HIV: Approach to CNS Disease

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AWACC
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- Nothing to disclose

Case

60 year-old man diagnosed with HIV one month prior (CD4 60, VL 541K) in the setting of fevers, chills, weight loss and declining cognitive status. He was started on cART two weeks prior, and his mental status has deteriorated.

PE: afebrile and well-appearing, worsened psychomotor slowing, no focal weakness.

Labs: viral load 2K.

MRI: Progressive symmetric bilateral white matter signal change.

Outline

- General diagnostic strategies in CNS syndromes
- Cases with syndromic differential diagnosis and treatment
- Questions and discussion

HIV Neurology Diagnostic Principles

- Context
  - Environmental factors (epidemiology)
  - Host factors (immune status, viral status, ART, prophylaxis)
- Clinical symptoms and signs
- Serological and other non-CNS studies
- CSF studies
- Imaging
- Response to treatment

Environmental Factors: Epidemiology

- Limited data due to lack of resources
- Little confirmatory evidence
- Malaria, tuberculosis, and neurocysticercosis increased in sub-Saharan Africa
- HIV prevalence impacts CNS infectious epidemiology

Environmental Factors: Epidemiology

- Meningitis in Johannesburg, South Africa[1]
  - Tuberculous meningitis (TBM) 25.4%
  - Bacterial meningitis (BM) 22.5%
  - Viral meningitis 14.1%
  - Cryptococcal meningitis (CM) 13%
- Meningitis in Harare, Zimbabwe[2]
  - CM 45%
  - Mononuclear meningitis (aseptic) 27%
  - BM 16%
  - TBM 12%
- Cryptococcal meningitis in Durban, South Africa[3]
  - Higher morbidity and mortality than rich countries

[1]Bergemann 1996; [2]Hakim 2000; [3]Moosa 1999.

Environmental Factors: Epidemiology

- Toxoplasmosis in Sub-Saharan Africa
  - Seroprevalence 20-80% but poor/outdated data[1]
- Focal mass lesions in resource poor settings
  - Some evidence for similar patterns to high resource countries (toxo most common focal brain lesion)[2]
  - Other studies suggest higher burden of TB (and neurocysticercosis)[3]

[1]Pappas 2009; [2]Bhigjee 1999; [3]Smego 2006

Host Factors: Immune Status

- CD4 count > 500 – “normal host”*
- CD4 200-500 – “mild immunosuppression”
- CD4 < 200 – differential expands
- CD4 rebound – all of the above plus IRIS

Host Factors: Immune Status

- ***CD4 count > 500 – "normal host"****
  - Dysimmune syndromes: Guillain-Barre, polymyositis, post-infectious encephalitis
  - Chronic low-grade meningitis
  - Mild neurocognitive disorders
- CD4 200-500 – "mild immunosuppression"
- CD4 < 200 – differential expands
- CD4 rebound – all of the above plus IRIS

Host Factors: Immune Status

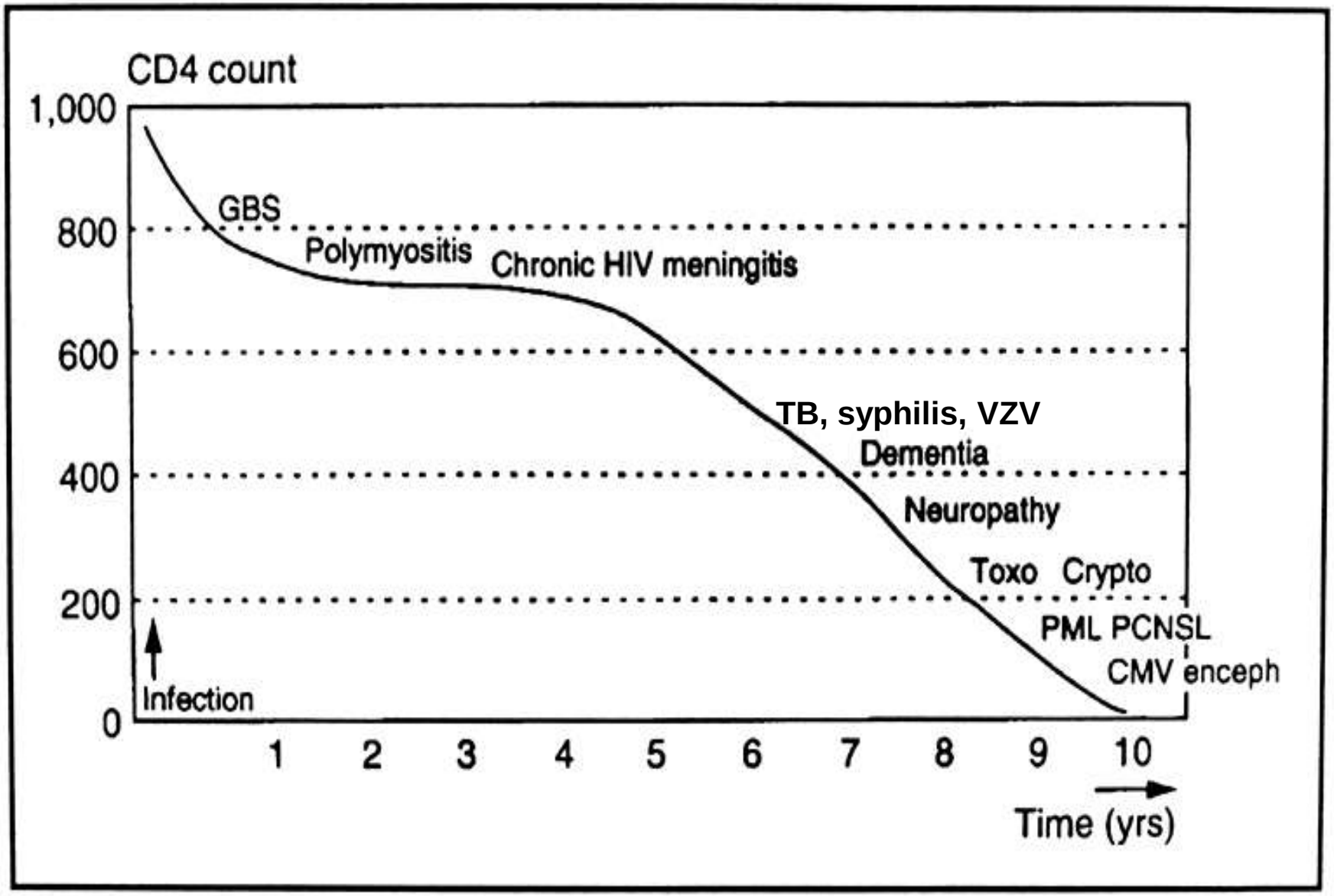
- CD4 count > 500 – “normal host”
- ***CD4 200-500 – “mild immunosuppression”***
  - TB, syphilis, VZV
  - Dementia, neuropsychiatric syndromes
  - Rarely PML
- CD4 < 200 – differential expands
- CD4 rebound – all of the above plus IRIS

Host Factors: Immune Status

- CD4 count > 500 – “normal host”*
- CD4 200-500 – “mild immunosuppression”
- ***CD4 < 200 – differential expands***
  - Moderate: Toxoplasma, cryptococcus, PML
  - Severe: PCNSL, CMV
- CD4 rebound – all of the above plus IRIS

Host Factors: Immune Status

- CD4 count > 500 – “normal host”*
- CD4 200-500 – “mild immunosuppression”
- CD4 < 200 – differential expands
- ***CD4 rebound – all of the above plus IRIS***
  - Most common: cryptococcus, TB, PML
  - Less common: toxoplasma, PCNSL, VZV, candida, MAC, HIV


CD4 count
1,000
800
600
400
200
0
GBS
Polymyositis
Chronic HIV meningitis
TB, syphilis, VZV
Dementia
Neuropathy
Toxo Crypto
PML PCNSL
CMV enceph
Infection
1 2 3 4 5 6 7 8 9 10
Time (yrs)

Host Factors: Viral Status/Prophylaxis

- High viral load, even with preserved CD4 count, carries increased risk for neurological complications
- ART effectiveness and timing changes differential, including IRIS
- Prophylaxis with TMP-SMX lowers risk of toxoplasmosis
- Prophylaxis with fluconazole lowers risk of cryptococcal meningitis (but not mortality)[1]
- Caveat that adherence to prophylaxis may be hard to confirm

[1]Parkes-Ratanshi 2009

Clinical Syndromes

Localization within nervous system

- Meninges
- Diffuse brain lesions
- Focal brain lesions
- Spinal cord
- Nerve root and peripheral nerve
- Muscle

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Clinical Syndromes

Localization within nervous system

- ***Meninges***
  - Headache, nucchal rigidity, photophobia, confusion (may overlap with encephalitis)
- Diffuse brain lesions
- Focal brain lesions

Clinical Syndromes

Localization within nervous system

- Meninges
- ***Diffuse brain lesions***
  - Encephalopathy, dementia, neuro-psychiatric, may also have meningismus
- Focal brain lesions

Clinical Syndromes

Localization within nervous system

- Meninges
- Diffuse brain lesions
- ***Focal brain lesions***
  - Hemiparesis, ataxia, dysphasia, visual field deficit, seizure, may also have meningismus

Clinical Syndromes

Localization within nervous system

- Meninges
- Diffuse brain lesions
- Focal brain lesions
- ***In practice, there is often overlap of syndromes (meningoencephalitis)***
  - Seizures, altered mental status, CSF abnormalities may be seen in each syndrome

Specific Etiologies of CNS Syndromes

- Meninges: ***acute meningitis***
  - Pyogenic
  - HSV-2
  - VZV
  - Neurosyphilis
  - HIV seroconversion
  - HIV rebound
  - HIV IRIS

Specific Etiologies of CNS Syndromes

- Meninges: ***subacute meningitis***
  - Cryptococcal meningitis
  - Tuberculous meningitis
  - Other fungal (histoplasma, coccidioides)
  - Neurosyphilis
  - Neoplastic (lymphomatous)
  - HIV (usu asymptomatic)

Specific Etiologies of CNS Syndromes

- Diffuse brain lesions: ***acute encephalitis***
  - HIV encephalitis
  - CMV encephalitis
  - VZV encephalitis
  - Post-infectious encephalitis/acute demyelinating encephalomyelitis (ADEM)
  - Neurosyphilis
- Diffuse brain lesions: ***encephalopathy*** (global brain dysfunction without prominent inflammation)
  - Toxic (efavirenz, illicit drugs, EtOH)
  - Cerebral malaria (HIV or non-HIV)

Specific Etiologies of CNS Syndromes

- Diffuse brain lesions: ***subacute-chronic encephalitis***
  - HIV-associated dementia
  - HIV rebound meningoencephalitis
  - Neuro-IRIS
  - Neurosyphilis

Specific Etiologies of CNS Syndromes

- Focal brain lesions ***with mass effect***
  - Toxoplasmic encephalitis
  - Primary CNS lymphoma
  - Tuberculoma or tuberculous abscess
  - Fungal abscess (crypto, aspergillus)
  - Bacterial abscess due to atypical organisms (e.g. Nocardia)

