

# HIV and Neurological complications

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**MNWR**

MORBIDITY AND MORTALITY WEEKLY REPORT

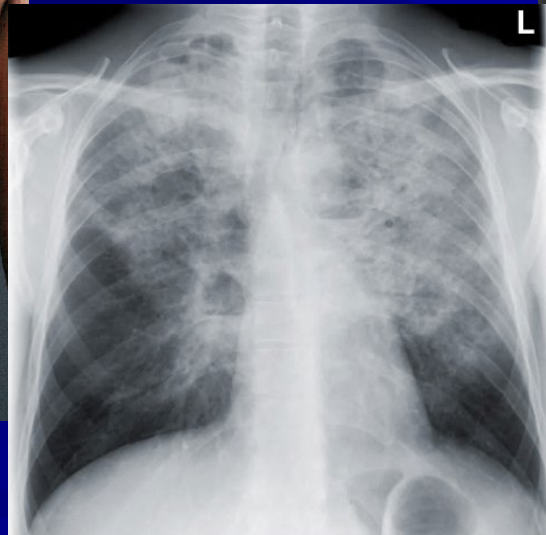
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Epidemiologic Notes and Reports***Pneumocystis* Pneumonia — Los Angeles**

In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. Case reports of these patients follow.

1981

**Pneumocystis pneumonia and Kaposi's sarcoma reported in 26 men in NYC and California**

**MNWR**

MORBIDITY AND MORTALITY WEEKLY REPORT

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Epidemiologic Notes and Reports**Kaposi's Sarcoma and *Pneumocystis* Pneumonia Among Homosexual Men — New York City and California**

During the past 30 months, Kaposi's sarcoma (KS), an uncommonly reported malignancy in the United States, has been diagnosed in 26 homosexual men (20 in New York City [NYC]; 6 in California). The 26 patients range in age from 26-51 years (mean 39 years). Eight of these patients died (7 in NYC, 1 in California)—all 8 within 24 months after KS was diagnosed. The diagnoses in all 26 cases were based on histopathological examination of skin lesions, lymph nodes, or tumor in other organs. Twenty-five of the 26 patients were white, 1 was black. Presenting complaints from 20 of these patients are shown in Table 1.

Skin or mucous membrane lesions—often dark blue to violaceous plaques or nodules

# 42 years later in 2023-----

## HCV, HBV and HIV Prevalence - USA

- **US Population: 331 million**
- **HIV:**
  - Estimated prevalence in the US- 1.1 million
  - About 1/350 Americans have HIV
  - Much higher in young males – about 1/150
  - About 35,000 new infections/year
- **Chronic HBV**
  - Estimated prevalence 880,000 -2.4.million
  - 4000 – 20,000 new infections per year
- **HCV:**
  - Estimated prevalence in the US- 2.4 – 4 million
  - About 50,000 new infections/year

# HIV and opportunistic infections

- The most important factor is the degree of immunosuppression in the host.
- Patients with CD4 cell counts  $>500/\text{microL}$ 
  - benign and malignant brain tumors
- Patients with CD4 cell :  $200 - 500/\text{microL}$ 
  - HIV-associated cognitive and motor
  - usually do not present with focal lesions.
- Patients with CD4 cell  $< 200/\text{microL}$ 
  - CNS mass lesions
  - Opportunistic infections
  - AIDS-associated tumors

# Lab evaluation in the setting of HIV and CNS lesions

- CD4 cell count and HIV viral load
- Syphilis testing (treponemal and non treponemal Ab)
- Serum cryptococcal antigen
- Toxoplasma IgG serology:
  - Negative IgG serology greatly reduces the likelihood of toxoplasmosis encephalitis (TE), although it does not rule it out completely
- Bacterial and fungal blood cultures
- Not diagnostic are:
  - Serum Interferon gamma release assays
  - Serum JC virus PCR
  - Serum cytomegalovirus (CMV)

# Space-occupying lesions in HIV

- **Toxoplasma encephalitis** — TE represents reactivation of disease from prior infection and is typically seen in patients with CD4 counts <100 cells/microL AND positive *Toxoplasma gondii* serology who are not taking ART.
- **Primary central nervous system lymphoma** — PCNSL is generally seen in patients with CD4 counts <50 cells/microL who are not on ART.
- **Progressive Multifocal leukoencephalopathy (PML)**
- **Bacterial/fungal brain abscess** — Brain abscesses secondary to *Staphylococcus* spp, *Streptococcus* spp, *Salmonella* spp, *Aspergillus* spp, *Nocardia* spp, *Rhodococcus* spp, and *Listeria*
- **Tuberculoma** — Rare in the US
- **Neurocysticercosis** — Rare in the US caused by the larval stage of the pork tapeworm *Taenia solium*

# Case

- 33 year male.
- AIDS, CD4- 40, Viral Load 102,000
  - Presents with 3 week H/O malaise, headaches, fever.
  - Drove to clinic
- On exam
  - T-99.5, Mild confusion, oral thrush, no neck stiffness or cranial N palsies
  - On occasional Bactrim for PCP prophylaxis

- Broad Differential
  - Anemia, uremia, electrolyte abnormalities,
  - Drug toxicity (recreational) or Bactrim
  - Other causes of encephalopathy/encephalitis
  - PML
  - Cryptococcal meningo-encephalitis
  - Disseminated Mycobacterium avium



# Next Steps

- History, Examination
- Labs: CBC, CMP, Serum Toxo IgG, Serum Cryptococcal Antigen, RPR
- Imaging: MRI better than CT
- Subsequently Lumbar Puncture, especially if Serum Cryptococcal antigen is positive
- CSF studies:
  - Cell count with diff, protein, glucose, CSF cryptococcal antigen, VDRL, May need to send CSF EBV PCR and JC Virus PCR if MRI abnormal

