Infections of central nervous system

Prof. Carlo Ferrarese

definitions

meningitis – inflammation of the meninges

encephalitis – inflammation of brain parenchyma

myelitis – inflammation of spinal cord

epidemiology

meningitis endemic in western countries

- incidence is 5-10/100,000 per year, winter
- 80% are Neisseria and Strept pneumoniae
- viral meningitis twice as common, summer

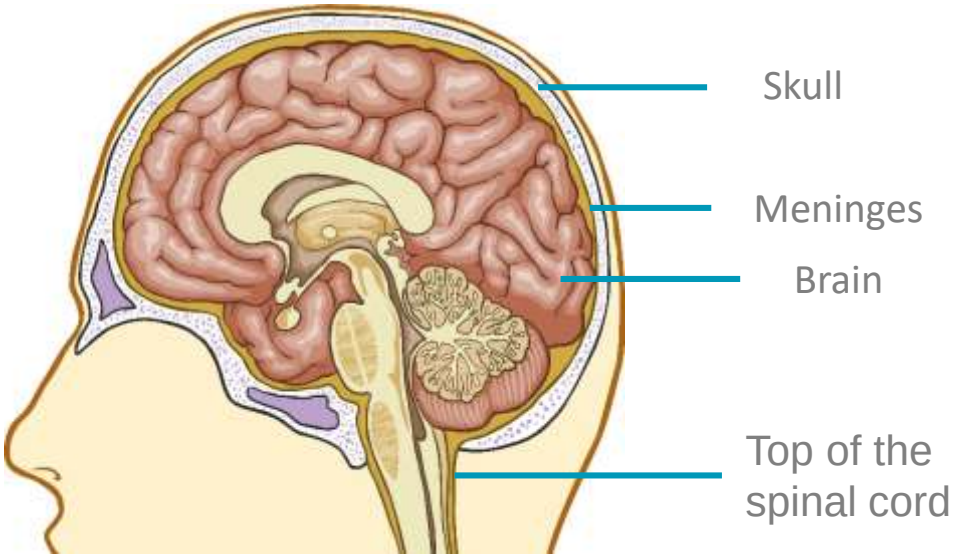
encephalitis less common but incidence rising due to West Nile Virus

rare brain abscesses due to sinusitis, otitis media, immunocompromised patients

MENINGITIS

What is meningitis?

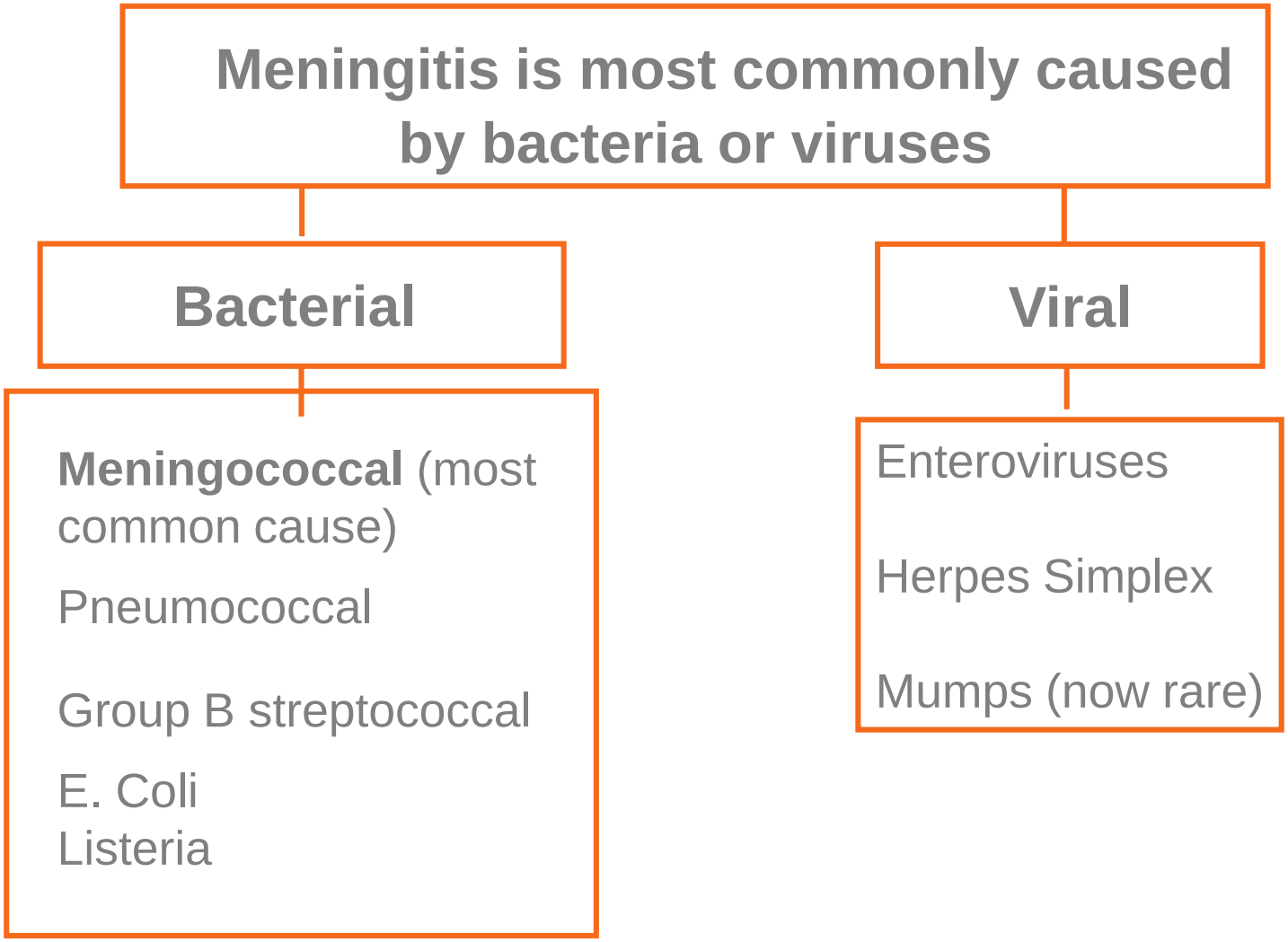
Inflammation of the protective layers (meninges) that surround the brain and part of the spinal cord



What is septicaemia?

Some bacteria that cause meningitis can also cause septicaemia. Septicaemia is a cause of sepsis - a life-threatening condition that arises when the body's response to an infection injures its own tissues and organs.

What causes meningitis?



Other aetiologies

- fungal – crypto, histo, blasto, coccidioides
- parasites – toxo, neurocyster., trichinosis
- rickettsiae
- non-infectious – post inf, drugs, autoimmune

Mollaret meningitis

- Mollaret meningitis is characterized by recurrent episodes of viral meningitis. The episodes of meningitis usually last from two to five days and then go away on their own, but the time in between episodes varies among people with the disease, from weeks to years.
- Some people have milder symptoms during recurrences, which do not necessarily require hospitalization.

Viral and bacterial meningitis

Viral meningitis

Rarely life-threatening

Pain relief, fluids and rest

Not considered to be contagious

After-effects include headaches, tiredness and memory loss

Bacterial meningitis

Life-threatening

Rapid admission to hospital, treated with antibiotics

Can be contagious and may require public health action

After-effects include deafness, acquired brain injury and limb loss (septicaemia)

Meningococcal disease

- A term used to describe two major illnesses – meningitis and septicaemia caused by meningococcal bacteria
- Meningococcal disease is the most common cause of bacterial meningitis
- There are five main groups of meningococcal bacteria that commonly cause disease - MenA, MenB, MenC, MenW, MenY
- MenB causes the majority of the disease

Recognising the signs and symptoms

- Meningitis and septicaemia often happen together. Be aware of all the signs and symptoms
- Symptoms can appear in any order. Some may not appear at all
- Someone with meningitis or septicaemia can get a lot worse very quickly. Keep checking them

clinical presentation

headache

fever

nausea/vomiting

seizures

altered mental status

nuchal rigidity

photophobia

many present atypically (old, young, immune compromised, aseptic)

Headache 87%

Neck stiffness 83%

Fever 77%

Change in mental status (GCS<14) 69%

clinical presentation

often have a primary source of infection on exam (sore throat, sinusitis, OM, etc.)

purpuric rash with menincococcemia

sudden acceleration of headache

Kernig Sign – can't extend knee to 180 while laying supine with hip in flexion

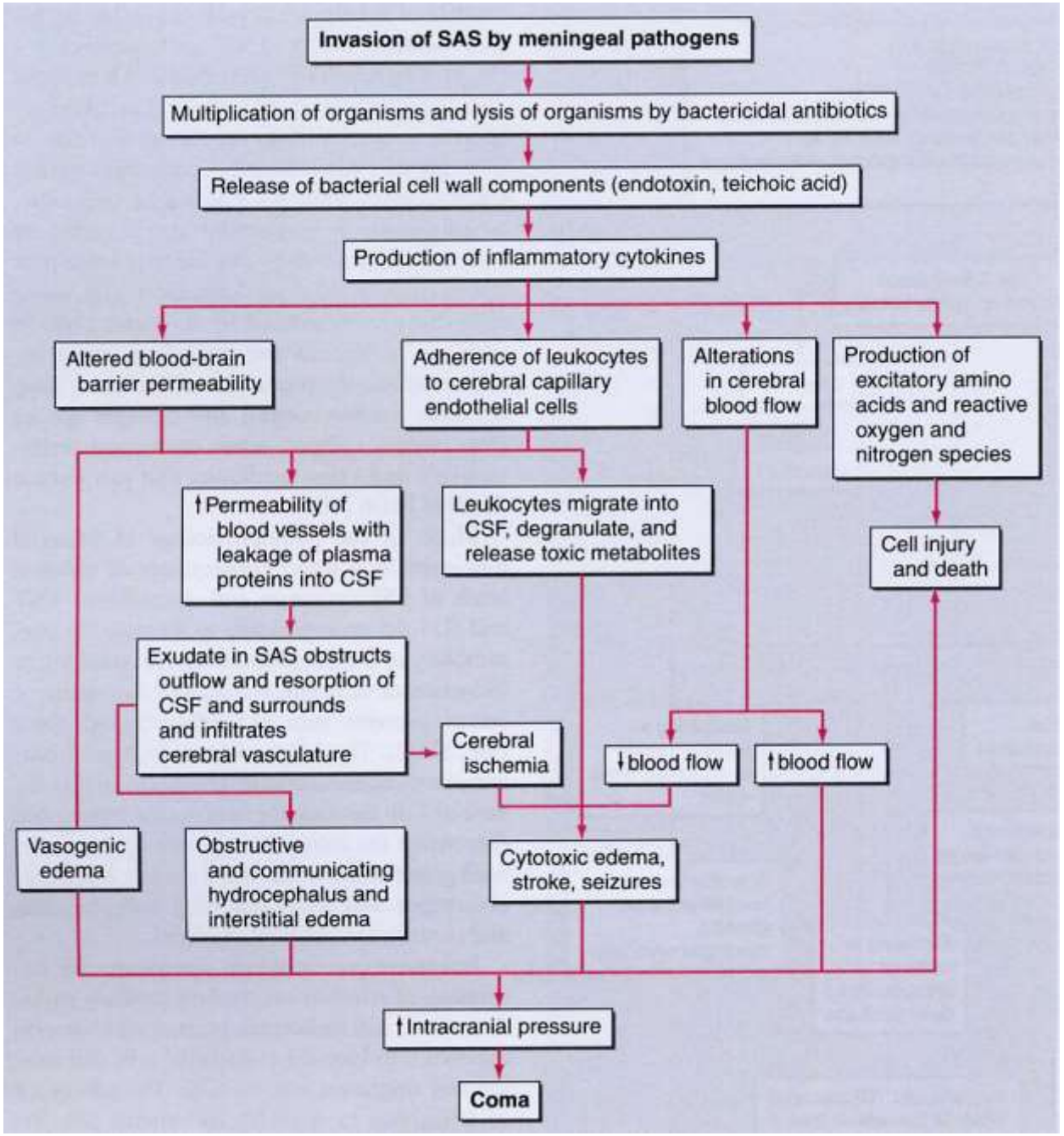
Brudzinski Sign –flexion of neck causes hip flexion

pathophysiology

nasopharyngeal colonization → mucosal invasion → enter blood stream → evade immune destruction → cross blood brain barrier into CSF

meningeal inflammation → increased permeability of BBB, vasculitis, edema, increased ICP

decreased cerebral perfusion, decreased CSF glucose, increased CSF protein


Invasion of SAS by meningeal pathogens
Multiplication of organisms and lysis of organisms by bactericidal antibiotics
Release of bacterial cell wall components (endotoxin, teichoic acid)
Production of inflammatory cytokines
Altered blood-brain barrier permeability
Adherence of leukocytes to cerebral capillary endothelial cells
Alterations in cerebral blood flow
Production of excitatory amino acids and reactive oxygen and nitrogen species
↑Permeability of blood vessels with leakage of plasma proteins into CSF
Leukocytes migrate into CSF, degranulate, and release toxic metabolites
Cell injury and death
Exudate in SAS obstructs outflow and resorption of CSF and surrounds and infiltrates cerebral vasculature
Cerebral ischemia
↓blood flow
↑blood flow
Vasogenic edema
Obstructive and communicating hydrocephalus and interstitial edema
Cytotoxic edema, stroke, seizures
↑Intracranial pressure
Coma

complications

acute – coma, seizure, loss of airway reflexes, respiratory arrest, cerebral edema, DIC, dehydration, death

delayed – seizures, paralysis, cognitive deficits, hydrocephalus, hearing loss, ataxia, blindness, death complications from viral meningitis are rare

DIAGNOSIS

CT before LP?