Specific Etiologies of CNS Syndromes

- Focal brain lesions ***without mass effect***
  - PML (except in IRIS, when inflammation can cause mild mass effect and enhancement on imaging)
  - HIV-associated stroke (usually no mass effect except at ~4 days w/peak cytotoxic edema)
  - Neurosyphilis (including optic neuritis)

Other CNS Syndromes – Cranial Neuropathies

- Common with any basal meningitis or brainstem process
  - May result from increased intracranial pressure (esp CN 6)
  - May result from extension of inflammation from CSF
  - Should prompt consideration of TBM, CM, syphilis

Other CNS Syndromes - Stroke

- Multiple possible mechanisms
  - Peri-arterial exudate with secondary vasculitis of cerebral arteries
  - Direct arterial infection
  - Immune-mediated parainfectious vasospasm or thrombosis
  - Infectious venous thrombosis
  - Hypercoagulable state + endothelial dysfunction from systemic infection
  - Endocarditis with emboli and aneurysms

Other CNS Syndromes - Stroke

- Possible causes
  - Opportunistic CNS infections
    - VZV vasculopathy
    - TB meningitis
    - Syphilitic meningovasculitis
    - Cryptococcal meningitis
    - Toxoplasmosis
  - HIV vasculopathy
  - Malignancy (hypercoagulable)
  - Endocarditis
  - HIV cardiomyopathy
  - Chronic systemic inflammation and coagulopathy
  - Accelerated atherosclerosis

Other CNS Syndromes - Stroke

- Compared to stroke in non-HIV patients
  - Epidemiology
    - Patients are younger
    - Lack typical vascular risk factors
  - Causes
    - Especially in developing countries, opportunistic CNS infection, malignancy, endocarditis, and HIV cardiomyopathy are more important
  - Evaluation
    - Typical stroke evaluation*
    - HIV immunological and virological status
    - Directed search for OI's, including possible LP

*See supplementary slides

Other CNS Syndromes - Seizure

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  - Epidemiology
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*See supplementary slides

Other CNS Syndromes - Seizure

- Causes of seizures in developed countries
  - **Idiopathic**
    - More than half of patients
  - Head trauma
  - Brain tumors
  - Stroke
  - Intracranial infection
  - Cerebral degeneration
  - Congenital brain malformations
  - Inborn errors of metabolism

Other CNS Syndromes - Seizure

- Causes of seizure in lower-middle income countries
  - Idiopathic
  - **Head trauma**
  - Brain tumors
  - Stroke
  - **Intracranial infection**
    - Neurocysticercosis, malaria, and other parasites; bacterial meningitis, TB; viral encephalitis, HIV
  - Cerebral degeneration
  - **Congenital brain malformations**
  - Inborn errors of metabolism

Other CNS Syndromes - Seizure

- Causes of seizure in HIV
  - HIV-related focal brain lesion
    - Toxoplasma, lymphoma, PML, TB, stroke
  - HIV-related diffuse brain lesion
    - HIV encephalitis, CMV
  - HIV-related meningeal lesion
    - Cryptococcal, TB
  - Unrelated focal, diffuse, or meningeal lesion
  - Unrelated epilepsy with HIV-related systemic disease

Other CNS Syndromes - Seizure

- Hepatic Drug Metabolism of ART[1]
  - PIs and NNRTIs
    - Metabolized in the liver by the CYP-450 system, particularly by the CYP3A4 isoenzyme
  - NRTIs
    - Do not undergo hepatic transformation through the CYP metabolic pathway
    - May have other routes of hepatic metabolism; significant pharmacodynamic interactions of NRTIs and other drugs have been reported

[1]http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf

Other CNS Syndromes - Seizure

- Interactions of ART and AED
  - Enzyme inducing anti-epileptic drugs (EI-AED)
    - Increase CYP-450 metabolism of other medications
    - Phenytoin, phenobarbital, carbamazepine
  - Coadministration may result in higher rates of virologic failure
  - Need to adjust (increase) PI and NNRTI dose for equivalent levels to pts not on EI-AED
  - Valproic acid is a mild enzyme inhibitor
    - Some evidence it may increase level of ZDV
    - Generally preferred agent in resource-limited settings

Diagnostic Studies: non-CNS

- CrAg 98% sens, 99% spec; may precede clinical symptoms by 22 days
- Toxo IgG sensitive (unless profound immunosuppression) but not specific (high baseline seroprevalence)
- Malarial smear
- Chest x-ray

Diagnostic Studies: CSF Profiles

Parameter	Bacterial	TB	Crypto	Aseptic
Opening Pressure (mmH_2O)	>180	Normal to elevated	>200 in 70% (may be much higher)	Normal to slightly elevated
Glucose (mg/dL)	<40	<45	Normal to slightly low	>45
Protein (mg/dL)	100-500	100-500 (2-6g w/CSF block)	Normal to slightly elevated	Normal to slightly elevated
WBC (cells/mm^3)	10-10,000	100-500	<50	10-2,000
Differential	PMN	Lymphocytic (PMN early)	Mononuclear	Lymphocytic
Microscopy	GS+ in 70-90%	AFB smear low sensitivity	India ink+ 70-90%	Neg
Culture		Up to 70%	Gold standard	Viral cultures
Other	Latex agglutination+	PCR+ ~60%, serum IGRA+	CrAg 93-100% sens, 93-98%	PCR's exist (esp HSV, VZV)

Diagnostic Studies: CSF Clues

- Very low glucose: carcinomatosis, lymphomatosis, gliomatosis, TB, fungal, sarcoidosis, hypoglycemia, chemical, SAH, LCMV
- High protein: TB with CSF block
- All lymphocytes: aseptic after 24 hours, TB, LCMV
- Elevated PMNs: bacterial, early TB, HSV
- Hemorrhagic: HSV, other rare viruses (Hantavirus, Ebola, Dengue), and ameba

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Diagnostic Studies: CSF Clues

Clue	Etiology
Very low glucose:	carcinomatosis, lymphomatosis, gliomatosis, TB, fungal, sarcoidosis, hypoglycemia, chemical, SAH, LCMV
Very high protein:	TB with CSF block
All lymphocytes:	Aseptic meningitis > 24h, TB, LCMV
PMN predominance:	bacterial, early TB, HSV
Hemorrhagic:	HSV, other rare viruses (Hantavirus, Ebola, Dengue), and ameba

Diagnostic Studies: CSF PCR

	JCV/PML	HSV	VZV	CMV
Sensitivity	Var (74-92%)	H	H	H
Specificity	Var (70-80%)	H (94-100%)	H	H

	Toxo	TB	EBV/PCNSL
Sensitivity	L (44-81%)	L (60%)	H (80-98%)
Specificity	H (100%)	H	H (88-100%)

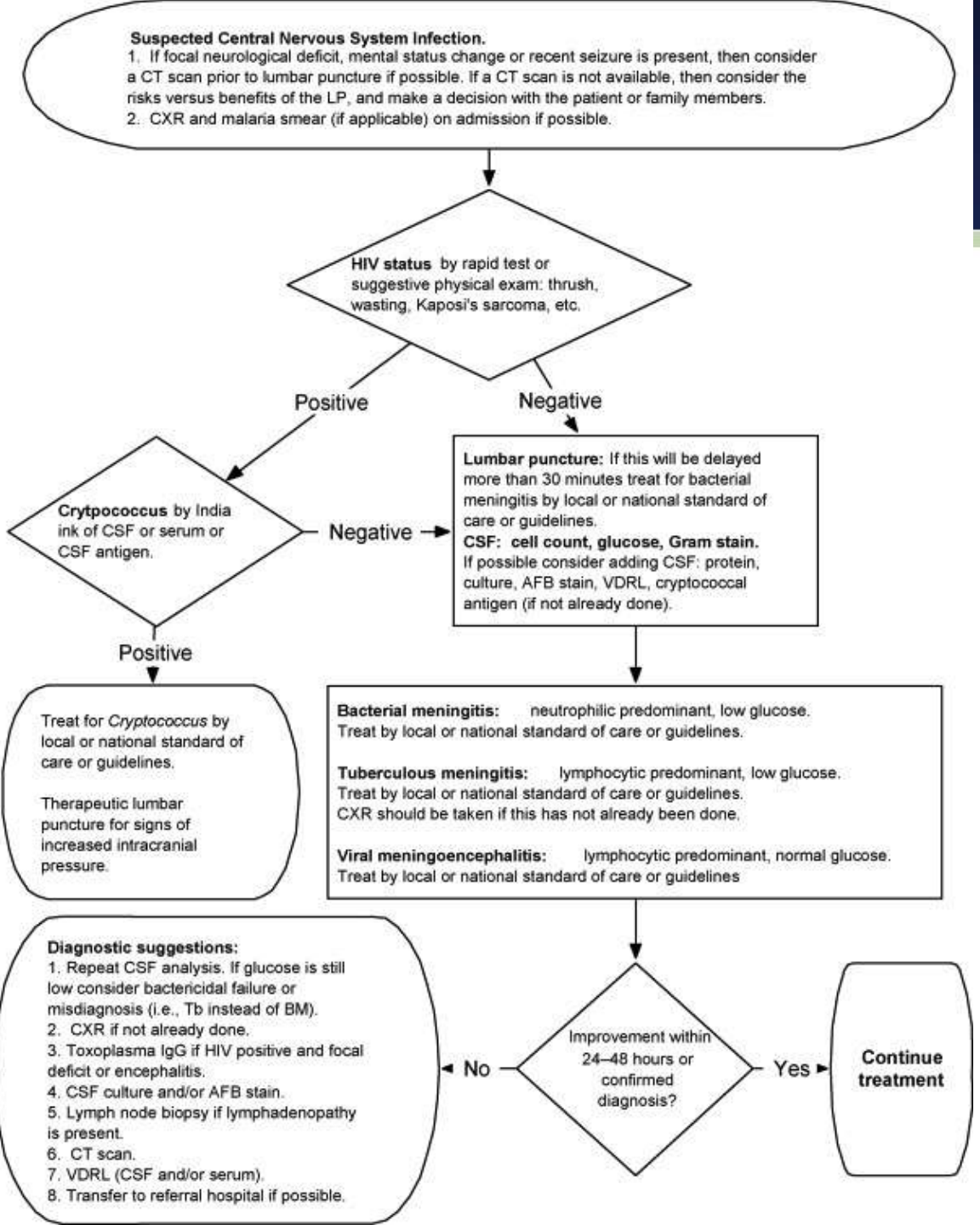
Resource-Limited CNS Infection

- Mortality much higher than in resource-rich countries
- Definitive diagnosis elusive
- Presentation delayed
- LP often delayed
  - Limited equipment or laboratory access
  - Patient response to empiric therapy or death prior to LP
  - Patient refusal
  - Concern for herniation
- Treatment delayed
  - Limitations on empiric use of antimicrobials
  - Overlap of syndromes
  - Delay in presentation
  - Delay in diagnosis

Resource-Limited CNS Infection

- Proposed algorithm for presumed CNS infection[1]
  - Immediate CXR and malarial smear
  - HIV +/-
  - CRAG +/-
  - If CRAG+, treat for CM
  - If CRAG-, then LP
  - Empiric Rx based on CSF profile
  - Concurrent adjunct studies: toxo IgG (focal signs), VDRL, lymph node biopsy (lymphadenopathy), CSF AFB & mycobacterial culture, head CT, transfer to tertiary care
  - Reassess based on response

