Clinicopathological Conference
Advanced Update in HIV Medicine and Clinical Research
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Neurology

Disclosures

- Dr. Mukerji reports no disclosures

Differential Diagnosis

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Historical Perspective

"Patients..[with this syndrome] ..present with a variable, yet characteristic constellation of abnormalities in cognitive, motor, and behavioral function…with time, intellectual impairment becomes more pervasive broadly affecting nearly all aspects of cognition, with further slowing and inaccuracy of performance. In parallel, gait unsteadiness gives way to frank weakness…variants of the syndrome occur..in some patients an agitated mental state with mania or other forms of organic psychosis may occur."

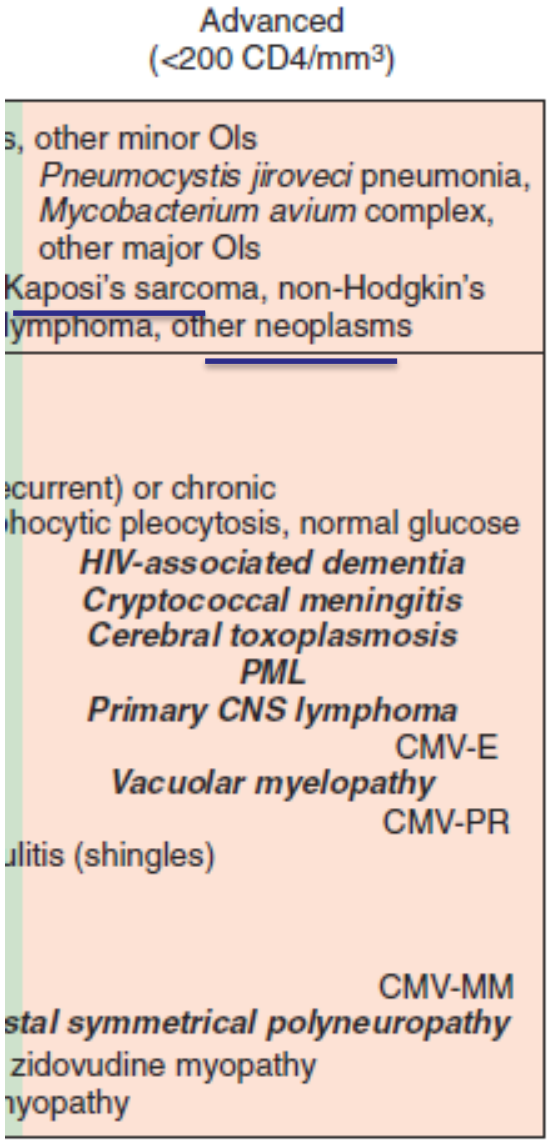
Price et. al *Science* 1988

Case Summary

- 48 year old man with a lifestyle at high-risk for HIV acquisition
- Weight loss for 1 year; painful lymphadenopathy; purple macules on his hard and soft palate; cytopenia; fever
- Behavioral Abnormalities (hyperactive agitation) and Encephalopathy
- Mild Motor Deficit and Gait Impairment
- Seizures

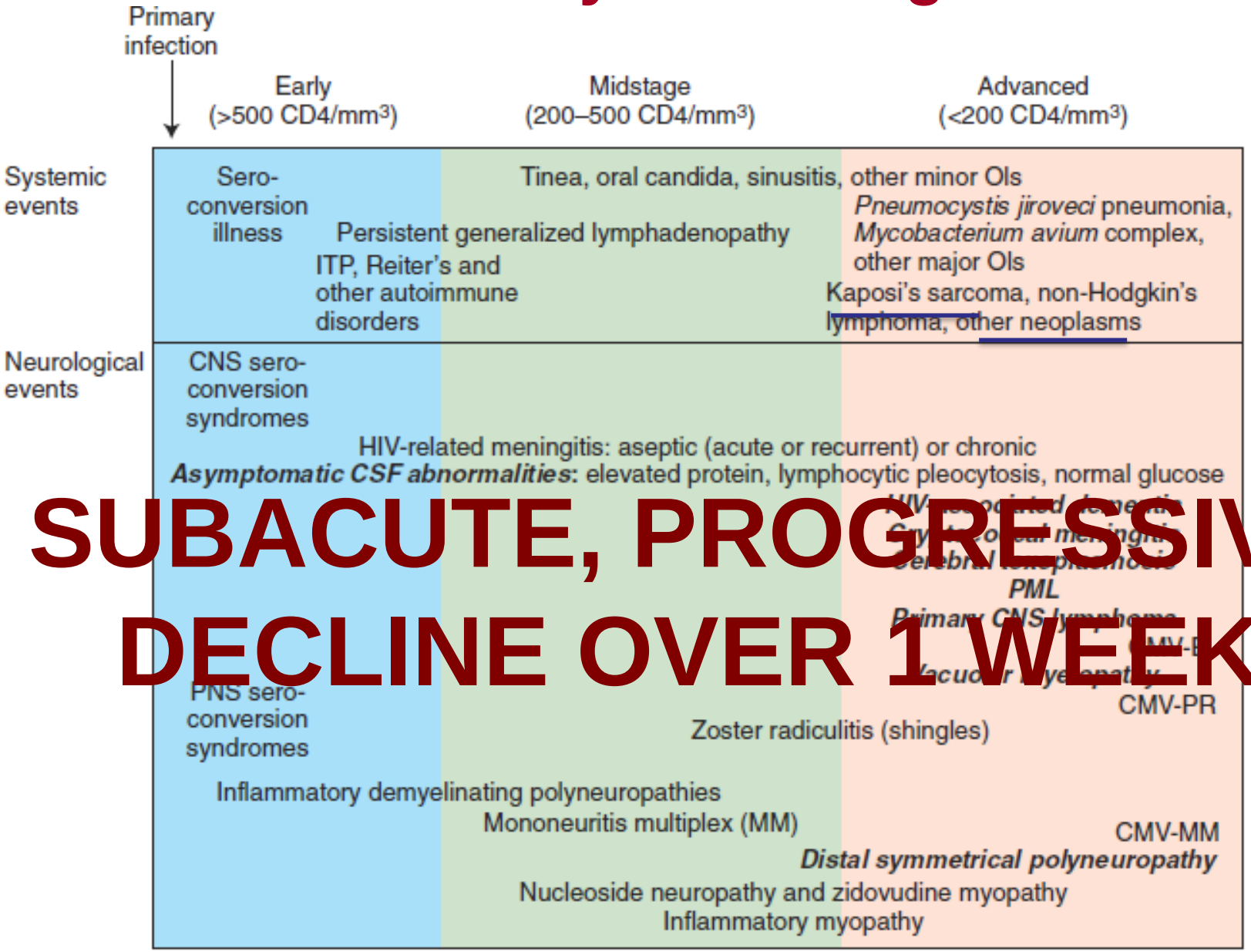
- CSF Pattern: **Normal opening pressure**, mild CSF pleocytosis (7 cells/ml; 80% L), **elevated total protein**, and **normal glucose**

