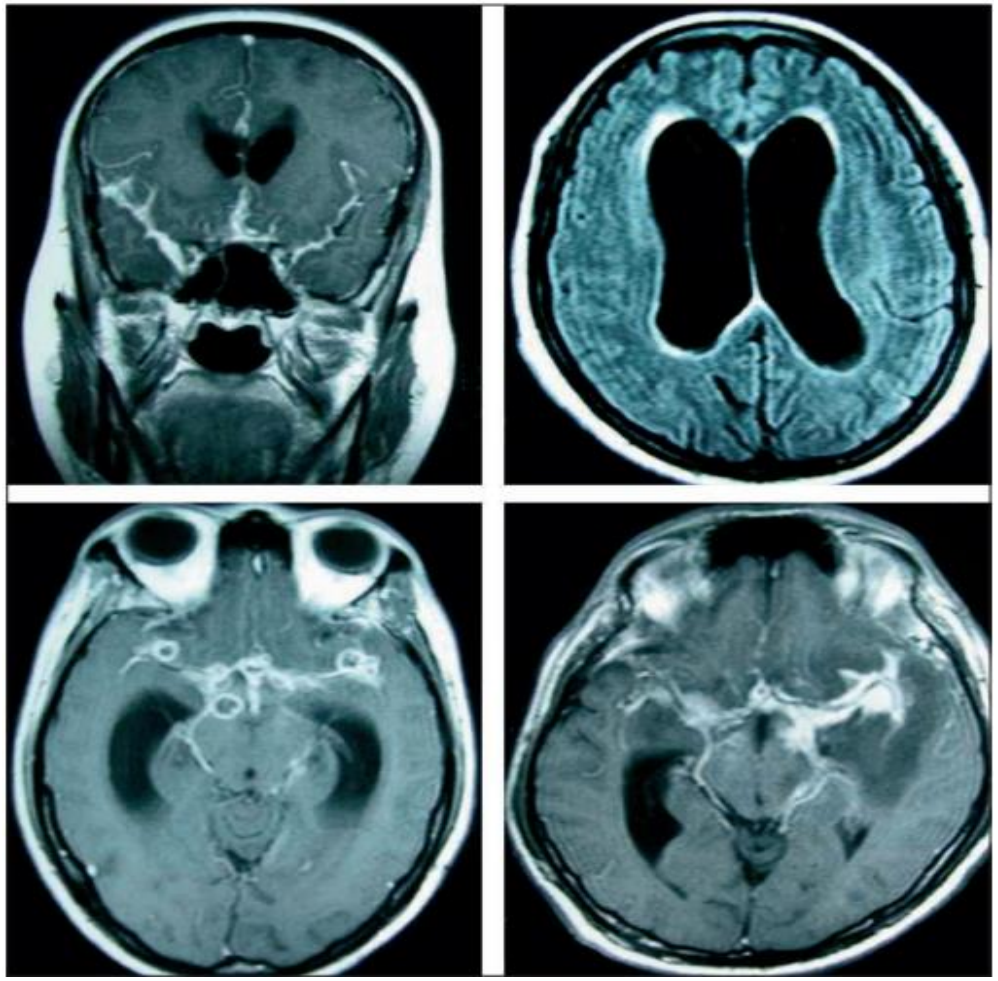


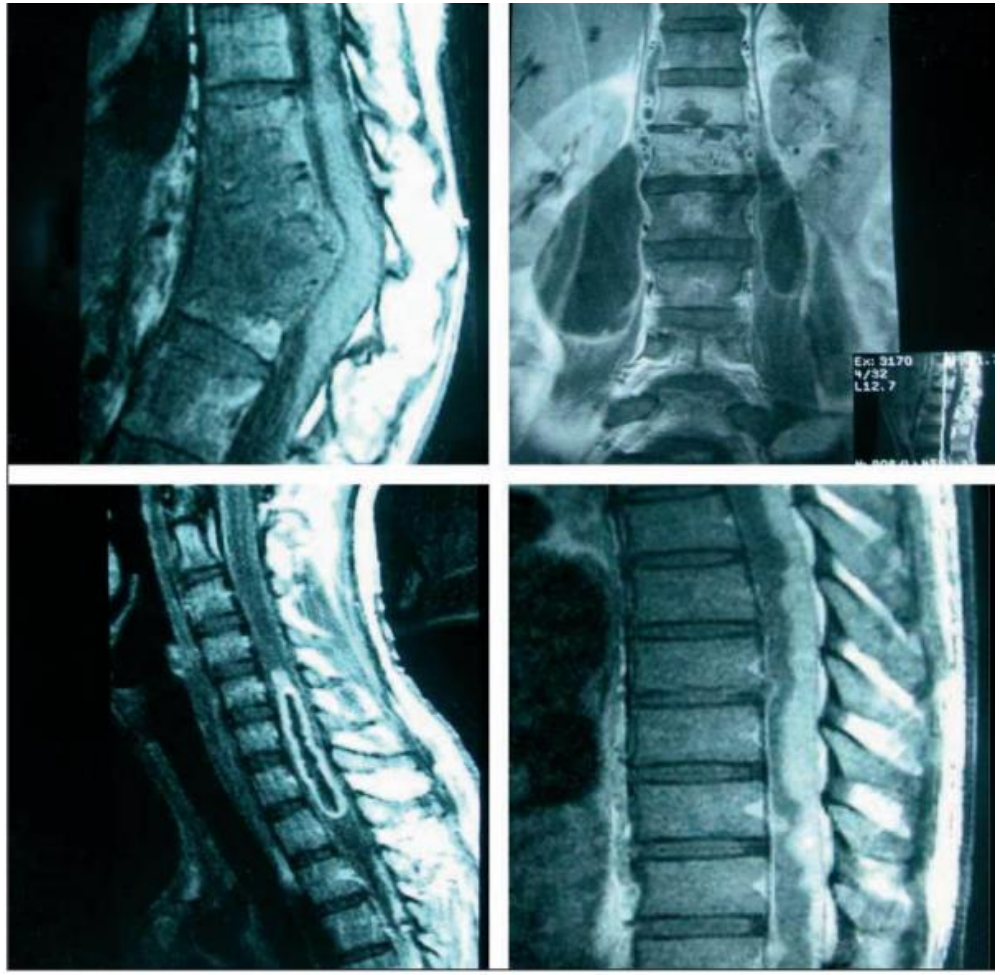
CSF CHANGES – TUBERCULOUS MENINGITIS

- Xanthochromic appearance
- Protein: 1–4 g/L
- Moderate pleocytosis (200–500 cells, 60–70% lymphocytes)
- **Very low glucose** (<50% of plasma)
- **Chlorides decreased** (2.0–3.0 g/L)
- Culture positive in ≈80% cases

TUBERCULOUS MENINGITIS: CLINICAL FORMS

1. Basal (cranial nerves)
2. Meningo-vascular (hemiparesis, hemianesthesia)
3. Meningo-medullary (paraparesis/tetraparesis)





MENINGITIS – KEY TAKE-HOME MESSAGES

Recognize early, treat fast — meningitis is a *neurological emergency*

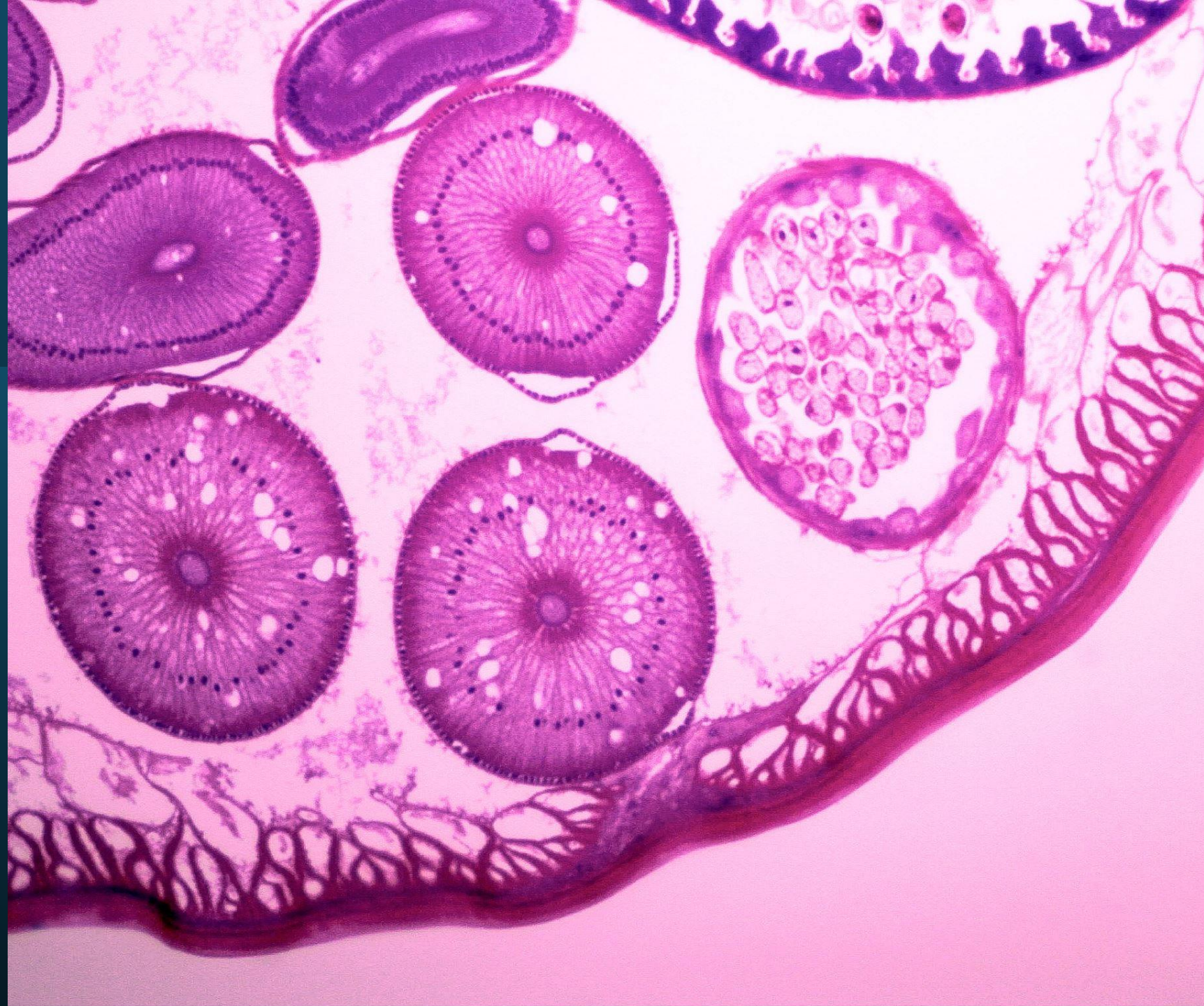
CSF analysis is the *cornerstone* of diagnosis

Empirical antibiotics must begin *immediately* after lumbar puncture

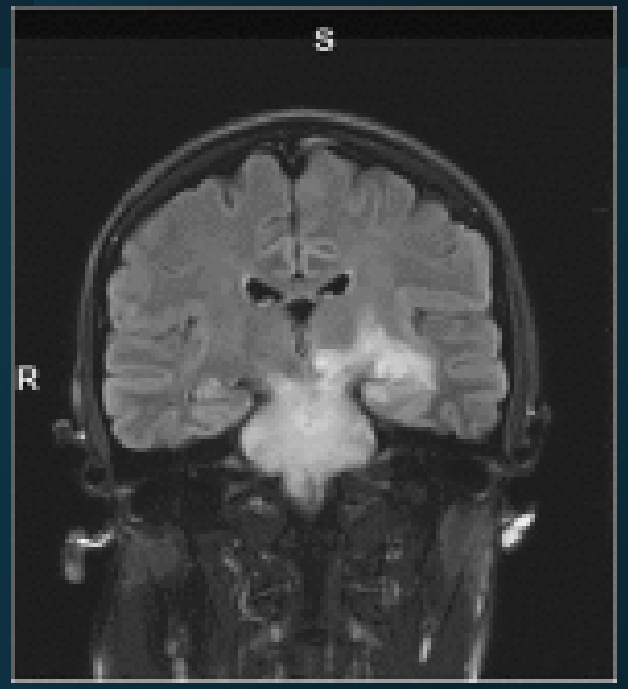
Adjunctive corticosteroids improve survival and reduce complications

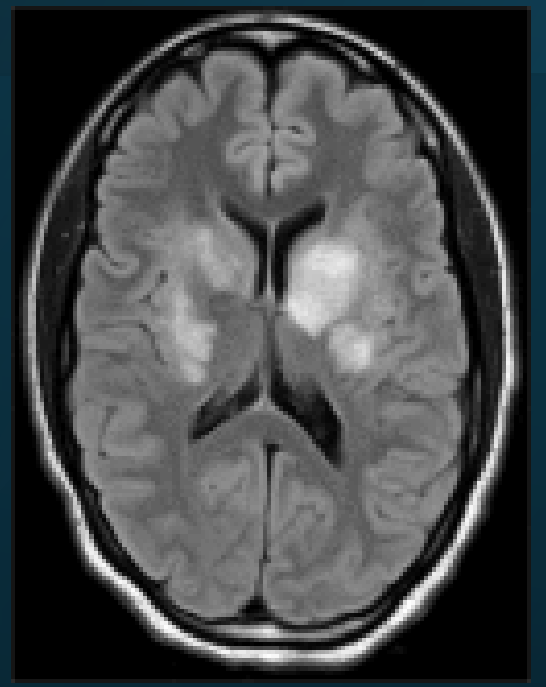
Vaccination saves lives — prevention is the most powerful therapy.