[1]Trachtenberg 2007


Suspected Central Nervous System Infection.
1. If focal neurological deficit, mental status change or recent seizure is present, then consider a CT scan prior to lumbar puncture if possible. If a CT scan is not available, then consider the risks versus benefits of the LP, and make a decision with the patient or family members.
2. CXR and malaria smear (if applicable) on admission if possible.
HIV status by rapid test or suggestive physical exam: thrush, wasting, Kaposi's sarcoma, etc.
Positive
Negative
Crytpococcus by India ink of CSF or serum or CSF antigen.
Negative
Lumbar puncture: If this will be delayed more than 30 minutes treat for bacterial meningitis by local or national standard of care or guidelines.
CSF: cell count, glucose, Gram stain.
If possible consider adding CSF: protein, culture, AFB stain, VDRL, cryptococcal antigen (if not already done).
Positive
Treat for Cryptococcus by local or national standard of care or guidelines.
Therapeutic lumbar puncture for signs of increased intracranial pressure.
Bacterial meningitis: neutrophilic predominant, low glucose.
Treat by local or national standard of care or guidelines.
Tuberculous meningitis: lymphocytic predominant, low glucose.
Treat by local or national standard of care or guidelines.
CXR should be taken if this has not already been done.
Viral meningoencephalitis: lymphocytic predominant, normal glucose.
Treat by local or national standard of care or guidelines
Diagnostic suggestions:
1. Repeat CSF analysis. If glucose is still low consider bactericidal failure or misdiagnosis (i.e., Tb instead of BM).
2. CXR if not already done.
3. Toxoplasma IgG if HIV positive and focal deficit or encephalitis.
4. CSF culture and/or AFB stain.
5. Lymph node biopsy if lymphadenopathy is present.
6. CT scan.
7. VDRL (CSF and/or serum).
8. Transfer to referral hospital if possible.
No
Improvement within 24–48 hours or confirmed diagnosis?
Yes
Continue treatment

Case

27 year-old man with advanced HIV (CD4 17, VL 63K) not on ART presents with vomiting, headache, neck pain, and mental status change worsening over weeks. He is reportedly taking TMP-SMX and azithromycin.

PE: T 39, poorly responsive, CN intact, moving all 4 limbs equally (GCS 11).

Labs: Toxo IgG+; CMV Ag -, CMV Ab +

CXR clear; head CT no mass lesions, edema, or abnormal enhancement

Case

27 year-old man with advanced HIV (***CD4 17***, VL 63K) not on ART presents with vomiting, headache, neck pain, and mental status change worsening ***over weeks***. He is reportedly taking ***TMP-SMX*** and azithromycin.

PE: T 39, poorly responsive, ***CN intact, moving all 4 limbs equally*** (GCS 11).

Labs: Toxo IgG+; CMV Ag -, CMV Ab +

CXR clear; ***head CT no mass lesions***, edema, or abnormal enhancement

Meningitis

- In pts with CD4<200: CM, TBM, BM, and syphilis
- Cryptococcal
  - Typically symptoms progress over 1-2 weeks
  - Fever, malaise, and headache are most common sx
  - Initial worsening may occur with ART (IRIS)
- TB meningitis
  - Like CM, TBM is more subacute than BM
  - Often associated with cranial nerve palsies
  - Prior or concurrent pulmonary TB in >50%
  - CSF glucose low, protein may be extremely high
  - Initial worsening may occur with TB treatment and/or with ART (IRIS)

Meningitis

Differential Considerations:

- BM more often acute, higher WBC count, PMN predominance
- Associated stroke should suggest meningovascular syphilis, TBM, or VZV
- HIV “aseptic” meningitis occurs at seroconversion
- HIV viral breakthrough (rebound) occurs with ART failure or non-adherence
- Non-HIV aseptic meningitis is common at all levels of immune function

Meningitis

Differential considerations:

- HIV pts are susceptible to the same causes of meningitis as the normal population, especially where bacterial meningitis is endemic.
- In advanced HIV, symptoms typical for meningitis may be mild due to lack of appropriate inflammatory response; CSF may be bland or minimally inflamed.

Meningitis

Diagnosis:

- Blood cultures; serum CrAg, RPR/TPPA
- CXR to look for pulmonary Tb
- LP for opening pressure (typically high in CM); glucose, protein, WBC with differential; bacterial and fungal cultures, India ink, CrAg, AFB and mycobacterial culture

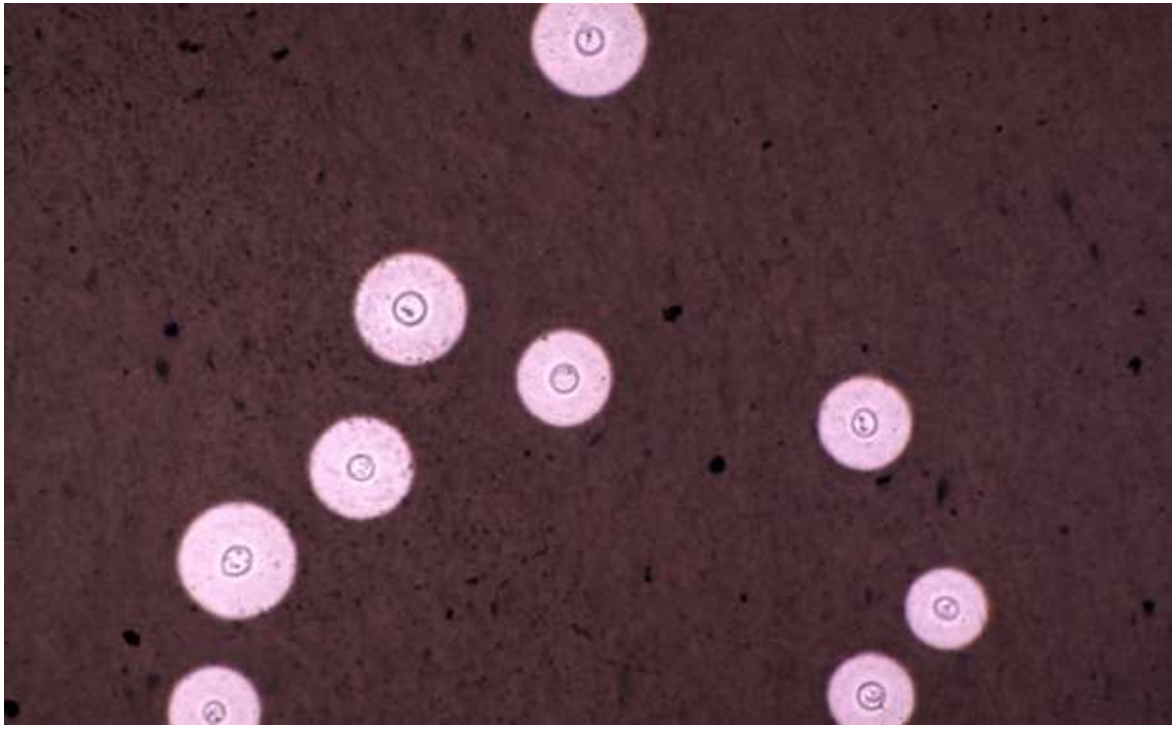
Meningitis

Diagnosis:

- CT is helpful as many pts with advanced HIV have multiple infections
- Presence of mass lesions would change differential
- Mass lesions causing downward pressure increase risk for herniation with LP
- In practice, CT is limited in resource-limited settings

Case

LP: opening pressure > 500 mmH2O; glucose normal and protein mildly elevated, WBC 91 (50%N, 17%L, 28%M); India ink stain showed encapsulated yeast; cryptococcal Ag+ at 1:500K



Case

38 year-old man with HIV (CD4 31, VL 112K) presents with 1 day of nausea and vomiting followed by a generalized convulsive seizure. He has been non-compliant with TMP-SMX prophylaxis.

PE: afebrile, white plaques on tongue, mild right hemiparesis.

Case

38 year-old man with HIV (***CD4 31***, VL 112K) presents with ***1 day*** of nausea and vomiting followed by a generalized convulsive ***seizure***. He has been ***non-compliant with TMP-SMX*** prophylaxis.

PE: afebrile, white plaques on tongue, ***mild right hemiparesis***.

Focal Brain Lesion

Differential:

- *Toxoplasma gondii*
- Primary central nervous system lymphoma (PCNSL)
- Progressive multifocal leuko-encephalopathy (PML)
- Tuberculosis
- Cysticercosis
- Bacterial abscess
- Stroke

Focal Brain Lesion

Differential:

- Symptoms in toxo generally develop rapidly over days, as opposed to PCNSL (over a few weeks) and PML (over weeks to months)
- Focal tuberculous lesions can present similarly over days to weeks
- NCC often presents first with headache and seizure
- Stroke in setting of infection may be preceded by headache and fever (meningitis)

Focal Brain Lesion

Diagnosis:

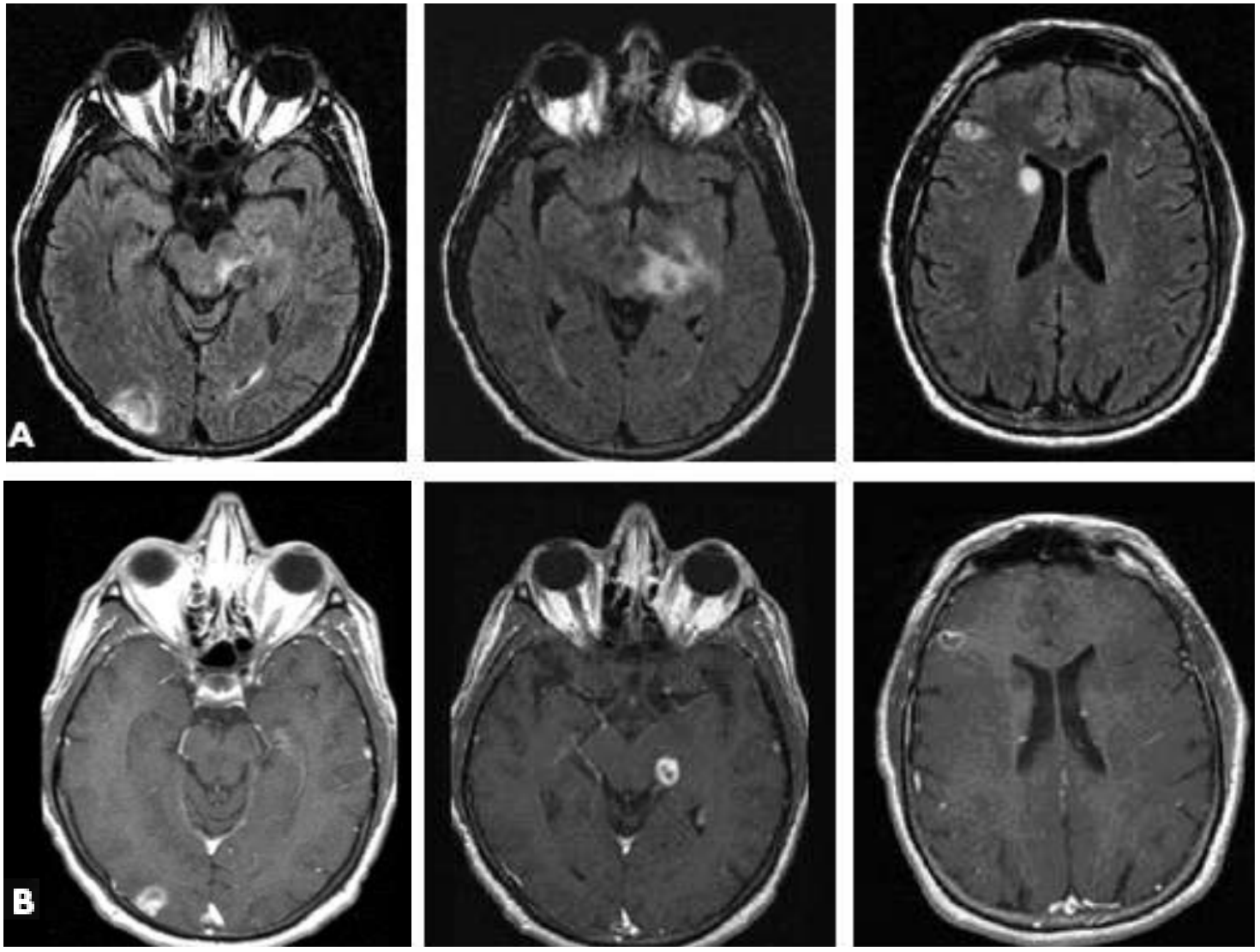
- Most patients with toxo are serum IgG positive (7-16% false negative), so a negative serology would make toxo much less likely
- Adherence to TMP-SMX makes toxo less likely
- CT helpful to assess safety for LP, characterize lesions
- Gold standard for diagnosis is brain biopsy, but rarely performed initially
- Therapeutic trial indicated if toxo IgG+
  - Approximately 70-80% of pts have clinical and radiographic response
  - Vast majority have at least 50% improvement from baseline at 14 days of treatment

