



Neuro Vignettes

Psychiatry Board Exam Preparation Resource

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1. Parkinson's Disease

A 59-year-old woman presents to your clinic with gait difficulty. Her family states that her steps have gotten shorter and more “shuffling.” It takes her significantly longer to do her daily activities and shopping as a result of these changes in her gait. She denies, however, any pain or instability when walking. In addition, she states that now she sometimes has difficulty preparing meals, as it takes her significantly longer to chop vegetables. Her family also notes the development of a tremor in her right hand when she is walking. The patient states that she is not bothered by the tremor and barely notices it. It does not occur when she is using her hand and it does not interfere with her eating or drinking. The patient claims that it is not the reason she has difficulty preparing meals. On examination you see a well-developed, well-nourished woman. You notice a slight paucity of expression while she talks. Cranial nerve exam and strength exam are unremarkable. However, there is rigidity in the right upper and lower extremities. The upper extremity has a ratchet-like quality to the rigidity. In addition, you note the presence of a resting tremor that disappears with movement and posture. Repetitive movements are slower in her right hand compared to her left, but remain fairly rhythmic. Her gait exam is significant for the presence of small steps and a slightly stooped posture, as well as a more pronounced tremor in her right hand during walking. Further, it takes her four steps to turn around.

BACKGROUND

- This patient has Parkinson's Disease (PD), a neurodegenerative disease of the dopaminergic cells of the nigrostriatal pathway in the basal ganglia. This degeneration leads to the extrapyramidal signs that are typical for this disease. These signs are captured with the acronym TRAP: Tremor (at rest), Rigidity, Akinesia, and Postural instability.
- The terms “Parkinsonism” and “extrapyramidal symptoms” may be used synonymously and refer to the symptoms of PD or another disturbance that leads to similar symptoms.

PATHOLOGY

- It is not clear how or why the nigrostriatal cells are preferentially affected in this disease. Multiple pathogenic mechanisms are hypothesized. Mitochondrial dysfunction and oxidative metabolism are the most accepted mechanisms based on observations that there is significantly decreased mitochondrial activity in the dopaminergic cells of the nigrostriatal pathway. This leads to energy failure of the cell, causes excessive oxidative stress, and increases susceptibility to other forms of damage. This hypothesis has been supported by heroin users who ingested MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a compound that is toxic to Complex I of the mitochondrial electron-transport chain of nigrostriatal dopaminergic cells, and leads to acute-onset Parkinsonism. Excitotoxicity from persistent activation of glutaminergic NMDA receptors can lead to toxic levels of intracellular calcium. Neurotrophic factors and immune factors may also play a role.
- The classical pathologic finding of PD is Lewy bodies, which are intracellular eosinophilic hyaline inclusion bodies. Their appearance varies depending on their location. Typical Lewy bodies that are found in degenerated nigrostriatal cells are spherical with a dense core and clear halo whereas Cortical Lewy bodies are smaller

and lack a distinct core. The role of Lewy bodies in the pathogenesis of PD remains unclear.

- Synuclein is a cell protein found in neurons and glial cells that forms the insoluble fibrils found in Lewy bodies.
- Degeneration of the dopaminergic cells of the nigrostriatal pathway leads to a dopamine-deficient state. This leads to reduced inhibition of GABAergic neurons via the direct pathway, and increased GABAergic excitation via the indirect pathway. These changes in basal ganglia circuitry lead to excessive inhibition of the motor cortex, which in turn leads to the tremor, akinesia, rigidity, and postural instability (TRAP) of PD.

CLINICAL PRESENTATION

- PD manifests clinically with resting tremor, cogwheel rigidity, and akinesia/bradykinesia. Postural changes are also typically included, but may be absent in early disease. Symptoms usually begin asymmetrically in PD, and the disease may progress insidiously at first. Handwriting becomes small and irregular. The sign of masked facies is due to bradykinesia of the face. Dementia is seen in late disease. PD is slowly progressive, and average lifespan after diagnosis does not exceed 10 years. Age is the most consistent risk factor. Interestingly, smoking has been shown to decrease the risk of PD.

DIAGNOSIS

- Diagnosis of PD is made clinically. Neuroimaging findings are commonly unremarkable in PD, but neuroimaging should be performed to rule out other causes of similar neurologic symptoms (e.g., stroke, tumor, normal pressure hydrocephalus). Obtaining a drug history is very important as drug-induced Parkinsonism is a common and reversible differential for PD. Parkinsonism-inducing drugs are dopamine-depletors and include neuroleptics (that is, first generation antipsychotics), atypical antipsychotics (to a lesser extent), centrally-acting antiemetics, and anti-cholinergics. Lithium and depakote are rare culprits, acting through unknown mechanisms. Good response of symptoms to treatment with levodopa is suggestive of PD, whereas minimal to poor response to levodopa is highly suggestive of other diagnoses.

TREATMENT

- Management is complex, involving a wide variety of medications available with varying mechanisms of action. The mainstay of therapy is levodopa, a precursor to dopamine. It is typically administered with carbidopa which blocks peripheral metabolism of levodopa to allow greater CNS bioavailability of levodopa. Levodopa is the most effective therapy in PD, but long-term use is associated with significant complications, such as the “wearing off” effect, peak-effect dyskinesias, and psychiatric disturbances such as hallucinations.
- Dopamine agonists may be used as initial monotherapy or as adjunctive therapy in PD. They are advantageous in that they have longer durations of action and, thus, lead to less dyskinesias and wearing-off effects. However, dopamine agonists are less potent than levodopa, and patients eventually progress to treatment with levodopa after several years of treatment with non-levodopa medications. The current dopamine agonists on the market are Bromocriptine (Parlodel) and Cabergoline (Dostinex). Pergolide has been withdrawn from use.

- Catechol-O-methyl transferase (COMT) is one of several enzymes that degrade catecholamines (i.e., dopamine, epinephrine, and norepinephrine). Inhibiting COMT thus increases the availability of these neurotransmitters at the synaptic cleft. Two COMT Inhibitors for the treatment of PD are available, tolcapone (Tasmar) and entacapone (Comtan). When used adjunctively with Levo-Dopa, COMT Inhibitors prolong its action and allow for lower levodopa doses. Tolcapone has been associated with acute fulminant liver failure and carries a black box warning to that effect. Due to this risk, it is a second line medication.
- MAO-B inhibitors also prolong the action of levodopa and are used adjunctively. Selegiline and a new MAO-B inhibitor, Rasagiline are available. The benefit of Rasagiline is that it's not metabolized into amphetamine.
- Amantadine and anticholinergics can be used symptomatically to help with dyskinesias and tremors. Atypical neuroleptics are used sparingly in PD patients given their chance of worsening the extrapyramidal effects, but may be required in patients with refractory psychotic symptoms. Deep brain stimulation (DBS) is a new and promising surgical option for patients with PD. Electrodes are implanted into deep grey matter and electrical stimulation is applied. Symptoms can improve dramatically. DBS targeting the ventrointermediate thalamic nucleus improves contralateral resting tremor and rigidity. DBS targeting bilateral globus pallidus internal segments improves all aspects of Parkinsonism and relieves levodopa-induced dyskinesias. Finally, as in all neurodegenerative diseases, social support is paramount for both the patient and the caretakers.

2. Wilson's Disease

A 36-year-old woman develops kinetic tremors in bilateral upper extremities. Over the course of several months, the tremor spreads to include her head and lower extremities. Over the course of several months, it develops to the point where it is quite debilitating. Physical examination is significant for yellowing of the sclera. The patient's ocular and oculomotor cranial nerves are intact and nystagmus is absent. The patient displays dysarthric speech with a strained voice quality. Strength is full, but with a significant high frequency, low amplitude kinetic tremor, slightly worse on the left upper extremity than the right. Tone is slightly increased with some cogwheel rigidity. The patient denies a family history of movement disorder and she has no atypical exposures to toxins. MRI of the brain reveals high T2 signal in the basal ganglia, especially in the globus pallidus and putamen. There is no contrast enhancement.

BACKGROUND

- The patient has Wilson's Disease (WD), a neurodegenerative disease of the brain and liver caused by abnormal liver metabolism of copper. Copper accumulates in the basal ganglia causing deterioration of the lenticular nucleus (i.e., putamen and globus pallidus). This accumulation leads to prominent tremor and/or dystonia with parkinsonian features. WD is also called hepatolenticular degeneration.

PATHOLOGY

- WD is due to a mutation in the amino acid copper-transporting P-type transmembrane ATPase, whose job is to incorporate copper into ceruloplasmin for secretion into bile. Failure of this enzyme leads to copper deposition in various body tissues, especially the liver and brain. This accumulation leads to oxidative damage.
- The disorder is autosomal recessive in inheritance.

CLINICAL PRESENTATION

- Clinically, the patient with WD presents with the triad of neurologic, psychiatric, or hepatic symptoms. Age of onset ranges from the teens to the fifth decade of life.
- Neurologic symptoms tend to be dominated by either dystonia or tremor. Younger patients tend to have more dystonic symptoms, while older patients tend to have more tremor symptoms. Dysarthria and Parkinsonism are also typical neurologic symptoms.
- Psychiatric symptoms include depression, disinhibition, irritability, and cognitive impairment including progression to dementia.
- Hepatic symptoms can present either insidiously, leading to chronic cirrhosis, or with acute fulminant failure. Hemolysis in the context of acute fulminant hepatic failure is a typical complication caused by the sudden release of a high amount of copper into the blood stream leading to red blood cell destruction.

DIAGNOSIS

- Diagnosis of WD is based on serum ceruloplasmin levels and 24-hour urine copper levels. A low ceruloplasmin level is consistent with WD – recall that the biochemical disturbance is in incorporation of copper into ceruloplasmin. The 24-hour urine copper is the more sensitive assay of the two, and in WD urine copper is high.
- A slit-lamp test can also detect the presence of Kayser-Fleischer rings, which are a deposition of copper in the cornea near the border of the sclera. Kayser-Fleischer

rings are typically seen in patients with neurologic or psychiatric presentations of WD, and more variably in patients with hepatic presentations.

- In patients with diagnostic uncertainty, the gold standard is measurement of copper in tissue obtained through liver biopsy.
- DNA tests are not available, as there are over 300 different mutations linked to WD.

TREATMENT

- Treatment of WD is divided into initial and maintenance therapy. Initial therapy consists of chelation – the chelating agent binds copper and allows it to be excreted. Tetrathiomolybdate, penicillamine, trientine, and zinc acetate are all copper chelating agents. Trientine and penicillamine can cause neurologic worsening. Conversely, Tetrathiomolybdate has a rapid response and is associated with less neurologic worsening compared to trientine and penicillamine, and is thus the preferred initial agent.
- The effect of zinc acetate is gradual, requiring four to eight months to reduce copper to non-toxic levels. For this reason, zinc is preferentially used as a maintenance therapy.
- Sequential 24-hour urine copper collections can be ordered to assess the effectiveness of therapy.
- In patients with fulminant hepatic failure, liver transplant may be the only option to save the patient's life.
- Prognosis in WD depends on prompt diagnosis and therapy. Untreated disease will progress to an akinetic-mute state with relatively preserved cognition. Symptoms can be reversed, which will be especially evident in the first several months of treatment. It is difficult to predict which patients will recover and which patients will stabilize at the level of symptoms present at the time of initiation of treatment.

3. Huntington's Disease

A 34-year-old woman presents to your clinic for involuntary movements of her hands and fingers. These movements started several months ago when she noticed a tremor in her hands while drinking coffee and eating meals. She denies presence of a tremor at an earlier point in her life. Several weeks ago, she began to note occasional, involuntary, brief flicking movements of her fingers. These movements have increased in frequency to the point that they now disrupt her ability to perform dexterous activities with her hands. She denies any other movement symptoms or other neurologic complaints. Her past medical history is significant for depression diagnosed four years ago. Her depressive symptoms included crying spells with episodes of irritability and agitation. Currently, she is taking a prescribed SSRI. When asked about control of her psychiatric symptoms, she states, "I don't really care." She denies presence of psychotic symptoms and has never been exposed to neuroleptics or antiemetics. Her family history is obscured since she is adopted, but she knows that her birth mother committed suicide. Apparently, her birth mother also had some history of movement disorders before her death. The patient has a 7-year-old son who is completely healthy. Her social history is negative for substances of abuse. Her physical examination reveals a thin, well-developed woman in no apparent distress. Her cranial nerve examination is unremarkable, and strength is full. You note brief, intermittent jerky movements in the fingers of both hands. There is a slight action tremor with intention only. Rapid alternating movement exam demonstrates a mild dysrhythmia as well. Gait is normal, as is the rest of the neurologic exam.

BACKGROUND

- The patient has Huntington's Disease (HD), a neurodegenerative disease of the neostriatum (i.e., caudate nucleus and putamen). HD is characterized by a trinucleotide expansion on chromosome 4 that leads to prominent involuntary movements and psychiatric disturbance. Dementia is a feature of mid to late disease. HD is a fully penetrant, autosomal dominant disease that typically manifests in adulthood. There is an inexorable progression towards death over a period of decades.

PATHOLOGY

- HD is a result of an unstable trinucleotide CAG expansion on chromosome 4. The gene product is called huntingtin, a protein whose function has yet to be determined. The CAG expansion leads to glutamine repeats in this huntingtin protein. The number of repeats is inversely associated with the age of onset: 60 or more repeats are seen in juvenile onset whereas 40 to 60 repeats are typical for adult onset disease.
- Due to the instability of trinucleotide, the number of CAG repeats increases with each successive generation, leading to earlier onset and worse severity of disease with each generation. This phenomenon is called genetic anticipation.
- Pathologically, cell death and inclusion bodies are seen, specifically in the spiny interneurons of the striatum. The exact pathogenic relationship between CAG repeats and striatal neuron cell death is unknown. Multiple mechanisms are postulated, with excitotoxicity via glutamate overexcitation thought to be one of the main mechanisms. Interestingly, the huntingtin gene is expressed ubiquitously in all

brain tissues. The selective vulnerability of striatal spiny interneurons is likely due to local factors that remain to be fully defined.

- In addition, the polyglutamine section of the abnormal huntingtin protein can crosslink with other proteins, leading to intranuclear inclusion formation.
- The mutant huntingtin protein is also suspected to interfere with function of transcription factors and production of neurotrophic factors as well.

CLINICAL PRESENTATION

- The most prominent feature of HD is the movement disorder, classically defined as choreoathetotic in character. The movement abnormality can begin as a tremor prior to the onset of the characteristic chorea. Chorea consists of small-amplitude, rapid movements, typically beginning in the fingers or face. Chorea is derived from the Greek word "to dance." It progresses to slower, larger, "writhing" movements called athetosis. More advanced disease can include flinging, ballismic movements. Eventually, the patient becomes dystonic and parkinsonian, leading to bradykinesia and immobility.
- Psychiatric symptoms can precede onset of movement abnormalities. Depression and apathy are the most common psychiatric manifestations. Suicide is a major concern, as 5 to 10 percent of HD patients commit suicide. Frank psychosis is relatively uncommon, however. Dementia becomes prominent in mid to late disease, but memory deficits, attention deficits, and problem-solving deficits can present early in the disease.
- The mean onset is in the fourth decade, with progression to death on average in 15 to 25 years. Juvenile onset can begin in the first or second decades, and is more rapidly progressive. Seizures can be a complication of late disease.

DIAGNOSIS

- Neuroimaging shows prominent caudate atrophy, but may be normal in early disease. Cortical atrophy is also seen in late disease.
- Genetic testing is available and is the key to diagnosis. Because it is fully penetrant and autosomal dominant in inheritance, a diagnosis of HD has significant implications to relatives as well. Genetic testing in asymptomatic individuals with affected family members is a highly personal decision, as the disease is uniformly fatal; there is no therapy that slows the progression of HD, and thus no benefit to early diagnosis.

TREATMENT

- Treatment of HD is entirely supportive. Multiple therapies have been examined to slow the progression of disease, including remacemide (a glutamate agonist), coenzyme Q12, and creatine. Treatment results with these agents have not been promising.
- Depression can be treated with SSRI's. Antipsychotics, due to their antidopaminergic effects, can be used to treat chorea, although they can worsen cognition at high doses. Levetiracetam (Keppra) may be used to control chorea as well.

PROGNOSIS

- HD is uniformly fatal, and there is no therapy that slows its progression. Thus, there is no treatment benefit to early diagnosis.

4. Alzheimer's Disease

A 76-year-old man comes to your clinic with complaints of memory and word-finding problems. He is a high-functioning, retired economics professor who is still active in the academic community. He is currently working on a publication with some of his peers, but finds that he has been having trouble "thinking of just the right word." He first started noting symptoms several years ago when he found it more difficult to recall more esoteric words, but he now has difficulty recalling even common words. His wife has noticed that he has some memory trouble as well. For instance, starting in the past year he often misplaces items, especially his keys, and sometimes reacts with anger when he cannot find them. There was one time that he left the stove on after heating water for tea. When he and his wife were on vacation in Florida five months ago, he became extremely confused when reading a map, a skill he never had trouble with before.

On mental status examination, he is alert and oriented to self, place, and time. His general knowledge seems intact and he is able to describe in detail the current status of the economy, albeit his language is circumstantial. It remains intact, however, in fluency, repetition, and comprehension. He made several paraphasic errors in the course of the examination such as using the word "speaking" rather than "listening," and "animal" rather than "plant." On memory testing, he scores a five out of five on registration. After 5 minutes, he recalls three of the memorized words spontaneously, and the other two only with prompting. Serial sevens were correct, but laborious and slow. In copying an illustration of two intersecting figures, he miscopies one of the figures, changing a pentagon to a rectangle. The rest of his neurological exam is unremarkable.