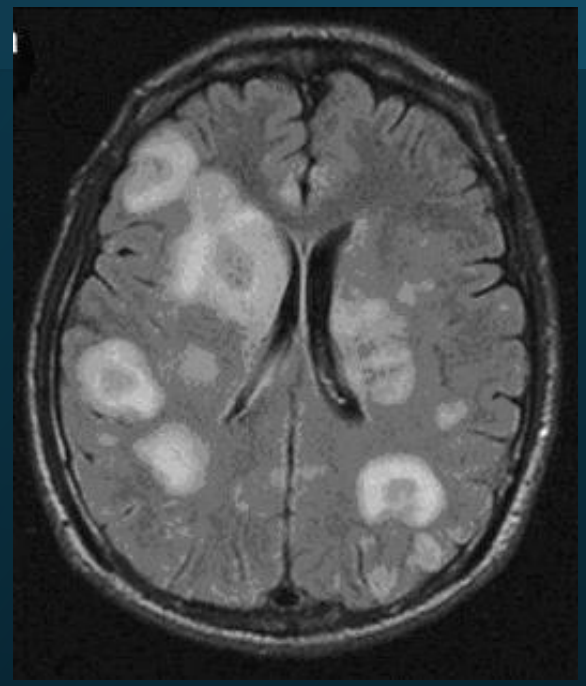
ENCEPHALITIS



ENCEPHALITIS is an **inflammatory lesion of the brain parenchyma** of **infectious or autoimmune** origin. It often involves both **gray and white matter**, and may affect **meninges or spinal cord**.







CLINICAL MANIFESTATIONS

Syndromic presentation may include:

- **ACUTE FEBRILE STATE** with meningeal irritation
- **ALTERED CONSCIOUSNESS:** lethargy, coma, confusion, delirium, disorientation
- **MENTAL CHANGES:** hallucinations, agitation, personality or behavioral disorders
- **FOCAL / DIFFUSE NEUROLOGICAL SIGNS:** seizures, aphasia, hemiparesis, ataxia, cranial nerve palsies

CLASSIFICATION OF ENCEPHALITIS

I. *Histological type:*

Polioencephalitis – gray matter predominance
Leukoencephalitis – white matter predominance
Panencephalitis – both gray and white matter

II. *Pathogenesis:*

Primary – due to direct viral invasion
Secondary – post-infectious or para-infectious (autoimmune)

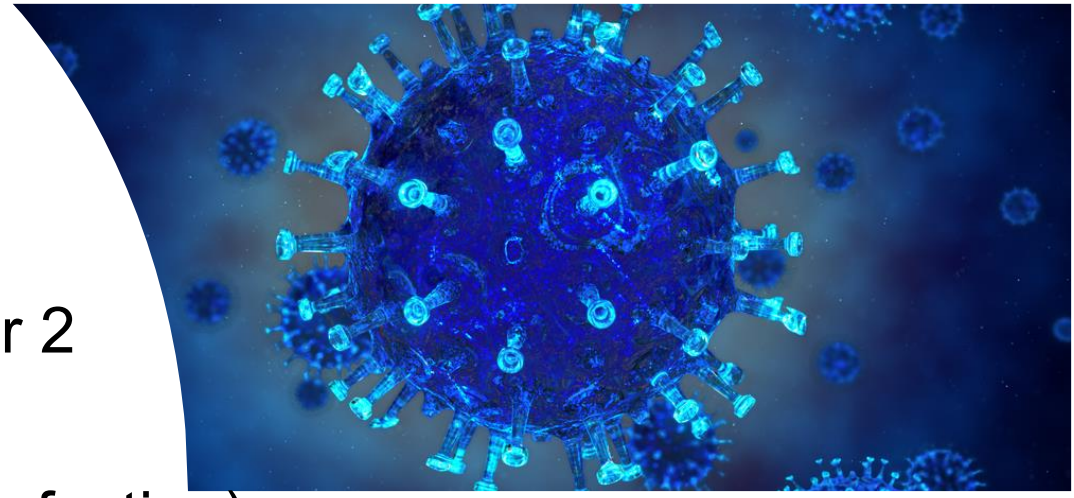
III. *Course*: acute, subacute, chronic

IV. *Etiology:*

Viral (herpes, enteroviruses, arboviruses, etc.)
Bacterial (staphylococci, streptococci, spirochetes)
Prions (Creutzfeldt–Jakob disease)

V. *Epidemiologic type:* Seasonal / endemic / epidemic / sporadic

HERPETIC ENCEPHALITIS



ETIOLOGY AND PATHOGENESIS

- **Causative agents:** Herpes simplex virus type 1 or 2

- **Entry points:** mucosa (gingivostomatitis, genital infection)

- **CNS involvement:**
  - Retrograde axonal transport via **cranial nerves I & V**
  - Hematogenous spread (rare)

- **Latency:** HSV may persist in neurons with possible reactivation

CLINICAL COURSE

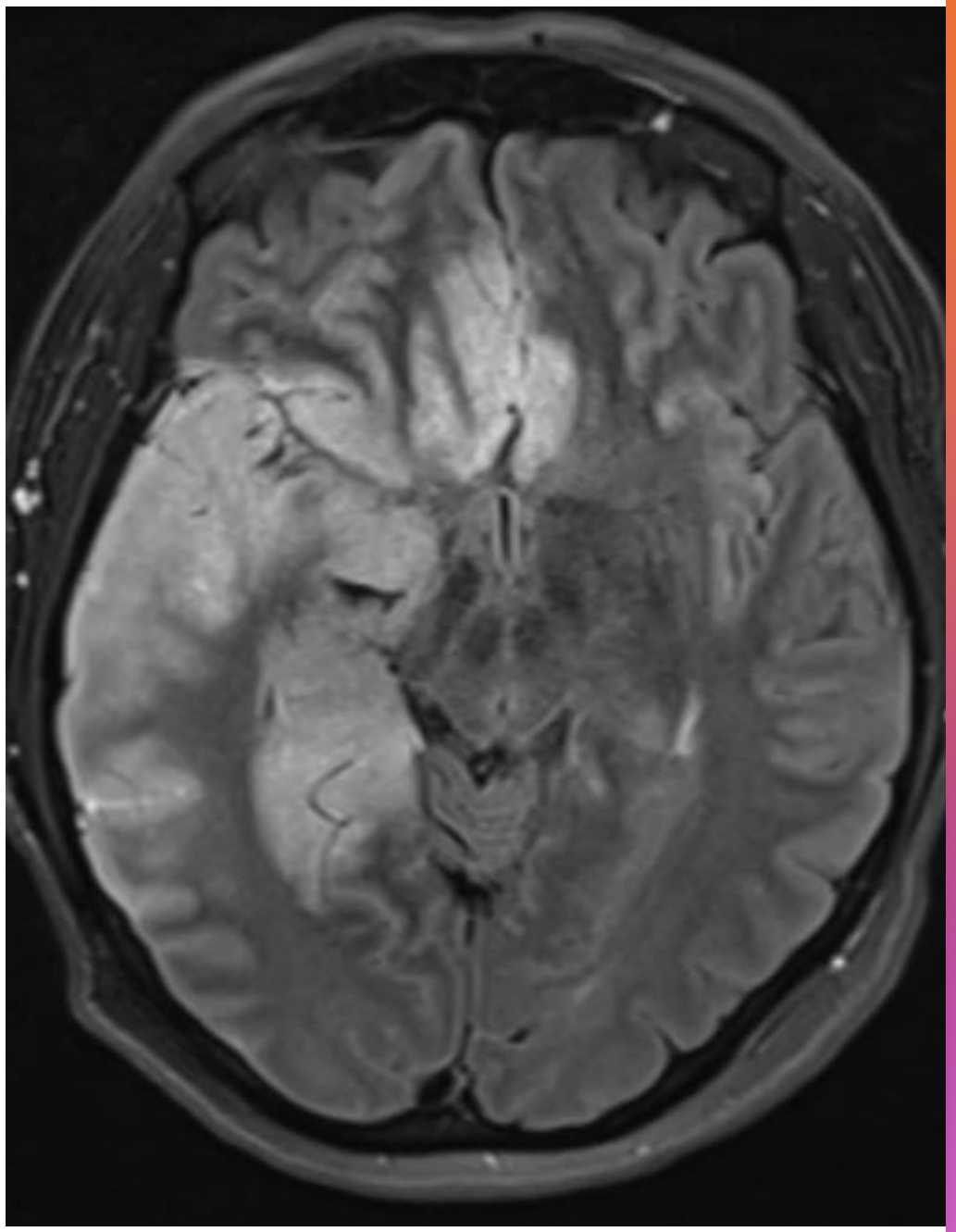
- Initial **respiratory or systemic infection**
- **Febrile state**, malaise, headache, myalgia
- **Herpetic lesions** in ~20% of patients
- **Focal neurological signs** appear 2–3 weeks later:

✓ Aphasia

✓ Central hemiparesis

✓ Seizures

✓ Memory, behavior, or cognitive changes



DIAGNOSIS: HERPETIC ENCEPHALITIS

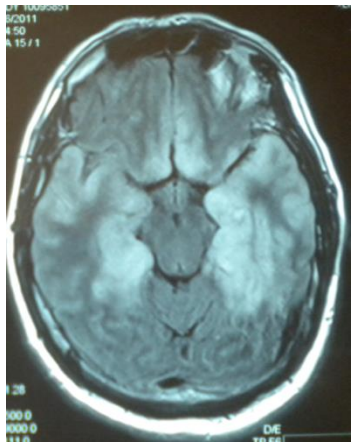
1. CLINICAL SIGNS: Fever, altered consciousness, focal deficits

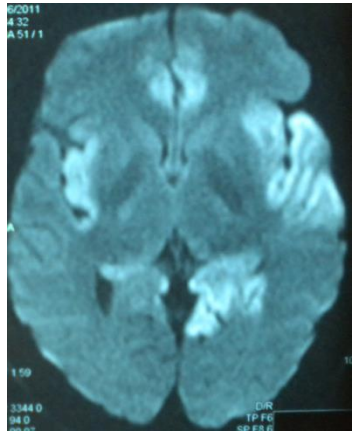
2. LABORATORY:

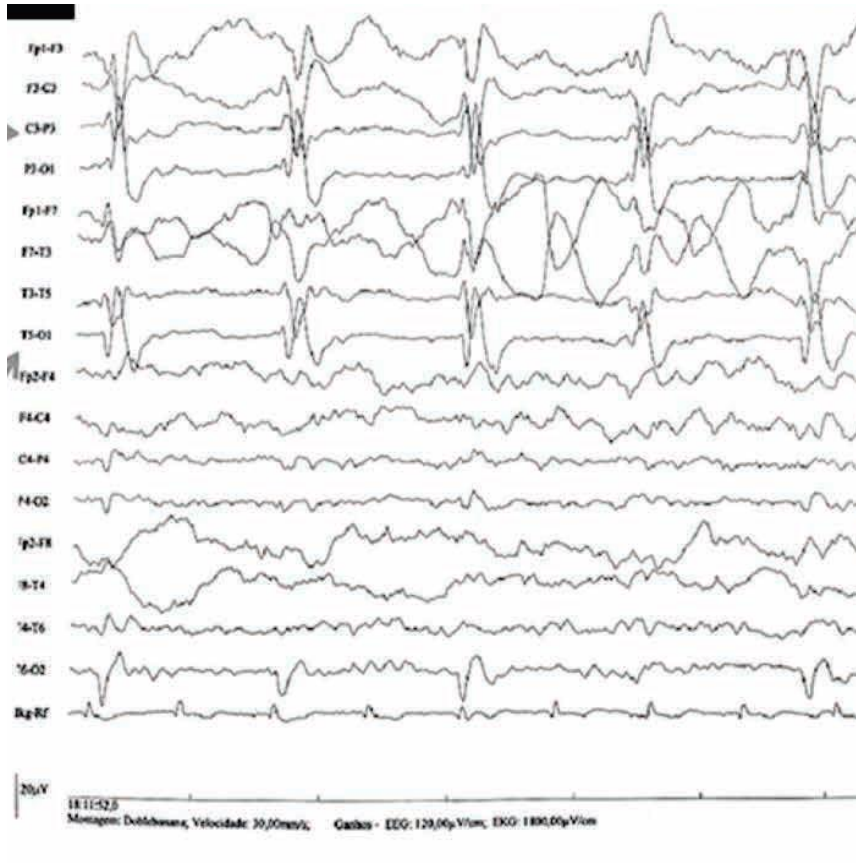
CBC: signs of inflammation

CSF:

- Clear, transparent
- Pressure: ~250 mmH_2O
- Proteins: ~0.8 g/L
- Cells: ~200 (90% lymphocytes, 10% neutrophils)
- Glucose: ~3.2 mmol/L
- Chlorides: ~7.0 g/L







Virology: anti-HSV1/2 antibodies (serum), PCR for HSV DNA (CSF)

3. NEUROIMAGING: MRI temporal and frontal lobe involvement (asymmetrical)

4. EEG: periodic sharp-wave complexes

5. BRAIN BIOPSY: in uncertain cases

TREATMENT: HERPETIC ENCEPHALITIS

ETIOLOGIC (antiviral): Acyclovir IV10 mg/kg every 8 hours for 14–21 d

ANTI-EDEMA THERAPY:

- Osmotic diuretics (mannitol)
- Head elevation at 30°
- Controlled hyperventilation / intubation if needed

SYMPTOMATIC:

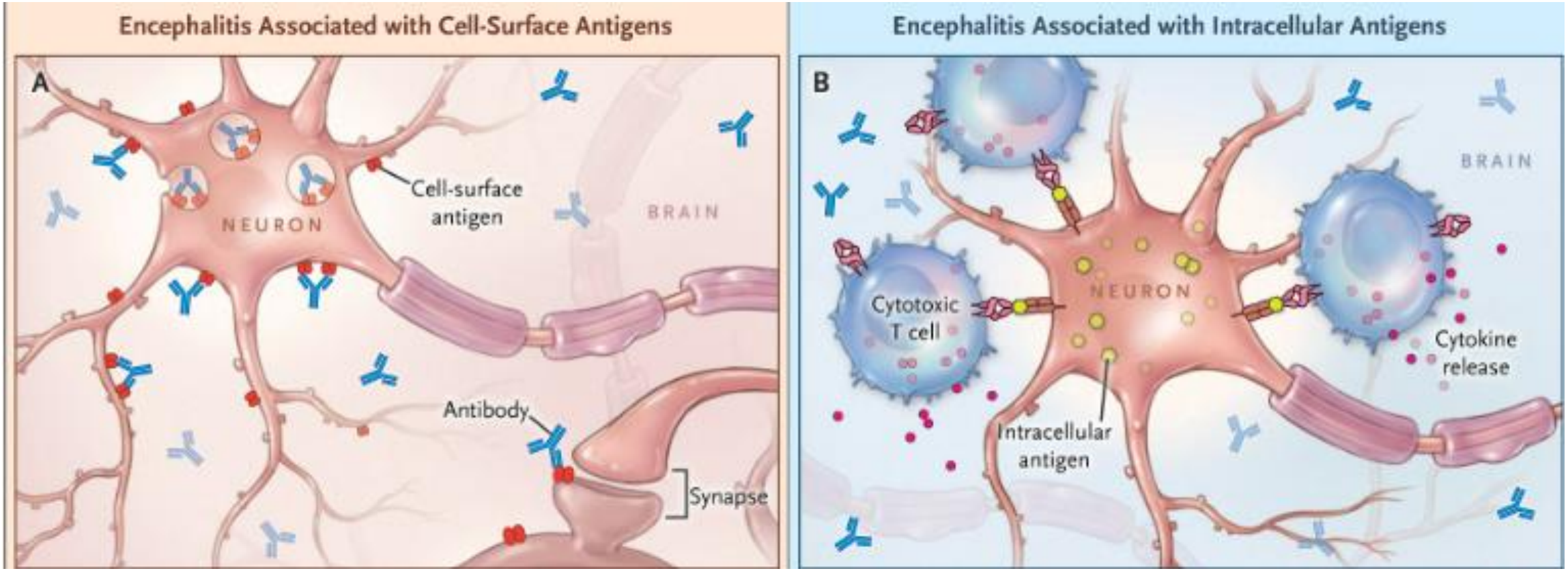
- Antiepileptics (phenytoin, carbamazepine, valproic acid, levetiracetam)
- Antipyretics
- Maintenance of fluid, electrolyte, and acid–base balance

AUTOIMMUNE ENCEPHALITIS

DEFINITION:

A group of **immune-mediated, noninfectious inflammatory disorders** of the brain parenchyma, involving **cerebral cortex or deep gray matter**, sometimes with **meningeal or spinal cord** involvement.

AUTOANTIBODIES



Autoimmune encephalitis is classified based on the **target antigen:**

Group I- **cell-surface antigens** (non-paraneoplastic)
Group II- **intracellular antigens** (paraneoplastic)

CLASSIFICATION:

CELL-SURFACE ANTIGENS

- Anti-NMDAr
- Anti-AMPAR
- Anti-GABA
- LGI1
- CASPR2

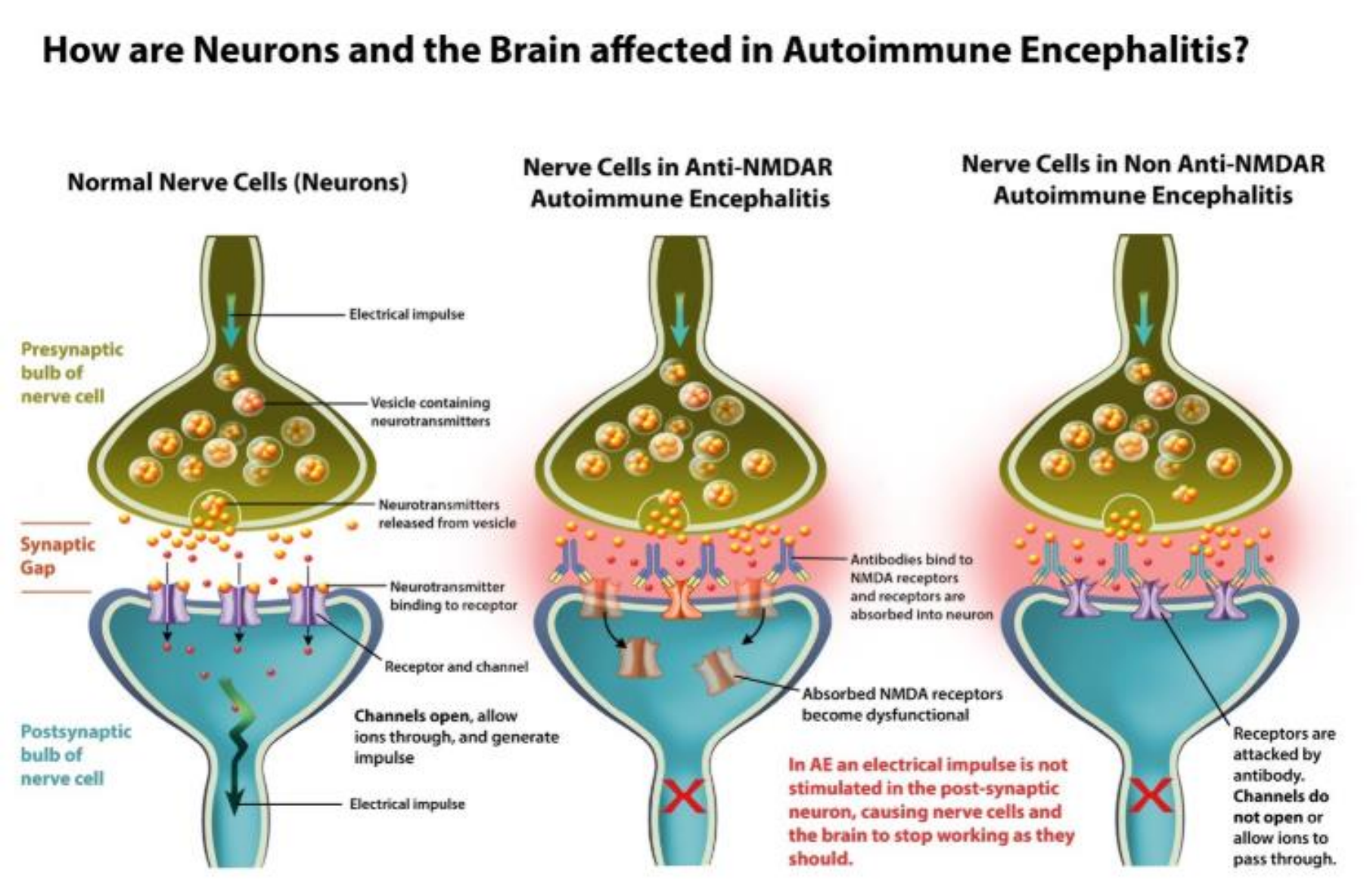
INTRACELLULAR ANTIGENS

- Anti-Yo
- Anti-Hu
- Anti-Ma2
- Paraneoplastic limbic encephalitis
- Brainstem encephalite
- Encephalomyelitis

NB! This distinction is clinically important - it predicts malignancy association, treatment response, and long-term prognosis

PATHOGENESIS

- Autoantibodies target **neuronal or synaptic antigens** (e.g., NMDA receptor)
- Induce **neuroinflammation and synaptic dysfunction**
- Predominant involvement of **hippocampus, cortex, basal ganglia**

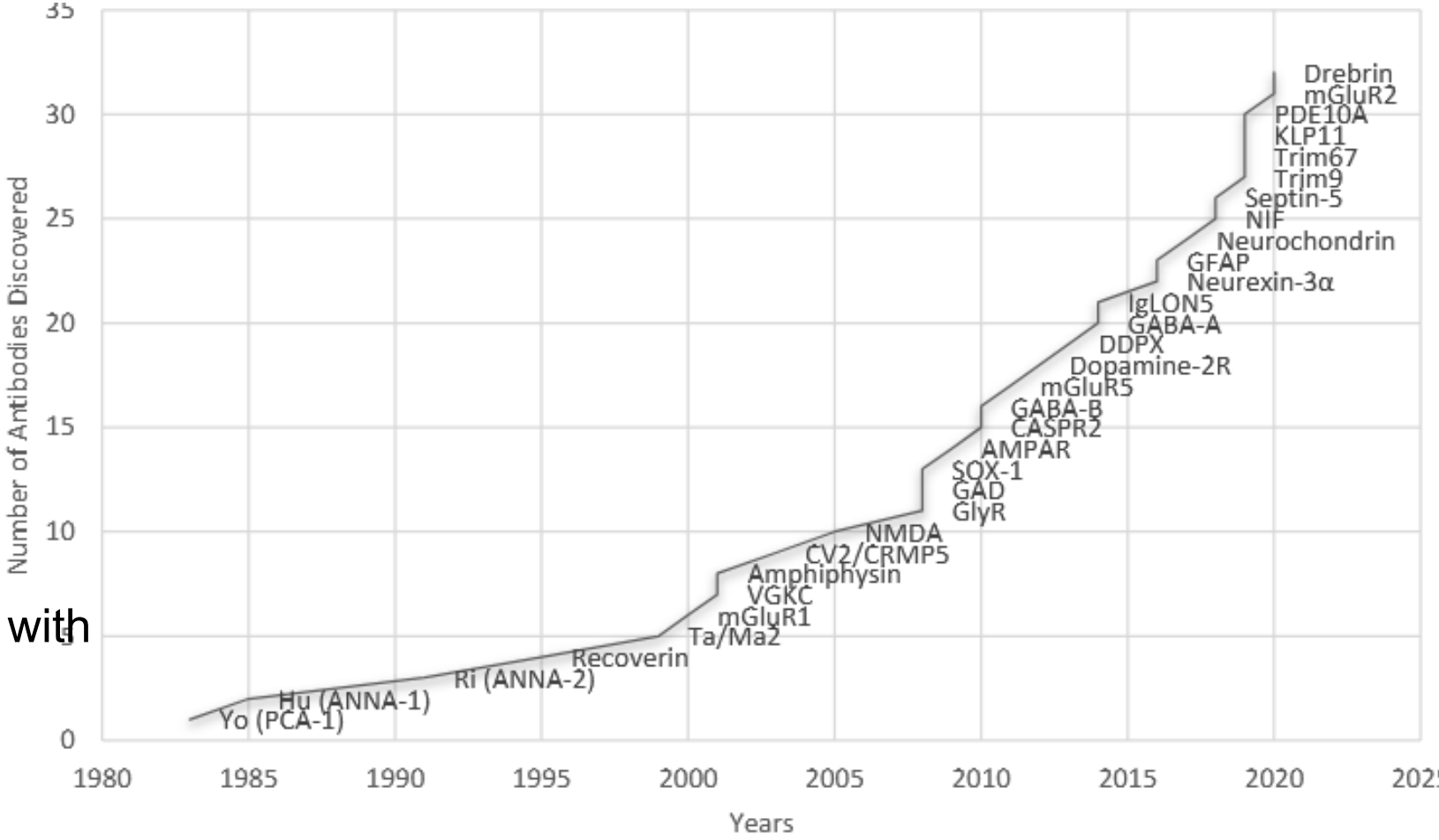


CHRONOLOGY OF ANTIBODY DISCOVERY

1988: Anti-GAD – first described in stiff-person syndrome

2005: Josep Dalmau identified anti-NMDAR Abs in 12 patients with encephalitis

2008–2010: Associations established with autoimmune encephalitis



CLINICAL MANIFESTATIONS

PSYCHIATRIC / BEHAVIORAL

agitation, irritability
emotional lability
hallucinations
disturbed sleep–wake cycles

COGNITIVE

Confusion, disorientation, amnesia (antero- & retrograde in LGI1 type)

SEIZURES

frequent focal seizures, occasional generalized
facio-brachial dystonic seizures (LGI1)
Status epilepticus (GABAa/b)

MOTOR

Chorea, dystonia, tremor, stereotypies (NMDAR)
Myoclonus, hypereplexia (DPPX, GlyR)
Rigidity (GlyR)

AUTONOMIC (ANS)