# CSF Characteristics of HIV associated OIs

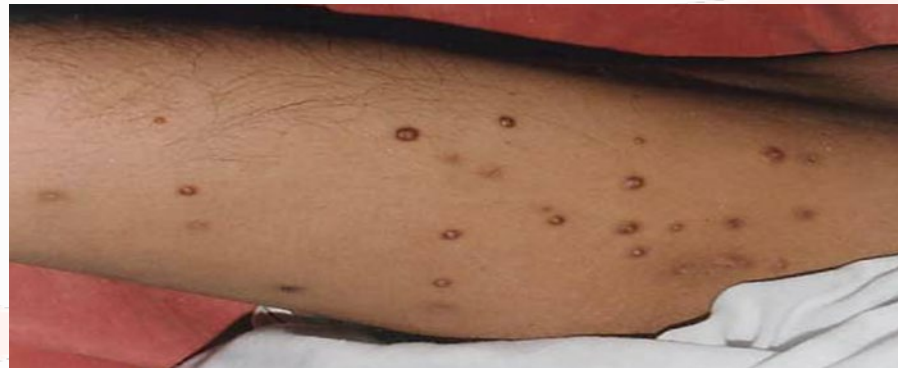
	White-blood-cell count	Glucose concentration	Protein concentration	Other
Toxoplasmic encephalitis <sup>21,22,36</sup>	Normal or increased lymphocytes	Decreased or normal	Normal or increased	<i>Toxoplasma gondii</i> PCR nearly 100% specific and 50–80% sensitive
PML <sup>23,24</sup>	Normal, rarely increased lymphocytes	Normal	Normal or increased	JC-virus PCR sensitivity variable at 50–90%, but specificity 90–100%
Primary CNS lymphoma <sup>25,26</sup>	Normal or increased lymphocytes	Normal	Normal	Epstein-Barr virus PCR nearly 100% sensitive and about 50% specific
Cytomegalovirus encephalitis <sup>27,28</sup>	Normal, rarely increased neutrophils	Normal	Normal or increased	PCR >90% sensitive and specific and <25% culture positive
Cryptococcal meningitis <sup>29,30,37</sup>	Normal, rarely increased lymphocytes	Decreased or normal	Normal or increased <sup>36</sup>	Opening pressure frequently raised; India ink stain 75% sensitive; CSF cryptococcal antigen sensitivity 92% and specificity 83%; high CSF antigen titre associated with poor prognosis, but change of titre with treatment has little correlation with prognosis
Tuberculous meningitis <sup>32–34</sup>	Increased lymphocytes	Decreased	Normal or increased	<i>Mycobacterium tuberculosis</i> culture has variable sensitivity, but use of microscopy for acid-fast bacilli and CSF NAAT can increase sensitivity to >80%
Herpes simplex virus <sup>35</sup>	Usually increased lymphocytes	Normal or increased	Increased	CSF PCR sensitivity 100%, specificity 99.6%

PML=progressive multifocal leukoencephalopathy. NAAT=nucleic-acid amplification test.

Table 4: CSF characteristics of HIV-associated CNS opportunistic infections

# Cryptococcal Meningoencephalitis

- Cryptococcal meningitis is the largest single cause of neurological mortality in HIV patients worldwide
  - Mortality rates of 25–50%
- The yeast is inhaled and then disseminates hematogenously and then crosses the blood brain barrier



# *C. neoformans* meningoencephalitis

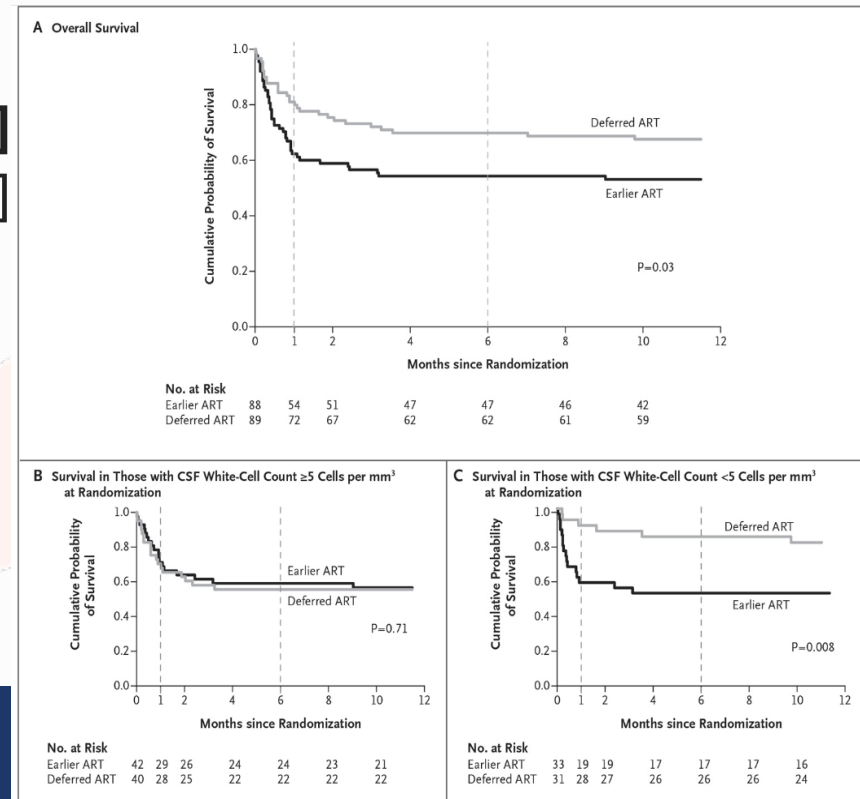
- Subacute presentation over several days or weeks
- Clinical features
  - Fever
  - Headache
  - Nausea
  - Mild – moderate Meningismus
  - Altered mental status
- CSF
  - Raised opening pressure
  - Minimally raised protein and WBC
  - Positive CSF cryptococcal Ag (98%)
- Blood
  - Positive cultures
  - Positive serum cryptococcal Ag (98%)

