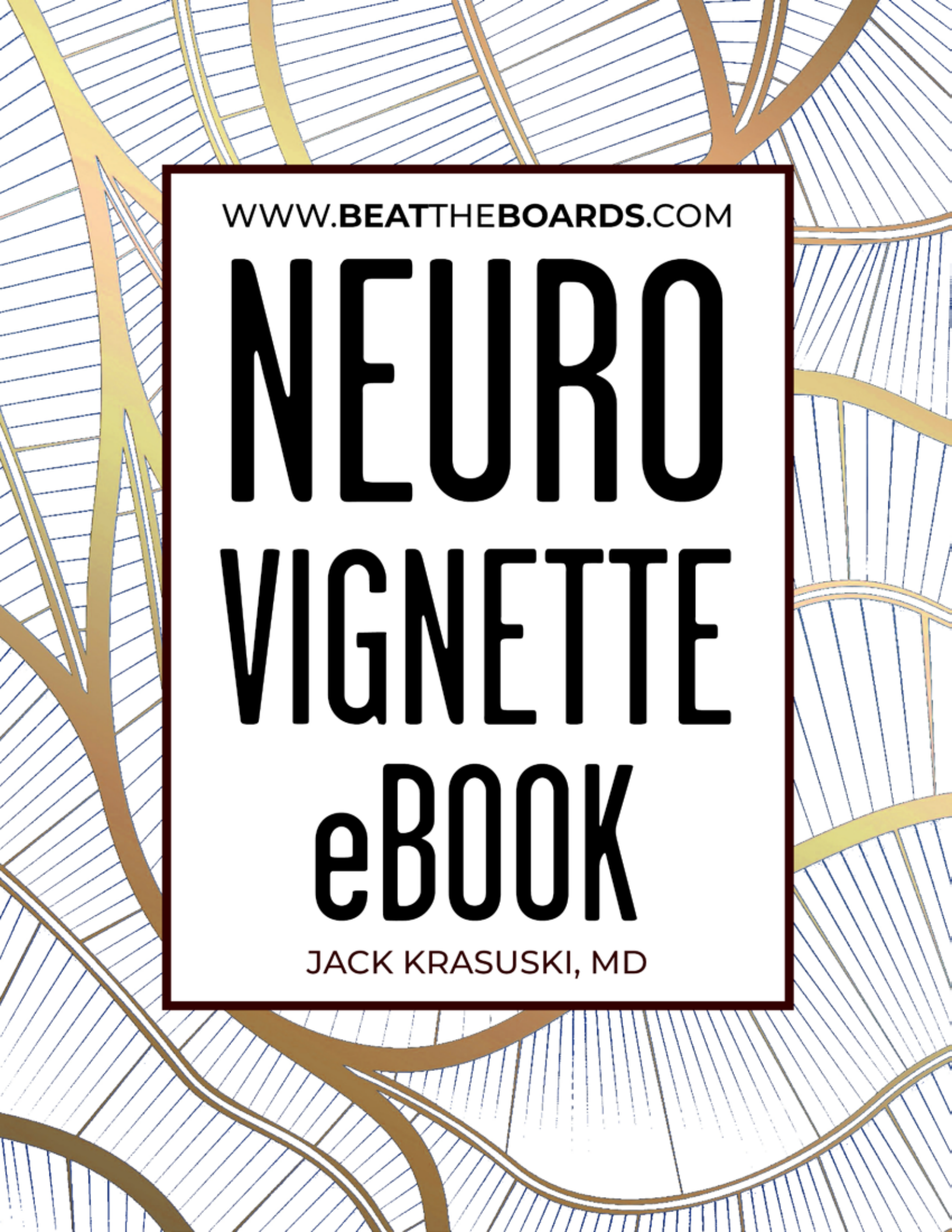
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NEURO VIGNETTES

PSYCHIATRY EXAM PREPARATION RESOURCE

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Introduction

This manuscript covers the neurologic disorders most commonly tested on the Psychiatry exam. Discussion of each disorder is organized as follows: clinical vignette, background, pathology, clinical presentation, diagnosis, treatment, and prognosis.

Note regarding diagnostic terminology: The DSM-5 has replaced the term 'dementia' with the term 'neurocognitive disorder.' Thus, when presenting the names of disorders, I use this DSM-5 term. However, when referring more generally to these conditions, I will at times use the term 'dementia,' which I use interchangeably with 'neurocognitive disorders.' Note also that when relevant terminology and diagnostic criteria are presented, they are consistent with the DSM-5.

Parkinson's Disease

CASE VIGNETTE

- 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 sustained 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 extrapyramidal signs are captured with the acronym TRAP: Tremor (at rest), Rigidity, Akinesia/bradykinesia, 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. The term extrapyramidal refers to the motor systems outside of the corticospinal tracts which resemble pyramids on axial cross sections through the brainstem.

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. MPTP is now used to create animal models of PD. Excitotoxicity from persistent activation of glutamatergic 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. Lewy bodies are not pathognomonic for PD as they can be found in other neurodegenerative disorders.
- 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/bradykinesia, 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 may be seen in late disease. PD is slowly progressive, and average lifespan after diagnosis often 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. Conventional 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). Functional imaging of the dopamine transporter (DaT scan) can demonstrate with high sensitivity presynaptic neuronal degeneration. This finding can assist with differentiating PD from other disorders with overlapping clinical presentations. DaT scans have been approved to differentiate PD from essential tremor.
- Obtaining a drug history is very important as drug-induced Parkinsonism is a common and reversible differential for PD. Parkinsonism-inducing drugs are dopamine-depleters and include first generation antipsychotics and, to a lesser extent, second generation antipsychotics. Other medications of concern include acetylcholine-increasing medications, such as bethanechol used to treat urinary retention, and the cholinesterase-inhibitors used to treat Alzheimer's disease. Lithium and valproate 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.
- Disorders in the differential include multisystem atrophy (with symmetrical presentation), progressive supranuclear palsy (with impaired downgaze and asymmetrical presentation), and corticobasal degeneration (with cortical impairments such as apraxia and agnosia).