Case Summary: Neurological Pace



Daroff 2013

Case Summary: Neurological Pace



SUBACUTE, PROGRESSIVE DECLINE OVER 1 WEEK

Daroff 2013

Reframing: Subacute, Progressive Encephalopathy With Seizures In Individual Presenting with AIDS

TABLE 1-2 Commonly Cited Etiologies of Altered Mental Status

- ▶ Vascular
  - Ischemic stroke[a]
  - Intracerebral or subarachnoid hemorrhage
- ▶ Infectious
  - Urinary tract infection
  - Pneumonia
  - Sepsis
  - Encephalitis
  - Meningitis
- ▶ Toxic
  - Intoxication and overdose
  - Withdrawal (alcohol, benzodiazepines, barbiturates, heroin)
  - Drugs (including prescription, over-the-counter, and herbal preparations)
- ▶ Traumatic
  - Concussion
  - Subdural hematoma
- ▶ Autoimmune
  - Neuropsychiatric lupus
  - Behçet syndrome
  - Vasculitis
  - Acute disseminated encephalomyelitis
- Hashimoto encephalopathy (also called steroid-responsive encephalopathy with autoimmune thyroiditis)
- Autoimmune limbic encephalitis (antibodies against VGKC[b], LGI1, NMDA receptors, AMPA receptors, $GABA_B$ receptors)
- ▶ Metabolic
  - Electrolytes
    - Hyponatremia/hypernatremia
    - Hypercalcemia
    - Hypermagnesemia
    - Hypophosphatemia
  - Endocrine
    - Hypothyroidism/hyperthyroidism
    - Hypocortisolism/hypercortisolism
    - Hypoglycemia/hyperglycemia
  - Hepatic encephalopathy
  - Uremic encephalopathy
  - Acute pancreatitis
  - Hypoxia and hypercarbia
  - Vitamin deficiencies
    - Thiamine
    - B_{12}
  - Hypothermia/hyperthermia
- Marchiafava-Bignami disease
- Porphyria
- ▶ Iatrogenic (see Table 1-3)
- ▶ Neoplastic
  - Large brain tumors
  - Carcinomatous meningitis
  - Paraneoplastic limbic encephalitis (antibodies against Ma2, Hu, CV2/CRMP5, Tr, VGKC, NMDA receptors, AMPA receptors)
- ▶ Seizure-Related
  - Postictal state
  - Nonconvulsive status epilepticus
- ▶ Structural
  - Hydrocephalus
- ▶ Degenerative
  - Dementia with Lewy bodies
  - Prion disease
  - Other neurodegenerative disorders usually are risk factors for delirium but another inciting cause is present
- ▶ Psychiatric Disease–Related

VGKC = voltage-gated potassium channel; LGI1 = leucine-rich glioma inactivated 1; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; GABA = γ-aminobutyric acid.

[a]Vascular lesions rarely lead to isolated delirium in the absence of other neurologic signs; rare exceptions include lesions of the thalamus and nondominant posterior parietal lobe.

[b]A recent study implicates LGI1 as the antigen in limbic encephalitis previously attributed to VGKC antibodies. Because LGI1 coprecipitates with VGKC, it is likely the commercial test for VGKC antibodies is actually detecting antibodies of LGI1. However, because direct testing for LGI1 antibodies is not yet available and because other disorders are associated with VGKC antibodies (eg, Morvan syndrome), it is still appropriate to order the commercial test for VGKC antibodies in patients with limbic encephalitis.[11]

Lymphomatous meningitis (metastatic)

BRAIN

Predominantly Nonfocal

HIV-associated dementia (HAD)
HIV-associated minor cognitive motor dysfunction (MCMD)
Toxoplasmic encephalitis
Cytomegalovirus (CMV) encephalitis
Aspergillus encephalitis
Herpes encephalitis
Metabolic encephalopathy (alone or concomitantly)

Predominantly Focal

Cerebral toxoplasmosis
Primary CNS lymphoma (PCNSL)
Progressive multifocal leukoencephalopathy (PML)
Cryptococcoma
Tuberculoma
Varicella-zoster virus (VZV) encephalitis
Stroke

SPINAL CORD

Vacuolar myelopathy (VM)

Douglas 2014; Daroff 2013

Salient Features of Patient's Confusion

Executive Dysfunction

- Fails to orient
- Perseverative Behavior
- Inability to follow two step commands
- Minimally goal-oriented tasks are **delayed**
- Rigidity of thought (abstract reasoning)