Should be performed in most patients with suspected meningitis, particularly with:

- focal neuro deficits
- altered mental status/coma
- papilledema
- seizures
- trauma

- Risk of herniation if increased ICP!

lumbar puncture

collect at least 3 tubes of 1 mL each

Normal features

opening pressure = 5-20 cm H2O

clear and transparent like water

cell count <5 WBC/mm3

differential <1 PMN/mm3

protein = 15-45 mg/dL

glucose = 60% blood glucose

Negative CSF Gram stain: distinguishing bacterial from viral meningitis

CSF glucose	<34 mg/dl
CSF/serum glucose ratio	<0,23
CSF protein	>50 mg/dl
CSF WBC count	>2000 WBC/mm^3
CSF neutrophil count	>1000 neutrophils/mm3

Bacterial meningitis with >99% certainty

adjuncts to LP

blood cultures

- often have higher yields for bacteria

Blood chemistry panel

- compare glucose to CSF, renal function

CXR

- 50% w/strep pneumo meningitis have pulmonitis

EEG – encephalitis (HSV)

MANAGEMENT

Resuscitation procedures

fulminant presentation

- septic shock
- seizures
- cerebral edema
- hypoxia
- loss of airway reflexes

standard supportive measures

- mannitol for cerebral edema
- empiric antibiotics as soon as possible

Empiric antibiotic regimen

vancomycin plus

- ceftriaxone or
- cefotaxime or
- meropenem or
- chloramphenicol

add ampicillin if >50 yrs

neonates: cefotaxime + ampicillin

special cases: penetrating trauma, post neurosurgery, VP shunt

Table 8. Duration of antimicrobial therapy for bacterial meningitis based on isolated pathogen (A-III).

Microorganism	Duration of therapy, days
Neisseria meningitidis	7
Haemophilus influenzae	7
Streptococcus pneumoniae	10–14
Streptococcus agalactiae	14–21
Aerobic gram-negative bacilli[a]	21
Listeria monocytogenes	≥21

[a] Duration in the neonate is 2 weeks beyond the first sterile CSF culture or ≥3 weeks, whichever is longer.

other medications

acyclovir for suspected HSV

INH, rifampin, etc. for TB

amphotericin B for fungal (not in ED)

flagyl for CNS abscess

- also early neurosurgical consultation

steroids in meningitis

dexamethasone has been shown to reduce cerebral edema, ICP, CSF lactate

past studies with variable results

- dexamethasone for strep pneumoniae

chemoprophylaxis

rifampicin 600 mg x4 doses in household contacts

ciprofloxacin 500 mg x1 dose in HCW with direct contact (intubation, suctioning)

CNS ABSCESS

etiology

usually invasion from more common head infections (otitis media, sinusitis, dental infections, etc.)

streptococcus most common

also bacterioides, staph aureus, propionbacterium, enterobacteriae

clinical presentation

similar to encephalitis, often difficult to differentiate clinically

usually subacute (>2 weeks onset) course of illness

often have papilledema

acute worsening can occur with rupture of abscess into ventricles or with uncal herniaton

can mimic intracranial hemorrhage

complications

mortality >50% without aggressive care

- <20% with surgical aspiration + abx

80% develop seizure disorder

cognitive deficits, focal neuro deficits common

epidural abscess → paralysis, motor & sensory deficits, bowel/bladder dysfunction

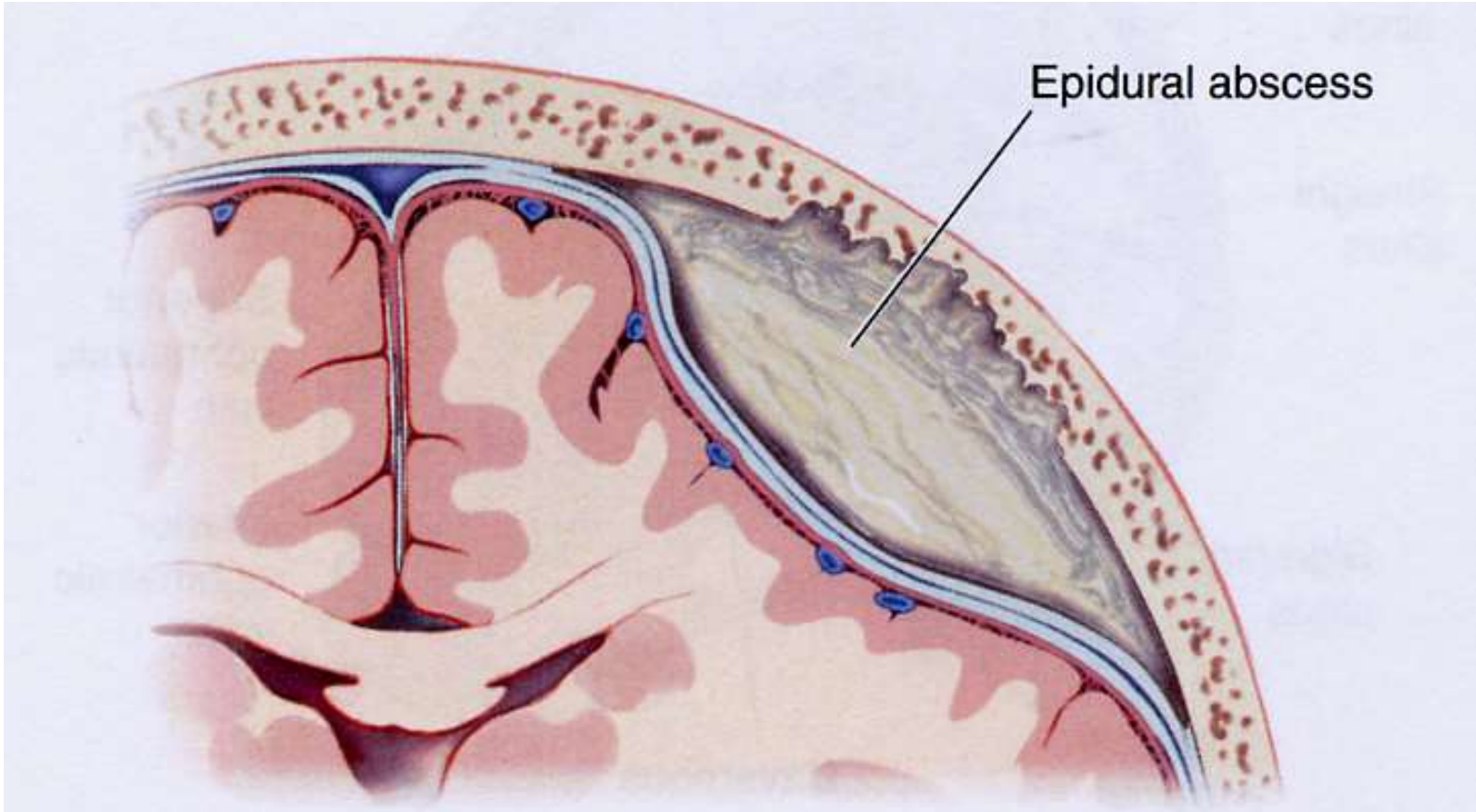


FIGURE 376-7 Cranial epidural abscess is a collection of pus between the dura and the inner table of the skull.