TREATMENT

- Management is complex, involving a variety of medications with varying mechanisms of action. The mainstay of therapy is levodopa, a precursor to dopamine. It is typically administrated 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 fewer dyskinesias and wearing-off effects. However, dopamine agonists are less potent than levodopa; patients eventually progress to treatment with levodopa after several years of treatment with non-levodopa medications. The current dopamine agonists 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 (Azilect) are available. The benefit of rasagiline is that it's not metabolized into amphetamine.
- Amantadine and anticholingeric medications can be used symptomatically to help with dyskinesias and tremors. Second generation antipsychotics should be used sparingly in PD patients given their risk of worsening the extrapyramidal effects, but may be required in patients with prominent and refractory psychotic symptoms.
- Deep brain stimulation (DBS) is a surgical option for patients with PD. Electrodes are implanted into deep gray matter and electrical stimulation is applied. Symptoms can improve dramatically. DBS often targets the subthalamic nucleus (STN) or the globus pallidus internal (GPi).
- Finally, as in all neurodegenerative diseases, social and emotional support is paramount for both the patient and caretakers.

SAMPLE EXAM QUESTION

A 67-year-old male patient presents to your clinic because of slowing of his movements, a tremor he notices when his hands are resting on the table or on his lap and, most concerning to him, his gait is slow and less steady. He often feels like he's about to fall over on his face, as if his "feet can't keep up." Medical history discloses moderate hypertension over the last 10 years, well controlled with the ACE inhibitor lisinopril. Family history is negative for tremor or gait instability. Physical exam discloses mild festinating gait, a resting high-amplitude tremor, and decreased facial expressiveness. On cognitive exam, patient is fully oriented, alert, and recalls 3 out of 3 words. He is noticeably slow in responding to questions and is not very elaborative. His answers are on-topic and accurate as confirmed by his wife who has accompanied him. Given this history and presentation, which medication would be most appropriate to start the patient on?

A. Amantadine

B. Levodopa/carbidopa

C. Selegiline

D. Tolcapone

E. Trihexyphenidyl

EXPLANATION

Initial treatment of Parkinson's disease is usually a choice between levodopa/carbidopa and a dopamine agonist, such as ropinirole, pramipexole, rotigotine, or apomorphine. Levodopa provides superior motor benefit but, because it is associated with a higher risk of dyskinesia, a dopamine agonist may be chosen as initial treatment, especially for milder disease. Since only levodopa/carbidopa is included as a response option, it is the correct answer.

Wilson's Disease

CASE VIGNETTE

- A 36-year-old woman develops bilateral kinetic tremors (that is, tremors when her limbs are in motion) in her upper extremities. Over the course of several months, the tremors spread to include her head and lower extremities. Over the course of several months, the tremors advance to the point that they are quite debilitating. Physical examination is significant for yellowing of the sclera. The patient's optic and oculomotor cranial nerves are intact and nystagmus is absent. The patient displays dysarthric speech with a strained voice quality. Motor 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 has no atypical exposures to toxins. MRI of the brain reveals high T2 signal in the basal ganglia, especially in the putamen and globus pallidus. 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 (ATP7B), 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 and cell death.
- The disorder is autosomal recessive inheritance.

CLINICAL PRESENTATION

- Clinically, the patient with WD presents with the triad of neurologic, psychiatric, and 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. Tremors are most commonly asymmetric and may be resting, postural or kinetic. Dysarthria also is a typical early neurologic symptom.
- 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-Fleisher 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 hepatic tissue as obtained through liver biopsy.

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, trientine, penicillamine, and zinc acetate are all copper chelating agents. Tetrathiomolybdate has a rapid response and is associated with less neurologic worsening compared to trientine and penicillamine, and is thus the preferred initial agent. Trientine and penicillamine, because they can cause neurologic worsening, are second line agents.
- 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 partially 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.

SAMPLE EXAM QUESTION

A 46-year-old male patient presents to your clinic, appearing tense and anxious, and complains that his "body isn't working right." As examples he reports problems getting up from a chair, unsteadiness when he walks, and clumsiness with his hands. He admits to feeling anxious and depressed because he feels his "body is falling apart and it feels like it's getting worse and worse." On personal history he reports first noticing these symptoms about three months ago but never before. He also denies any previous symptoms of anxiety or depression, or any past or current symptoms of psychosis, substance abuse, or suicidal or homicidal thoughts. He does feel his memory is worse but thinks it may be related to his anxious state. On family history he denies knowledge of any family member with similar symptoms other than his mother who suffers from chronic depression. On exam he exhibits mask-like facies, an ataxic gait, an action tremor in his left upper extremity, and dysarthric speech. He displays brownish-yellow rings at the junction of his sclera and cornea bilaterally. Which of the following lab abnormalities is most likely to be found when a thorough lab assessment is conducted?

A. High serum ceruloplasmin level
B. High urine ceruloplasmin level
C. Low serum ceruloplasmin level
D. Low urine copper levels
E. Presence of the 14-3-3 protein in cerebral spinal fluid

EXPLANATION

In Wilson's disease, serum ceruloplasmin is low, 24-hour urine copper excretion is high, and hepatic copper levels are high (the latter is ascertained by liver biopsy). Over 90% of patients with WD have serum ceruloplasmin levels less than 20mg/dl while normal levels are 20-40mg/dl. The 14-3-3 protein is a marker for classic Creutzfeldt-Jakob disease.