Disinhibition/Apathy

- Agitation
- Frenzied
- Disinhibited social behavior
- Apathy to self appearance

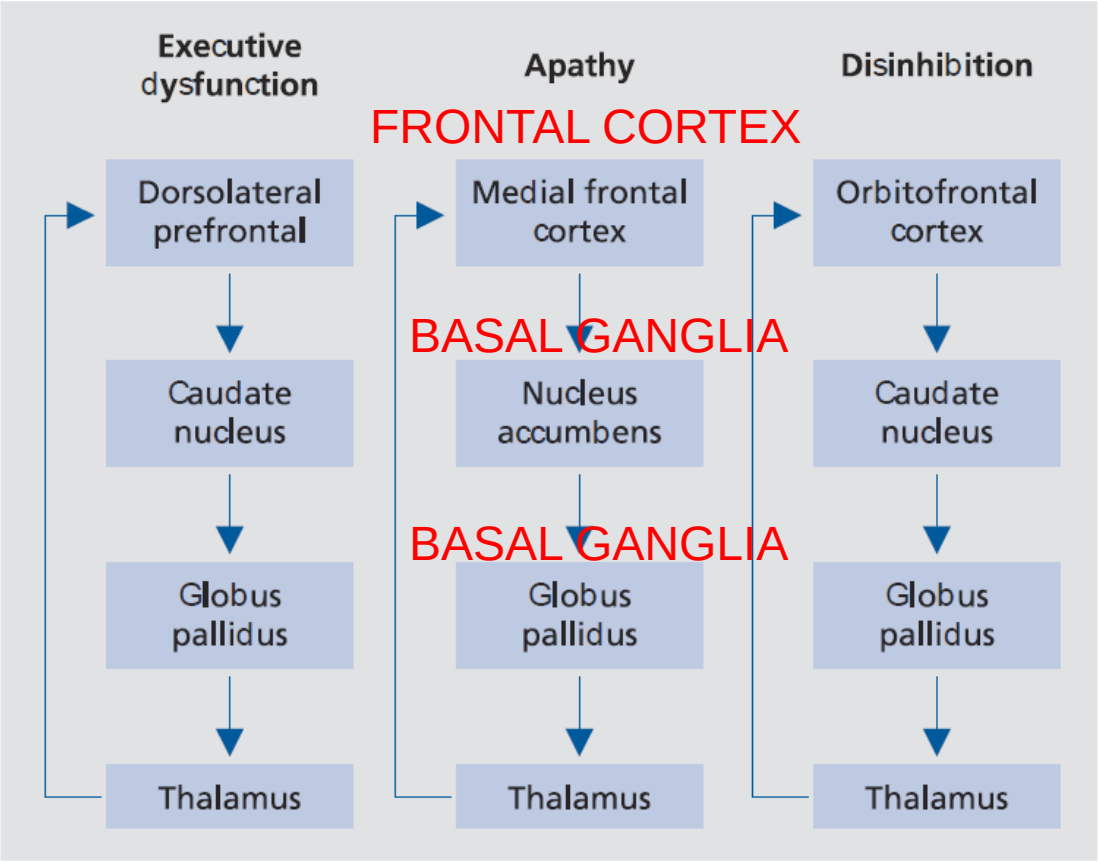
Gait Disturbance

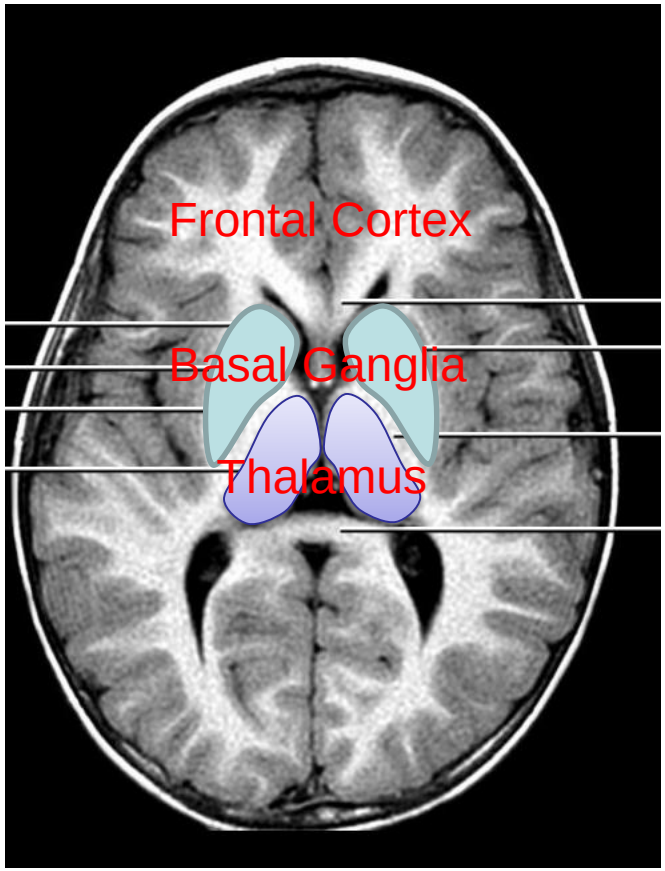
- Ataxia of Gait: The act of walking is impaired/slowed not explained by weakness, loss of sensation or spasticity

