# NEUROPATHOLOGY V - DISEASES OF MYELIN

**Mahlon Johnson, MD, PhD and Christopher Tarolli, MD**

Myelin sheaths in the central nervous system myelin are formed by **oligodendrocytes**, which myelinate long internodes of multiple axons. While there are a number of pathological processes that can affect the oligodendrocytes, there are essentially only two pathological reactions of oligodendrocytes: neoplasia and cell death. The pathology of oligodendroglial neoplasms (**oligodendrogliomas**) will be discussed in the Neoplasms TBL, and here we will focus exclusively on processes that result in oligodendrogial cell destruction and the resultant impaired myelination. This may occur in the form of **demyelination**, characterized by normal myelin formation and a subsequent infectious, inflammatory, or metabolic destruction, or **dysmyelination**, characterized by abnormal myelin formation with resultant premature cell death.

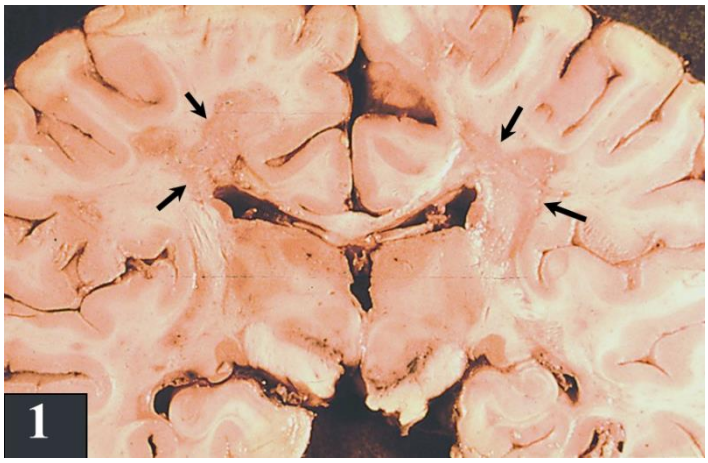
## ACQUIRED INFLAMMATORY DEMYELINATING CONDITIONS:

### *Multiple Sclerosis*

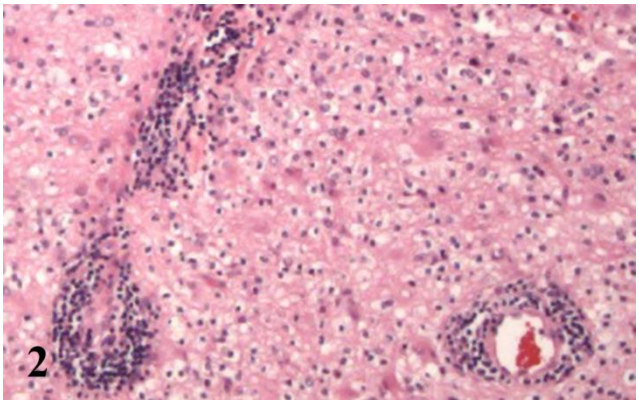
Multiple sclerosis (MS) is the classic acquired demyelinating condition, and is characterized by episodes focal demyelination within the central nervous system. Here, we will focus on the underlying pathophysiology and pathological findings. For further review of the clinical presentation, epidemiology, and possible etiologic factors, review the lecture syllabus on Disorders of Myelin.

MS is generally considered a T-cell mediated autoimmune disease, characterized by the inflammatory destruction of oligodendrocytes. While no specific CNS-directed auto-antibodies have been consistently identified in patients with MS, patients with a history of demyelination frequently have elevated levels of IgG in their CSF, termed **oligoclonal bands**. Regions of demyelination in MS tend to be **sharply defined**, and while any CNS myelin can theoretically be impacted by the inflammatory process in MS, the areas most commonly affected tend to be:

- Optic nerve [optic neuritis]
- Periventricular (including in the brainstem)
- Juxtacortical (next to the cortex)
- Spinal cord [transverse myelitis]The name multiple sclerosis comes from the gross pathological findings of chronic MS lesions, termed "**MS plaques**." **Figure 1** demonstrates the multifocal areas of hardened (sclerotic) and sunken white matter (**Figure 1**). Note the predilection for the periventricular region.

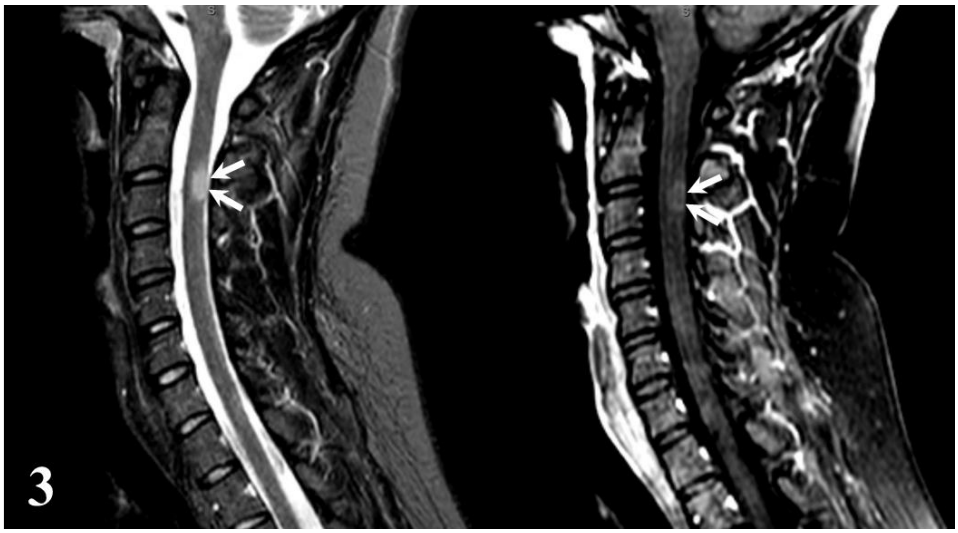


Histopathologically, MS plaques vary based on their age. Areas of acute inflammation, termed **active plaques**, are characterized by a **hyper-cellular, perivascular inflammatory infiltrate** composed of primarily T-lymphocytes and macrophages (**Figure 2**). Macrophages within this inflammatory infiltrate are primarily present to clear the destroyed cellular debris, and if stained with Luxol fast blue (myelin stain), may demonstrate intracellular phagocytosed myelin.




Chronic MS lesions, termed **inactive plaques**, are hypocellular and demonstrate astrogliosis with a loss of oligodendrocytes/myelin. Classically, the demyelinated axons are intact in a chronic MS plaque, though axon loss is possible.

Biopsy of MS lesions is extremely uncommon today given the invasiveness of the procedure and the presence of highly reliable neuro-radiologic correlates of the pathological changes described above. Imaging in MS primarily relies on the use of MRI. Active plaques are characterized by local inflammation with an associated breakdown of the blood-brain barrier. Administration of IV contrast takes advantage of this breakdown, with **acute MS lesions demonstrating contrast enhancement**, as well as **hyperintensity on T2-weighted MRI**. **Figure 3** demonstrates a characteristic acute MS lesion in the cervical spinal cord; the left panel is a T2-weighted image demonstrating a small, well-circumscribed hyperintensity around the C3 level (**white arrows**), and the right panel is a T1-weighted image with contrast demonstrating contrast enhancement in the same region (**white arrows**). As the inflammatory process subsides, the contrast enhancement resolves, but **T2 hyperintensities remain**. Patients with longstanding MS may additionally develop T1-hypointensities (**black holes**) in regions of chronic plaques, corresponding to underlying axon loss.



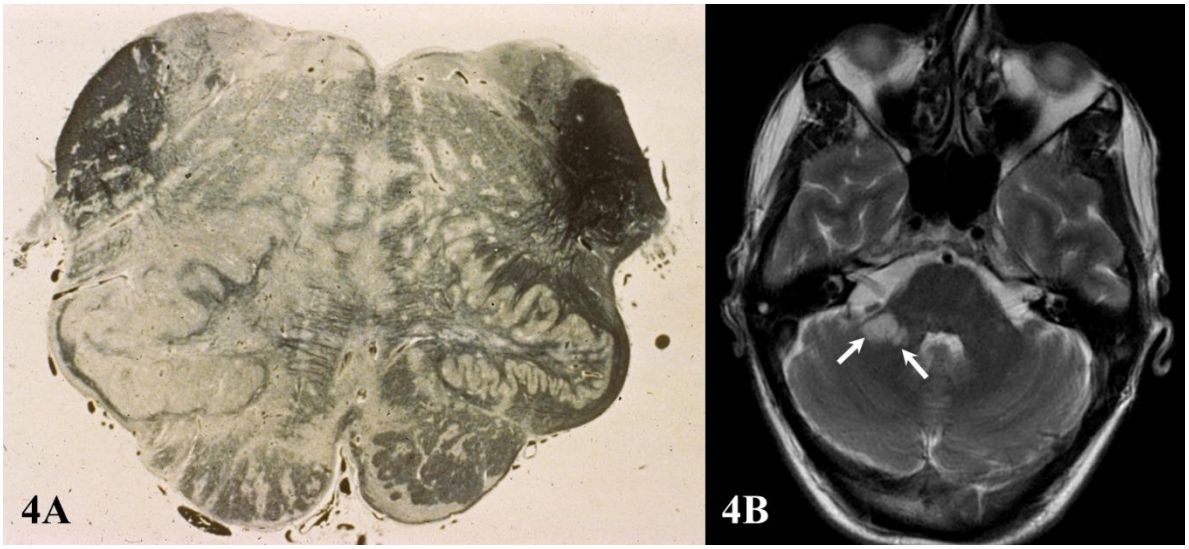
*Neuromyelitis Optica Spectrum Disorder*

**Neuromyelitis optica spectrum disorder (NMOSD)**, formerly termed **Dévic disease**, is a less common but frequently more progressive inflammatory demyelinating disorder. As the name implies, the most common areas to be involved in inflammatory demyelinating attacks are the spinal cord (myelitis) and optic nerve. Unlike in MS, attacks in NMOSD tend to more fulminant, frequently with **long-segment (>3 spinal levels) transverse myelitis** or **bilateral optic neuritis**. Beyond these areas, other common regions of demyelination in NMOSD include the brainstem (particularly around the 4$^{th}$ ventricle), while the cerebral hemispheres tend to be relatively spared.