Note also that the Kayser-Fleischer rings consist of copper deposits in Descemet's membrane of the cornea. Approximately 95% of patients with WD with neurological signs will have evident Kayser-Fleischer rings on slit lamp exam while only 65% of patients with WD and predominantly hepatic signs will have visible Kayser-Fleischer rings.

Huntington's Disease

CASE VIGNETTE

- 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 a history of previous tremors. 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 the severity of her psychiatric symptoms, she states, "I don't really care." She denies presence of psychotic symptoms and has never been exposed to antipsychotic or antiemetic medications. 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 of a gene 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 within a single gene on chromosome 4. The gene is the Huntingtin gene and its product is a protein called the huntingtin protein (often written as Htt); this protein functions in vesicle formation in neurons. The trinucleotide sequence CAG in the gene codes for the amino acid glutamine in the gene product.
- All individuals have a certain number of CAG repeats in their Huntingtin gene, usually 36 or fewer repeats. However, due to the mutation that causes Huntington's disease, the CAG repeats are increased in number, leading to large number glutamine repeats that are incorporated into the huntingtin protein. These glutamine repeats lead to the formation of a mutant protein (mHtt) that cannot be cleared from the neuron, leading to its accumulation and causing excitotoxic damage, and eventually leading to cell death. The number of repeats is inversely associated with the age of onset: 60 or more repeats are seen in juvenile onset disease 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. (Note that glutamine is converted to glutamate, a powerful excitatory neurotransmitter.) 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

- HD presents with a classic clinical triad: with a movement disorder, dementia, and psychiatric disturbance.
- 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.
- Patients with juvenile-onset disease may have a predominantly hypokinetic/rigid clinical presentation known as the Westphal variant of HD.
- 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. Subcortical cognitive features usually predominate.
- 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 atrophy of the caudate nucleus, but may be normal in early disease. Generalized cortical and cerebellar atrophy is seen in late disease.
- Genetic testing is available at any stage of development and is the key to diagnosis. Because HD is fully penetrant with an autosomal dominant pattern of 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 pathologic progression of HD, and thus no benefit to early diagnosis. Prenatal genetic testing also is available through the methods of chorionic villus sampling or amniocentesis.

TREATMENT

- Treatment of HD is entirely supportive. Multiple therapies have been examined to slow the progression of disease, including the use of remacemide (a NMDA glutamate antagonist), coenzyme Q12, and creatine. Treatment results with these agents have not been promising.
- Treatments to decrease chorea include the FDA-approved monoamine depletor tetrabenazine (Xenazine). Of clinical importance, tetrabenazine, due to its monoamine-depleting effects, greatly increases the risk of depression and suicide. Levetiracetam (Keppra) is also used off-label for control of chorea. Antipsychotics, due to their antidopaminergic effects, can be used to treat chorea, although they can worsen cognition at high doses. And last, benzodiazepine can sometimes lessen chorea severity.
- Depression should be treated with SSRI's or other antidepressants.

PROGNOSIS

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

SAMPLE EXAM QUESTION

When the symptoms of a genetic disorder occur earlier and with greater severity in each successive generation, this phenomenon is known by which of the following terms?

A. Epigenetics
B. Genetic anticipation
C. Meiotic non-disjunction
D. Pharmacogenomics
E. Trinucleotide repeats

EXPLANATION

- A type of genetic mutation, a trinucleotide repeat expansion, is the genetic mechanism that leads to several genetic disorders, including Huntington's disease, Fragile X syndrome, myotonic dystrophy, Friedreich's ataxia and others.
- In regard to Huntington's disease: all normal individuals have a certain number of CAG repeats in their Huntingtin gene, usually 36 or fewer repeats. However, due to the mutation that causes Huntington's disease, the CAG repeats in the gene are increased in number, leading to a long string of glutamine molecules incorporated into the gene's protein, called the huntingtin protein. These glutamine repeats lead to the formation of a mutant protein (mHtt) which, because it cannot be cleared from the neuron, ultimately leads to neuronal death.
- Genetic anticipation occurs as result of an increasing number of trinucleotide repeats in the Huntingtin gene that are passed on to successive generations. This makes the symptoms of HD appear at earlier ages and with greater severity in affected individuals in later generations.
- Meiotic non-disjunction is the mechanism that leads to trisomy 21 or Down's syndrome. Epigenetics refers to the study of changes in gene expression that are not due to alterations in the underlying DNA sequence. Epigenetic modifications change an organism's phenotype without changing its genotype. Pharmacogenomics is the study of how differences in individuals' genomes modify their responses to pharmacologic agents.

Alzheimer's Disease

CASE VIGNETTE

- 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 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. He has been having greater difficulty remembering to pay the bills and has transferred this responsibility to his wife.
- 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 was noted to make 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 two of the memorized words even

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 disease that progresses to dementia. It is associated with deposition of amyloid plaques and formation of 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 atrophy becomes global in late disease. The pathogenesis of AD is secondary to three pathogenic mechanisms.
  - Accumulation of senile plaques in the extracellular space
  - Accumulation of neurofibrillary tangles inside neurons
  - Neuronal cell loss in the cerebral cortex
- Senile (also known as neuritic) plaques are spherical aggregated deposits of β-amyloid peptide interwoven with distorted neuronal processes. β-amyloid is abnormally cleaved into a form, β-amyloid 42 (written as A β42), that facilitates formation of beta-pleated amyloid sheets. These sheets then aggregate into senile plaques that collect over the limbic and parietal lobes.
- 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.
- Early Onset Familial Alzheimer's disease: Three genetic loci are associated with abnormal β-amyloid metabolism and early onset AD. The gene for Amyloid Precursor Protein (APP), the precursor to the β-amyloid protein, is located on chromosome 21. Patients with Down 's Syndrome (trisomy 21) have abnormally enhanced APP production and early onset AD. Presenilin 1 & Presenilin 2 are genes that code for proteins involved in cleaving APP into smaller peptides. The abnormal Presenilin 1 and Presenilin 2 gene products lead to the formation of elevated concentrations of Aβ42 which leads to senile plaque formation. Genetic mutations of these three proteins – APP, Presenilin 1 and Presenilin 2 – have autosomal dominant heritable transmission and are associated with early-onset familial Alzheimer's disease.
- The metabolism of cholesterol is also involved in the pathogenesis of AD, specifically through the activity of apolipoprotein E (ApoE), a lipoprotein involved in cholesterol transportation. The epsilon 4 allele of ApoE gene 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. AD first impairs 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 apraxia, that

is, an inability to mimic hand gestures, such as brushing teeth or combing hair, 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

