Imaging of Tumefactive Demyelination: A Comprehensive Review

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Purpose

- Describe the definition, history, and epidemiology of tumefactive demyelination
- Discuss the clinical presentation of tumefactive demyelination and briefly review the multiple neurological diseases in which it manifests
- Review imaging appearance of tumefactive demyelination in multiple neurological diseases with a variety of cases with pathologic correlations
- Summarize management and treatment options for patients with tumefactive demyelination

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Definition

- Tumefactive demyelination (TFD) is demyelination presenting as an acute, large (≥ 2 cm), tumor-like lesion in the CNS
- TFD may occur with mass effect, surrounding edema, and varied post-contrast enhancement
- TFD is seen in multiple disorders that exhibit demyelination:
  - Multiple sclerosis (MS)
  - Balo's concentric sclerosis
  - Balo-like lesion in MS
  - Myelinoclastic diffuse sclerosis (Schilder's disease)
  - Marburg variant
  - Neuromyelitis optica spectrum disorders (NMOSD)
  - Spectrum of acute disseminated encephalomyelitis (ADEM)
  - Autoimmune encephalitis

History and Epidemiology

- First reported in 1979 by van der Velden et. al with the lesion seen on non-contrast head CT in a patient with pathologically confirmed MS
- The term “tumefactive MS” has been used in the past to describe these lesions indiscriminately and is still seen in the literature
- However, the more general term “tumefactive demyelination” is used in this presentation to be more inclusive and highlight the fact that it is seen in disease processes separate from MS
- TFD is relatively uncommon and exact epidemiology statistics are difficult to accurately obtain due to under-reporting or misdiagnosis, especially in patients without established inflammatory demyelinating disease
- TFD is most well-studied and commonly reported as a subset of MS
  - Reported prevalence of TMD in 1-3/1000 cases of MS
- Estimated incidence of 0.3/100,000 people for TFD based on two small hospital studies
- Affects patients of any age, but more commonly the younger population (age 20-30’s)
- Possible female predominance for TFD has been reported

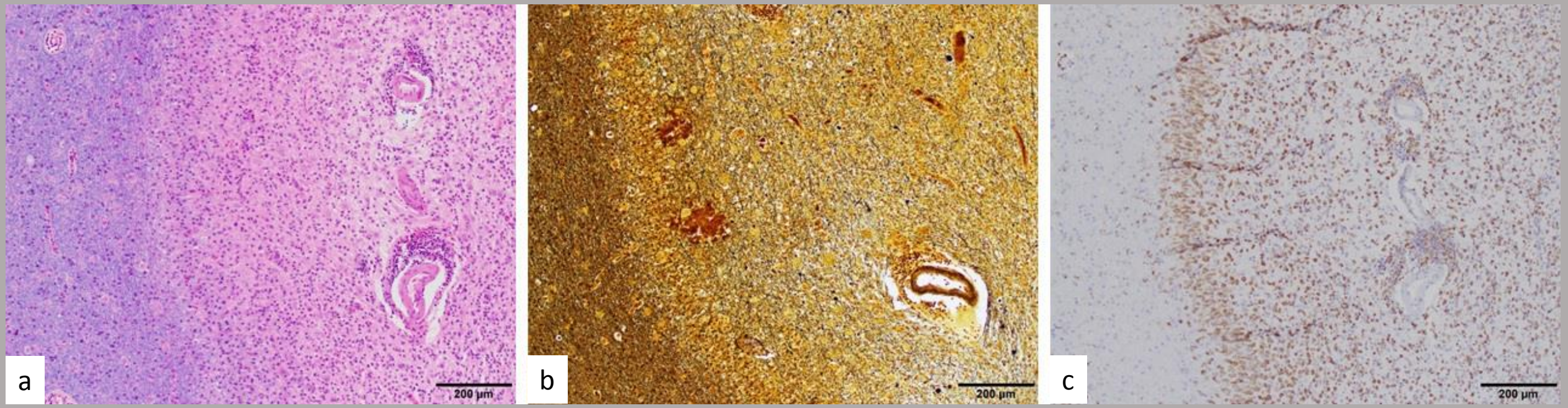
Clinical Manifestations

- TFD may present as:
  - An isolated event of demyelination due to viral infections, autoimmune disease, drugs, or malignancy
  - First clinical event in a patient without established demyelinating disease, who will later be confirmed to have demyelinating disease
  - An acute demyelination episode in a patient with known demyelinating disease
- Clinical symptoms are variable and dependent on lesion size and location
- TFD is often supratentorial and neurological deficits include motor, sensory, cognitive, and cerebellar functioning
  - Due to the large size of the lesion, multiple symptoms are usually present
- Symptoms can develop over a varied amount of time from days to weeks
- Some presentations include:
  - Stroke-like symptoms of dysphasia, hemiparesis, or visual field deficits
  - Headache and seizure, with vomiting often reported in children
  - Progressive encephalopathy and memory changes
- In severe cases, large amounts of edema and mass effect can lead to increased intracranial pressure and herniation

Pathological Appearance

- The typical pathological appearance of TFD is characterized by:
  - Numerous macrophages
  - Demyelination
  - Relative axonal preservation
  - Reactive astrocytes
  - Chronic inflammatory perivascular infiltrate (T-lymphocytes)
- Pathological appearance may differ depending on if the sample was taken from the edge or center of the lesion
- Pathology of TFD lesions may also be misleading and contain areas of necrosis, nuclear atypia, and mitotic figures
- Therefore, not all lesions should be biopsied if MRI and other imaging modalities are sufficient to make the diagnosis of TFD

Pathological Appearance



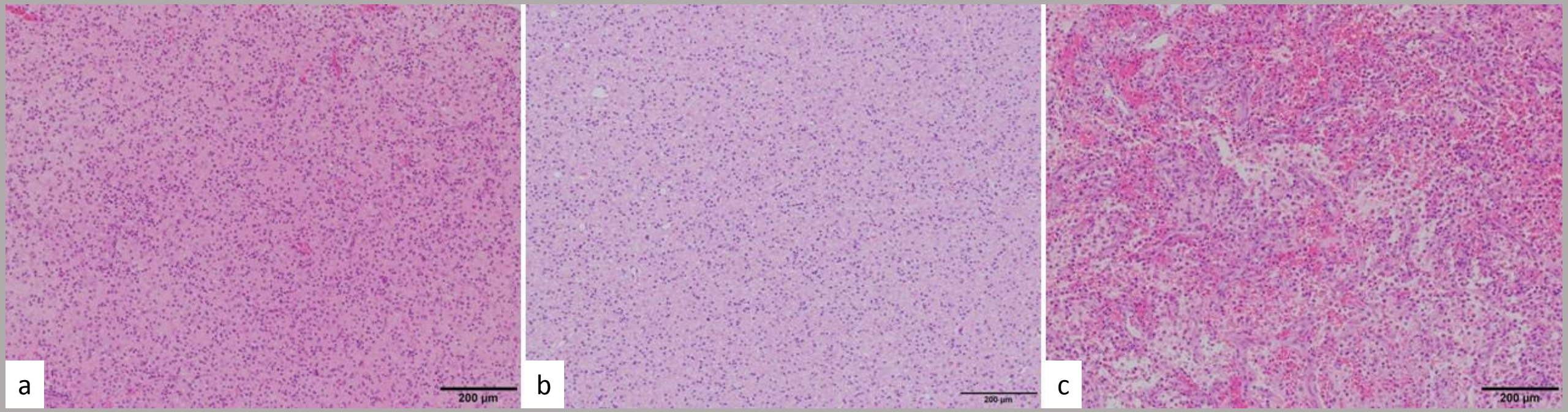
Histology of active demyelination

a) Luxol fast blue/H&E shows white matter on left with myelin highlighted blue and sharp demarcation of demyelinated area on right. Note sea of macrophages and perivascular lymphocytes associated with demyelination.

b) Bielschowsky silver stain shows black/brown axons that are *relatively* preserved in the area of demyelination.

c) CD68 immunostain confirms the presence of macrophages in the area of demyelination.

Pathological Look-Alikes

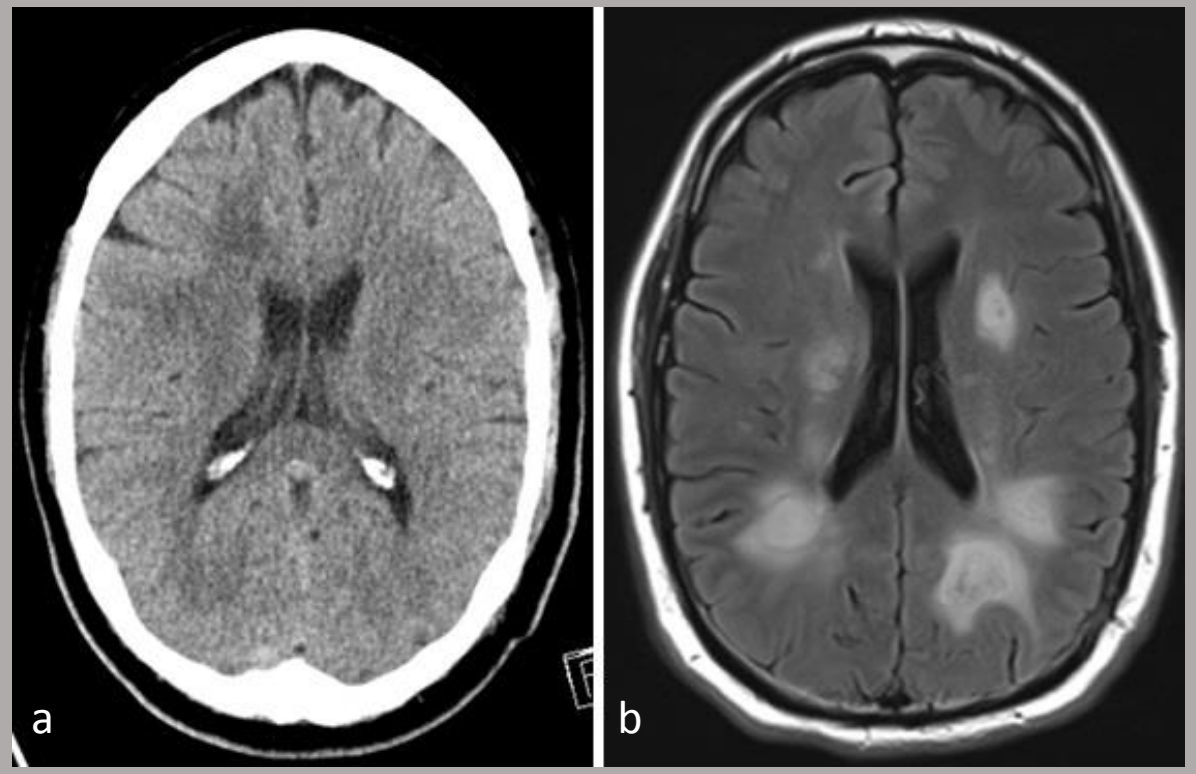


Histology of active demyelination and common look-alikes.
a) Demyelination with sheets of macrophages in a background of demyelinated white matter (H&E).
b) Oligodendroglioma, WHO grade II with tumor cells diffusely infiltrating white matter (H&E).
c) Subacute infarction with sheets of macrophages and proliferating microvasculature (H&E).

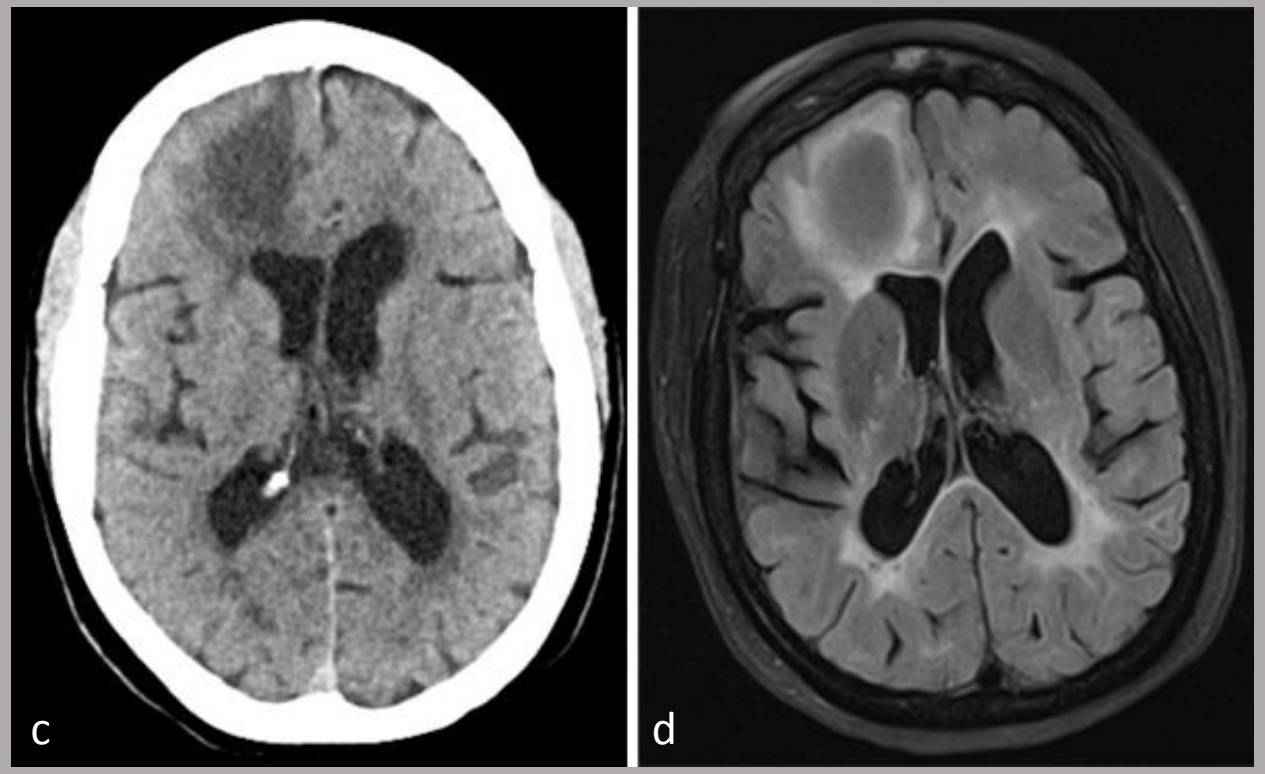
Imaging Appearance in Multiple Modalities

- MRI is the best imaging modality for diagnosis of TFD
- However, sometimes non-contrast CT is the first imaging study obtained, especially in patients with milder, non-specific neurological symptoms and without pre-existing neurological disease
  - Depending on size and location, the mass effect and edema of TFD may be seen on CT
  - Follow-up MRI should be obtained for further evaluation if there is an abnormality on CT or if there is high clinical suspicion for neurological process even on a negative CT
- MR spectroscopy (MRS), MR cerebral perfusion, and FDG-PET are less often used imaging modalities, but may help narrow the differential in certain cases

CT vs MRI Appearance of TFD



a) Non-contrast CT shows some subtle areas of hypodensity in the periventricular white matter.
b) FLAIR image on MRI demonstrates the hyperintense lesions much more avidly.