Case

Diagnostic studies:

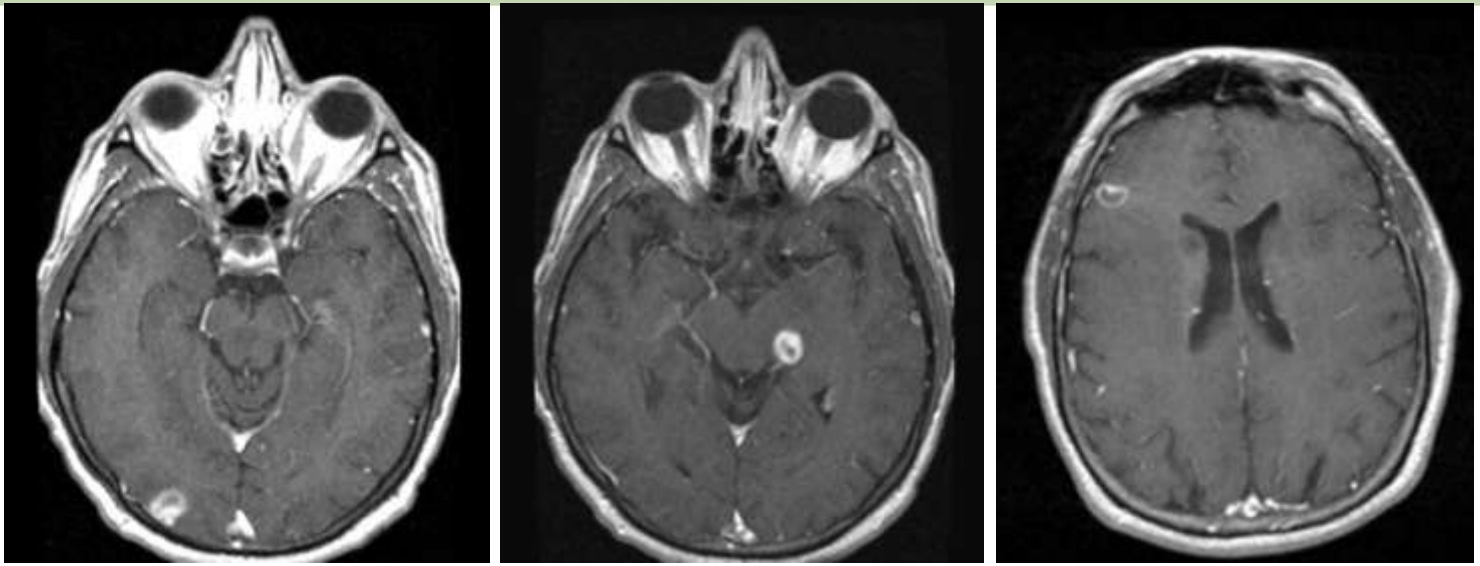
- Serum toxo IgG+, IgM-
- Chest X-ray clear
- MRI with multifocal rim-enhancing mass lesions
- CSF normal; EBV and JCV PCR negative
- Empiric toxo treatment led to rapid clinical and radiographic improvement

Case

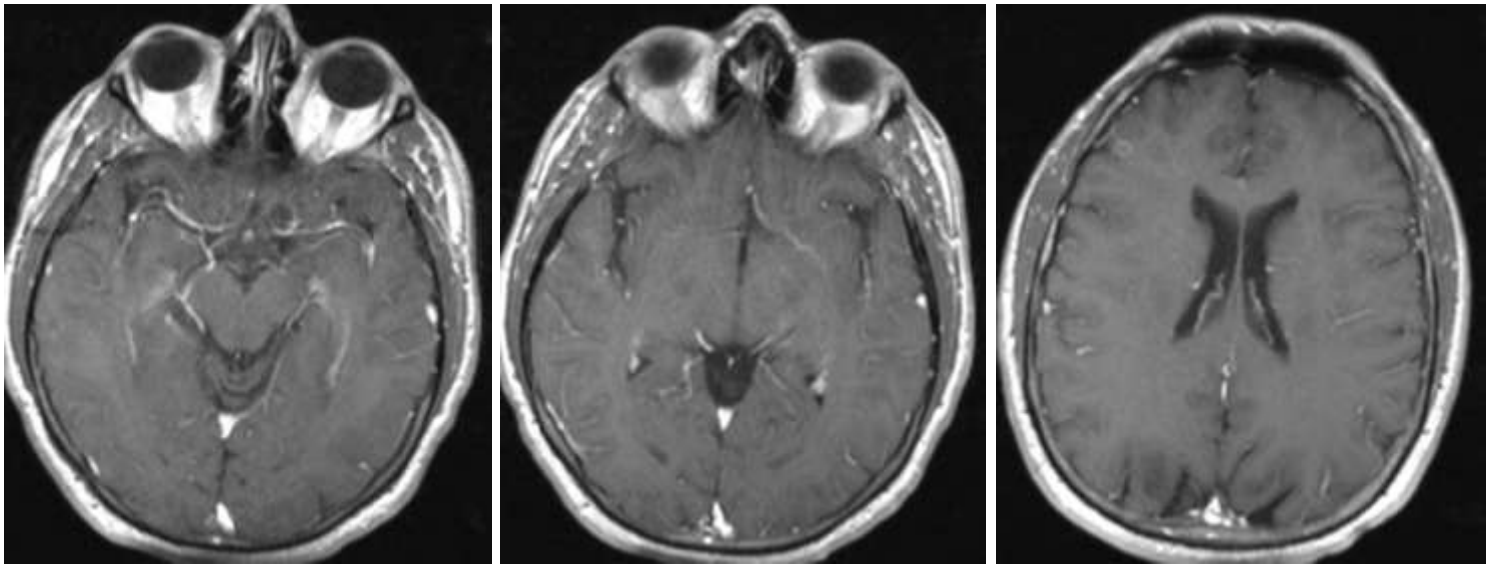


Case

Pre-Rx



Post-Rx



Case

52M with a history of HIV presents with 5 weeks of right arm clumsiness, unsteady gait. Not on TMP-SMX.

PE: afebrile and well-appearing, right upper extremity dysmetria.

Labs: CD4 130, viral load 803K, toxo IgG (-)

CXR: clear

MRI: mutlifocal right pons and cerebellum signal abnormality without enhancement or mass effect

CSF: OP, glucose, protein normal; 10 WBC (lymphocyte predominance); CrAG (-); AFB, fungal & mycobacterial cultures (-)

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Labs: ***CD4 130***, viral load 803K, ***toxo IgG(-)***

CXR: clear

MRI: mutlifocal right pons and cerebellum signal abnormality ***without enhancement or mass effect***

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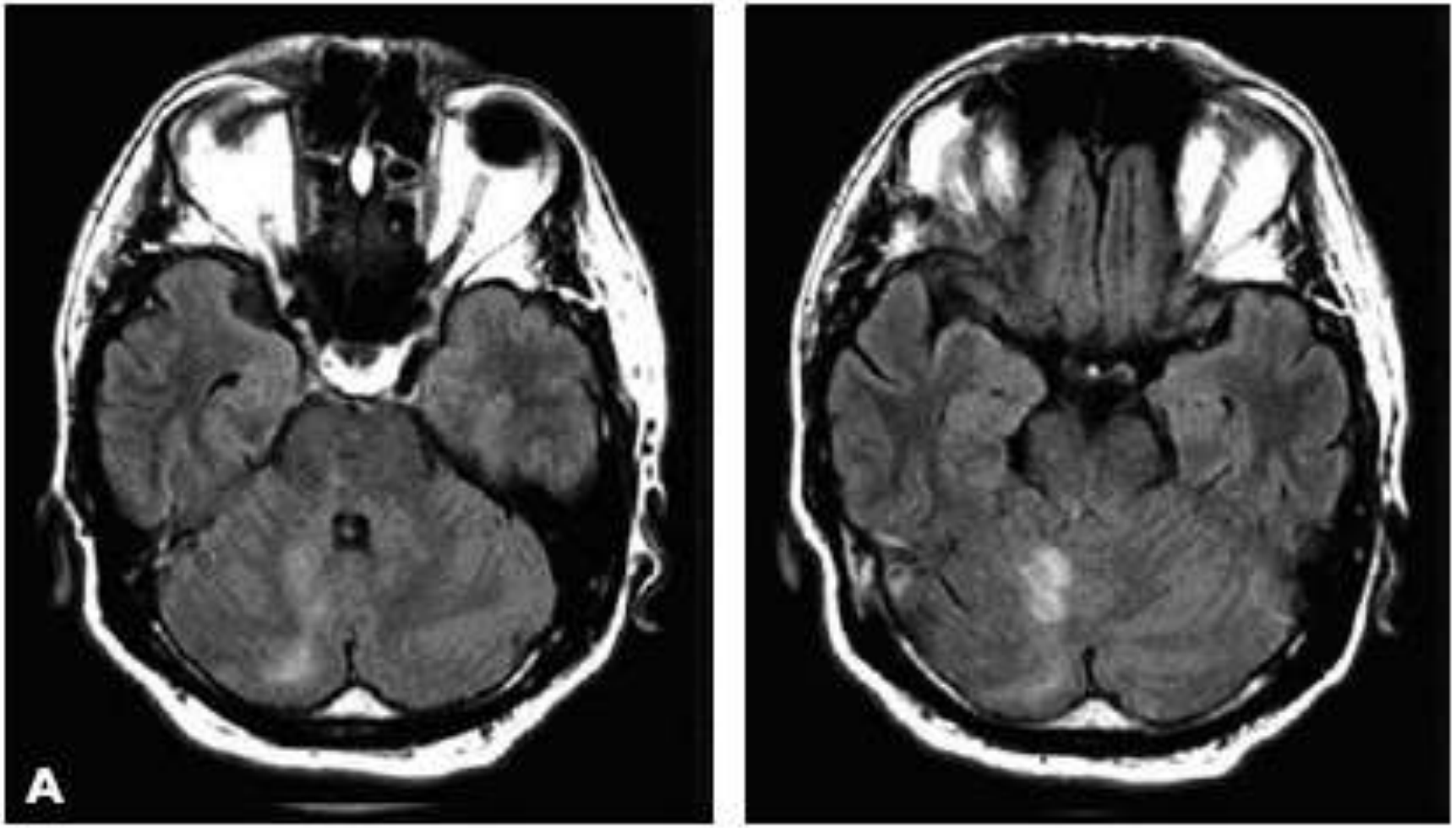
Case



