

Infections of the central nervous system

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Clinical significance

- Feared illnesses!
- Might be
 - septic
 - w/ a shocking speed of development
 - indistinguishable in the beginning
- Possible sequelae – neurological or psychiatric symptoms, seizures, dementia, psychomotor retardation
- Contracted easily – ubiquitous agents

Signs and symptoms

- High fever
- Headache
- Vomiting
- Exhaustion
- Convulsions
- Altered level of consciousness
- Meningeal signs
- Psychiatric symptoms (especially in slower infections)

Be careful!

Babies and elderly might lack clinical symptoms like neck stiffness or fever

Encephalitis

- Diffuse inflammation of the brain
- The most dangerous neuroinfection
 - can be necrotizing - herpes, molds

The agent is mostly UNKNOWN!

- Of the known agents, most cases are caused by herpes virus or other viruses

Meningitis

- Inflammation of the meninges
- Spectrum of bacteria changes with age:
 - newborns: *S. agalactiae*, *E. coli*, *L. monocytogenes*
 - *N. meningitidis*, *S. pneumoniae*, *H. influenzae*
 - elderly: *S. pneumoniae*, *L. monocytogenes*, *E. coli*
- Enteroviruses
- *C. neoformans* (HIV), *Candida* sp.

Brain abscess

- Local inflammation with overall symptoms
- Pyogenic membrane
- Breakdown of the leukocytes – osmotic pressure – increasing volume – damage of the surrounding tissue
- Anaerobic bacteria
- Odontogenic, sinusitis, otogenic, bacteremia

Septic syndrome

- **Proven infection + 2 of these:**
 - Hypotension (systolic BP < 90 mm Hg or fallen by >40 from baseline)
 - Lactate > 1 mmol/L
 - Mottled skin (polka-dot) :D
 - Decreased capillary refill of nail beds or skin
 - Fever > 38.3 degrees C
 - Hypothermia < 36 degrees
 - Heart rate > 90
 - Tachypnea
 - Change in mental status
 - Significant edema or positive fluid balance
 - Hyperglycemia without diabetes
 - White blood cell count > 12,000 or less than 4,000
 - Elevated C-reactive protein in serum
 - Elevated procalcitonin in serum
 - Arterial hypoxemia
 - Acute drop in urine output
 - Creatinine increase
 - INR > 1.5 or aPTT > 60 seconds
 - Absent bowel sounds (ileus)
 - Platelet count < 100,000
 - High bilirubin

Meningeal signs!

Signs of Meningeal Irritation



Opisthotonos.



Assessing for Kernig's sign.



Assessing for Brudzinski's sign.

Tests and expected results

Blood analysis

- Cell count - leukocytosis
- Biochemistry primarily - High CRP, PCT, FW (markers of inflammation)
- Further biochemistry - active search for markers of sepsis and organ failure
- Blood culture (bacteria, fungi: positive / or not!)
- PCR of the serum can be done, but w/ a low effectivity

Urinalysis – pneumococcal antigen

CSF

- Cytology - High amount of leukocytes
 - Normal: $5/\text{mm}^3$, 70% LYM, 30% MON
 - General increase
 - Under 100 – viral
 - Up to 1000 – bacterial
 - Change of composition
 - Neutrophils – bacterial inflammation (not always)
 - Eosinophils – parasites, fungal, viral
- Pneumococcal antigen!
 - (use the same kit as for urine)

CSF Biochemically...

High protein

⊕ (in bacterial inflammation)

Low glucose



...normal when viral!