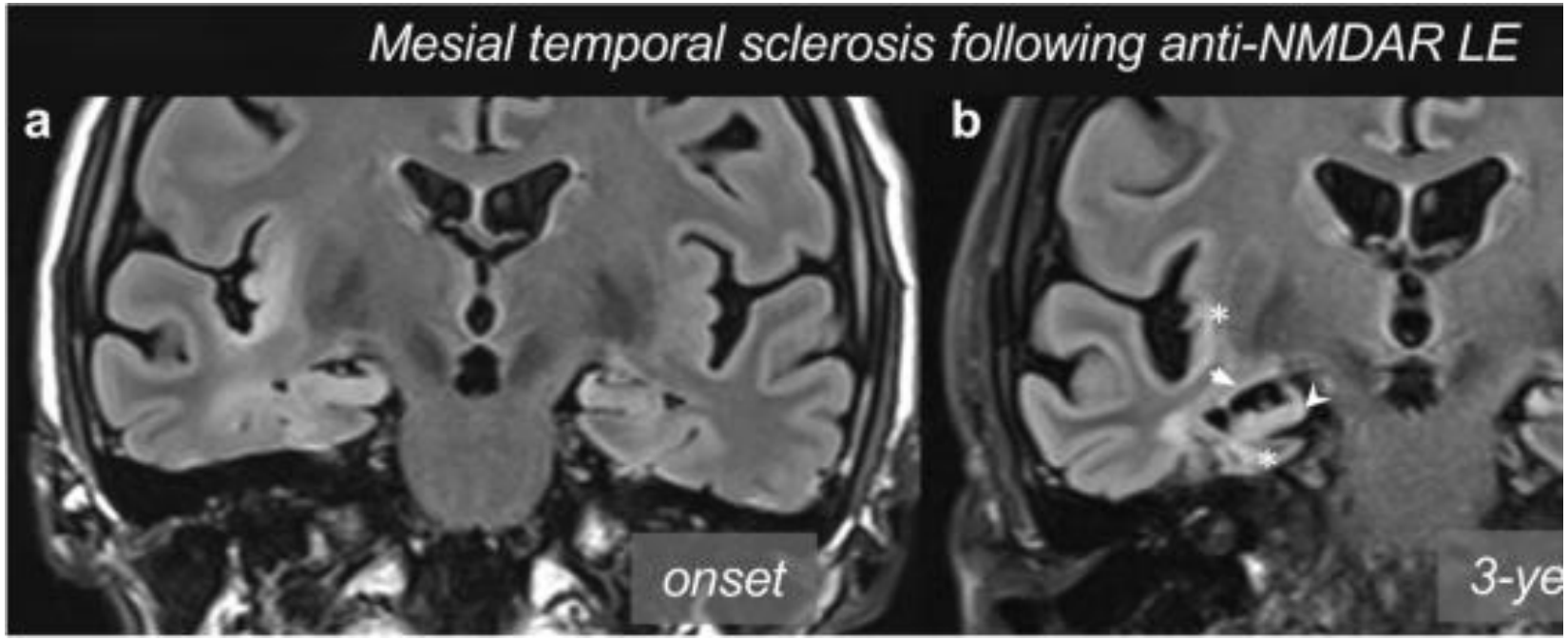
Fluctuating BP and HR, arrhythmias
Orthostatic hypotension, constipation
Abnormal sweating

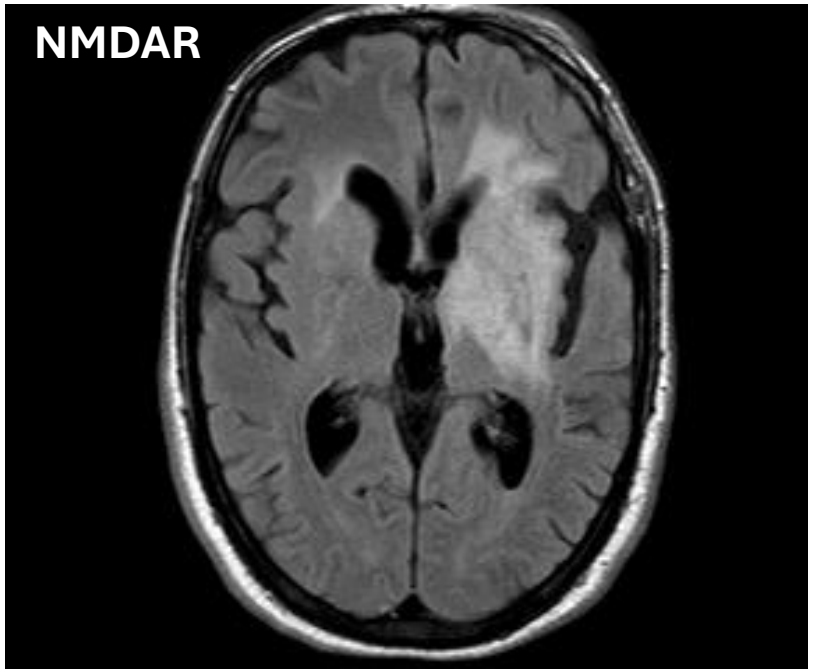
PAIN

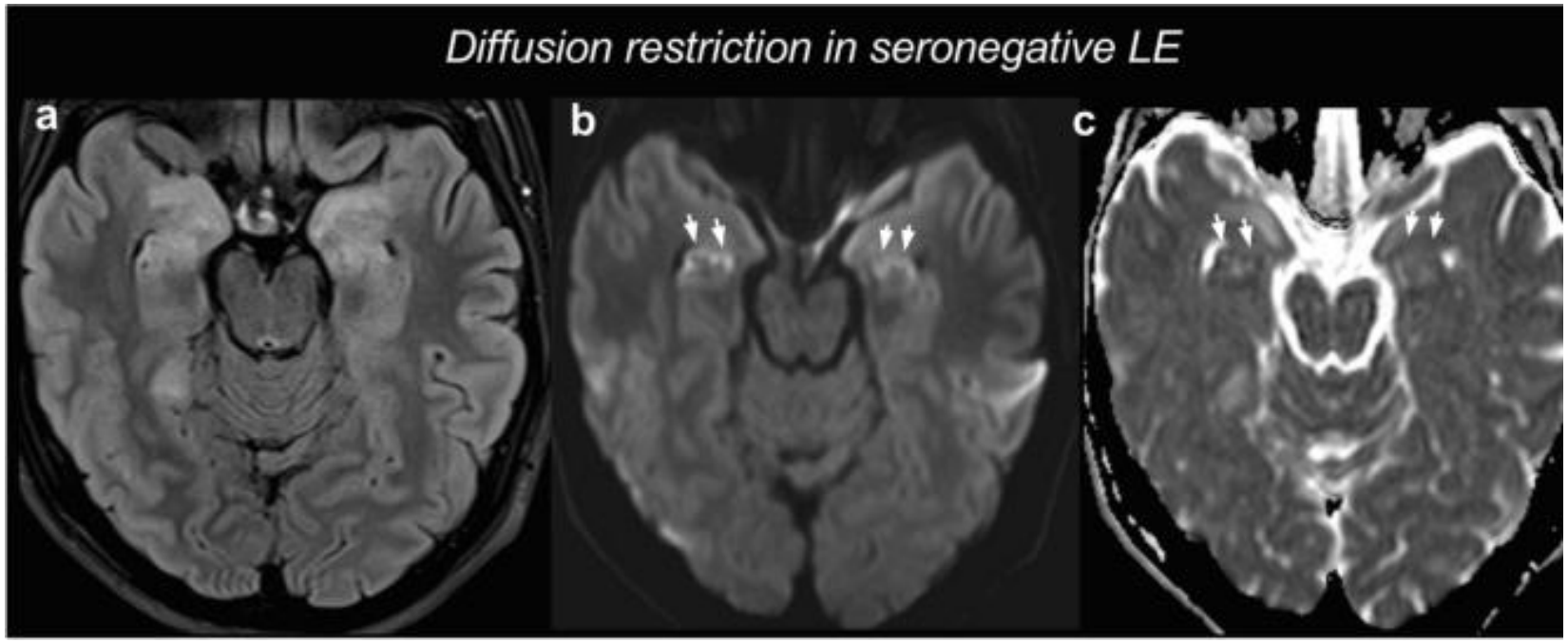
Neuropathic pain, allodynia, dysesthesia, or pruritus

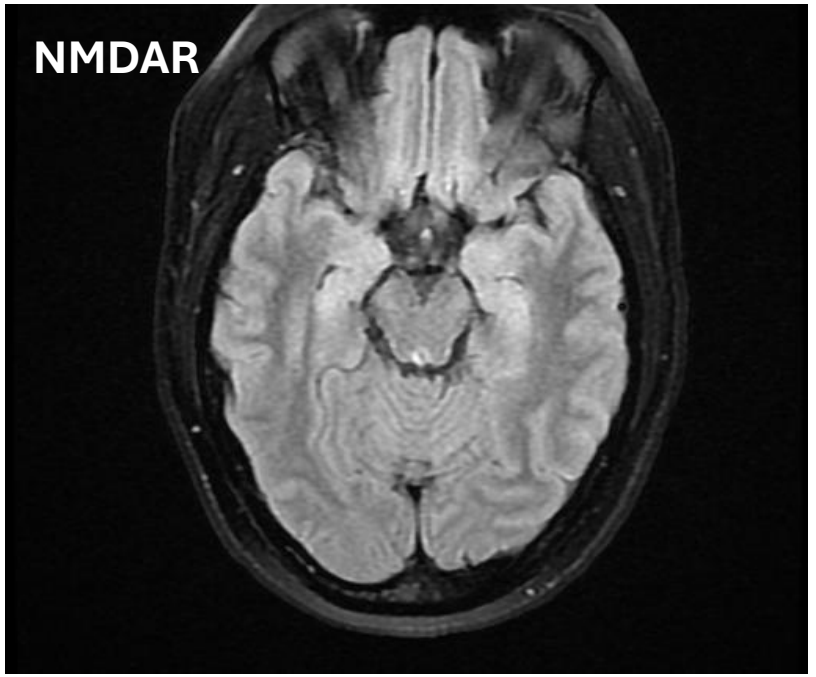
DIAGNOSTIC CRITERIA – AUTOIMMUNE ENCEPHALITIS

- **Clinical picture** compatible with autoimmune encephalitis
- **MRI**: medial temporal or multifocal lesions
- **CSF**: mild pleocytosis, oligoclonal bands
- **EEG**: epileptiform discharges
- Detection of **specific antibodies** (serum & CSF)
- Exclusion of infectious causes


Mesial temporal sclerosis following anti-NMDAR LE
a
b
onset
3-ye


NMDAR


Diffusion restriction in seronegative LE
a
b
c


NMDAR

TREATMENT – AUTOIMMUNE ENCEPHALITIS

1. INTENSIVE CARE MANAGEMENT

- Refractory status epilepticus
- Severe dysautonomia or respiratory distress

2. EMPIRICAL ANTIMICROBIAL THERAPY

Acyclovir + broad-spectrum antibiotics until infection is ruled out

3. ACUTE IMMUNOTHERAPY

- High-dose corticosteroids: Methylprednisolone 1 g/day × 5–7 days
- Intravenous immunoglobulin (IVIg): 2 g/kg over 5 days
- Plasma exchange: 5–10 sessions (every 2 days)
- 2nd-line immunosuppressants: Rituximab, Cyclophosphamide, Bortezomib, Tocilizumab

4. SYMPTOMATIC TREATMENT

Management of cerebral edema, electrolyte imbalance, etc.

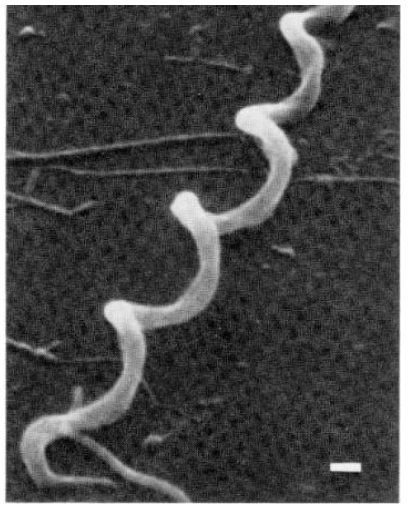
ENCEPHALITIS – KEY TAKE-HOME MESSAGES

- Suspect early in any patient with fever + confusion + seizures
- MRI & PCR are diagnostic pillars
- Start acyclovir immediately
- Think autoimmune if infectious tests are negative
- Early immunotherapy saves neurons

NEUROSYPHILIS & NEUROBORRELIOSIS: COMMON FEATURES

✓Both caused by **spirochetes** (Gram-negative, difficult to culture):

Treponema pallidum → Neurosyphilis
Borrelia burgdorferi → Neuroborreliosis (Lyme disease)



<u>Shared characteristics</u>:

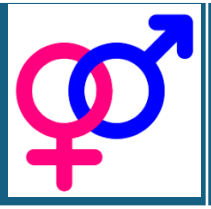
✓Usually **subacute or chronic onset**

✓**Polymorphic neurological presentation** and **multisystem involvement**

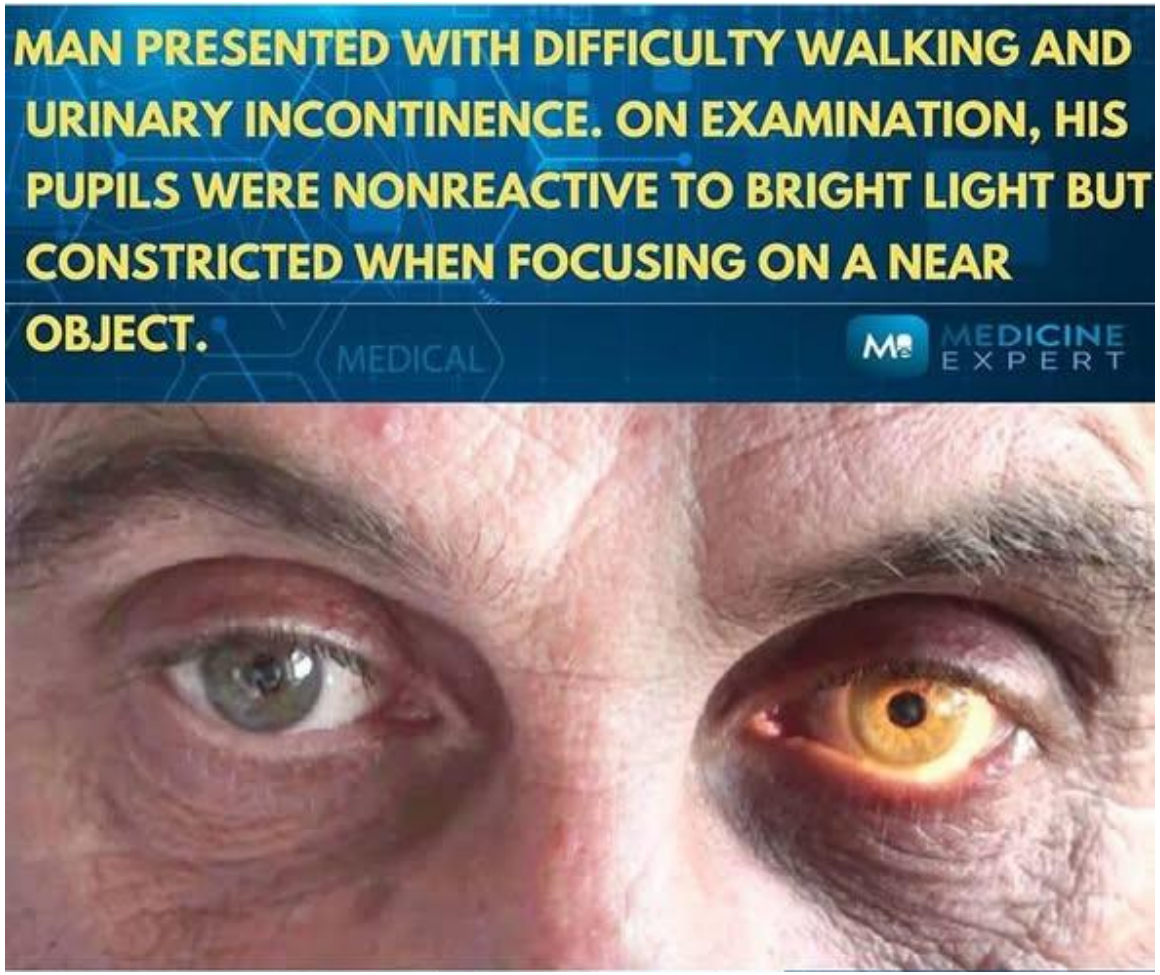
✓May cause **meningitis**, **cranial nerve palsies**, **cognitive decline**, **peripheral neuropathies**