The majority of patients with NMOSD will have an identifiable antibody to a cell membrane water channel known as Aquaporin 4 (**anti-Aquaporin 4 IgG**). These water channels are known to be present on astrocytic foot processes, and the immune attack can result in breakdown of the blood brain barrier with a resultant inflammatory response in the affected area. Similar to MS, acute lesions will demonstrate contrast enhancement and T2-hyperintensities on MRI.

*Acute Disseminated Encephalomyelitis*

**Acute disseminated encephalomyelitis (ADEM)** is a multifocal inflammatory disease of the CNS possibly due to a T cell-mediated hypersensitivity reaction. The CNS changes are usually preceded by systemic viral infection or, more rarely, vaccination, with a latent period of a few days to weeks. Pathologically, ADEM is characterized by an **inflammatory infiltrate surrounding small veins and venules**. ADEM can affect any portion of the CNS, and unlike MS, ADEM tends to be a **monophasic illness with diffuse CNS demyelination**. **Figure 4A** demonstrates demyelination in a myelin-stained section through the lower brainstem; note the **"moth-eaten" appearance** with patchy but diffuse demyelination. **Figure 4B** demonstrates a T2 hyperintensity in the right middle cerebellar peduncle. Note that the lesion has a "fluffy" or cloud-like appearance without well-circumscribed edges. Acute lesions in ADEM may or may demonstrate contrast enhancement.

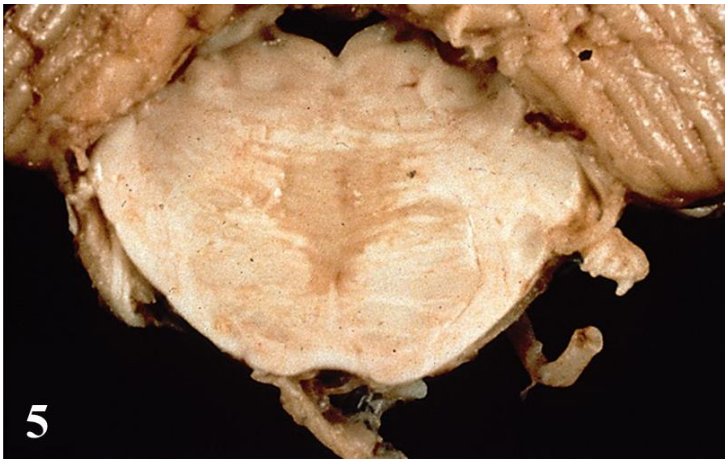


***Subacute Combined Degeneration ($B_{12}$ Deficiency)***
Vitamin $B_{12}$ deficiency can result in symmetric demyelinating degeneration of the spinal cord, termed **subacute combined degeneration**. This disorder and its associated pathology is described in the syllabus on toxic and metabolic disorders.

***Progressive Multifocal Leukoencephalopathy***
**Progressive multifocal leukoencephalopathy (PML)** is a disease characterized by the infection and destruction of oligodendrocytes by the **JC virus**, most commonly in the setting of immunosuppression. This disorder is discussed in the syllabus on infectious diseases.

## ACQUIRED MYELINOLYTIC DISORDERS

***Central Pontine and Extra-pontine Myelinolysis***
While the net effect of both pathological processes is the same, the term *demyelinating* is typically reserved for pathological processes resulting in the *inflammatory, infectious, or nutritional* destruction of myelin, while **myelinolysis** is typically used to describe myelin destruction in the setting of **osmotic injury**. This occurs as a result of changing intra- and extracellular ion gradients, resulting in fluid shifts and rapid changes in cellular size, with associated destruction. The most common clinical scenario where this is seen is in the patient with **chronic hyponatremia with rapid correction of the serum sodium to near normal levels**. In chronic hyponatremia, central oligodendrocytes become equilibrated to the low sodium levels in the extracellular milieu. A rapid increase in the extracellular sodium concentration results in the egress of water from the intracellular compartment to the extracellular compartment with cell injury and death. Myelin in the central pons tends to be most susceptible to this injury (**central pontine myelinolysis**), with the dreaded **locked in syndrome** occurring as a result due to demyelination of the bilateral corticobulbar and corticospinal tracts (**Figure 5**); vertical eye movements are classically spared. Injury can also happen elsewhere in the nervous system, and is termed **extra-pontine myelinolysis**. These can be demonstrated with brain MRI, demonstrating T2 hyperintensities without contrast enhancement in the affected areas.




## INHERITED WHITE MATTER DISORDERS: LEUKODYSTROPHIES

Beyond the acquired demyelinating disorders, there are a number of rare inherited, mostly autosomal recessive disorders that cause progressive myelin destruction. These disorders are collectively referred to as the **leukodystrophies**

(leuko = white; dystrophy = wasting/loss) and are secondary to mutations in proteins involved in myelin formation, maintenance, turnover, and catabolism. **Table 1** lists some of the more common leukodystrophies and the associated abnormal protein products. Each of these disorders causes a characteristic set of symptoms and pattern of white matter loss. The specifics of these findings largely go beyond the scope of this syllabus. However, in general, the disorders cause a relatively symmetric, progressive loss of white matter. As an example, X-linked adrenoleukodystrophy tends to cause prominent myelin loss in the parietal and occipital lobes with relative sparing of the anterior cerebral hemispheres.

In gross specimens, the white matter appears grey and sunken. Note the symmetry of the white matter loss in **Figure 6**. Classically, there is **sparing of the arcuate fibers**, which are the fiber bundles connecting adjacent gyri. These findings can be seen on imaging, with **T2-weighted MRI demonstrating diffuse, symmetric hyperintensities** with sparing of the arcuate fibers (termed **subcortical U-fibers** on imaging). There may be contrast enhancement. Clinically, the disorders most commonly present in childhood or adolescence, but presentations from the infantile stage until adulthood have been described with most of the disorders. Further information on the clinical presentations and specifics of each of the syndromes below is discussed in the lecture (and associated syllabus) on Disorders of Myelin.

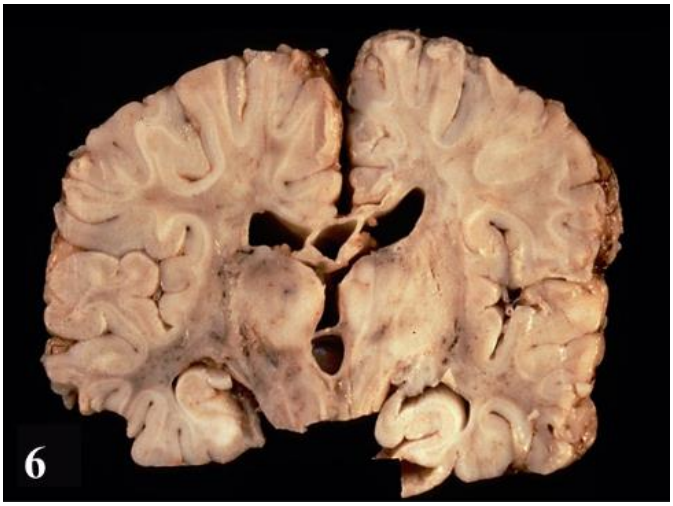



**Table 1 – Leukodystrophies and Associated Protein Deficiencies**

| Leukodystrophy | Abnormal Protein |
|---|---|
| **X-linked adrenoleukodystrophy** | ALD (*ABCD1* gene) |
| **Metachromatic leukodystrophy** | Arylsulfatase A |
| **Krabbe disease** | Galactocerebroside β-galactosidase |
| **Alexander disease** | GFAP |
| **Canavan disease** | Aspartoacyclase |
| **Pelizaeus-Merzbacher disease** | Myelin proteolipid protein |

**NOTES**

# NEUROPATHOLOGY VI – TOXIC AND METABOLIC DISEASES

**Mahlon Johnson, MD, PhD and Christopher Tarolli, MD**

## OVERVIEW

Central to understanding the pathophysiology and distribution of metabolic and toxic diseases is the concept of **selective vulnerability**, which states that specific cell types or populations are more susceptible to a particular insult than others. If the insult is lethal and the neuron is susceptible, then one should recall that neurons are post-mitotic cells and irreplaceable. The following abridged classification is offered to facilitate the management of these myriad diseases.