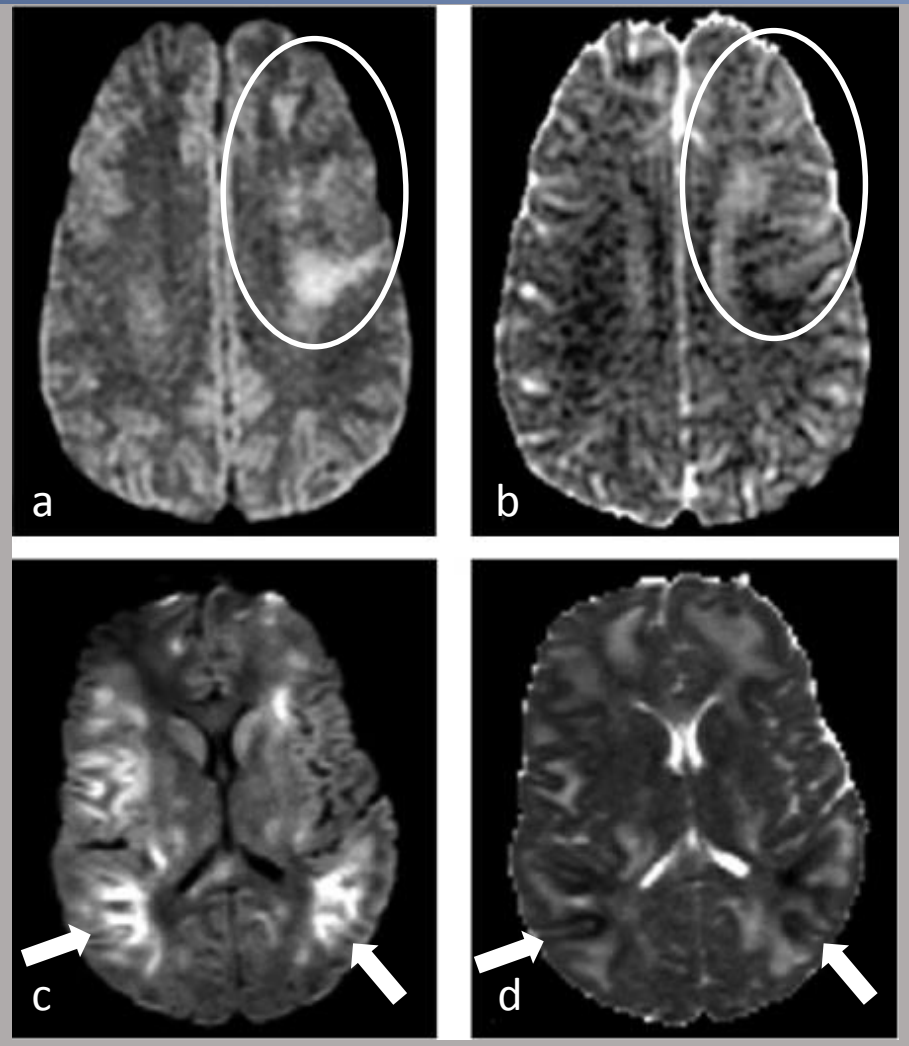
c) Non-contrast CT shows mass effect and edema in the right frontal lobe from the large mass lesion.
d) FLAIR image on MRI provides further characterization of the right frontal lesion.

MRI Appearance

- Lesion size ≥ 2 cm
- Predominant involvement of white matter and absence of cortical involvement
- Varying amounts of mass effect and/or edema
- Most commonly supratentorial lesions, with a tendency toward frontal and parietal lobes
- Nearly all TFD lesions show enhancement and incomplete ring enhancement is considered pathognomonic
  - However, varying post-contrast enhancement patterns are seen
  - Multiple examples of incomplete ring enhancement are shown in the following cases

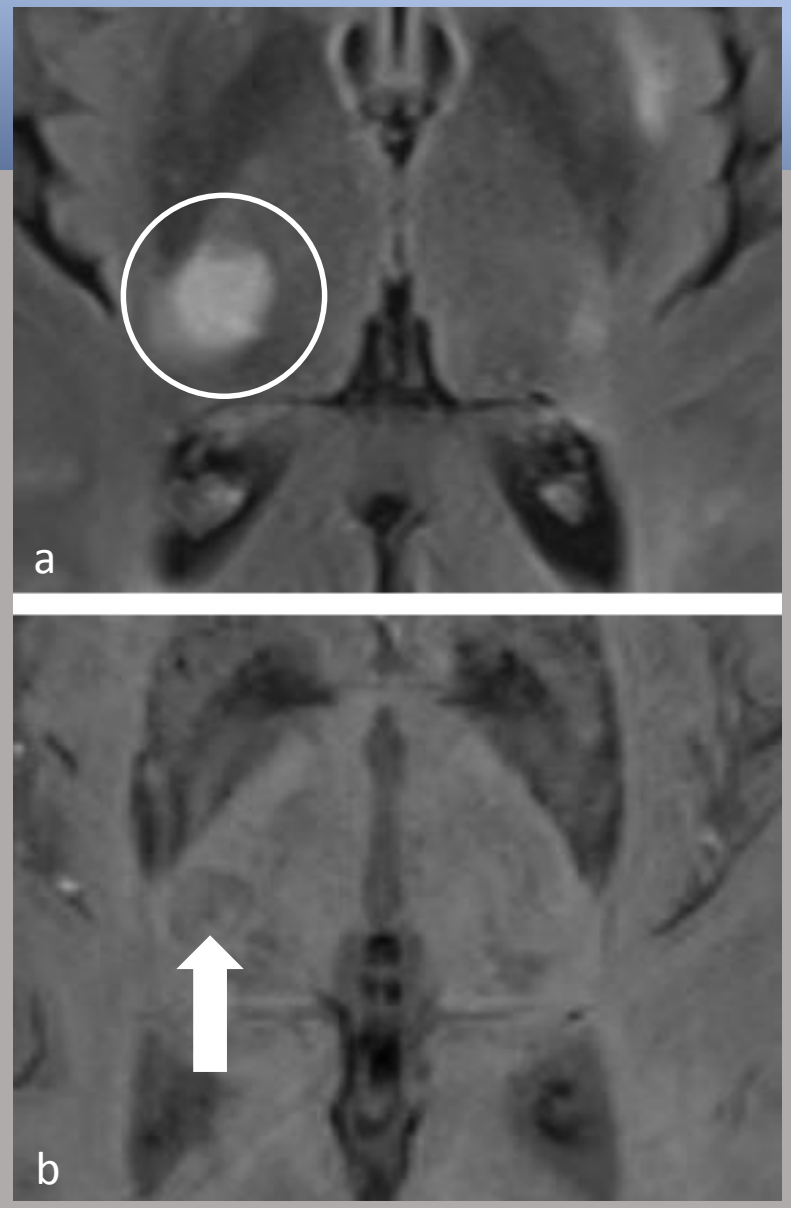
MRI Appearance

- DWI and ADC in TFD are most commonly hyperintense due to expanded extracellular space with axonal loss, demyelination, and vasogenic edema
  - Although, in the acute demyelination stage, edema within the myelin can cause decreased ADC instead
  - **Image a)** DW image shows hyperintense demyelinating lesion (circle)
  - **Image b)** ADC map shows increased signal (circle)
- Peripheral restricted diffusion (high DWI and reduced ADC) is often seen due to ischemic/hypoxic injury at the leading edge of the lesion
  - **Image c)** DW image shows hyperintense signal in multiple areas of demyelination (arrows)
  - **Image d)** ADC map shows increased signal with peripherally partially decreased signal (arrows)



MRI Appearance

- The central vein sign is suggestive of demyelination and can also be used in recognizing TFD
  - Demyelination is peri-venous in distribution
  - T-cells and macrophages enter the brain parenchyma from these veins to contribute to the demyelination process
  - On SWI, the vein is represented by a hypointense linear structure running through the center of the lesion
    - **Image a)** FLAIR image shows the hyperintense demyelinating lesion (circle)
    - **Image b)** SWI image shows central hypointense linear structure within the lesion (arrow)
  - Seen in both active and inactive demyelinating lesions, most commonly in MS



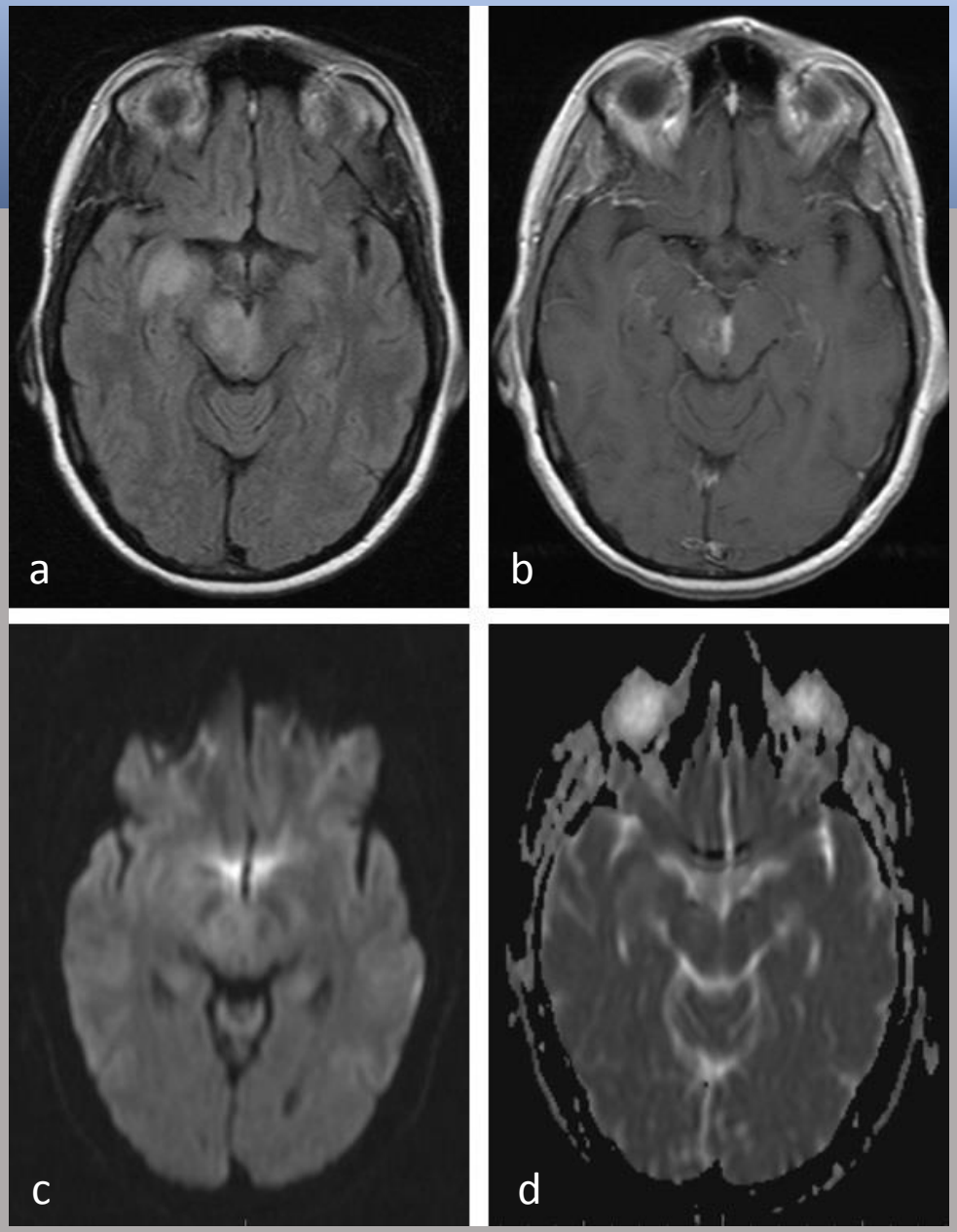
TFD

56 yo F, previously healthy, presenting with 1 week of diplopia and 1 day of acute left eyelid droop and right hand tingling/numbness. Originally, glioma was the most favored diagnosis, but biopsy was performed and showed demyelination.

a) FLAIR images shows hyperintense lesion in the right insula and right midbrain.

b) Post-GAD T1 images shows patchy peripheral enhancement of the lesion.

c) and d) DWI and ADC images show slight hyperintense signal of the lesion.