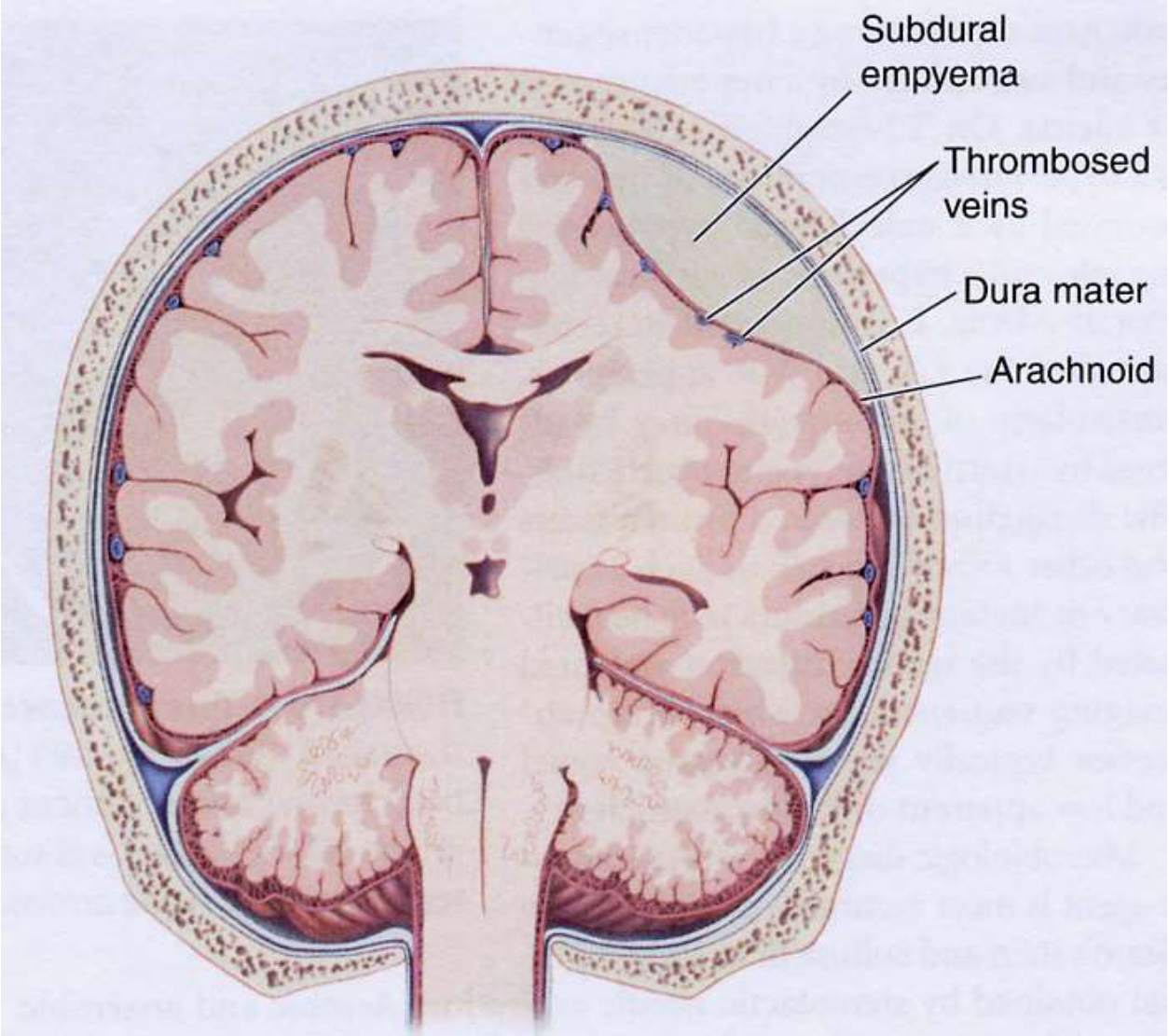


FIGURE 376-5 **Subdural empyema.**

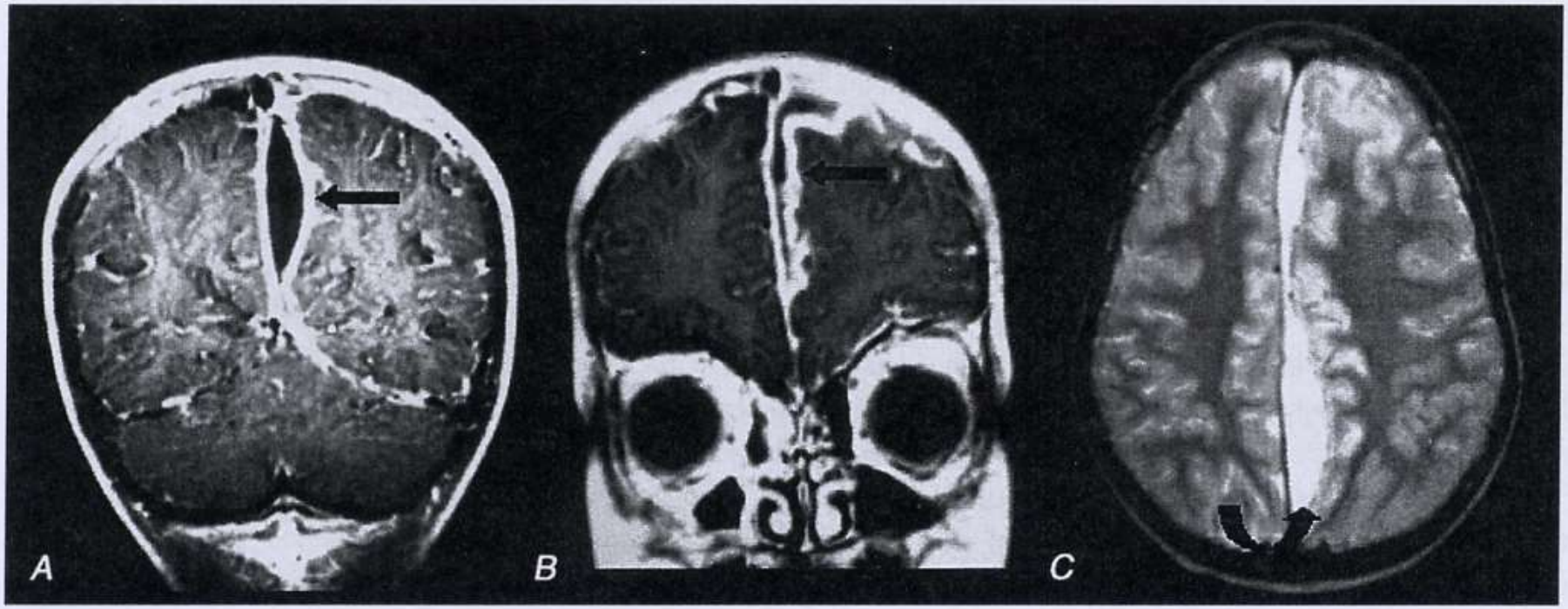


FIGURE 376-6 Subdural empyema. There is marked enhancement of the dura and leptomeninges (***A***, ***B***, *straight arrows*) along the left medial hemisphere. The pus is hypointense on T1-weighted images (***A***, ***B***) but markedly hyperintense on the proton density–weighted (***C***, *curved arrow*) image. *(Courtesy of Joseph Lurito, MD; with permission.)*

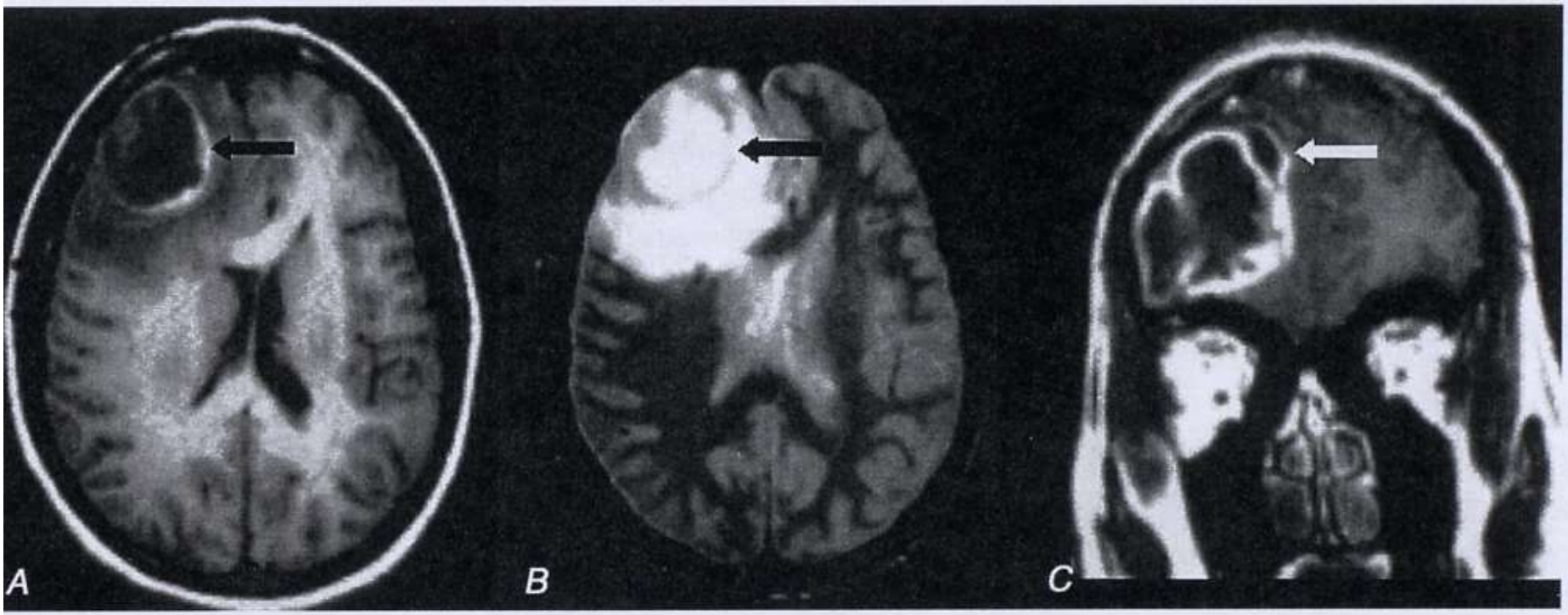


FIGURE 376-4 Pneumococcal brain abscess. Note that the abscess wall has hyperintense signal on the axial T1-weighted MRI (***A***, *black arrow*), hypointense signal on the axial proton density images (***B***, *black arrow*), and enhances prominently after gadolinium administration on the coronal T1-weighted image (***C***). The abscess is surrounded by a large amount of vasogenic edema and has a small "daughter" abscess (***C***, *white arrow*). (*Courtesy of Joseph Lurito, MD; with permission.*)

Epidural Spinal Abscess

Definition

- Infection of epidural space of spinal cord leading to compression of spinal cord and/or nerve roots
- Classical clinical symptoms include:
  - **Back or neck pain**
  - **Fever**
  - **Neurologic simptoms and signs**
- Rapid diagnosis and treatment are necessary to avoid permanent neurologic deficits

Etiologies

- Hematogenous diffusion from:
  - Skin Infections
  - Deep visceral infections (bacterial endocarditis)

- Direct diffusion to epidural space from local infection
  - Vertebral osteomielitis
  - Decubitus ulcer
  - Iatrogenic complications of
    - Spinal surgery
    - Epidural anesthesia
    - Lumbar puncture

- Bacteria involved
  - Most cases due to *Staphylococcus aureus* or other *Staphylococcus*.
  - Other causes
    - Gram-negative bacteria
    - Anaerobic bacteria
    - Fungi
    - Micobacterium Tubercolosis
  - In some cases multiple bacteria are involved

Diagnosis

- In a patient with bilateral weakness of legs and back pain it is mandatory to perform urgent MRI of column.

Treatment

- Surgical and AbTx

Chronic meningitis

- **Tuberculosis**
- **Borreliosis**
- **Syphilis**

Sneaky and underhand clinical presentation

CSF: lymphocitic increase, protein increase, glucose decrease

Tubercular meningitis: pathogenesis

- Initially small tubercular foci in brain, spinal cord and meninges.
- Rupture of a follicle spreads bacteria and their antigens in subaracnoid space inducing immune reaction.
- This leads to proliferative aracnoiditis and meningeal essudate particular in basal and posterior brain areas
- Vasculitis of small and medium vessels and subsequent infarcts
- Abnormal drainage of CSF due to block of flow in Silvius acqueduct and impaired rebsorption in aracnoideal villi, leading to hydrocephalus

Tubercular meningitis: clinical presentation

- Usually aspecific symptoms (tiredeness, light recurrent fever) precedes slow onset of headache.
- In child the most prominent symptoms are irritability or sleepiness, in adult headace is the most common simptom.
- Gradually neurologic picture becomes manifest with meningeal signs, somnolence, headache (due to increased intracranial pressure), then epileptic seizures may occur and onset of focal neurologic deficits
- Cranial nerve involvement is common, in decreasing order : VI, III, IV, VII, II, VIII, X, XI, XII.

Neuroborreliosis (Lyme disease)

- Zoonosis trasmitted by mint, caused by Borrelia Burgdorferi (Bb).
- Affects at different stages skin, heart, joints and nervous system.
- *Stage 1 (locale skin reaction)*- eritema migrans, from 3 to 30 days after mint bite, lasting few weeks.
- *Stage 2 (early disseminated stage)*- within 3 months, characterized by heart problems (pericarditis, rhytm abnormalities), muscular and joint pain, finally a variety of NS disorders, manifesting as:
- meningitis, cranial neuritis, radiculitis, mono and polineuropaties

Stage 3 (neuroborreliosi tardiva)

- 70% of untreated cases, characterized by:
  - Atrofic chronic Acrodermatits
  - Chronic axonal Neuropaty
  - Chronic Meningitis, progressive mieloradiculopathy, progressive encephalomyelitis
  - Subacute Encephalopathy

- The latter is characterized by alterations of memory, behaviour, sleep-wake cycle, marked asthenia.

  If untreated, progressive course with onset of piramidal, cerebellar signs and dementia.

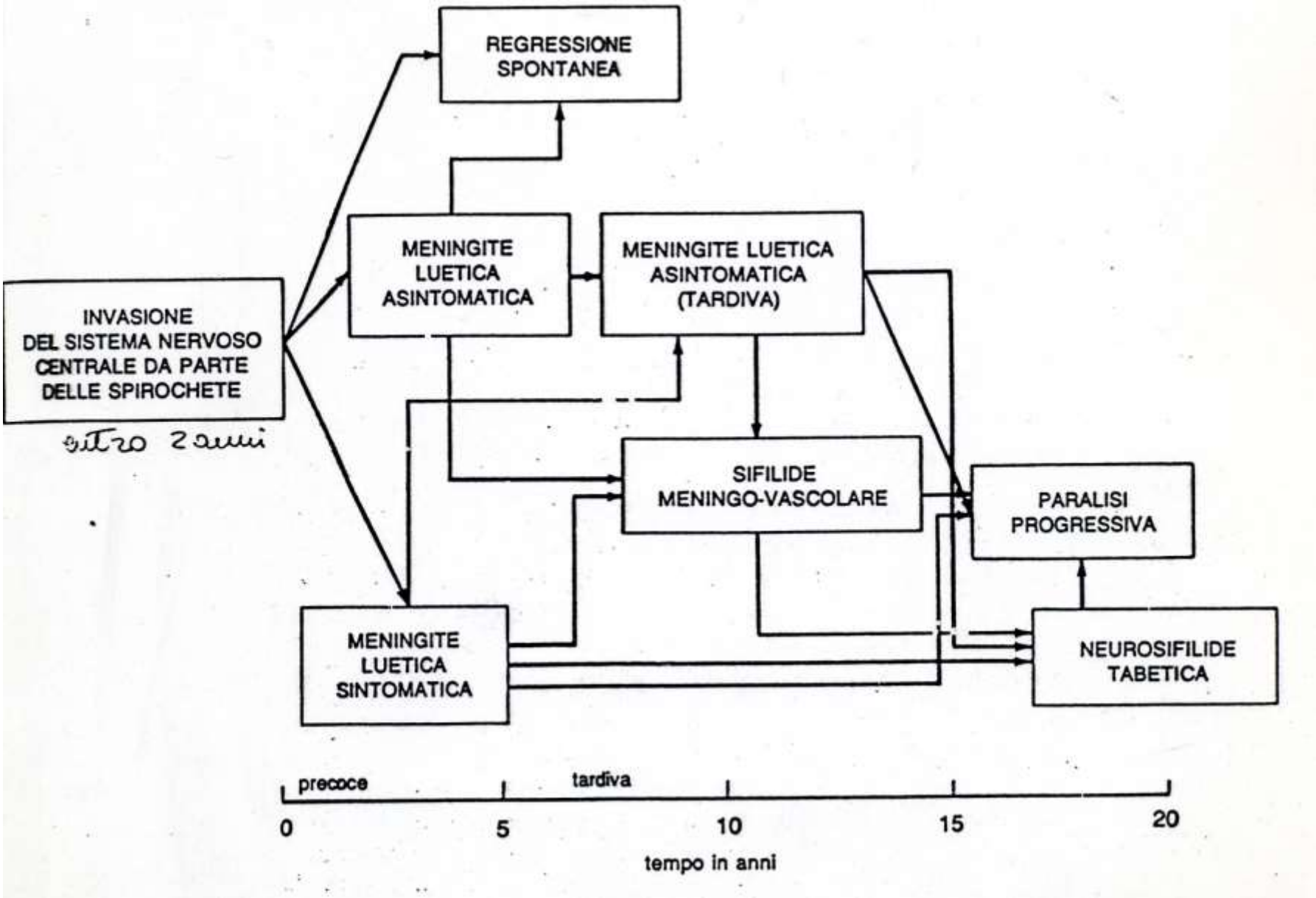
DIAGNOSIS

- seric levels of IgM and then IgG specific for *Bb*
- CSF antibodies against *Bb* (intratecal production)
- Quantitative analysis by PCR of Bb DNA, both in serum and in CSF
- Active phase: increased CSF lymphocytes and slight decreased glucose

Therapy

- penicillines, erytromicines, cephalosporines and e tetracyclines more effective in early stages

Neurosyphilis



Meningovascular syphilis

- Appears as focal signs of brain or spinal cord involvement 5-10 years after infection.
- Sudden onset, sometimes preceeded by aspecific signs (memory impairment, weakeness).
- Most common focal signs are: aphasia, emiparesis, epileptic seizures.
- Spinal infarcts manifest as paraparesis and sfinter problems, with sub-lesional anaesthesia
- Diagnosis is by positivity of VDRL on blood and CSF.
- CT and NMR may show ischemic lesions.
- Penicilline therapy may prevent onset of new ischemic lesions.