BACKGROUND

- The patient has Alzheimer's Disease (AD), a neurodegenerative dementia associated with deposition of amyloid plaques and neurofibrillary tangles. Clinically, the disease manifests as cortical dysfunction leading to impairment in memory, language, visuospatial function, and praxis. Alzheimer's Disease, the prototypical dementia, is the most common dementia in the world, accounting for about two-thirds of all dementia cases.

PATHOLOGY

- Gross pathology of an Alzheimer's brain shows significant cortical atrophy, most predominant in the mesial temporal lobes and the association cortices of the frontal, parietal, and temporal lobes, although it becomes global in late disease. The pathogenesis of AD is secondary to three pathogenic mechanisms. First, is the accumulation of senile plaques in the extracellular space. Second, is the accumulation of neurofibrillary tangles inside neurons. Third, is neuronal cell loss in the cerebral cortex.
- Senile plaques are aggregated deposits of β -amyloid peptide associated with multiple other proteins, including ubiquitin, tau protein, apolipoprotein E, and others. β -amyloid is abnormally cleaved into a form that facilitates formation of beta-pleated sheets. These sheets aggregate into senile plaques that collect over the limbic and parietal lobes.

- Several genetic loci have been associated with abnormal β -amyloid metabolism and early onset AD. The gene for Amyloid Precursor Protein, the precursor to the β -amyloid protein, is located on chromosome 21. Patients with Down's Syndrome (trisomy 21) have abnormally enhanced Amyloid Precursor Protein production and early onset AD. Presenilin 1 & Presenilin 2 are proteins of unknown function that are thought to increase formation of β -amyloid depositions through unknown mechanisms.
- Neurofibrillary tangles are composed of hyperphosphorylated tau peptides arranged in paired helices. Although neurofibrillary tangles are seen in other dementias, such as progressive supranuclear palsy, the paired helical formation is unique to AD.
- In addition to these unique findings, there is widespread neuronal loss seen throughout the brain, especially with cholinergic neurons. However, pathways involving dopamine, norepinephrine, and serotonin neurotransmission are also affected.
- The metabolism of cholesterol is also involved in the pathogenesis of AD, specifically with apolipoprotein E (ApoE), a protein involved in cholesterol transportation. The epsilon 4 allele of ApoE increases the risk of late onset AD, especially if the patient is homogenous for that allele.

CLINICAL PRESENTATION

- As the pathological processes described above have an affinity for the mesial temporal lobe, memory loss is an early complaint. It first involves short-term memory and the ability to incorporate new knowledge into working memory and, subsequently, into long-term memory. Remote memory is preserved until late in disease. Language impairments are also an early manifestation, including word-finding, naming difficulty, and decreased vocabulary. Fluency, comprehension, and repetition are relatively uninvolved until late in the disease process. Visuospatial dysfunction can be an early symptom which includes visual agnosia and spatial disorientation. Ideomotor apraxias also can be seen.
- Psychiatric complaints consist of apathy and depression in early disease. Agitation, psychosis, and hallucinations occur in late disease.
- Seizures and myoclonus may be noted in 10 to 20 percent of patients in late disease. The disease progresses insidiously over years to a vegetative state. Aspiration pneumonia due to impaired swallowing is the most common proximal cause of death.

DIAGNOSIS

- Diagnosis is clinical with supportive evidence from laboratory, neuropsychiatric, and neuroimaging tests. Clinical diagnosis of probable AD is made when there are deficits in two or more areas of cognition affecting activities of daily living, a progressive course, and the absence of other possible etiologies.
- B12, TSH, and other reversible causes of dementia should be ruled out. MRI can show frontal, parietal, and temporal lobe atrophy bilaterally in early to moderate disease, and global atrophy in late disease. Neuropsychiatric testing is used to help define and quantify areas of cognitive difficulty.
- Pathological confirmation is the only way to make a diagnosis of definite AD, but this is not clinically relevant or practical in the vast majority of cases.

TREATMENT

- Cholinesterase inhibitors are the mainstay of treatment, although they are purely symptomatic and not disease-modifying. The most commonly used agents are donepezil (Aricept), rivastigmine (Exelon), and galantamine (Razadyne). These agents improve cholinergic transmission and are efficacious in slowing cognitive and functional decline. The three agents are thought to be equal in efficacy. They are associated with nausea and vomiting, but GI side effects can be avoided by taking the medications with meals.
- Memantine (Namenda) is an NMDA antagonist that improves function of hippocampal neuronal transmission, and is thought to be both a symptomatic and a disease-modifying therapy.
- The combination of donepezil and memantine has been shown to be more efficacious in delaying cognitive decline than donepezil alone.
- Vitamin E and selegiline therapy have been studied as disease-modifying agents, and have been shown to slow the rate of neuronal death.
- SSRI's are used for depressive symptoms and behavioral dysfunction such as resistant and defiant behaviors.
- Nonpharmacologic therapies are of great import, which include daycare programs, community resources, visiting nurses, and occupational therapy.

PROGNOSIS

- The interval from diagnosis to death is on average 10 years, although the variability in the progression among patients is significant, with some patients living over two decades. The cognitive and functional decline tends to proceed at a gradual and even pace over the years of illness for individual patients.

5. Frontotemporal Dementia

A 62-year-old man is brought to your clinic by his family for “acting strangely.” He is a retired accountant and a deacon at his church. However, starting about a year ago, he has made inappropriate sexual advances towards women. At first his sons attributed this behavior to their father being a “dirty old man,” but his behavior has increased in frequency and lewdness. In addition, he has taken to swearing often, something he has never done before in his life. On his first clinic appointment, his mental status exam is significant for a normal level of alertness, orientation and level of current knowledge. His memory remains intact for three out of three objects after 5 minutes. He can clearly recount details of his breakfast the morning of the evaluation, as well as his actions from the previous day. His ability to produce words that begin with a specific letter within a minute is moderately reduced. In addition, you note that he makes some paraphasic errors, such as substituting the word “clock” when he means “watch.” An MRI of the brain shows increased gyral space and atrophy of the left frontotemporal lobes.

BACKGROUND

- The patient has frontotemporal dementia (FTD). FTD is a group of neurodegenerative diseases causing atrophy of the frontotemporal cortex, leading clinically to a progressive cortical dementia. Behavioral changes dominate in early disease while memory is relatively spared, which is the opposite to Dementia of Alzheimer’s Type. There are several clinical subtypes of frontotemporal degeneration, including primary progressive aphasia, semantic dementia, corticobasal degeneration syndrome, progressive supranuclear palsy, FTD with Parkinsonism, and FTD associated with motor neuron disease.
- Terminology surrounding FTD and Pick’s Disease can cause confusion. Pick’s Disease refers to a specific disease etiology which manifests with signs and symptoms of frontotemporal dementia. (Consider FTD as a clinical diagnosis, while Pick’s Disease is a pathological one). Frontotemporal Degeneration refers to the spectrum of subtypes and variants which include primary progressive aphasia, FTD associated with motor neuron disease, etc.

PATHOLOGY

- Pick’s Disease is one etiology of FTD. The pathogenic etiology of most cases of FTD remains undiagnosed and unknown. There are three pathologic subtypes of Pick’s Disease based on pathological findings.
- Ubiquitin-positive, tau-negative inclusions are the most common pathological finding in FTD, and are also seen in FTD with motor neuron disease. Tau-positive inclusions are nonspecific entities seen in various neurodegenerative dementias, including Alzheimer’s Disease. They are also seen in Pick’s Disease, corticobasal degeneration, progressive supranuclear palsy, and FTD with Parkinsonism. FTD with Parkinsonism is associated with dysfunction of tau metabolism due to a mutation in chromosome 17 (FTDP-17).

CLINICAL PRESENTATION

- Behavior and personality change are the defining features of FTD. Disinhibition is a prominent manifestation which includes childishness, rudeness, inappropriate sexual remarks and behaviors, careless driving, reckless spending, shoplifting, or undressing in

public. The patient may seem inattentive, impulsive, and amotivated. Insight is lost early in the disease. Recent episodic and autobiographic memory is remarkably preserved until late in the disease.

- In the “Semantic Dementia” variant of FTD, a semantic aphasia predominates, with frequent word substitutions exhibited within the context of retained fluency. This level of impairment progresses to an incomprehensible fluent aphasia.
- In the Primary Progressive Aphasia variant of FTD, language disturbance is the primary symptom for the first several years. This aphasia is typically nonfluent and progresses eventually to mutism.
- Corticobasal Degeneration and Progressive Supranuclear Palsy have significant extrapyramidal signs and may be thought as being a combination of FTD and Parkinsonism.
- The classical triad of Corticobasal Degeneration is: 1) unilateral rigidity, 2) apraxia, and 3) alien hand syndrome.
- Progressive Supranuclear Palsy is a Parkinson-plus syndrome with prominent vertical gaze palsy.
- FTD is also seen in motor neuron disease, particularly familial Amyotrophic Lateral Sclerosis.
- FTD with Parkinsonism is an inherited dementia with behavioral changes together with parkinsonian motor symptoms.
- It is not uncommon for patients to have features of varying subtypes of FTD, or to progress from one subtype to another.

DIAGNOSIS

- FTD is primarily a clinical diagnosis that is confirmed via pathology. MRI is the neuroimaging test of choice given higher definition over CT. Imaging shows asymmetric frontal and temporal atrophy, although it can be negative in early disease and more diffuse in late disease. T2 hyperintensity can be seen in the subcortical white matter adjacent to the areas of atrophy.

TREATMENT

- There is no specific treatment for FTD, which is symptomatic only. SSRI's have been used to improve obsessive symptoms, emotional lability, and aggressivity. Cholinesterase inhibitors have been unreliable in improving symptoms, and may worsen them. Atypical antipsychotics can be used for restlessness and hyperactivity.
- Speech therapy can be offered to patients with aphasias, who may benefit by developing compensatory language skills. As the disease process continues, however, gains are eventually lost. Family and patient education is important as well.

PROGNOSIS

- FTD is a uniformly fatal presentation. Duration of illness and speed of decline are highly variable given that FTD is not a unitary disease, but rather a clinical presentation of various neuropathological processes.

6. Dementia with Lewy Bodies

A 66-year-old man is brought to your clinic by his wife and son for declining mental abilities. The family members tell you that they are particularly concerned because the patient's mental state changes frequently and dramatically. He can fluctuate from being completely coherent to not recognizing where he is in a matter of minutes. His wife reports that he has developed movements of his legs during sleep, of which he is not aware. Also, he had a sleep episode during which he yelled and thrashed about until his wife woke him. Earlier in his life, he had never experienced such an event.

In addition, his family is quite concerned because he seems to see people and animals when none are visible. He is not distressed by these occurrences, however, and states, "My eyesight isn't so good anymore. Sometimes when it gets dark I get a little confused. I know these people aren't there and they don't bother me."

On examination, his memory is intact to registration and he is able to recall three out of three objects at 5 minutes. His language is normal in fluency, repetition, and comprehension. On serial sevens, he correctly states, "100, 93, 86, 79, 72, and 65." However, he is quite slow in calculation and requires frequent prompting due to lapses in his concentration. His motor exam reveals a slight spasticity in the right upper extremity, but the rest of the neurologic exam is unremarkable.

BACKGROUND

- This patient has Dementia with Lewy Bodies (DLB), a neurodegenerative dementia marked by the presence of Lewy bodies diffusely distributed in the brain. Typical clinical features include fluctuations of mental status, recurrent visual hallucinations or illusions, and extrapyramidal motor signs such as those seen in Parkinson's Disease (PD). DLB is the second most common dementia after Alzheimer's Dementia.

PATHOLOGY

- Lewy bodies are seen in PD, PD with dementia, and Dementia with Lewy Bodies. Lewy bodies are formed by aggregates of alpha-synuclein, ubiquitin, and neurofilament protein. They are more widespread in DLB than in PD. In PD, Lewy bodies are deposited mostly in the nigrostriatal pathways of the basal ganglia. In contrast, they are deposited diffusely in the brainstem, subcortical areas, and cortex in DLB. An ascending pattern of Lewy body progression has been observed from the brainstem to the basal brain.
- Coexisting pathological findings include neurofibrillary tangles and senile plaques similar to Alzheimer's Dementia. Degeneration of cholinergic neurons may predispose the patient to hallucinations.

CLINICAL PRESENTATION

- Symptoms are a progressive, cognitive impairment with a fluctuating course, recurrent visual hallucinations, and Parkinsonism. Cognitive impairment is of the subcortical type, characterized by significant psychomotor slowing, visual-spatial deficits, and decreased attention. Memory impairment is seen primarily in acquisition and retention of new information. However, items that are well-learned may be retained. Fluctuations of level of consciousness and cognition may last from minutes to days.

- Hallucinations are typically well-formed and usually are of people or animals. They may occur sporadically. They can be either distressing or benign to the patient, and the patient may recognize them as being products of his own mind. Other neuropsychiatric features include agitation, depression, and emotional lability.
- Extrapyramidal symptoms include rigidity and bradykinesia, but to a lesser degree than seen in PD. Interestingly, rest tremor is not common in DLB.
- Sleep disturbances are also typical and include acting out one's dreams, restless leg syndrome, and insomnia.
- Differentiation between PD with dementia and DLB is based on the onset of cognitive symptoms relative to motor symptoms. Patients with DLB have cognitive symptoms that begin prior to or within one year of motor symptoms. Since one year is an arbitrary cut-off, there is significant overlap in the clinical and pathological features of these two diseases. In general, however, patients with DLB have predominantly cognitive symptoms, with motor symptoms being relatively mild in the early disease.

DIAGNOSIS

- Diagnosis is made clinically. This can be difficult given the clinical and pathological overlap between DLB, PD with dementia, and Alzheimer's Disease. Neuroimaging shows nonspecific cortical atrophy.

TREATMENT

- There is treatment that slows or reverses the course of the disease. Cholinesterase inhibitors such as rivastigmine improve cognitive symptoms, and may be even more effective than in Alzheimer's Disease. Typical neuroleptics should be avoided, as they worsen Parkinsonism, especially haldol. Atypical neuroleptics, particularly clozapine, may be used to control hallucinations as they are less likely to worsen parkinsonian symptoms. Levodopa can be used in patients with significant motor dysfunction. However, clinical response is less than that seen in typical PD. In addition, it can worsen hallucinations. Social support is important to patients and their caregivers.

PROGNOSIS

- The course is slowly progressive and leads to death with an average survival time of eight years after diagnosis.

7. Binswanger's Dementia

A 67-year-old man presents to your clinic for a progressive decline in cognitive status over the course of many years. His medical history is significant for hypertension, hypercholesterolemia, coronary artery disease, and two prior strokes. His family relates that the patient "sits around all day" and seems "slow" overall in conversation and function. He requires assistance to dress and groom himself, but is able to ambulate on his own, albeit with supervision.

On physical examination, the blood pressure is 154/94. The patient is awake and oriented to self and place. Time is incorrect to date and month. His speech is dysarthric. He is a poor historian, and his speech is noticeably slowed with prominent inattention. Memory is three of three with immediate recall, and one of three after 5 minutes. Language is intact to fluency, repetition, and comprehension. Cranial nerve exam is unremarkable except for nasolabial flattening on the left. Extremities are slightly spastic on the left side with 4/5 weakness with increased reflexes. Gait exam is spastic.

You order an MRI which shows significant atrophy with hydrocephalus *ex vacuo* of the ventricles. T2 weighted imaging shows significant confluent hyperintensity in the white matter, especially in the periventricular region.

BACKGROUND

- The patient has a subcortical type of Vascular Dementia, a disease historically referred to as Binswanger's Dementia. It is a progressive decline in cognitive function caused by subcortical dysfunction from ischemic damage to the deep white matter. Longstanding uncontrolled hypertension is thought to be the major risk factor for development of this disease. A history of prior strokes is typical, but not universal.

PATHOLOGY

- Although the true pathogenesis remains under debate, pathology reveals pronounced lipohyalinosis of arterioles of deep white matter with surrounding ischemic demyelination. Lacunar infarcts are commonly seen as well. For this reason, vascular risk factors, especially hypertension, are thought to lead to this disease. This is verified in studies showing high prevalence of hypertension among patients with Binswanger's Dementia. The cortex is remarkably spared on pathological examination.

CLINICAL PRESENTATION

- The dementia of Binswanger's Disease is predominantly one of subcortical features, such as apathy, amotivation, and slowed cognition. Cortical features such as aphasia, memory loss, and neglect may be present but are less common than they are in Dementia of Alzheimer's Type. Cognitive deficits may be step-wise with periods of stabilization in early disease, but typically the condition becomes chronically progressive even without further obvious vascular events. Dysarthria, focal motor signs, and gait abnormality are also common, but not universal. Extrapyramidal and ataxic features can also be seen. The disease typically begins in the sixth and seventh decades of life and progresses over 5 to 10 years.

DIAGNOSIS

- Neuroimaging is required to demonstrate extensive changes of the deep white matter, best seen on MRI. These changes are demonstrated with T2-weighted hyperintensities predominantly in the centrum semiovale, corpus callosum, and internal capsule, and spare the U-fibers. It is also common to see lacunar infarcts in the basal ganglia, thalamus, and pons.
- Binswanger Disease is a term that predates MRI which refers to the clinical picture of subcortical cognitive impairment from arteriosclerosis resulting from vascular and non-vascular risk factors. Multi-infarct dementia refers to subcortical cognitive impairment from arteriosclerosis caused by vascular risk factors. Subcortical arteriosclerosis without vascular risk factors is seen in CADASIL, an inherited disease causing migraines, strokes, and eventually dementia. CADASIL is due to deposition of a periodic acid-Schiff positive material into the smooth vessel walls of cerebral vessels. Amyloid angiopathy and antiphospholipid antibody syndrome are also causes of Binswanger Disease without traditional vascular risk factors.