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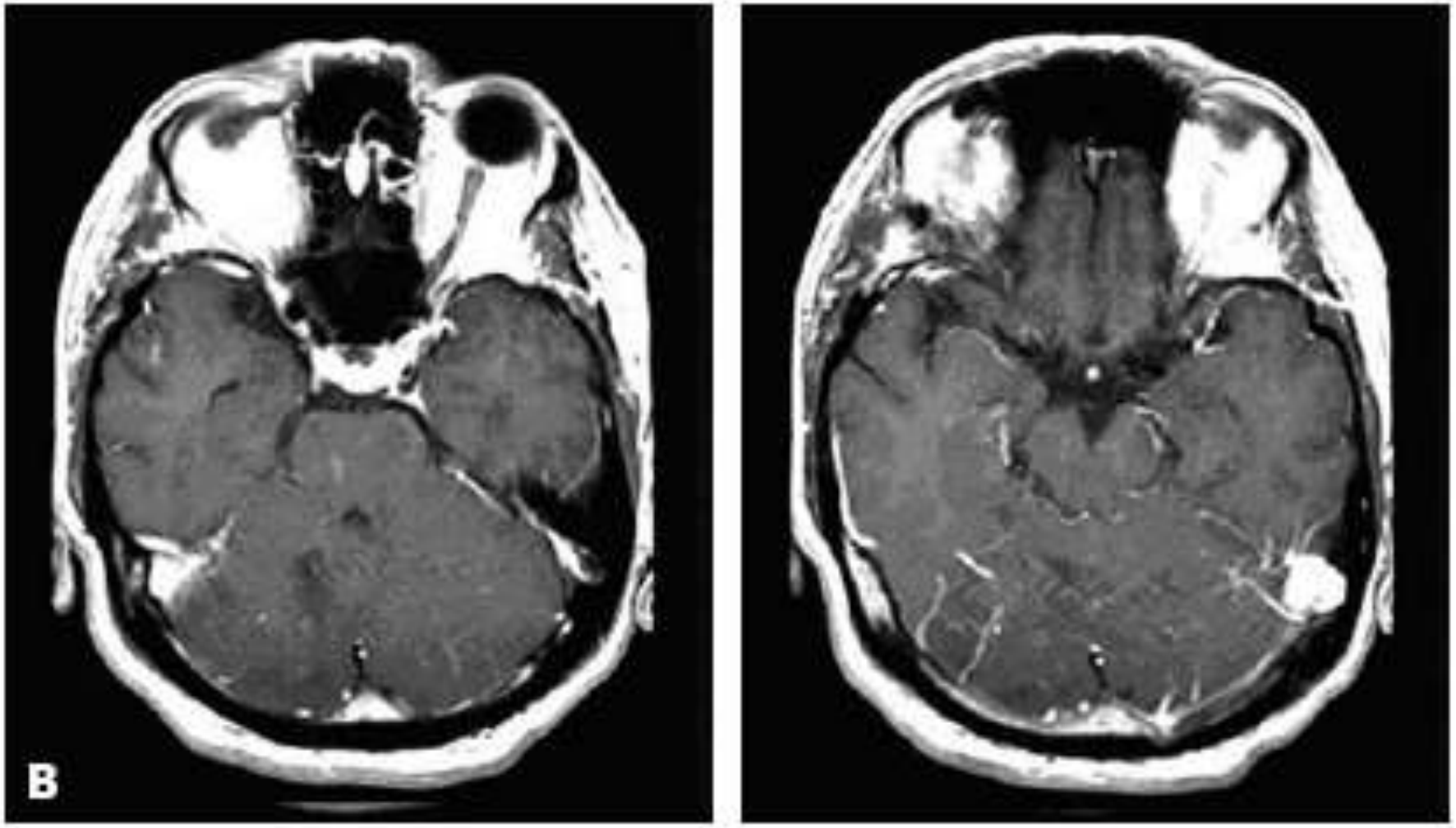


Focal Brain Lesion

Differential:

- Subacute (weeks to months) onset of focal neurological symptoms
- Without contrast-enhanced imaging, differential remains the same as other focal brain lesions
- Toxo IgG (-), moderate CD4 count make toxo and PCNSL less likely
- Stroke less likely given subacute progression
- PML, PCNSL, tuberculous abscess or tuberculoma, bacterial abscess all possible

Focal Brain Lesion

Diagnosis:

- For PML, CSF JCV PCR 72-92% sensitive and 92-100% specific in the pre-ART era (less sensitive w/cART)
- Diagnosis of PML in resource-rich countries usually based on clinical and radiographic patterns combined with CSF PCR studies and (lack of) response to other treatments
- ART is only effective therapy for PML
- Survival in PML with ART has improved from 10 to 50% in resource-rich countries

Case

The patient is started on cART and TMP-SMX. Over 2-4 weeks he develops worsening symptoms.

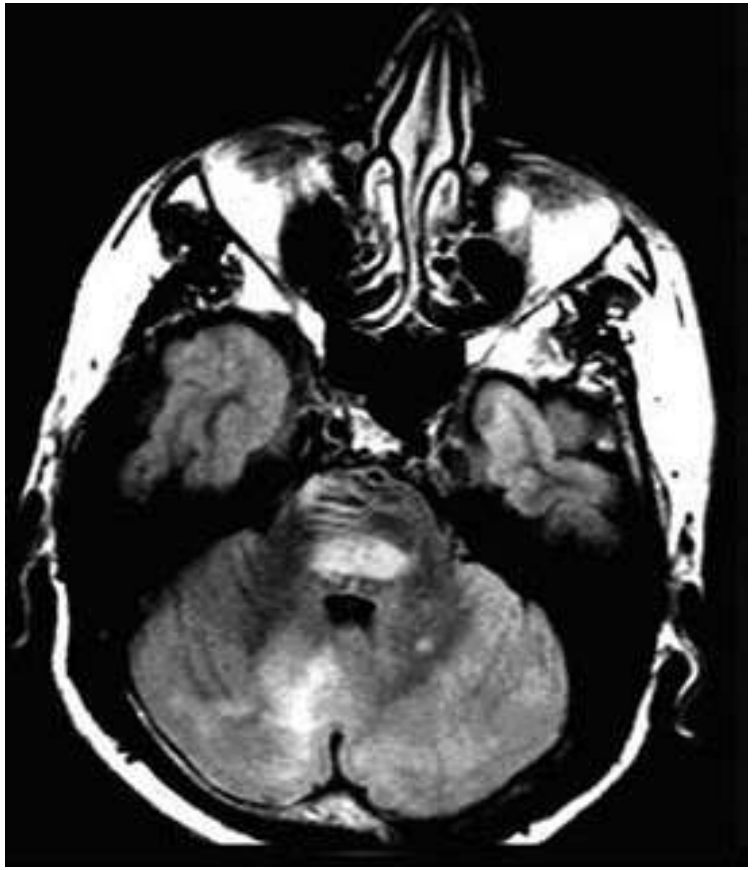
PE: new brainstem signs.

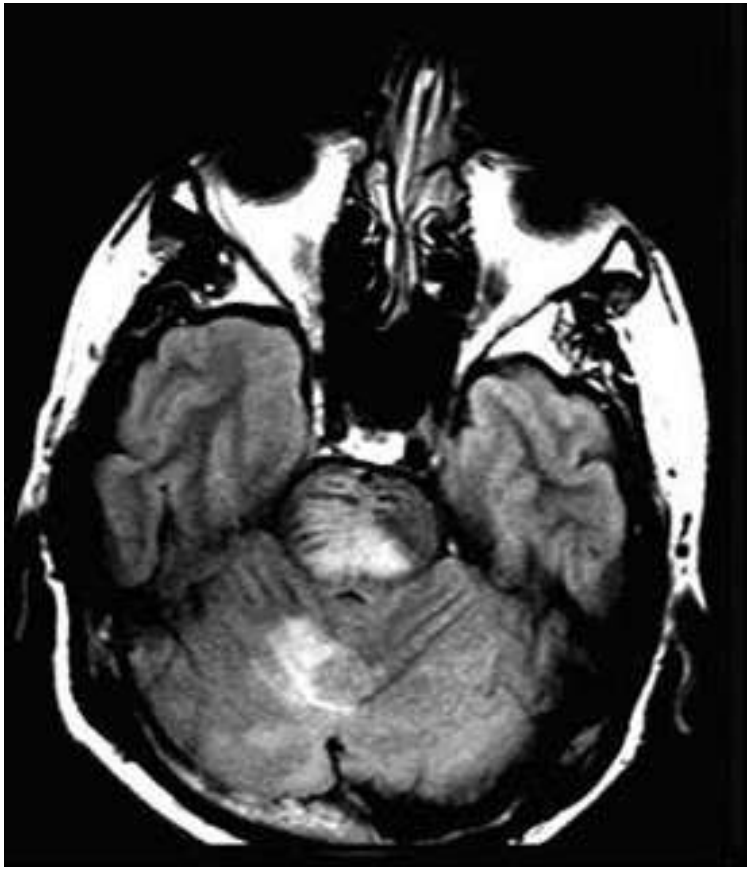
Labs: stable CD4 count, decrease in VL from 803K to 4K.

Repeat MRI w/worsening, enhancement.