✓Diagnosis: **serological testing + CSF analysis**

✓Both require **prolonged antibiotic therapy** and **careful follow-up**

Caracteristics	NEUROSYPHILIS 	NEUROBORRELIOSIS 
Etiologic agent	*Treponema pallidum*	*Borrelia burgdorferi*
Transmission	Sexual, transplacental (vertical)	Tick bite *(Ixodes),* zooanthroponosis
Rezervoar of infection	Strictly human	Rodents, deer, birds
Incubation	Long (months–years)	Weeks–months
Pathogenesis	***T. pallidum:*** ➢skin, mucous membranes ➢hematogenous ➢host cell attachment ➢inflammation ➢neuronal damage ➢demyelination ➢obliterating endarteritis of terminal arterioles	***B. burgdorferi:*** ➢skin ➢hematogenous ➢peripheral nerves ➢CNS ➢direct inflammatory, immune-mediated or vasculitic response

NEUROSYPHILIS: *CLINICAL MANIFESTATIONS*



➢**ASYMPTOMATIC NEUROSYPHILIS:**
abnormal CSF without symptoms.

➢**MENINGEAL NEUROSYPHILIS (1-2 years):**
occurs early; headache, cranial nerve palsies.

➢**MENINGOVASCULAR FORM (5-12 years):**
chronic meningitis + stroke-like episodes.

➢**<u>PARENCHYMATOUS FORMS</u>** (**15-20 years**):

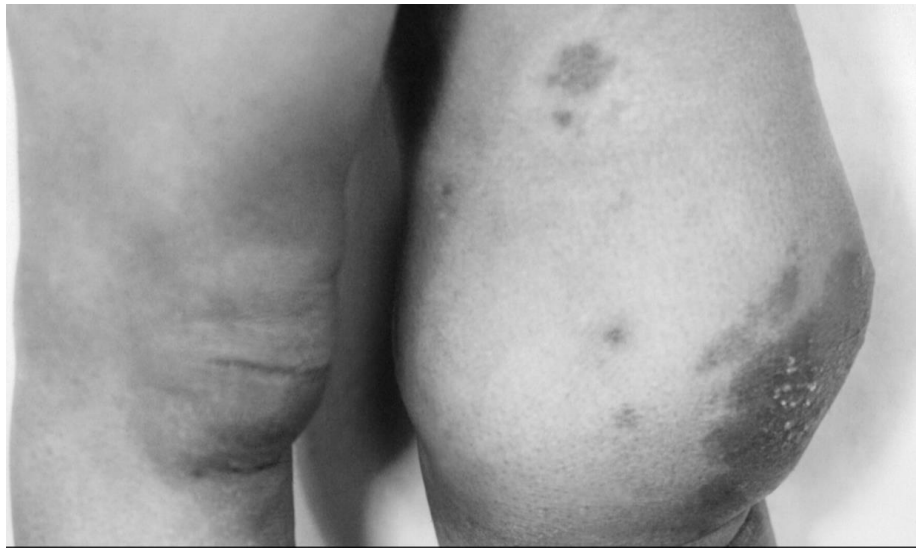
TABES DORSALIS – dorsal column degeneration → ataxia, lightning pains, **Agyll Robertson pupil**.

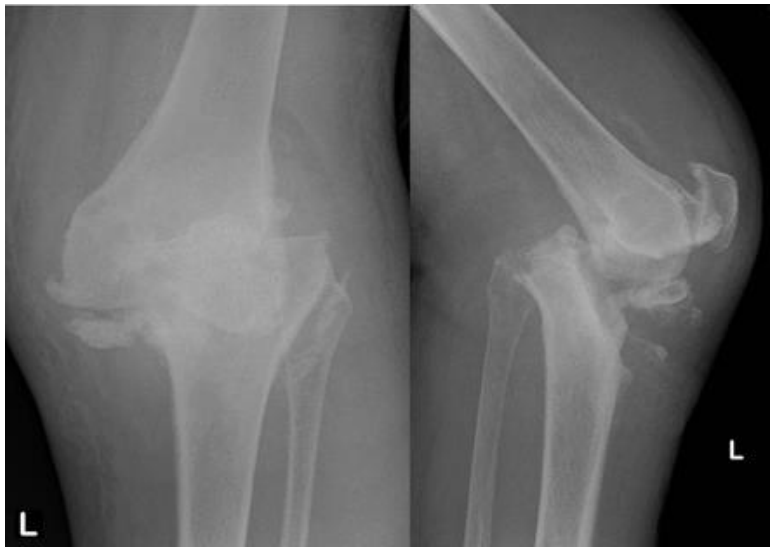
GENERAL PARESIS – progressive dementia, psychiatric symptoms, tremor, dysarthria

✓**ANY STAGE**: ocular syphilis, oto-syphilis

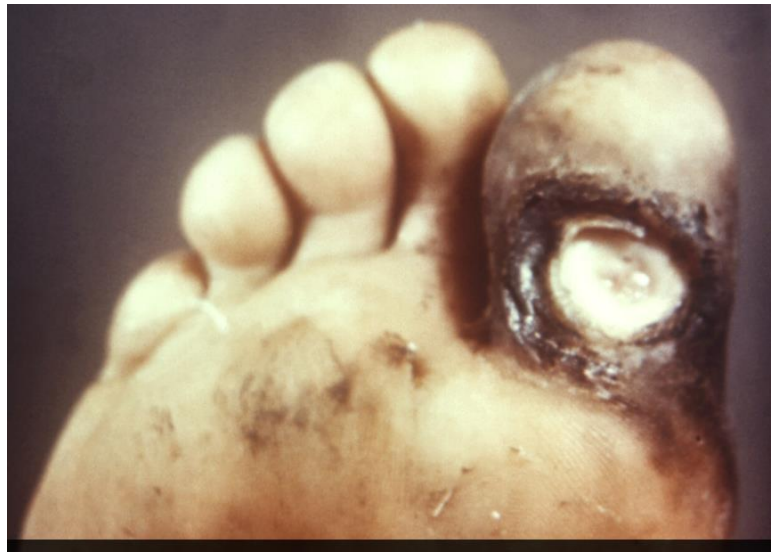
✓**MULTISYSTEMIC INVOLVEMENT**: skin, carditis (aortitis), osteoarthritis

CHARCOT JOINT (neuropathic arthropathy)





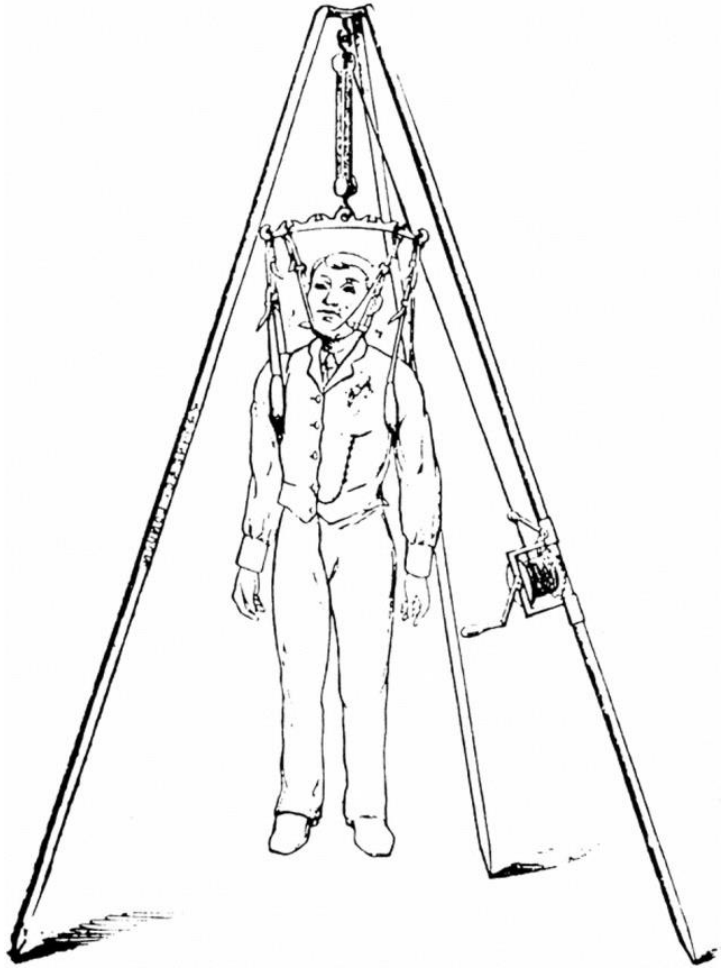
MAL PERFORANS



NEUROSYPHILIS: *DIAGNOSIS*

- **Serology**: RPR, VDRL, TPHA
- **CSF** exam: lymphocytic pleocytosis, ↑ protein, ↓ glucose, positive VDRL

SUSPENSION THERAPY (1889)



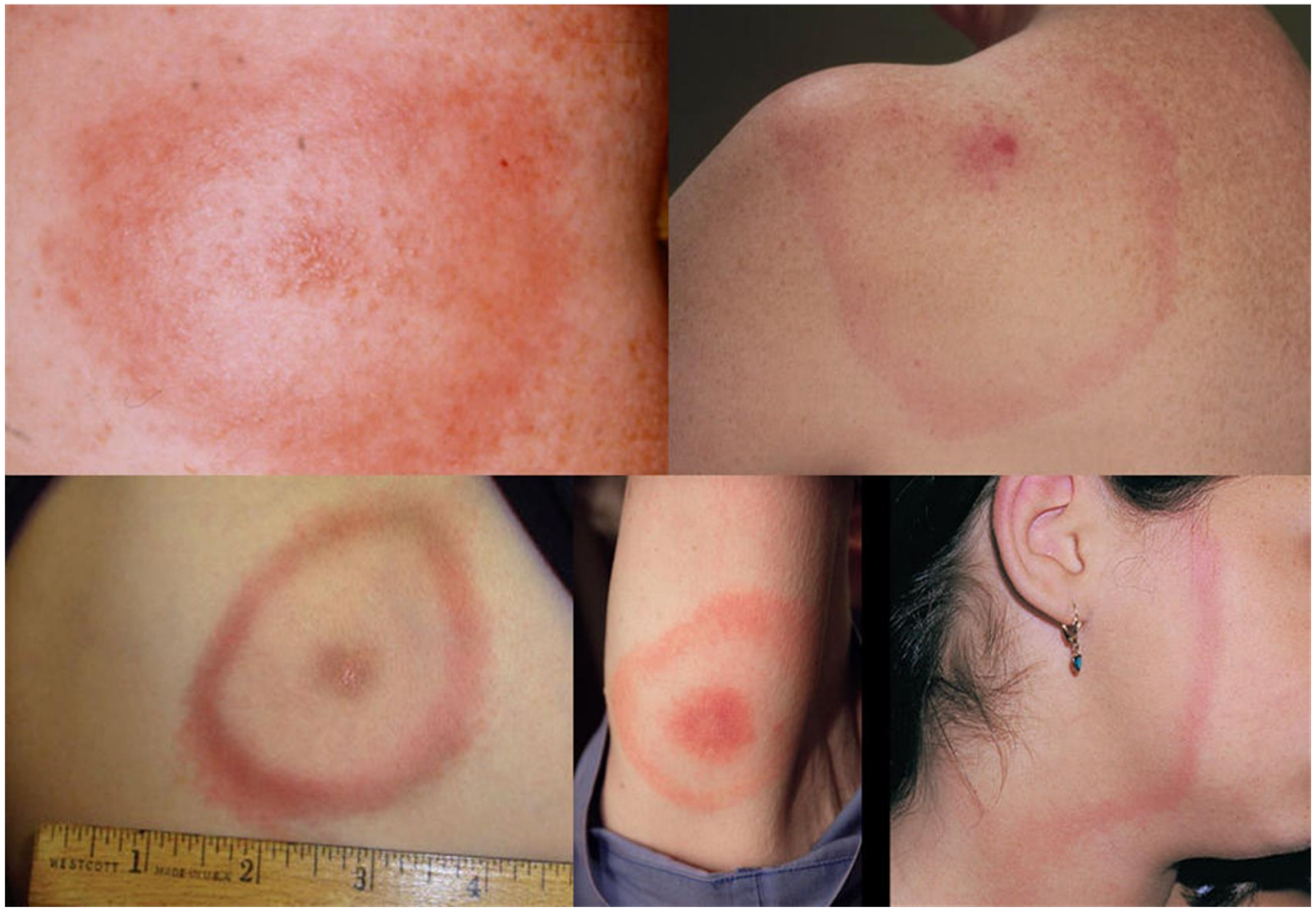
TREATMENT:

- ✓**Penicillin G IV** 18–24 million units per day, 10-14 days.
- ✓Alternative: **Procaine penicillin** G 2.4 million units IM once daily

  PLUS **Probenecid** 500 mg orally 4 times/day
- ✓Penicillin Allergy: **Ceftriaxone** (1–2 g daily IV or IM for 10–14 days)
- ✓**Follow-up Testing:** CSF analysis recommended every 6 months to monitor treatment success, along with periodic blood tests.
- ✓**Steroids:** Prednisolone are sometimes used for ocular syphilis.