Microscopy

- Detritus
- Red blood cells
- White blood cells
- Search for microbes
 - 1 or 2 are not enough – might be wrong (contamination)

Microscopy: microbes

- Think of typical species
 - G- diplococci – *Neisseria* sp.
 - G+ diplococci (Batman's eyes) – *Streptococcus pneumoniae*
 - G- rods – *E. coli* etc.
 - Yeasts? Burri! (*Cryptococcus* sp.)
 - Parasites – amoebae
 - Mould hyphae – thin or ribbons? (Mucorales)

Special microscopy

- Ziehl-Neelsen in suspect TB
- Fluorescence microscopy in suspect mycosis
- Immunofluorescence microscopy or Wright-Giemsa stain in suspect *Naegleria*

Serology

- Always take 2 specimens: CSF + serum!
- Indirect detection of the agents – antibodies
 - IgM – rather acute
 - IgG – rather chronic
- Antibodies in the CSF needn't be intrinsic!
 - HE barrier can be damaged (unexpectedly)
 - Ab index – we can compare blood and CSF levels of antibodies
- Diagnostic window - antibodies need time to develop!
 - Depending on the agent, type of antibody and the detection method
 - days, weeks or even months (during that time the patient might be infectious!)

Molecular methods

- Direct detection of the DNA with PCR
 - Might be false negative (inhibition by ubiquitous chemicals)
 - Might be false positive (the agent is dead for a long time)
- Galactomannan – detection of Aspergillus-like fungi
- Beta-D-glucan – panfungal antigen

Always think mathematically.

- If you request:
 - Gram stained mount
 - Fluorescence mount
 - Bacteriological cultivation
 - primary
 - enrichment
 - Mycological cultivation
 - primary
 - enrichment
 - Parasitological microscopy
 - Antibody levels
 - Galactomannan + Beta-D-glucan
 - PCR

...DO YOU DO IT WITH 0,1 ML OF CSF? WE DON'T.

Differential diagnosis

- Other causes of fever – all kinds of infections
- Other causes of headache – migraine, sinusitis...
- Other causes of neurological symptoms – drugs, neurological illnesses, stroke...
- Non-infective inflammation (autoimmunity)

Acute complications

- Sepsis – MODS – MOF – exitus lethalis
- Intracranial hypertension – compression of the brain stem
- Intracranial bleeding
- Dissemination of the infection – organ abscesses, heart valves etc.

Chronic complications

- Epilepsy
- Psychological changes
- Dementia
- Vision loss
- Headache

Gram-positives

S. pneumoniae – ubiquitous!

Normal flora of the oropharynx

S. aureus – susceptible and MRSA

Normal on the skin, nasal cavity, etc.

S. agalactiae – newborns, babies

Normal in stools of healthy people

L. monocytogenes – newborns, elderly

Food-borne pathogen (cheese, mayo)

Gram-negatives

H. influenzae – mainly kids

Normal flora of the upper respiratory tract

N. meningitidis – babies, teenagers

Unpredictable!

E. coli + enterobacteriaceae

Normal flora of the gut

P. aeruginosa – immunocompromised people

...and the others

M. pneumoniae – neuroinfection or neurological complication of pneumonia

B. burgdorferi – tick-borne

slow development, often w/o skin rash

T. pallidum – neurosyphilis („risky“ patients like pornographers)

Anaerobic bacteria (tooth/implant-borne brain abscess) – often mixed

Mycobacteria

- *M. tuberculosis* - basilar meningitis
 - 100% deadly if untreated
- MDR – TB!
- Vaccination

Viruses

- Herpes simplex (herpesviridae, DNA)
- Tick-borne encephalitis (flaviviridae, RNA)
- Measles (paramyxoviridae, RNA)
 - acute or SSPE
- Chickenpox (herpesviridae, DNA)
- Adenovirus (adenoviridae, DNA)
- Rotavirus (reoviridae, RNA)
- Lyssa (rhabdoviridae, RNA)

Fungi

- *Candida* sp. (newborns)
- *Cryptococcus neoformans* (HIV)
 - pigeons?
- Molds
 - Aspergilli
 - Mucorales

Parasites

- Naegleria fowleri
 - warm natural waters
 - swimming pools with broken tiles
 - invades the organism through the olfactory nerves
 - fast and deadly