## SUBSTRATE OR COFACTOR DEFICIENCY

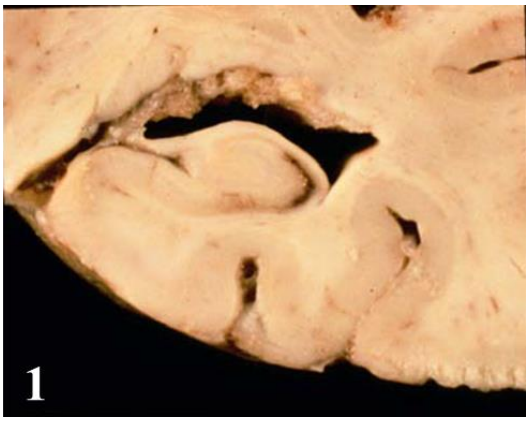
### *Global Hypoxic Ischemic Injury*

Hypoxia is reduced oxygen supply or utilization, while ischemia is defined as a reduction of blood supply (with a resultant failure of oxygen delivery). Interestingly, **pure hypoxemia** (low oxygen in blood) of the brain can occur as in the case of anaphylaxis, asthma, bronchitis, and epiglottitis. This is most common in young people, and may be reversible, with prolonged coma of 2 weeks from which a complete recovery is possible. In contrast, in patients with **global states of hypoperfusion** (e.g. in cardiac arrest with reduced cerebral blood flow), hypoxia and ischemia are invariably linked. Because of this overlap, when considering a patient with a hypo-perfusive brain injury, the generic term **global hypoxic-ischemic encephalopathy** is frequently used. In addition to **tissue hypoxia**, ischemia, and infarction, reduced cerebral perfusion also results in decreased removal of metabolic waste products ($CO_2$ and $H^+$) causing secondary injury.

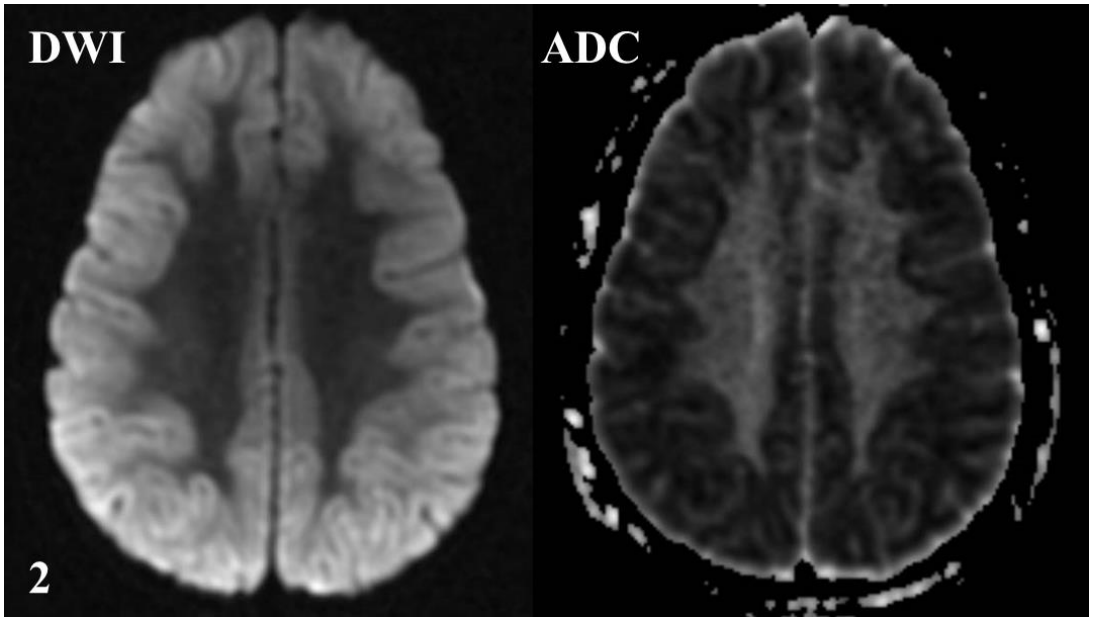
Generally, two variations of brain injury can occur as a result of a hypo-perfusive brain injury: **infarction** and **selective neuronal necrosis**. Infarction is covered in previous notes under CNS vascular diseases. Recall that global hypoperfusion is most likely to cause infarction in the **border or watershed zones**.

**Selective neuronal necrosis** refers to the selective vulnerability of certain regions of the brain to the hypoxic-ischemic state, likely due to the high metabolic demand of these areas. In adults, these include (in order of likelihood of involvement):

1) CA1 region of the hippocampus (Figure 1)
2) Pyramidal neurons in laminae 3 and 5 of the cerebral neocortex [recall the laminar necrosis discussed in the Vascular Pathology syllabus]
3) Purkinje cells in the cerebellum
4) Basal ganglia



The severity of a hypoxic-ischemic brain injury can vary substantially based on the duration of reduced cerebral perfusion and the patient's age and baseline brain health. However, the most severe injuries result in permanent global ischemia and **brain death**. This is evident clinically by the absence of all volitional and brainstem reflex responses (spinal reflexes may remain intact). Radiographically, severe hypoxic-ischemic brain injury will typically demonstrate diffuse cerebral edema and diffusion restriction throughout the entirety of the cerebral cortex on MRI (**Figure 2**).

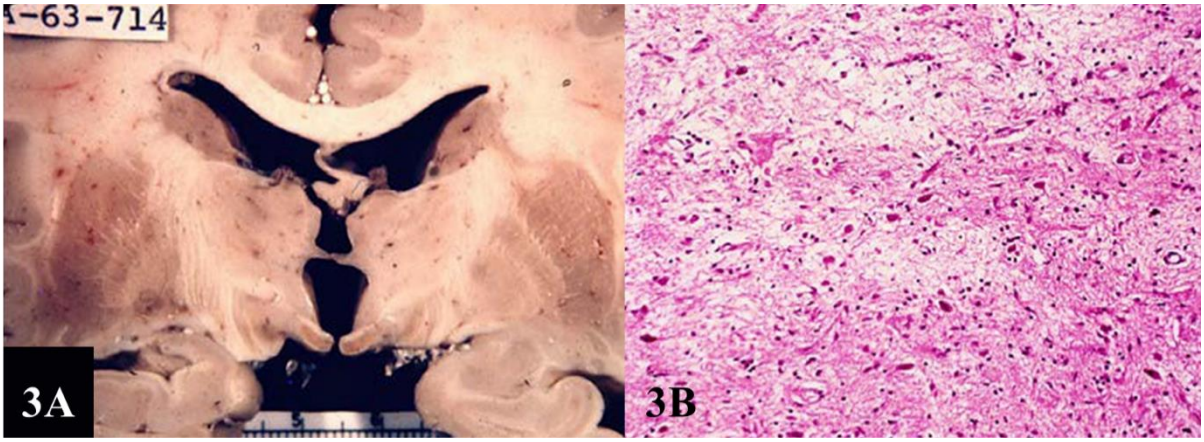



***Hypoglycemic injury***
Since the brain requires glucose and oxygen for its energy production, the cellular effects of diminished glucose resemble those of oxygen deprivation; however, Purkinje cell necrosis is not noted in hypoglycemic injury.

***Thiamine (Vitamin $B_1$) deficiency***
Thiamine deficiency is relatively rare among patients with a balanced diet, as many grains are fortified with the nutrient in the United States. Given this, individuals at risk of thiamine deficiency include those with a severely restricted caloric intake (classically seen in patients with chronic alcohol use disorder) and those who have impaired nutrient absorption (e.g. following gastric bypass surgery). Thiamine deficiency can cause both CNS and systemic pathology (cardiac disease, polyneuropathy).

In the CNS, **Wernicke encephalopathy** is the classic manifestation, and is characterized by the clinical triad of **ophthalmoplegia, ataxia, and mental status changes**. It usually is reversible if treated early with thiamine. There are typically minimal gross pathological changes; however, among those with more severe disease, there may be **petechial hemorrhage or atrophy of the mammillary bodies** evident on pathological section.

Compared to the largely reversible Wernicke encephalopathy, **Korsakoff syndrome** represents a dreaded and largely irreversible complication of chronic thiamine deficiency. Thiamine acts as an essential co-factor in the metabolism of glucose. Given this, if a patient with insufficient stores of thiamine receives a bolus of intravenous glucose, the resultant up-regulation of these pathways causes a toxic buildup of intermediate products, resulting in excessive lactic acid production and cellular toxicity. Pathological changes in Korsakoff syndrome are most prominent in the **mammillary bodies and dorsomedial thalamic nuclei**. Chronically, these lesions appear **atrophic with a brownish discoloration** due to hemosiderin deposition (**Figure 3A**), and by histology, **gliotic tissue with depletion of myelinated fibers and scattered hemosiderin-laden macrophages** may be present (**Figure 3B**).




Clinically, the syndrome is characterized by both **anterograde and retrograde amnesia, confabulation** (inventing historical memories to fill in amnestic gaps), **eye movement abnormalities**, and **profound apathy**. Because of the risk of this condition, any patient with altered mental status receiving glucose should first be administered intravenous thiamine.

***Vitamin $B_{12}$ (Cobalamin) deficiency***

Vitamin $B_{12}$ deficiency is most commonly seen in the setting of insufficient dietary intake (vegan diet, chronic alcohol use disorder) and in the setting of insufficient absorption (e.g. following gastric bypass surgery or in the setting of **pernicious anemia** with antibodies against gastric intrinsic factor). While there are myriad systemic effects of $B_{12}$ deficiency (macrocytic anemia, neuropathy, gastrointestinal symptoms), the most common effect in the central nervous system is the development of subacute neuropsychiatric changes ranging from irritability and depression to frank dementia. The pathological underpinnings of these changes are not clearly understood.