<u>Psychomotor Underactivity</u>

<u>Behavioral Disturbance</u>

Frontal Lobe Syndrome Helps Explain Most of Dominating Salient Features

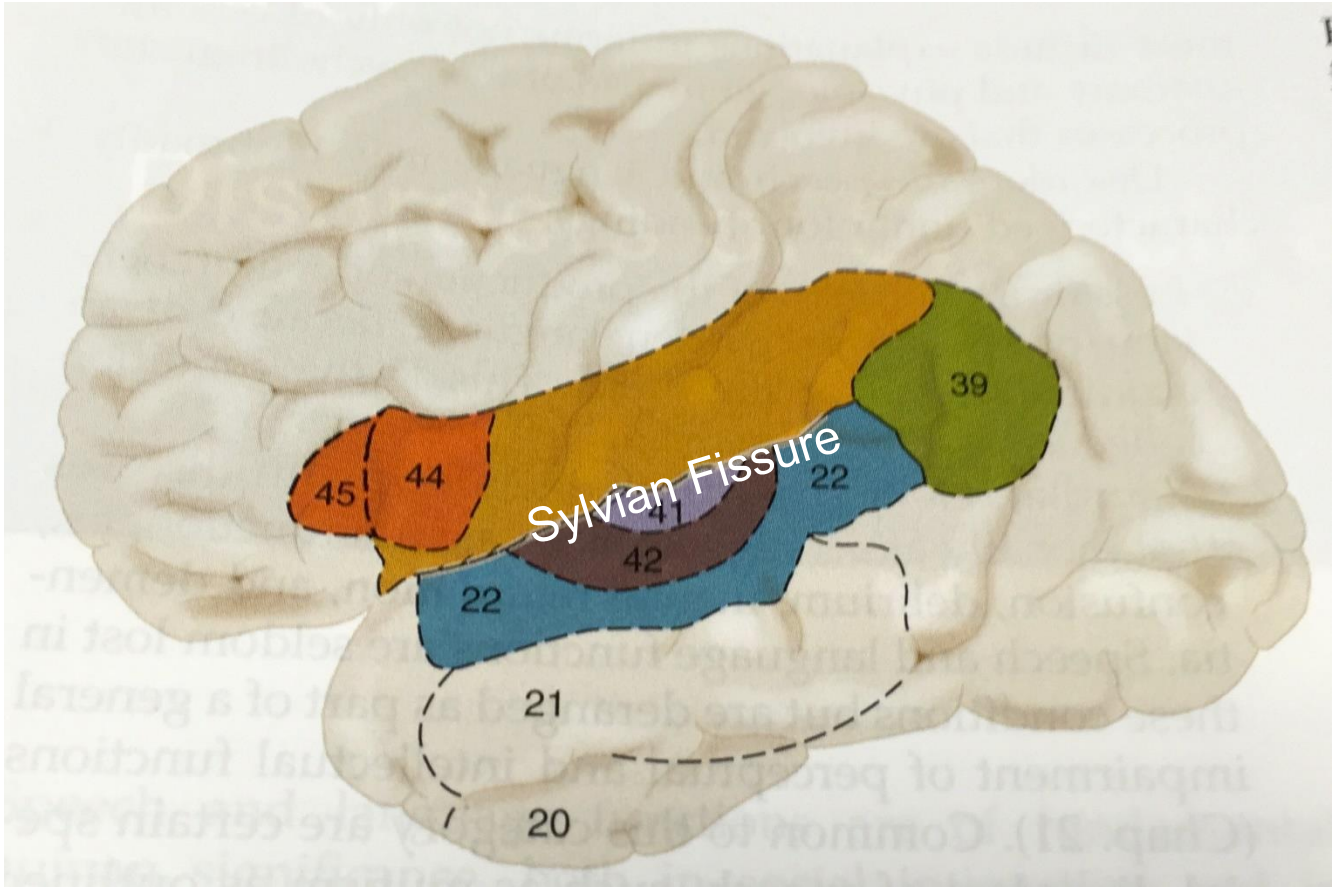




Likely dealing with Frontal lobe syndrome and the circuits or white matter tracks to subcortical tissues (Basal Ganglia and Thalamus)

Bonelli 2007; statdx

Patient's Speech Disorder Stems from the Frontal Lobe



Principles of Neurology 10th Ed

OUR PATIENT

- **Perseverative;**
- Maintained recall, naming, and basic comprehension

Patient's Speech Disorder Stems from the Frontal Lobe

1. Loss of impairment with the production or comprehension of spoken/written language: Aphasia
2. Disturbances of speech and language stemming from altered higher-order processes (delirium, confusion)
3. Defect in articulation with intact mental functions: Dysarthria
4. Alteration or loss of voice: aphonia