TREATMENT

- There is no specific treatment for Binswanger's Dementia. Prevention is thought to be consistent with control of vascular risk factors, especially hypertension. Hypertension should be lowered cautiously, as chronic hypertension shifts autoregulation of perfusion pressure in the brain. Thus, reducing the patient's blood pressure to normotensive levels may actually cause CNS hypoperfusion and precipitate a stroke.
- Given the role of cerebral ischemia in the development of this disease, it is reasonable to use antiplatelets such as aspirin for stroke prevention in these patients. Aricept and nimodipine can be used symptomatically to treat the cognitive symptoms and are thought to be of modest benefit.

8. New Variant Creutzfeldt-Jakob Disease

A 32-year-old man with no significant past medical history presents to your clinic with cognitive complaints, having seen multiple doctors prior to his visit with you. His symptoms began several months ago when he first noticed difficulty falling asleep and decreased appetite. He states that his work performance as an accountant has begun to suffer; he blames this on increasing difficulty maintaining his concentration. His concentration is now so poor that he is quite distressed.

He was initially evaluated by his primary care physician who diagnosed him with depression, although there were no clear social and environmental triggers, or positive family history. After a month, he developed severe feelings of dysphoria and agitation. He began to develop intermittent paranoia and felt that he was being controlled by signals from his television. He was referred to a psychiatrist and diagnosed with schizophrenia. His symptoms were temporarily and relatively well-controlled with antipsychotic medications, but several weeks ago he began to notice a gait imbalance. He states that he feels unsteady when walking and standing, and has difficulty with fine movements because his limbs “just aren’t coordinated.” In addition, he states that he has diffuse “pins and needles” sensations over his entire body. They are persistent in nature, although they vary in location and intensity.

His social history is negative for tobacco or illicit drugs of abuse, and his consumption of alcohol is minimal. The patient was born and raised in Britain, but received a job transfer to the United States in the year 2000.

Examination reveals a visibly anxious young man who appears exhausted. He is a good historian and responds appropriately. Language is intact to fluency, repetition, and comprehension. However, he occasionally makes paraphasic errors, such as mistaking “foot” for “shoe.” He also displayed an instance of right-left confusion, which he immediately corrected. He has an action tremor on bilateral finger-to-nose that worsens as his finger approaches the target. Rapid, repetitive movement is significantly arrhythmic and irregular. Sensory exam reveals diffuse parasthesias that are not restrained to any specific anatomical distribution.

BACKGROUND

- The patient has New Variant Creutzfeldt-Jakob Disease (vCJD), a spongiform encephalopathy transmitted via prions. vCJD is a recently-defined clinical entity marked by transmission of prion via exposure to Bovine Spongiform Encephalopathy (Mad Cow Disease). Unlike classical CJD, vCJD manifests marked psychiatric and sensory symptoms early in the disease. The first cases of vCJD were reported during the early 1990s in the United Kingdom, where an outbreak of Bovine Spongiform Encephalopathy had occurred. The defined period of risk for exposure to Bovine Spongiform Encephalopathy in the UK is 1980-1996.

PATHOLOGY

- CJD and its various subtypes (vCJD and Gerstmann-Straussler-Scheinker syndrome, fatal familial insomnia) are neurodegenerative diseases of prion transmission in

humans and other primates. Prion diseases of animals includes Scrapie (in sheep), Bovine Spongiform Encephalopathy (in cows), and Chronic Wasting Disease (in deer and elk), among others.

- Prions are pathological conformations of normal proteins that induce transformation of the normal protein into the pathological isoform. Pathologic prions are designated Pr^{Sc} (for scrapie) and their normal conformational counterparts are designated Pr^C. Amino acid sequencing of Pr^C shows either methionine or valine at codon position 129. Interestingly, vCJD is exclusively confined to patients that are homozygous for methionine at codon 129.
- Prions are noted for their transmissibility via consumption, and it is believed that vCJD is caused by consumption of beef from cows infected with Bovine Spongiform Encephalopathy. They are unique in the world of infectious agents, considering that they mediate their infectivity without nucleic acids. Since prions do not contain any nucleic acids and are resistant to proteases, they cannot be degraded by normal biological means. The prion isoform aggregates to produce amyloid, which leads to vacuolization and cell death. Unlike vCJD, classic CJD occurs spontaneously (80 percent of cases) or is inherited.

CLINICAL PRESENTATION

- The average age of onset for vCJD is 20 to 30 years old. Once the patient becomes symptomatic, decline is rapid with death occurring in months to a year. The incubation period of vCJD is still unknown, but is likely years to span decades.
- Psychiatric or sensory symptoms predominate in early disease, with myoclonus, cerebellar ataxia, and dementia occurring later in disease. An exaggerated startle myoclonus is common.
- Conversely, classic CJD typically has an onset in the sixth to seventh decades of life and progresses even more quickly. Typical symptoms of classic CJD paint a picture of an extremely rapid progressive dementia with memory loss, confusion, and behavioral changes. Other significant neurologic symptoms are myoclonus, ataxia, aphasia, visual changes, and lower motor neuron signs.

DIAGNOSIS

- The typical EEG finding of classic CJD is periodic or pseudoperiodic paroxysms of sharp waves and spikes against a slow background. This finding is usually not seen in vCJD. However, MRI of vCJD patients shows T2-weighted hyperintensity on the posterior thalamus, or the “pulvinar sign.” This finding is less often seen in classic CJD. Spinal fluid is remarkable for a lack of inflammatory markers in either disease. Testing for CSF 14-3-3 protein is sensitive and specific for classic CJD. Measurement of neuron-specific enolase and S100 proteins in CSF is not useful diagnostically, as these proteins are nonspecific and nonsensitive for CJD.
- Pathological analysis is the gold standard of diagnosis and shows vacuolization, neuronal loss, and gliosis. Amyloid plaques are common in vCJD, but are only present in 10 percent of classic CJD. Prion protein can be detected via electrophoresis.

TREATMENT

- There is no treatment for prion disease that slows or alters the disease course. Social and educational support for the patient and the patient’s caretakers is important.

- Transmissibility is a major concern in prion disease. Prions are resistant not only to biological mechanisms of degradation, but also to standard sterilization procedures as well. From this, iatrogenic cases of CJD following dura mater graft or intracerebral electrode implantation have been reported. There is one case of vCJD reported in the United Kingdom in which the source of exposure was thought to be from a blood transfusion. Also, an inoculation with blood of patients with CJD has led to development of that disease in mice. Therefore, blood and tissue from patients with CJD must be treated with extreme caution. Intracerebral implantation is the most efficient route of transmission, leading to death more quickly than transmission via prion consumption. Sterilization procedures should include autoclaving, soaking in phenols or detergents, and exposure to extremes of pH.

PROGNOSIS

- Prognosis is uniformly fatal. Death occurs within about one year for vCJD and within half a year or less in classic CJD.

9. Tay Sachs Disease

A 2-month-old boy is brought to your clinic for an evaluation for developmental delay. His birth was uncomplicated and his APGAR scores were normal. However, the patient remained hospitalized for a week due to poor feeding. After being brought home, the parents noted a significant generalized weakness. He only lies on his back and is unable to change position on his own. When he is sat up, the patient is unable to hold up his head and slumps to his side.

On examination, his eyes follow your penlight from side to side, and he seems to respond to his mother's voice. He has a brisk startle response with arm extension, and clonus to even mild touch that does not attenuate with repetition. A fundiscopic examination reveals pale nerve discs and a distinctive red circular lesion on the fovea. The parents are non-consanguineous Ashkenazi Jews. Both mother and father have first degree relatives who have died of this condition. You continue to follow the patient, and at 1 year of age his pupils are no longer reactive to light. The fundiscopic exam at this point reveals pale white optic nerves with little vascularization. The initial flaccidity has now become spasticity. At 18 months, the patient develops generalized tonic-clonic seizures. At 3 years of age, the patient dies of pneumonia.

BACKGROUND

- The patient has Tay Sachs Disease (TSD), an inborn error of metabolism. TSD is caused by a genetic mutation that leads to loss of an enzyme called hexosaminidase A. This enzyme, found in the lysosomes, catalyzes the biodegradation of fatty acid derivatives known as gangliosides. When hexosaminidase A function is insufficient, as it is in TSD, the gangliosides accumulate and damage the brain.
- Patients and carriers of TSD can be identified by a simple blood test that measures hexosaminidase A activity.
- Infantile TSD is a particularly devastating disease, with infantile onset and death occurring by 3 to 5 years of age. It is autosomal recessive in inheritance.

PATHOLOGY

- There are two beta-hexosaminidase isozymes. Beta-hexosaminidase A is composed of an alpha and a beta subunit whereas beta-hexosaminidase B is composed of 2 beta subunits. The gene mutation of TSD leads to loss of the alpha subunit, leading to loss of beta-hexosaminidase A, while beta-hexosaminidase B remains biologically active. (The closely-related Sandhoff Disease is caused by a mutation in the beta subunit, causing a loss of both A and B isozymes.)
- The genes that encode for beta-hexosaminidase A and B are HEXA (chromosome 15) and HEXB (chromosome 4), respectively. Beta-hexosaminidase A cleaves N-acetyl-galactosamine from gangliosides, and disruption of this function leads to accumulation of GM2 ganglioside in cortical neurons, Purkinje cells, and retinal cells.
- Pathology reveals an abnormally large brain of significant gliosis and neurons distended with glycolipids two to three times their normal size. Histology shows accumulation of gangliosides in the cytoplasm. TSD is rarely caused by mutations in the hexosaminidase genes. Instead, causation stems from a mutation in the gene

coding for an GM2 activator protein, which is used in the degradation of GM2 ganglioside.

- Sandhoff Disease is a closely related disease caused by deficiency of beta-hexosaminidase A and B isozymes. This is due to a genetic mutation causing a defect in the beta subunit (TSD occurs due to a defect in the alpha subunit causing a loss of beta-hexosaminidase A only). The major ganglioside of storage in this disease is globotetraosyl ceramide (globoside). Symptoms are similar to classic TSD with the addition of ganglioside accumulation in visceral organs, causing hepatosplenomegaly and bony malformations.

CLINICAL PRESENTATION

- The classical form of TSD begins within a few weeks to months of birth. Often, the first abnormality noticed is an excessive startle response to a visual, auditory, or tactile stimulus that does not attenuate with repetition. Generalized weakness becomes evident quickly, with delayed development of motor skills, and loss of other learned motor skills. Patients are unable to roll over or sit on their own. Hypotonia is present initially, but is replaced by spasticity as the disease progresses.
- Visual failure develops through damage to the retinal ganglion cells. The cherry red spot on the macula is a classic finding in TSD, but is not due to an abnormality in the macula itself. Rather, in TSD patients the retina surrounding the macula is paler than normal due to the presence of lipid-distended retinal ganglion cells. Therefore, the normally red macula (showing the redness of the chorioidal circulation) stands out in greater contrast in TSD patients due to the pale halo surrounding it. Note that TSD is not the only disease in which the cherry red spot is seen. It can be seen also in Niemann Pick Disease.
- Seizures begin in the second year of life, and can be partial or generalized tonic-clonic. Macrocephaly occurs without hydrocephalus or other disturbances of the ventricles. By 3 to 5 years of age, the patient is severely and cognitively impaired, blind, and decerebrate. Death occurs through cachexia or respiratory failure.
- There exists juvenile-onset and adult-onset variants of TSD in which the disease is associated with mutation of the GM2 activator protein. Patients with the adult/late-onset variant have a slow progressive course with generally preserved motor development. Ataxia, muscle atrophy, and psychiatric symptoms begin in childhood. However, patients can still have a normal lifespan.
- Ashkenazi Jews are the cohort typically associated with this disease, secondary to the propagation of recessive alleles within a closed community.

DIAGNOSIS

- There are three prominent genetic mutations among the Ashkenazi Jewish population. Two of which will cause classic TSD, while the other is seen in 95 percent of late-onset TSD. These mutations, along with other less common mutations, can be screened via genetic tests. Enzyme analysis is the screening test, which is followed by confirmatory DNA mutational analysis in suspected cases. Patients with identified TSD should screen family members to identify asymptomatic carriers.
- Prenatal testing is available as early as 8 to 12 weeks of gestation. This testing has been effective in lowering the incidence of TSD in Ashkenazi Jewish populations.

- MRI studies show diffuse atrophy with T1-weighted hyperintensity in the deep grey matter. Nerve conduction studies are normal, but EMGs show fasciculation's, fibrillations, and neurogenic pattern of muscle damage.

TREATMENT

- There is no treatment available for TSD. Enzyme replacement, bone marrow transplantation, and cellular infusion have all been tried with limited success. The only effective therapy has been prevention via carrier screening, elective abortion, and alternative reproduction methods.

PROGNOSIS

- Patients with Infantile TSD usually die by age 5. The adult/late onset patients may have a normal life span, albeit they live with multiple symptoms and dysfunction.

10. Friedrich's Ataxia

A 9-year-old girl is brought to your clinic for gait difficulty. Several months ago the patient began to note difficulty in running while playing soccer. Her family states she would fall without reason, and initially attributed it to clumsiness. Over the course of time, it seems to have worsened slowly but progressively. Recently, she had a viral illness which seems to have worsened the unsteadiness to the point where she cannot even stand. This condition persists even after the illness resolved. The father states that he may have a cousin with a similar symptom who died many years ago. The mother is unsure of her family history. On examination, you note a slight foot deformity with high plantar arch. There is a mild scoliosis as well. Her sensory exam reveals absent vibration and reflexes in the lower extremities. There is significant dysmetria in bilateral legs. Upper extremities show mildly decreased vibration only. Over the course of a decade, the disease worsens to the point when she is severely disabled and wheelchair-bound. She sways and teeters on standing, even with feet wide apart. Lower extremities are spastic with upgoing toes, even though reflexes are lost diffusely elsewhere. The foot deformity progresses to cause extension at the metatarsophalangeal joint and flexion at the interphalangeal joints. Sensation reveals diminished vibration and proprioception in all extremities. Cerebellar findings are present in the upper extremities as well. Her speech is dysarthric and scanning. The patient passes away at age 25 from complications of heart failure.

BACKGROUND

- The patient has Friedrich's Ataxia (FA), a metabolic disorder leading to neurodegeneration of the peripheral nerves and spinal cord. It is autosomal recessive in inheritance, and is the most commonly inherited ataxia overall. Classically, it is associated with cardiac and orthopedic abnormalities. There is a wide spectrum of inherited ataxias in their age of onset, clinical severity, and associated symptoms. Inherited ataxias can be autosomal dominant, autosomal recessive, X-linked, and mitochondrial in inheritance.

PATHOLOGY

- FA is caused by GAA triplet expansion in chromosome 9. This results in an abnormal conformation of the DNA that impedes transcription and translation of the frataxin protein. As it is autosomal recessive in inheritance, both alleles must show expansion. However, in 5 percent of cases, there is only expansion in one allele, with a point mutation in the unexpanded allele. Frataxin is a mitochondrial enzyme involved in iron removal and respiratory chain function. Decreased levels of frataxin lead to iron buildup and oxidative damage to mitochondria. Certain tissues are particularly affected by frataxin dysfunction, including the peripheral nerves, the dorsal root ganglions, the posterior columns of the spinal cord, the pyramidal tracts, and the spinocerebellar tracts. The size of the GAA expansion is associated with age of onset and clinical severity. However, there are other predictive factors, as there is significant variability within the same range of GAA expansion. Pathology reveals a thin spinal cord with degeneration of the posterior columns, as well as the corticospinal and spinocerebellar tracts. Dorsal root ganglia have decrease numbers of nerve bodies, and the peripheral nerves are demyelinated. There is decreased size of the cerebellar peduncles, but significant

cerebellar atrophy is not a feature of FA. Myocardial tissue shows heavy fibrous replacement.

CLINICAL PRESENTATION

- Onset of symptoms is typically from 5 to 25 years of age, with the mean age of onset around 15 years old. Gait ataxia is the primary presenting symptom. Sensory loss and diminished reflexes are also present at presentation. These symptoms are secondary to loss of large myelinated peripheral nerves and neurons in the dorsal column tract. Pes cavus, hammer toes, and kyphoscoliosis may exist at presentation, or develop several years afterwards. There are a number of movement abnormalities seen in FA, the most common being rhythmic involuntary movements of the eyes. Dystonic postures, myoclonus, and postural tremor have also been described. Pyramidal tract involvement leads to amyotrophy and weakness in the lower extremities. Extensor plantar reflexes are seen, even with loss of ankle and knee jerks. Speech becomes slow and uncoordinated, leading to “scanning” speech. Hypertrophic cardiomyopathy develops over time in 50 percent of patients, leading to symptoms of cardiac failure and dysrhythmia. Death occurs in the second to fourth decades of life from cardiac etiologies or complications of immobility. Diabetes Mellitus is associated with 10 percent of FA. Other associated symptoms include optic nerve atrophy and hearing impairment. Of note, there is a variant of FA in which tendon reflexes are preserved, and in some cases, brisk. Kyphoscoliosis and heart disease are not seen in this variant. The late-onset variant occurs after the age of 25. Both of these variants are associated with the typical GAA expansion.