NEUROBORRELIOSIS: *CLINICAL MANIFESTATIONS*

ERYTHEMA MIGRANS: 3-30 days, flu-like symptoms



"bull's-eye“ rash

NEUROLOGICAL SYMPTOMS ~15% of untreated pts.

EARLY PHASE (1-6 Mo):

Bannwarth’s syndrome

- Lymphocytic meningitis
- Cranial neuritis (especially facial palsy)
- Radiculoneuritis (pain, paresthesia)

LATE PHASE (>6 Mo):

- polineuropathy
- stroke
- encephaloptahy
- myelitis / encephalomyelitis,

Multisystemic involvement: skin, carditis, arthritis

NEUROBORRELIOSIS: *DIAGNOSIS*

- **SEROLOGY:** ELISA + Western blot confirmation
- **CSF:** lymphocytic pleocytosis, ↑ protein, intrathecal antibodies against *B. burgdorferi*
- **MRI:** may show nonspecific white matter lesions

TREATMENT:

14–21 DAY COURSE OF ANTIBIOTICS

- Oral **doxycycline** (200 mg/day)
- Intravenous **ceftriaxone**, **cefotaxime**, or **penicillin G**
- **Supportive Care:** for neurological pain (numbness, shooting pain), medications like **gabapentin or pregabalin** may be used

MYELITIS: Inflammatory disease of the **spinal cord**, which may be **infectious** (viral, bacterial, parasitic) or **non-infectious** (autoimmune, demyelinating).

Inflammatory
- Multiple sclerosis
- Neuromyelitis optica
- Transverse myelitis
- Sarcoidosis
- Sjögren-related myelopathy
- Systemic lupus erythematosus
- Vasculitis

Infectious
- Viral: VZV, HSV-1 and -2, CMV, HIV, HTLV-I, others
- Bacterial and mycobacterial: *Borrelia*, *Listeria*, syphilis, others
- *Mycoplasma pneumoniae*
- Parasitic: schistosomiasis, toxoplasmosis

CLINICAL FEATURES

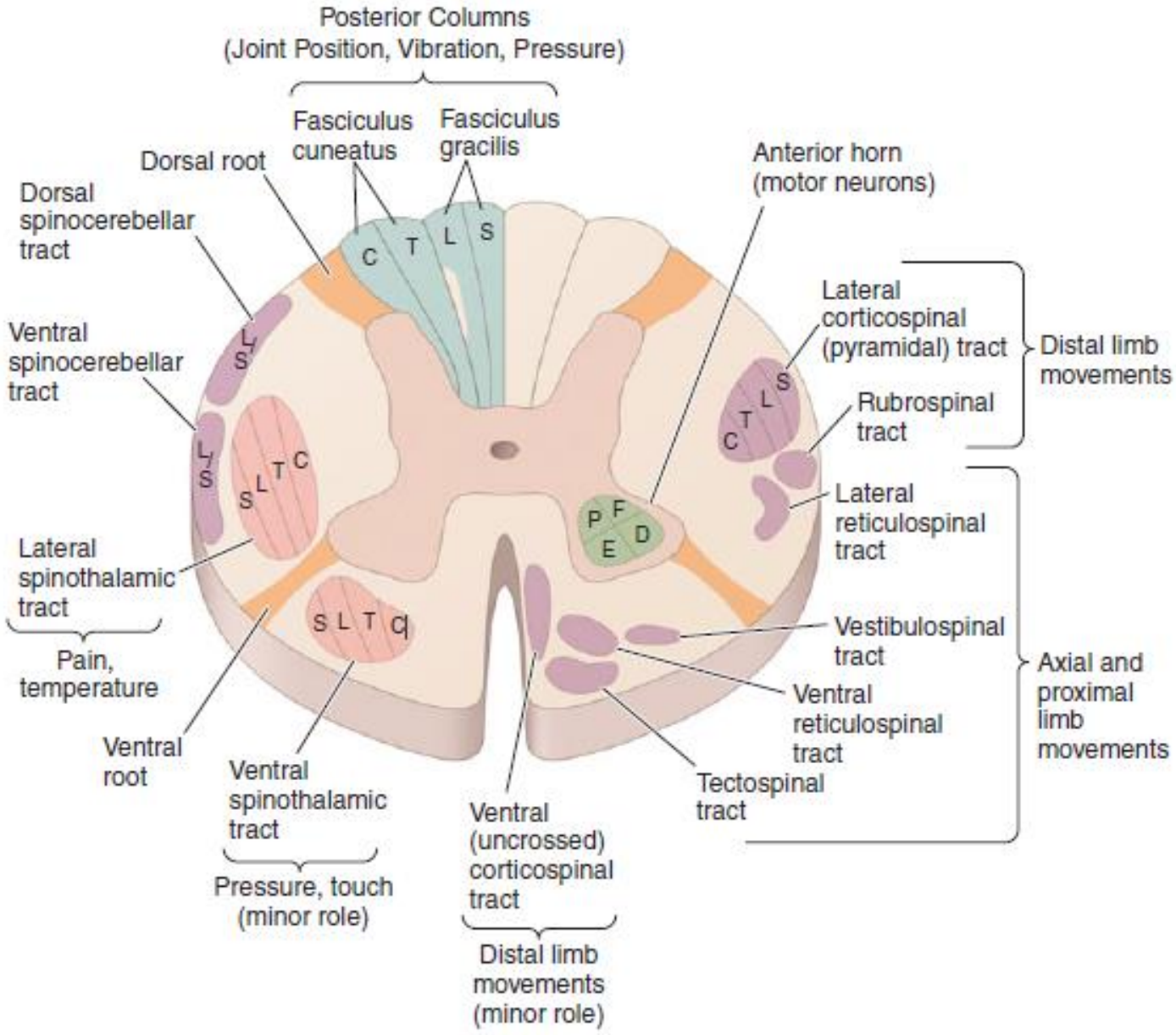
1. **Systemic infectious syndrome**

2. **Motor deficits:** paraparesis or tetraparesis

3. **Sensory disturbances:** sensory level, conduction-type deficits

4. **Sphincter dysfunction:** urinary/fecal retention or incontinence

5. **Autonomic involvement**



MYELITIS: DIAGNOSIS

1. MRI of the spinal cord detects inflammatory lesions

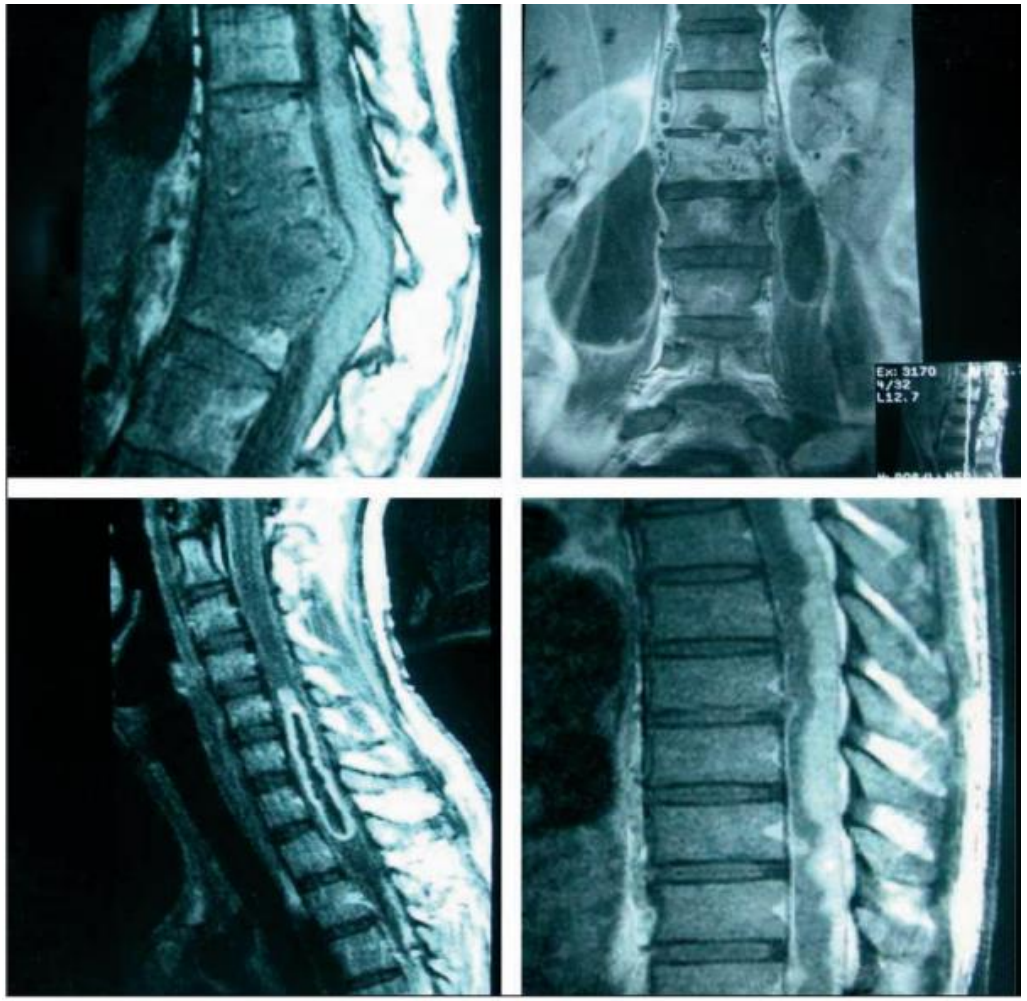
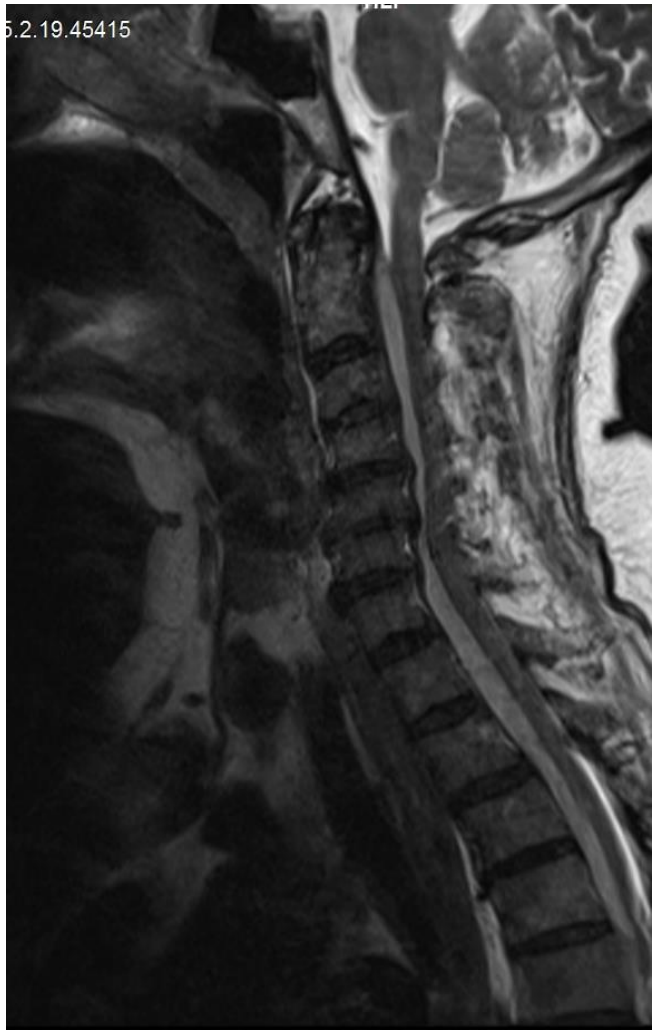
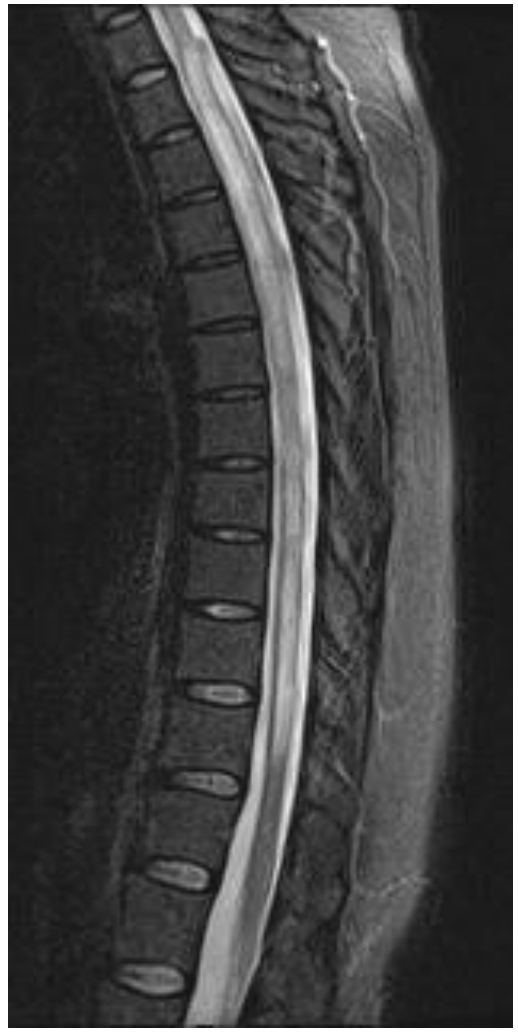


Figure 3: MRI showing spinal tuberculosis associated with TM
Vertebral tuberculosis causing impingement on the spinal cord (top left); extensive vertebral tuberculosis with bilateral fusiform tuberculous paravertebral abscesses (top right); cervical-cord tuberculoma causing quadriplegia (bottom left); tuberculous radiculomyelitis showing loculation and obliteration of the spinal subarachnoid space with nodular intradural enhancement (bottom right).