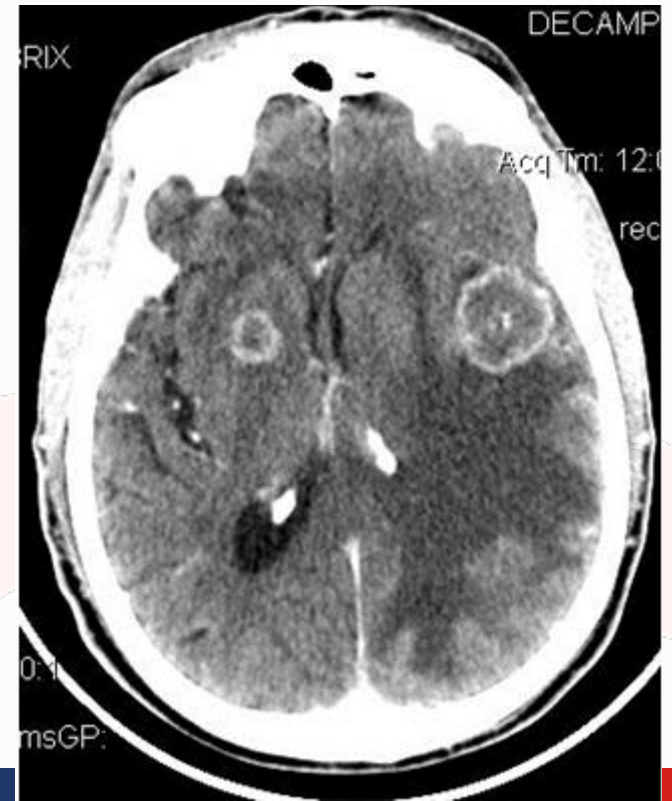
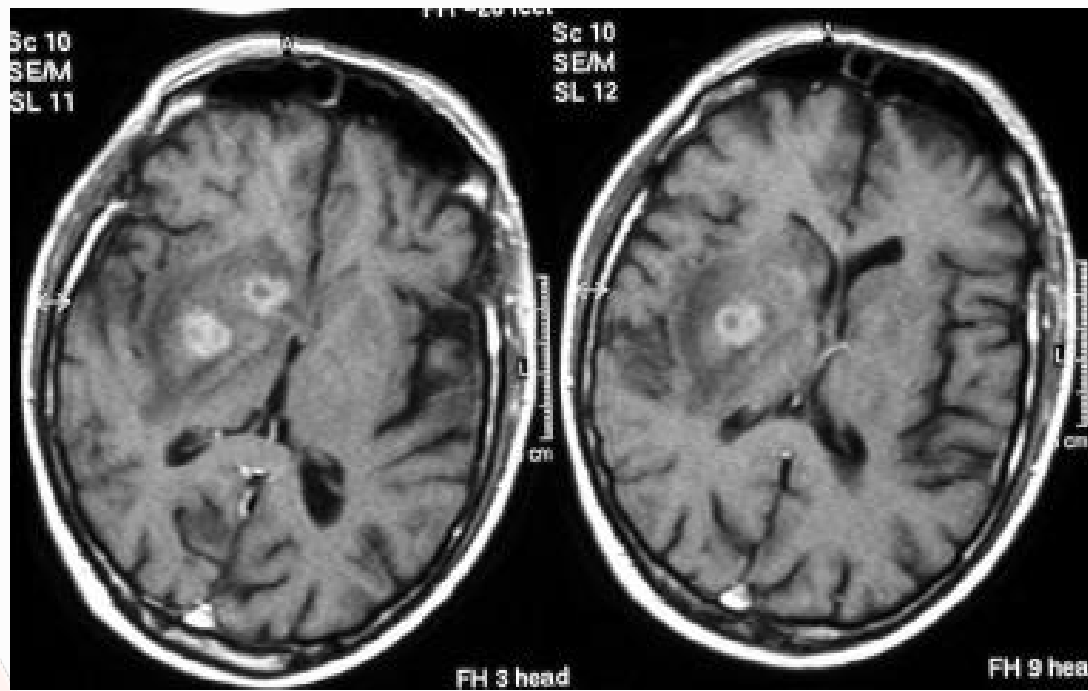
# Treatment in HIV infected patients

- Management of cryptococcal meningoencephalitis includes all of the following:
  - Antifungal therapy: Liposomal amphotericin and Flucytosine X 2-4 weeks followed by fluconazole
  - Control of intracranial pressure
    - Increased ICP in patients with cryptococcal meningoencephalitis should be managed aggressively to decrease mortality
    - LP should be performed to reduce the opening pressure to <20 cm CSF
  - ART
    - antiretroviral therapy (ART) should be started between 2 and 10 weeks after antifungal therapy has

# COAT Trial- timing of ART with Cryptococcal meningoencephalitis

- South Africa and Uganda
- assigned study participants to undergo
  - earlier ART initiation (1 to 2 weeks after diagnosis)
  - Or deferred ART initiation (5 weeks after diagnosis).
- Results:
- 26-week mortality
  - **Earlier ART -45% [40 of 88 patients]**
  - **Deferred ART-30% [27 of 89 patients]**





## Case 2

# Toxoplasma gondii

- Transmission
  - Ingestion of food or water
  - Eating undercooked or raw meat
  - Via transplacental transfer
  - Accidentally swallowing the parasite through contact with cat feces that contain *Toxoplasma*.
- Prevalence
  - **11%** in the United States
  - 50% to 80% in Latin American & African countries



# Cerebral toxoplasmosis

- Presentation
  - Fever, altered sensorium, focal neurologic deficits, seizures
- Diagnosis
  - Cerebrospinal fluid may be normal
- Best “screening” test for cerebral toxoplasmosis in a patient with AIDS and ring enhancing lesions :
  - **Serum Toxoplasma IgG**
  - Positive in > 95% AIDS
    - higher risk for titers  $\geq 150$  IU/ml.
  - *Derouin F, et al. AIDS. Nov 1996;10(13):1521-1527*
  - CSF Toxoplasma PCR

# Treatment for toxoplasma encephalitis (cerebral toxoplasmosis)

- Therapy

- Pyrimethamine plus sulfadiazine plus leucovorin

- Pyrimethamine

- penetrates the brain parenchyma efficiently
      - Pyrimethamine toxicities: rash, nausea, and bone marrow suppression

- Leucovorin

- reduces the likelihood of pyrimethamine toxicity

- Sulfadiazine toxicities

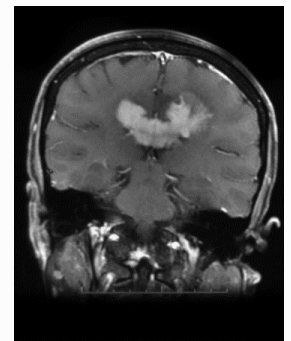
- rash, fever, leukopenia, hepatitis, diarrhea, renal insufficiency, and crystalluria.

TMP/SMX is an alternative for treatment and prophylaxis

# Monitoring

- Clinical response to empirical treatment in 14 days
- MRI usually better in 2 -4 weeks
- Acute therapy for TE
  - At least 6 weeks
- Maintenance therapy till CD4 > 100
- Primary Prophylaxis
  - *Toxoplasma*-seropositive patients (Serum Toxo IgG +) and CD4 counts <100 cells/ $\mu$ L should receive prophylaxis against TE
    - Primary Prophylaxis can be safely discontinued in patients with CD4 100 -200 cells/mm<sup>3</sup> and HIV plasma RNA < 400

# CNS Lymphoma



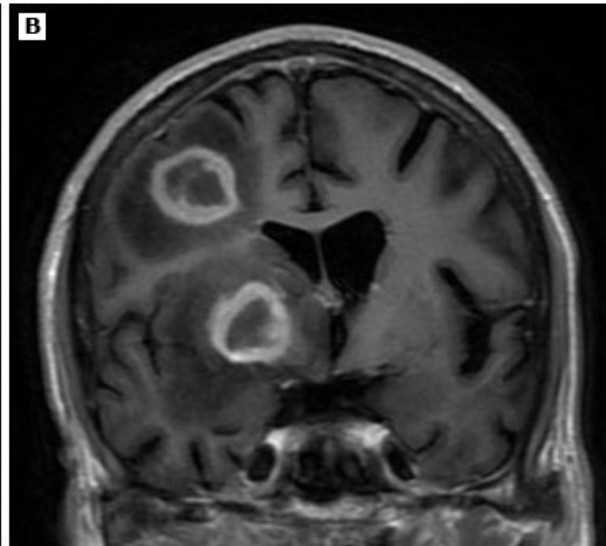
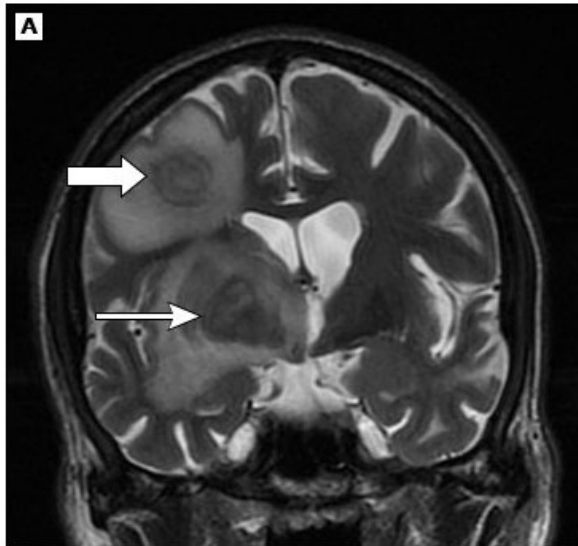
- HIV-related NHL is generally divided into three types
- Systemic NHL, PCNSL, and primary effusion ("body cavity") lymphomas
  - Diffuse large B cell Non Hodgkins lymphoma is the commonest
  - Primary CNS Lymphoma
    - The incidence of PCNSL has declined with widespread ART
    - EBV infection is central to the pathobiology of HIV-related PCNSL.
    - Varying sensitivity and specificity of CSF EBV PCR
      - High NPV > 75%
      - Low PPV- 30%
    - In the right setting a positive EBV PCR can avoid a biopsy but lesions need close monitoring