DIAGNOSIS

- Neuroimaging is underwhelming. Cerebellar atrophy is not typically seen on MRI or CT, although the spinal cord may appear thin on MRI. EMG findings are consistent with a diffuse demyelinating sensory neuropathy. DNA testing is available and can identify GAA triplet repeats in chromosome 9. Once the diagnosis has been made, gene testing should be offered to the patient’s family to identify asymptomatic carriers. Prenatal testing is also available. Echocardiogram must be done every two years to evaluate cardiac status.

PROGNOSIS

- Management is supportive only. Prostheses, walking aids, wheelchairs, antispastic medications, and therapy can help prolong mobility. Diabetes Mellitus and congestive heart failure are treated in the typical fashion. Feeding and respiratory support may be required in late disease. Coenzyme Q has been used for its antioxidant effects and may show a benefit in cardiomyopathy.

11. Metachromatic Leukodystrophy

A previously healthy, intelligent 16-year-old male is brought to the attention of the school guidance counselor for behavioral problems. He is getting into fights and his grades decline from As to Cs over the course of a year. There is no clear social issue to precipitate this change. After episodes of intense agitation and paranoia, he is diagnosed as having a primary psychiatric disorder. Over the next several years, the patient becomes involved in multiple illicit substances, including marijuana, ecstasy, and cocaine. He attends college, but drops out after a year. After five years, he is brought to the attention of a neurologist for cognitive problems by his parents, whom he lives with. His family is concerned about his ability to drive, as he had two recent minor accidents. They report his memory is quite poor, and recently he has been getting lost on the way from his house to the grocery market where he works. His social history is significant for a pack of tobacco per day, occasional alcohol use, and occasional marijuana use. He denies recent usage of other illicit substances. His family history is significant for a maternal uncle who died of "some sort of dementia" in his 30s, but further details are unavailable. On physical exam, he is well-nourished without any craniofacial abnormalities. He is polite and well-behaved, although restless and with poor concentration. The mental status exam reveals poor memory registration and recall at 5 minutes, but otherwise he is a good historian and responds appropriately. He has mildly diminished vibration and proprioception at the toes and ankles, with one reflex at the ankles. The rest of his neurologic exam is unremarkable. You order an MRI and EMG. MRI shows bilateral diffuse white matter hyperintensities on T2-weighted imaging, predominantly in the frontal lobes. There is no contrast enhancement and grey matter is spared. EMG showed diminished conduction velocity but normal amplitudes at the sural nerves.

BACKGROUND

- The patient has metachromatic leukodystrophy (MCL), an inherited disease of lysosomal enzyme deficiency, characterized by central and peripheral demyelination and metachromatic granules in white matter on pathology. The disease is caused by a deficiency of arylsulfatase A activity leading to sulfatide accumulation. Clinical features vary depending on age of onset, which ranges from infantile (1 year old) to adult (greater than 12 years old), but typically includes loss of learned motor and cognitive skills. The lack of dysmorphic features helps differentiate from other inherited enzyme deficiencies.

PATHOLOGY

- Arylsulfatase A is a lysosomal enzyme that hydrolyzes galactose-3-sulfate from sulfatides. Dysfunction of this enzyme leads to accumulation of sulfatides which, through unknown mechanisms, leads to demyelination of the CNS and PNS, as well as deposition of metachromatic granules in the CNS and PNS white matter. It is thought that the accumulation products are neurotoxic, although the exact mechanism is still controversial. There are over 100 known mutations of this enzyme that leads to MCL, with many unidentified mutations as well. Mutations can cause complete or partial loss of enzymatic activity, which leads to varying degrees of clinical severity. It is autosomal recessive in inheritance. The key pathological feature is the deposition of metachromatic granules, from which the disease derives

its name. These are inclusion bodies that stain a different color than the dye used (i.e. metachromia). They are present not only in the central and peripheral neurons, but also microglia, oligodendrocytes, Schwann cells, kidney, gallbladder, and other non-neurologic tissues.

CLINICAL PRESENTATION

- The clinical syndromes are classified according to age of onset, with earlier onset disease being more severe. Late infantile form (1 to 2 years old) begins with loss of learned motor function, specifically walking. The patient develops flaccid weakness and hypotonia. After a few months to a year, the cognitive symptoms begin with loss of speech. Ataxia, nystagmus, and spasticity begin to develop. This leads to a spastic quadriplegia with various forms of posturing. Eventually, the child becomes blind, deaf, and is unable to interact meaningfully with the environment. This progresses over the course of several years, and sometimes over a decade. The juvenile form (4 to 12 years old) begins with behavioral disruption and cognitive impairments, first noticed at school. It evolves to include incontinence, gait disturbance, and extrapyramidal symptoms, eventually ending with a spastic, bedridden patient lacking any meaningful interaction with the environment. This can progress over the course 20 years or more. The adult onset form can range from 12 to 70 years in age of onset. Behavior and psychiatric symptoms predominate the early course, with anxiety, disorganized thinking, and psychosis. Symptoms can also begin with signs and symptoms of a peripheral neuropathy. More neurologic features develop, eventually ending in spastic quadriplegia and death over the course of 5 to 10 years. Seizures are a common symptom, as is gallbladder problems.

DIAGNOSIS

- MRI is a key component to diagnosis, and is often the first test that can differentiate between the multiple other inherited enzymic deficiency syndromes. MRI shows diffuse symmetric T2-weighted hyperintensities reflective of CNS demyelination. It begins periventricularly but can progress to the corpus callosum, cerebellum, and internal capsules. Lesions do not enhance. The lack of dysmorphic features also helps differentiate MCL from other inherited enzymatic deficiencies. EMG shows evidence of segmental demyelinating neuropathy, but neuropathy may be absent in patients with late juvenile or adult onset. Diagnosis is based on testing of enzymatic activity and accumulation products. It can be confirmed by genetic sequencing. Direct analysis of arylsulfatase A activity can be performed, and sulfatides can be measured in urine sediment via 24-hour urine collection. Mutation analysis of the most frequent arylsulfatase A mutations can also be performed for confirmation if necessary.

TREATMENT

- Treatment is symptomatic with antispasticity, antiepileptic, and antipsychotic medications. Bone marrow transplantation or hematopoietic stem cell transplant is an increasing acceptance as therapy for lysosomal enzyme disorders. Donor bone marrow cells migrate to target organ, leading to replacement of the deficient enzyme. In cases of juvenile or adult onset MCL without neurologic decline, this therapy has been shown to slow or delay onset of the disease. This selection criteria is further limited by the availability of HLA-matched donors.

12. Coma

A 17-year-old female presents to the ER after a significant motor vehicle accident in which she was thrown through the windshield. Upon arrival, she's completely unarousable to deep stimulation, has a large unreactive right pupil, and has decorticate posturing to stimulus. The head CT shows a large left hemispheric hemorrhage with significant edema and downwards herniation of the brainstem. The patient is treated with emergent intubation involving hyperventilation, and mannitol infusion while an intracranial pressure monitor is placed. The ICP stabilizes at 15-20 mmHg without any surgical treatment, and over the course of several days decreases to 10-15 mmHg. Her examination at this point shows complete lack of arousal to noxious stimuli (she is not on any sedatives), but intact pupillary light reflex, oculocephalics, and gag reflex. An MRI shows not only the hemorrhage and surrounding edema, but also white matter changes at the grey-white interface in multiple areas. An SSEP shows intact N20 responses bilaterally. Over the next two weeks, she is weaned off the ventilator and IV medications. Three weeks after the trauma, she still lacks spontaneous eye opening and movement with noxious stimulation. She is discharged to a nursing care facility in this condition. At the facility, she begins to exhibit spontaneous eye opening. At four months post trauma, she moves her limbs non-purposefully, makes incomprehensible sounds to stimuli, and even smiles occasionally. However, she does not display any meaningful interaction with her environment or her family. She displays a sleep-wake cycle. At six months, she begins to localize to environmental sounds and stimuli. She presents brief, but consistent visual tracking, and reaches for objects. She begins to verbalize single words, although she is not using them appropriately in context. At one year, she is walking with assistance and speaking in full, fluent sentences. Other than memory loss anterograde and retrograde from the trauma, she displays her full mental faculties.

BACKGROUND

- This patient was in a coma secondary to closed-head trauma with diffuse axonal damage. Over the course of a year, her clinical status progressed from coma to persistent vegetative state (PVS), to minimally conscious state (MCS), and finally, to recovery.

PATHOLOGY

- Disorders of consciousness occur as responses to global or multifocal brain injury. Consciousness depends on the interaction of the reticular activating system in the dorsal pons and midbrain with its wide-spread projections to subcortical and cortical structures. Given the multitude of injuries that can cause coma, pathologic features diffuse in different situations. In trauma, shearing of the axons at the grey-white junction and termed diffuse axonal injury leads to functional isolation of the cortex. Metabolic and hypoxic injury lead to global depression of neuronal function. Diffuse laminar necrosis is seen on autopsy after hypoxic damage.

CLINICAL PRESENTATION

- Consciousness is defined as wakefulness with awareness of self and the environment. There is a spectrum of disorders of consciousness, with one end consisting of complete lack of awareness and wakefulness, and the other end consistent of wakefulness with impaired awareness. Coma is a state of complete

unconsciousness in which the patient does not respond to any stimuli. It has been described as “unarousable unawareness.” It is the result of multiple etiologies of brain injury, including trauma, tumors, developmental abnormalities, medication toxicity, metabolic disorders, and neurodegenerative diseases. Patients in PVS are awake, but show no meaningful interaction with the environment. Patients in MCS are awake and show consistent, reproducible evidence of awareness of self or environment.

- Coma is the state of unarousable unawareness. The patient is unconscious, and there is no response to noxious stimuli. There is no eye opening or spontaneous movements. Any limb movements observed are secondary to spinal or brainstem reflexes. Cranial nerves can be present. PVS occurs after several weeks of coma, following the recovery of some brainstem function. The patient is still unconscious, but may now exhibit spontaneous eye opening and posturing, or withdrawal to noxious stimuli. Smiling or other emotional responses may be seen, but they are secondary to deep subcortical reflexes and not conscious effort. There is no meaningful interaction with the environment. A sleep-wake cycle is observed in this state, as are other hypothalamic and brain-stem autonomic functions. Orientation to environment may be seen, but is brief and inconsistent. MCS occurs as the brainstem and cortex continue to recover, and is marked by partial consciousness in the patient. The patient localizes noxious and auditory stimuli, reaches for objects, and demonstrates sustained visual fixation. Communication is intelligible but inconsistent.

DIAGNOSIS

- Diagnosis is through clinical criteria. Clinical criteria for PVS and MCS may be confusing for clinicians not accustomed to these patients. EEG’s do not reliably distinguish between disorders of consciousness. In general, EEG’s of patients with coma or PVS show slow delta or theta activity, with attenuation to noxious stimuli. Occasionally, persistent alpha activity that does not attenuate with stimuli is seen. This is called alpha coma. As the patient transitions from coma to PVS, the change from wakefulness to sleep is accompanied by desynchronization of the background. Somatosensory evoked potential may play a role in prognostication in coma patients. The absence of bilateral N20 responses one week after a hypoxic event is highly predictive of failure to recover consciousness. There are currently no prognostic factors that indicate a good chance of recovery.
- Locked-in state must be ruled out in making diagnoses for disorders of consciousness. Locked-in state is defined by patients who are completely or almost completely paralyzed but with intact consciousness. This can occur with large brainstem strokes affecting the lower pons, affecting the motor tracts of the face, limbs, and extraocular muscles, but sparing the reticular activating system and the cortex. Brain death is a separate entity than coma. It is defined as the complete cessation of all brain function. Like coma patients, those experiencing brain death are unaware and unarousable. However, brain death implies loss of all brainstem function, leading to lost cranial nerve reflexes, lost apneic drive, and lost cardioregulatory function. By definition, there is no recovery from brain death.

TREATMENT & PROGNOSIS

- Trauma is the most common acute cause of coma and PVS. Hypoxic-ischemic encephalopathy is the most common non-traumatic etiology. Coma progresses to

PVS after several weeks. PVS and MCS can be transitory as the patient continues towards recovery, or could be permanent. Likelihood of recovery depends on the cause. In general, prognosis for recovery is poor. However, patients with acute traumatic brain injuries have a higher likelihood of recovering than nontraumatic brain injuries. Recovery of consciousness in patients who have not demonstrated improvement by 12 months is unlikely. Patients with dementias or neurodegenerative diseases of metabolic origin do not ever display recovery. Patients who do not recover have a lifespan of about two to five years, and eventually succumb to complications of immobility. Treatment for these patients consists of supportive care which can include mechanical ventilation, IV hydration, and artificial means of feeding.

13. Subdural Hematoma

A 65-year-old man presents to the ER after a moderate-speed motor vehicle accident. He was an unrestrained front passenger and hit his head on the dashboard. On arrival, his Glasgow Coma scale is 15 and his neurological exam is unremarkable. However, he complains of severe bifrontal headache. A head CT shows a moderate amount of atrophy with a small concave hyperintensity overlying the right frontal lobe. There is no skull fracture. The patient is admitted for monitoring and is started on dilantin for seizure prophylaxis. The nurse reports that the patient is lethargic and not oriented to time or place 8 hours later. The repeat head CT shows expansion of the hyperintensity leading to compression of the underlying hemisphere. There is a 3mm falcine shift. The neurosurgeon is consulted emergently. The patient undergoes a right hemisphere craniotomy, where a large collection of blood is seen underneath the dura. The blood is evacuated and the patient is monitored in the ICU, where he is stable for several days. Eventually, he is discharged in good condition without neurologic deficits.

BACKGROUND

- The patient had a traumatic subdural hematoma (SDH). Subdural hematomas are extra-parenchymal accumulations of blood underneath the dura. Classically, it is thought to be secondary to the rupture of bridging veins. However, in one-third of patients, arterial rupture has been found during surgery. SDH can occur via trauma or spontaneously. Risk factors for SDH include age and chronic alcoholism since they lead to brain atrophy, stretching the bridging veins. Anticoagulants and chronic dialysis increase the risk. Subdural hematomas cause brain damage through compression of the underlying tissue which leads to mass effect, and shifts if significant enough in volume. In addition to compression, SDH decreases metabolism and blood flow of the underlying parenchyma, leading to further deficits. It is the underlying brain injury that has the most prognostic significance in recovering from the deficits.

PATHOLOGY

- The composition of the SDH evolves with time. Following 24 hours after the initial hemorrhage, the blood clot is covered with a layer of fibrin. Over days to weeks, a membrane encapsulates the clot, and phagocytic cells liquefy it. By the time the SDH has reached the chronic stage, the hematoma is fluid in consistency. This accounts for the changes seen on CT during the evolution of the SDH.

CLINICAL PRESENTATION

- Severe acute SDH can lead to brain herniation, shift, coma, and death. In less severe SDH, clinical symptoms depend on the location and size. SDH that is localized to the poles of the frontal lobes, particularly on the non-dominant side, may not produce any focal deficit. It is not uncommon for patients to present with symptoms of a chronic SDH without ever having had symptoms of an acute SDH. These patients may present with transient ischemic attack (TIA) symptoms that are caused by intermittent cortical vessel compression or vascular displacement. Seizures may also be an initial presentation of SDH. These may be secondary to modest head trauma or may be spontaneous. Syndrome of Inappropriate Secretion of Antidiuretic Hormone (SIADH) can result from SDH.

DIAGNOSIS

- CT scan is the study of choice, as it can detect hemorrhages and bony fractures with high sensitivity. Acute SDH appears as a hyperintense signal overlying the brain parenchyma in a crescent shape. As the clot is resorbed after one week, the SDH appears isodense to the brain. After three weeks, the SDH is hypodense.

TREATMENT

- Treatment can be either medical or surgical, with surgical options usually reserved for emergent cases. Surgical evacuation involves craniotomy with evacuation of the entire hematoma, control of the source of hemorrhage, and resection of nonviable, underlying brain tissue.
- Burr holes may be used early in treatment prior to more extensive surgery. Post-operative reaccumulation of blood must be expected with repeat CT's.
- Medical management consists of close monitoring and seizure prophylaxis. Mannitol may be used to reduce intracranial pressure.
- Patients with symptomatic chronic SDH should undergo surgical drainage. Evacuation can be done via burr holes. Craniotomy should be reserved for patients with recurrences, or SDH with fresh clot. Patients on anticoagulants should have their coagulopathy reversed with vitamin K, fresh frozen plasma, platelets, or cryoprecipitate as needed. Anticoagulation can be restarted in about three weeks.

14. Epidural Hematoma

A 6-year-old girl presents to the ER after falling from a swing. She was being pushed by her sister when she fell off at the peak of her swing, hitting her head. Her sister tells you that the patient was unconscious for a few seconds, and returned to normal. The two returned home several hours later when the parents noted that she was “acting dazed.” She declines on the way to the hospital. She is currently unconscious and difficult to arouse. Her GCS is 7 (opens eyes to pain, makes incomprehensible sounds, and flexes to pain). An emergent head CT shows a lens-shaped hyperdensity in the right hemisphere which is causing surrounding cortical edema and midline shift of the septum pellucidum by 3 mm. A small fracture of the right temporal bone is also noted. A neurosurgical consult is placed, and the patient is brought to the OR emergently.