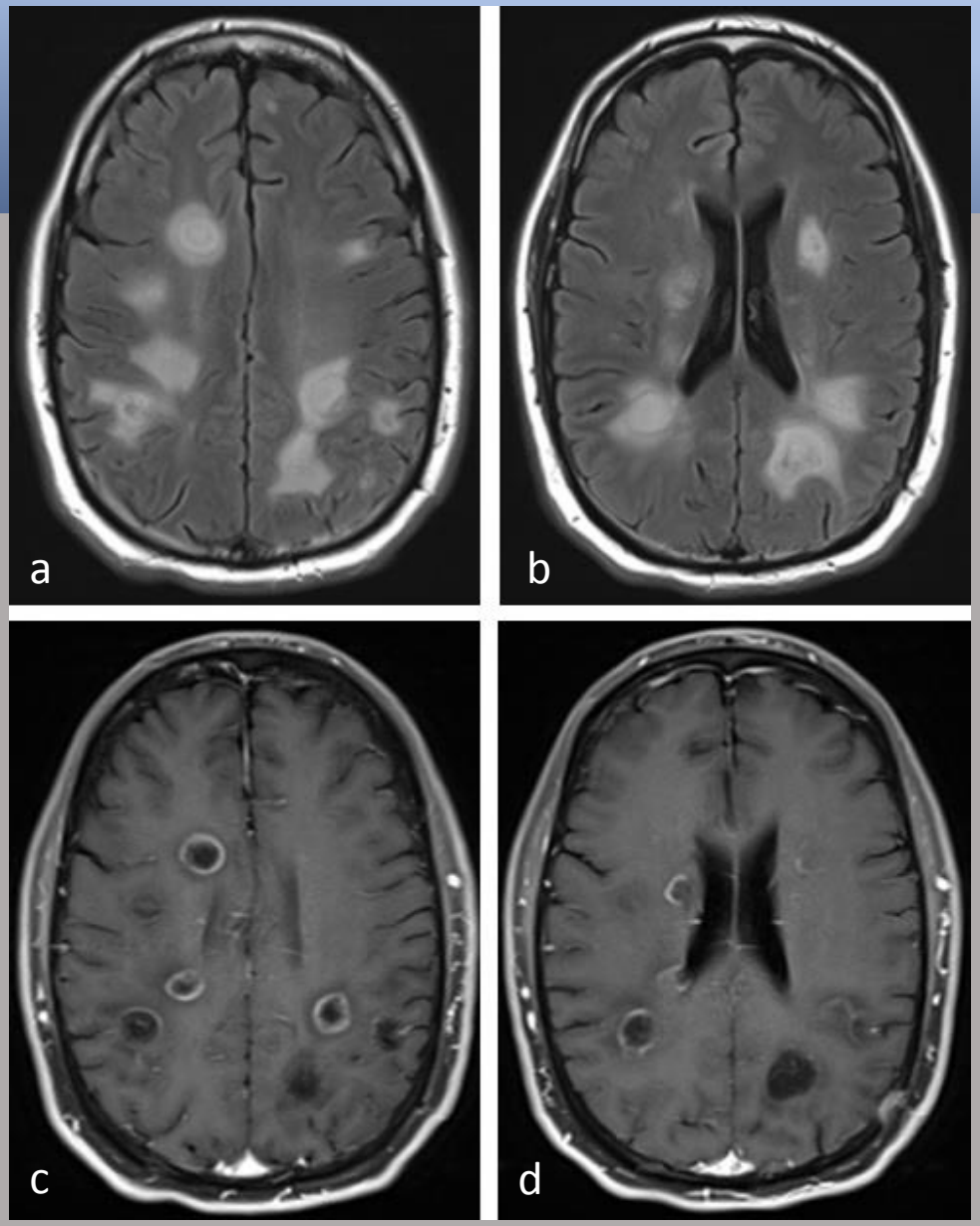
Multiple TFD Lesions

63 yo M, previously healthy, presenting with acute left-sided weakness, and progressively worsening gait, left foot drag, lightheadedness, and dizziness.

a) and b) FLAIR images show multiple hyperintense lesions in the subcortical whiter matter bilaterally.

c) and d) Post-GAD T1 images show ring enhancement and incomplete ring-enhancement of these lesions.

Biopsy showed demyelination **(continued on next slide).**



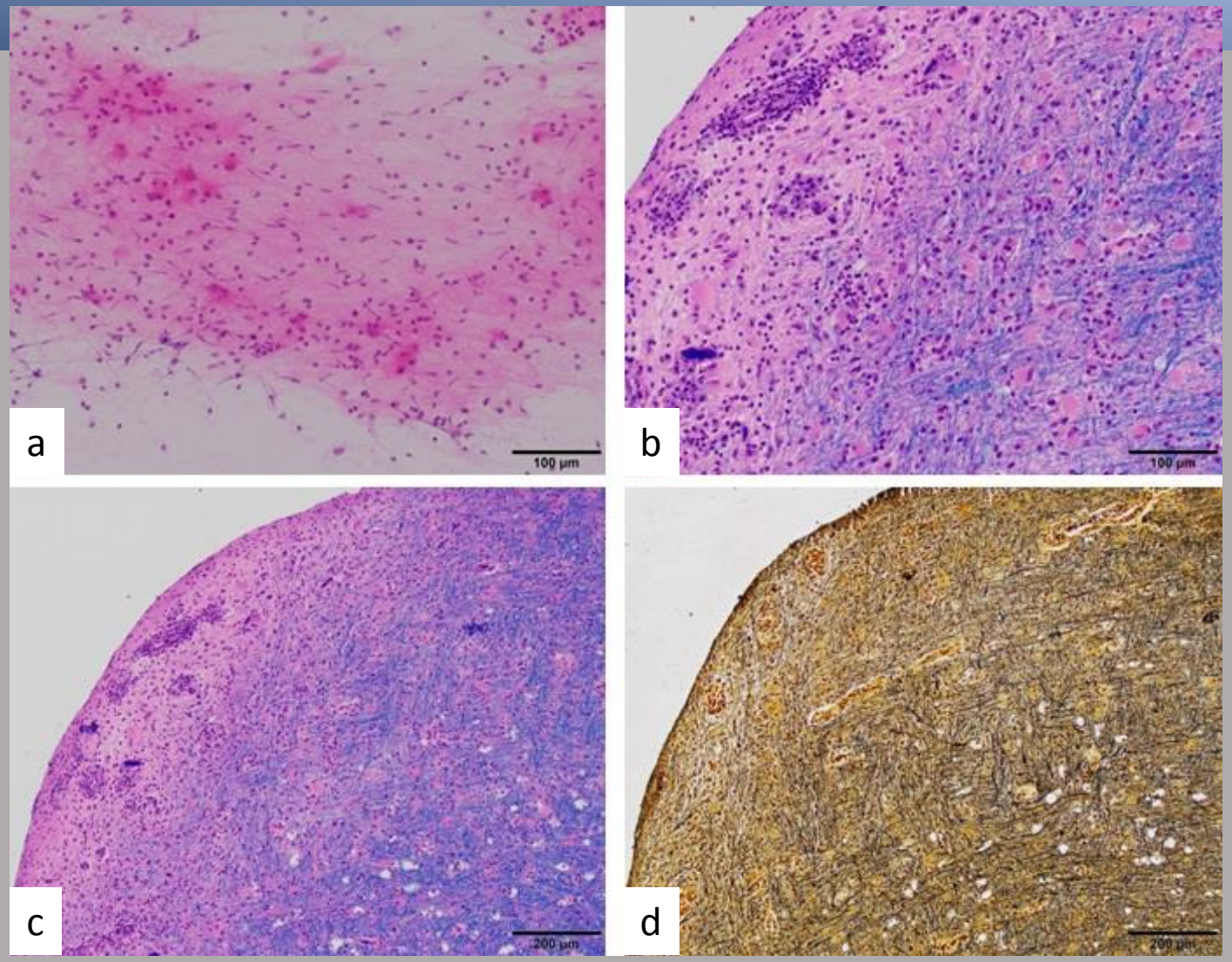
Multiple TFD Lesions

63 yo M, previously healthy, presenting with acute left-sided weakness, and progressively worsening gait, left foot drag, lightheadedness, and dizziness. (Continued from previous slide)

a) Intraoperative smear preparation shows reactive astrocytosis (H&E).

b) and c) Normal white matter on right with myelin highlighted blue and area of demyelination on the left with loss of myelin, macrophages, and perivascular lymphocytes (Luxol fast blue/H&E).

d) Relative axonal preservation in the area corresponding to demyelination (left) (Bielschowsky silver stain).

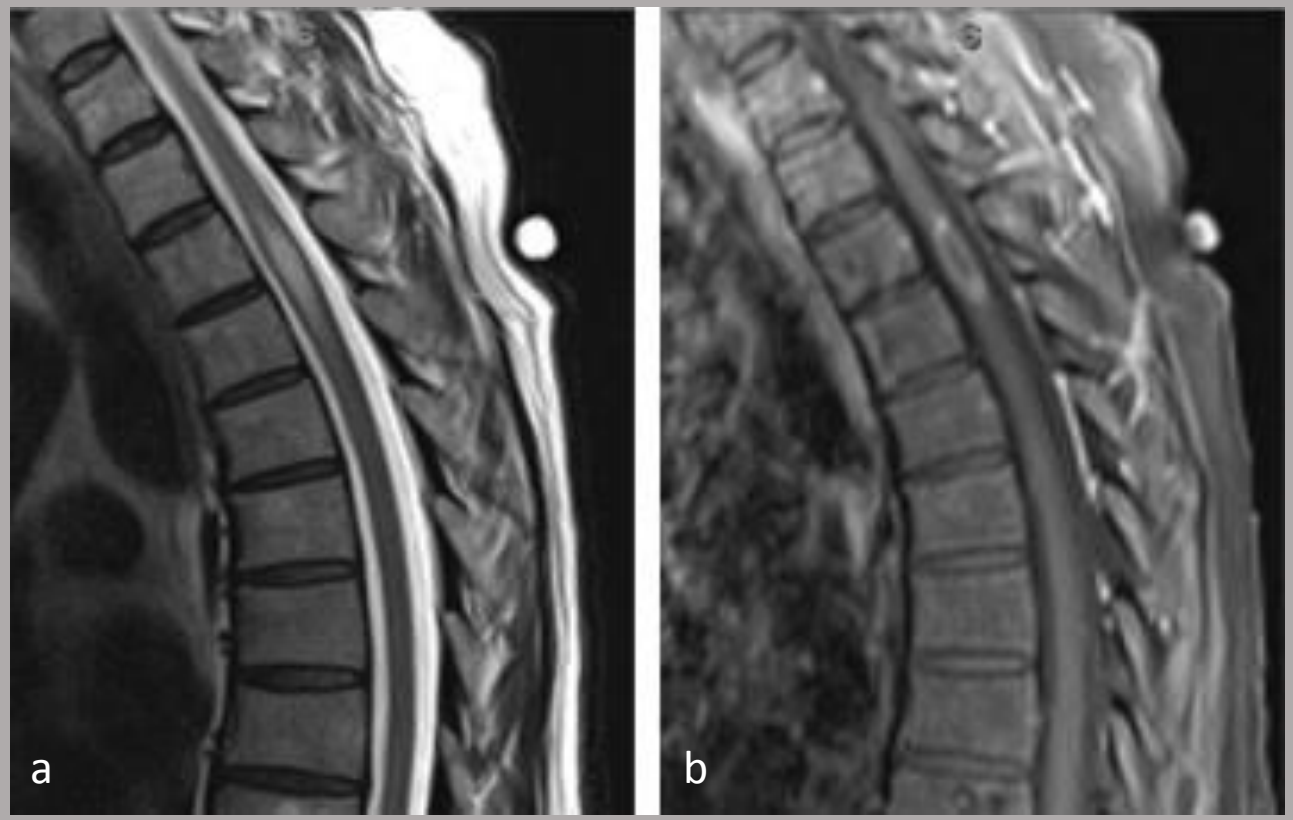


Multiple TFD Lesions

63 yo M, previously healthy, presenting with acute left-sided weakness, and progressively worsening gait, left foot drag, lightheadedness, and dizziness. (Continued from previous slide)

a) T2 image shows the same patient also had a hyperintense lesion in the upper thoracic spinal cord.

b) Post-GAD T1 image with ring enhancement of the same lesion.



MS

- Chronic disease of the CNS with loss of motor and sensory function due to immune-mediated inflammation, demyelination, and axonal damage
- There are recurrent clinical episodes with cumulative neurological injury and deficits that become permanent and irreversible
- Diagnosis made by McDonald criteria that combines clinical, laboratory, and radiologic findings
- Prevalence depends on population and ranges from 15 to 250/100,000 people
- Reported prevalence of TMD in 1-3/1000 cases of MS
- There are four forms classified by different clinical disease courses: 1) relapsing-remitting (RR), 2) secondary-progressive (SP), 3) primary-progressive (PP), and 4) progressive-remitting (PR)
- There are variant types of MS that are considered separate from typical MS that may present with TFD
  - Clinical presentations are atypical of MS
  - Distinct but often overlapping radiologic and pathological findings

TFD in MS

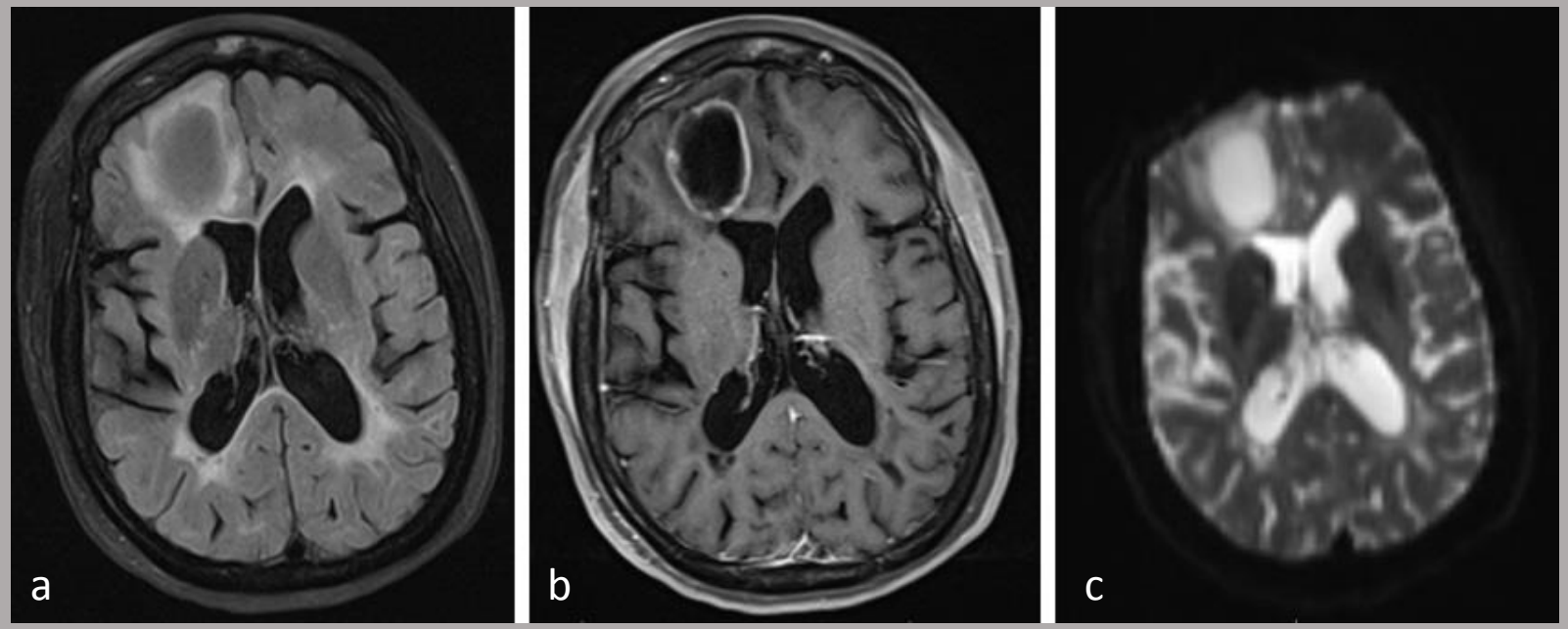
50 yo F with history of progressive MS diagnosed at age 20, presented with seizure without return to baseline mentation.

a) FLAIR image shows large right frontal lesion with hyperintense rim and isointense center.

b) Post-GAD T1 images show incomplete ring-enhancement of the lesion.

c) DW image shows hyperintense signal of the lesion.