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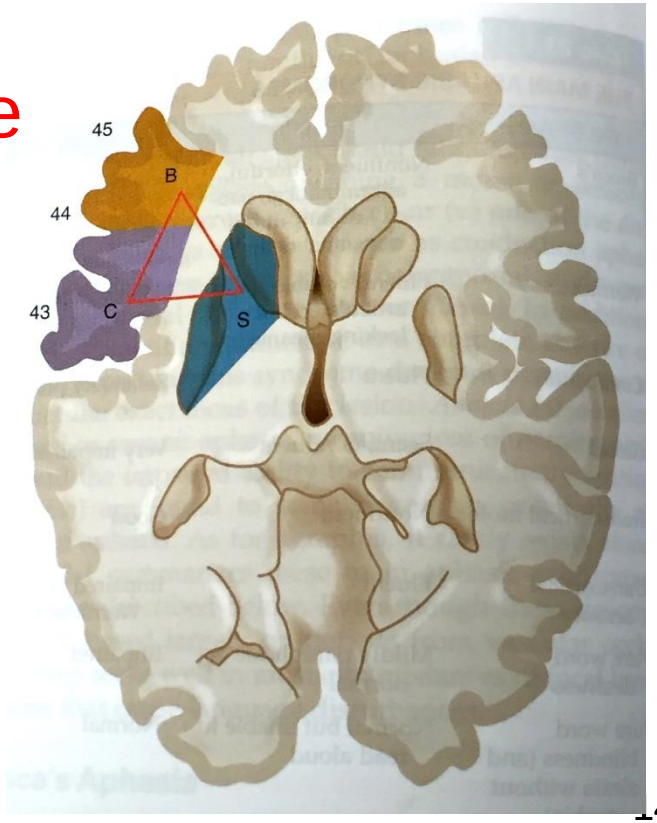
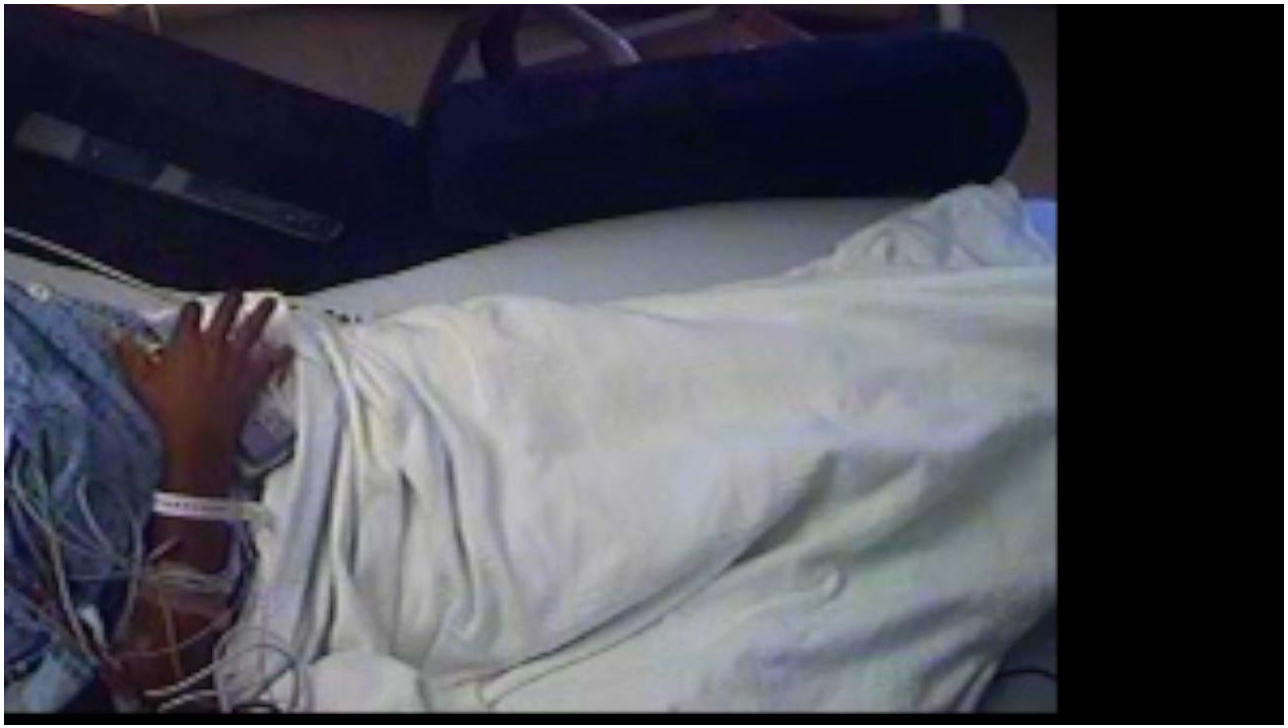
Patient's Speech Disorder Stems from the Frontal Lobe

Loss of impairment with the production or comprehension of spoken/written language: Aphasia

Hypothesis: Restricted Language Output Consistent with Psychomotor Underactivity and Frontal Lobe Dysfunction



Epilepsia Partialis Continua of Right Face



Seizures

- 2 minute episode of aphasia
- 2nd episode of staring, twitching, inability to speak with confusion

Symptoms

Progressive Subacute (<7 days)

Executive Dysfunction/ Psychomotor Underactivity/ Behavioral Disturbances

Bilateral Frontal Lobe and Inputs to Deeper Subcortical Structures

Possible Right Motor Deficits

Left Frontal Lobe

EPC+ Partial Complex Seizure

Suspect Frontal or Temporal Lobes

Multifocal Process Affecting **Frontal Lobes Bilaterally** and **Deeper White Matter** Structures, Potentially Temporal Lobes with a Constellation of Psychomotor Slowing/Behavioral Disturbances/Motor Impairment and Seizures in the setting of AIDS

Differential Diagnosis for Frontal Lobe Dysfunction

- Nutritional Abnormalities
  - Weirnicke's encephalopathy due to thiamine deficiency.
  - Vitamin B12

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- Prion Disease

MRI Read: Abnormal T2 hyperintense signal within the **frontoparietal white matter**, slightly more prominent in the right frontal lobe, **extending into the genu of the corpus callosum**, **without significant local mass effect or abnormal restricted diffusion**.