- This patient's level of cognitive and functional impairment is consistent with major neurocognitive Disorder due to Alzheimer's disease, mild severity.
- Diagnosis of neurocognitive Disorder due to Alzheimer's disease 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 (DSM-5). Dementia/NCD due to AD includes an impairment of the activities of daily living (ADLs).
- Laboratory measurement of 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. PET scanning of glucose metabolism can be used to differentiate AD from frontotemporal dementia etiologies in patients who have clinical features of both types of dementia.
- 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 effective in slowing cognitive and functional decline. The three agents are thought to be equal in efficacy. They are associated with the adverse effects of 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 a symptomatic and possibly a disease-modifying therapy. Memantine is approved for moderate to severe AD.
- The combination of donepezil and memantine has been shown to be more efficacious in delaying cognitive decline than donepezil alone. But memantine can be used safely and effectively with any cholinesterase inhibitor.
- Caprylidene (Axona), is a FDA-approved medical food (available by prescription only) that increases ketones in brain, an alternate energy source that protects neurons. It is FDA approved for treatment of mild to moderate AD.
- Vitamin E and selegiline therapy have been studied as disease-modifying agents, and some evidence suggests they slow cognitive decline. Other studies, however, have not found this benefit. Therefore, these agents are not universally recommended for all patients. High doses of vitamin E may increase the rate of falls, cardiac disease, and hemorrhagic stroke.
- SSRI's are used to treat depressive symptoms and behavioral dysfunction such as resistant and defiant behaviors.
- Nonpharmacologic therapies are of great import, which include exercise, 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.

SAMPLE EXAM QUESTION

A 79-year-old male patient with neurocognitive disorder due to Alzheimer's disease diagnosed seven years has recently developed increased level of defiant and aggressive behaviors. His wife, his main caretaker, states that if his behavior does not improve, she will no longer be able to manage the patient at home with help from the couple's children. She reports that he at times becomes loud and vaguely threatening. He is uncooperative when she tries to help him dress, bathe, and eat. His sleep is reduced at night and he often takes short naps during the day. His mood is 'unpredictable' and his irritated mood often gives way to tearfulness and fear. He now often has trouble navigating around the house and must be monitored closely so he does not wander off. On exam, he has no focal motor or sensory deficits. Gait is stable and no tremors are noted. On cognitive exam his memory, expressive language, constructional skills, and praxis are more impaired than during an evaluation conducted six months earlier. The patient is currently on rivastigmine 6mg bid and sertraline 100mg qam and is tolerating the medications well. What change in treatment regimen would you recommend to the patient and his family member that would have the greatest potential benefit?

A. Add memantine
B. Add selegiline
C. Add vitamin E
D. Switch rivastigmine to donepezil
E. Switch sertraline to fluoxetine

EXPLANATION

Adding selegiline (a selective MAOI) to sertraline is contraindicated. A two week washout period of sertraline is required prior to starting selegiline.

Switching from one cholinesterase inhibitor to another or from one SSRI to another, although safe, is unlikely to make a large clinical difference. Starting Vitamin E may provide marginal benefit; the dose should not exceed 400 I.U. qd.

Given the patient's diagnosis, his greater impairment in behavior and cognition are most probably an expected progression of his disease state (although a more thorough work-up is indicated). The vignette suggests progression of illness to a moderate- severe level. Memantine is now a natural addition to the medication regimen. It is well tolerated and safe to use in conjunction with the patient's current medications.

Frontotemporal Neurocognitive Disorder

CASE VIGNETTE

- 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 becoming 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 frontotemporal lobes.

BACKGROUND

- The patient has frontotemporal neurocognitive disorder which, by DSM-5 criteria, has two syndromal variants, the behavioral variant and the language variant.
  - The behavioral variant can present with symptoms of disinhibition, inappropriate social or sexual behaviors, abulia, utilization behavior, and hyperorality, as well as executive function impairment.
  - The language variant can present with various language deficits such as with a nonfluent/agrammatic aphasia characterized by sparse and halting speech; with a semantic aphasia characterized by loss of meaning and recognition of words and objects; or with a logopenic aphasia characterized by impaired naming and repetition.
- Frontotemporal neurocognitive disorder is caused by any one of a group of neurodegenerative diseases that lead to frontotemporal lobar degeneration (FTLD).
  - Terminology surrounding frontotemporal neurocognitive disorder and FTLD can be confusing: frontotemporal neurocognitive disorder refers to the clinical presentation caused by any one of the different disease states that lead to degeneration of the frontal and/or temporal lobes, that is, that lead to a FTLD.
- FTLD etiologies include Pick's disease, amyotrophic lateral sclerosis, progressive subcortical gliosis, and five currently-identified genetic mutations. The two most important ones are:
  - GRN (or PRGN) Progranulin gene mutation
  - MAPT (Microtubule-Associated Protein Tau) gene mutation