Progressive Paralysis

- Caused by invasion of brain by Treponema Pallidum, leading to frontal and temporal atrophy 15 years after primary infection.
- Characterized by progressive cognitive impairment with memory deficits and behavioural disorders, personality change, leading to severe dementia, disartria, epilaptic seizures, piramidal and extrapiramidal signs may also occur.
- Characteristic Argyll Robertson sign, characterized by loss of direct fotomotor reflex with preservation of miosis with accomodation reflex.
- Treatment may block worsening, but does not induce regression of symptoms

tabes dorsalis

- 35% of neurosyphilis cases, within 10 years from primary infection.
- M*eningoradicolitis caused by localization of* Treponema in sensitive ganglia of dorsal roots with degeneration of sensitive roots and rear cords with loss of epicritic sensitivity.
- Symptoms are sensitive ataxia and painful dysaesthesias with "tabetic chrisis", or sudden episodes of abdominal pain.
- Therapy may block progression, but ataxia may persist

ENCEPHALITIS

etiology

usually viral – HSV, HZV, west nile virus, arbovirus, EBV

occasionally idiopathic, post infectious, or bacterial (mycoplasma pneumoniae)

pathophysiology

innoculation occurs via various mechanisms depending on the virus

viremia, proliferation within neurons, or invasion via nasal mucosa

CSF invasion similar to meningitis but less of an immune response if viral → fewer neurologic sequelae in most patients

clinical presentation

symptoms similar to meningitis, except:

almost all have neurological symptoms:

personality changes

focal neurologic signs

higher incidence of seizure

hallucinations, bizarre behavior

- may precede other signs → psych dx

complications

dependent on etiologic agent

West Nile Virus infects few but has significant mortality

HSV mortality dropped from 70% to 30% with acyclovir

- survivors: seizure, motor/cognitive deficits

Anatomical lesions distribution may give hints for diagnosis

- HSV: **frontotemporal regions:**
  - Loss of smell and taste, smell allucinations
  - Aphasia
  - Behavioral and personality changes
  - Mnesic problems
  - Epileptic seizures

- Flavivirus (WNV, Japanes encephalitis), rabies, *Listeria monocytogenes*
  Rapidly progressive symptoms involving **brainstem**
  Movement disorders (tremor, myoclonus) or parkinsonian like

- WNV, enterovirus 71, or other enterovirus: **spinal cord**
  - Paralysis poliomyelitis-like

- Rabies (hydrophobia)
  Fobic spasm of larynx faringe, neck and chest; autonomic hyperactivity, mental fluctuations

Main diagnostic test: CSF PCR

- For HSV, sensitivity (~98%) and specificity (~94%) equal brain biopsy.
  - Test negative within first 72 hrs ore, may become positive in 1-3 giorni
  - Negative test does not esclude the possibility of infection
- EBV: low specificity
- WNV: ~70% sensitivity

EEG

- May be aspecific or patognomonic.

- Aspecific: **slow waves (theta e delta)** usually diffuse; with epileptic seizures tipical EEG patterns (spikes, sharp waves).

- Patognomonic:
- **herpetic encephalitis - periodic focal slow waves (**temporal periodic slow sharp waves) .

- **Subacute sclerosing panencephalitis (SSPE): periodic difasic delta waves**

Imaging

NMR with fluid-attenuated inversion recovery (FLAIR) and diffusion sequences

- HSV
  - Increased signal intensity in frontotemporal, cingular or insular areas in T2, FLAIR and DWI
- WNV
  - Important alterations in deep gray matter (basal ganglia, thalamus)
- VZV
  - Hemorragic lesions
- Rabies
  - Hyperintens signal in T2 in brainstem, hippocampus, hypothalamus

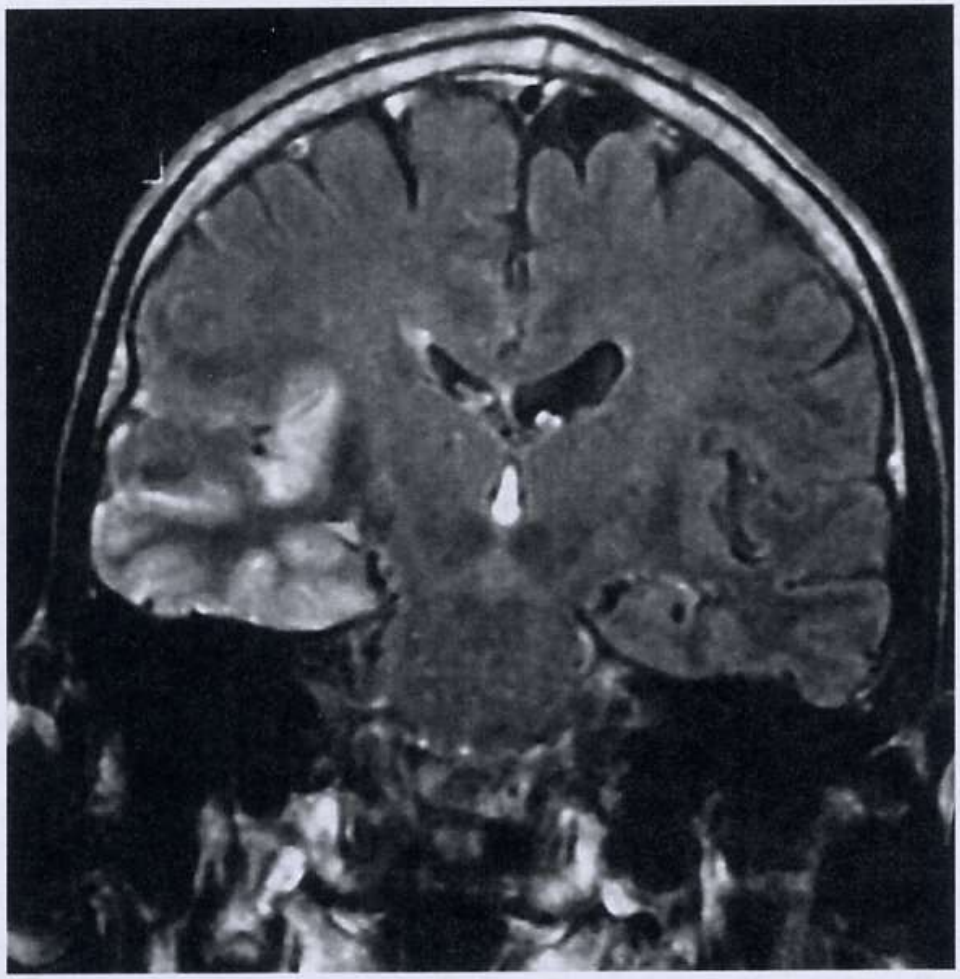


FIGURE 376-3 Coronal FLAIR magnetic resonance image from a patient with herpes simplex encephalitis. Note the area of increased signal in the right temporal lobe (left side of image) confined predominantly to the gray matter. This patient had predominantly unilateral disease; bilateral lesions are more common but may be quite asymmetric in their intensity.

“lentivirus” encephalitis

- Progressive Multifocal Leucoencephalopaty (PML)
  - JC virus
- Subacute sclerosing Panencephalitis (SSPE)
  - Measles Virus
- Rubella Encephalitis

- **PML**
  - Linked to immunosuppression (HIV, natalizumab therapy)
  - Visual (45%) and mental alterations (38%) (dementia, confusion, personality disorders)
  - Paresis

- **PESS**
  - Measles virus infection in infancy, followed by latency for 6-8 years and then slow onset of cognitive decline and personality changes (schizophrenic-like)
  - Focal or generalized epileptic seizures, mioclonus, ataxia with disease progression

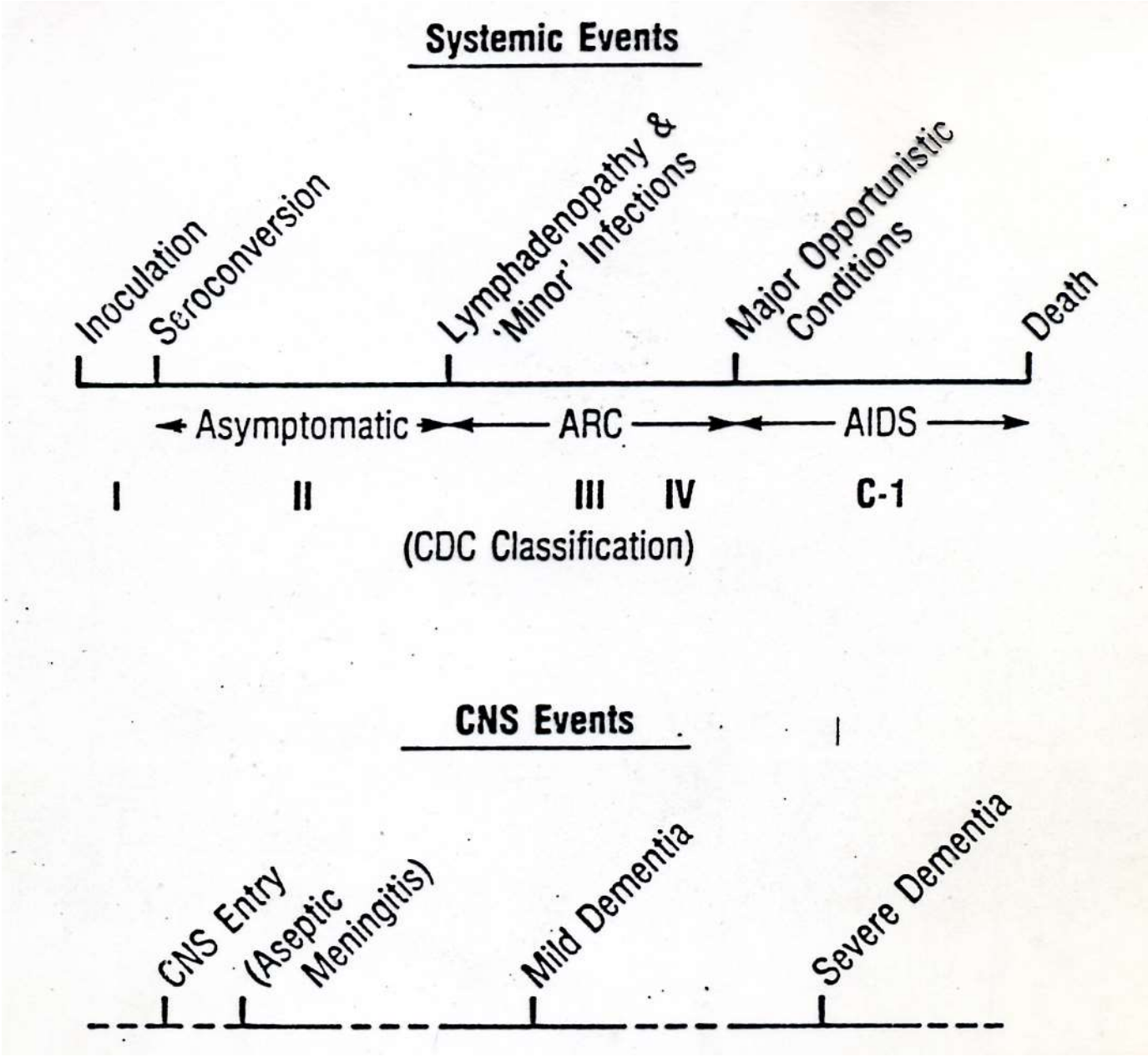
- **Progressive Rubella encephalitis**
  - 8–19 years latency from rubella infection, followed by progressive neurological deterioration, PESS-like

HIV

Table 16–1. Classification of HIV Infections

GROUP I: Acute infection (transient symptoms with seroconversion)
GROUP II: Asymptomatic infection (seropositive only)
GROUP III: Persistent generalized lymphadenopathy
GROUP IV: Other disease
- Subgroup A. Chronic constitutional disease
- Subgroup B. Neurologic disease
- Subgroup C. Specified secondary infections
  - Category C–1. Diseases listed in the CDC definition for AIDS
  - Category C–2. Other specified secondary infections
- Subgroup D. Specified secondary cancers (includes cancers fulfilling CDC definition of AIDS)
- Subgroup E. Other conditions

(From Centers for Disease Control, Morbidity and Mortality Weekly Report. 1986; 35:334–339)