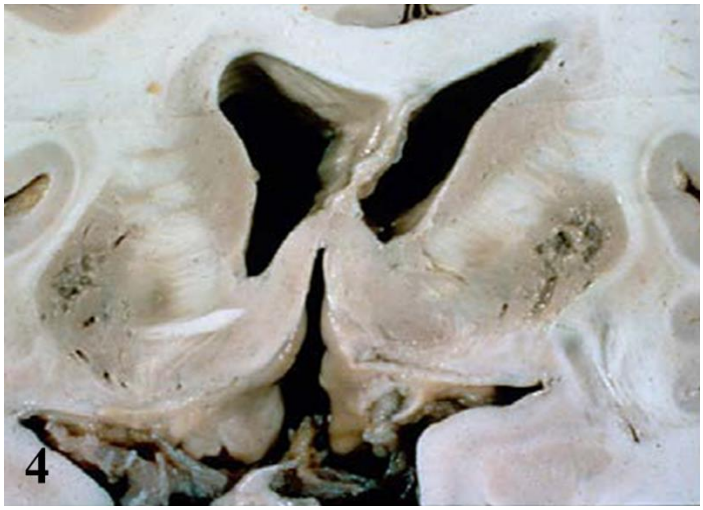
Substantially less common but more specific for $B_{12}$ deficiency is the clinical syndrome of **subacute combined degeneration of the spinal cord**. The disorder is seen with chronic $B_{12}$ deficiency, and is associated with a symmetric demyelinating degeneration of the **dorsal columns** and **lateral funiculi**

(corticospinal tracts) of the spinal cord. Clinically, this produces a spastic diplegia and profound sensory loss with sensory ataxia. Repletion of B12 may result in some improvement in symptoms, though much of the damage is irreversible.

## ENDOGENOUS TOXINS

### *Wilson disease/hepatolenticular degeneration*

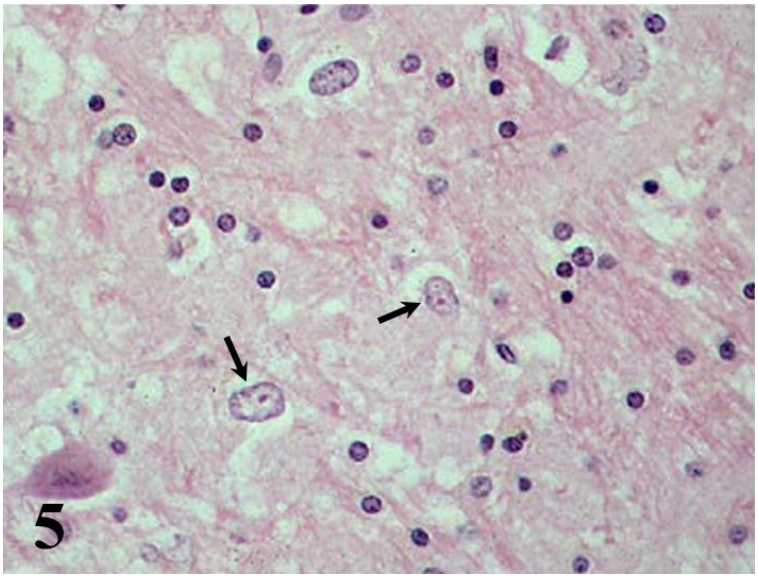
Wilson disease is an autosomal recessive disorder characterized by improper copper metabolism. The disease is caused by mutations in a copper transporting ATPase gene (***ATP7B***) on chromosome 13q14.3. The net effect of impaired copper metabolism is reduced copper clearance, and the **toxic accumulation of copper in many tissues, principally the liver, brain, and eye**. Accumulation of copper within the central nervous system is most prominent in the basal ganglia, particularly the **putamen and caudate nucleus,** which become brown and shrunken with central cavitation due to copper deposition and resultant cellular toxicity (**Figure 4**). Histopathology is relatively non-specific and may demonstrate findings associated with hepatic encephalopathy (described below), or may demonstrate the presence of scattered pigment-laden macrophages.




Clinically, patients typically develop liver dysfunction first, but a failure to chelate copper can result in substantial CNS toxicity. The most common neurological symptoms include **neuropsychiatric manifestations** (ranging from mild behavioral changes to frank psychosis) and **movement disorders** including parkinsonism, dystonia, and a characteristic tremor that is most prominent in the wing-beating position (**wing-beating tremor**). In addition, patients with neurologic involvement develop eye lesions called **Kayser-Fleischer rings**, green-brown deposits of copper granules in Descemet's membrane in the corneal limbus. Fingernail deposition of copper may also be noted. Diagnosis is based on typical clinical manifestations (with or without a family history), laboratory findings (**hepatic dysfunction, elevated serum copper, low serum ceruloplasmin**), and genetic testing. Long term copper chelation therapy is used to reduce tissue deposition; liver transplant represents a definitive therapy, as the transplanted organ has normal hepatic copper transporters.

***Hepatic encephalopathy***

Hepatic encephalopathy refers to non-specific alterations of mental status seen in the setting of chronic hepatic disease (e.g. chronic alcohol use disorder, Wilson disease, non-alcoholic steatohepatitis). As a result of poor hepatic synthetic and clearance function, there is an accumulation of toxic metabolites in the bloodstream, including ammonia (**hyperammonemia**), resulting in selective neuronal dysfunction and pathological changes in the CNS. While the cerebral cortex is certainly involved, these changes are most prominent in the **globus pallidus, caudate nucleus, and dentate nucleus of the cerebellum**. Histopathologically, one can see **Alzheimer type II astrocytes**, demonstrating vesicular nuclei with marginated chromatin and scanty cytoplasm (**Figure 5**), and are fairly specific for the presence of **hyperammonemia**.




***Kernicterus***

Kernicterus is most commonly found in newborn premature infants with **maternal-fetal Rh blood incompatibilities** (fetus Rh positive, mother Rh negative) with resultant hemolysis and **hyperbilirubinemia** due to the transmission of maternal antibodies directed against fetal/infant Rh-positive red blood cells. Its incidence has been reduced dramatically due to the development of **Rh$_O$(D) Immune Globulin** (RhoGAM), which neutralizes the maternal antibodies. Gross abnormalities consist of yellow discoloration of specific nuclei: **globus pallidus, subthalamic nucleus, hippocampus, superior and inferior colliculi, vestibular nuclei, inferior olives and dentate nucleus**. The pigment is lethal to neurons. Clinically, these infants also have superimposed anemic and oligemic hypoxia due to hemolysis and problems with cardiac function. Surviving the kernicteric episode leads to the classical triad of **opisthotonus, sensorineural deafness, and impaired upgaze.**

## EXOGENOUS TOXINS

A large number of substances are toxic to the nervous system. Toxicity may be secondary to environmental exposure or intentional ingestion (e.g. prescription and illicit substances). Given the heterogeneity of nervous system toxins, a comprehensive listing is beyond the scope of this material. Here, we will focus exclusively on two of the most common substances to cause CNS toxicity. For a more extensive review of exogenous toxins and their impact on the nervous system, you should review **Chapter 9 (Acquired Metabolic Disorders)** in Escourolle and Poirier's *Manual of Basic Neuropathology*.

### *Carbon monoxide*

Carbon monoxide (CO) is a colorless odorless gas produced by incomplete combustion of carbon fuels that can cause fatal poisoning. In the presence of hemoglobin, CO will bind at the oxygen binding site, forming the highly stable compound, **carboxyhemoglobin**. Because of the substantially higher affinity for CO, it cannot be displaced, **preventing oxygen binding and delivery to target tissues**. This causes tissue hypoxia, with the **globus pallidus (particularly the pars interna)** most frequently and severely affected. Beyond the pathological changes associated with hypoxia of any cause (described above), CO poisoning causes the brain to become swollen, congested, and **cherry red** (due to the bright red color of carboxyhemoglobin) within the first few hours. After 24-48 hours **petechial hemorrhages develop in white matter and pallidum**.

Clinically, mild and short-term CO poisoning may produce headache, dizziness, nausea, and visual disturbances, while more prolonged exposure will result in convulsions, coma, and death. Because of the preferential involvement of the basal ganglia, survivors of severe CO poisoning most commonly experience a variety of non-progressive movement disorders.

### *Ethanol*

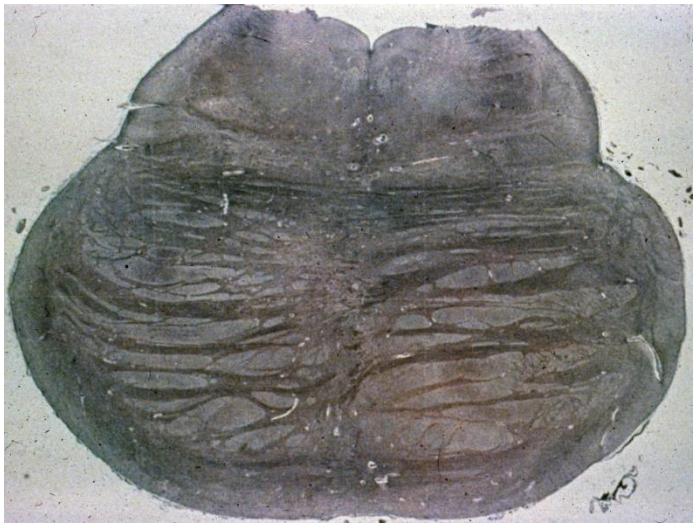
The deleterious effects of ethanol on the nervous system are widespread and may be primary (e.g. direct toxicity) or secondary (e.g. due to nutritional deficiencies that are commonly comorbid with alcohol use disorder). Here, we will focus on the direct toxic effects of alcohol on the CNS. **Acute alcohol intoxication** is associated with reversible dysfunction of the cerebellum, but does not cause specific neuropathologic changes. In contrast, **chronic heavy alcohol use** results in direct toxicity to the **Purkinje and granular cells** of the cerebellum, with associated **selective atrophy of the anterior cerebellar vermis**. Similar toxicity and pathological findings are associated with the chronic use of sodium channel blocking anti-convulsant drugs like **phenytoin**. This can produce profound and irreversible truncal ataxia.