PATHOLOGY

- 40% of frontotemporal neurocognitive disorder cases are familial and half of these familial cases are due to currently-identified genetic mutations. The five known genetic mutations involve these genes: MAPT, GRN, VCP, TARDBP, CHMP2B.
- The FTLDs can be divided into the tauopathies, in which the neuronal inclusions are positive for the protein tau; and the non-tauopathies, in which the inclusions are tau-negative and ubiquitin positive.
  - A mutation in the MAPT (Microtubule-Associated Protein Tau) gene, located on chromosome 17, causes a tauopathy. The MAPT mutation has an autosomal dominant inheritance pattern and causes clumping of the tau protein that eventually leads to cell death. Clinically, the MAPT mutation presents with frontotemporal cognitive impairment and parkinsonian motor symptoms and, thus, this condition is called 'FTD with Parkinsonism' or FTDP-17. Despite the use of the word 'parkinsonian' in the name, this is not an α-synucleinopathy (like Parkinson's disease) but rather, as stated previously, a tauopathy.
  - The most common pathological finding in cases of frontotemporal dementia, however, are ubiquitin-positive, tau-negative inclusions. These conditions are named FTLD-U. Clinically, FTLD-U may present with or without Parkinsonian motor symptoms. A mutation on the GRN (or PRGN) Progranulin gene, located on chromosome 17, accounts for the majority of the FTLD-U cases.
- Frontotemporal NCD overlaps clinically and pathologically with several neurologic diseases. Thus, both frontotemporal NCD and the specific neurologic disease can be diagnostically coded.
  - Corticobasal Degeneration presents with a classical triad of: 1) unilateral rigidity, 2) apraxia, and 3) alien hand syndrome.
  - Progressive Supranuclear Palsy is characterized by cognitive impairment and

Parkinsonism, as well as supranuclear gaze palsy.

- Amyotrophic Lateral Sclerosis, the upper and lower motor neuron disease is associated with features of frontotemporal NCD in approximately 20% cases.

CLINICAL PRESENTATION

- Behavioral and personality change are prominent features of the behavioral variant of frontotemporal NCD. Disinhibition, a common symptom, presents as 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 language variant of frontotemporal NCD, various language impairments may develop and are grouped into three syndromic variants.
  - Nonfluent/agrammatic aphasia characterized by sparse and halting speech with intact comprehension and object recognition. This level of impairment may progress to mutism.
  - Semantic aphasia characterized by loss of meaning and recognition of words and objects. Frequent word substitutions occur within the context of retained fluency. This level of impairment may progress to an incomprehensible fluent aphasia.
  - Logopenic aphasia is characterized by impaired naming and repetition.
- It is not uncommon for patients to have features of the different subtypes of frontotemporal NCD, or to progress from one clinical presentation to another as the underlying pathology progressively worsens.

DIAGNOSIS

- FTD is primarily a diagnosis made clinically that can be confirmed by pathologic assessment and, in familial cases, by DNA testing. 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. PET imaging can be used to help distinguish between FTD and AD and is Medicare approved for diagnosis in cases in which AD and FTD clinical features overlap.

TREATMENT

- There is no specific treatment for FTD, which remains 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 and further language rehabilitation may become frustrating or overwhelming to patients. Family and patient education is important as well.

PROGNOSIS

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

SAMPLE EXAM QUESTION

A 63-year-old male presents to clinic with a progressive three year history of decrements in expressive language. His speech is sparse and halting; he is acutely aware of his language difficulty and appears frustrated and tense. His wife reports that his mood goes through inexplicable changes and he becomes agitated at times, in a way that scares her. Also, his behavior is odd in other ways. For example, he was walking down a neighborhood street last week and noticed a lawnmower in his neighbor's open garage and started mowing his neighbor's lawn. Also, he seems to want to eat sugary cereal three times a day and gets agitated when this is denied him. His wife reports that the patient's father, whom he did not know well because his parents divorced early, also developed 'odd symptoms' before he died in his 60's. On exam the patient is noted to have a resting tremor, mild rigidity, and unsteady gait. Motor strength is full and reflexes are within normal. On cognitive exam patient has three out of three word registration and recall but with hesitation; full orientation; ability to follow a three step command, and intact copying of intersecting pentagons. He is alert and cooperative. Which of the following etiologies is the most likely cause of this patient's clinical presentation?

A. Alzheimer's disease

B. Vascular disease

C. Amyotrophic lateral sclerosis

D. MAPT gene mutation

E. Prion disease

EXPLANATION

This patient presents with a mixture of the behavioral and language variants of frontotemporal NCD. He has a dramatic change in diet and displays environmental dependency (or utilization behavior) as evidenced by inexplicably mowing his neighbor's lawn when he saw a lawnmower.

His motor symptoms are suggestive of Parkinson's disease and the differential should include NCD due to Lewy bodies and NCD due to Parkinson's disease. NCD with Lewy bodies usually has a cortical presentation of cognitive impairment that affects memory, praxis, recognition, as well as the language impairment that the patient present with.

NCD due to Parkinson's disease more frequently presents with a subcortical presentation that is somewhat more consistent with this patient's presentation. Thus, a more careful cognitive and motor exam is indicated as well as evaluation with labs and neuroimaging studies to rule out a Parkinson's disease etiology.

This patient is unlikely to have prion disease because classic Creutzfeldt-Jakob disease (CJD) usually leads to death within half a year of symptom onset and variant CJD (due to bovine spongiform encephalopathy) usually leads to death usually close to one year of symptom onset. More definitive assessment with EEG, MRI, and of CSF could help rule out classic and variant CJD.

Given that the patient has normal motor strength and reflexes and a three year history of progressive language impairment, ALS is unlikely.

The patient's father is reported to have developed similar symptoms. So, given his family history and a frontotemporal presentation, the most likely cause, from the options presented, is a MAPT gene mutation which has an autosomal dominant pattern of inheritance.