BACKGROUND

- The patient had an epidural hematoma secondary to head trauma. Epidural hematomas are neurosurgical emergencies given their rapid expansion, which can lead to death.
- Epidural hematomas are accumulations of blood in the space between the dura mater and the skull. They occur most commonly secondary to rupture of the middle meningeal artery. Because the high arterial pressure is opposed only by brain tissue, blood accumulation is rapid and leads to parenchymal compression on the order of hours to days. On rare occasions, rupture of the dural venous sinuses can cause an epidural hematoma. In such causes, onset of symptoms can be delayed by days to weeks.

PATHOLOGY

- Epidural hematomas are typically caused by head trauma and are associated with a lucid period prior to clinical decline. The lucid interval can last hours to days in the case of an arterial rupture, or days to weeks with a venous rupture. Symptom onset is typical for increasing intracranial pressure – headache, lethargy, nausea, and vomiting. The hematoma may precipitate a seizure. Consciousness declines to coma as brain structures are shifted past midline, and hemiparesis occurs contralateral to the side of the hematoma. Signs of herniation occur as the hematoma continues to expand, leading to decorticate or decerebrate posturing, cranial nerve defects, and respiratory failure. Death follows if untreated.

DIAGNOSIS

- Diagnosis is made via head CT. Epidural hematomas are lens-shaped accumulations that are restricted by suture lines in the skull, but not by falx divisions. This is the opposite of subdural hematomas, which can cross suture lines but must respect the boundaries of the tentorium. It is common to see fractures of the skull along the path of the middle meningeal artery.

TREATMENT

- Treatment consists of burr holes for surgical drainage, or craniotomy for drainage and repair of the bleeding vessel.

PROGNOSIS

- Prognosis depends on the state of the patient prior to the surgery. Coma, bilateral Babinski signs, and decerebrate posturing are negative prognostic factors.

15. Cortical Ischemic Stroke

A 56-year-old man with a history of long-standing hypertension and congestive heart failure presents with acute onset of right sided weakness and language disturbance. He was at the golf course when he suddenly dropped his golf club and found himself unable to speak. His friends describe it as if he was incapable of producing words, yet he was able to gesture appropriately to their questions. They also note that his face seemed asymmetric as well. He was able to walk back to the club house with them, where they called 911. He is brought to the ER within 2 hours of symptoms. On arrival, weakness appears limited to the face and arm on the right. Language is intact to comprehension, but not fluency or repetition. There is no sensory neglect, acalculia, or left-right confusion. His NIH Stroke Scale is 13; he is unable to answer questions of month or age, he has partial gaze palsy with gaze preference to the right, complete left hemianopsia, a partial right facial palsy, no effort against gravity in his right arm, mild-to-moderate sensory loss on the right side, mild-to-moderate aphasia, and there is mild-to-moderate dysarthria. A head CT shows blurring of the grey-white junction at the right frontal cortical ribbon and basal ganglia. An EKG shows atrial fibrillation, which he has never been diagnosed with before. Coagulation studies and platelet count are normal, and IV TPA is given. He has immediate and dramatic improvement. On discharge three days later, he displays only mild weakness in his right arm and intermittent word-finding difficulties.

BACKGROUND

- The patient had a cortical ischemic stroke of the right frontal MCA distribution, most likely secondary to cardioembolism in the setting of new-onset atrial fibrillation.

PATHOLOGY

- Strokes that involve cortical structures are typically due to occlusion of major feeding vessels such as the MCA, ACA, or PCA. This leads to infarction of large territory, depending on the proximity of the occlusion.
- The most common cause of large vessel strokes is cardioembolism. Atrial fibrillation, heart wall movement abnormalities, stenotic valves, and vegetations are risk factors for formation of cardiac emboli. Right-to-left shunts such as patent foramen ovale, or in some cases pulmonary arteriovenous malformations, may allow a venous clot to travel to the brain by bypassing the pulmonary system.
- Plaques and atherosclerotic disease of large vessels such as the carotid arteries introduce another embolic risk, and can also cause local thrombi as well. Less commonly, large vessel dissections lead to stroke, either via occlusion of the true lumen, or by formation of clot at site of intimal tearing.
- Small-territory strokes can occur with occlusion of the end-arterioles. This is termed lacunar strokes. These strokes are strongly associated with uncontrolled hypertension, causing smooth muscle hypertrophy of the vessel walls and lipohyalinosis.
- Determining the etiology is important for deciding therapy. Once the clot has occluded the vessel, a core infarcted brain tissue forms. There is larger area of “stunned” brain where blood flow is insufficient to sustain dependant brain tissue, but the ischemic tissue is not yet infarcted. This is called the ischemic penumbra, and saving this zone of brain is the centerpiece of acute stroke therapy.

CLINICAL PRESENTATION

- Symptoms depend on the location and size of the stroke. Complex neurologic deficits such as aphasia, apraxia, neglect, and hemianopsia localize to cortical structures, and thus are termed cortical signs.
- Involvement of the primary motor cortex leads to contralateral weakness in the distribution of the affected homunculus.
- Aphasias localize to the left hemisphere; Wernicke's aphasia localizes to the superior temporal lobe, and Broca's aphasia localizes to the posterior frontal lobe. In practice, patients rarely have aphasias that fall neatly into the Broca-Wernicke semiology.
- Agraphesthesia localizes to the contralateral primary sensory cortex.
- Neglect is a feature of right parietal infarct.
- Apraxia can be difficult to localize, and can be seen in frontal and parietal strokes.
- Subcortical strokes have a predilection to occur in the periventricular subcortical white matter, the internal capsule, the basal ganglia, the thalamus, or the brainstem, producing different syndromes. Typical lacunar stroke syndromes include pure hemiplegia, pure hemisensory loss, mixed hemiplegia-hemisensory loss, clumsy hand-dysarthria, and ataxic hemiparesis. Spasticity and hyperreflexia develop later in the course of the stroke, the initial weakness is a placid paralysis. The vascular territory of the stroke can be deduced via the constellation of the patient's symptoms.

DIAGNOSIS

- Noncontrast head CT or brain MRI should be done within 30 minutes of patient arrival in an acute stroke. Signs of ischemia are subtle in early infarcts and involve the loss of grey-white differentiation at the cortical ribbon, or blurring of the deep grey-matter structures. Older strokes are more obviously hypodense. Diffusion-Weight Imaging and Apparent Diffusion Coefficient sequences on MRI are highly sensitive for acute ischemia. Hemorrhagic stroke must be ruled out via either of these methods before proceeding to treatment. Angiography can be done to evaluate for intravascular disease, stenosis, or dissection. Conventional cerebral angiogram produces the clearest image, but is the most invasive. CT and MR angiograms are options to evaluate for disease of large vessels. An EKG should be done on arrival to the ER to evaluate for rhythm abnormalities. All ischemic stroke patients should have at least 24 hours of cardiac monitoring to evaluate for paroxysmal rhythms. Basic chemistry and liver panels are checked to rule out metabolic diseases that imitate stroke. Platelets and coagulation factors are checked to evaluate for bleeding risk. Once the patient is admitted, carotid dopplers can be checked from intravascular disease, and echocardiogram is done to evaluate for risk factors of cardiac emboli.

TREATMENT

- Treatment of acute strokes (less than 3 hours after onset) consists of IV tissue plasminogen activator (tPA). Strokes greater than 3 hours but less than 6 hours can be treated with intraarterial tPA. Patients who are at risk for major bleeds (coagulopathies, recent surgery, history of intracranial bleed) are excluded from this therapy. tPA has been shown to improve functionality at three months, regardless of stroke type. Although it significantly increases the number of intracranial hemorrhages, mortality is not increased. Blood pressure is allowed to run high

during the first 24 hours up to 220/120, and then should be gradually tapered down. If tPA is given, BP should be maintained below 185/110. Hyperglycemia and hyperthermia should be avoided. Patients with stroke from cardioemboli should be on anticoagulation, which can be initiated three to five days after the stroke. Patients with carotid stenosis greater than 70 percent ipsilateral to the side of the stroke benefit from carotid endarterectomy or stenting. Secondary stroke prevention involves control of vascular risk factors, including smoking cessation, strict glucose, cholesterol, blood pressure control, and antiplatelet agents. Diuretics and ACE-inhibitors are the options of choice in blood pressure control, as statins are for cholesterol control. Aspirin has been shown to have a small but significant reduction in stroke risk. Aggrenox and Plavix are both antiplatelet agents that are superior to aspirin in stroke reduction, but carry heavier price tags and an increased risk of side effects. All are reasonable options.

16. Brainstem Ischemic Stroke

A 66-year-old woman with a long history of tobacco use and hypertension presents to the ER with acute onset dizziness and numbness on the right side of her body. An ER resident finds no evidence of weakness and she is sent home with a prescription for Reglan. She comes to your clinic two days later, stating a continuation of these complaints without relief. You note on examination asymmetric pupils, with the left eye greater than the right by 2 mm. Both are reactive. There is a slight ptosis over the left eye. There is sustained nystagmus on left gaze. Facial sensation is decreased to temperature and pinprick on the left, while it is decreased on the right side of the body. You note a subtle dysarthria. Gag reflex is diminished on the left. There are no weaknesses in the limbs. Finger-to-nose and rapid-alternating movements are clumsy on the left upper extremity. Gait appears unsteady in primary gait. After the exam, you call the hospital to directly admit this patient to a room.

BACKGROUND

- The patient has a brainstem stroke presenting as lateral medullary syndrome, aka Wallenberg Syndrome. This is a stroke syndrome affecting the spinothalamic tract, trigeminal nucleus, vestibular system, sympathetic tracts, nucleus ambiguus, and inferior cerebellar peduncle as they converge in the lateral medulla. It is secondary to an occlusion of the PICA.

PATHOLOGY

- The brainstem is subject to the same pathological mechanisms of other strokes, including cardioembolism, thrombus or embolism from large vessel atherosclerotic disease, lipohyalinosis, and dissection. Dissection should be especially considered in young patients without vascular risk factors with a history of sudden acceleration-deceleration trauma or chiropractic manipulation. Lacunar strokes in the brainstem tend to involve the pons and are secondary to occlusion of perforating vessels off the basilar artery.

CLINICAL PRESENTATION

- As the brainstem is a compacted area of numerous structures and tracts, strokes in this area can cause various syndromes. Important structures include the cranial nerve nuclei and tracts, the descending corticomotor and corticobulbar tracts, the ascending medial lemniscus and spinothalamic tracts, crossing cerebellar tracts, and the reticular formation. Oculomotor palsies, facial palsies, dysarthria, or dysphagia are common cranial nerve symptoms. Interruption of the corticobulbar tracts above the nuclei leads to contralateral cranial nerve palsies. Cranial nerve symptoms are ipsilateral when the nuclei is involved. Since the decussation of the corticospinal fibers occurs in the medulla, an infarct involving a cranial nerve nuclei or tract and corticospinal fibers leads to an ipsilateral cranial nerve palsy and a contralateral limb weakness. This is an example of “crossed signs,” which typically localizes to the brainstem. Sensory symptoms can be crossed as well, as in the case of lateral medullary syndrome. Infarcts of the cerebellar fibers leads to ipsilateral ataxia. The reticular formation is located in the dorsal portion of the pons and midbrain. Involvement of this structure leads to decreased consciousness. Given the small area and compressed nature of the various tracts, even small infarcts can cause

devastating effects. Edema not only compresses nearby structures, but collapse of the fourth ventricle or cerebral aqueduct can cause life-threatening hydrocephalus.

DIAGNOSIS

- Brainstem strokes are evaluated more or less in the same manner as other strokes. Head CT is insensitive to brainstem strokes given the large amount of bony artifact and poor resolution. MRI is preferred in this case. MRA and CTA are available to evaluate large vessels, although formal angiogram may be preferred in specific situations requiring evaluation of small vessels. Echocardiogram is required to look for cardioembolic risk factors. Carotid ultrasounds are not necessary to evaluate posterior circulation strokes.

TREATMENT

- Treatment of brainstem strokes is similar to treatment of cortical strokes with several exceptions. In general, more caution should be exercised given the tight packing of critical structures. Patients with brainstem strokes are at higher risk of aspiration, given paralysis of oropharyngeal muscles or depressed consciousness. Patients at high risk of aspiration should be formally evaluated with a swallow evaluation prior to onset of PO intake. IV and intraarterial tPA are options for patients presenting within 3 or 6 hours of onset, respectively. Given the devastating nature of large brainstem strokes and an invariable progression towards death or severe disability if left untreated, intraarterial tPA has been used successfully in basilar artery occlusions up to 12 hours after presentation in selected patients. Secondary stroke prevention consists of tobacco cessation, control of cholesterol, hypertension, hyperglycemia, and appropriate antiplatelet therapy. Aspirin, Plavix, and Aggrenox are appropriate therapies in non-brainstem strokes. Anticoagulation is not indicated for non-cardioembolic strokes in brainstem or non-brainstem strokes.

17. Hemorrhagic Stroke

A 65-year-old man with a history of longstanding tobacco use and poorly controlled hypertension presents to the ER with acute onset dizziness, gait imbalance, and nausea. He was at church during the onset of his symptoms when he felt a sudden occipital headache, blurry vision, and dizziness. He tried to get up and leave, but found that his gait was “like a drunk person’s.” He fell and was immediately brought to the ER. On examination, he is lethargic but easily arousable. He answers questions of orientation correctly. His cranial nerves are unremarkable, as is his strength. However, he has severe dysmetria on finger-to-nose and dysdiadokinesia on the left side. His vital signs are significant for a blood pressure of 180/99. The acute stroke protocol is activated. IV antihypertensives bring his blood pressure down to 135/76. The head CT reveals a 3 cm by 5 cm parenchymal hemorrhage in the left cerebellum. After returning from the CT, he vomits twice. Neurosurgery is consulted, and he is taken to the OR for craniotomy and resection. The procedure goes without complications, and after 48 hours post-op he is released from the ICU with mild residual left-sided ataxia. A cerebral angiogram of the posterior circulation is negative for vascular abnormalities.

BACKGROUND

- The patient had a spontaneous hemorrhagic stroke secondary to uncontrolled hypertension. There are several types of spontaneous hemorrhagic strokes, including parenchymal hemorrhages as in this case, and extraparenchymal hemorrhages such as subarachnoid or subdural hemorrhages. In addition, parenchymal hemorrhages can occur secondary to other etiologies, such as tumor or ischemic stroke.

PATHOLOGY

- Spontaneous hemorrhagic strokes are most commonly caused by uncontrolled hypertension in the elderly and cerebral amyloid angiopathy. However, important causes of hemorrhage that must be ruled out include arteriovenous malformations and aneurysms, as they are treatable and have a high rate of recurrent bleed if they are left untreated. Other etiologies include venous sinus infarct, tumor, cavernous angiomas, and vasculitis. Tobacco use, excessive use of cocaine or alcohol, and coagulopathy increase the risk of spontaneous intracranial hemorrhages. Uncontrolled hypertension results in rupture of small perforating arterioles, leading to typical locations as follows.

Location	Perforating Vessel
Basal Ganglia	Lenticulostriate arteries off MCA
Thalamus	Thalamogeniculate arteries off PCA
Pons	Paramedian perforators off basal artery
Cerebellum	Perforating arteries of SCA, AICA, or PICA

- When the hemorrhage occurs, the blood spreads between the planes of neuronal axons, leaving it relatively intact around the perimeter of the hematoma. The majority of expansion occurs quickly within the first hours before compression by surrounding brain tissue causes a tamponade effect. Vasogenic and cytotoxic edema occurs in the surrounding tissue, leading to tissue damage. It is felt that this neuronal injury is the major cause of persistent neurologic deficit, as the stretch from the hematoma mass itself leaves neurons relatively viable.

CLINICAL FEATURES

- Clinical features depend on the area of the brain affected and the size of the hemorrhage. Hypertensive hemorrhages affect small vessels similar to lacunar infarcts and may present with a lacunar syndrome. Hemorrhages from amyloid angiopathy tend to be lobar and can present with cortical signs.
- The only way to determine between ischemic and hemorrhagic stroke is via neuroimaging; there is no consistent way to differentiate between the two clinically.
- As hemorrhages produce significant cytotoxic and vasogenic edema in the surrounding tissue, symptoms of shift and herniation are common and must be treated emergently. The hemorrhage can expand from the parenchymal tissues into the ventricular system, which is a feared complication as it increases mortality. Once inside the ventricular system, the blood can clot off normal flow of CSF, leading to increased intracranial pressure and hydrocephalus.

DIAGNOSIS

- Head CT is the modality of choice in looking for intracranial blood, although MRI with T2* is shown to be highly sensitive for acute blood as well. Once a hemorrhage is found, the etiology must be determined. Cerebral angiogram should be done in selected patients with lobar hemorrhages, or in young patients without significant hypertension. This study is used to rule out arteriovenous malformations, aneurysms, and vasculitis. Older patients with known uncontrolled hypertension in typical locations of hypertensive hemorrhage may not necessarily need to undergo the risks of conventional angiography. The sensitivities of CTA and MRA are not established, but are probably not comparable to conventional angiogram. Cerebral angiogram may be negative in the acute setting due to the hematoma, and should be repeated two to four weeks after resolution in order to reevaluate for a vascular anomaly.