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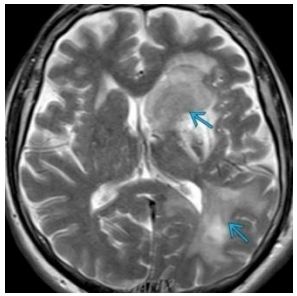
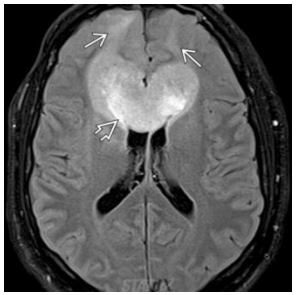
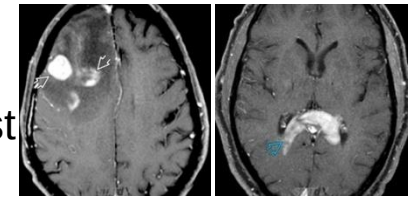
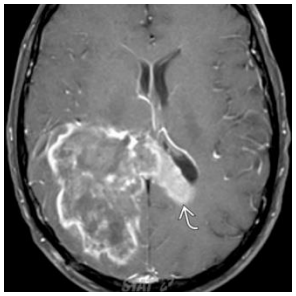
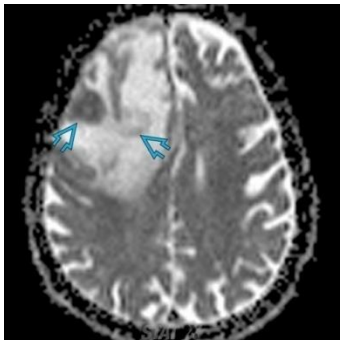
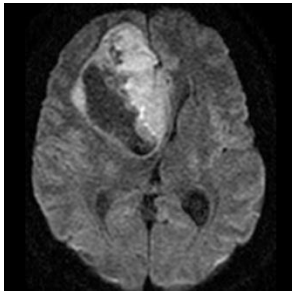
- Intracranial Lesions
  - Infiltrative Neoplasms

MRI Read: Abnormal T2 hyperintense signal within the **frontoparietal white matter**, slightly more prominent in the right frontal lobe, **extending into the genu of the corpus callosum**, **without significant local mass effect or abnormal restricted diffusion**.

Infiltrative Neoplasms

	CNS Lymphoma	Glioblastoma
T2/ FLAIR		
T1 +Contrast		
DWI		
Mass Effect	Yes	Yes

Unlikely based on the MRI read

Statdx; Dr Hani Al Salam, Radiopaedia.org, rID: 8945

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- Prion Disease
- Intracranial Lesions
  - Infiltrative Neoplasms
  - Infectious Organisms

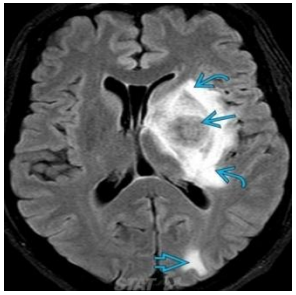
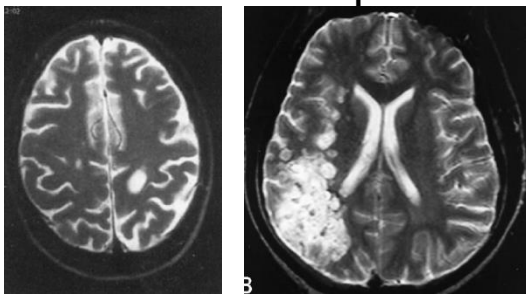
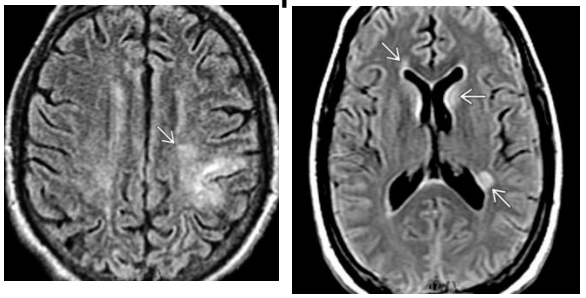
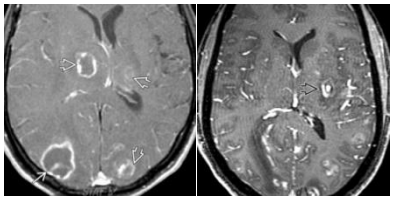
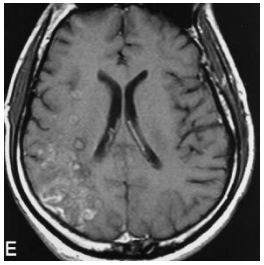
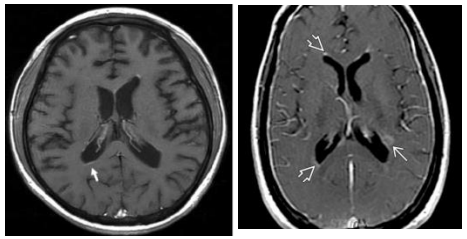
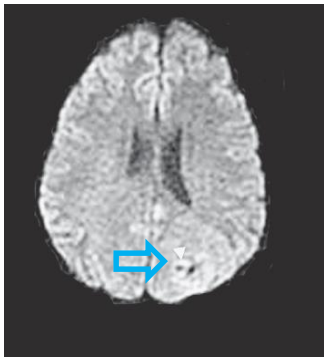
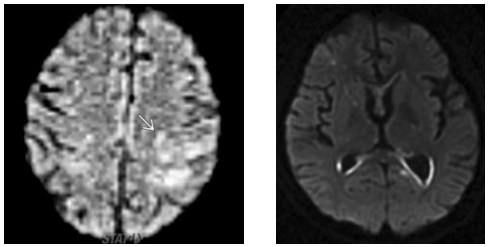
MRI Read: Abnormal T2 hyperintense signal within the **frontoparietal white matter**, slightly more prominent in the right frontal lobe, **extending into the genu of the corpus callosum**, **without significant local mass effect or abnormal restricted diffusion**.