Patient proceeded to surgery **(continued on next slide)**.



TFD in MS

50 yo F with history of progressive MS diagnosed at age 20, presented with seizure without return to baseline mentation. (Continued from previous slide)

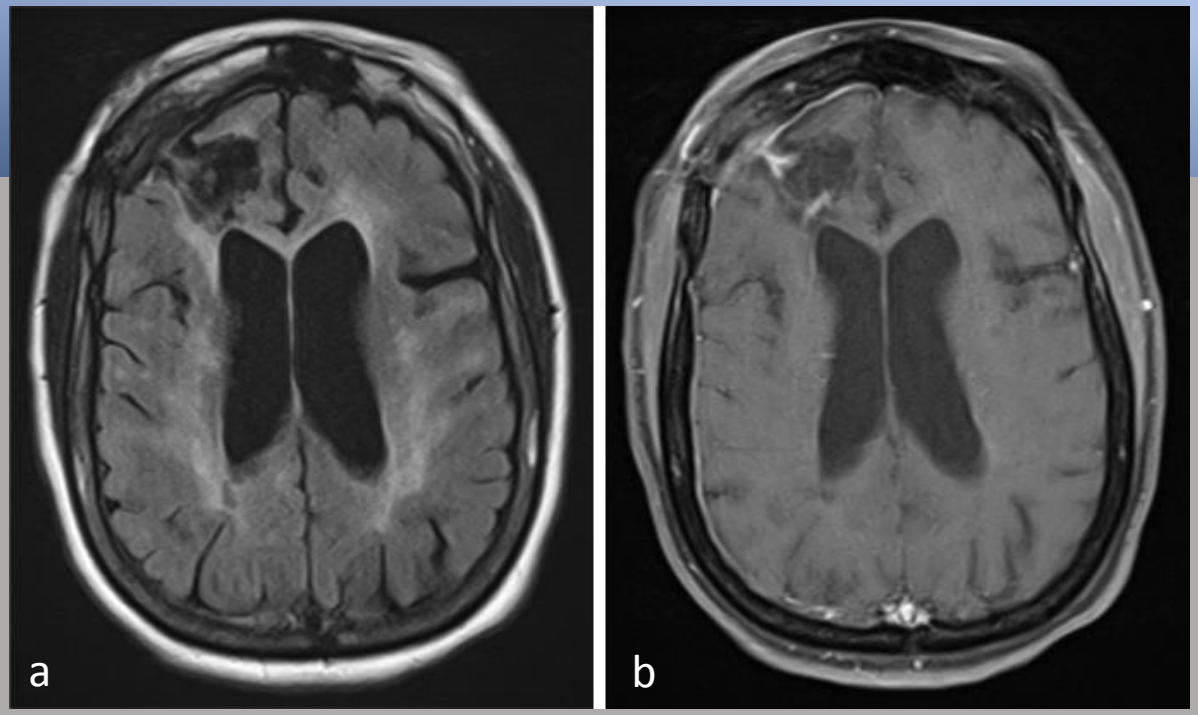
a) FLAIR image shows post-resection changes of the right frontal lesion.

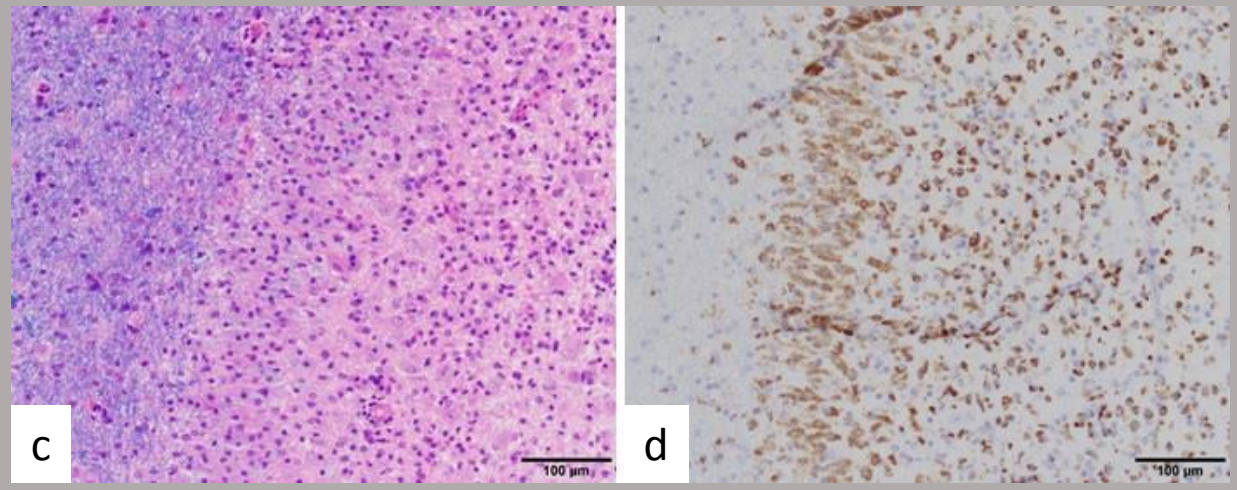
b) Post-GAD T1 image shows some peripheral enhancement of the resection cavity and enhancement of the overlying dura, likely post-surgical changes.

Pathology from the resected tissue shows demyelination.

c) Luxol fast blue/H&E stain shows sharp border between blue myelin and pink demyelination.

d) CD68 immunostain shows macrophages in the area of demyelination.





Rare Tumefactive MS Variants

- Balo's concentric sclerosis
  - First described by Joseph Balo in 1928 and characterized by unique concentric rings of demyelination
  - Lesions tend to spare cortical U-fibers and may be small or occupy large sections of the cerebral hemisphere
  - Concentric ring appearance is due to alternating rings of demyelination and relatively normal myelin
  - Although very suggestive of Balo's, concentric demyelinating rings can also be seen in other diseases
- Myelinoclastic diffuse sclerosis
  - First described in 1912 by Paul Schilder and also called inflammatory diffuse sclerosis and Schilder's disease
  - Characterized by large cerebral hemisphere lesions and development of new, progressively larger lesions
  - More specific diagnostic radiologic criteria state that there must be a single or 2 symmetrically arranged lesions measuring at least 2 x 3 cm with involvement of the centrum semiovale
  - Lack typical oligoclonal bands seen in MS
- Marburg variant
  - First described by Otto Marburg in 1906 with large cerebral hemisphere lesions
  - Fulminant and progressive disease course ending in death between 1 month to 1 year after onset
  - Histologically, the lesions are more destructive than typical MS and patients have different mutations in myelin basic protein (MBP) compared to traditional MS; this is proposed to lead to structural instability of myelin
  - Not well-studied due to rarity, but currently considered a distinct clinical entity from MS due to pathologic differences and different MBP mutations

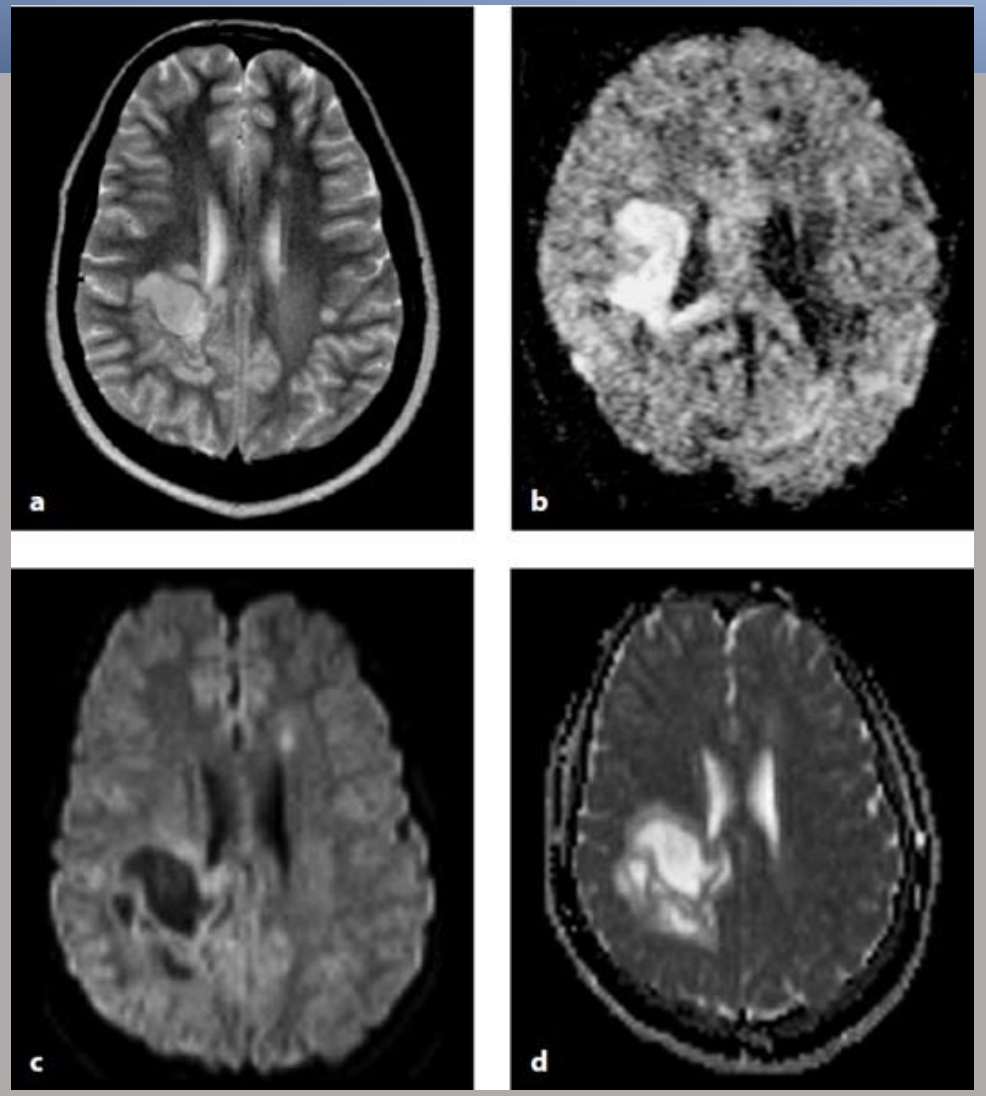
TFD in Balo's Concentric Sclerosis

17 yo F who presented with stroke-like symptoms. Pathologically proven Balo's concentric sclerosis.

a) T2-weighted image shows a large hyperintense mass with a multilayered appearance in the right posterior periventricular and deep white matter.

b) DW image shows the lesions as very hyperintense. ADC map not obtained at this time.

c) and d) A 2-month follow-up DW image shows the lesions as hypointense with increased ADC.



TFD in Myelinoclastic Diffuse Sclerosis

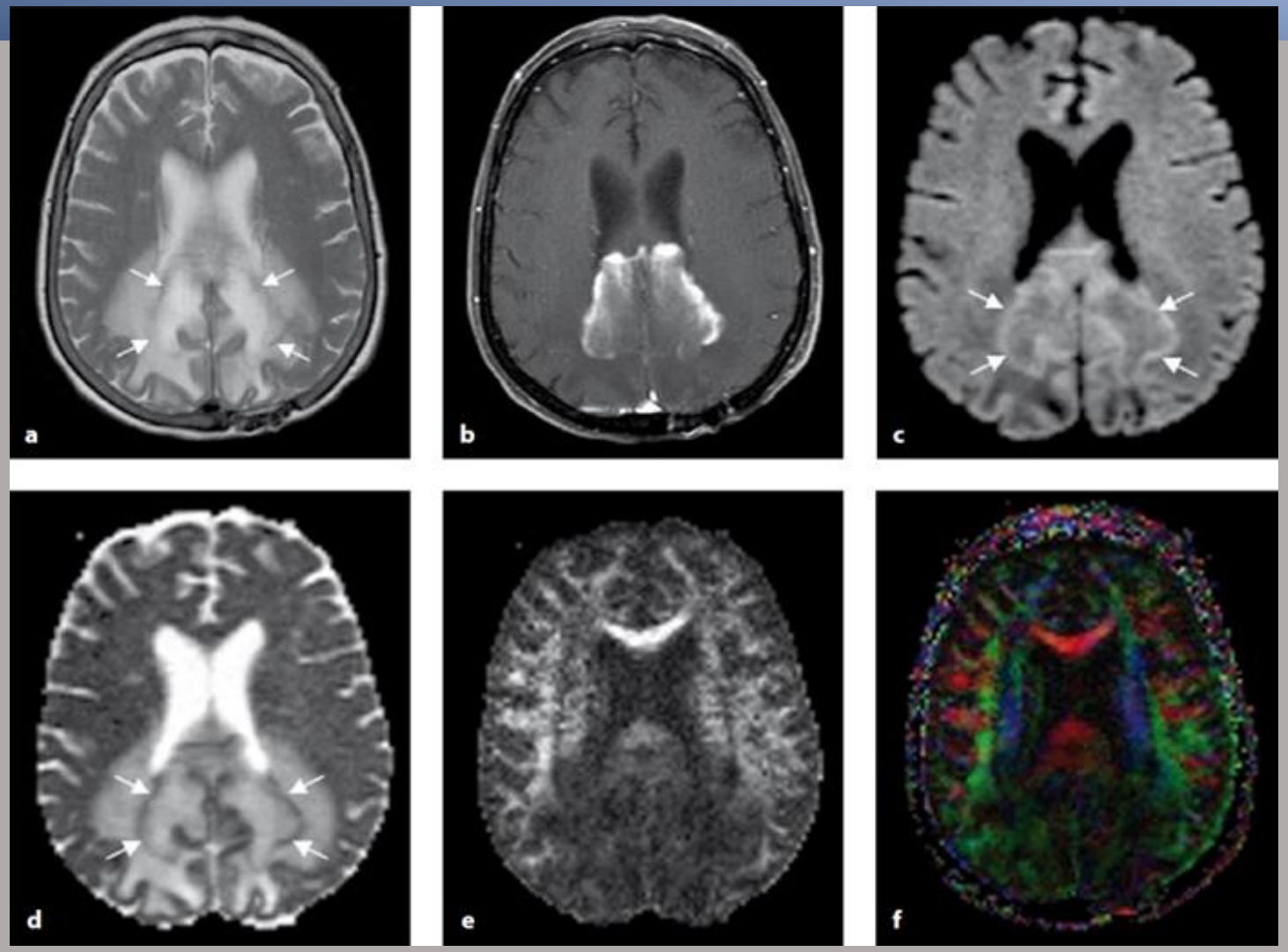
80 yo F with confusion. Pathologically proven myelinoclastic diffuse sclerosis.

a) T2 image shows symmetric large hyperintense lesions with slightly low signal curvilinear areas (arrows) involving the posterior corpus callosum and occipital white matter bilaterally.

b) Post-GAD T1 image shows symmetric irregular enhancement along the curvilinear T2 low signal areas.

c) and d) DW image shows the curvilinear areas as isointense with iso ADC, corresponding to active demyelination (arrows). There is likely surrounding vasogenic edema.

e) and f) FA and color maps show decreased anisotropy in both areas.