# Primary CNS Lymphoma

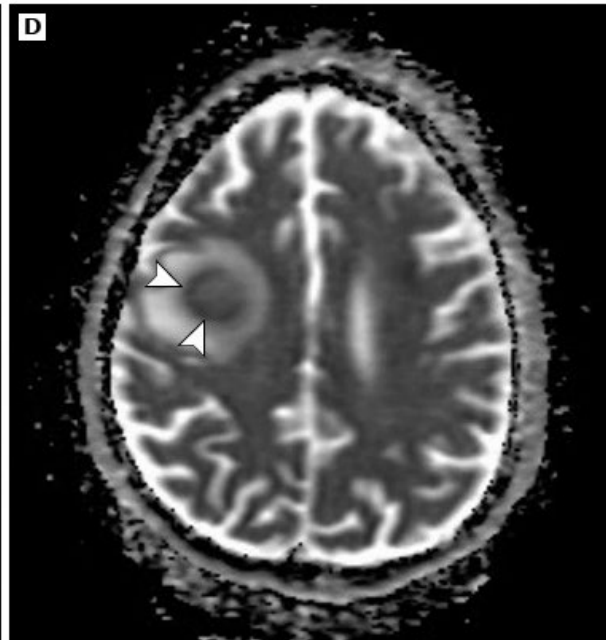
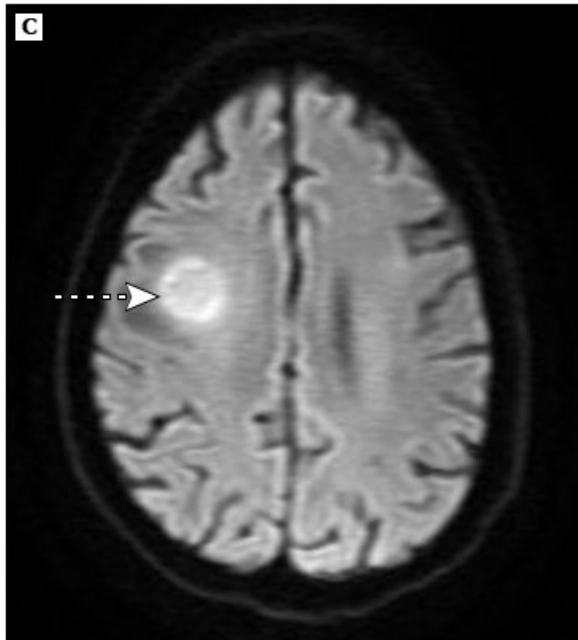
- Presentation
  - Confusion, memory loss, hemiparesis, aphasia, seizures
  - Fever, night sweats, weight loss, in > 80 percent of patients.
- Lumbar puncture
  - Should be performed in all patients
    - unless contraindicated by mass effect or midline shift
  - CSF studies
    - Cell count, differential, glucose, total protein, and culture, cytology, flow cytometry, EBV PCR, JC virus PCR.
    - EBV DNA in CSF is used as a marker of PCNSL
- Radiological findings
  - Single or multiple lesions
  - Involve the corpus callosum or the periventricular areas

AIDS-related primary central nervous system lymphoma

T2



T1



# Progressive multifocal leukoencephalopathy (PML)

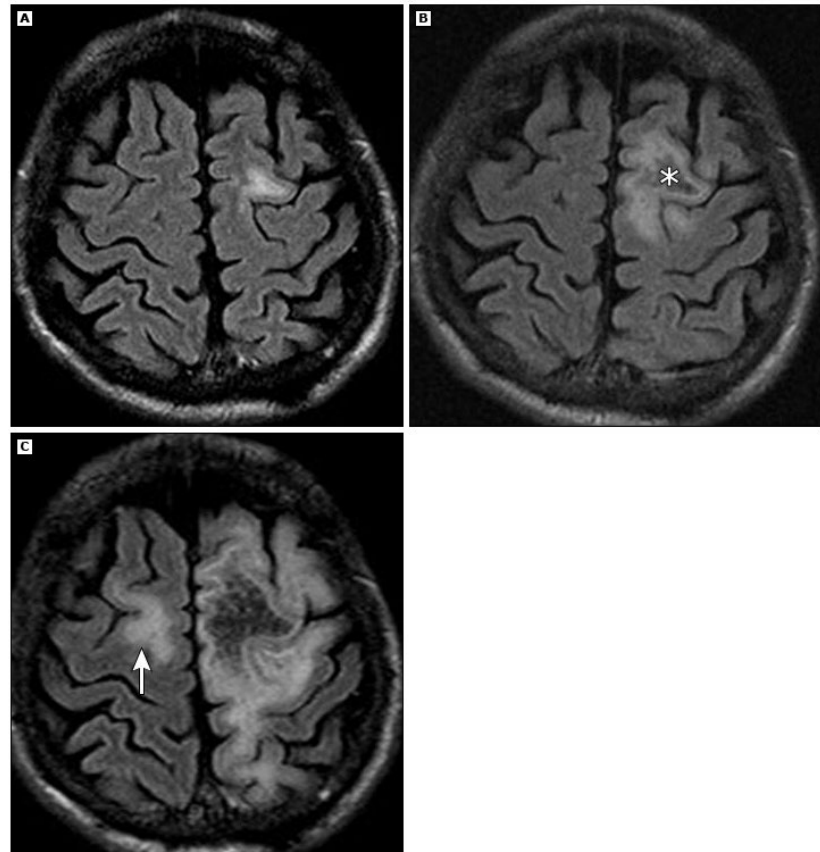
- PML is a severe demyelinating disease of the CNS
  - Caused by reactivation of the polyomavirus JC
  - Asymptomatic infection with JCV occurs in childhood
    - Antibodies can be found in 86 % of adults
  - Replication in the setting of immune suppression may lead to rearrangement of the viral genome
    - Produces neurotropic variants that replicate in CNS