TREATMENT

- Treatment may be surgical or medical, and depends on the size and location of the stroke. Patients with cerebellar hemorrhages should undergo evacuation as the patient is at high risk of compressing the brainstem, and the cerebellum is relatively easy to access surgically. Large lobar hemorrhages, clinical deterioration, expanding hematoma, and volume over 30 mL are all indications for surgical evacuation. Surgical evacuation via craniotomy is difficult in patients with bleeds of deep structures such as the pons, basal ganglia, and thalamus. Patients with ventricular extension should have an intraventricular catheter placed for CSF drainage and ICP monitoring. Medical management includes strict high blood pressure control with a goal of mean arterial pressure < 130 mmHg. Mechanical intubation should be used for patients with depressed mental status, brainstem compression, or herniation. Hyperventilation, mannitol and hypertonic saline should be used to decreased ICP, with a goal cerebral perfusion pressure > 70 mmHg. Patients who suffer a seizure

should be started on an anticonvulsant, which can be discontinued in 30 days if there is no subsequent seizure. For hematomas in difficult to access regions of the brain, emerging surgical techniques include stereotactic or endoscopic approaches. Another novel therapy is injection of thrombolytics into the hematoma via catheter and subsequent aspiration.

18. Status Epilepticus

A 23-year-old woman with a history of complex partial epilepsy presents to the ER with continuous seizure activity. She woke up in the morning feeling “not quite right” and shortly afterwards began to have a generalized tonic-clonic seizure in the kitchen. Her boyfriend calls 911. An ambulance arrives in 15 minutes and finds her unconscious but not experiencing active seizures. Her boyfriend states that she had been seizing for 10 minutes before it ended spontaneously. On the way to the hospital, she has another seizure lasting for 2-3 minutes. Upon arrival to the ER, she has another seizure lasting for approximately 5 minutes before it is broken by 2 mg of Ativan x 2 doses. Her boyfriend states that she usually takes Tegretol, but ran out of her prescription two days ago. She is given a dilantin load of 15 mg/kg and intubated for airway protection.

BACKGROUND

- She has status epilepticus (SE) secondary to noncompliance of medications. SE is a life-threatening condition defined as continuous seizure activity for greater than 30 minutes, or multiple seizures without return to consciousness lasting greater than 30 minutes. However, continuous seizures become much more refractory if unabated for greater than 5 minutes, so treatment for SE is initiated after 5 minutes of continuous seizure activity or two or more discrete seizures with incomplete recovery of consciousness.

PATHOLOGY

- Seizures occur from imbalance of excitatory and inhibitory inputs in the cortex that synchronizes to produce abnormal rhythmic electrical activity. The main excitatory and inhibitory neurotransmitters in the CNS are glutamate and GABA, respectively. Most seizures spontaneously resolve secondary to poorly understood mechanisms in the brain that abort isolated seizures. SE is thought to result in a failure of that mechanism leading to persistent, excessive excitation, or diminished inhibitory input. Another mechanism postulated to cause SE is shifting seizure foci. No matter the cause, continuous seizure activity leads to cerebral injury to the CNS after 30 minutes secondary to glutamate excitotoxicity. The metabolic demands of continuous, repetitive neuronal firing may also contribute to cortical damage.

CLINICAL PRESENTATION

- SE is typically associated generalized tonic-clonic, tonic, or clonic movements. If untreated for prolonged periods of time, the phenomenon of electromotor dissociation occurs in which cortical seizure activity does not translate into motor movements. The obvious movement abnormalities abate into small-amplitude twitching of the face or extremities, or nystagmus of the eyes. Patients with continuous cortical seizure activity without obvious motor movements are said to be in subclinical, or nonconvulsive, SE. It is estimated that SE is the initial presentation in up to 30 percent of new diagnoses of epilepsy. SE is triggered by metabolic, toxic, and infectious etiologies, as well as stroke, tumor, head trauma, and hypoxia. Noncompliance with antiepileptics in patients with known epilepsy is the most common cause of SE. Myoclonic SE occurs after hypoxic injury of the brain and is a significant negative prognostic indicator.

DIAGNOSIS

- SE is diagnosed clinically and treatment should be initiated without further confirmatory testing, although subclinical SE can only be diagnosed with EEG. Basic chemistries and blood count, an ABG, urine toxicology, and antiepileptic levels if the patient is on antiepileptics, should be sent off on arrival. A non-infused head CT should be done to evaluate for bleed. An infused MRI should be done in patients without a known history of seizures.

TREATMENT

- SE is a neurologic emergency. It is associated with 20 percent morbidity, and about 55,000 deaths are attributed to it each year. Initial evaluation consists of airway and ventilation assessment. Emergent intubation is indicated in patients with respiratory compromise seen clinically or on ABG. Pharmacologic treatments should not be delayed as unabated seizure activity leads not only to increased CNS damage, but also to increasing refractoriness to treatment. Lorazepam, a short-acting benzodiazepine with a 12-24 effect duration, is the first line treatment, usually given at 0.1 mg/kg or 2 mg IV. Diazepam, another short-acting benzodiazepine, is another option and can be given per rectum in children, but has an effect duration of only 15-30 minutes. Further antiepileptic medications may not be indicated if the seizure stops and the etiology of the seizure is rectified. If this is not the case, phenytoin or fosphenytoin are next line agents, given at 20 mg/kg loading dose. Fosphenytoin is a prodrug of phenytoin with the advantage of a faster infusion rate. Phenytoin is limited by a infusion rate of 50 mg/min, usually taking 20-25 minutes to finish the infusion. Exceeding this infusion rate leads to hypotension and arrhythmias. If seizures persist after infusion of phenytoin or fosphenytoin, either another 5-10 mg/kg infusion can be given, or Phenobarbital can be tried. Phenobarbital is a long-acting barbituate with significant CNS and respiratory depressant effects. For this reason, Phenobarbital is recommended only after failure of benzodiazepines and phenytoin. Loading dose is 20 mg/kg infused at 50-75 mg/min. SE that is refractory to these therapies requires usage of continuous IV drips. Midazolam, a benzodiazepine, is administered at 0.2 mg/kg bolus followed by 0.75 to 10 micrograms per kg/min. Propofol is another option, given at 2-10 mg/kg/hr. Patients at this point should be on continuous EEG monitoring, with propofol or midazolam titrated to suppression of spikes or burst-suppression pattern. These medications can be titrated down in 12-24 hours, and resumed for a longer period of time if EEG shows recurrence of epileptic activity. Thiopental and pentobarbital are last-line treatments, given their association with severe hypotension requiring pressors.
- Most patients with SE do not have respiratory distress unless their airway is obstructed. Metabolic derangements secondary to SE consist of hyperthermia, metabolic, and respiratory acidosis. Metabolic acidosis can be observed unless profound, in which case sodium bicarbonate can be infused.
- SE is a term reserved for generalized seizures. Prolonged focal motor seizures are called *epilepsia partialis continua*.

19. Partial Complex Seizure

A 28-year-old man presents to the ER with “strange behavior.” He awoke in the morning feeling “off.” He was giving a presentation at work when he suddenly halted his speech, appeared glazed and distant, and developed an abnormal movement described by his coworkers as “picking at his shirt” with his left hand and “smacking his mouth.” This activity lasted for several minutes before the patient collapsed into his chair. He was lethargic and answering inappropriately when EMS arrived 20 minutes afterwards. The patient states that he does not remember the incident and work-up in the ambulance. He states that the last thing he remembers was smelling “something burning” when he was giving the presentation. In review of systems, he states that he did not get much sleep the night before so he could work on the presentation, but denies any recent illnesses or intoxications. The patient has no significant past medical history except for a head trauma he sustained several months ago playing football. He had a head-on collision with another player and lost consciousness for several minutes. Since he recovered without deficits, he decided not to go to the hospital at that point in time. Basic chemistries and blood counts are negative, and urine toxicology is negative. A head CT is negative.

BACKGROUND

- The patient had a complex partial seizure (CPS), likely secondary to the head trauma. Given the symptomatology, it is likely that the seizure origin is the left mesial temporal lobe. Partial seizures are the most common seizure disorder in adults as they arise from focal lesions such as strokes, tumors, trauma, and infection.
- Seizures can be classified by several different schema. The generalized vs focal/partial classification refers to origin of the seizure, while the simple vs complex classification describes mental status. Simple seizures do not affect mental status as they are isolated to one hemisphere. Complex seizures cause abnormal mentation as epileptic involves both hemispheres. Complex partial seizures thus start focally and spread to both hemispheres.

PATHOLOGY

- Most partial seizures in adults are acquired from focal lesions. This leads to abnormal synaptic reorganization predisposing to hypersynchronous discharges. CPS of the mesial temporal lobe is associated with hippocampal sclerosis. Hippocampal sclerosis is an entity that consists of selective neuronal loss, gliosis, and aberrant innervation leading to a recurrent excitatory circuit. The electrical activity of this circuit propagates to other nearby structures leading to seizures. Hippocampal sclerosis is associated with a childhood history of febrile seizures, CNS infection, or head trauma. It is not clear if hippocampal sclerosis is a cause or an effect of seizures.

CLINICAL PRESENTATION

- CPS may begin with an aura. Auras are manifestations of focal epileptic activity in the brain, and may consist of visceral sensations, such as nausea, fear, or a rising epigastric feeling. Less common auras are olfactory or gustatory hallucinations, déjà vu, or visual distortions. As the epileptic activity spreads, the patient stares blankly and automatisms are initiated, commonly consisting of lip smacking or chewing, picking at clothes, or buttoning motions. Interestingly, limb automatisms localize

ipsilaterally to the seizure focus. The patient is unresponsive during this time and amnesic for the event. CPS can begin in other lobes as well. Seizures that originate in the motor cortex begin as localized twitching of part of a limb. As the electrical activity spreads up the motor cortex, the twitching “marches” up the body, a phenomenon called “Jacksonian march.” CPS can generalize into general tonic-clonic seizures. Triggers for seizures include stress, sleep deprivation, and hormonal changes of the menstrual cycle. Patients with CPS of the temporal lobe are at high likelihood of developing memory problems, behavior abnormalities, and depression.

DIAGNOSIS

- An EEG may show interictal epileptiform activity, but only 50 percent of EEGs are abnormal in patients presenting with a first seizure. The sensitivity can be brought up to nearly 90 percent with three isolated EEGs. Continuous EEG monitoring for several days with maneuvers to trigger seizures, such as sleep deprivation, is the most sensitive test for seizures at this time. Mesial temporal sclerosis may be seen on MRI with thin cuts through the hippocampus. It is best visualized on coronal T1 views.

TREATMENT

- Antiepileptic medications can be classified as broad-spectrum or narrow spectrum. Broad-spectrum medications are efficacious regardless of seizure type, while narrow-spectrum medications are less effective in primary generalized epilepsies and should be restricted to usage in focal onset epilepsy. Broad spectrum medications include depakote, lamotrigine, levetiracetam, and topiramate. Narrow-spectrum medications include carbamazepine, oxycarbazepine, phenytoin, gabapentin, tiagabine, and pregabalin. Head-to-head trials suggest no advantage of one medication over another in CPS. Choice of medication is based on side effect profile (see table below*). Carbamazepine or phenytoin are both reasonable choices as first line agents for CPS given practitioners’ longer experience with these medications. If these agents fail as monotherapy, they can be titrated up to side effects, limit tolerability, and another agent can be added. Patients who fail three or more agents are likely to be medically refractory to other agents as well. Surgical resection as an option of seizure foci is surgically accessible and not near “eloquent” areas of cortex. Patients treated with surgery can become seizure free, or have a significant reduction in the number of seizures. Often these patients will still need to continue antiepileptic medications, but at a reduced dose.

Medication	Common Side Effect	Serious Side Effects
Carbamazepine	Dizziness, diplopia, blurry vision, weight gain, ataxia	Agranulocytosis, aplastic anemia, hepatic failure, hyponatremia
Gabapentin	Sedation, fatigue, dizziness, ataxia	None
Lamotrigine	Dizziness, blurry vision	Rash, Stevens-Johnson syndrome, multi-organ failure
Levetiracetam	Fatigue, dizziness, irritability, anxiety	Psychosis

Oxcarbazepine	Fatigue, dizziness, ataxia, nausea	Rash, Steven-Johnson Syndrome
Phenytoin	Fatigue, dizziness, ataxia	Blood dyscrasias, conduction block, lupus-like syndrome
Phenobarbital	Fatigue, dizziness, ataxia, confusion, hyperactivity in children	Blood dyscrasias, hepatic failure, Steven-Johnsons syndrome
Pregabalin	Fatigue, dizziness, ataxia	None
Tiagabine	Fatigue, dizziness, ataxia, somnolence	Spike-wave status epilepticus
Topiramate	Drowsiness, ataxia, difficulty concentrating, weight loss	Metabolic acidosis, renal calculi, acute glaucoma
Valproic acid	Drowsiness, ataxia, weight gain, thrombocytopenia	Hepatic failure, hyperammonemia, aplastic anemia
Zonisamide	Drowsiness, ataxia, difficulty concentrating	Aplastic anemia, renal calculi

* Adapted from French, JA et al. N Engl J Med 2008; 259:166-76.

20. Grand Mal Seizure

You are consulted for a new onset seizure on a 47-year-old woman who is on the general surgery service for an appendectomy. She presented two days prior with severe acute abdominal pain, where a CT of the abdomen showed an inflamed appendix. The surgery went without complications, and the patient has been doing well post-op, albeit the nurses report she is demanding and difficult to get along with. That night, while having vitals checked, the patient extends both arms and emits a strangled groan. Her eyes roll up into her head, and her extremities begin jerking in large-amplitude, rhythmic fashion. This lasts for about 2 minutes before subsiding and spontaneously resolving. The patient is unresponsive during this event. A glucometer reading immediately after the event shows a reading of 98. When you see the patient 15 minutes after the event she is lethargic, but there are no focal neurologic deficits on examination. There is some trauma to her tongue. Since she has a foley catheter, you cannot assess for bladder incontinence. You speak to her family and find that prior to this hospitalization, she has been "healthy as a horse." She has not had a history of head trauma or CNS infection. Her family does report that she drinks one bottle of wine nightly. However, they were not concerned since it is red wine, which they say is "supposed to be good for you, right?" A head CT is negative, and basic chemistries, liver function panel, and blood count are negative. A urine toxicology and serum ethanol level are negative as well.

BACKGROUND

- The patient had a generalized tonic-clonic seizure (GTC), aka a grand mal seizure, secondary to alcohol withdrawal. Generalized tonic-clonic seizures are the most common type of seizures. Other types of convulsive generalized seizures include clonic, tonic, and myoclonic seizures. Nonconvulsive generalized seizures include atonic and absence seizures. Generalization refers to epileptic activity that occurs throughout the cortex bilaterally. By definition, generalized seizures affect mental status. Seizures can be primarily generalized. They start diffusely throughout the cortex simultaneously, or secondarily generalized, in that the epileptic discharges start at a focus that propagates and spreads diffusely.

PATHOLOGY

- The pathological mechanism of seizures remains unclear, but is thought to be due to imbalance between excitatory and inhibitory inputs that predispose to hypersynchronous discharges. Several ion channel abnormalities have been associated with primary generalized seizures that lead to cortical hyperexcitability. In the case of absence seizures, the specific abnormality is associated with hyperactive T-type calcium channels that lead to thalamocortical excitation and seizure.

CLINICAL PRESENTATION

- Generalized tonic-clonic seizures often progress through phases. A prodrome is a pre-ictal sensation occurring hours prior to the onset of the seizure and are nonspecific. They may consist of a feeling of apathy, depression, or irritability. Most often generalized seizures begin without warning. Primary generalized seizures do not begin with an aura, as an aura is a simple partial seizure producing non-motor symptoms prior to the onset of motor abnormalities. However, focal seizures with

secondary generalization may begin with auras. GTC's begin with an initial tonic phase with extremities and trunk extension. There may be a cry as air is forced through the vocal cords via contraction of the respiratory muscles. This phase transitions to the clonic phase with repetitive relaxation of the tonic contraction. This gives way to rhythmic flexor spasms of the extremities and trunk. Tongue-biting may occur in this stage. After seconds to minutes, the clonic jerks decrease in amplitude and frequency. After movement abnormalities cease, the patient remains unresponsive or lethargic. They are confused as they awake, and are amnesic to the event. This is the post-ictal stage. Urinary incontinence can occur in any stage of the seizure.

DIAGNOSIS

- Diagnostic evaluation includes EEG and neuroimaging. An EEG is abnormal in 50 percent of patients with a first diagnosis of seizures. Thus, multiple EEGs or multiple days of continuous video and EEG monitoring may be required to find interictal abnormalities. An MRI should be performed to look for structural abnormalities. Metabolic abnormalities and infections should be investigated as the causative agent.

TREATMENT

- Broad-spectrum antiepileptic medications are recommended for primary generalized seizures, although any antiepileptic can be used to treat focal seizures with secondary generalization. Broad spectrum antiepileptics include valproate, topiramate, lamotrigine, and levatiracetam. Surgical therapy is not an option for generalized seizures.

21. Multiple Sclerosis

A 32-year-old woman presents to the ER with acute onset vision loss in her right eye. She reports that over the course of several hours she developed pain and "darkening" of her vision in that eye, although she denies having a curtain come down over her vision. She also reports having had "stiffness" of her right leg two years ago lasting for several months. She saw a chiropractor who ordered an MRI of the L-spine, which apparently shows some mild disk bulges. On examination, she has decreased visual acuity on the right eye, 20/70 compared to left 20/20. Pupils are bilaterally brisk and reactive 6mm to 3mm on light exam to the left eye, but both eyes dilate to 6mm on light exam to the right eye. Extraocular movements are normal bilaterally, but the patient reports increased retroorbital pain on the left eye with movement. Other pertinent exam findings include bilateral spasticity in both legs with three beats of clonus in the ankles, and an extensor toe reflex on the right.

