الحُمّى في عالم الدماغ

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A scenario

- Patient with few days history of headache, fever, vomiting.
- Has neck stiffness
- CT brain : negative
- LP: Pleocytosis, high pr, low glu
- This is meningitis
- Differential Diagnosis (etiology):

Hold it: would your DDx be the same if this patient:

- Lives in Saudi Arabia vs. switzerland
- HIV vs. post renal transplant
- 18 yrs old vs. 75 yrs old
- On steroids for lupus or took ritoximab for RA
- Has chronic otitis media or has abnormal heart valves S/P teeth extraction

Another scenario

- Patient with headache, fever and vomiting
- MRI: ring enhancing lesions in brain
- This is brain abscess
- Differential Diagnosis (etiology):

Hold it: would your DDx be the same if this patient:

- Lives in Saudi Arabia vs switzerland
- HIV vs post transplant
- 18 yrs old vs 75 yrs old
- On steroids for lupus on took ritoxamab for RA
- Has chronic otitis media or has abnormal heart valves S/P teeth extraction

What is the message here

- The same clinical, biochemical & radiologic findings can mean completely different diagnoses in different patient populations
- The relationship between pathogens and CNS is changing into a very dynamic one

What is behind the change?

Patients populations are changing:

- **More Transplants (solid organ & HSCT)**
- **More Neutropenics (post chemotherapy)**
- **HIV epidemic**
- **Aging population**
- **More use of new immunosuppressive drugs: TNF antagonists**

What is behind the change?

- **Newer pathogens are emerging:**
  - ✓ **Transmissible spongiform encephalopathy**
  - ✓ **SARS?**
  - ✓ **Avian flu?**

- **Already existing ones are changing susceptibility:**
  - ✓ **Pneumococcal resistance to penicillins and to 3rd generation cephalosporins**

What is behind the change?

- **Development of potent vaccines,with subsequent change in epidemiology of CNS infections: H.Influenza, meningococcus,& ??pneumococcus**

- **Identification of efficacy of agents other than antimicrobials in the therapy of infections: steroids**

More sophisticated diagnostic technology

- **Nucleic acid testing (PCR) of CSF:**
  - **HSV,TB, Enteroviruses**
- **Antigen detection in CSF:**
  - **Cryptococcus, CMV**
- **Protein detection in CSF:**
  - **14-3-3 for CJD**

The first case

- Meningitis, Yes.
- But what kind?
- Bacterial, viral, Mycobacterial, or fungal?
- Should we administer antivirals (which ones?), antibiotics (which ones?), or antifungals?
- The answer is in patient characteristics & in where he/she lives

Immunocompetent : Bacterial meningitis

- **No change in the etiologic agents**
  - ✓ Less than 1 month: Strep.B, E.coli, Listeria (SLE)
  - ✓ 1month-50 years:Pneumococci,meningococci
  - ✓ More than 50 years:Pneumococci, listeria
- **There is change in the recommended antibiotics**
  - ✓ Less than 1 month: Ampicillin + cefotaxime
  - ✓ 1month-50 years: Ceftriaxone or cefotaxime + Vancomycin
  - ✓ More than 50 years:Ampicillin + Ceftriaxone + vancomycin

Why add vancomycin?

- **Increasing in vitro pneumoccal resistance to 3rd generation cephalosporins**
- **Reports of clinical failure on ceftriaxone alone**

Bacterial meningitis
Steroids: to give or not to give?

- **The rationale is based on animal studies which showed that subarachnoid space inflammation was a major factor contributing to morbidity and mortality**
- **Initially, there were conflicting results in humans**
- **Dexamethasone was shown to reduce neurologic deficit as compared to placebo in infants and children**

N Engl J Med 1988;319:964-71
N Engl J Med 1991;324:1525-31
Lancet 1993;342:457-61.

Bacterial meningitis
Steroids: to give or not to give?

- Dexamethasone (10mg) given 15-20min.before the first dose of antibiotics, & then Q 6hrs,was shown to reduce unfavorable outcomes and death as compared to placebo in adults.

N Engl J Med 2002;347:1549-56

- Risk of adverse events did not differ significantly between the 2 groups
- Benefit was most striking with pneumococcus
- There was some concern about steroids impairing penetratin of vancomycin into CSF. That was not substantiated in later pharmacokinetic studies

Bacterial meningitis: special conditions

- **Immunosuppressed (neutropenic/ transplant):**
  Cover for listeria with ampicillin. If allergic, use trimethoprin/sulfa

- **Patients with V-P shunts:**
  - ✓**Staph. Epidermidis & aureus, Gram(-) ,P.acnes**
  - ✓**Vancomycin + ceftazidime**
  - ✓**Early shunt removal is necessary for cure**