Notably, chronic alcohol exposure to the developing brain (so-called **fetal alcohol syndrome**) causes its own unique set of neuropathological abnormalities including micrencephaly, neuroglial heterotopia, hydrocephalus and hypoplasia of centrum semiovale and cerebellum.

**NOTES**

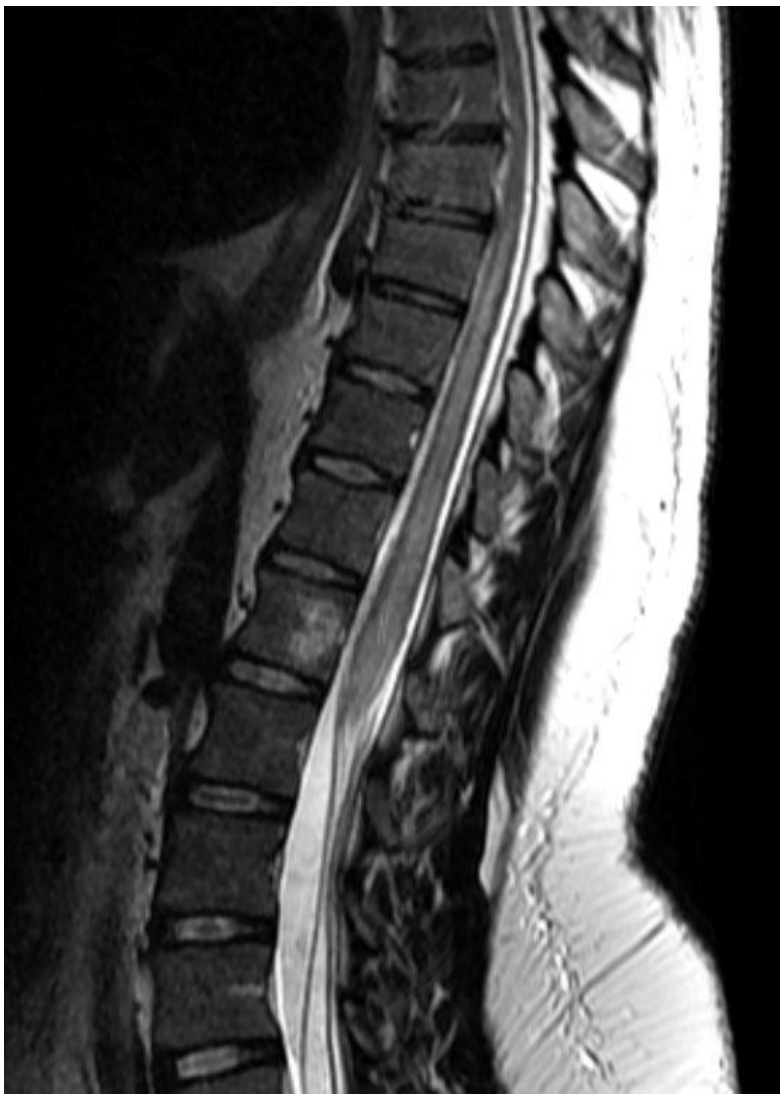
**DISORDERS OF MYELIN AND TOXIC, METABOLIC DISORDERS**
**IRAT/GRAT**

1. A 67-year-old woman with a longstanding history of multiple sclerosis dies after being hospitalized for a hip fracture following a fall. Her family requests an autopsy. Sections through a chronic plaque in the brainstem are shown with a myelin stain (left) and axonal stain (right). Which of the following histopathological features is most supportive of a diagnosis of multiple sclerosis over another demyelinating disease?

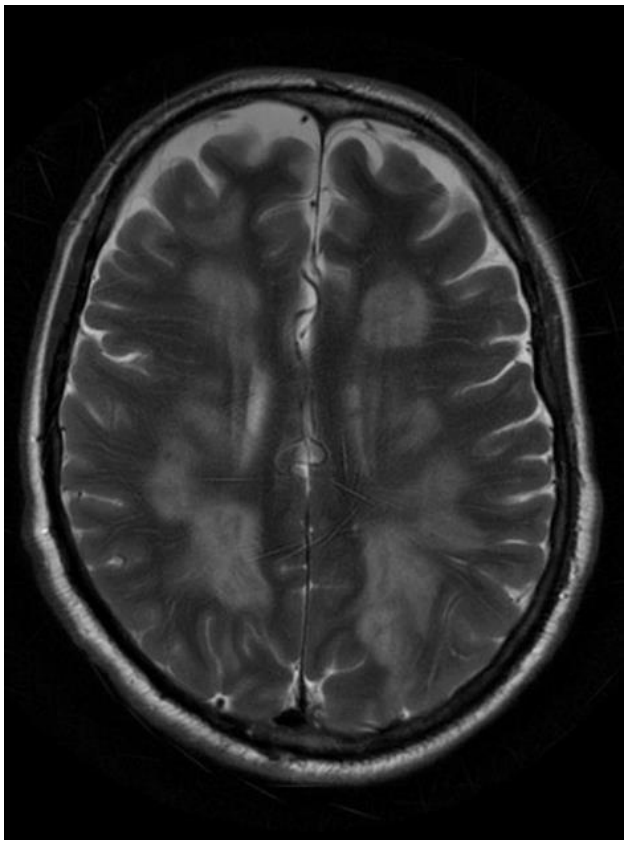
A. Absence of inflammatory cells
B. Axon loss
C. Brainstem localization
D. Limitation to a single vascular territory
**E. Well-demarcated lesion**

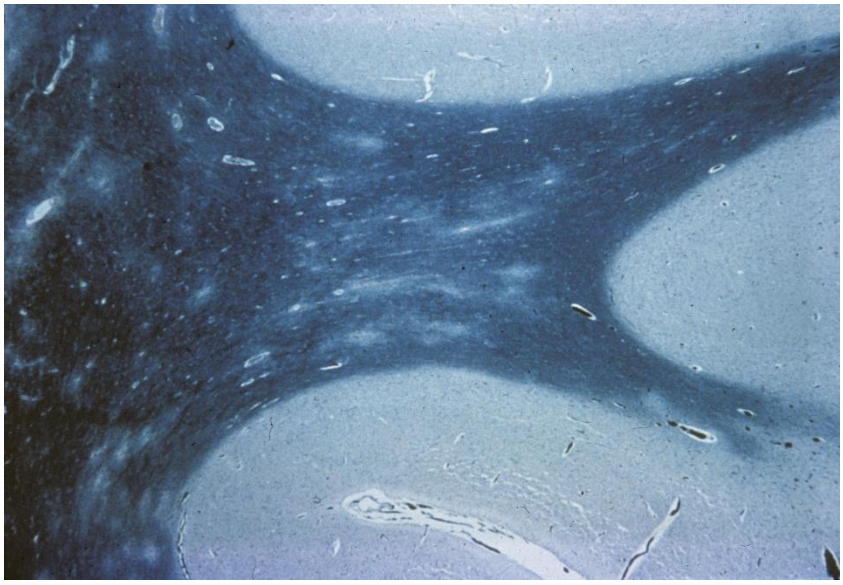
2. A 41-year-old man presents to the hospital with progressive gait instability and leg weakness over 5 days. On exam, he has grade 1-2 strength throughout the lower extremities with 3+ patellar reflexes, clonus at the bilateral ankles, and bilateral extensor plantar responses. He has a sensory level at the umbilicus. A T2-weighted MRI of the spinal cord is shown. CSF analysis is most likely to demonstrate which of the following:



**A. Antibodies to Aquaporin-4**
B. Elevated CSF lactate and pyruvate
C. No abnormalities
D. Positive JC virus PCR
E. Positive Angiotensin Converting Enzyme (ACE)

3. An 8-year-old boy with no history of developmental delay or other past medical history presents to the hospital with increasing confusion over around 1 day. His father describes the patient having an upper respiratory infection around a week before and the development of difficulty walking starting 3 days ago. On initial exam, the patient requires loud voice to maintain his attention and he is able to only follow simple commands. He has multidirectional nystagmus and is clumsy when reaching for objects, particularly with his right hand. The patient's T2 MRI is shown below (left), as well as a myelin-stained histopathological slice from the cerebral hemisphere of a patient with a similar presentation (right). Which of the following is the most likely diagnosis?





**A. Acute disseminated encephalomyelitis (ADEM)**
B. Adrenoleukodystrophy
C. Extra-pontine myelinolysis
D. Multiple sclerosis
E. Progressive multifocal leukoencephalopathy

4. A 57-year-old man presents to the hospital with increasing confusion. On initial exam, he requires loud voice to maintain his attention, but he is able to move all extremities symmetrically and follow simple commands. Laboratory analysis identifies a serum sodium of 117 mEq/L (normal 135-145 mEq/L). The patient is started on a hypertonic (3%) saline infusion, and the sodium increases to 132 mEq/L over around 12 hours. On repeat assessment, the patient is unable to move his limbs or face. However, he is able to move his eyes vertically on command. Which of the following is the most likely mechanism for the patient's neurological deficits?