BACKGROUND

- Multiple sclerosis (MS) is a chronic autoimmune demyelinating disease affecting the central nervous system. It has a predilection to affect the periventricular white matter, the optic nerves, as well as the white matter tracts of the brainstem and spinal cord. Typical presentations of MS include optic neuritis and transverse myelitis, although numerous other manifestations may occur. Classically, the patient has multiple neurologic deficits "separated by time and space."

PATHOLOGY

- The exact pathogenetic mechanism of MS remains to be completely defined, but it is thought to be due to autoimmune dysregulation and invasion of CD4 T-cells into the CNS. Once inside the blood-brain barrier, these activated T-cells initiate an attack on the neurons through multiple proposed mechanisms. It is thought that autoantibodies are formed against multiple myelin antibodies, including myelin basic protein and myelin-associated glycoprotein. This leads to activation of the complement pathway leading to demyelination and cytolysis. Macrophages and microglial cells may play a role as well.
- Although MS is classically thought of as a demyelinating disease, secondary axonal injury is prevalent and leads to longstanding disability.
- Histologically, areas of demyelination and remyelination are seen in MS lesions, causing the so-called "shadow plaque." The inciting autoimmune event also remains a mystery, as it is thought to be a combination of environmental and genetic factors.
- MS is seen with increasing prevalence in areas further away from the equator, supporting an environmental factor. However, the HLA-DR2 allele has been found to increase the risk of MS. In addition, the risk of MS in first degree family members of MS patients, especially in monozygotic twins, is significantly higher than the risk in the general population.

CLINICAL PRESENTATION

- Like most autoimmune diseases, MS is seen in women more often than men. Onset is typically in the first to third decades of life. Classically, MS manifests in acute "flares" of neurologic disability that resolves without treatment over weeks, usually leaving little remaining disability. This is the typical "relapsing-remitting" course seen in 80 percent of MS patients. Over time, flares leave increasing neurologic deficits,

eventually leading to severe disability. In 70 percent of relapsing-remitting MS patients, the flares eventually disappear and disability progresses at a steady rate without obvious acute declines. This is called "secondary progression." Twenty percent of MS patients have a "primary progressive" course, in which disability progresses insidiously without acute flares.

DIAGNOSIS

- MS affects areas of high myelin content in the CNS. Periventricular white matter tracts, brainstem, optic nerves, cerebellum, and spinal cord are typically affected. Involvement of the optic nerve produces optic neuritis, which manifests as decreased visual acuity, pain with movement, afferent papillary defect, and pale discs on fundoscopic exam. Lesions in the spinal cord cause transverse myelitis which can lead to loss of sensation, strength, urinary dysfunction, and sexual dysfunction. Cerebellar ataxia, eye movement abnormalities (especially intranuclear ophthalmoplegia), and trigeminal neuralgia are typical brainstem and cerebellar manifestations. Depression and decline in cognitive function are prevalent in MS, and are under-recognized. Eventually, the patient progresses to significant motor disability. Fifteen percent of patients require assistance with walking in 15 years. Spasticity, neurogenic bladder, and neuropathic pain become increasingly difficult to treat. Eventually, death occurs from complications of immobility.
- MRI is both sensitive and specific for MS. MS lesions are hyperintense on T2-weighted imaging. They are typically small, discrete ovoid lesions. Periventricular lesions are perpendicularly oriented to the ventricle, the so-called Dawson's fingers. Enhancement occurs in areas of breakdown of the blood-brain barrier and represents active MS lesions. Areas of chronic axonal damage are hypointense on T1-weighted imaging and are termed "black holes." Multiple MS lesions are typically seen at the time of diagnosis. The presence of both enhancing and non-enhancing lesions fulfills the requirements for lesions separated by "time and space." CSF is confirmatory if the presence of oligoclonal bands is found, but the finding is not specific to MS and may occasionally be absent. Evoked potential tests may also be confirmatory if patterns of demyelination are found, but this testing may be difficult to perform and is highly technician-dependant.

TREATMENT

- Mainstay of treatment is immunomodulation or suppression. Treatment of acute MS flare is typically high dose corticosteroids with an oral taper. Maintenance therapy is interferons, which have been shown to reduce clinical and radiologic attacks, most likely reducing progression to disability as well. There are three interferon treatments in market at present (Avenox - IFN-B1a, Betaseron - IFN B1b, and Rebif - high dose IFN-B1a) that have been shown to decrease frequency of MS attacks. Efficacy of treatment is thought to be dose-dependent, meaning that Betaseron and Rebif are of higher efficacy than Avenox. In addition, glutamir acetate (Copaxone) is a random polymer of myelin basic protein, which has also been shown to decrease clinical and radiologic evidence of attacks. The exact mechanism of action for the medications is unknown, but they are thought to shift T-cell balance towards suppression of inflammation and remyelination. Unfortunately, primary progressive and secondary progressive MS have only marginal benefit from these agents. Only Betaseron has shown to have efficacy with delaying disability in secondary progressive MS, and there are no proven therapies for primary progressive MS.

Supportive medications include gabapentin and pregabalin for neuropathic symptoms, muscle relaxants for spasticity, and SSRI's for depression. Physical and occupational therapy, home nursing care, and community support are critical for the patient and the caregivers.

22. Amyotrophic Lateral Sclerosis

A 67-year-old man presents with a three-month history of “right hand clumsiness.” He first noted that he was having occasional difficulty signing his name and buttoning clothes, but now is having difficulty opening doors and using his keys. He states that his right arm is getting weaker, and he has had increasing fatigue in general. On questioning, he reports noticing occasional muscle twitching in his right deltoid and forearm. He denies any tremor. He does report that having tripped once going up the stairs, feeling that his right leg “wouldn’t get up.” On examination, you notice that there is spasticity in the right upper extremity with hyperreflexia in the right upper and lower extremity. There is thenar wasting on the right hand compared to the left. There is a flexor plantar response on the right. Over the course of several years, the patient’s symptoms generalize to include all extremities, and he passes away from respirator failure in five years.

BACKGROUND

- The patient has amyotrophic lateral sclerosis (ALS), previously known as Lou Gehrig’s Disease. It is a neurodegenerative disease affecting both the upper and lower motor neurons, leading to progressive muscle wasting and spasticity.

PATHOLOGY

- The disease mechanism of ALS selective targets motor neurons, leading to motor neuron death in the motor cortex and anterior horns of the spinal cord. Multiple mechanisms have been proposed in the pathogenesis of ALS, and it is likely to be multifactorial. Free radical oxidative damage, calcium and glutamate excitotoxicity, and neurofilament disorganization are among the mechanisms proposed in the pathogenesis of ALS. Genetic factors have been identified in some cases. A mutation in SOD1, an antioxidative enzyme, is seen in 20 percent of familial ALS. CD4 and CD8 cells have been seen in the anterior horns of the spinal cord, suggesting an immune mechanism, but immunomodulators therapies have not been shown to have any effect on the disease. No environmental factors have been convincingly proven. Pathological examination shows gliosis and degeneration of the motor neurons in the cortex, brainstem, and spinal cord.

CLINICAL PRESENTATION

- ALS presents as a combination of upper (spasticity, hyperreflexia, positive Babinski sign) and lower (fasciculations, muscle atrophy) motor neuron signs. Weakness is commonly the first complaint, and is usually asymmetric. Although limbs are commonly affected first, bulbar symptoms may be the presenting symptoms in some cases. Bulbar symptoms include dysarthria, dysphagia, tongue atrophy and fasciculations. Sensory complaints are inconsistent with ALS, although patients will sometimes report subjecting sensations of muscle cramps and tightness. The bladder and bowels are unaffected. There is high prevalence of cognitive impairment in ALS patients, with 5 percent proceeding to dementia. Familial ALS is associated with frontotemporal dementia via a mutation in chromosome 9.

DIAGNOSIS

- Diagnosis of ALS is based on clinical findings and electrophysiologic criteria. EMG shows denervation patterns consisting of large amplitude motor units and delayed recruitment. Nerve conduction studies are normal, although motor nerve

conduction velocities can be diminished in severely atrophic muscles. Findings of denervation in three out of four segments (bulbar, cervical, thoracic, lumbosacral) are consistent with ALS. Fasciculations and fibrillations should be seen. MRI of the affected spinal territories should be done to rule out spinal cord and root compression, which can also give a mix of upper and lower motor neuron signs. An important differential is multifocal motor neuropathy, a chronic motor neuropathy that is imminently treatable by IVIG. The EMG of multifocal motor neuropathy is unique for its multiple conduction blocks on motor nerve conduction study. A serum GM1 ganglioside is also diagnostic for multifocal motor neuropathy.

TREATMENT

- ALS is an unremittingly progressive disease leading to immobility and death in 10 years. Patients with prominent bulbar symptoms have worse prognosis and are at risk for respiratory failure. Riluzole is a glutamate antagonist that prolongs survival by three to six months, but does not improve function or quality of life. Treatment is usually palliative. Long-term mechanical ventilation and artificial feeding can prolong life at the cost of total immobility, in addition to heavy family burden.

NOTE

- Neuronopathy is a term that implies a primary pathological process at the cell body. This is different from neuropathies, which implies a pathological process in the nerve process, either axonal or demyelinating. The sensory equivalent of motor neuronopathy is a ganglionopathy.

23. Guillain-Barre Syndrome

An 18-year-old man presents to the ER with complaints of weakness in his legs. Symptoms began one day prior, with feelings of weakness in his feet. This morning, the patient began “tripping over my own feet,” and by early afternoon he was having difficulty picking up his legs to walk up stairs. He reports sensations of numbness in his legs, which is minor in comparison to his motor complaints. On examination, toe flexion and extension is 1/5 bilaterally, ankle flexion and extension is 3/5, and hip flexion and extension is 4/5. Tone is flaccid, and reflexes are absent in the lower extremities. Upper extremities are normal to strength, tone, and reflexes. There are no cranial nerve or mental status abnormalities. The patient denies any recent respiratory or GI symptoms. You admit the patient to begin treatment. An EMG shows slow conduction velocities and prolonged F-waves in the lower extremities. Over the course of the hospitalization, it comes out that the patient has been engaging in high-risk sexual activity for the past year. An HIV test comes back positive.

BACKGROUND

- The patient has Acute Inflammatory Demyelinating Polyneuropathy (AIDP), a form of Guillain-Barre Syndrome (GBS). GBS is a syndrome that consists of a subacute ascending paralysis. It was once considered a single disorder, but is now recognized as having multiple variants with unique pathological mechanisms. AIDP is the classic form of GBS, and is a demyelinating disease of the peripheral nerves that causes predominantly motor symptoms. It is commonly preceded by a febrile illness, and is especially associated with recent C. Jejuni gastroenteritis, CMV, and EBV infection. Symptoms of GBS begin two to four weeks after the illness. GBS is rarely associated with influenza vaccine at a rate of one case per million vaccines.

PATHOLOGY

- The disease is caused by an autoimmune attack on the myelin in the peripheral nerve and nerve roots. Given its association with antecedent infection, it is thought that molecular mimicry between an antigen on the infectious agent and myelin component of the nerve leads to sensitization against self. This is demonstrated in the similar epitopes (antigenic sites against which antibodies react) between the cell surface of C. Jejuni and the gangliosides that compose myelin. Prolonged autoimmune attack against the myelin leads to secondary damage of the underlying axons. Axonal damage is a negative prognostic factor for motor recovery, given the incomplete nature of axon repair.

CLINICAL PRESENTATION

- Motor symptoms are the predominant finding and classically begin distally with an ascending paralysis. In practice, weakness may begin proximally and spread distally as the disease attacks nerve roots, as well as the distal processes. The disease progresses rapidly over the course of hours to days, and can lead to complete flaccid paralysis. Life-threatening paralysis occurs when respiratory and bulbar muscles are affected. Sensory abnormalities are common, but relatively minor component, consisting of pain, tingling, and numbness. Areflexia is an important feature, and other diagnoses should be considered if reflexes are retained. Autonomic symptoms including cardiac, bowel, and bladder abnormalities occur in over 50 percent of patients. The disease is self-limited, and will begin to resolve in

three to four weeks. As the disease is demyelinating, prognosis of functional recovery is good as long as the nerve axons are relatively spared. The bulk of motor recovery occurs over weeks to months as the nerves are remyelinated.

DIAGNOSIS

- EMG and CSF are the cornerstones of diagnostic testing. However, they may not show positive findings until days to weeks after onset of illness. EMG shows demyelinating patterns of nerve damage with slowed conduction velocity, prolonged distal latencies and F-waves, and temporal dispersion. Motor nerves are affected earlier and more severely than sensory nerves. Multifocal conduction blocks are common, and the lack of that feature should point towards hereditary neuropathies. CSF shows elevated protein with normal WBC's, termed the cytoalbuminologic dissociation. This finding is not specific to GBS and can be seen in other inflammatory diseases. The search for antecedent infection is not critical given the benign nature of most of these infections. However, the consideration of HIV is especially important, as GBS may be the initial presentation after seroconversion, after which the HIV virus will go into an asymptomatic, latent phase for years.

TREATMENT

- Treatment consists of IVIG or plasmaphoresis, typically for five days. It is thought that they have similar efficacies. Although the disease is self-limited, early treatment hastens recovery and limits secondary axonal damage, leading to better motor recovery. Mechanical ventilation may be required to support the patient through the nadir of the disease. Gabapentin and pregabalin are useful in controlling neuropathic symptoms.

NOTE

- Besides AIDP, GBS has several other variants. Acute Motor Axonal Neuropathy presents with a similar clinical picture but displays an axonal pattern on EMG, and has a lower rate of recovery. It is seen mostly in northern China and is strongly associated with recent C. Jejuni infection. It is associated with antibodies against GM1, GM1b, and GD1a gangliosides. The Miller Fisher variant is a syndrome of acute ophthalmoplegia, ataxia, and areflexia which spreads to produce a more diffuse polyneuropathy. It is associated with antibodies against the GQ1B ganglioside. Acute Motor and Sensory Axonal Neuropathy is a rare form of GBS that has prominent motor and sensory symptoms with an axonal pattern of damage.

24. Myasthenia Gravis

A 36-year-old woman presents to your clinic for “fatigue” and “weak eyelids” for the past year. She states that she can barely keep her eyes open at the end of the day, even though she is wide awake. Her husband concurs that her eyelids are always droopy, but worse at the end of the day. In addition, she reports occasional double vision. The two images are side by side and one disappears after covering one eye. This also worsens at the end of the day. She denies any dysarthria or dysphagia. She reports a generalized weakness, and notices that she has decreasing energy. She was previously a long-distance runner, but for the past month cannot even run one mile before feeling fatigued. On examination, pupils are equally round and reactive. There is bilateral ptosis coming down to the upper border of the iris. You note a moderate constriction in extraocular movements in all directions that seems symmetric and bilateral. Limb strength is normal, as is tone. Reflexes are one’s throughout. You assess for fatigability by having her keep her arms raised perpendicular to her body for 1 minute. At 45 seconds, there is bilateral moderate drift downwards. You send her for a CT scan of the chest, which is positive for a mediastinal mass.

BACKGROUND

- The patient has myasthenia gravis (MG), an autoimmune disorder of the neuromuscular junction leading to premature weakness and fatigability of the limbs and bulbar muscles.

PATHOLOGY

- MG is secondary to the production of autoantibodies against the postsynaptic nicotinic acetylcholine receptors (AChR). This blocks binding of acetylcholine released from the presynaptic vesicles. The reduced acetylcholine activation leads to reduced muscle membrane depolarization to the point where the depolarization threshold for muscle contraction is not met. This causes the clinical findings of weakness and fatigability. MG is associated with disorders of the thymus, typically thymoma or hyperplasia. Of those with myasthenics, 10-15 percent have thymomas, while 40 percent of patients with thymomas will develop MG. The thymus produces autoantigenic T-cells that produce antibodies against the acetylcholine receptors. It is unclear how the thymus sensitizes against the acetylcholine receptor, especially in patients without obvious abnormalities of the thymus.

CLINICAL PRESENTATION

- Ocular symptoms are common, causing ptosis and diplopia secondary to weakness of the extraocular and palpebral muscles. Ophthalmoplegia of MG can mimic deficit of cranial nerves 3, 4, 6, or any combination thereof, as well as intranuclear or supranuclear lesions. In some patients, MG symptoms will be confined to the ocular muscles, termed ocular MG. Most patients will go on to develop further symptoms. Dysarthria and dysphagia are particularly concerning as they predispose to aspiration pneumonia and respiratory failure. Weakness of neck flexion and extension, dyspnea on exertion, and inability to count from 1 to 20 in a single breath are concerning for impending respiratory distress. Fatal respiratory dysfunction can develop over hours in a myasthenic crisis. Limb weakness and fatigability can be presenting symptoms. The weakness of MG tends to be the worst at the end of the day, and improves with rest. Myasthenic crisis occurs with a sudden exacerbation of

MG symptoms, which can lead to fatal respiratory distress. Metabolic derangements or infectious agents trigger myasthenic crisis.