# PML

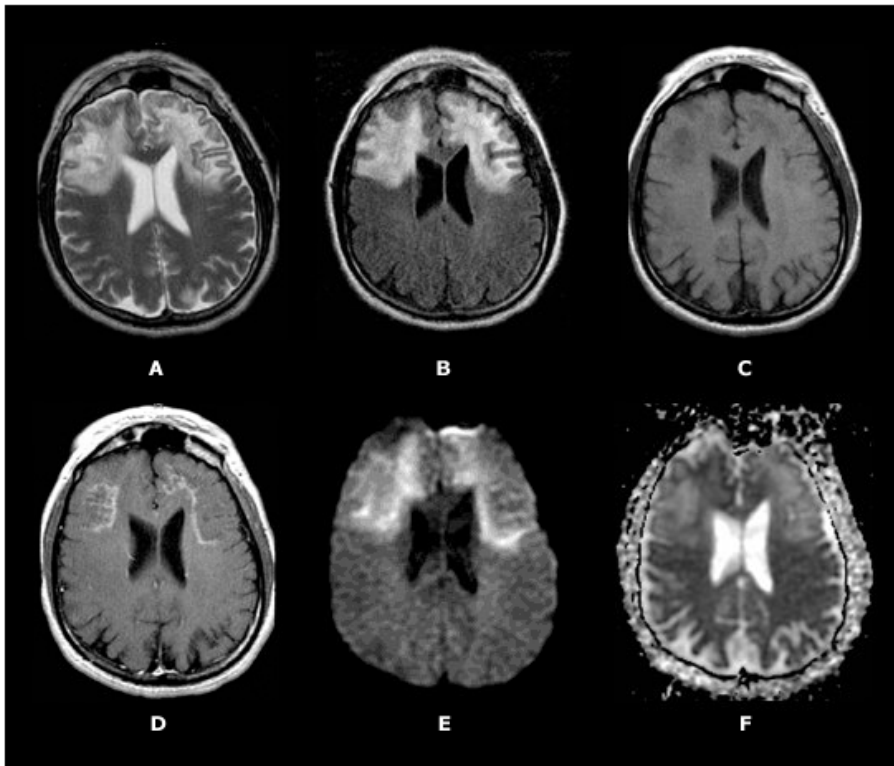
- Risk Factors
- **HIV (CD4 < 100)**
- **Malignancy**
- Organ transplantation
- Immunomodulatory therapy
  - Natalizumab
    - And other drugs
- Autoimmune disorders (in 20% of non-HIV PML)
- Primary immunodeficiency



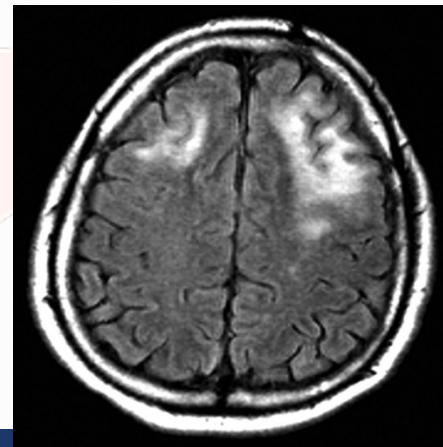
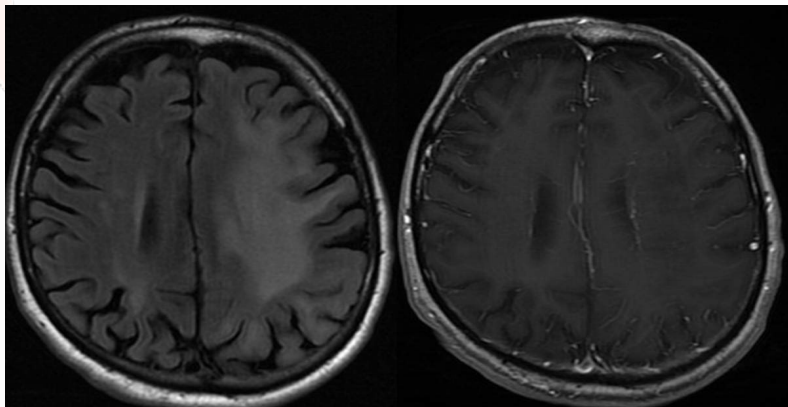
Brain MRI showing progression of PML over four months



Brain MRI of progressive multifocal leukoencephalopathy after cardiac tran



- **Progressive Multifocal Leukoencephalopathy-HIV**
- Presentation is subacute
- focal neurological deficits
  - Cognitive impairment, focal deficits, ataxia
  - weeks to months
- The lesions are
  - hyperintense (white) on T2
  - hypointense (dark) on T1
  - **non-contrast enhancing** and produce **no mass effect**



# Diagnosis of PML

- Serum Antibody for JC virus NOT reliable for active PML
  - Estimated 86% of adults are seropositive
- CSF
  - Typically, normal with absence of leukocytes
  - Protein is mildly elevated, but < 100 mg/dl
- **CSF PCR for JC virus - best non-invasive test**
- CSF JCV assay in HIV infected patients
  - Positive in 70% - 90% of patients not taking ART
  - Quantitative assay had a diagnostic sensitivity of 76% and specificity of 100%.
  - Patients on ART may be falsely negative for CSF JC Virus

# Patient , 34 years old, with PML

B/L Dysdiadochokinesia, dysmetria, intention tremor, nystagmus



# Immune reconstitution inflammatory syndrome (IRIS)

- Half-life of HIV is between 1-4 days
  - ART : >90 % reduction in the HIV viral load within 2 weeks
- IRIS:
  - Spectrum of inflammatory disorders associated with paradoxical worsening of preexisting infectious processes following the initiation of ART in HIV-infected individuals
- Usually Within 4-8 weeks of starting ART
  - Seen with an increase in CD4 & decrease in Viral load
  - Due to Worsening of an existing or unrecognized OI
- Incidence 7%-15%