Infectious Differential Diagnosis for Frontal Lobe Dysfunction

- Toxoplasmosis Encephalitis
- Abscess
- Varicella-zoster leukoencephalitis
- CMV encephalitis
- Progressive Multifocal Leukoencephalopathy
- HIV-associated Leukoencephalopathy

(CNS tuberculoma or cryptococcus) unlikely given CSF studies and lack of positional headache

Infectious Agents

	Toxoplasmosis	Varicella encephalitis	CMV encephalitis
T2/ FLAIR			
T1 +Contrast			
DWI		Yes	
Mass Effect	Yes	No	No

Clinical presentation + Imaging Read does not fit the pattern for our patient

Statdx;Aygun 1998

Infectious Differential Diagnosis for Frontal Lobe Dysfunction

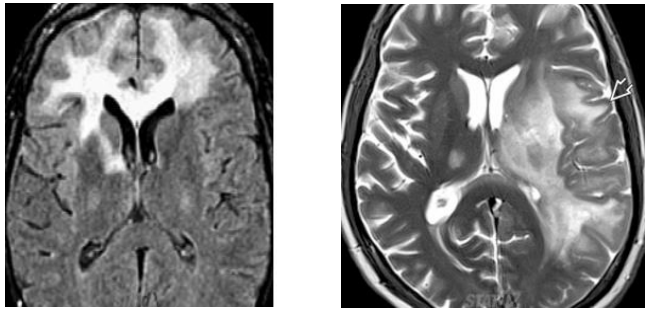
- Toxoplasmosis Encephalitis
- Frontal Lobe Abscess
- Varicella-zoster leukoencephalitis
- CMV encephalitis
- Progressive Multifocal Leukoencephalopathy
- HIV-associated Encephalitis

(CNS tuberculoma or cryptococcus) unlikely given opening pressure, normal glucose and lack of headache

Classic PML Patterns in AIDS

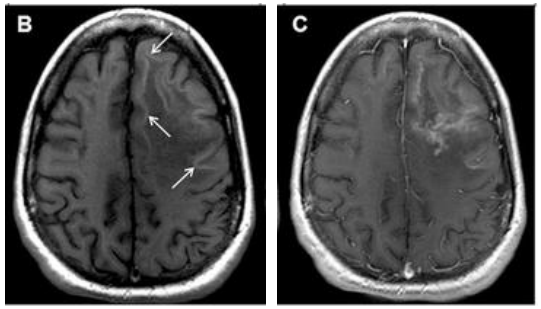
PML

T2/
FLAIR



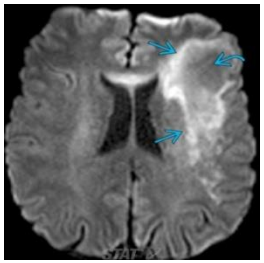
T2 Hyperintensity involving the subcortical U fibers; “Scalloped” cortex

T1
+Contrast



T1 hypointensity; 15% of HIV-associated PML may have enhancement

DWI



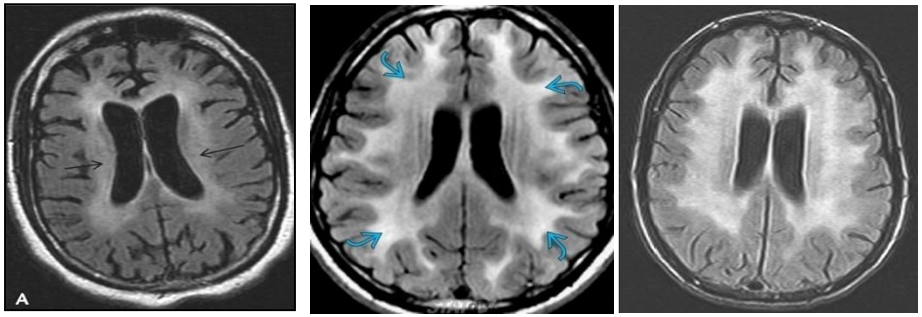
DWI: Newer lesion has slightly restricted diffusion along its margins; older lesion is unrestricted

Mass
Effect

NONE

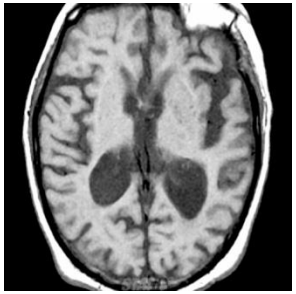
HIV-1 Encephalitis Pattern in AIDS

T2/ FLAIR



T2 hyperintensity (“hazy”) appearance; Periventricular and centrally located

T1 +Contrast



T1 imaging is typically without abnormalities in white matter. Atrophy is usually present. No contrast enhancement

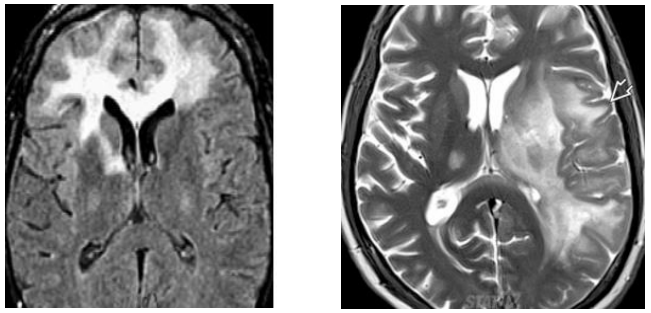
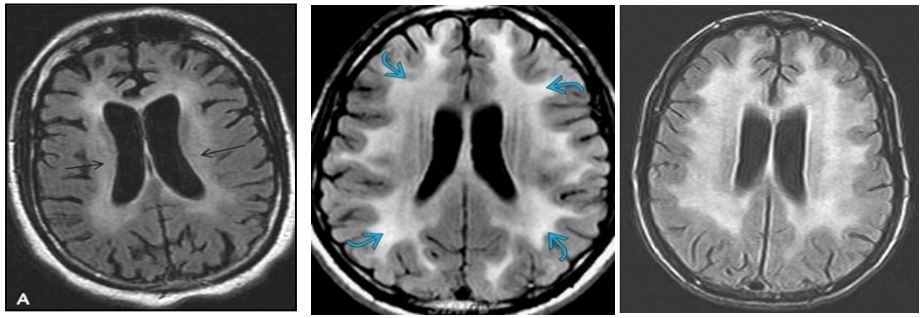
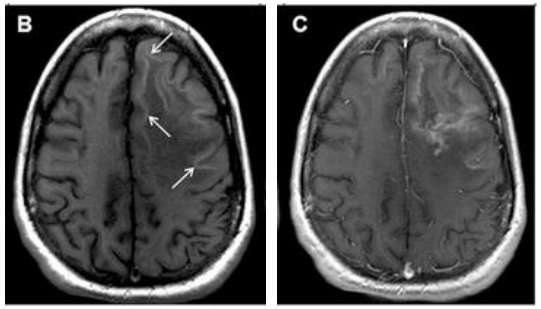
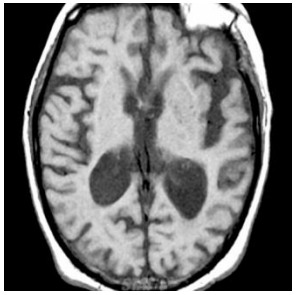
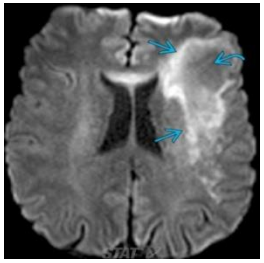
DWI