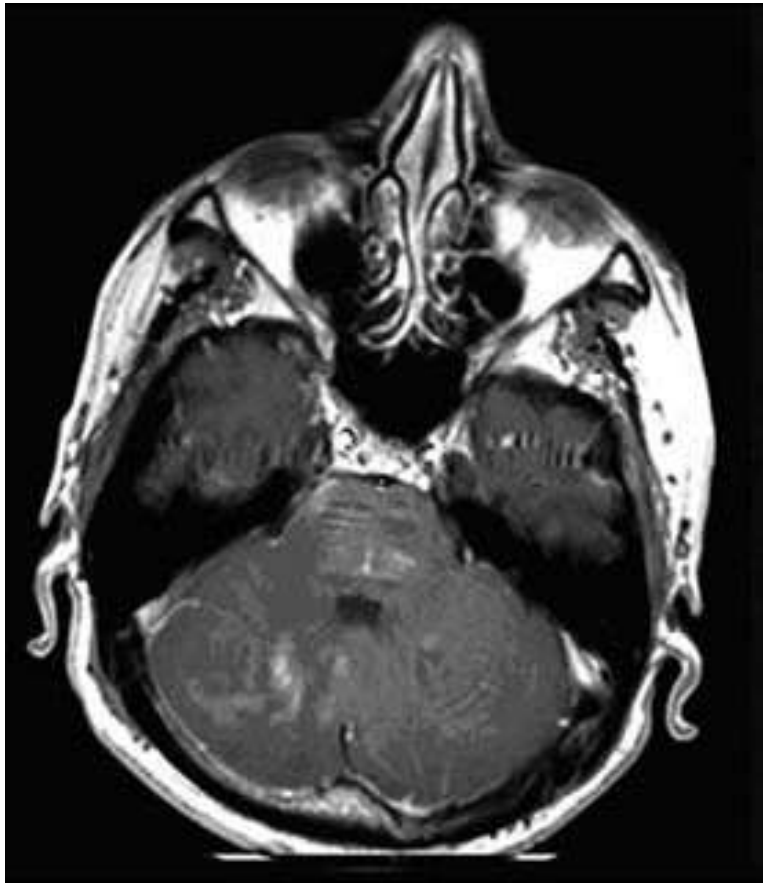
Treated with prednisone 60mg tapered over 2 weeks, with stabilization but little recovery.

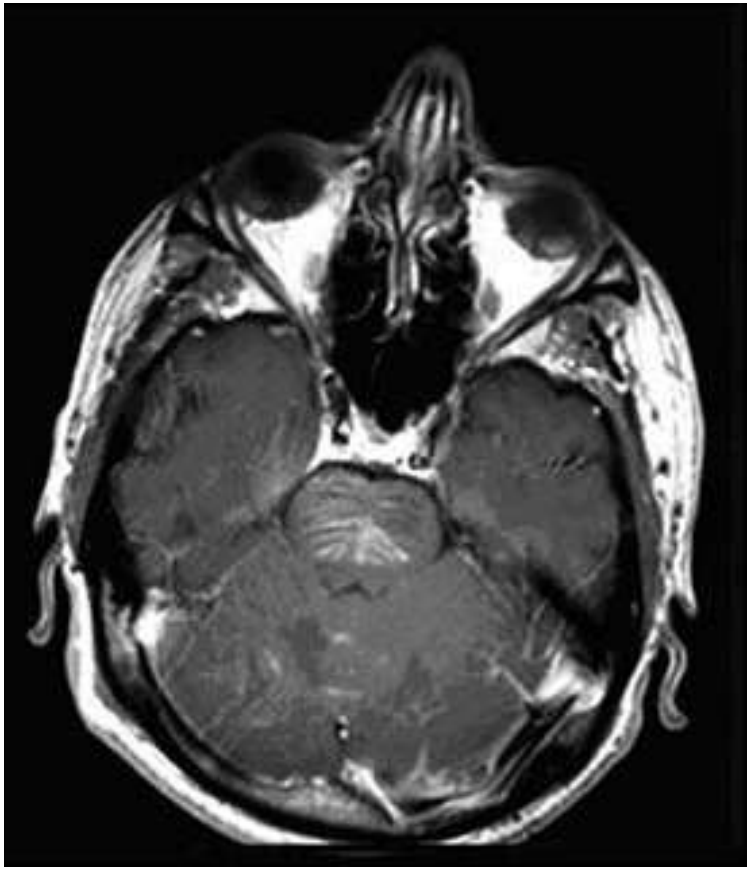
Case





Case





Focal Brain Lesion

Treatment:

- PML-IRIS may have enhancement, edema
- Steroids controversial but may be considered for severe cases

Case

23 year-old woman with HIV (vertical transmission, diagnosed age 10, recently noncompliant with ART, CD4 75, VL>100K, prior zoster) presents with acute onset right then left facial tingling, lightheadedness, followed by left-sided weakness and horizontal diplopia

PE: left hemiparesis involving face but 0/5 in upper extremity

MRI, CTA…

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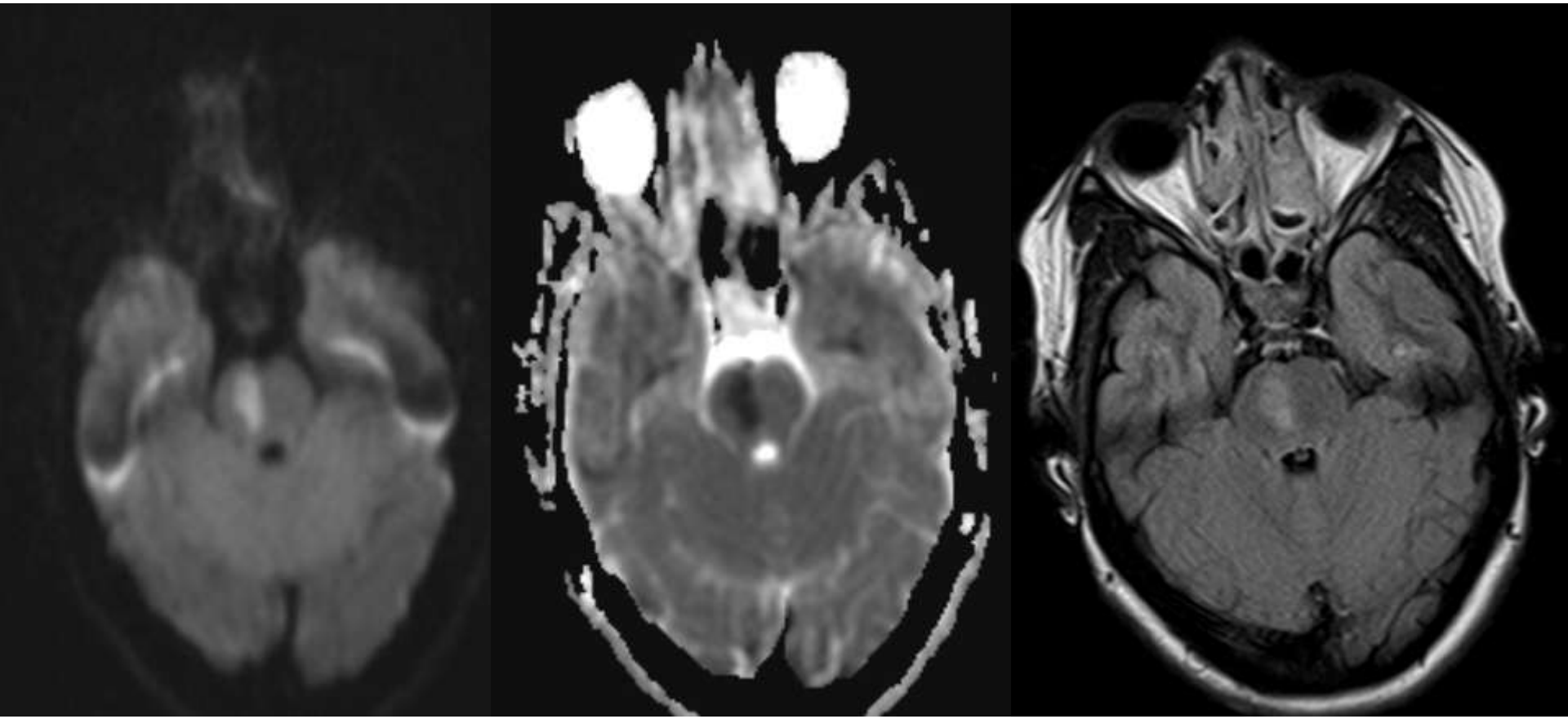
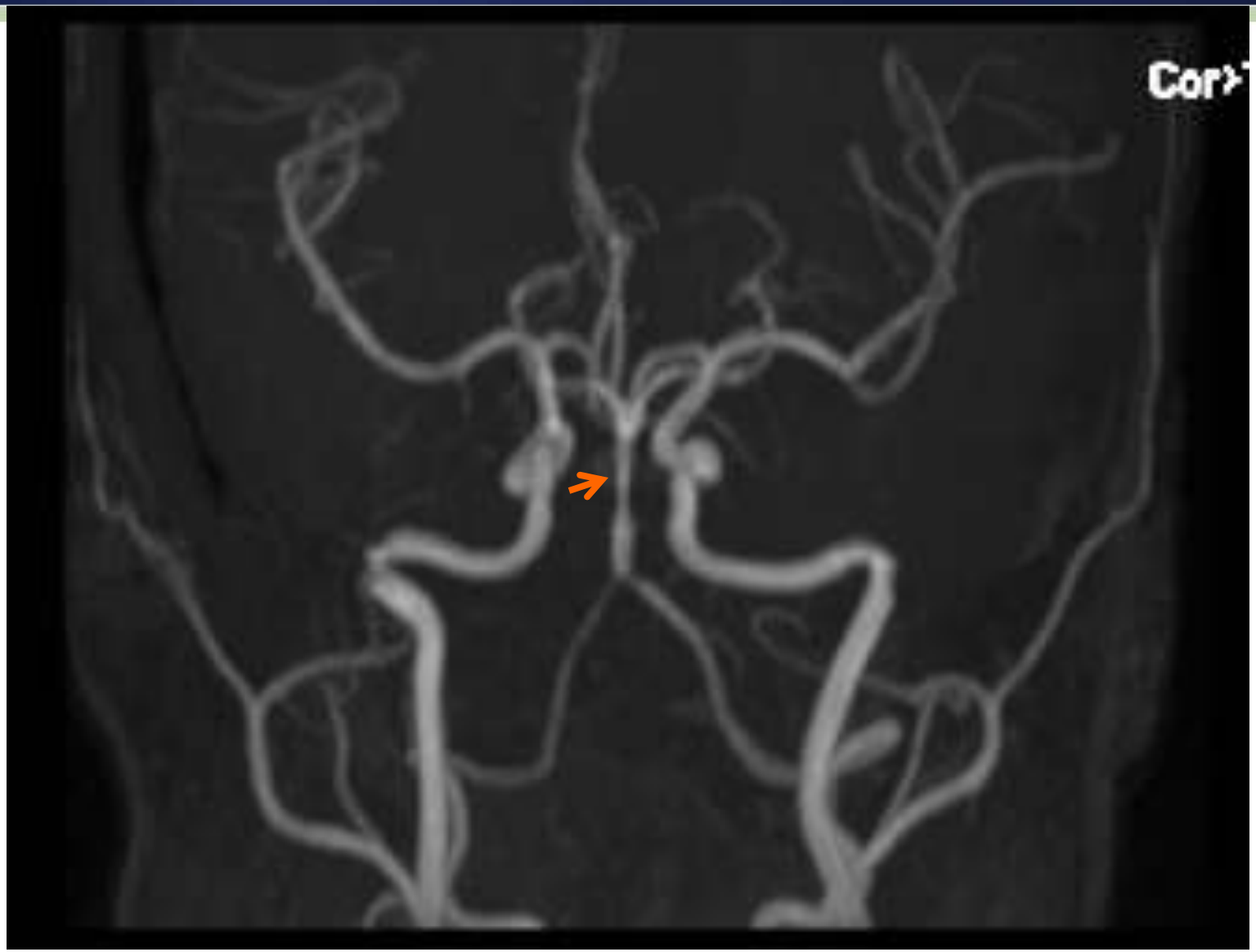
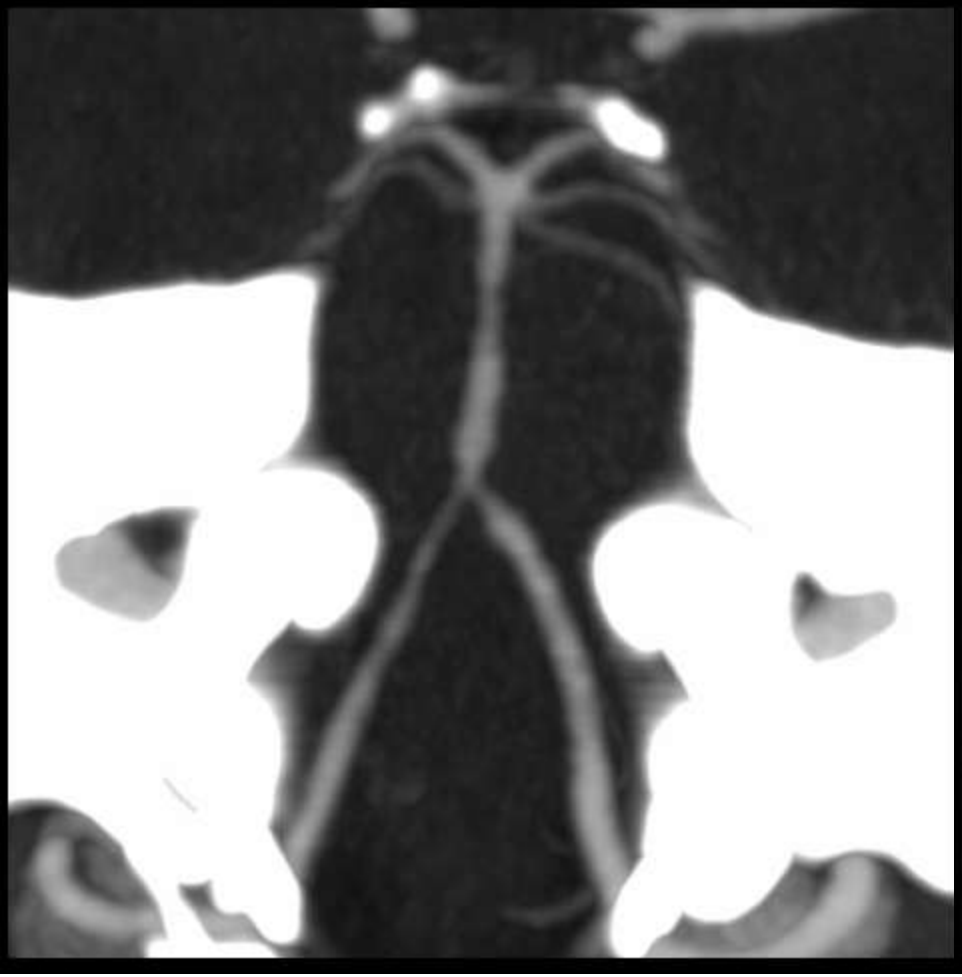
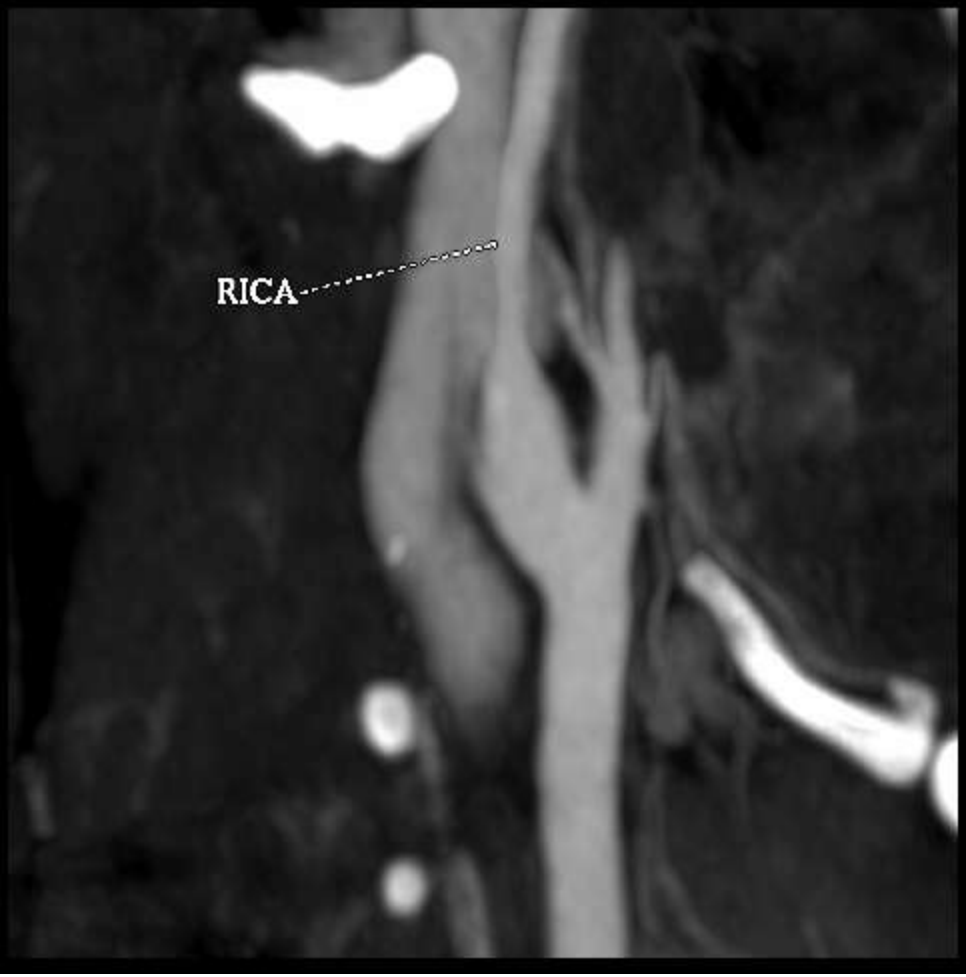