Systemic Events
Inoculation
Seroconversion
Lymphadenopathy & 'Minor' Infections
Major Opportunistic Conditions
Death
Asymptomatic
ARC
AIDS
I
II
III
IV
C-1
(CDC Classification)
CNS Events
CNS Entry
(Aseptic Meningitis)
Mild Dementia
Severe Dementia

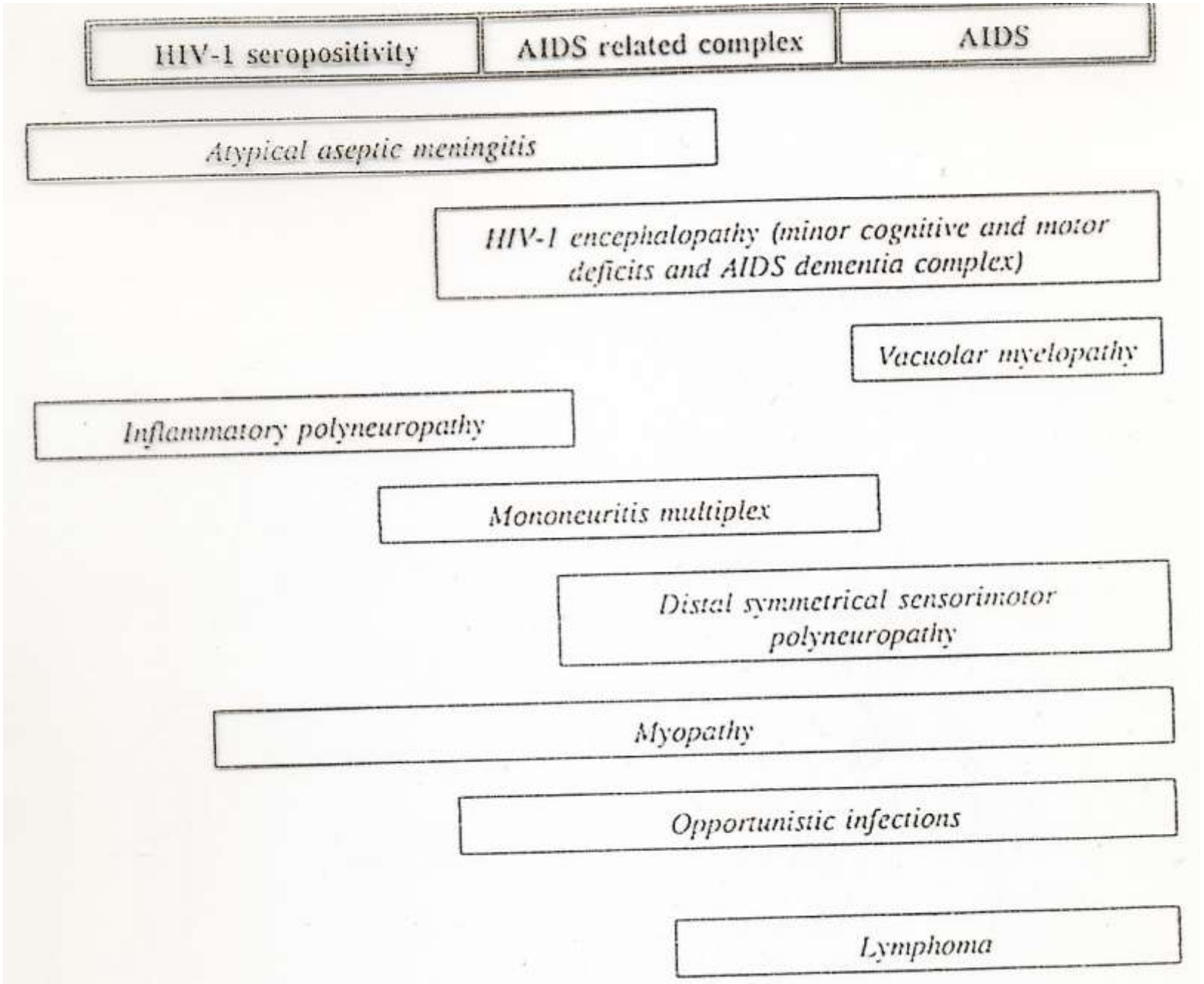

HIV-1 seropositivity
AIDS related complex
AIDS
Atypical aseptic meningitis
HIV-1 encephalopathy (minor cognitive and motor deficits and AIDS dementia complex)
Vacuolar myelopathy
Inflammatory polyneuropathy
Mononeuritis multiplex
Distal symmetrical sensorimotor polyneuropathy
Myopathy
Opportunistic infections
Lymphoma

Table 1. AIDS-Related Central Nervous System Diseases

PRIMARY VIRAL (HUMAN IMMUNODEFICIENCY VIRUS) SYNDROMES
Human immunodeficiency virus encephalopathy
Atypical aseptic meningitis
Vacuolar myelopathy

OPPORTUNISTIC VIRAL ILLNESSES
Cytomegalovirus
Herpes simplex virus, types I and II
Herpes varicella zoster virus
Papovavirus (progressive multifocal leukoencephalopathy)
Adenovirus type 2

NONVIRAL INFECTIONS
Toxoplasma gondii
Cryptococcus neoformans
Candida albicans
Aspergillus fumigatus
Coccidioides immitis
Mucormycosis
Rhizopus species
Acremonium alabamensis
Histoplasma capsulatum
Mycobacterium tuberculosis
Mycobacterium avium intracellularis
Listeria monocytogenes
Nocardia asteroides

NEOPLASMS
Primary central nervous system lymphoma
Metastatic systemic lymphoma
Metastatic Kaposi's sarcoma

CEREBROVASCULAR DISORDERS
Infarction
Hemorrhage
Vasculitis

COMPLICATIONS OF SYSTEMIC AIDS THERAPY

Neuromuscular Complications of Infection with Human Immunodeficiency Virus

Peripheral Neuropathies
- Acute Guillain-Barré syndrome
- Chronic, progressive, inflammatory demyelinating polyneuropathy (CIDP)
- Mononeuritis multiplex, including polyneuritis cranialis or plexopathies
- Small fiber, axonal, often painful sensory neuropathy
- Large fiber ataxic neuropathy (ganglioneuronitis)
- Progressive inflammatory polyradiculoneuropathy of lower extremities with sphincteric loss (cauda equina syndrome)

Polymyositis

Other
- Proximal muscle weakness with type II muscle fiber atrophy
- Amyotrophic lateral sclerosis (?)
- Subclinical neuromuscular involvement
- Rods (nemaline myopathy)

Table 1. Proposed nomenclature for HIV-1-associated central nervous system disorders and terms currently in use for the same disorders*

HIV-1-associated cognitive/motor complex
AIDS dementia complex[7]

I. Severe manifestations

A. HIV-1-associated dementia complex
Subacute encephalitis[1]
HIV encephalopathy[8]
AIDS-related dementia[4]

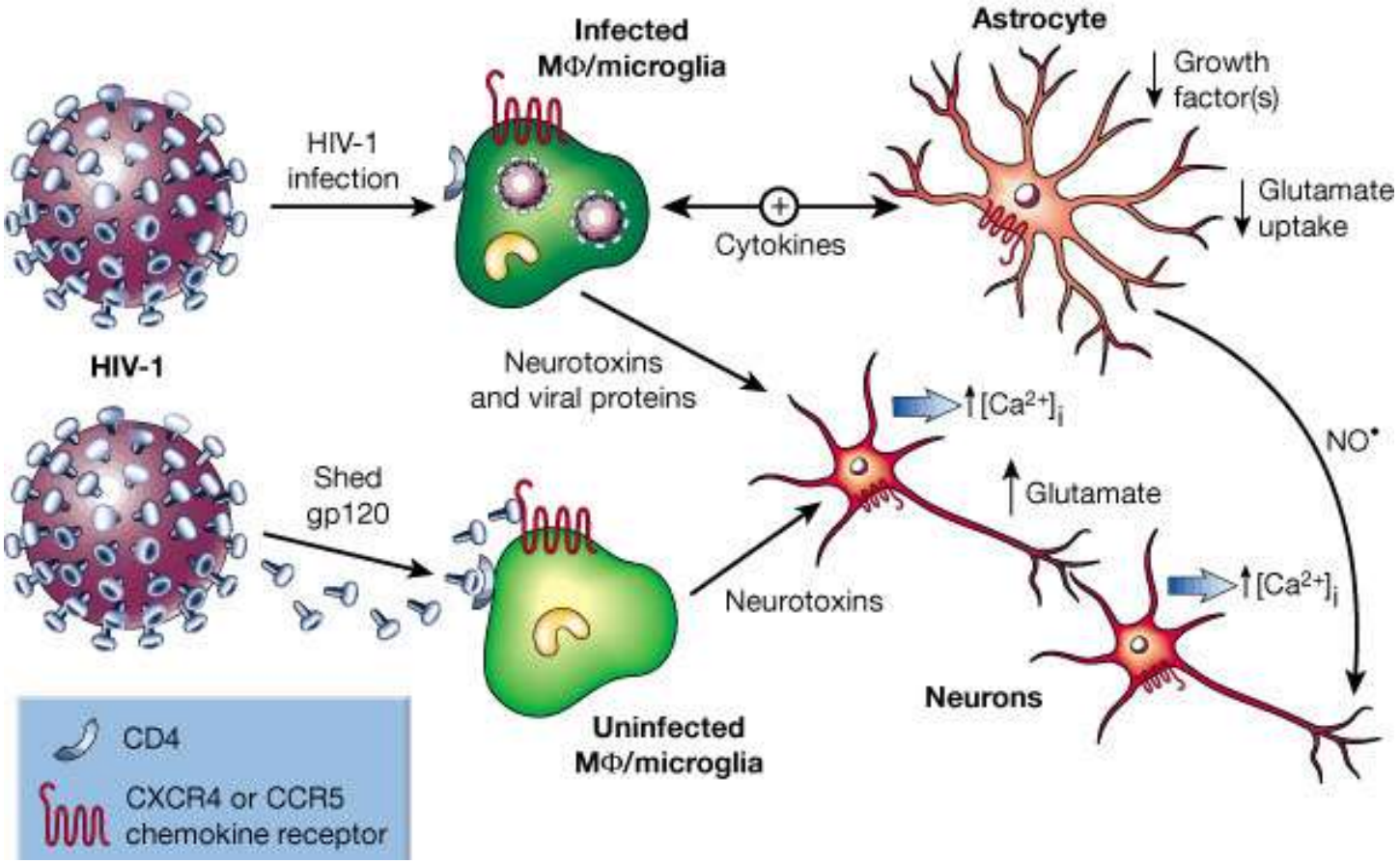
B. HIV-1-associated myelopathy
HIV encephalopathy[8]

II. Mild manifestations

HIV-1-associated minor cognitive/motor disorder
HIV-1-associated neurocognitive disorder[9]
HIV-associated neurobehavioral abnormalities[19]

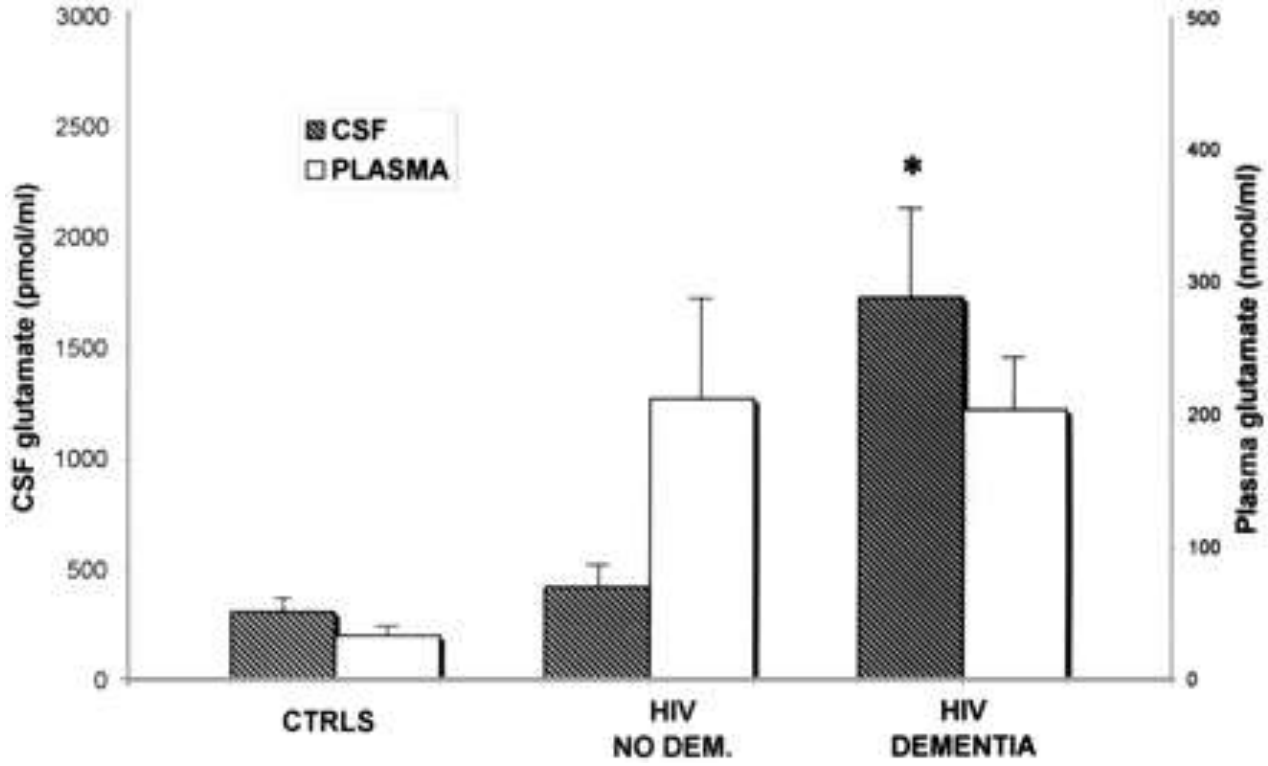
* Proposed nomenclature is shown in boldface.