None

Mass Effect

None

PML vs. HIV encephalitis

	Peripheral Extension PML	Central/Periventricular HIV encephalitis
T2/ FLAIR		
T1 +Contrast		
DWI		NONE

Must request read of T1 images and determine the extent of white matter abnormalities on T2 images

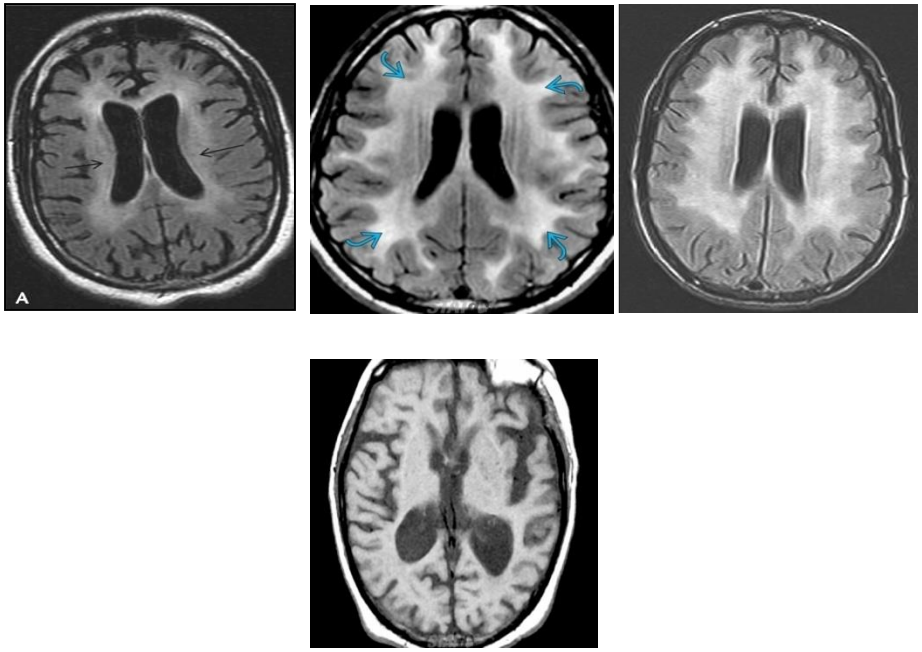
Gheuen 2014; StatDx

Imaging

HIV encephalitis

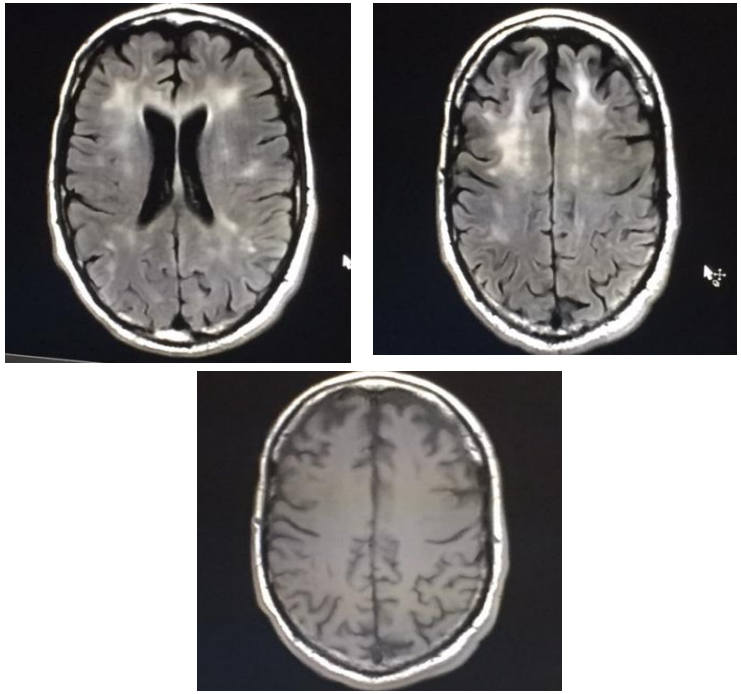
HIV encephalitis

Cognitive dysfunction
Symmetrical Motor Abnormalities
Gait Impairment
Variant: mania and agitation



Our patient

Cognitive dysfunction
Asymmetric Motor Abnormalities
Gait Impairment
Mania and agitation



Given abundance of frontal motor system and visual pathway involvement on imaging without true focal weakness or visual deficits,
- HIV encephalitis is preferred

Dr. Mukerji's Diagnosis

HIV encephalitis in setting of advanced immunosuppression