Neurocognitive Disorder with Lewy Bodies

CASE VIGNETTE

- 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 one 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. He also scores very poorly on the Trail Making Test. 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 Neurocognitive Disorder with Lewy Bodies (or DLB, for dementia with Lewy bodies), 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, eventually, extrapyramidal motor signs such as those seen in Parkinson's Disease (PD). DLB may be the second most common dementia etiology after Alzheimer's disease.

PATHOLOGY

- Lewy bodies are seen in Parkinson's disease (PD), PD with dementia, and DLB . Lewy bodies are formed by aggregates of alpha-synuclein, ubiquitin, and neurofilament protein. They are more widely distributed in DLB than in PD. In PD, Lewy bodies are deposited mostly in the nigrostriatal pathways of the basal ganglia. In contrast, in DLB they are deposited diffusely in the brainstem, subcortical areas, and cortex. 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 AD. Degeneration of cholinergic neurons may predispose the patient to hallucinations.

CLINICAL PRESENTATION

- Symptoms are a progressive, cognitive impairment with a fluctuating course (at times suggestive of delirium), recurrent visual hallucinations, Parkinsonian motor symptoms, and psychiatric symptoms, especially of visual hallucinations and depression. Cognitive impairment in DLB overlaps substantially with that seen in Alzheimer's disease, but displays more severe impairment in visual-spatial function and spatial working memory. The Trail Making Test Part B is sensitive to impairments in spatial working memory. 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 dreams (REM sleep behavior disorder), 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 start of motor symptoms. Patients with PD with dementia have Parkinsonian motor symptoms present for a minimum of one year prior to start of cognitive 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 AD. Neuroimaging shows nonspecific cortical atrophy similar to that seen in AD.

TREATMENT

- Treatment can slow the progression or decrease the symptoms of the disease, but no curative treatment is available. Cholinesterase inhibitors such as rivastigmine may improve cognitive symptoms, and may be as effective as in AD. Use of antipsychotics, especially high potency ones such as haloperidol, should be minimized since they often worsen Parkinsonism. Some second generation antipsychotics, particularly clozapine, may be used at low doses 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, dopamine-increasing medications can worsen hallucinations. Social support is important to patients and their caregivers.

PROGNOSIS

- The course of DLB is slowly progressive and leads to death with an average survival time of eight years after diagnosis; thus, the progression is faster than that seen with AD. No treatment is curative or disease-modifying.

SAMPLE EXAM QUESTION

A 69-year-old female presents to clinic with new onset visual hallucinations of miniature people that she sees in on her counter and tables, and at the foot of her bed. The patient's daughter reports that the patient is different 'from one day to the next. Sometimes she's calm and almost like her normal self, and other days she's confused, anxious and irritable." On a couple of occasions the daughter slept at her mother's house and was wakened by her mother speaking and moving about on her bed while asleep. On cognitive exam, the patient shows short-term memory impairment, poor clock copying ability, constructional deficits, and ideomotor apraxia. The latter was tested by asking her to show how she would brush her teeth and comb her hair. Which of the following medications should be avoided when treating the symptoms of this patient?

A. Risperidone
B. Donepezil
C. Clozapine
D. Rivastigmine
E. Memantine

EXPLANATION

This patient presents with symptoms most consistent with dementia with Lewy bodies. She is, therefore, likely to have antipsychotic medication sensitivity and react with severe extrapyramidal symptoms when exposed to such a medication. Out of the antipsychotics, clozapine is least likely to cause severe EPS, while high potency medications such as haloperidol and risperidone are most likely to trigger it. When psychotic symptoms, such as visual hallucinations or delusions, are prominent and distressing, then pharmacotherapy is indicated. Initial management should be with a cholinesterase inhibitor or SSRI. If these medications fail, then low dose antipsychotics can be cautiously initiated. If clozapine is not a viable first choice due to its side effect profile and need for frequent blood tests, then low doses of an alternate antipsychotic medication such as quetiapine can be initiated.

Binswanger's Subcortical Vascular Disease

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, because otherwise he has frequent falls.

On physical examination, 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 slow with prominent inattention. Memory is three of three for immediate recall, and one of three after 5 minutes. Language is intact for 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 shows unsteadiness and inability to shift his feet accurately to maintain a center of gravity and prevent falls.

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 presentation of dementia caused by subcortical dysfunction from ischemic damage to the deep white matter, a condition known historically as Binswanger's disease and now more frequently referred to as subcortical arteriosclerotic encephalopathy. This condition leads to a progressive decline in cognitive function. 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, that is, strokes that leave an area of damage one centimeter or less in diameter, 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 disease. 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 hemineglect may be present but are less common and less severe 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.
- Additionally, signs of pseudobulbar palsy are also commonly seen. These symptoms include

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, while sparing 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.

- Vascular dementia or neurocognitive disorder is caused by different types of vascular cortical and subcortical pathology.
  - Subcortical: Binswanger's disease causes subcortical brain damage and presents with a subcortical presentation. Also, 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. Also, amyloid angiopathy and antiphosphilid antibody syndrome leads to Binswanger's disease without traditional vascular risk factors.
  - Cortical: multi-infract dementia results from large thromboembolic cortical strokes.

TREATMENT

- There is no specific treatment for Binswanger's disease or, more broadly, vascular neurocognitive disorder. 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 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. Off-label use of cholinesterase inhibitors, such as donepezil, can provide symptomatic improvement of cognitive symptoms and is of modest benefit.

PROGNOSIS

- Patients who have vascular risk factors optimally controlled can arrest progression of their cognitive and non-cognitive symptoms. Some patients may even show slight improvement when the continued insults to the brain cease.