Bacterial meningitis-
Diagnostic pearls

- **CSF WBC differential may be misleading early in meningitis: >10% of cases of bacterial meningitis will have an initial lymphocytic predominance, and viral meningitis may initially be dominated by neutrophils**

- **Bacterial antigen testing is going out of favor: low yield and not shown to impact patients management**

Immunocompetent in endemic areas: TB meningitis

- **CSF : lymphocytic pleocytosis, high protein, low glucose**
- **A negative PPD does not exclude the diagnosis**
- **A negative acid fast bacilli stain, Tb Culture or PCR also do not exclude the diagnosis: the sensitivity of each respectively is: 10%, 60-80%, and 60-80%**

TB meningitis

- **Steroids to be started with the first dose of Tb Rx drugs, and to be tapered over 2 months;as compared to placebo improved survival , but not neurologic deficits**
  (N Engl J Med 2004;351:1741)

- **In KSA, Start with 4 first line anti-tuberculous drugs**

- **Duration of therapy is 12 months if initial regimen had pyrazinamide and 18 months if it did not.**
- **Quinolones: Moxifloxacin?**

HIV: Cryptococcal meningitis

- Mostly seen with HIV (+) and post transplant, but can occur in immunocompetents: accounts for 7% of chronic meningitis
- CSF cryptococcal antigen is a highly sensitive and specific test
- Therapy consists initially of amphotericin B followed by Fluconazole

In all patient populations: Do Not Forget viral meningitis

- **Mostly benign self limited**
- **Enteroviruses account for than half of the cases, and usually cause disease during summer & fall in temperate areas.**
- **In the pre-vaccine era, Mumps virus was the most common cause in USA.**
- **Mosquito-borne viruses are important etiology in endemic areas (St Louis encephalisis, WNV)**

Herpes meningitis

- Can be caused by both HSV-1 & 2
- Can occur with primary or activation diseases
- Absence of herpetic lesions does not exclude disease
- 36% of women & 15% of men had aseptic meningitis with primary genital herpes.
- Self limited & without sequelae
- Link between HSV-2 & Mollaret's meningitis
- Chichenpox & zoster can be also associated with meningitis

The second case

- **Brain abscess, Yes.**
- **What Kind?**
- **Bacterial (which bacteria?), Mycobacterial, fungal, protozoan, or may be not of infectious etiology at all?**
- **Again, the answer is in patient characteristics & in where he/she lives**

Ring enhancing lesions

- **Immunocompetent patients:**
  - ✓ **Bacterial brain abscesses (streptococci,anaerobs, G-)**
  - ✓ **Tuberculoma**
- **Patients on steroids:**
  Nocardia
- **HIV positive patients, depending on CD4 Count:**
  - ✓ **>500 copies/cc, as immunocompetent**
  - ✓ **<100 copies/cc :**
    - ✓ **Toxoplasma Gondi**
    - ✓ **Cryptococoma**
- **Post transplant patients:**
  - ✓ **Aspergillus**

Ring enhancing lesions

- **The approach depends on :**
  - ✓ **The patients immune status**
  - ✓ **The level of endemicity of infections in the country**
  - ✓ **Availability of invasive diagnostic tests**
  - ✓ **Accessibility of the lesions**

Ring enhancing lesions
Diagnostic Pearls

- **Look for suggestive etiologies elsewhere: e.g. lungs**

- **Run appropriate Serologic tests:**
  - ✓**Galactomannan Ag**
  - ✓**Cryptococcal Ag**
  - ✓**Toxoplasma Ab**

- **Biopsy/drainage remain the ultimate diagnostic tool:**
  - ✓**Confirm etiology**
  - ✓**susceptibility**

Bacterial brain abscesses

- Can be primary or contiguous (sinusitis, otitis)
- Underlying endocarditis should be excluded
- Empiric therapy should include a 3rd generation cephalosporin + metronidazole
- If size of abscess is > 2.5 cm, surgical drainage should be considered.

In endemic areas: Tuberculoma

- Intracranial tuberculomas are space-occupying lesions that mimic pyogenic abscesses
- They are most frequently multiple but can be single, appearing on imaging studies as avascular masses with surrounding edema
- Anti tuberculous vs surgery
- Duration of therapy: 12 months vs. Until resolution

HIV or post transplant: Toxoplasma encephalitis

- **Multiple ring enhancing lesions, associated with edema, mainly at Gray-white junction**
- **Normal CSF in around 30%**
- **Toxo-IgG is negative in up to 16%**
- **Rx: Pyremethamine + sulfadiazine/ clindamycin/ azithromycin/ Trimethprin/ sulfa**
- **Clinical response in 1 week, radiological response in 2 weeks**