# IRIS

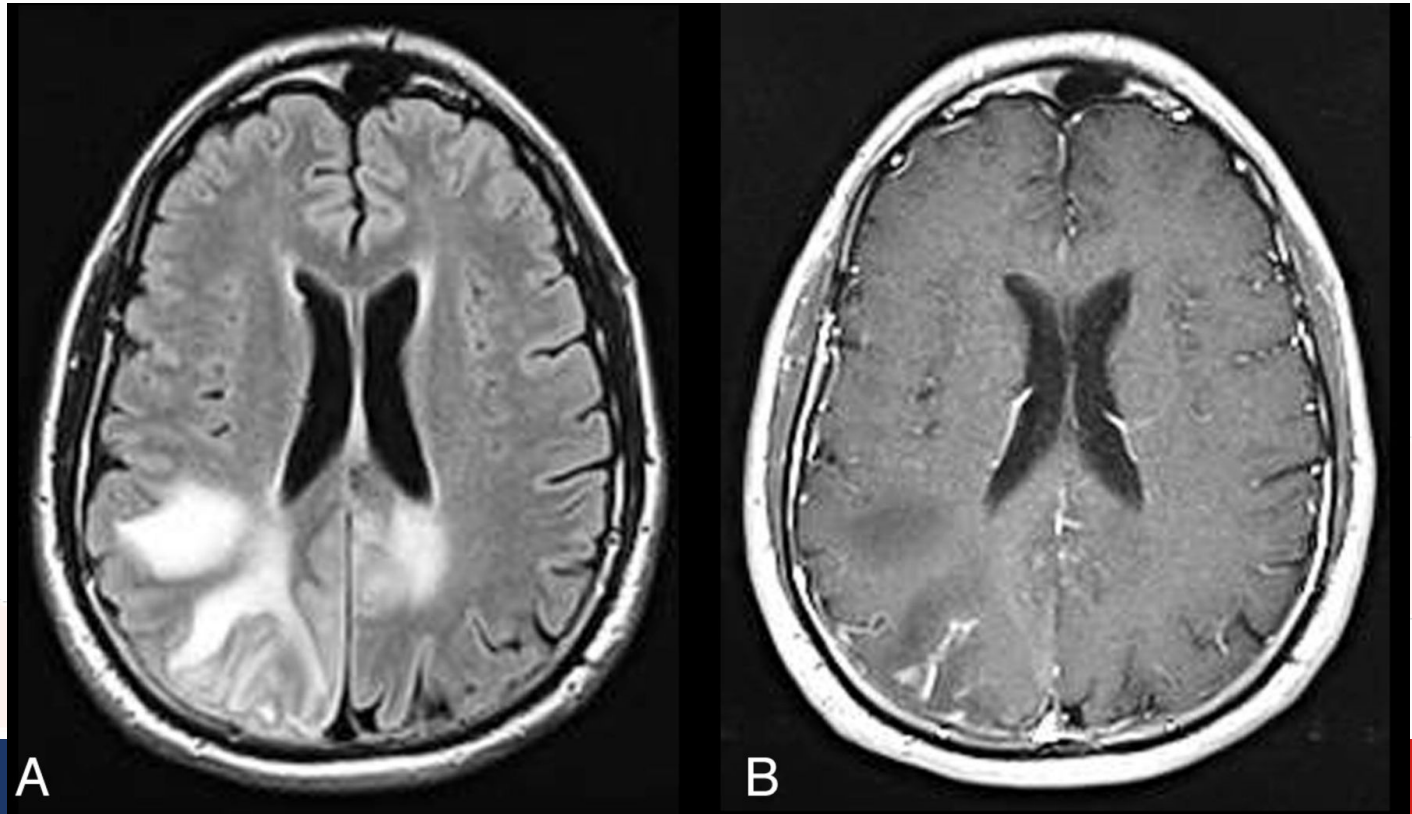
- Inflammatory reactions to many pathogens have been described
  - Mycobacteria: TB, MAC
  - Fungi: Cryptococcal meningitis, Pneumocystis pneumonia
  - Viruses: CMV , PML from JC, HSV, VZV, Hep B/C, HPV
  - Bacteria: Bartonella, T. pallidum
  - Parasites: Toxoplasma, Strongyloides
- May include worsening of some malignancies
  - Kaposi's sarcoma, Castleman's disease

# IRIS presentations



# PML-IRIS

- PML-IRIS occurs in patients with HIV who start ART
  - Can enhance
  - Can have mass effect





# Cytomegalovirus Retinitis

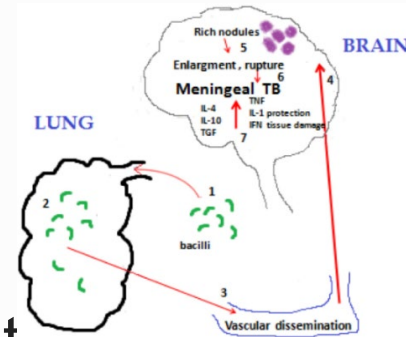
- CMV Retinitis
  - Usually with  $CD4 < 50$
  - Necrotizing retinitis
  - High rates of disease in contralateral eye
- CMV Colitis :
  - in 5% to 10%



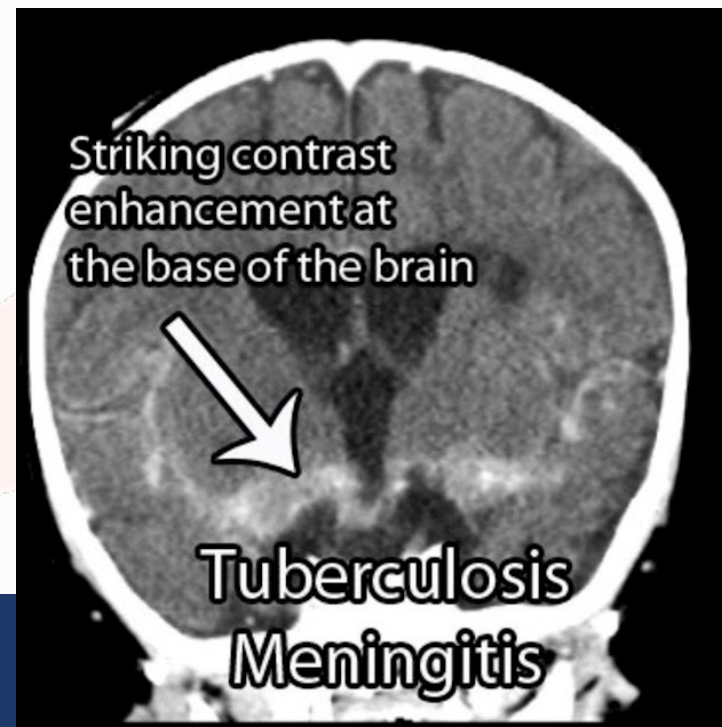
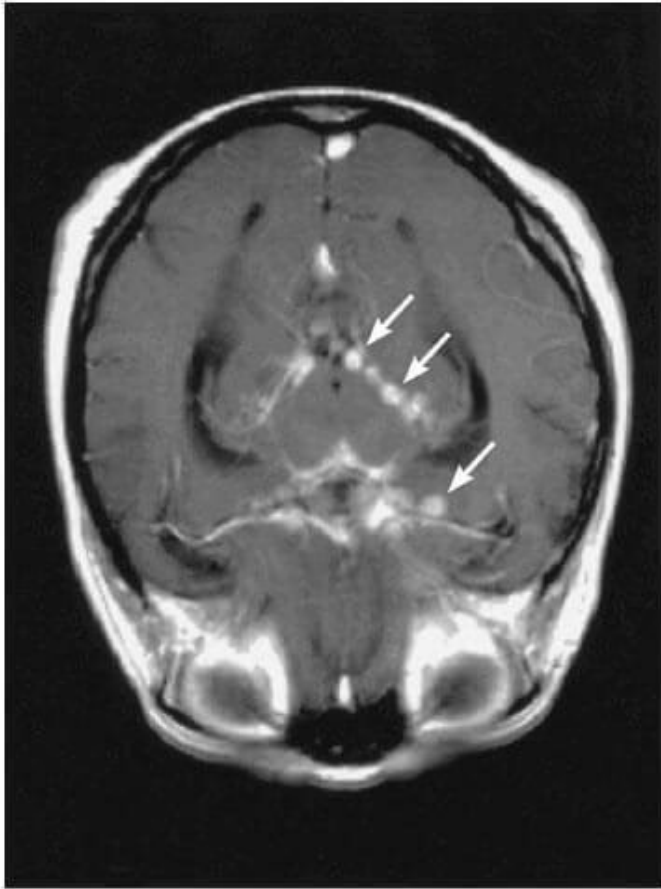
# Diagnosis and Treatment of CMV