SAMPLE EXAM QUESTION

A 64-year-old male presents to clinic. His family members who accompany him report a history of depression, apathy, and cognitive decline over the last 10-15 years characterized by 'slow thinking and slow movements.' On exam, he is unshaven and disheveled and has urine stains on his pants. His blood pressure is 200/110 with a pulse of 84. The patient speaks slowly, softly and hard to understand due to a 'mumbling speech.' His gait is unsteady with a stiff walk and odd placement of his feet, which leads to swaying and near falls. He has clumsy and slow limb movements, left sided weakness and an extensor plantar sign on his left. He has incomplete gaze paresis. At one point in the interview when a clinic door closed loudly, the patient started crying although he could not describe why and denied feeling sad or distressed. Given this patient's presentation, in which region or brain structure is brain damage most likely present?

A. Amygdala

B. Cerebellum

C. Hippocampus

D. Periventricular white matter

E. Thalamus

EXPLANATION

This patient presents with subcortical arteriosclerotic encephalopathy or Binswanger's disease. This condition is characterized by the 4 D's: dysmnesia (impaired recall that is improved with cuing), dysexecutive syndrome, delay (slowness), and depletion (apathy and amotivation). This patient also shows signs of a 'frontal' or 'magnetic' gait characterized by impaired limb placement and frequent falls. Further, he has signs of pseudobulbar or suprabulbar palsy that occur due to interruption of the corticobulbar tracts as they descend through the corona radiata and internal capsule, and present with deficits in cranial nerve function and, additionally, can present with 'emotional incontinence.'

Variant Creutzfeldt-Jakob Disease

CASE VIGNETTE

- 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, nor a 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 paresthesias that are not restricted to any specific anatomical distribution.

BACKGROUND

- The patient has variant Creutzfeldt-Jakob Disease (vCJD), a spongioform encephalopathy, transmitted via prions. It occurs from exposure to contaminated beef products derived from cows with Bovine Spongioform Encephalopathy (Mad Cow Disease). Unlike classical (also known as sporadic) 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 Spongioform Encephalopathy had occurred.

PATHOLOGY

- CJD and its various subtypes (vCJD,Gerstmann-Straussler-Scheinker syndrome, fatal familial insomnia) are neurodegenerative diseases of prion transmission in humans and other primates. Prion diseases in animals include Scrapie (in sheep), Bovine Spongioform Encephalopathy (in cows), and Chronic Wasting Disease (in deer and elk), among others.
- Prions are pathological conformations of normal proteins found in neurons. They lead to the disease state by inducing progressive transformation of normal prion proteins (PrPs) into a pathological (misfolded) isoform called a prion.
- Prions are unique in the world of infectious agents, since that they mediate their infectivity without nucleic acids. Since prions do not contain any nucleic acids and also are resistant to cellular proteases, they cannot be degraded by normal biological means. The prion isoform molecules increase exponentially and begin to form insoluble aggregates within cells that cannot be processed or cleared. These aggregates accumulate and eventually lead to vacuolization and cell death.

- Unlike vCJD, classic or sporadic CJD occurs spontaneously (85 percent of cases) or is inherited (in about 15% of cases).

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 within months to a little over one year. The incubation period of vCJD is still unknown, but infection may have occurred years or decades earlier.
- Psychiatric or sensory symptoms predominate in early vCJD, 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 decade of life and progresses even more quickly. Typical symptoms of classic CJD present as 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

- Typical findings in classic CJD are 1) EEG periodic sharp and slow wave complexes, and 2) presence of 14-3-3 protein in cerebrospinal fluid. The 14-3-3 protein is released into CSF when neurons die. It also may be present in CSF in vCJD but less commonly.
- A typical finding in vCJD is a prominent hyperintensity in the posterior thalamus, or the "pulvinar sign," visible on T2-weighted MRI. This finding is due severe spongiform changes in the thalamus. The pulvinar sign may also occur in classic CJD but much less commonly.
- Pathological analysis of brain tissue is the gold standard of diagnosis. Biopsy will show vacuolization, neuronal loss, and gliosis. Amyloid plaques are common in vCJD, but are only present in 10% of classic CJD cases. Prion protein can be detected directly 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.

SAMPLE EXAM QUESTION

A 34-year-old male presents to emergency room with agitation and visual hallucinations. Acute management includes IM haloperidol and lorazepam. He is admitted to the psychiatric unit with a presumptive diagnosis of psychosis not otherwise specified. When lab results become available, all results are within normal limits and urine toxicology is negative for drugs of abuse. His family members are now available and report no history of medial or psychiatric symptoms other than changes in his behavior evident over just the last few weeks. Also, there is no known family history of psychiatric or cognitive disorders. On the unit the patient is noted to have an unsteady wide based gait and a slight intention tremor evident when eating. His cognitive exam demonstrates 1 out of 3 word recall at 5 minutes, impaired clock drawing, impaired attention and poor trail making test results. An MRI is ordered and a prominent hyperintensity is visible in the posterior thalamus bilaterally. A full neurological work-up is pursued: EEG shows generalized slowing, and CSF obtained from lumbar puncture is negative for protein 14-3-3 while showing increased tau protein levels. Given this patient's presentation what is the patient's most likely diagnosis?

A. Classic Creutzfeldt-Jakob disease

B. Variant Creutzfeldt-Jakob disease

C. Multiple Sclerosis

D. Huntington's disease

E. Thalamic tumor

EXPLANATION

This patient's presentation is consistent with variant Creutzfeldt-Jakob disease. Elevated tau protein levels in CSF may be seen in vCSF although they are non-specific. Many patients with vCJD have 14-3-3 protein present in their CSF (about 50%) but this rate is lower than in classic CJD (over 80%).

Tay Sachs Disease

CASE VIGNETTE

- 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 fundoscopic 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 fundoscopic 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. TSD is in a class of disorders known as lysosomal storage disorders.
- 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 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 with significant gliosis and neurons distended with glycolipids two to three times their normal size. Histology shows accumulation of gangliosides in the cytoplasm.
- 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 infantile 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 TSH 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 choirodal 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 cognitively impaired, blind, and decerebrate. Death occurs through cachexia or respiratory failure.
- There exist 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 infantile TSD, while the other is seen in 95% 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 to12 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.