    A. Basilar artery occlusion
    B. Brainstem herniation
    **C. Cellular fluid shifts**
    D. Immune-mediated destruction of oligodendrocytes
    E. Persistent hyponatremia

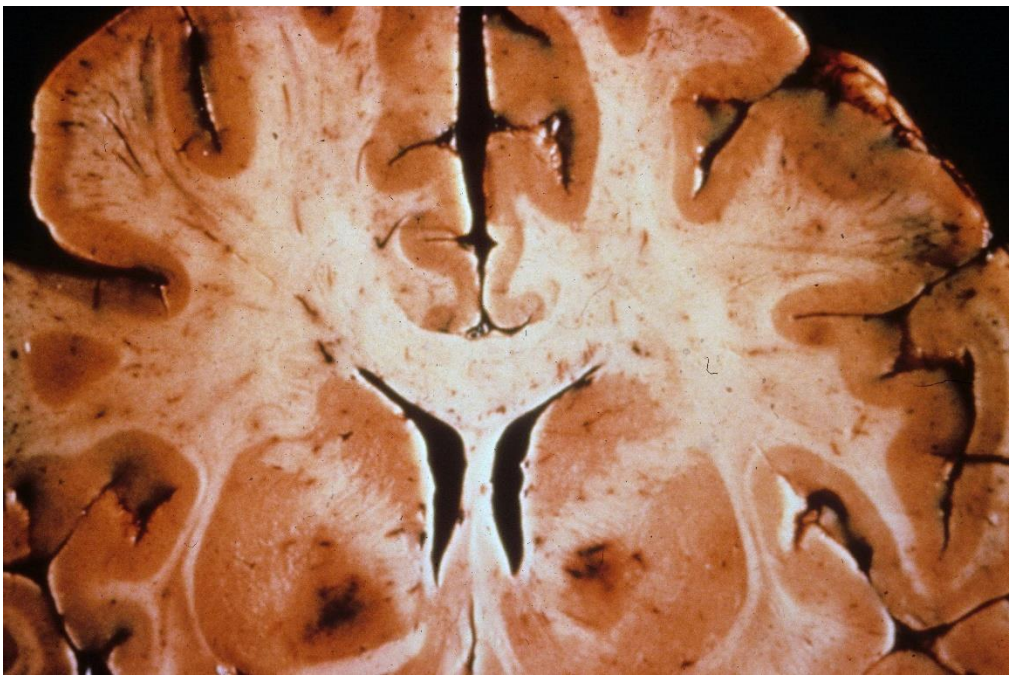
5. A 48-year-old woman with a history of gastric bypass surgery presents to the neurology office for evaluation of increasing difficulties walking over the past few months. She reports she transitioned to a vegan diet around 8 months ago. On exam, she has bilateral lower extremity spasticity, grade 4 strength throughout the lower extremities, 4 beats of clonus at the bilateral ankles, extensor plantar responses, and absent vibratory sense at the great toes and medial malleoli. Pinprick sensation is intact. Demyelination in which of the following neuronal pathways is responsible this patient's symptoms?

    A. Corticospinal tracts, dorsal columns, and spinothalamic tracts
    **B. Corticospinal tracts and dorsal columns**
    C. Corticospinal tracts and spinothalamic tracts
    D. Dorsal columns and spinothalamic tracts

6. A 41-year-old woman with a history of alcohol use disorder with associated malnutrition presents to the hospital after being found unresponsive outside. Initial laboratory analysis reveals a blood alcohol level of 173 mg/dL and a blood glucose of 57 mg/dL (normal 60-99 mg/dL). She receives IV fluids and an infusion of dextrose. The following day, she is fully awake, but has difficulty following complex commands and has horizontal nystagmus and difficulty tracking to the left with her left eye. MRI head reveals microhemorrhages in the bilateral mammillary bodies. Deficiency of which of the following likely underlies this patient's presentation?

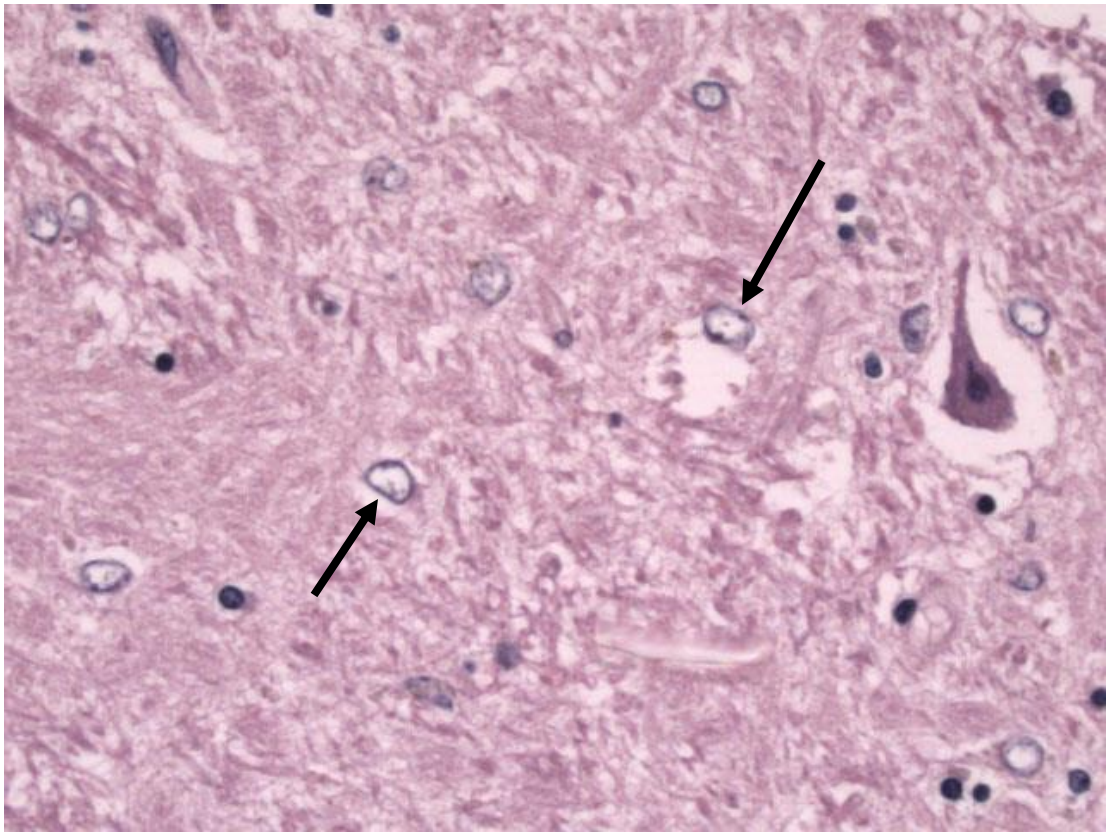
    A. Copper
    B. Riboflavin (vitamin B2)
    **C. Thiamine (vitamin B1)**
    D. Vitamin B12
    E. Vitamin E

7. A 21-year-old man is brought to the hospital unresponsive following a house fire. Despite aggressive medical management, he dies, and autopsy is performed with a gross brain specimen shown. The red appearance of the brain is due to the presence of which of the following?



    A. Carbon dioxide
    **B. Carboxyhemoglobin**
    C. Diffuse cerebral hemorrhage
    D. Hemoglobin S
    E. Lipohyalinosis

8. A 61-year-old man with a history of end-stage non-alcoholic liver disease dies following a cardiac arrest. Autopsy is performed, and a histopathological specimen from the putamen is shown. The abnormal cells indicated by the black arrows are derived from which of the following cell lines?



**A. Astrocytes**
B. Ependymal cells
C. Microglia
D. Neurons
E. Oligodendrocytes

# MBB Team Based Learning 3:
# Disorders of Myelin and Toxic, Metabolic Disorders

Application Exercises

## CASE #1

A 22-year-old man with no significant medical history presents to the hospital with complaints of painful and blurred vision in his right eye over the past 2 days. On examination, visual acuity is 20/100 in the right eye, and 20/20 in the left eye. He has an afferent pupillary defect on the right, but his eye movements are full. He reports that his blurred vision improves with covering the right eye, but remains when covering the left eye. He is treated with 5 days of intravenous methylprednisolone with improvement in vision symptoms.