DIAGNOSIS

- Signs of fatigability aid clinical diagnosis. Upgaze at a fixed target or holding arms outstretched for 60 seconds can provoke fatigue. Antibodies can be detected in most patients with MG. There are three different AChR receptor antibodies. Binding antibodies are the most common, and thus are useful for an initial screen. Blocking antibodies are found in only one percent of patients who are negative for binding antibodies. Modulating antibody may be more sensitive in patients with ocular MG. Anti-MuSK antibody is useful in AChR antibody negative patients, and may be positive in up to 40 percent of that cohort. EMG with repetitive nerve stimulation shows a pattern of electrical decrement, with decrements greater than 10 percent as being diagnostic. This is secondary to decreased binding of ACh to AChR during maximal contraction. Single fiber EMG can be performed, with increased jitter consistent with MG. Edrophonium, a short-acting acetylcholine esterase inhibitor, is rarely used in the clinical setting due to its low sensitivity. It works by temporarily increasing acetylcholine in the synaptic cleft, thus improving AChR binding and clinical strength. It is better known as the Tensilon test. A chest CT with infusion should be done in every MG patient to look for thymomas.

TREATMENT

- Oral corticosteroids are a proven maintenance therapy, limited by the many side effects of long-term steroid use. Steroid-sparing immunomodulatory therapies should be used as monotherapy, or in conjunction with steroids to decrease effects of chronic steroids. Azathioprine and mycophenolate mofetil are reasonable first choices as steroid-sparing agents. Cyclosporin and cyclophosphamide are reserved for refractory cases that have failed other immunomodulatory agents.
- Thymectomy is a safe and effective therapy for MG, leading to remission of MG in up to 50 percent of patients in conjunction with immunomodulatory medications. However, peak effects are delayed for over one year. Thymectomy is not recommended for children because of its role in the developing immune system, or elderly older than 65 years old secondary to surgical risks. Myasthenic crises should be treated with IVIG or plasmaphoresis.
- High dose steroids are contraindicated for their risk in paradoxically worsening weakness. Intubation and mechanical ventilation may be necessary in patients with respiratory distress, and should be done preventatively to avoid emergent intubations. Forced vital capacities and negative inspiratory force should be followed serially in the hospital. Values of less than 1 L and greater than - 60 cc H2O are indications for intubation, respectively.

25. Duchenne Muscular Dystrophy

A 3-year-old boy presents to your clinic with gait difficulty. He is the nonconsanguineous product of an unremarkable childbirth. His APGAR scores were 8 and 10 at birth, and he had no difficulties with feeding. At 1 year, he was sitting without support, crawling, and saying his first word. He began walking at 22 months. His parents are concerned because he frequently falls without seemingly any provocation. At this point, he is still unable to walk up stairs. His parents note that he walks on his tip-toes. On his examination, you see an active, happy boy. You see that as he ambulates around the room, he brings his hips in towards the center of gravity, resulting in a “waddling” gait. In addition, he arches slightly backwards and stands on his tip-toes to compensate in balance. When asked to get up from a supine position, he rolls over until prone, gets on his elbows and knees, and uses his hands to push up off his legs in order to reach a standing position. His calves seem abnormally enlarged. Proximal reflexes are absent, but ankle jerks are preserved. The mother has a brother who died at the age of 7 from some “wasting illness,” but does not know any further details. The parents are concerned because they have a 1-year-old girl as well, and they want to know the risks of her developing this syndrome.

BACKGROUND

- The patient has Duchenne Muscular Dystrophy (DMD). This is an X-linked recessive inherited myopathy which is caused by mutations in the dystrophin gene. It is the most common muscular dystrophy in children (1 in 3,500 male births), and one of the most common lethal genetic diseases. DMD shares a clinical spectrum with Becker Muscular Dystrophy, of which DMD is the more severe disease. Becker Muscular Dystrophy is caused by the same gene and protein defect as DMD.

PATHOLOGY

- The DMD gene is extremely large (2.5 million base pairs), and encodes the dystrophin protein. Because of the large size of the gene, it is at high risk for spontaneous new mutations. It is thought that up to one-third of cases are secondary to spontaneous mutations. Mutations in DMD are typically out-of-frame deletions leading to decreased amounts of altered forms of dystrophin. Dystrophin is a structural protein that stabilizes the membranes in muscle cells. Mutations in dystrophin lead to oxidative damage to the cell, calcium excitotoxicity, and cell death. This leads to a chronic necrotizing myopathy with a pattern of myofiber degeneration and regeneration on histology.

CLINICAL PRESENTATION

- Patients with DMD present with progressive proximal muscular weakness, typically with childhood onset. Symptoms may not be recognizable until the patient begins walking. The gait is described as “waddling” secondary to weakness in the hip extensors. This leads to a forward tilt of the pelvis with a compensatory lordosis. The tip-toe walking develops as a mechanism to balance the center of gravity, and precedes weakness of the anterior tibialis muscle. Gower’s sign is the classical finding in DMD and consists of the child first lying at a supine position, then getting up as fast as he can. The full Gower’s maneuver consists of the child turning from supine to prone, pulling himself up to his knees and elbows, and using his hands to push himself up off his legs to reach a standing position. Calf enlargement is another

typical feature, and is described as “inverted champaign glasses.” Intellectual impairment is seen in about one-third of patients. DMD is a progressive disease that eventually leads to loss of ambulation, degenerative bony changes, and respiratory failure. Cardiac muscles are involved in late disease, leading to dilated cardiomyopathy. Progression of the disease is inevitable, and patients lose ambulation by 15 years of age. Most patients die by their second decade. Patients with DMD who are exposed to halothane anesthetics are at risk for developing malignant hyperthermia. As the disease is inherited through the X-chromosome, women are symptomatic carriers. They may, however, be asymptomatic for elevated CK levels.

DIAGNOSIS

- CK levels are strikingly elevated at birth, ranging from 5,000 to 150,000 IU/L. CK is a common lab checked at birth, possibly alerting family and physicians to the disease. DMG is confirmed by gene deletion testing, and can be performed prenatally. However, not all DMD mutations are secondary to gene deletion, as some are due to point mutations. Rapid sequencing of the dystrophin protein can also be performed. Confirmatory DNA testing can be offered to patients with a typical presentation and clear family history, but is not necessary. In non-deletional cases of DMD, a muscle biopsy is necessary to evaluate the dystrophin production. Dystrophin levels less than five percent of normal are diagnostic of DMD. Decreased amounts of dystrophin higher than five percent are a diagnostic of Becker Muscular Dystrophy. Once a patient has been identified with DMD, the females in the family must be screened for carrier status. Once the diagnosis has been made, serial transthoracic echocardiograms should be checked annually to evaluate the cardiac status.

TREATMENT

- There is no cure for DMD. However, corticosteroids have been shown to slow the progression of disability. It can prolong ambulation for years, but does not affect overall outcome. Its use must be tempered by the chronic side effects. It is thought to work via membrane stabilizing effects rather than an anti-inflammatory mechanism. Braces and physical therapy are necessary to prevent contractures. ACE-inhibitors are thought to be beneficial to the dilated cardiomyopathy of late disease. Mechanical ventilation is an option for prolonging life in the end-stage of disease.

NOTE

- Becker’s Muscular Dystrophy another dystrophinopathy that presents with proximal muscular weakness. Symptoms are milder than that seen in DMD and begin later in life. Progression is slower and mild cases may not require assistance in ambulation. In addition, CK levels are typically not as highly elevated. Mutations are generally in-frame deletions leading to production of a functional form of dystrophin, either in normal or decreased quantity. Differentiation between DMD and Becker’s is done on the basis of clinical presentation, family history, and if necessary, dystrophin protein testing. The presence of gene deletion is insufficient to determine between the two diseases.

26. High Grade Glioma

Mr. X is a 53-year-old, right-handed male who was brought to the hospital after generalized tonic clonic seizure activity was witnessed. When questioned, his family states he had no prior medical problems, but noted subtle personality changes over the past three weeks. They state that occasionally the patient would become frustrated because he felt clumsy when using his left hand, and would sometimes drop objects he was holding with that hand. Non-contrast CT imaging of the brain revealed a right frontal mass. Follow up of an MRI with and without infusion demonstrated a heterogeneously enhancing lesion in the frontal lobe with surrounding edema.

BACKGROUND

- The patient has an illness categorizing in CNS malignancy, most likely high grade glioma, specifically glioblastoma (also known as grade IV astrocytoma or GBM).

PATHOLOGY

- Glioblastoma has no clear environmental etiologic factors, except for prior history of ionizing radiation. Histologically, the two cardinal features are pseudopalisading necrosis, and endothelial proliferation.

CLINICAL PRESENTATION

- It is the most common *primary* brain tumor. Clinical features often include new onset seizures and headaches. The seizures are focal in onset, but can become secondarily generalized. The headaches are often worse when lying down and can awake individuals from sleep. Other clinical findings depend on the anatomic location of the tumor. Oftentimes in glioblastoma, the symptoms are relatively quick in onset.

DIAGNOSIS

- Non-infused head CT will demonstrate the mass lesion. This is often obtained in the ER initially. An MRI with and without infusion (also called pre/post) is obtained to better characterize the lesion. Typically, glioblastomas are heterogeneously enhancing because of the areas of necrosis within them. Tissue for pathologic assessment is necessary for diagnosis via a craniotomy or stereotactic biopsy.

TREATMENT

- Treatment of glioblastoma is multi-modality. Treatment begins with surgery (maximum safe surgical resection), followed by radiation therapy with concomitant chemotherapy, then adjuvant chemotherapy (temozolomide). There are multiple therapeutic options if individuals progress on one regimen.

PROGNOSIS

- The mean survival with surgery and radiation is 12.1 months, with surgery/radiation/temozolomide is 14.6 months. Some patients can survive for much longer. Favorable prognostic factors include young age, good "performance" status, and extensive resection.

NOTES

- Points of confusion include the multiple names for the same thing: glioblastoma, glioblastoma multiforme, GBM, and grade IV astrocytoma.
- It is important to distinguish between primary brain tumors (which begin in the brain), such as glioblastoma from metastatic brain tumors that spread to the brain.

Metastatic brain tumors and abscesses (infections) often appear as ring-enhancing lesions on CT and MRI. These lesions may be multiple. Patients with metastatic cancer will often have lesions elsewhere in the body, or have histories which include smoking and weight loss. Patients with abscesses will often have fevers, a preceding invasive surgical procedure, or infection in their histories.

27. Astrocytoma

Ms. X is a 34-year-old, right-handed female who began to bump into objects on her left over the last 10 months. She ascribed this to being inattentive. Also, she's been having headaches intermittently for about two years. These were most pronounced when first awakening in the morning, and would worsen anytime she would Valsalva. She subsequently was in a motor vehicle accident in which another car ran into hers from the left side. This prompted imaging with a non-infused, which revealed a right parietal mass. Subsequent MRI with and without infusion demonstrated a non-enhancing area of low signal on T1 and high signal on T2/FLAIR.

BACKGROUND

- The patient has CNS malignancy, most likely grade II astrocytoma (also known only as astrocytomas).

PATHOLOGY

- Grade II astrocytomas have no clear environmental etiologic factors, except for previous history of ionizing radiation. Histologically, they demonstrate moderately increased cellularity and occasional nuclear atypia. They lack the necrosis and endothelial proliferation, which define glioblastoma.

CLINICAL PRESENTATION

- Clinically, lower grade (i.e. grade II) astrocytomas is seen in slightly younger patients. Oftentimes they have a longer history of symptomatology. Again, location of the tumor determines what specific symptoms the patient may have. All patients with brain tumors may have headaches which are often worse upon first awaking in the morning or with Valsalva, as well as seizures of focal onset with the possibility of becoming secondarily generalized.

DIAGNOSIS

- Imaging is the same as with other brain tumors; head CT usually initial in the ER, followed by the more definitive MRI with and without infusion. The tumors usually do not enhance. They are typically low signal on T1 and high signal on T2/FLAIR. To diagnose the grade II astrocytoma, a surgery is needed (craniotomy with tumor resection or stereotactic brain biopsy).

TREATMENT

- In certain scenarios these lesions are followed radiographically, but in most cases the largest safe surgical resection is performed. There is controversy regarding the subsequent treatment of radiation, chemotherapy, or following treatment radiographically.

PROGNOSIS

- The mean survival for a grade II astrocytoma is 6 to 8 years. Grade II astrocytomas can progress to become grade III (anaplastic astrocytoma) and grade IV (GBM) tumors.

NOTE

- The nomenclature is confusing; astrocytoma, or grade II astrocytoma. The term "astrocytomas" is also used as the name for the category encompassing tumors ranging from grade I to grade IV. Sometimes these tumors are called "benign" to

distinguish them from “malignant” (i.e. grade III and IV tumors), however the mean overall survival is less than 10 years.

28. Medulloblastoma

Jason is an 8-year-old boy whose gym teacher noticed that he has been quite clumsy for the past two months. He has also been complaining of headaches every morning when he awakes. His parents have felt he was merely trying to avoid school. After he awoke one morning with a severe headache, nausea, and vomiting, his parents took him to his pediatrician. While at the pediatrician's office, his level of alertness began to diminish. He was rushed to the ER, and a non-infused head CT revealed a large mass in the posterior fossa with evidence of hydrocephalus.

BACKGROUND

- The patient has developed a posterior fossa, in which the differential includes medulloblastoma, as well as pilocytic astrocytoma (grade I).

PATHOLOGY

- There are no definitive etiologic factors for medulloblastoma. On histopathology there is a dense number of small, round blue cells. Homer-Wright rosettes may be seen. There is typically high mitotic activity.

CLINICAL PRESENTATION

- Medulloblastomas occur in the cerebellum (usually midline). They can grow into the fourth ventricle and obstruct CSF flow, causing hydrocephalus. They most often occur in children with a peak incidence at 7 years of age. They can spread via the CSF to other parts of the neuraxis. Oftentimes, patients present with headaches that are worse in the morning and may awake patients during sleep. Patients may also develop nausea and vomiting, as do other brain tumor patients. However, they typically do not develop seizures as in other brain tumor patients. These patients usually have cerebellar findings (clumsiness, ataxia, dysmetria, etc).

DIAGNOSIS

- As with most brain tumors, a non-infused head CT is performed in the ER. However, an MRI of the brain with and without infusion is the definitive study which you would order. It usually demonstrates a heterogeneously enhancing mass arising in the cerebellum. In medulloblastomas, an MRI of the spine should also be performed to evaluate for drop mets. Complete resection of the tumor should be the means by which tissue is available for pathologic evaluation. Subsequent to surgery CSF is evaluated by LP to assess for CSF spread.

TREATMENT

- Initial management is complete surgical resection, followed by radiation (often craniospinal radiation) and chemotherapy.

PROGNOSIS

- The five year survival for average-risk medulloblastomas is 80 percent. This is a marked improvement compared to the 1960s, when it was 30 percent.

NOTE

- There is sometimes confusion regarding the etiology of the tumor before there is tissue. Pilocytic astrocytomas (grade I) can also appear in the posterior fossa. They are often ring enhancing, sometimes cystic.

29. Brain Death Evaluation

A 68-year-old male recently had a myocardial infarction three days ago. He develops an arrhythmia, followed by cardiac arrest. CPR was initiated, and a stable rhythm was established approximately 20 minutes later. The patient was noted by staff to not be “breathing over the vent” after 24 hours passed. The patient did not respond to voice or painful stimuli. Primary service is requesting a consult to evaluate for brain death.

BACKGROUND

- The patient has likely suffered a cardiopulmonary arrest with a resultant anoxic injury to the brain. The patient’s clinical exam 24 hours after the arrest shows evidence of loss of cortical and brainstem function. Evaluation is as follows.
- Neuro Exam:
 - State: Unresponsive to verbal/painful stimuli
 - Cranial nerve exam:
 - Pupils 3mm bilaterally and unreactive to light.
 - No movement of eyes with passive movement of head, or “doll’s head maneuver”
 - No corneal reflex
 - Absent vestibular cochlear reflex
 - No gag reflex
 - Tone: Flaccid
 - Strength: No spontaneous movements
 - Stimuli: No response to painful stimuli
 - Reflexes: 0/4 in upper and lower extremities bilaterally
- Studies:
 - Head CT: no hemorrhage, no masses

For the diagnosis of brain death, there are certain criteria that must be fulfilled. Criteria are listed below:

- Criteria for Determination of Brain Death
 - 1) Must have a known and irreversible cause
 - 2) No severe electrolyte or acid base abnormalities
 - 3) Temperature of at least 36.5 degree Celsius and a blood pressure of at least 90mmHg systolic
 - 4) Clinical Exam:
 - a. Absent response to painful stimuli
 - b. Decreased tone in all extremities with absent reflexes
 - c. Absent brain stem reflexes
 - i. No pupillary response to light
 - ii. No oculocephalic reflex (“doll’s eyes maneuver”)
 - iii. No corneal reflex
 - iv. No vestibular cochlear reflex (“cold caloric”)
 - v. No gag
 - vi. Apnea Test
 1. Preoxygenate the patient to PO₂ of >200 and PCO₂ <40
 2. Hold ventilations for 8 minutes

3. Abort test if respiratory mvmts seen, systolic Bp<90mmHg, significant desaturation or cardiac arrhythmia
4. Draw ABG
5. => Test positive if PCO₂ >60mmHg or 20mmHg increase above baseline

5) Optional Confirmatory Tests

- a. Cerebral angiogram, Transcranial Dopplers (TCDs)-no filling past carotid bifurcation/circle of Willis
- b. EEG-electrocerebral silence
- c. Technetium 99hexamethylpropyleneamine brain scan-no uptake

Important Points to Remember:

1. Patients must have absence of cortical and brain stem function. Hence, both cortex and brainstem must be injured.
2. Patient cannot be “cold” and dead. Pt must have temp > 36.5.
3. Tone must be flaccid, with absent reflexes in extremities.
If tone is present, increased, or hyperreflexia is noted, the patient cannot be diagnosed as brain dead. In that clinical situation, an upper spinal cord/brainstem injury must also be considered.

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