NMOSD

- Group of closely related demyelinating diseases (including NMO) caused by autoantibody to aquaporin-4 water channel (AQP4)
- Classic presentation of NMO:
  - Optic neuritis
  - Transverse myelitis (extending ≥ 3 vertebral bodies)
  - Anti-AQP4 antibody positive
- Additionally, brain lesions are common and seen in 85-89% of cases
- Brain lesions often involve the subcortical deep white matter, corticospinal tracts, dorsal brainstem, thalamus/hypothalamus, periventricular, and callosal regions
- TFD is uncommon, but present in 29% of cases

TFD in NMO

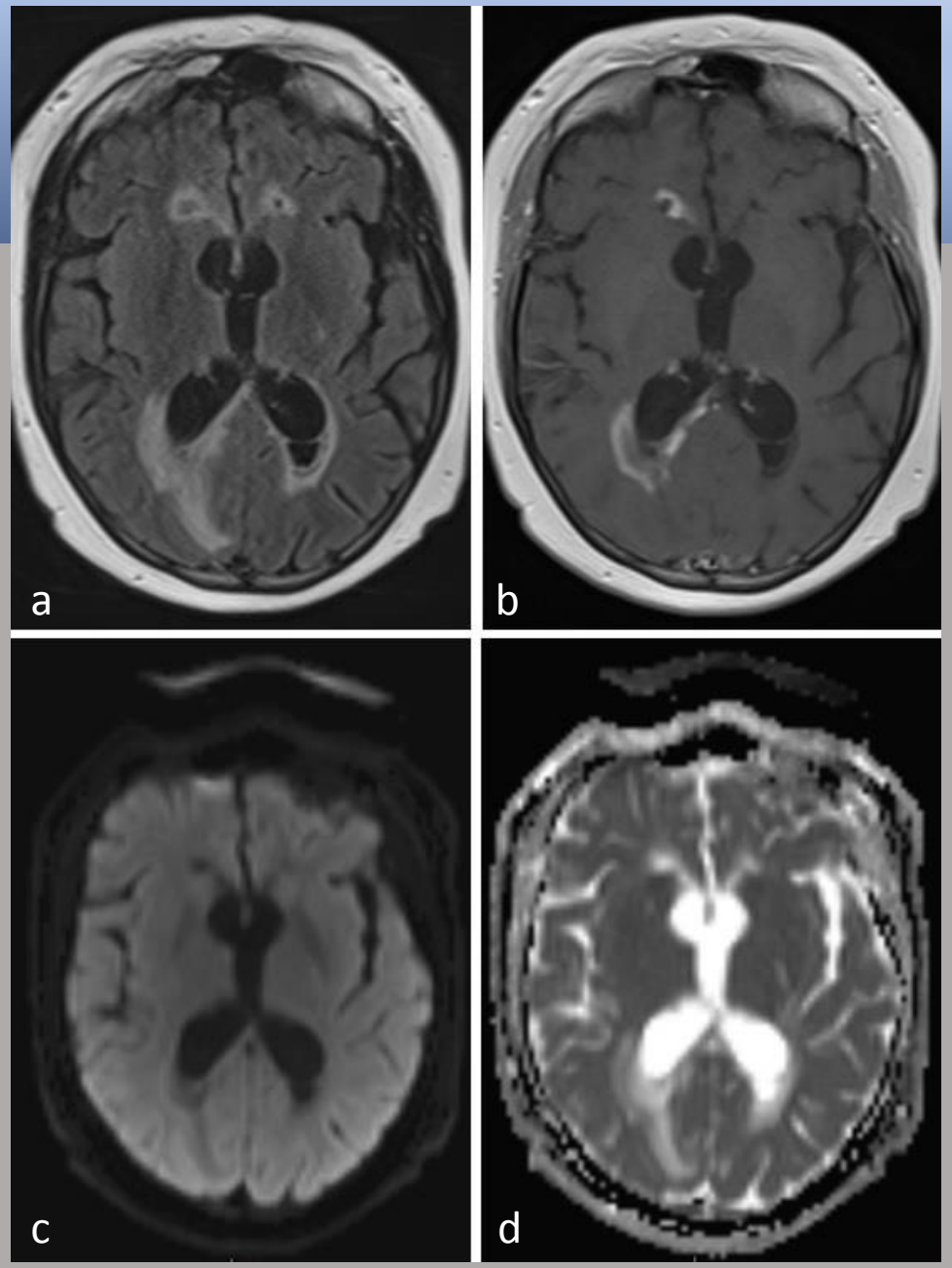
35 yo F, diagnosed with NMO at 7 years of age and paraplegic, presenting with increased sleepiness and decreased alertness as well as less ability to move and assist with transfers.

a) FLAIR image shows multiple hyperintense lesions in the periventricular regions, worse along the occipital horn of the right lateral ventricle. There is also hydrocephalus that required ventriculostomy placement.

b) Post-GAD T1 image shows incomplete peripheral enhancement of the right-sided lesions.

c) and d) DW images shows hypointense signal of the larger periventricular lesions with increased ADC.

Biopsy showed demyelination **(continued on next slide)**.



TFD in NMO

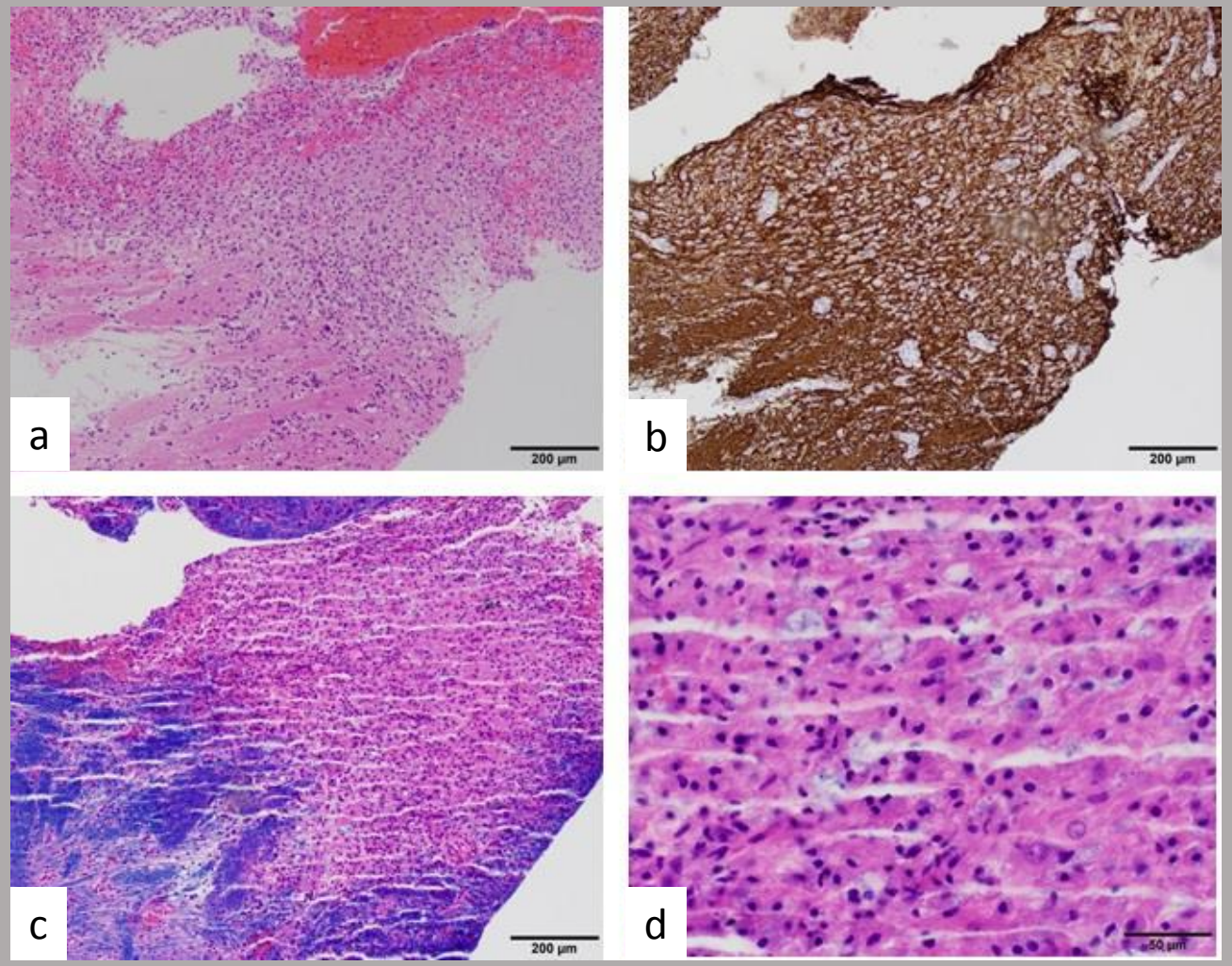
35 yo F, diagnosed with NMO at 7 years of age and paraplegic, presenting with increased sleepiness and decreased alertness as well as less ability to move and assist with transfers. (Continued from previous slide)

a) Sheets of macrophages in the area of demyelination in the top right with preserved white matter in the bottom left (H&E).

b) Neurofilament stain shows relative preservation of axons throughout both areas.

c) Luxol fast blue/H&E shows white matter with axons highlighted blue in the bottom left and the area of demyelination with loss of myelin in the top right.

d) Higher power of LFB/H&E stain shows macrophages with ingested myelin (blue) in their cytoplasm.



ADEM Spectrum

- ADEM: Immune-mediated inflammatory demyelinating disorder, usually triggered by viral infections or vaccinations
  - Multifocal, but monophasic, without the reoccurrences seen in MS
  - Demyelinating lesions almost always occur in the subcortical white matter, but are also seen in the brain stem, spinal cord, thalami, and basal ganglia
  - Most commonly occurs in the pediatric population
- Acute hemorrhagic leukoencephalitis (AHL): Hyperacute form of the maximum variant of ADEM that is acute and rapidly progressive, usually triggered by upper respiratory infections
  - Since there are large white matter lesions with surrounding edema, TFD is often seen
  - There is also acute vasculitis with vessel occlusion that causes hemorrhage
  - Death from brain edema is common and patients must be treated aggressively

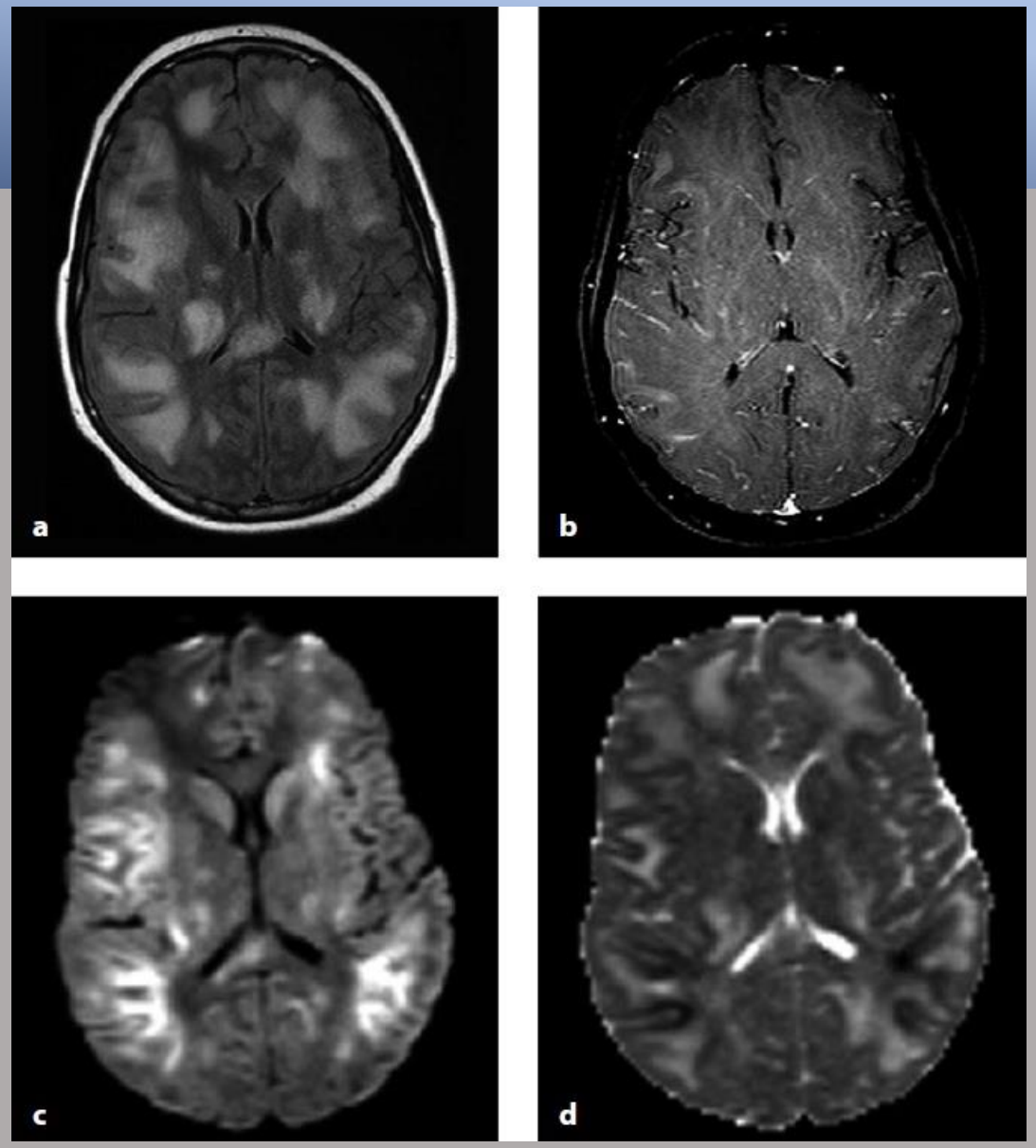
TFD in ADEM

11 yo M presenting with altered mental status. Pathologically proven ADEM.

a) FLAIR image shows multiple ill-defined, hyperintense lesions in the white matter, corpus callosum, basal ganglia, and thalami.

b) Post-GAD T1 image shows mild enhancement in the subcortical white matter lesions.

c) and d) DW image shows multiple hyperintense lesions with increased ADC and partially decreased ADC in the peripheral area of the lesions, likely representing a combination of vasogenic cytotoxic edema with demyelination.