Mechanisms of neuronal damage in AIDS-dementia



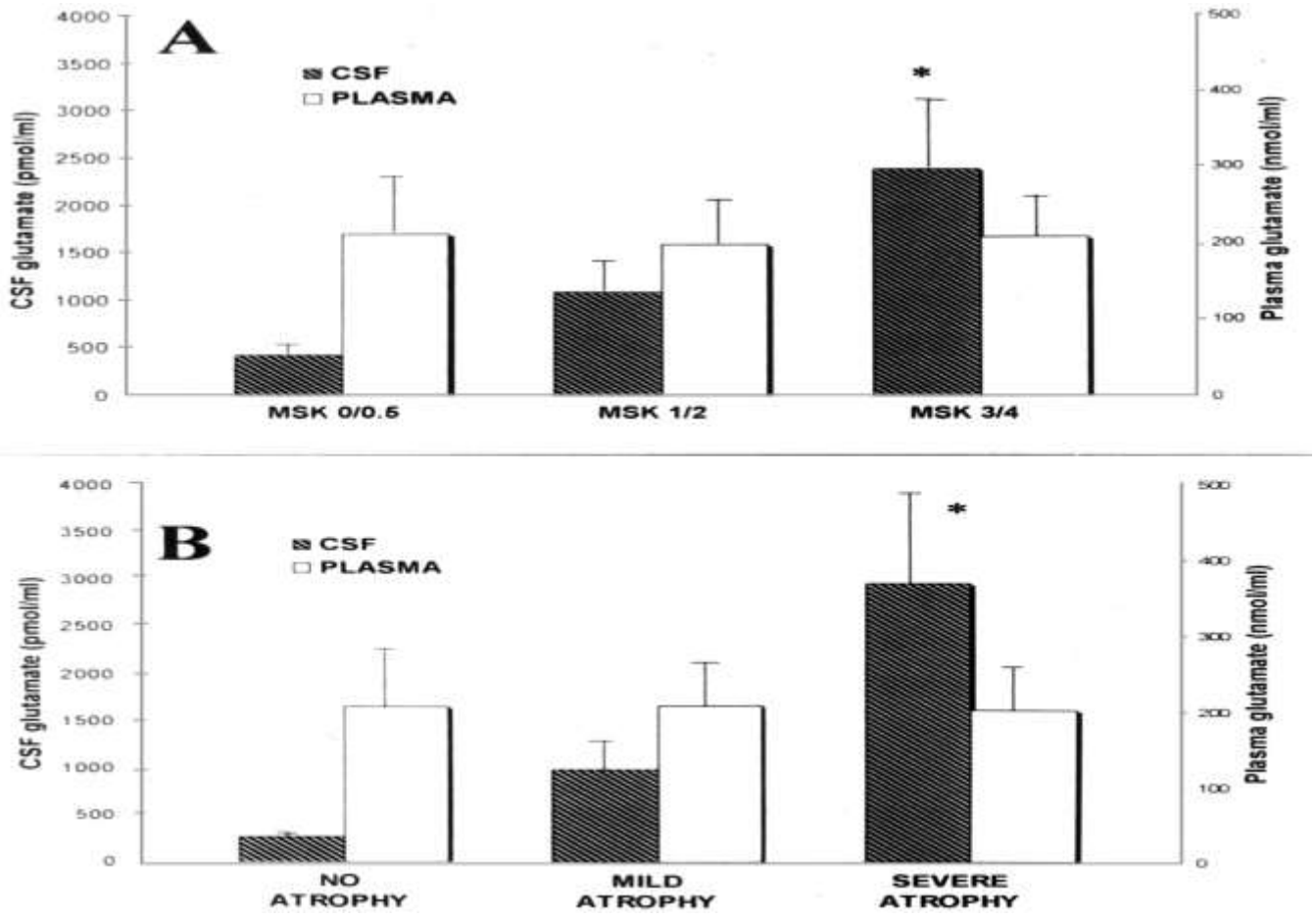
Lipton, Nature 2001

CSF and plasma glutamate in HIV-dementia



Ferrarese et al. , Neurology 2001

CSF and plasma glutamate in HIV-dementia: relation to dementia severity and brain atrophy



Ferrarese et al., Neurology 2001

ADEM:
Acute Disseminated Encephalomyelitis

- ADEM is a rapid onset demielinating pathology with a monofasic course.

- Symptoms and signs of multifocal localizations

- Usually follows viral infections or vaccinations

Epidemiology

- Prevalence
  - 100 every 100.000 measles cases
  - 1–2 every 100.000 anti-measles vaccination
  - 10–25 every 100.000 chickenpox vaccination
- Incidence
  - ~ 0,8 over 100,000/year
- World-wide distribution
  - Measles vaccine decreased incidence
- Age
  - Children and young
- Sex
  - Same prevalence males and females

Physiopathology

- Autoimmune reaction to mielin basic protein (MBP)
- Sometimes antibodies in CSF
- Small and diffuse foci of demielination and perivenular inflammation
- More severe form: acute hemorragic leucoencefalitis (Weston Hurst)

Simptoms & Signs

- Onset
  - Rapid onset and progression (few hours or days)
  - Subacute onset (few days or weeks)
- Fever and headache more common in children
- Motor and sensitive symptoms more common in adults
- Epileptic seizures common

- CSF
  - Slightly Increasead proteins (50–150 mg/dL)
  - Increased lymphocytes >200 cells/µL
  - Transient presence of oligoclonal bands in CSf: intratecal synthesis
- MRI
  - Multiple areas of altered signal in white matter of brain and spinal cord
  - Gadolinium enhancement: active disease

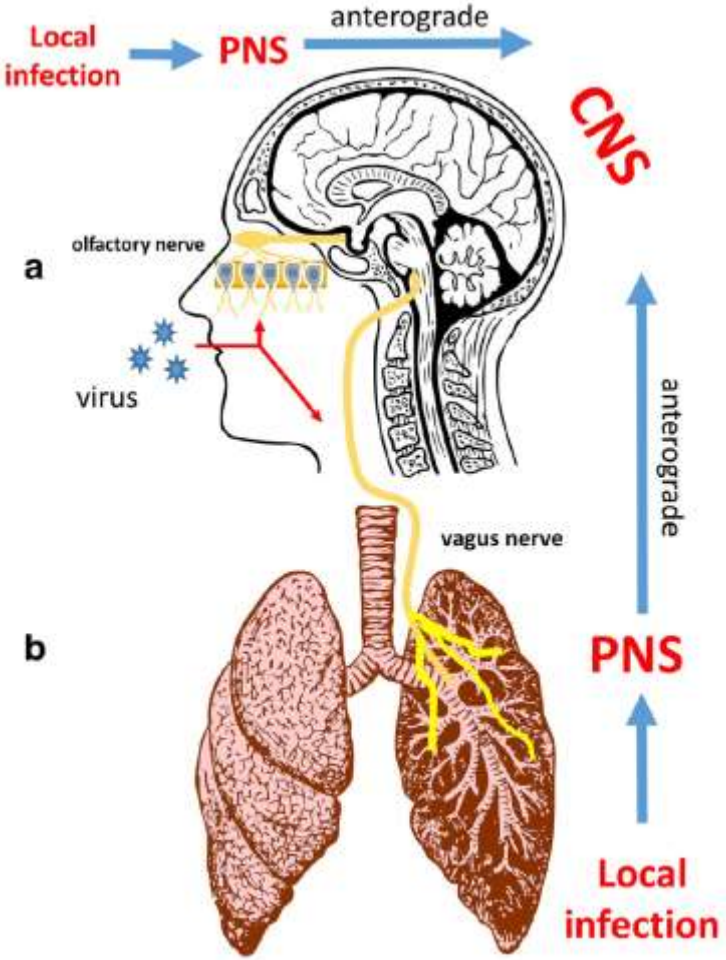
Treatment

High dose steroids

- Metylprednisolone ev, 500–1000 mg/die for 5 days
  - Sometimes followed by oral prednisone

Patients not responding to steroids:

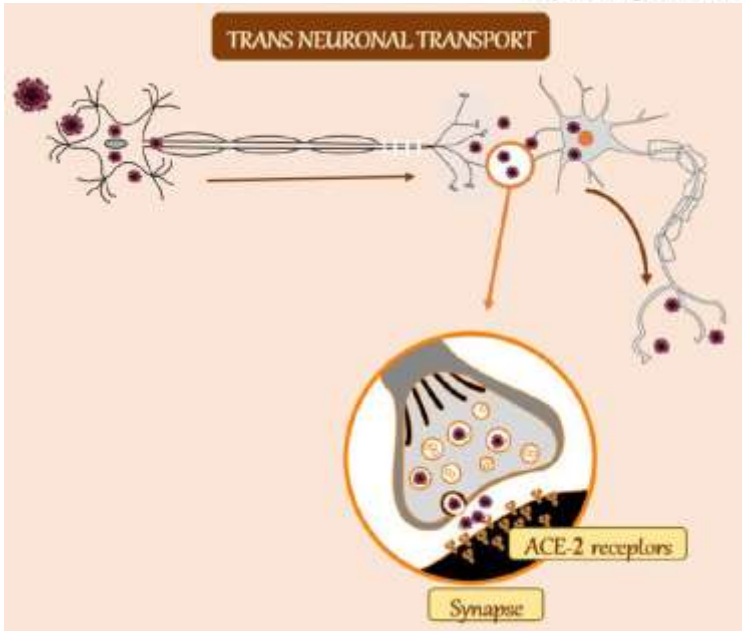
- Plasmapheresis
- Intravenous Immunoglobulines
  - 0.4 g/kg/die for 5 days



Neuroinvasion, neurotropic, and neuroinflammatory events of SARS-CoV-2: understanding the neurological manifestations in COVID-19 patients

Yassine Yachou[1] · Abdeslem El Idrissi[2] · Vladimir Belapasov[1] · Said Ait Benali[3]

Neurological Sciences
https://doi.org/10.1007/s10072-020-04575-3



Potential neurological impact of coronaviruses: implications for the novel SARS-CoV-2

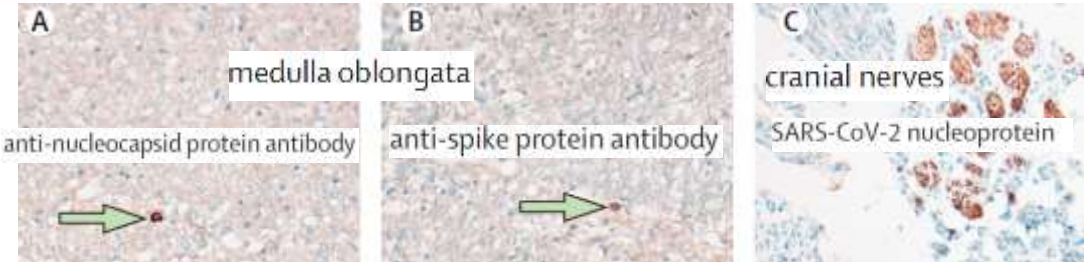
Neurological Sciences (2020) 41:1329–1337
https://doi.org/10.1007/s10072-020-04469-4