Case



Case





Case

- Evaluation
  - Hypercoagulation studies (-)
  - Transthoracic echocardiogram normal
  - Serum treponemal antibody (-)
  - PPD (-)
  - CSF bland, VZV IgG and DNA (-)
  - Serum HIV viral load 259,000 copies/μL
  - CSF HIV viral load 21,600 copies/μL
  - Started ASA, cART, acyclovir until VZV (-)
- Diagnosis: VZV vs. HIV vasculopathy

Case

60 year-old man diagnosed with HIV one month prior (CD4 60, VL 541K) in the setting of fevers, chills, weight loss and declining cognitive status. He was started on cART two weeks prior, and his mental status has deteriorated.

PE: afebrile and well-appearing, worsened psychomotor slowing, no focal weakness.

Labs: viral load 2K.

MRI: Progressive symmetric bilateral white matter signal change.

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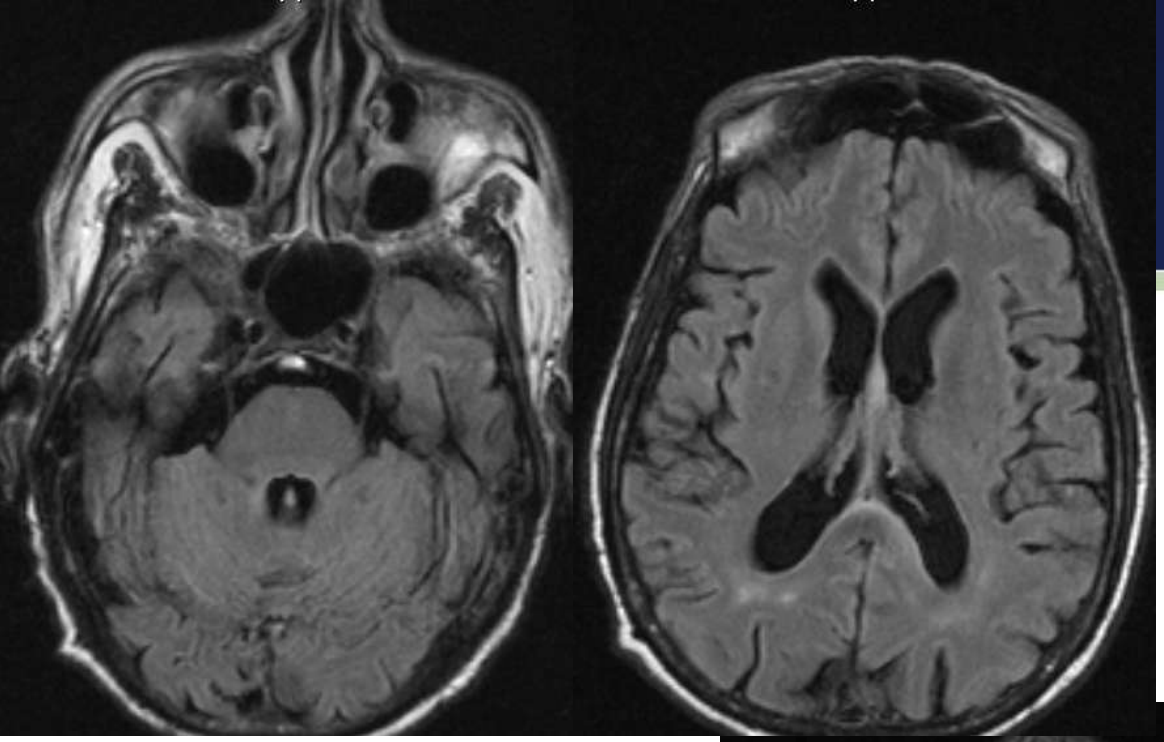
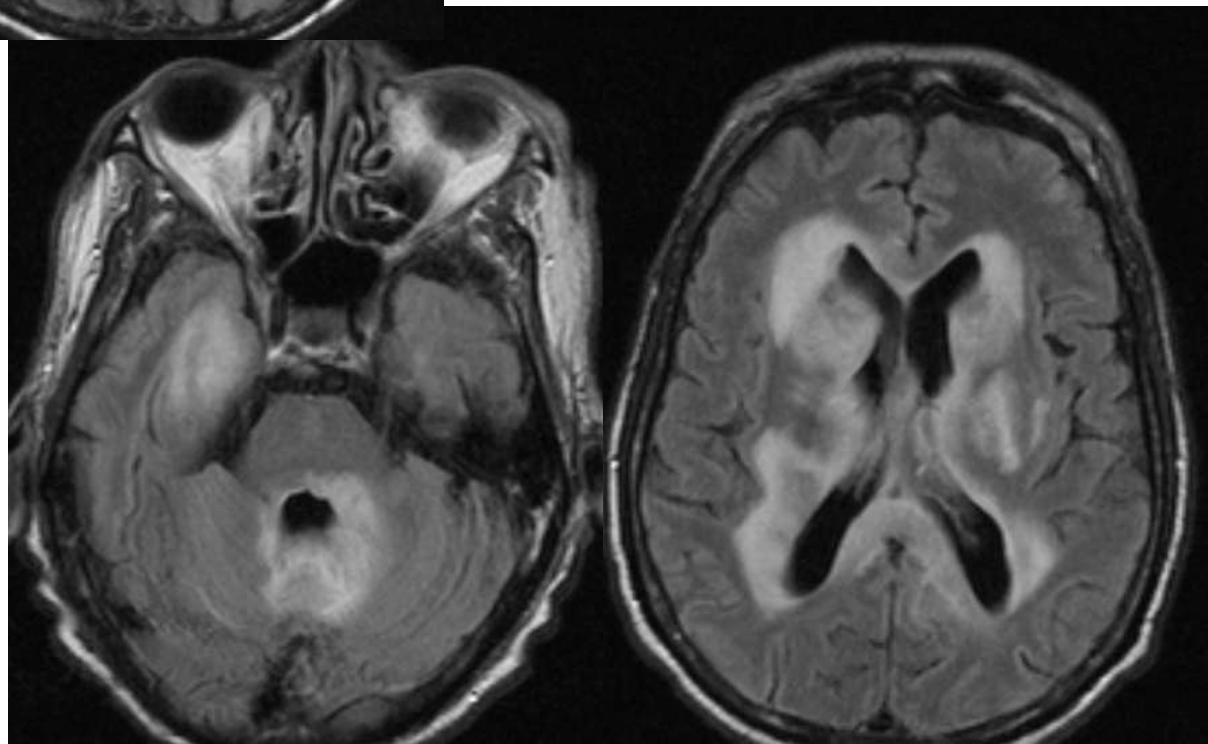
Labs: viral load ***2K***.