- Diagnosis:
    - NO Role of CMV IgG in HIV infected patients
    - Use PCR: blood and CSF.
    - Tissue biopsy if available is **best** as denotes CMV end-organ disease rather than colonization
  - Treatment
    - ART
  - Anti-virals:
    - IV ganciclovir
    - OR PO valganciclovir (this is a prodrug with good bioavailability)
    - Intravitreal injections of ganciclovir or foscarnet
- Concomitant treatment with systemic anti-CMV therapy

# CNS TB



- CNS tuberculosis (TB) includes three clinical categories
  - tuberculous meningitis
  - intracranial tuberculoma
  - Spinal tuberculous arachnoiditis
- Meningitis develops most commonly as a complication of progressive primary infection in
  - Infants and young children
  - In older adults with immune deficiency
- Sequelae in children with tuberculous meningitis
  - Death in upto 20%
  - Neurological sequelae > 50% of patients.



# Neurosyphilis

- CNS invasion in early disease – occurs in about 50%
- Majority are asymptomatic
- 80% will clear the CNS infection spontaneously
- 20 % develop tertiary syphilis in 10- 20 years
- Serum RPR (VDRL) positive in
  - 70-80% of primary
  - 99% of secondary
  - 56-70% of late syphilis

# Neurosyphilis

- Diagnosis of neurosyphilis
  - Presence of any of the following in the CSF
    - Elevated protein
    - Pleocytosis
    - VDRL
- Presentations:
  - Syphilitic meningitis : 5% of Early neurosyphilis is symptomatic-meningitis, cranial N palsy (within 1-10 years)
  - Meningo-vascular- focal signs due to infarction
  - Parenchymatous- combination of vascular and ischemic changes- GPI, Tabes dorsalis
- Treatment
  - Aqueous crystalline penicillin G, 18- 24 million units IV in divided doses a day for 10-14 days

# Rash of Secondary Syphilis



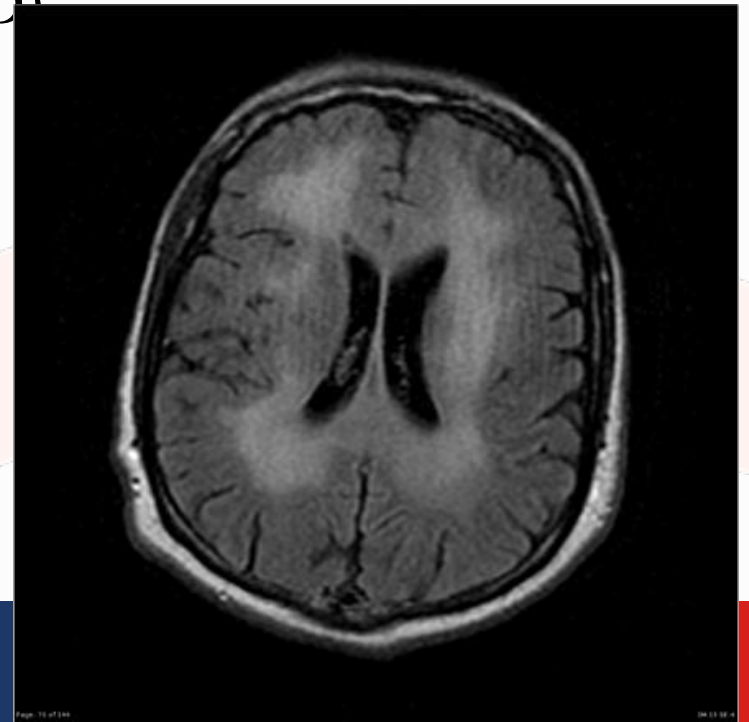
# HIV Neuropathy

- HIV can affect
  - Peripheral sensory and motor nerves
  - Thoracic nerves
  - Cranial nerves or autonomic nerves.
- **HIV polyneuropathy** (distal symmetric polyneuropathy)
- Symptoms include:
  - Paresthesia
  - Numbness and pain in their hands and feet.
  - Weakness of the muscles in the feet and hands
- **HIV mononeuropathy**
- Guillain-Barre Syndrome (AIDP)



# HIV dementia

- HIV-associated neurocognitive disorders (HAND)
- Spectrum of neurologic and cognitive symptoms.
- NIH Classification
  - Asymptomatic neurocognitive impairment (ANI)
  - Minor neurocognitive disorder (MND)
  - HIV-associated dementia (HAD).



## 2023- Initiate ART immediately (or as soon as possible)

DHHS <sup>[1]</sup>	WHO <sup>[2]</sup>	IAS-USA <sup>[3]</sup>
<ul style="list-style-type: none"><li>Initiate ART immediately (or as soon as possible) after HIV diagnosis</li></ul>	<ul style="list-style-type: none"><li>Recommended where feasible</li></ul>	<ul style="list-style-type: none"><li>Start ART as soon as possible, <b>including immediately after diagnosis</b>, if patient is ready</li></ul>

1. DHHS Guidelines. 2019. 2. WHO Guidelines. July 2017. 3. Saag. JAMA. 2018;320:379.

# Recommendations for Initiating ART for a person infected with HIV

- ART (Antiretroviral therapy) is recommended for all HIV-infected individuals
  - As soon as possible after diagnosis
- HIV is easier to treat than Diabetes, COPD or CHF
  - (And HIV is one of the only conditions where the federal and state governments pay for : provider visits, labs, vaccines, medications etc. for all unfunded patients)
- Effective ART reduces transmission to uninfected partners to “0”
  - Undetectable= Untransmissible