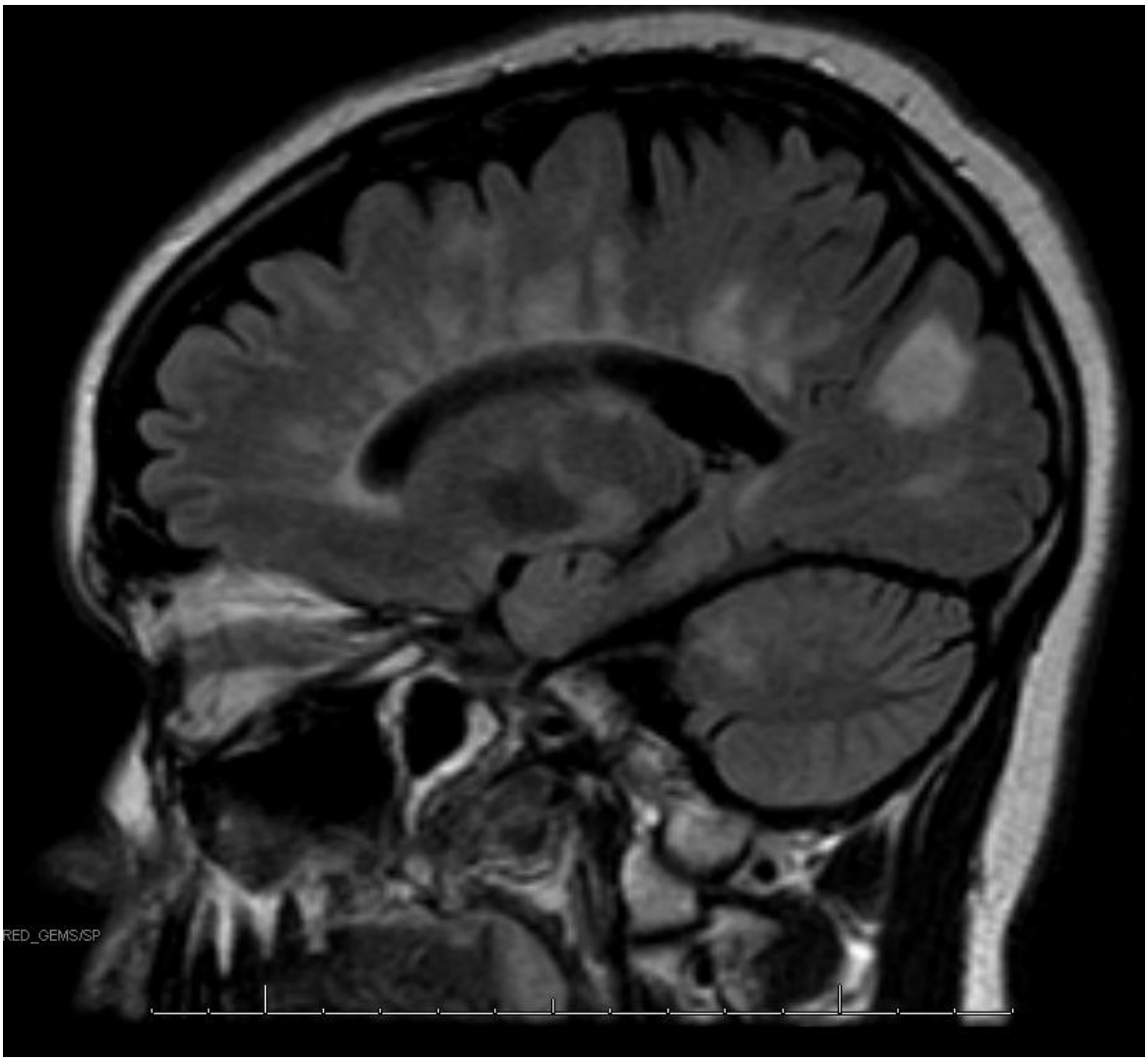
**Question 1:**
Which of the following CSF patterns is most supportive of a diagnosis of multiple sclerosis?

| | **WBC** | **RBC** | **Protein** | **Oligoclonal bands** | **Aquaporin 4 antibodies** |
|---|---|---|---|---|---|
| A. | ↔ | ↔ | ↑ | Absent | Absent |
| B. | ↑ | ↔ | ↑ | Absent | Present |
| **C.** | ↑ | ↔ | ↑ | **Present** | **Absent** |
| D. | ↑ | ↑ | ↑ | Absent | Absent |
| E. | ↑↑ | ↔ | ↑ | Absent | Absent |

**Question 2:**
Over the following 8 years, the patient has 3 additional episodes with focal neurological deficits including a presentation with double vision, a presentation with bilateral leg weakness and urinary retention, and a presentation with sensory loss in his right face and arm. During each presentation, imaging demonstrates focal regions of enhancement that correspond to his deficits, and he is treated with intravenous steroids with improvement in symptoms. Which of the following pathophysiologic mechanisms underlies each presentation?

A. Immune-mediated attack on cell surface water channels
B. Ischemic neuronal destruction
C. Latent viral reactivation
**D. Perivascular lymphocytic infiltration**
E. T-cell mediated hypersensitivity reaction

**Question 3:**
The patient is started on disease-modifying therapy to manage his relapsing-remitting multiple sclerosis, and he has only one additional clinical presentation over the following 10 years. Sagittal T2-FLAIR MRI obtained as a part of routine neuroimaging to monitor for subclinical disease progression is shown below. In addition to the prominent lesions noted in the corpus callosum (periventricular region), demyelination in which of the following additional regions are most common in patients with multiple sclerosis (select all that apply)?

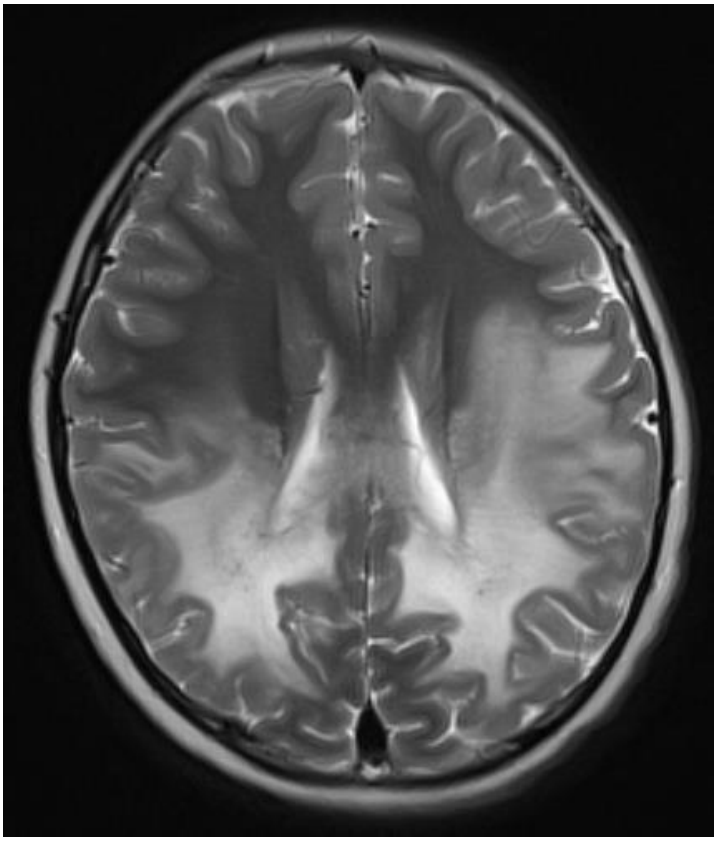



A. Basal ganglia
**B. Brainstem**
**C. Juxtacortical**
**D. Spinal cord**
**E.** Thalamus

# CASE #2

A 6-year-old boy with a history of attention deficit hyperactivity disorder presents to the pediatric neurology office for evaluation of increasing challenges at school and at home. His mother describes that he was previously very active, but has been having increasing challenges with kicking and throwing a ball over the past few months. His behavior deteriorated in class with increasing hyperactivity and challenges with both reading and math. His mother is adopted, but believes her biological brother had a "brain disease," and died at an early age. On exam, he has mild weakness and spasticity in the bilateral lower extremities with grade 3 reflexes at the patellae, 4 beats of clonus at the bilateral ankles, and extensor plantar responses bilaterally.

**Question 1:**
MRI head is obtained, and the T2-weighted image is shown below, which demonstrates bilaterally symmetric T2 hyperintensities with linear contrast enhancement around the edges of the lesion, and relative sparing of the subcortical U-fibers (arcuate fibers). These imaging features are most consistent with which of the following pathological processes of myelin?

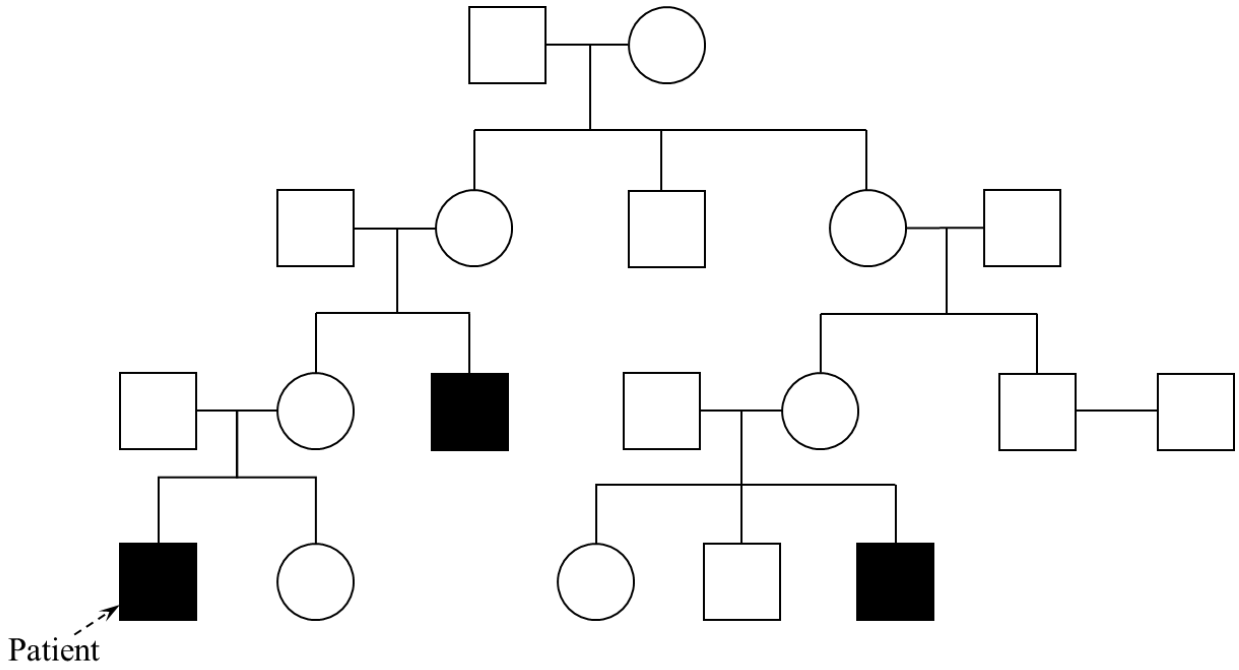


**A. Inherited abnormality of myelin maintenance**
B. Destruction in the setting of rapid fluid shifts
C. Antibody-mediated myelin destruction
D. Infectious destruction of oligodendrocytes
E. T-cell hypersentivity reaction

**Question 2:**
The patient has bloodwork, which demonstrates an elevation in very long chain fatty acids (VLCFA), and genetic testing confirms a mutation in the *ABCD1* gene. Which of the following is the most likely diagnosis?