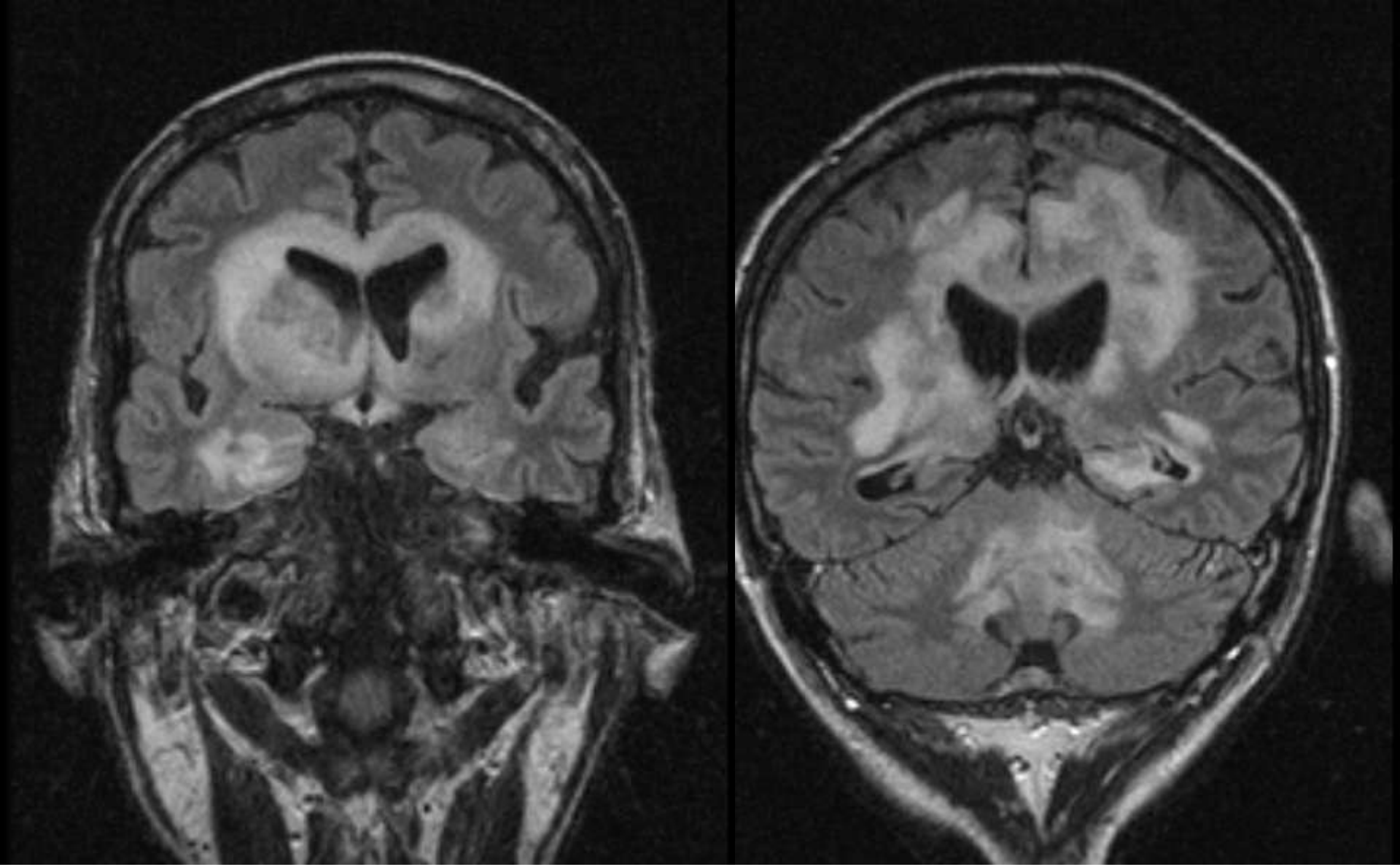
MRI: ***Progressive*** symmetric bilateral white matter signal change.



Initial MRI



MRI after ART



MRI after ART

Case

LP: bland, all microbiology negative including HIV viral load

Brain biopsy: multinucleated giant cell and a polyclonal lymphocytic infiltrate

Diagnosis: Neuro-IRIS (against HIV)

Treated with oral prednisone in addition to cART with improvement in cognitive function.

CNS-IRIS

- May present as worsening of known OI or unmasking of previously undiagnosed OI
- Risk factors include baseline low CD4 and high viral load
  - ***Resource-limited settings may have increased incidence***
- Precipitous drop in viral load and/or increase in CD4
- Signs of inflammation, usually atypical for underlying OI presentation in HIV

CNS-IRIS

- Most common CNS IRIS syndromes
  - Cryptococcal meningitis
  - TB meningitis or tuberculoma
  - PML
- Less common CNS IRIS syndromes
  - Toxo, PCNSL, VZV, candida, MAC
  - HIV
- Treat OI specifically if not already
- Delay ART in CM for 2-4 weeks
- Case by case, but given poor CNS recovery to injury and confined intracranial space, consider corticosteroids early

ART issues in CNS

CNS Penetration-Effectiveness (CPE) Ranks (2010)

Table 1.	4	3	2	1
NRTIs	Zidovudine	Abacavir	Didanosine	Tenofovir
		Emtricitabine	Lamivudine	Zalcitabine
			Stavudine	
NNRTIs	Nevirapine	Delavirdine	Etravirine	
		Efavirenz		
PIs	Indinavir-r	Darunavir-r	Atazanavir-r	Nelfinavir
		Fosamprenavir-r	Atazanavir	Ritonavir
		Indinavir	Fosamprenavir	Saquinavir-r
		Lopinavir-r		Saquinavir
				Tipranavir-r
Fusion/Entry Inhibitors		Maraviroc		Enfuvirtide
Integrase Inhibitors		Raltegravir		

Letendre S. et al. , 17th Conference on Retroviruses and Opportunstic Infections, poster n°430

ART issues in CNS

- Conflicting data regarding importance of “neuro-ART”
  - CSF levels are not necessarily indicative of brain levels
  - Some evidence that cognitive performance improves off ART
  - CNS “escape” when serum viral load suppressed is rare, but may constitute a scenario in which ART is changed to target CNS
  - More evidence is needed!

End

Supplementary Slides

Evaluation of Stroke

- History and physical
  - Differentiate stroke from mimics (seizure, CNS infection, migraine, metabolic, trauma)
  - Differentiate ischemic from hemorrhagic stroke (precipitant, headache, vomiting, decreased alertness, evolution)
  - Assess for stroke risk factors (prior stroke/TIA, HTN, hyperlipidemia, diabetes, smoking, cardiac disease)
  - Localize syndrome and determine stroke subtype
- Imaging
  - CT without contrast (hemorrhage, mass lesion, old stroke)
  - Vessel imaging
  - MRI if available

Evaluation of Stroke

- Basic blood tests
  - CBC, coagulation (thrombocytopenia, coagulopathy)
  - Chemistries (hypoglycemia and other metabolic disturbances)
  - Hemoglobin A1c
  - Lipid panel
- Cardiac studies
  - EKG, telemetry, Holter monitor (atrial fibrillation)
  - Echocardiogram (LV thrombus, LA dilatation, endocarditis)
- Other studies targeted to above results and demographic
  - ESR
  - Hypercoagulable studies
  - Infectious studies including LP

Stroke in HIV compared to non-HIV patients

- Treatment
  - Acute and long term care per typical stroke guidelines
  - Antiplatelet (ASA) or anticoagulation depending on etiology
  - Beware interaction between statins and ART (PI's increase statin toxicity, NNRTI's reduce statin efficacy)
  - Watch for IRIS
  - Consider ART with lower risk for atherosclerosis (evolving area)

HIV Vasculopathy

- First recognized in pediatric HIV patients with stroke
- Fusiform aneurysm of intracranial ICA and circle of Willis
- Thrombotic rather than hemorrhagic
- Chronic lymphocytic infiltration of vascular wall, without evidence of virus
- Question of VZV as underlying etiology although not identified in all

HIV Vasculopathy

- Some cases of extra-cranial involvement revealed vaso vasorum vasculitis, while intracranial medium sized vessels have shown intimal involvement
- May have pro-thrombotic effect or accelerated atherosclerosis
- Protein S deficiency and antiphospholipid antibodies are likely epiphenomena
- As HIV population ages, interplay of HIV, cART, and traditional vascular risk factors will be more complicated

HIV Vasculopathy

- Response to cART is mixed but there are some reports of vasculopathy resolution
- ASA indicated in most
- Some anecdotal reports of ongoing strokes until anticoagulated

VZV Vasculopathy

- Classically: History of recent zoster
- Neurologic symptoms and signs attributable to ischemia, infarct, or hemorrhage
- Unifocal large vessel vasculopathy after ophthalmic zoster in elderly adults or childhood chickenpox
- Multifocal large or small arteries in immunocompromised

VZV Vasculopathy

- Diagnosis may be complicated due to:
  - Neurologic disease develops weeks to months after zoster
  - Not all VZV vasculopathy patients have zoster or chickenpox
  - Findings resemble other causes of vasculopathy
  - CSF VZV DNA is often negative, as opposed to IgG

VZV Vasculopathy

- Given that virus particles are found in the vessel wall, experts argue that acyclovir should be used even when CSF is bland and no DNA detected (and IgG detected)
- No consensus, but reasonable to use acyclovir for 14-21 days, steroids if severe