# ART initiation in the setting of an opportunistic infection

- Initiation of ART ASAP with :
  - Cryptosporidium, Kaposi's sarcoma, PML
- ART :within 2 weeks of treatment for most other opportunistic infections like- PCP, Candidiasis, Toxoplasmosis
  - ART is recommended immediately in the setting of a new diagnosis of cancer with attention to drug-drug interactions
- Two exceptions for holding off on ART initiation immediately
  - **Active tuberculosis** with or without tuberculous meningitis
    - ART should be initiated within 2 weeks **after** initiation of tuberculosis treatment, especially for those with CD4 < 50/ $\mu$ L
  - **Cryptococcal meningoencephalitis:**
    - ART should be initiated 2 - 4 weeks after starting antifungal therapy

# Case

- 38 year woman, 2 day H/O fever, headache, neck stiffness, sexually active with husband.
- Has 2 children at home
- T-99.8, meningismus, alert, oriented
- CSF:
  - **WBC-70, 80% lymphocytes, glucose-60, Protein-70, gram stain negative,**

# Aseptic Meningitis

- Viral
- Parasitic
- Mycobacterial- TB meningitis- high protein, low glucose
- Bacterial
  - Syphilis- usually secondary syphilis but can present at any stage
  - Lyme meningitis- late summer, mild fever , may include CN palsies
- Neoplasm
- Fungal- Cryptococcus and coccidiomycoses
- Drug induced- sulfa drugs, phenytoin, IVIG, OKT3 antibodies,

# Viral Meningitis

- Commonest aseptic meningitis
  - Enteroviruses- summer or fall, PCR is a good test
  - Mumps- Most frequent extrasalivary complication (10-20%)
  - Herpes virus ( Including HSV, VZV)
  - Measles
  - Influenza (Non Polio Enteroviruses)
  - EBV
  - Lymphocytic choriomeningitis virus
  - **HIV- primary HIV (Fever, rash, lymphadenopathy, pharyngitis)**

# Viral Meningitis

## ■ Viral Meningitis

- Not distinguishable from bacterial meningitis based on symptoms
- Duration usually less than 1 week
- Most commonly caused by enteroviruses, HSV-2, and arboviruses

## Treatment

- Empiric antimicrobials until CSF profiles and cultures finalize
- Symptomatic and supportive management

CSF Parameter	Viral Meningitis <sup>a</sup>
Opening pressure	≤250 mm H <sub>2</sub> O
Leukocyte count	50-1000/μL (50-1000 × 10 <sup>6</sup> /L)
Leukocyte predominance	Lymphocytes <sup>d</sup>
Glucose	>45 mg/dL (2.5 mmol/L)
Protein	<200 mg/dL (2000 mg/L)
Gram stain	Negative
Culture	Negative



# CSF- PCR Panel

## Meningitis Encephalitis Panel

Sample Type: Cerebrospinal Fluid (CSF)

### 14 TARGETS IN ONE TEST

The FilmArray Meningitis/Encephalitis (ME) Panel tests for a comprehensive set of 14 bacteria, viruses and yeast. The FilmArray ME Panel identifies the most common viral, bacterial and yeast pathogens that cause infections in the central nervous system which in some cases can be life-threatening. The diagnosis of meningitis and encephalitis can allow faster decisions on appropriate therapy to be made to prevent complications.



### ME PANEL MENU

#### BACTERIA:

- *Escherichia coli* K1
- *Haemophilus influenzae*
- *Listeria monocytogenes*
- *Neisseria meningitidis*
- *Streptococcus agalactiae*
- *Streptococcus pneumoniae*

#### VIRUSES:

- Cytomegalovirus (CMV)
- Enterovirus
- Herpes simplex virus 1 (HSV-1)
- Herpes simplex virus 2 (HSV-2)
- Human herpesvirus 6 (HHV-6)
- Human parechovirus
- Varicella zoster virus (VZV)

#### YEAST:

- *Cryptococcus neoformans/gattii*

<http://www.biofiredx.com/products/the-filmarray-panels/>

# Case

- 56 year female presented with a 2 day history of fever, chills headache confusion
- Headache, stiff neck, fever, purpuric rash
- Platelets 20 K, WBC 30K
- CSF
  - **WBC 2800, 99% Neutrophils, Glucose 20**

# Bacterial Meningitis

- Fever, HA, meningismus, cortical dysfunction are hallmarks
  - Most have 2/4
- Absence of all four almost rules out meningitis
- **Lab evaluation:**
- Culture
  - positive in 70% to 85% (if no previous antibiotics)
- Gram stain
  - positive in 30% to 90% (Listeria 30% and pneumococcus 90%)
- Latex agglutination
  - May help in culture negative or pretreated meningitis but not routinely recommended
- PCR:

# Treatment for Community acquired Bacterial meningitis in an immunocompetent individual

- Dexamethasone + vancomycin + ceftriaxone

# Mucor infections

- 50 year old healthy male
- COVID-- received steroids and tocilizumab
- 3 weeks later developed fungal sinusitis
- Progressive orbital involvement led to left eye exenteration

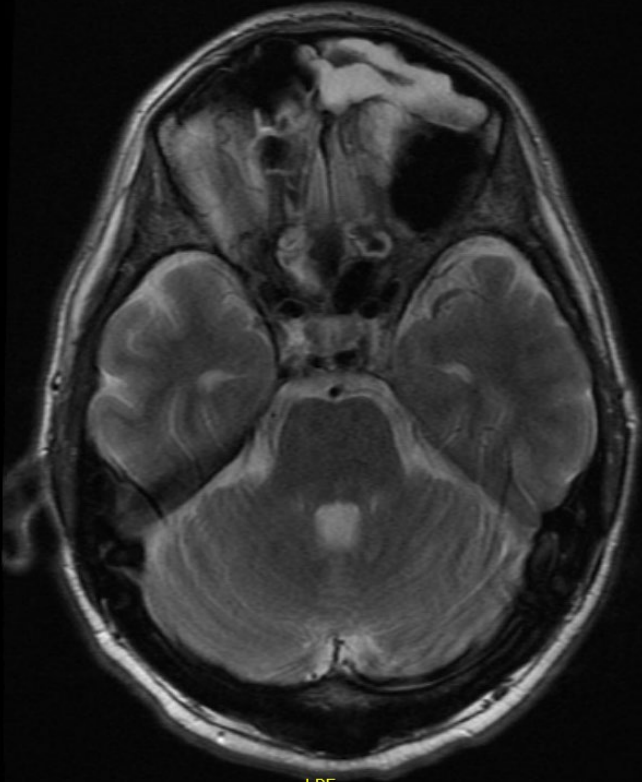


- This is not his picture but similar!
- 3 months later is getting his 5<sup>th</sup> sinus surgery

MRI BRAIN W WO CONTRAST

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17 of 24

ax T2 FSE

MRI BRAIN W WO CONTRAST

RAN

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LPF

# India

- In 2019,
  - 2.3 million people with HIV
  - 0.22% adult HIV prevalence
  - 69,000 new HIV infections
  - 58,000 AIDS-related deaths
  - 64% people on ART