TFD in AHL

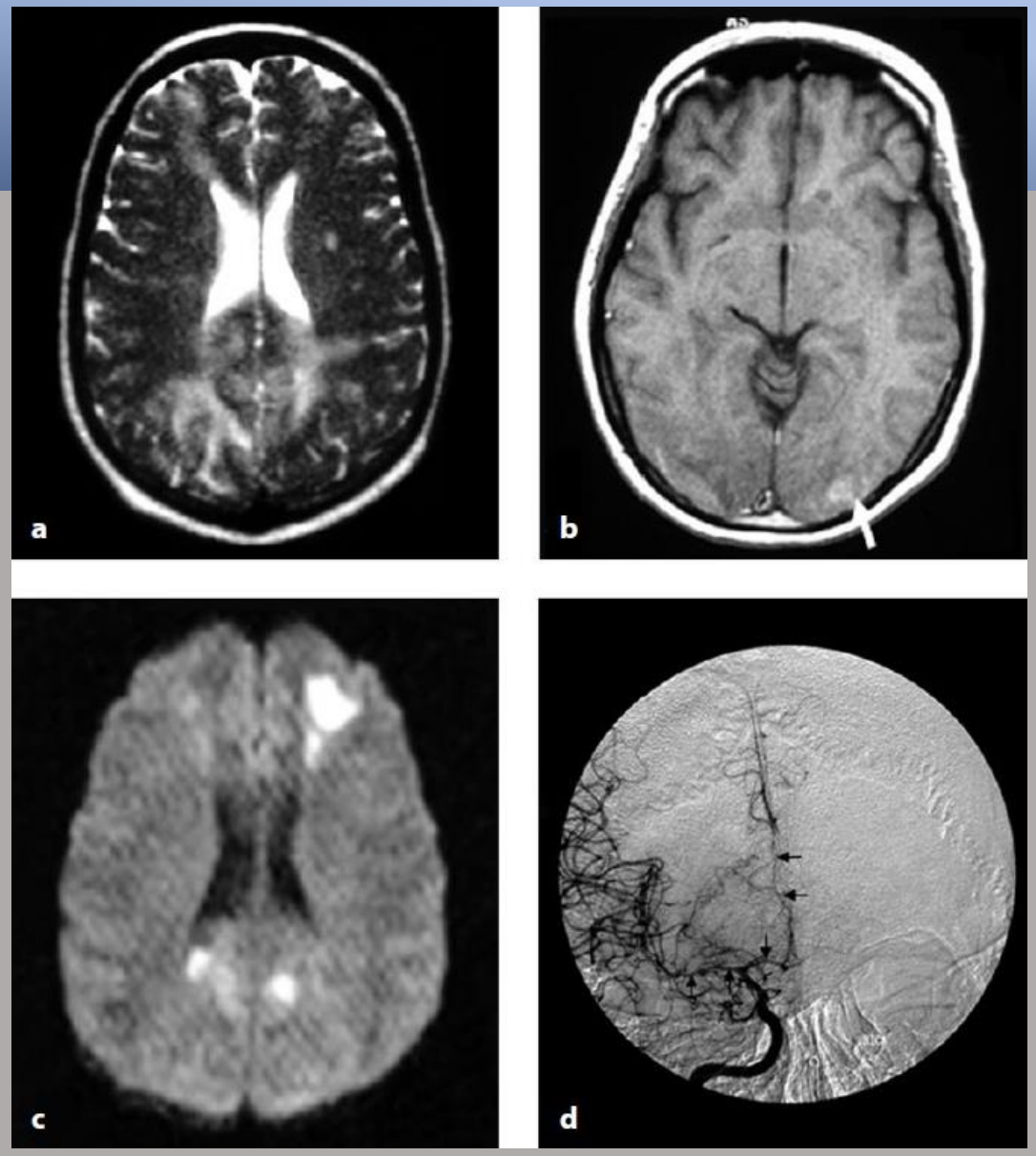
48 yo F presenting with altered mental status. Patient died within a week of presentation. Pathologically proven AHL.

a) T2 image shows multiple hyperintense lesions in the anterior and posterior white matter bilaterally.

b) T1 image shows hyperintense area in the left occipital lobe consistent with intracerebral hemorrhage (arrow).

c) DW image shows the lesions as mildly low or isosignal areas with multiple very hyperintense foci consistent with a combination of vasogenic and cytotoxic edema.

d) DSA shows multiple stenosis in the anterior and middle cerebral arteries (arrows).



Autoimmune Encephalitis

- Large group of neurological diseases associated with systemic and CNS autoimmune disorders and paraneoplastic syndromes
- Immunopathogenesis of these diseases is modulated by autoantibodies to CNS proteins
- Although rare, anti-MOG (myelin oligodendrocyte glycoprotein), anti-NMDA, and anti-Ma2 related encephalitis have been reported to show demyelinating lesions
- Anti-MOG antibodies are seen in subsets of patients with NMOSD and also patients suspected to have NMOSD but who are seronegative for anti-AQP4 antibody
  - Patients who are anti-MOG antibody positive often have a different disease course and are demographically different from the typical NMOSD population
  - Further research is required to more clearly define this association
- Anti-Ma2 encephalitis: Paraneoplastic syndrome with antibodies against the Ma2 protein that is widely distributed in normal brain parenchyma
  - Known association with testicular cancer

TFD in Anti-Ma2 Encephalitis from Nonseminomatous Germ Cell Tumor

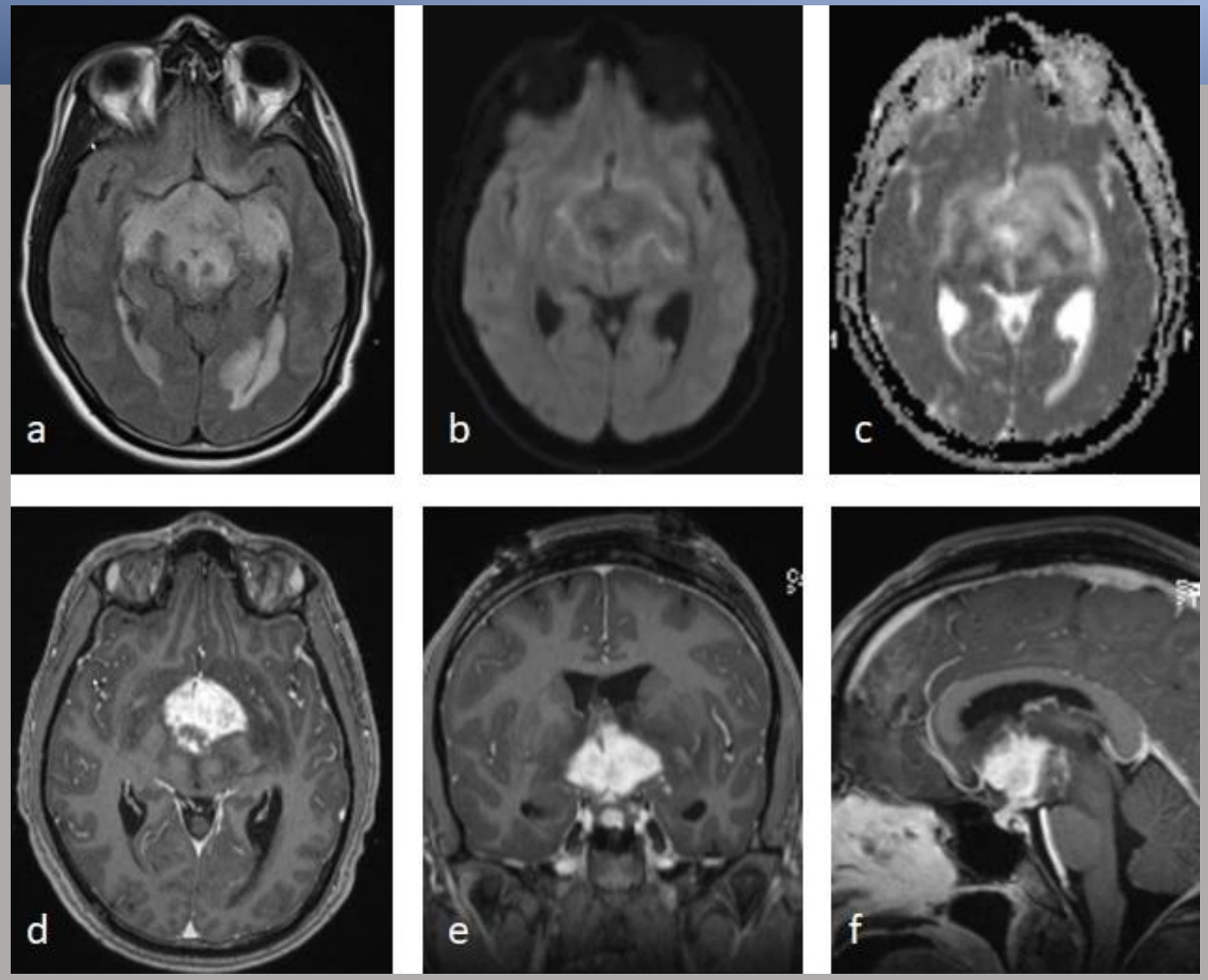
30 yo M presenting with altered mental status, incontinence and history of headaches. Patient had a testicular mass.

a) FLAIR image shows extensive edema extending from the suprasellar region to the temporal lobes and insula bilaterally.

b) and c) DW images show restricted diffusion along the periphery.

d), e), and f) Post-GAD T1 images show the avid enhancement in the suprasellar region.

Testicular mass was nonseminomatous germ cell tumor. Brain biopsy showed demyelination **(continued on next slide)**.



TFD in Anti-Ma2 Encephalitis from Nonseminomatous Germ Cell Tumor

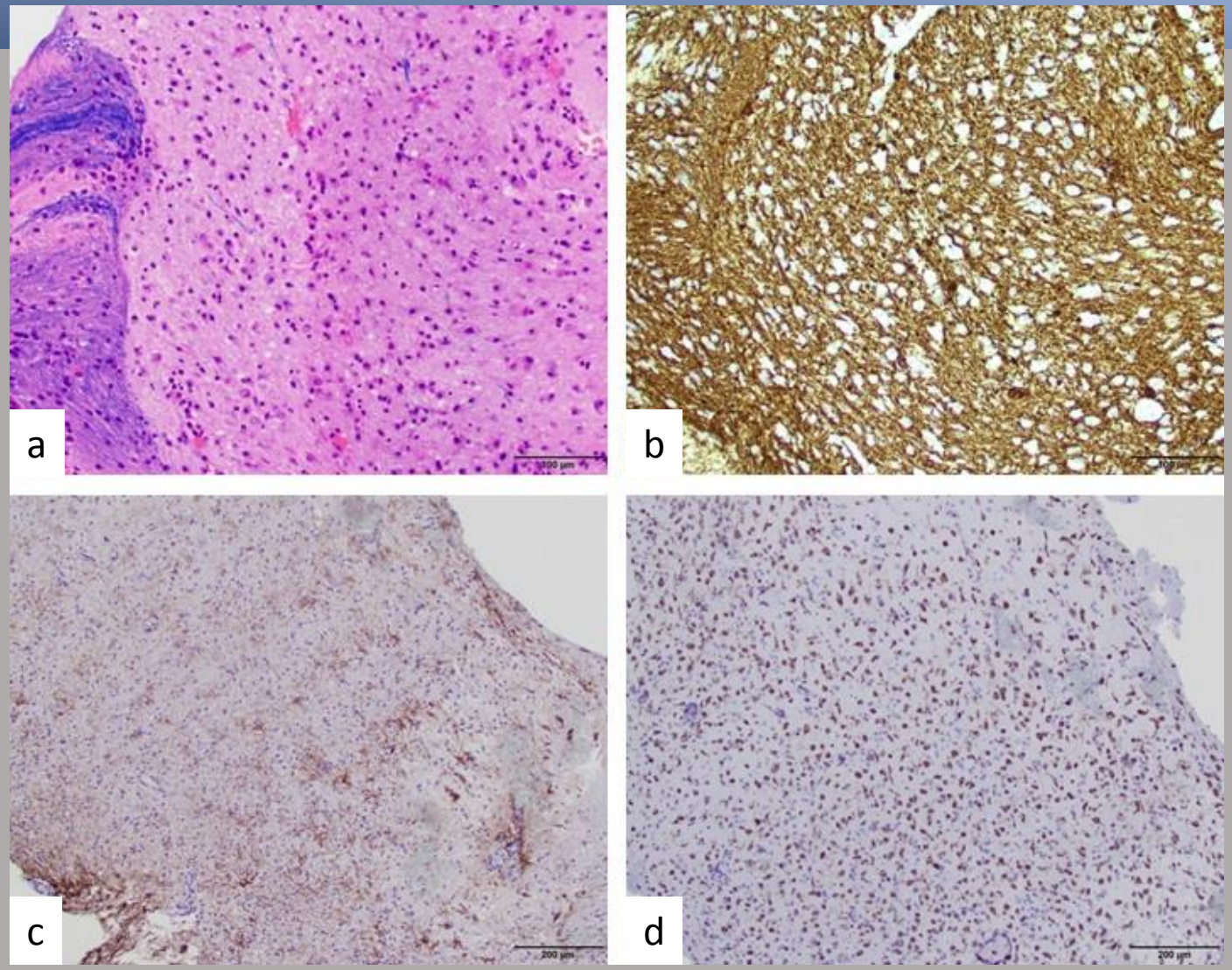
30 yo M presenting with altered mental status, incontinence and history of headaches. Patient had a testicular mass. (Continued from previous slide)

a) Sharp demarcation between area of demyelination and adjacent normal white matter tract with intact myelin highlighted blue (Luxol fast blue/H&E).

b) Neurofilament stain confirms relative axonal preservation in the area of demyelination.

c) GFAP stain highlights reactive astrocytes in the background of the demyelinative lesion.

d) CD68 stain shows the sheets of macrophages in the area of demyelination.