TB



Cervico-toracic empiema



Postinfectious myelitis

MYELITIS: DIAGNOSIS

2. CSF analysis:

- Pleocytosis, elevated proteins
- Oligoclonal bands
- CSF PCR for viruses, serology
- Ab: *HTLV, B. Burgdorferi, Mycoplasma pneumoniae, Chlamidia etc.*

3. Blood analysis:

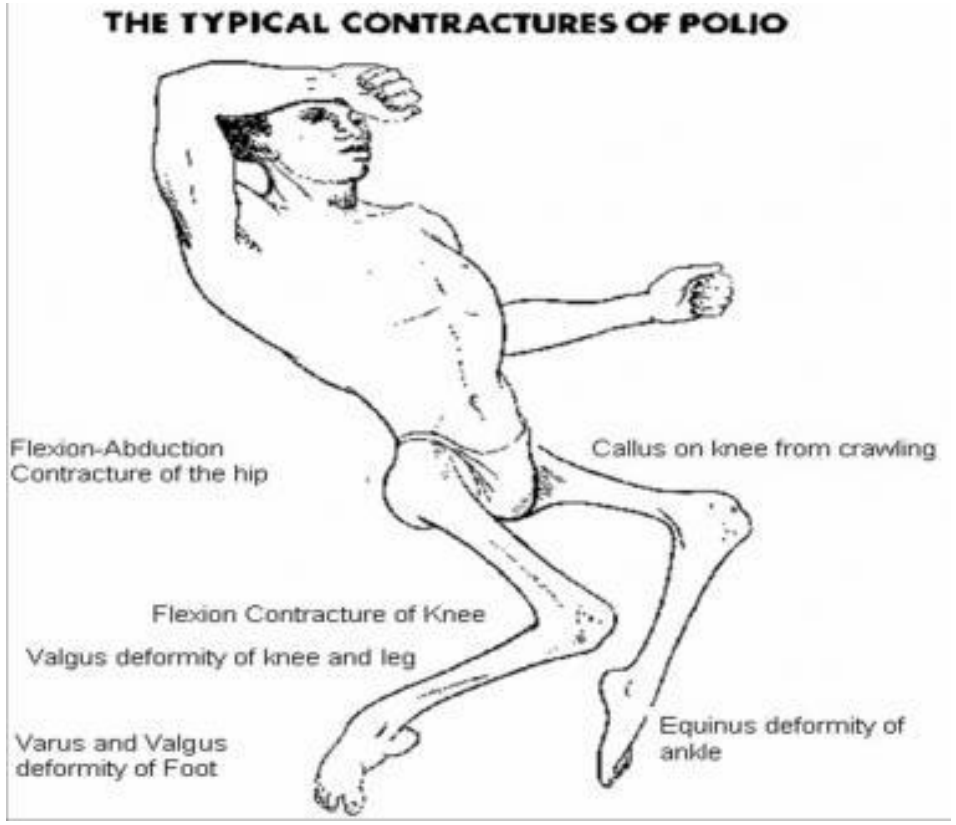
- Infectious agents
- autoimmune diseases (sarcoidois, Sjogren …)

4. Exclusion of demyelinating diseases (MS, NMO)

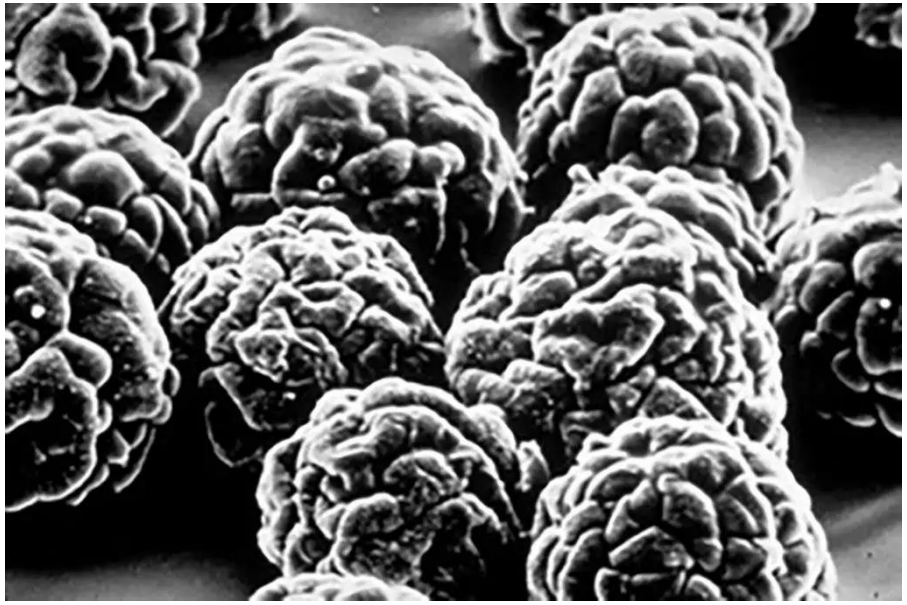
5. Exclusion of vascular causes (AVM, dural fistula)

POLIOMYELITIS

Infectious disease of the CNS, caused by the poliomyelitis virus, with predominant damage to the medullary gray matter (anterior horns) and the brainstem.



POLIOMYELITIS: GENERAL INFORMATION



Causative agent: *Poliovirus* (enterovirus, family *Picornaviridae*), 3 serotypes
Transmission: fecal–oral or airborne
Risk factors: lack of vaccination, travel to endemic areas

PATHOGENESIS

Virus colonizes **pharynx and intestine**
95% – asymptomatic or mild (pharyngitis/enteritis)
5% – CNS involvement
- Selective destruction of **anterior horn motor neurons** in spinal cord
- Possible involvement of **brainstem (bulbar form)**

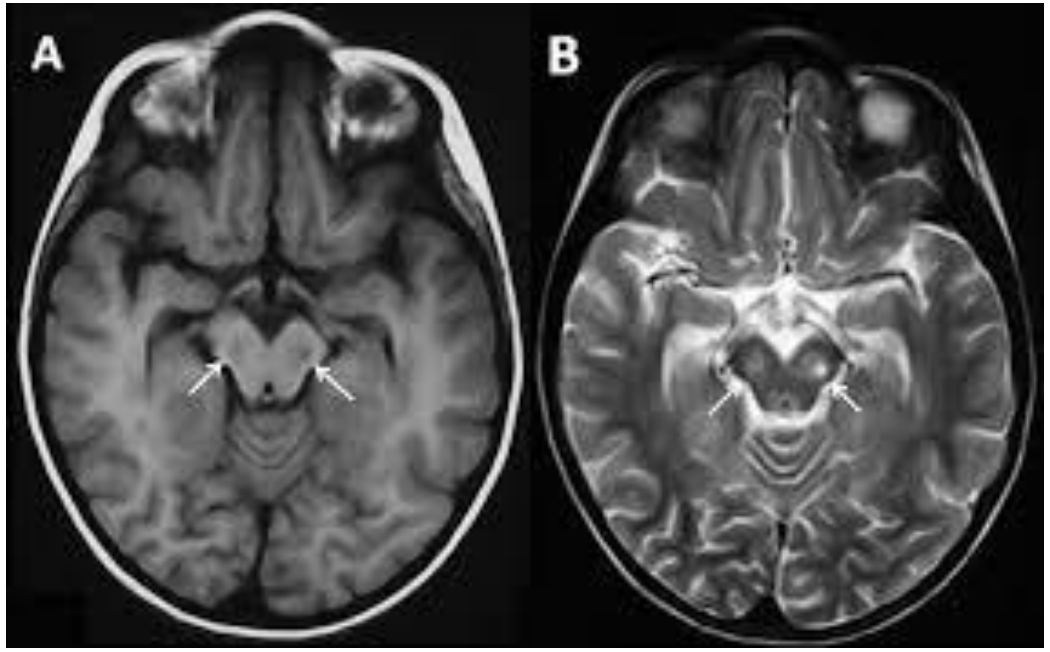
CLINICAL FORMS

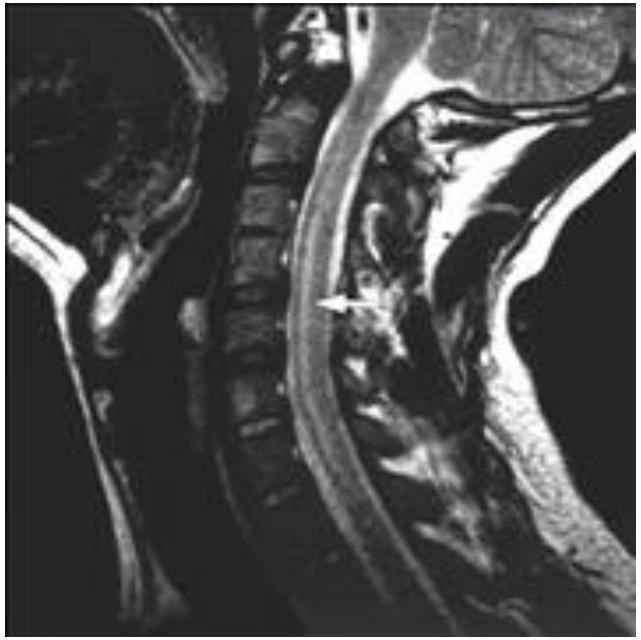
***Non-paralytic* (meningitic / pre-paralytic):** headache, stiff neck, mild meningeal signs

***Paralytic*:**
- Muscle pain, cramps → asymmetric weakness
- Peak within 48 h
- **Lower limbs** > upper limbs
- **Bulbar involvement:** dysphagia, respiratory failure

POLIOMYELITIS: *DIAGNOSIS, TREATMENT*

- **CSF:** meningitic pattern (pleocytosis, moderate protein rise)
- **Blood:** inflammatory markers
- **Virology:** virus isolation from pharynx, stool, blood, or CSF
- **MRI:** spinal cord anterior horn lesions





TREATMENT:

➢No specific antiviral therapy

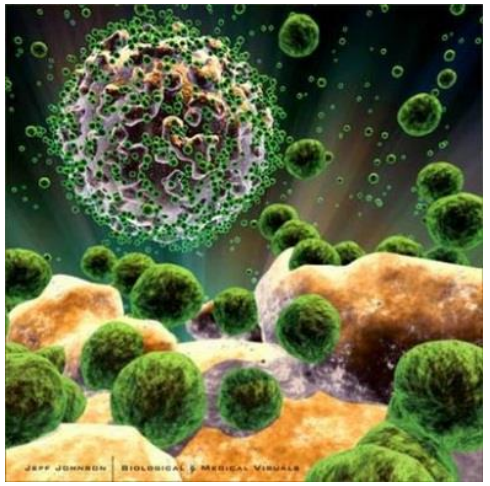
➢Supportive: respiratory care, physiotherapy, prevention of deformities

PREVENTION:

Vaccination (OPV/IPV – oral or inactivated polio vaccine)

Strict hygiene in endemic zones

HIV/AIDS AND THE NERVOUS SYSTEM



Agent: Human Immunodeficiency Virus (HIV-1), family *Retroviridae*, genus *Lentivirus*

Target: cells with **CD4 receptors** (T-helper lymphocytes), macrophages, microglia, astrocytes, oligodendrocytes