A. Acute disseminated encephalomyelitis
**B. Adrenoleukodystrophy**
C. Autism spectrum disorder with intellectual disability
D. Juvenile Alexander disease
E. Metachromatic leukodystrophy

**Question 3:**
The patient's mother is able to obtain a more detailed family history, and a pedigree is shown below. This condition demonstrates which of the following inheritance patterns?

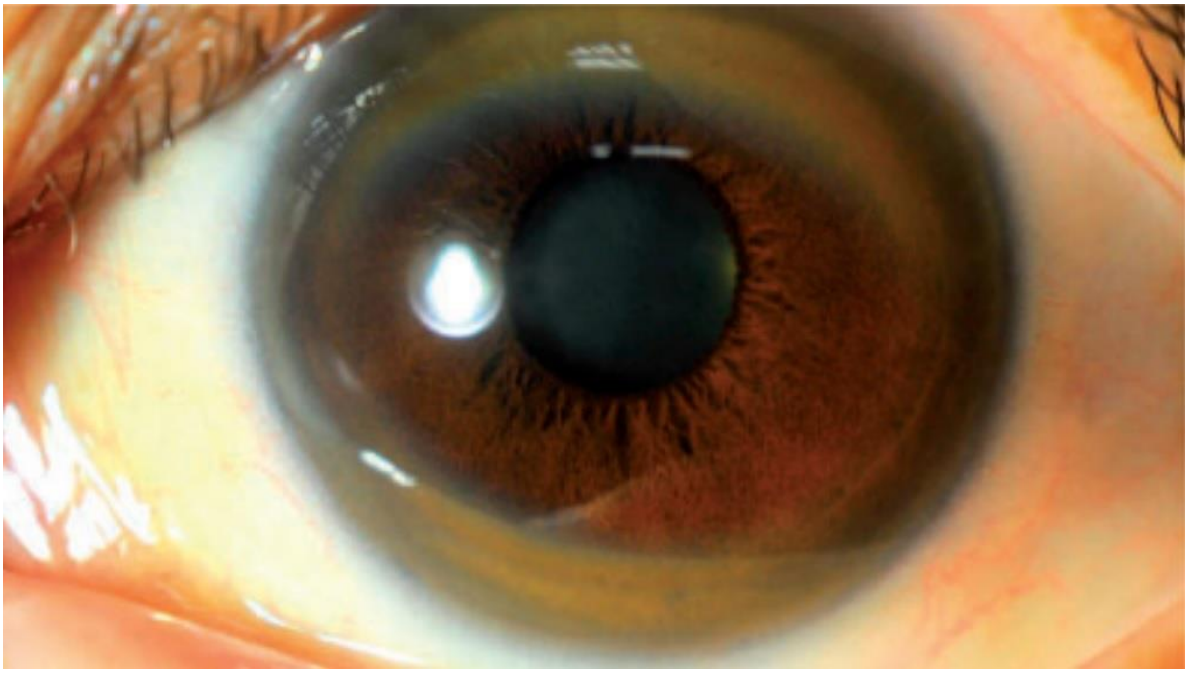



A. Autosomal dominant
B. Autosomal recessive
C. Non-Mendelian inheritance
D. X-linked dominant
**E. X-linked recessive**

# CASE #3

A 24-year-old non-binary nursing student presents to the neurology office for evaluation of abnormal movements over the past 6-8 months. They describe increasing challenges with reaching for objects, eating, and drinking because of a prominent upper extremity tremor. On exam, they have a prominent postural and action tremor in the bilateral arms, and they develop dystonic posturing of the right hand while walking. In reviewing their family history, their parents and three older siblings have no symptoms; however, they think their maternal great aunt developed abnormal movements and difficulty walking in her 20's and died in her 40's.

**Question 1:**
A slit lamp ocular examination is performed and shown below. The patient's presentation is most likely secondary to improper metabolism of which of the following substances?



A. Bilirubin
**B. Copper**
C. Ethanol
D. Vitamin A
E. Vitamin E

**Question 2:**
On laboratory testing, serum ceruloplasmin is 7 mg/dL (normal >20 mg/dL) and genetic testing confirms the presence of a homozygous mutation in the *ATP7B* gene. Neuroimaging is most likely to demonstrate abnormalities in which of the following structures?

A. Cerebellar hemispheres
B. Hippocampus
C. Optic nerves
D. Pre-frontal cerebral cortex
**E. Putamen**

**Question 3:**
If left untreated, this patient is likely to die as a complication of which of the following?

A. Dilated cardiomyopathy
**B. Liver failure**
C. Pancreatic insufficiency
D. Renal failure
E. Seizures and status epilepticus

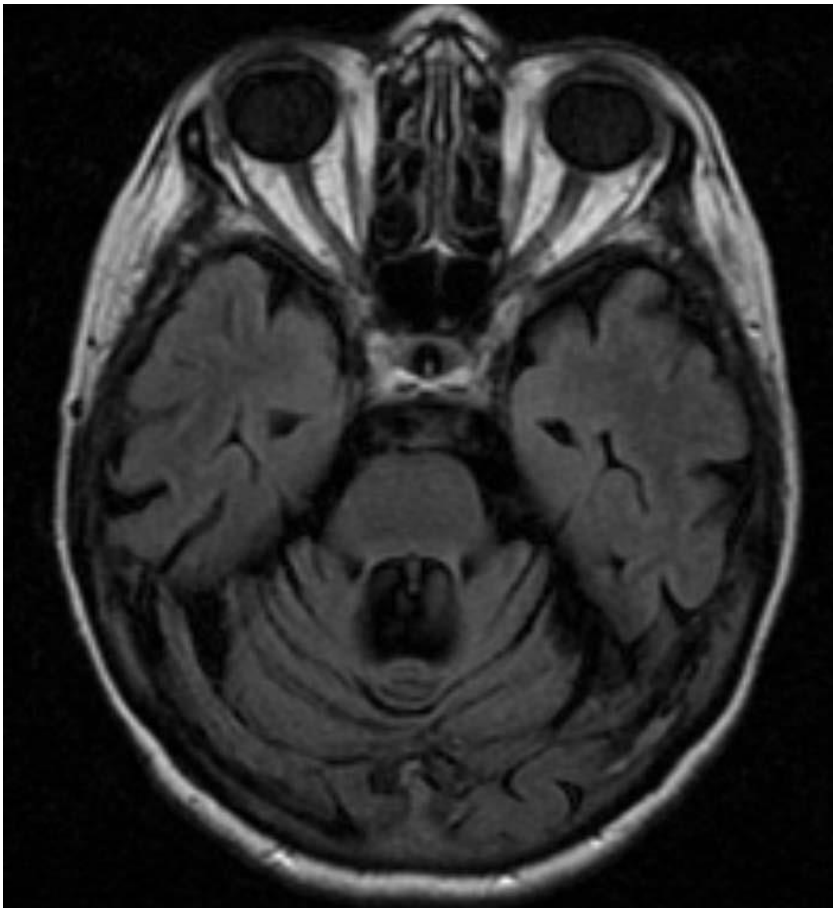
# CASE #4

A 61-year-old man with a history of alcohol use disorder, now in remission, presents to the neurology clinic for evaluation of unsteadiness and frequent falls. The patient describes challenges with walking and reports feeling unsteady both on his feet and when sitting down. He has a history of multiple prior falls with head injury in the setting of alcohol intoxication, including admissions for traumatic subdural and subarachnoid hemorrhages in the past. However, he has not had a drink in the past 8 months, and has not had a fall with head injury in more than three years. On exam, he is unable to sit upright without supporting himself with his hand. He has a mild ataxic dysarthria and on standing, has a wide-based stance and substantial postural instability with his eyes open that worsens with closing his eyes. He has mild ataxia with finger-to-nose and heel-to-shin movements bilaterally.

**Question 1:**
The patient's clinical presentation is most likely secondary to dysfunction in which of the following structures?

**A. Cerebellar vermis**
B. Dorsal spinocerebellar tracts
C. Middle cerebellar peduncles
D. Primary motor cortex
E. Substantia nigra, pars compacta

**Question 2:**
MRI brain is obtained, and the T2-FLAIR image is shown below. Dilation of the fourth ventricle noted on the imaging is most likely secondary to which of the following?



A. Communicating hydrocephalus due to meningeal scarring
B. Communicating hydrocephalus due to prior subdural hematoma
C. Non-communicating hydrocephalus due to aqueductal stenosis
D. Non-communicating hydrocephalus due to occlusion of the foramina of Luschka
**E. Secondary dilation in the setting of cerebellar atrophy**

**Question 3:**
A similar clinical presentation and neuropathological findings can be seen in the setting of chronic use of which of the following substances?

A. Fluoxetine
B. Haloperidol
C. Lamotrigine
D. Methamphetamine
**E. Phenytoin**