Post transplant: CNS Aspergillosis

- **Aspergillus is the most common cause of brain abscesses in transplant Patients (solid organ, SOT & hematopoeitic stem cells, HSC)**
- **Median time to onset is 24 days in SOT, and 70 days in HSC**
- **Fronto parietal cerebral lobes are mainly involved (80-89%)**
- **Rx: Voriconazole +/- Caspofungin > liposomal ampho B**
- **Mortality remains around 100%**

On steroids: Nocardia abscesses

- G(+) that are also Acid fast staining
- Cause abscesses in skin, lung & brain
- Main risk factor is steroids intake, but also transplant
- Rx: trimethoprin/ sulfa

Encephalitis

- **Viruses are the most likely etiology.**
- **Exact viral etiology is again determined by patients characteristics & by where he/she lives.**
- **Natural course of Viral encephalitis is not as benign as that of viral meningitis**
- **In immunocompetent, mainly HSV , arboviruses, less likely rabies**
- **In immunosuppressed, HHV-6, HIV, JC virus, CMV.**
  - ✓ **Listeria cause bacterial encephalitis**

HSV encephalitis

- Most common acute sporadic viral CNS disease
- Beyond neonatal period, HSV-1 is the main etiology
- Mortality in untreated cases is 60-80%
- >90% of survivors are left with severe neurologic sequel
- PCR for HSV in CSF is now the gold standard for Dx of herpes encephalitis: Specificity and sensitivity are almost 100%
- Acyclovir is the recommended empiric therapy until HSV PCR results are out. Once diagnosis confirmed, duration of therapy is 21 days

HHV-6

- **The most neuroinvasive of all herpesviruses**
- **Serologic studies showed prevalence in up to 80%**
- **Exanthem subitum(roseola infantum) in immuno-competent children and classical mononucleosis illness in adults.**
- **In immunosuppressed (transplant) , HHV-6 encephalitis:**
  - ✓ **Mental status changes (confusion-coma):92%**
  - ✓ **Seizures, fever, Speech disturbances : 25%**

HHV-6

- **CSF: No pleocytosis in 50%**
  High protein: 88%
  Normal glucose

- **Diagnosis: Detection in CSF of HHV-6 DNA by PCR**

- **Overall mortality is around 60%**

- **Rx: Ganciclovir and foscarnet**

HIV dementia

- Chronic progressive encephalitis caused by HIV, seen with CD4<200
- Incidence: 7% in pre HAART and 2% more recently. Despite decrease in incidence, the prevalence is icreasing due to prolonged survival
- Early Symptoms: Apathy, memory loss and cognitive slowing
- Late Symptoms: severe psychomotor retardation , mutism, and seizures
- Rate of progression is variable, but average from onset of symptoms to death was 6 months in pre HAART era

HIV dementia

- **MRI shows cerebral atrophy, with rarefaction of white matter**
- **CSF shows high protein, has 0-15 wbc/cc**
  65% have no pleocytosis
- **No specific diagnostic test is available**
- **HAART is associated with significant increase in survival & decreased incidence of dementia .**

JC virus

- A polyoma virus. It causes a demyelinating process: Progressive multifocal leukoencephalopathy
- JC virus is Acquired during childhood; Seroprevalence 60%- 90%
- PML occurs mainly in HIV and transplant patients
- Presenting symptoms: alteration in personality, aphasia, gait disturbances,& headache
- MRI:lesions involve the cerebral cortex, multifocal, asymmetric, Spare the gray matter,lack edema & lack enhancement

JC virus

- **CSF is typically unremarkable**
- **PCR in CSF ; sensitivity up to 90%**
- **In situ hybridization for JC virus in brain biopsy samples is The gold standard for diagnosis**
- **Rx: HAART, cidofovir ?**

CMV encephalitis

- In immunocompetent, CMV rarely causes self limited encephalitis
- CMV encepahalitis is more common in HIV with CD4<50
- Rapidly progressive disease causing delirium, CN defects , nystagmus, & ataxia.
- CSF: high protein and mononuclear pleocytosis
- PCR in CSF: sens:80%, spec:90%
- MRI: periventricular enhancement
- Rx: Ganciclovir or foscarnet
- Preterminal event:with Rx survival is 94 days vs 42 days in historical control

AIDS 2000;14:517

Listeria encephalitis

- **Meningitis is the most common form of CNS infection with listeria, often associated with bacteremia**
- **In transplant patients, listeria causes Brain stem encephalitis with cranial nerves palsies .**
- **Rx: Ampicillin and Trimethoprin/sulfa**

Take home message

The relation between the nervous system and microbes is Getting More sophisticated

- **The same presentation will have different differential diagnosis Depending on:**
  - ✓ **Patient's level of Immunity**
  - ✓ **Geography**
- **The same etiology may need different treatment strategies depending on which part of the world you are practicing**