MRS, Perfusion, and FDG-PET

- Using myoinositol levels, Cho/NAA ratio, and lipid/lactate peaks, MRS can be used to exclude other differential diagnoses for cerebral lesions that may potentially represent TFD
  - However, TFD lesions can often mimic MRS findings seen in neoplasms
- Cerebral perfusion studies show TFD lesions have less perfusion than that seen for tumors
  - However, there is some overlap as differing tumor types also have differing amounts of perfusion
- There is very limited data for the usage of FDG-PET, but one study showed glucose metabolism in TFD lesions was increased compared to normal brain parenchyma, but not as increased as most cerebral tumors

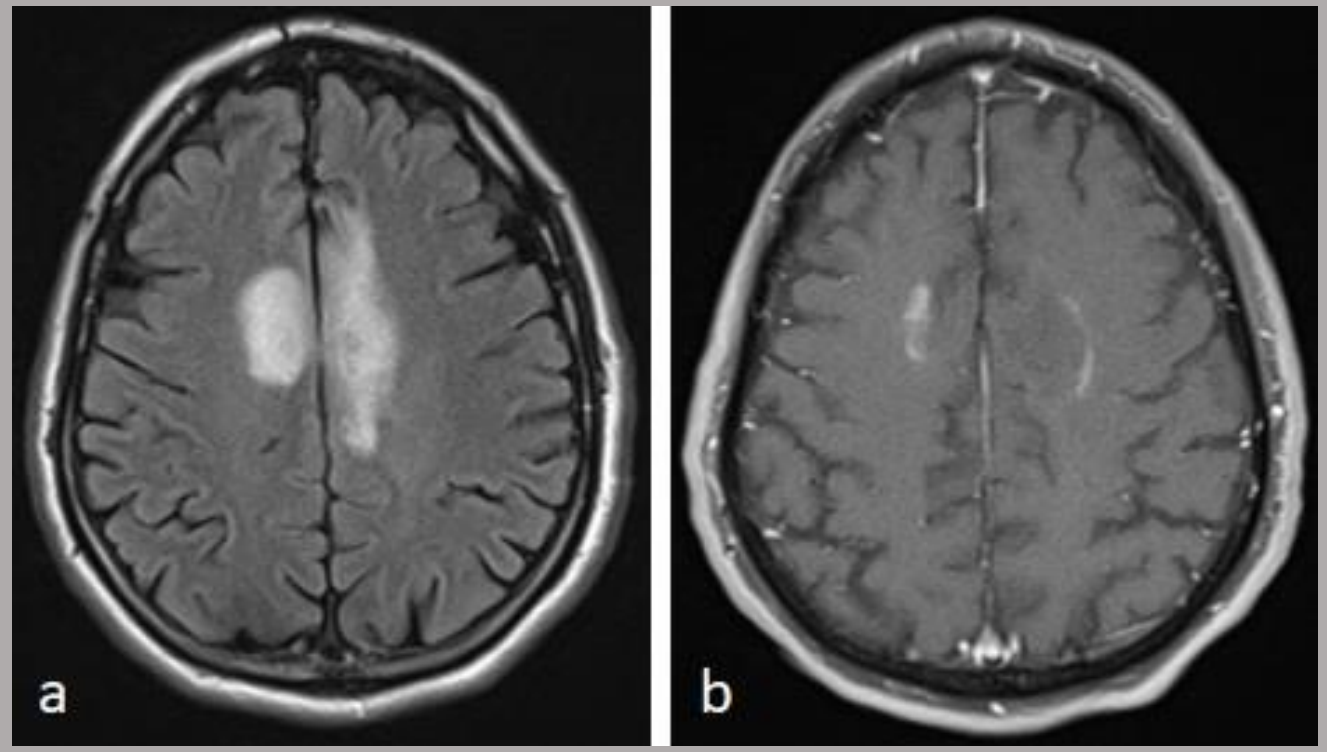
Usage of MRS in Diagnosis of TFD

68 yo M with progressive confusion, dysarthria, and right-sided weakness.

a) FLAIR image shows hyperintense lesion in the corpus callosum and cingulate gyrus.

b) Post-GAD T1 image with the lesion demonstrates incomplete peripheral enhancement.

Differential included lymphoma or glial neoplasm versus tumefactive demyelination. **MRS was used in this case (continued on next slide).**



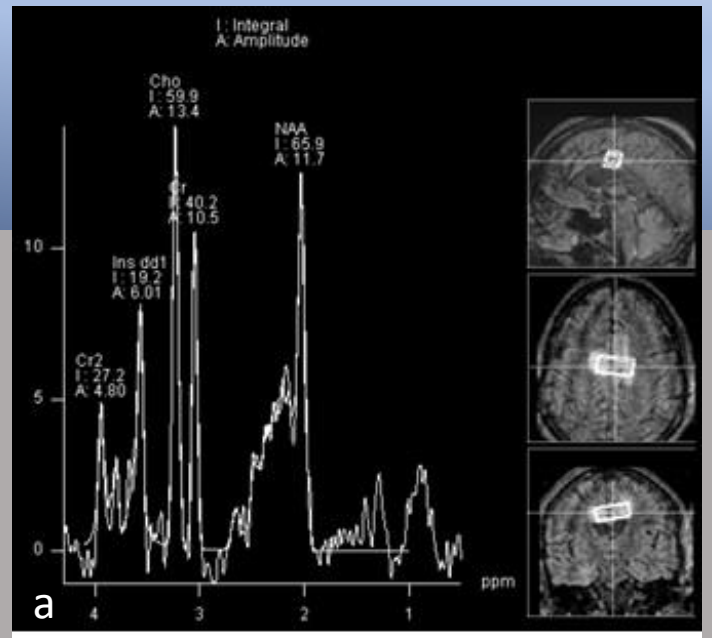
Usage of MRS in Diagnosis of TFD

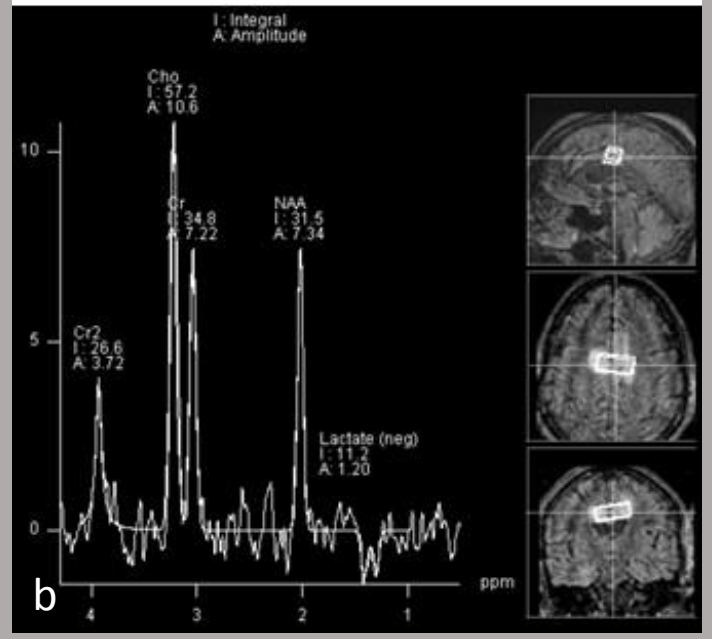
68 yo M with progressive confusion, dysarthria, and right-sided weakness. (Continued from previous slide).

Differential included lymphoma or glial neoplasm versus tumefactive demyelination.

a) and b) MR spectroscopy excludes both lymphoma (observed myoinositol level) and glial neoplasm (measured Cho/NAA ratio < 2.1). Pathologic lipid/lactate peaks support active disease process.

Overall, findings were most consistent with TFD lesion.





Differential Diagnosis

- CNS tumors
  - High-grade gliomas
  - CNS lymphoma
- Various infections
- Progressive multifocal leukoencephalopathy (PML)
- PML-related immune reconstitution inflammatory syndrome (IRIS)
- Neurosarcoidosis
- Immune-mediated encephalitides

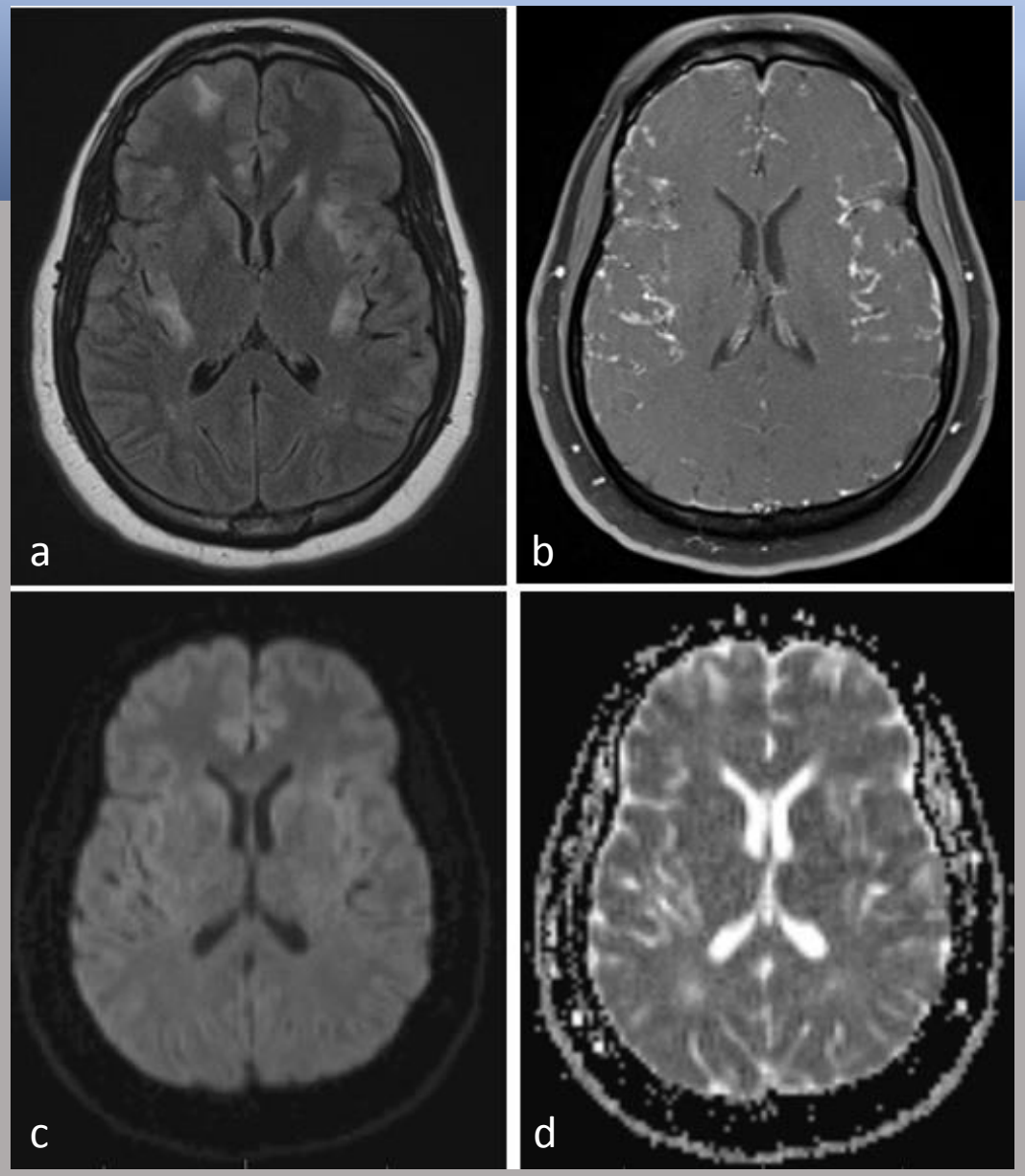
DDx: Neurosarcoidosis

32 yo M with 9 month history of enlarging skin papules. Skin punch biopsy showed non-caseating granulomatous inflammation consistent with sarcoidosis. Presented with confusion and agitation.

a) FLAIR image shows subcortical hyperintense FLAIR signal abnormalities in the bilateral frontal, parietal, and temporal lobes.

b) Post-GAD T1 image shows diffuse leptomeningeal enhancement, typical of neurosarcoidosis and not seen in the TFD.

c) and d) No significant abnormalities on DWI and ADC.