1985 - HIV-1 - isolated from: brain, spinal cord, CSF, peripheral nerves

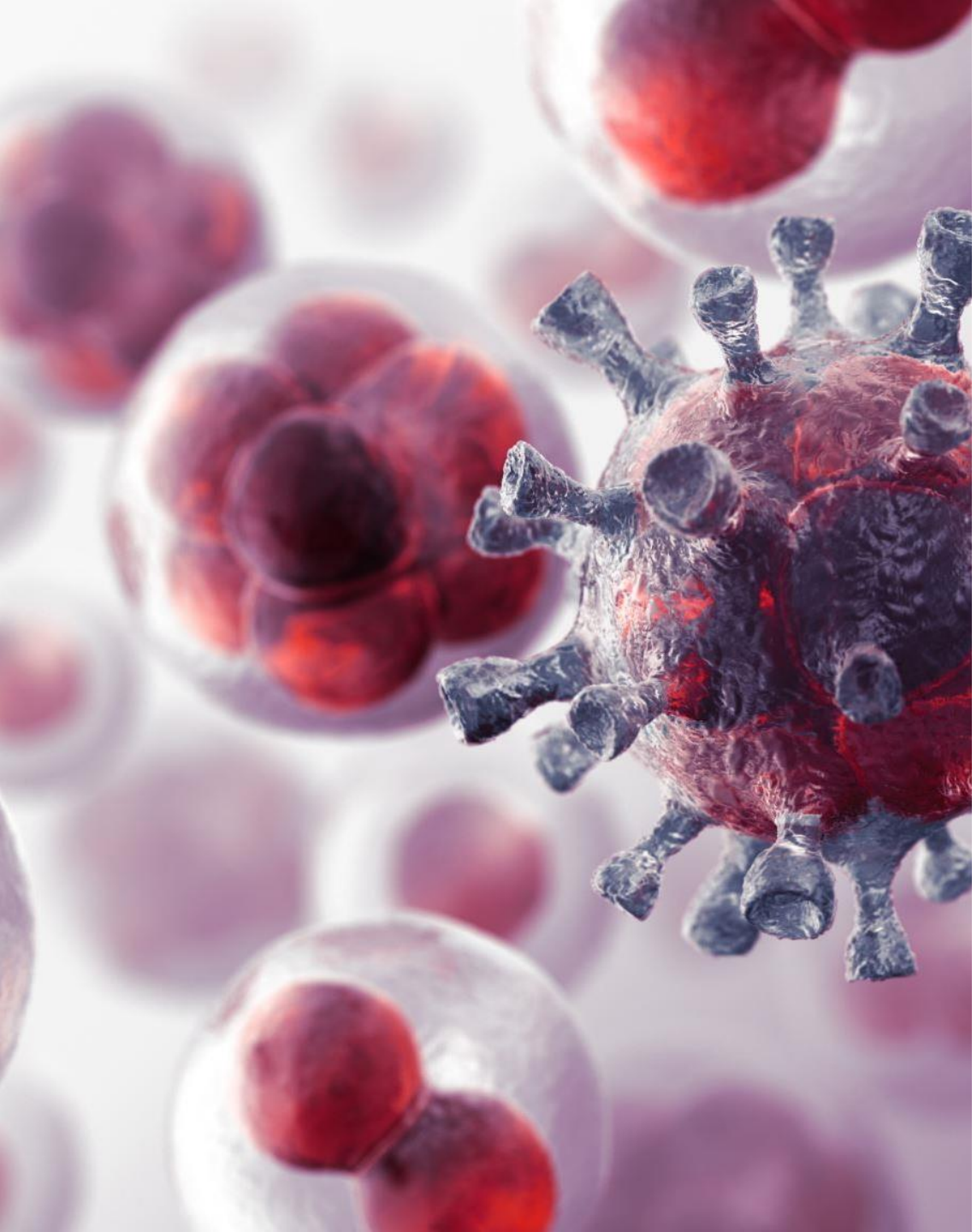
1985-1988 – clinical, virological, morphopathological studies:

discovery of viral RNA, DNA in the brain

demonstration of intrathecal synthesis of anti-HIV antibodies

localization of HIV-1 antigens in brain macrophages and monocytes

increased levels of HIV-1 DNA in the brain compared to other organs



NEUROTROPIC PROPERTIES OF HIV

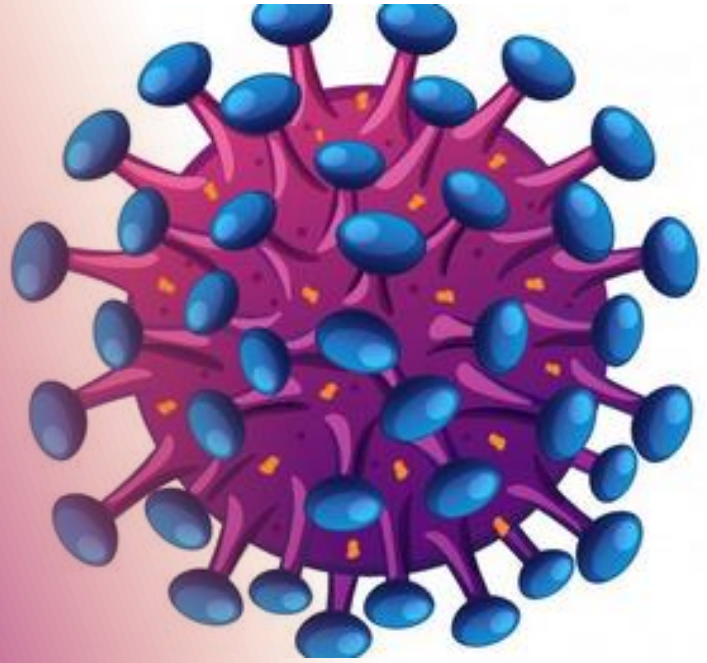
NEUROINVASIVE: enters CNS early after infection

NEUROVIRULENT: causes diverse neurological disorders

≈70% of HIV/AIDS patients develop neurological manifestations

In **≈10%**, these are the **initial presentation** of HIV infection

HIV-RELATED NEUROLOGICAL MANIFESTATIONS



DIRECT VIRAL EFFECTS:

- Meningitis
- Peripheral neuropathy
- HIV dementia (HIV-associated neurocognitive disorders)
- HIV-associated myelopathy
- HIV myopathy

OPPORTUNISTIC INFECTIONS

- Toxoplasmosis
- Cryptococcosis
- Tuberculosis
- Citomegalovirus meningitis / encephalitis
- Progressive multifocal leukoencephalopathy (PML)

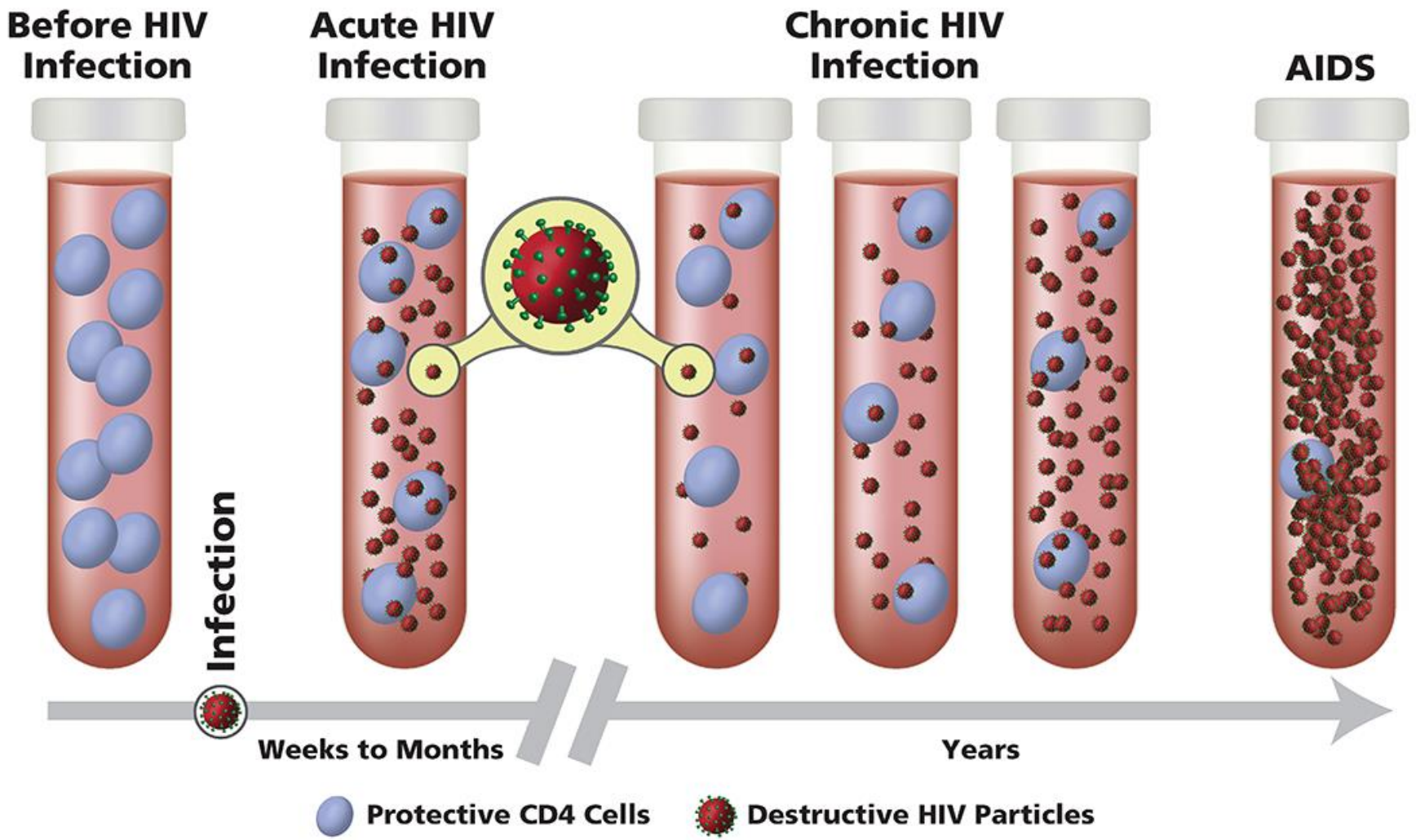
MEDICATION SIDE EFFECTS:

- Peripheral neuropathy
- Myopathy

MALIGNANCIES

- Primary central nervous system (CNS) lymphoma
- Metastatic lymphoma

DIRECT CORRELATION BETWEEN CD4 LEVELS AND NEUROLOGICAL MANIFESTATIONS



HIV INFECTION MANIFESTATIONS ACCORDING TO CD4 LEVEL

CD4 Level	Nervous System Manifestations	Systemic Manifestations
Regardless of CD4 count	▪ HIV meningitis ▪ Herpes simplex virus meningitis ▪ Mononeuropathy (cranial nerve VII) ▪ Guillain–Barré syndrome	▪ Pulmonary tuberculosis ▪ Varicella-zoster infection ▪ Bacterial pneumonias ▪ Kaposi's sarcoma ▪ Non-Hodgkin lymphoma
<250 /ml	▪ PML – Progressive multifocal leukoencephalopathy ▪ HIV-associated dementia ▪ Distal sensory polyneuropathy	▪ Pneumocystis pneumonia ▪ Oropharyngeal candidiasis ▪ Herpetic infection
<100 /ml	▪ Cerebral toxoplasmosis ▪ Cryptococcal meningitis ▪ CNS tuberculosis	▪ Miliary tuberculosis
<50 /ml	▪ CMV meningoencephalitis ▪ Primary CNS lymphoma	▪ Cytomegalovirus retinitis ▪ Atypical bacterial infections

TREATMENT

ANTIRETROVIRAL THERAPY (ART)

(regardless of CD4 count or clinical stage, to reduce morbidity, mortality, and transmission risk)

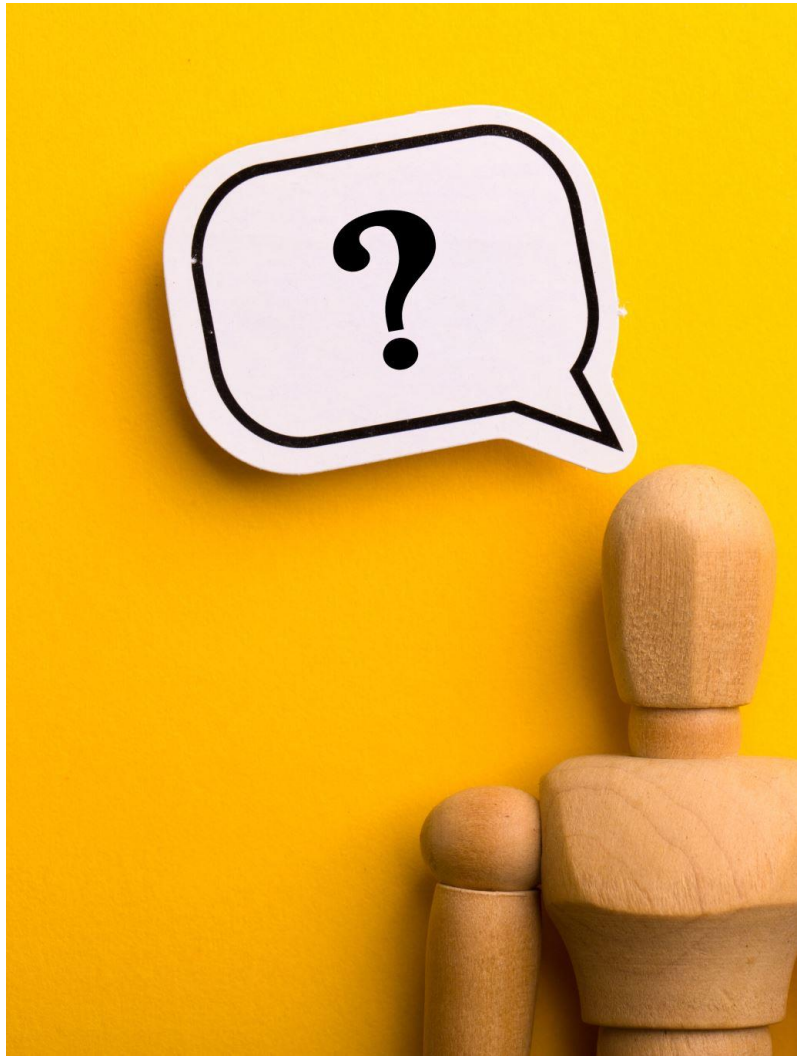
- Tenofovir disoproxil fumarate / Emtricitabin / Lamivudinum / Abacavirum / Zidovudinum

  Dolutegravirum / Efavirenzum

MANAGING OPPORTUNISTIC INFECTIONS, CO-INFECTIONS AND CO-MORBIDITIES

EQUITY AND HUMAN RIGHTS

- ✓ Test for syphilis in unexplained neurological disease
- ✓ Suspect neuroborreliosis in tick-endemic areas with facial palsy
- ✓ MRI + steroids are first-line in acute myelitis
- ✓ Vaccination prevents paralysis — polio is nearly eradicated
- ✓ ART (antiretroviral therapy) saves the brain — controlling HIV prevents opportunistic CNS infections.



NEUROINFECTIONS: KEY TAKEAWAYS

Neuroinfections shaped the history of medicine and microbiology.

Progress depends on early diagnosis and specific therapy.

Vaccination remains the cornerstone of prevention.

Despite advances, timely clinical recognition is still the greatest challenge.