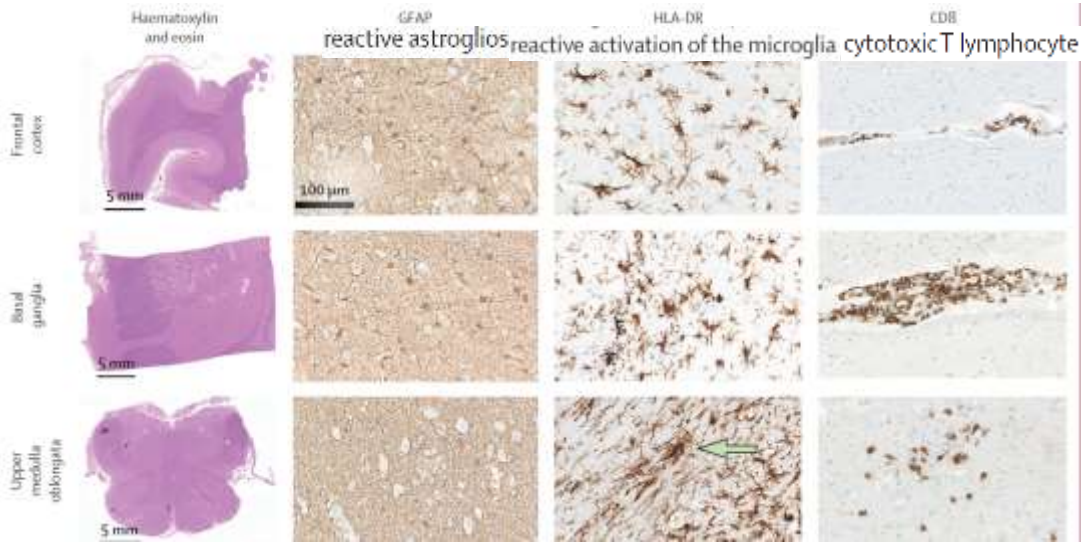
Joy D. Iroegbu[1] · Chibuzor W. Ifenatuoha[1] · Omamuyovwi M. Ijomone[1,2]

Neuropathology of patients with COVID-19 in Germany: a post-mortem case series

Jakob Matschke, Marc Lütgehetmann, Christian Hagel, Jan P Sperhake, Ann Sophie Schröder, Carolin Edler, Herbert Mushumba, Antonia Fitzek, Lena Allweiss, Maura Dandri, Matthias Dottermusch, Axel Heinemann, Susanne Pfefferle, Marius Schwabenland, Daniel Sumner Magruder, Stefan Bonn, Marco Prinz, Christian Gerloff, Klaus Püschel, Susanne Krasemann, Martin Aepfelbacher, Markus Glatzel

SARS-CoV-2 within the CNS





- **Reactive astrogliosis**
- **Reactive microglia**
- **Cytotoxyc T lymphocytes**

Clinical Presentation and Outcomes of Severe Acute Respiratory Syndrome Coronavirus 2–Related Encephalitis: The ENCOVID Multicenter Study

The Journal of Infectious Diseases

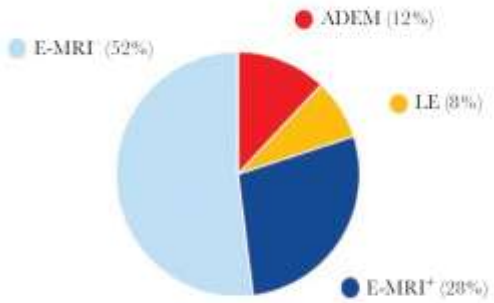
MAJOR ARTICLE

Andrea Pilotto,[1,2] Stefano Masciocchi,[1] Irene Volonghi,[1] Massimo Crabbio,[3] Eugenio Magni,[3] Valeria De Giuli,[4] Francesca Caprioli,[4] Nicola Rifino,[5] Maria Sessa,[5] Michele Gennuso,[6] Maria Sofia Cotelli,[7] Marinella Turla,[7] Ubaldo Balducci,[8] Sara Mariotto,[9] Sergio Ferrari,[9] Alfonso Ciccone,[10] Fabrizio Fiacco,[11] Alberto Imarisio,[1] Barbara Risi,[1] Alberto Benussi,[1] Enrico Premi,[12] Emanuele Focà,[13] Francesca Caccuri,[14] Matilde Leonardi,[15] Roberto Gasparotti,[16] Francesco Castelli,[13] Gianluigi Zanusso,[9] Alessandro Pezzini,[1] and Alessandro Padovani[1]; for the SARS-CoV-2 related encephalopaties (ENCOVID) Study Group[a]

Twenty-five cases of encephalitis

(ADEM; n = 3), limbic encephalitis (LE; n = 2),

ADEM and LE cases showed a delayed onset



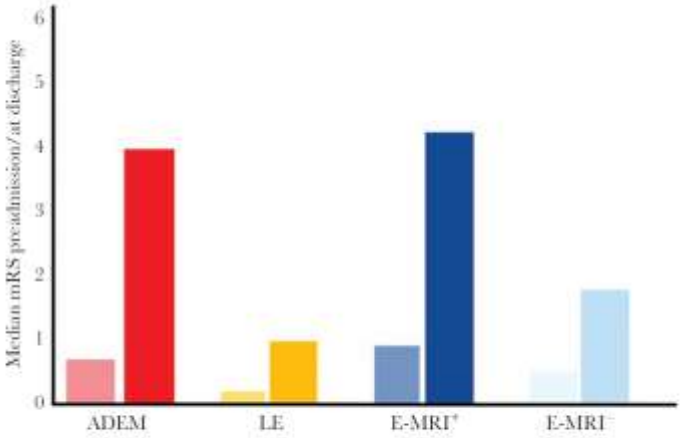
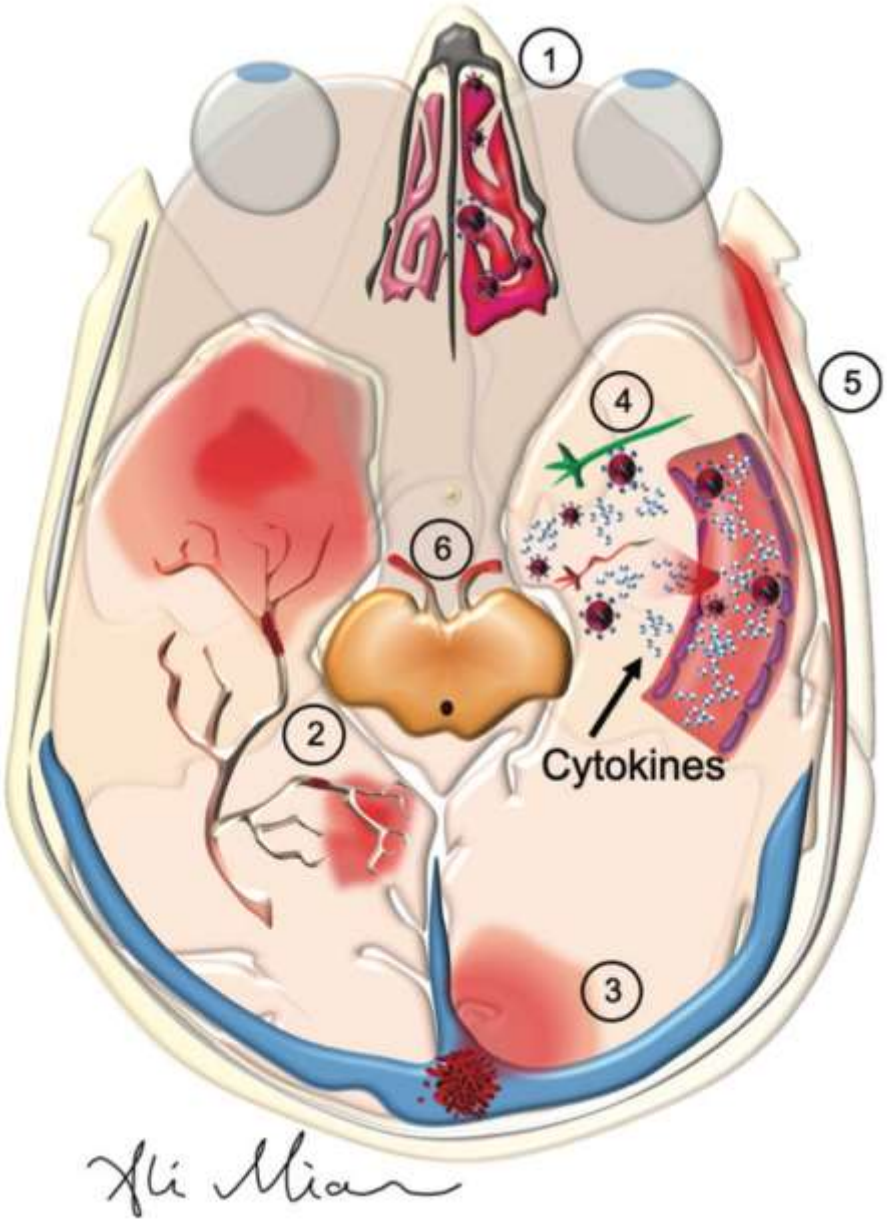


Figure 2. Outcome measures according to encephalitis subtype. The histograms showed premorbid modified Rankin scale (mRS) (light colors) and final mRS (enhanced colors). Abbreviations: ADEM, acute disseminated encephalomyelitis; E-MRI⁻, encephalitis with negative MRI; E-MRI⁺, encephalitis with MRI alterations; LE, limbic encephalitis; mRS modified Rankin scale.

Table Acute neurologic complications of coronavirus infections

Viral meningitis
Anosmia
Encephalitis
Postinfectious acute disseminated encephalomyelitis
Postinfectious brainstem encephalitis
Guillain-Barré syndrome
Myositis
Acute necrotizing hemorrhagic encephalopathy



1. passaggio lungo i nervi olfattori
2. alterazioni delle pareti vasali
3. alterazioni della coagulazione
4. tempesta citochinica
5. vasculiti
6. autoanticorpi per molecular mimicry

Neurological Sciences (2020) 41:1355–1359
https://doi.org/10.1007/s10072-020-04450-1

COVID-19

An Italian multicenter retrospective-prospective observational study on neurological manifestations of COVID-19 (NEUROCOVID)

Carlo Ferrarese[1] · Vincenzo Silani[2] · Alberto Priori[3] · Stefania Galimberti[4] · Elio Agostoni[5] · Salvatore Monaco[6] · Alessandro Padovani[7] · Gioacchino Tedeschi[8] · on behalf of Italian Society of Neurology (SIN)

Received: 2 May 2020 / Accepted: 5 May 2020 / Published online: 19 May 2020

Study objective

To collect detailed information on any neurological manifestation of COVID-19:

1) the appearance of neurologic symptoms and/or signs at COVID-19 onset or during the disease course
2) the exams performed for the diagnosis of the neurological involvement
3) the clinical course of both the COVID-19 infection and the neurological events
4) the occurrence of possible long-term neurological complications within a 6 months period of follow-up

Recruiting: March 1, 2020- June 30, 2021
Follow-up: Dec 31 2021
50 Neurological Centers involved at national level

#1030 NEUROLOGICAL DISORDERS ASSOCIATED WITH COVID-19 INFECTION: AN ITALIAN MULTI-CENTER COHORT STUDY (NEURO-COVID)

S. Beretta[1], V. Cristillo[2], B. Viti[3], C. Morotti Colleoni[1], E. Bianchi[4], V. Silani[5], A. Priori[6], A. Padovani[2], A. Pilotto[2], S. Guttmann[3], E. Barvas[3], P. Palumbo[7], E. Bartolini[7], M. Turla[8], M.S. Cotelli[8], F. Bax[9], G.L. Gigli[9], M. Viganò[10], M. Sessa[10], L. Ciolli[11], S. Maffei[11], S. Meletti[11], L. Tancredi[6], V. De Giuli[12], B. Censori[12], L. Benedetti[13], M. Pardini[13], A. Schenone[13], M. Orrico[14], G. Sferruzza[14], M. Filippi[14], M. Braga[15], S. Beretta[15], N. Calcagno[5], F. Trogu[5], G. Primiano[16], S. Servidei[16], P.C. Ranchicchio[17], S. Caproni[17], M. Gentile[18], P. Cortelli[19], A. Zini[18], E. Beghi[4], G. Tedeschi[20], C. Ferrarese[1]

Results:

904 patients with confirmed COVID-19 infection and concomitant newly diagnosed neurological disorders were recruited. The median age was 68 years (IQR 56-78) and 57.5% were males. Severe acute respiratory syndrome occurred in 35.9%. The most common new neurological diagnoses were hypogeusia (21.1%), hyposmia (20.5%), acute ischemic stroke (19.6%), delirium (14.4%), headache (12.3%), cognitive impairment (11.3%), abnormal behaviour or psychosis (8.9%), seizures (5.9%), Guillain-Barrè syndrome (5.1%), severe encephalopathy with stupor or coma (3.7%), dizziness (3.0%), encephalitis (2.3%) and haemorrhagic stroke (2.3%). Overall, the onset of neurological disorders occurred during the presymptomatic-asymptomatic phase in 45.9%, during the acute respiratory illness in 37.5% and after recovery in 16.6%. In-hospital mortality was 12.2% and was mostly due to COVID-related respiratory failure (9.1%).