DDx: PML

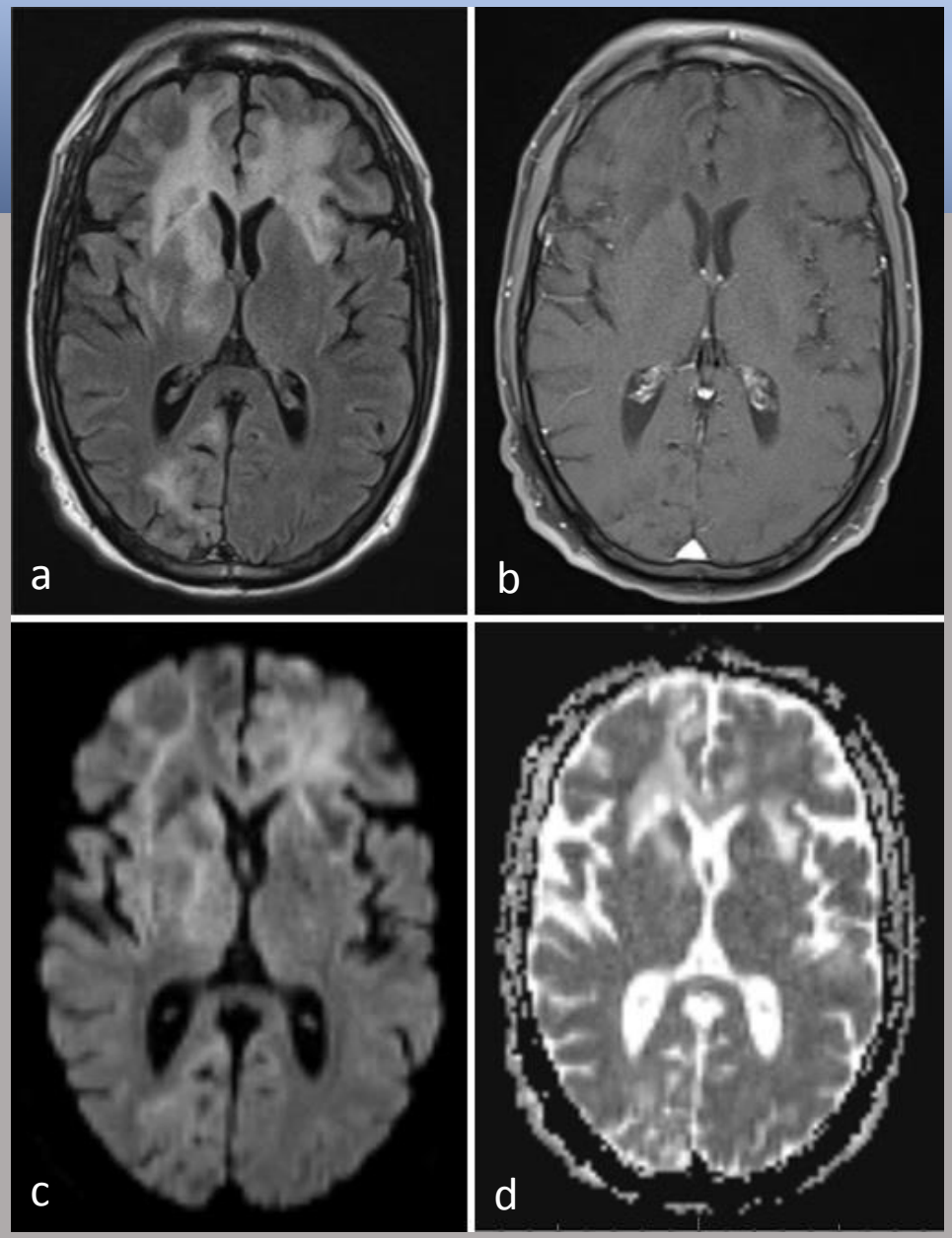
40 yo M diagnosed with AIDS (CD4 count 15, viral load 157,000) and positive JC virus in CSF 2 months prior to presentation with altered mental status and left-sided homonymous hemianopsia.

a) FLAIR image shows multiple areas of hyperintense signal abnormality in the subcortical white matter, most noticeably the confluent region that crosses the midline in the frontal lobes.

b) The lesions do not show any significant enhancement on post-GAD T1 images, which is usually seen in TFD.

c) and d) DWI and ADC show that the lesions have regions of peripheral and central diffusion restriction.

PML should be considered in patients with HIV/AIDS and tests performed for JC virus in the CSF.



DDx: Diffuse Large B-Cell Lymphoma (DLBCL)

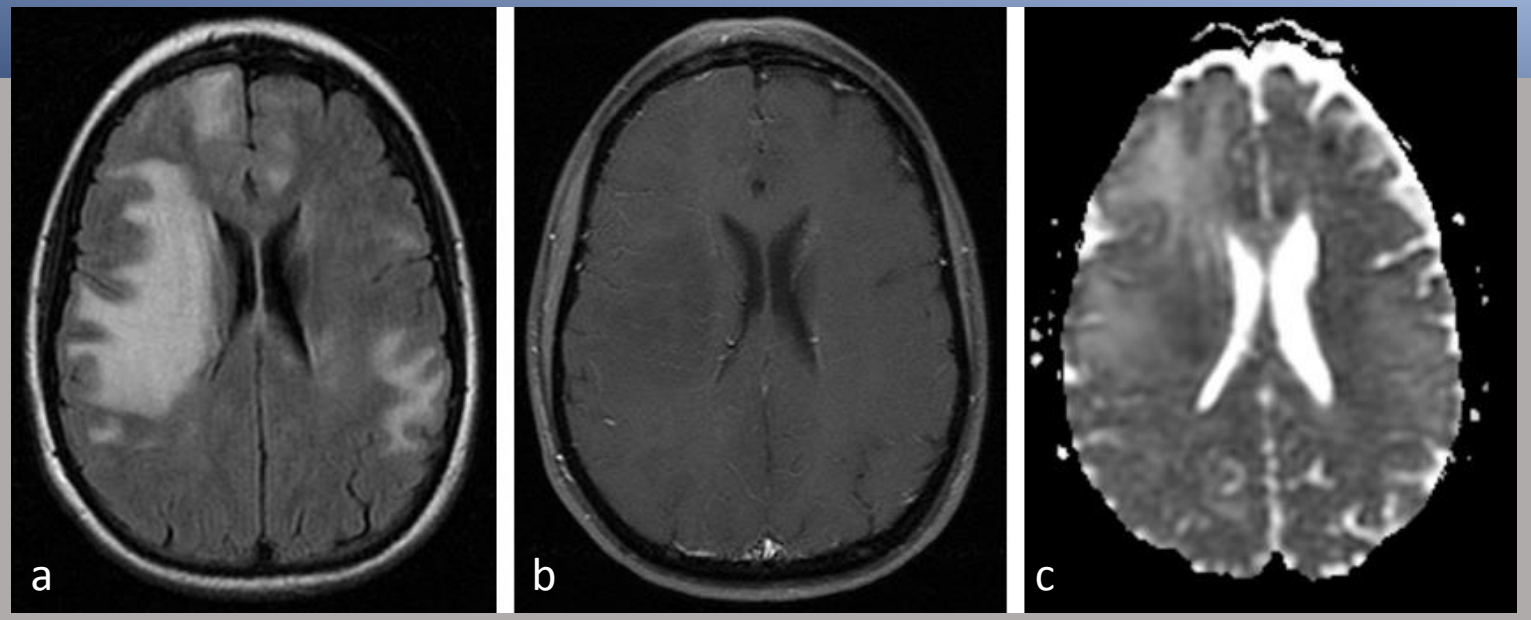
55 yo M with months of progressive memory, gait disturbance, insomnia, left-sided face and arm weakness. Pathologically proven DLBCL.

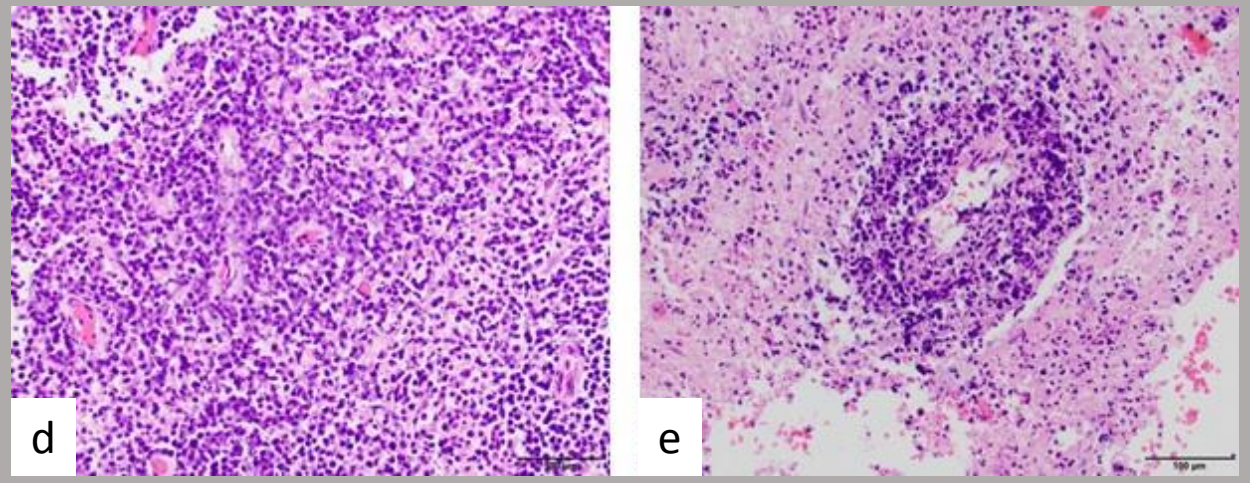
a) FLAIR image shows multiple regions of hyperintense signal abnormality in the subcortical white matter, most prominent in the right frontoparietal lobe.

b) The lesions do not show any significant enhancement on post-GAD T1 images, which is usually seen in TFD.

c) DW images show hyperintense signal.

d) H&E stains show neoplastic large B-cells infiltrating brain, often with an angiocentric pattern as seen in **e)**.





Management

- Lumbar puncture and CSF studies can be a first step to exclude infection and malignancy
- Consider biopsy if there is high suspicion for malignancy, especially if there is concern for lymphoma, as this tumor can also show response to high dose steroids
- Patients will require supportive care if hospitalized, and sometimes even require ICU admission
- In severe cases with large amounts of mass effect and edema, primary teams will have to aggressively manage increased intracranial pressure
- High dose intravenous corticosteroids are first line treatment for acute symptomatic TFD
- Follow-up MRI should be obtained approximately 4-6 weeks or sooner if symptoms worsen
- Treat any underlying demyelinating disease with disease modifying agents and patients should continue outpatient neurology follow-up
- If corticosteroids are ineffective, consider plasma exchange therapy
- Certain immunomodulatory agents can also be used for acute episodes of demyelination if previous interventions were ineffective

Response to Steroids

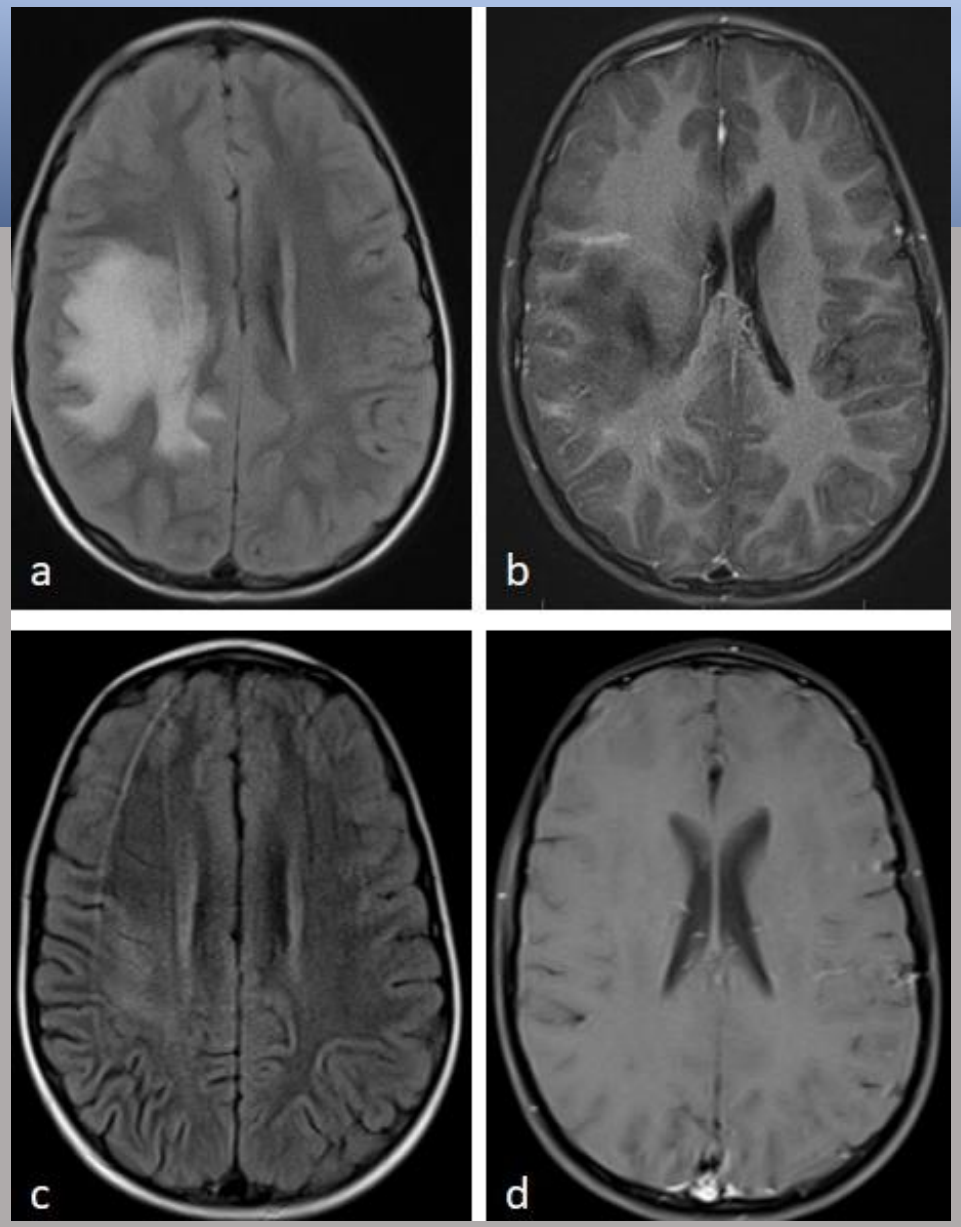
8 yo M with 1 day of left-sided weakness and 1 week of headaches. This patient showed a good response to steroid treatments, seen in most cases of TFD.

a) FLAIR image shows large hyperintense lesion in the right frontoparietal lobe.

b) Post-contrast T1-image shows incomplete peripheral enhancement of the lesion.

c) 5 week follow-up MRI shows significantly decreased FLAIR signal abnormality in the right frontoparietal lobe after treatment with IV steroids.

d) Post-GAD T1 image on follow-up exam after treatment shows no areas of abnormal enhancement.



Conclusion, Considerations, and Future Work

- TFD is an uncommon but important manifestation of multiple neurological diseases that can be difficult to diagnose accurately
- Even if the exact disease cannot be diagnosed on imaging, identifying that the abnormality may represent demyelination rather than malignancy or infection is critical in guiding further work-up and treatment
- Misdiagnosis may lead to delay in proper treatment as well as treatment modalities such as brain biopsy, resection, or brain irradiation that could exacerbate the demyelination process
- There is clinical overlap between many of the CNS disorders that cause TFD and the differences in symptomology, disease course, and radiological findings in these disorders are often subtle
- This raises the question of whether certain disorders are truly distinct entities or simply representing the expected phenotypic variance of presentation for the same underlying disease process
- Continued research into these demyelinating diseases to understand their immunopathogenesis on a molecular level will help to more clearly define variants vs. distinct entities
- Classification of these disorders may change, either by more clearly defining distinct variants or consolidating multiple entities into a spectrum of the same disease
- As our understanding in this field evolves, the terminology and definition of TFD may also change

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