Prions

- Not only organisms are infective
- DNA is not needed
- misfolded proteins causing misfolding of other proteins (normal variants of themselves)
 - BSE (bovine spongiform encefalopathy)
 - Creutzfeldt-Jakob disease (amyloid and cell death)

Prevention

- Vaccination
 - *Haemophilus influenzae* b
 - *S. pneumoniae*
 - *M. tuberculosis*
 - *N. meningitidis*
 - measles
 - rotavirus
 - tick-borne encephalitis
 - chickenpox
 - Lyssa virus

Preventative application of antimicrobials

- Adequate treatment of suppurative infections of the neighbouring cavities
 - sinusitis
 - otitis
 - dental surgery
- Aciclovir for infants from mothers with genital herpes
- „Covering“ of immunocompromised patients

Hygiene

- Washing hands
 - No kissing people with herpes
 - Avoiding interactions with ill people
- = it is no heroism if you go sick to work

Treatment

1) Antibiotics

- Empirical combined treatment
(never wait for cultivation!)
- Bactericidal first!
- The brain is the priority
- CAVE hematoencephalic barrier

- Ceftriaxone!
- Cefotaxim
- Ceftazidim
- Cefepime
- Ampicillin
- Co-trimoxazole
- Chloramphenicol is obsolete
(but has an excellent penetration to the CNS
through the HE barrier)
- Combine with vancomycin or aminoglycosides

Valid combinations

- Ceftriaxon + aciclovir (knowing nothing)
 - Ampicillin + cefotaxime
 - Ceftriaxone + gentamicine
 - Meropenem + vancomycin
- and many others

(Don't hesitate to call the antibiotic center!)

Neuroborreliosis

- Doxycycline
- Ceftriaxone
- Cefotaxim
- Penicillin G in hospital settings

- The treatment must be longer than usual –
2-3 packages are normal

2) Antivirotics

- Only for herpes viruses
 - HSV 1
 - HSV 2
 - CMV
 - VZV...
- aciclovir, ganciclovir, foscarnet
- quite toxic, VIROSTATIC
- poor penetration to the CNS

3) Antimycotics

- Prior extraction of any hardware
- Candida
 - Amphotericin B + flucytosin
 - more reliable but toxic
 - Fluconazole
 - less reliable, less toxic
- Molds: amphotericin B
- Individual treatment

4) Antiparasitic treatment

- *Naegleria*: intrathecal amphotericin B or miconazole + rifampicin
- Worms: don't use antihelmintics!
 - inflammatory reaction to dying worms might kill the patient (surgery preferred)

5) Surgery

- Necessary for abscess and worms
- Might be beneficial in brain swelling
- Necessary in persisting focal infection of the neighbouring spaces
- Might be necessary if the draining spaces are stuck after infection (outflow of the CSF!)

6) Antiinflammatory and anti-swelling therapy

- not always needed
- dexamethasone (corticosteroid)

Should be applied after or concurrently with the antibiotics.

Never without them.

What to remember?

- Any symptomatic infection of the central nervous system is an urgency. Treat now!
- It might be fatal.
- It might have lifelong sequelae.
- Meningeal signs are easy to examine.
„Kiss your knee, baby!“
- The treatment should be fast and complex.

Case study

- A boy, 12 y/o
- Fever, vomiting, convulsions, altered level of consciousness, neck stiffness
- Suppurative otitis media during past week, mother refused to administer antibiotics
- Brought to emergency dpt.
- 40 kg
- Given ceftriaxone 2g i.v./12h + 30 mg dexamethasone i.v.
- Gentamicin 200 mg daily added (sepsis), serum level monitoring
- Lumbar puncture – CSF was cloudy, sent for testing
 - Antigen *S. pneumoniae* positive
 - Microscopy: gram-positive diplococci
 - Cultivation: *S. pneumoniae*, susceptible