Transmissible spongiform encephalitis

- Creutzfeldt-Jakob (CJ):
  - sporadic
  - iatrogenic
  - familial
- Kuru
- Gerstmann-Straussler-Scheinker
- Fatal familial insomnia
- New variant Creutzfeldt-Jakob

Sporadic Creutzfeldt-Jakob disease

- 85% of CJ cases
- 1 case/1.000.000 person/year
- Onset between 55 and 75 anni
- Mean survival: 5 months; 80% die within 1 year

Creutzfeldt-Jakob: caratteristiche cliniche

Symptoms and signs:	prevalence %
Rapid onset dementia	100
Myoclonus	>80
Piramidal	>50
Cerebellar	>50
Extrapiramidal	>50
Cortical vusual defects	>20
Epileptic seizures	<20
Autonomic	<20

Diagnostic citeria for Creutzfeldt-Jakob

- **CJ probable:**

  Rapidly progressive dementia with at least two clinical features:

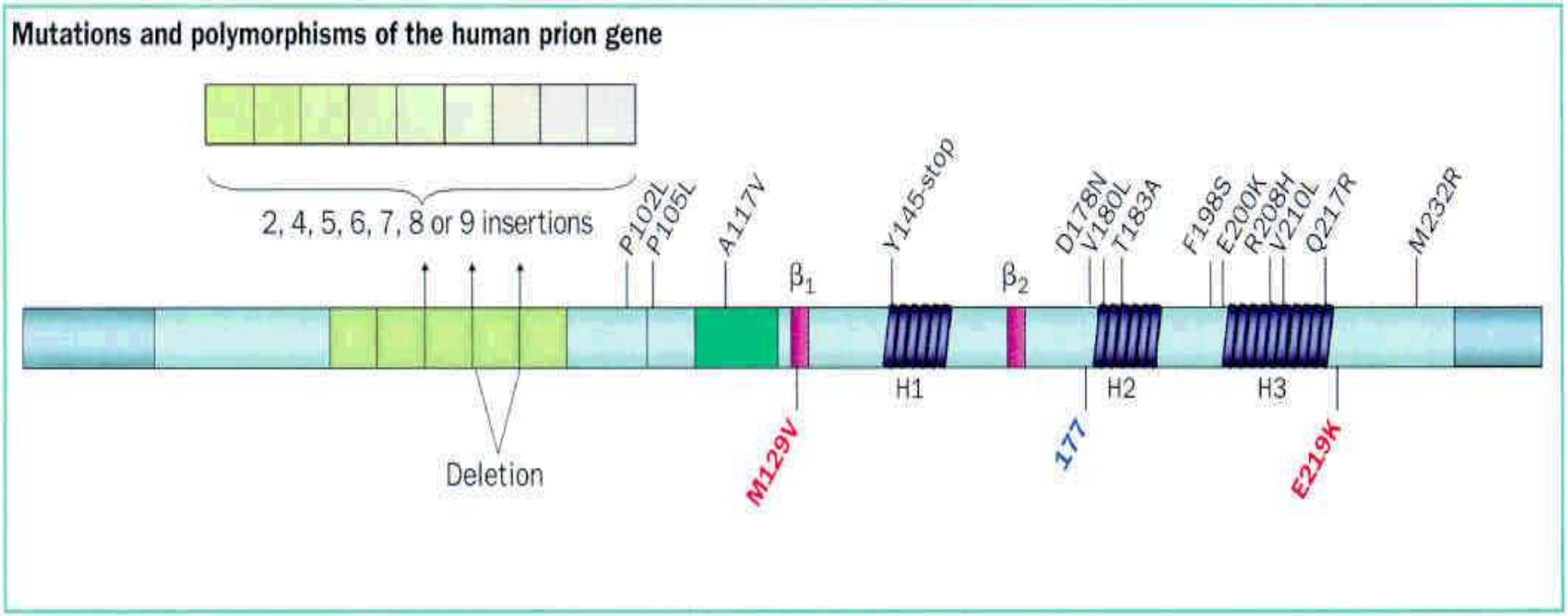
  1. **Mioclonus**
  2. **Visual or cerebellar**
  3. **Piramidal or extrapiramidal**
  4. **Acinetic mutism**

  Periodic spikes and sharp waves at EEG and

  Protein 14-3-3 in CSF and disease duration less than 2 years

(Now: RTQuick test on CSF or nose brush)

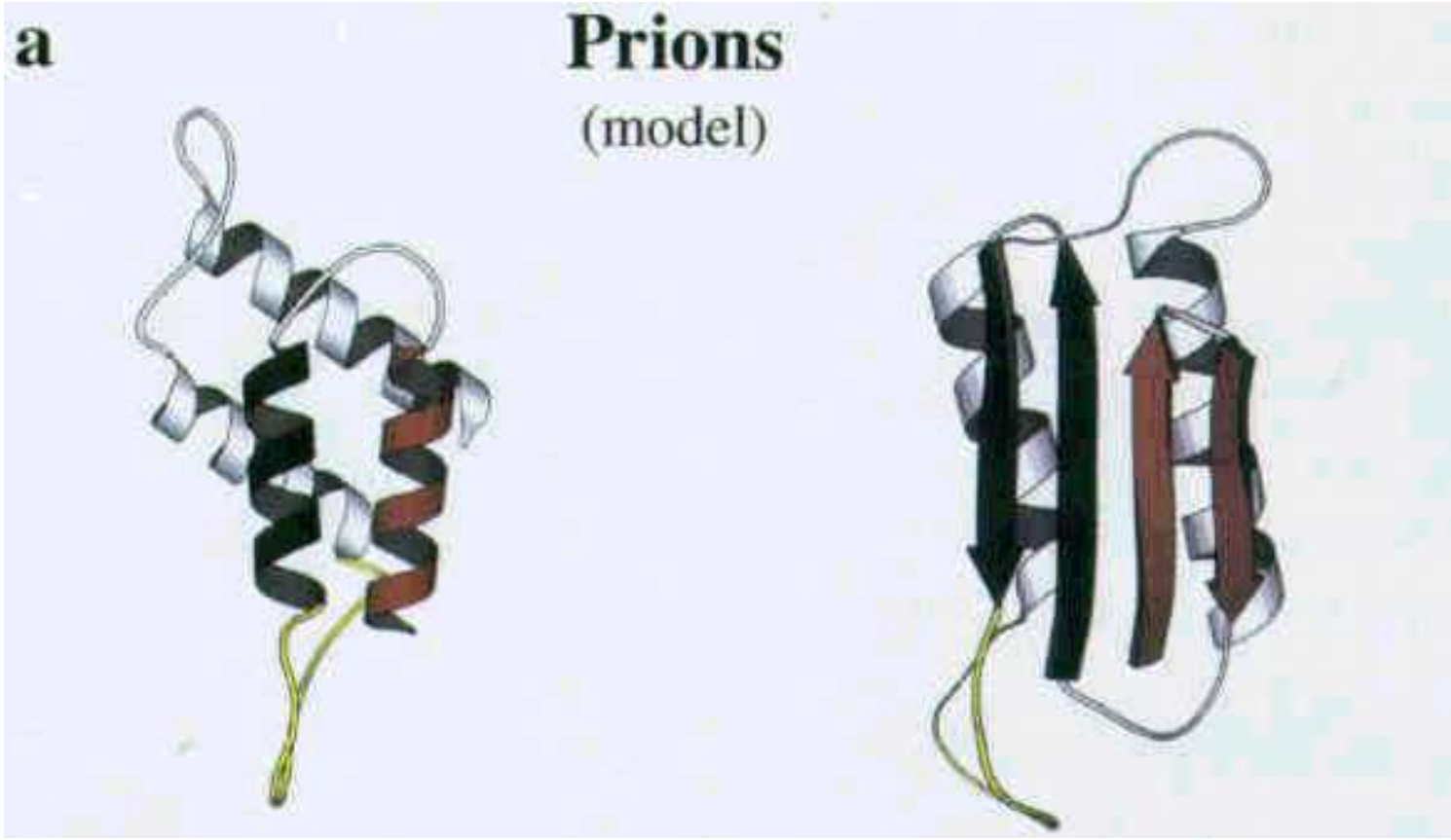
Prion protein, mutations and polymorphisms



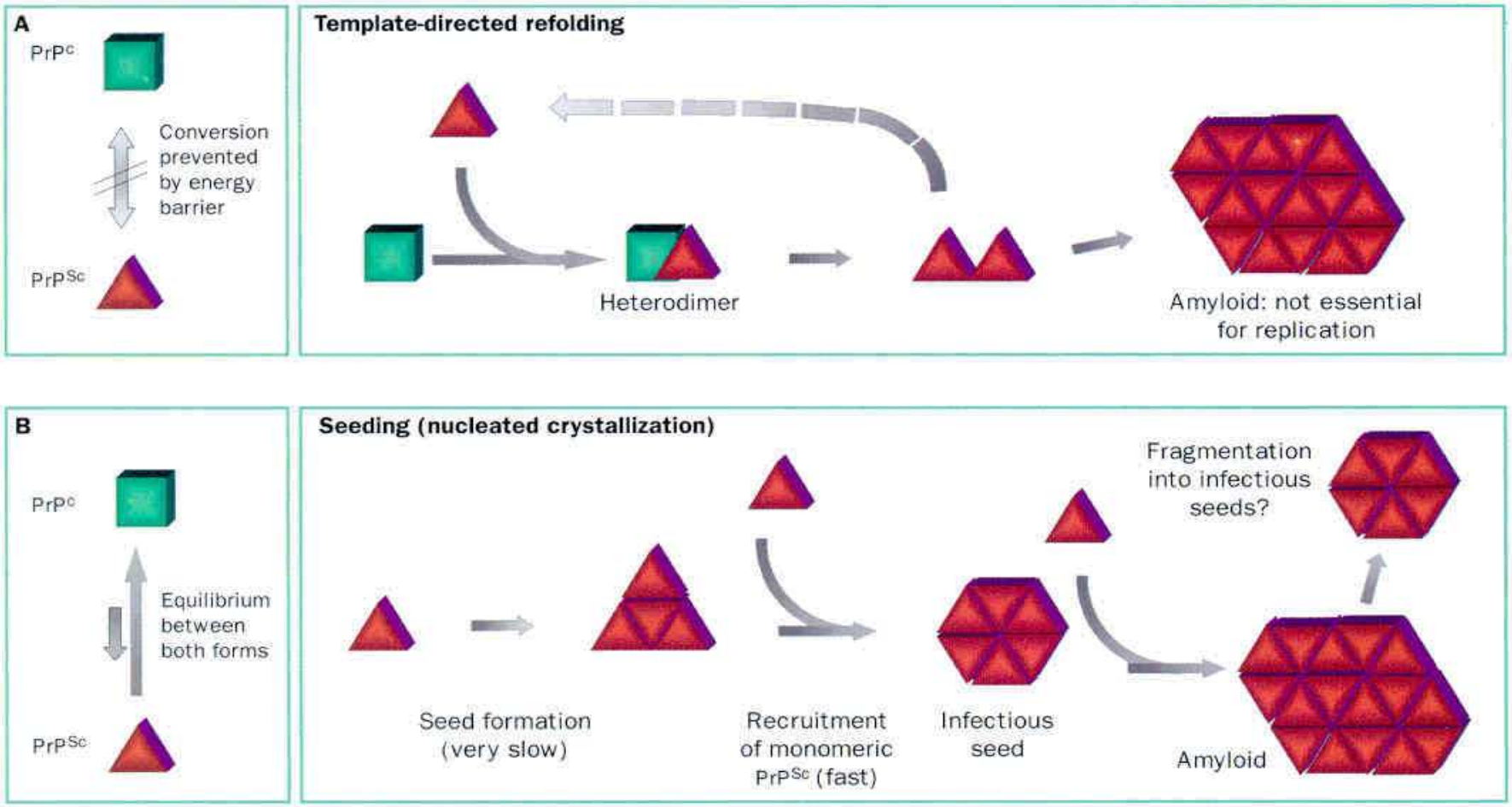
Da Aguzzi e coll, Lancet 1999

Prpc

Prpsc



(da R. W. Carrell Lancet 1996)



Aguzzi e coll, Lancet 1999

Fatal familial insomnia

- First description of a 58 yo man, in 1986 (Lugaresi and coll.)
- Onset characterized by progressive insomnia and dysautonomic symptoms (hyperydrosis, hyperthermia, tachycardia, hypertension)
- Later onset of dysartria, tremor, myoclonus and hormonal alterations (melatonin, GH, Prl)

nvCJ: link with bovine spongiform encephalitis (BSE)

- Cluster in UK, 10 years after BSE onset
- Peculiar clinical picture
- Neuropathology “Kuru-like”
- Similar neuropathology in monkeys with BSE inj.
- PrP at Western-blot similar for BSE and nvCJ

nvCJ: clinical presentation

- **Early onset : mean age 28 yrs**
  range 16-52
- **Onset with: Depression**
  Anxiety
  Social withdrawal
  Hallucinations
- **Neurologic symptoms after 6 months:**
  Mnesic defects
  Dysesthesias and painful paresthesias
  Ataxia
  Myoclonus-involuntary movements
  Dementia

nvCJ: diagnostic criteria

I **A) Progressive psychiatric symptoms**
B) Onset > 6 months
C) No alternative explanation
D) No iatrogenic exposure

II **A) Progressive psychiatric symptoms**
B) Persistent painful dysesthesias
C) Ataxia
D) Myoclonus, chorea or dystonia
E) Dementia

III **A) EEG: no sporadic CJ pattern**
B) Bilateral pulvinar hyperintensity or diffusion at MRI

Will RG Ann Neurol 2000