SAMPLE EXAM QUESTION

A 15-month-old boy is brought to clinic by his parents, recent immigrants from Central America, due to the child's pneumonia. On seeing the child the Emergency Physician notices multiple neurological disturbances and consults with neurology. A formal neurological exam reveals generalized weakness with spasticity, inability to walk, gross incoordination of movements, absent pupillary reflexes and horizontal nystagmus bilaterally. The boy does not speak and does not follow commands. He does not track objects through space. The boy is admitted to Pediatrics for treatment of pneumonia. The next day he is noticed to have a tonic-clonic seizure. Beta-hexosaminidase A enzyme assay is ordered and reveals deficient activity of this enzyme. What is this child's most likely diagnosis?

A. Canavan disease

B. Duchenne muscular dystrophy

C. Niemann Pick disease

D. Sandhoff disease

E. Tay Sachs disease

EXPLANATION

- This patient's presentation is suggestive of Tay Sachs disease, a lysosomal storage disease. The deficiency of Beta-hexosaminidase A found on assay establishes the diagnosis. However, DNA testing would be ordered next to confirm the diagnosis. Lysosomal storage diseases number in the 50s and are all caused by a genetic mutation that leads to deficiency of a key enzyme, leading to accumulation of various metabolic products in the cell lysozyme that eventually kill the cell. The background carrier rate for this autosomal recessive mutation is 1/250 individuals, certain ethnic groups have much higher rates. These groups include Ashkenazi Jews, French Canadians, and Louisiana Cajuns; the carrier rate in these groups is approximately 1/27 individuals.

Friedreich'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 Friedreich's Ataxia (FA), a metabolic disorder leading to neurodegeneration of the peripheral nerves and spinal cord. It is autosomal recessive 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 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 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. FA often leads to shortened life expectancy.

SAMPLE EXAM QUESTION

An 11-year-old boy presents to his pediatrician with slowly progressive muscle weakness. He noticed that he couldn't run as fast, and that he was tripping while walking. Parents report that there is a family history on both sides of the family of a disease that made "the people weaker and weaker, and lasted decades until they could no longer walk or care for themselves." Genetic testing confirms the diagnosis of Friedreich's Ataxia. Given this disease, a mutation in which of the genes is expected?

A. Frataxin
B. HEXA
C. HEXB
D. DMD
E. SMPD1

EXPLANATION

Genetic mutation and their corresponding diseases: Frataxin leads to Friedreich's ataxia, HEXA leads to Tay-Sachs disease, HEXB to Sandhoff disease, DMD to Duchenne's muscular dystrophy, and SMPD1 to Niemann Pick disease.

Metachromatic Leukodystrophy

CASE VIGNETTE

- 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 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 enzymatic 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. Doner 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.

Coma

CASE VIGNETTE

- 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 intracranial pressure (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, oculocephalic (doll's eyes) reflex, and gag reflex. An MRI shows not only the hemorrhage and surrounding edema, but also white matter changes at the gray-white interface in multiple areas. A SomatoSensory Evoked Potentials (SSEP) study, a method of non-invasively assessing somatosensory system functioning, 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 normal 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 regains 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, sheering 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 nerve function can be intact. 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 established 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 to 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 (supratentorial and infratentorial) 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 (pupils are mid-sized and non-reactive), 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 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.

SAMPLE EXAM QUESTION

Following a brain injury, a patient who is able to localize noxious and auditory stimuli, reach for objects, demonstrate sustained visual fixation, and communicate intelligibly at times but inconsistently, is best described as suffering from which of the following conditions?

A. Brain death
B. Coma
C. Locked-in state
D. Minimally conscious state
E. Persistent vegetative state

EXPLANATION

The question stem describes a minimally conscious state. Brain death refers to absence of all brain activity, cortical as well as of the brain stem. Coma is the state of unarousable unawareness without response to noxious stimuli, eye openings, or spontaneous movements. A persistent vegetative state is characterized by unconsciousness , but with spontaneous eye opening and posturing, withdrawal to noxious stimuli and presence of a sleep-wake cycle. No meaningful interaction with the environment continues. Orientation to environment may be seen, but is brief and inconsistent. A locked-in state is characterized by complete or almost complete paralysis with intact consciousness.

Subdural Hematoma

CASE VIGNETTE

- 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 right windshield post. 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 convex-concave hyperintensity overlying the right frontal lobe. There is no skull fracture. The patient is admitted for monitoring and is started on phenytoin for seizure prophylaxis. The nurse reports that the patient, now 8 hours later post-accident, is lethargic and not oriented to time or place. 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 mater. Classically, SDH occurs due to rupture of bridging veins. However, in one-third of patients arterial rupture has been found during surgery. SDH can occur via trauma or spontaneously in vulnerable individuals. Risk factors for SDH include older age and chronic alcoholism since they both lead to brain atrophy and stretching of the bridging veins. Anticoagulants and chronic dialysis also increase the risk.
- SDHs cause brain damage through compression of the underlying tissue which leads to mass effect, possibly resulting in herniation if the SDH is significant enough in volume. In addition to compression, SDH decreases metabolism and blood flow of the underlying parenchyma, leading to further damage.

PATHOLOGY

- The composition of the SDH evolves with time. Acute SDH is the most common form of SDH and develops within minutes to hours to days following injury. Acute SDH is somewhat arbitrarily defined as a SDH that presents up to 3 days post-injury. Acute SDH is associated with the most severe brain damage; it can present with the patient being in a comatose state; and it has the worst outcome. On CT, acute SDH appears as a hyperintense signal overlying the brain parenchyma in a crescent shape.
- Subacute SDH is one that presents between 4-21 days post-injury. 24 hours after the initial hemorrhage, the blood clot begins to be covered with a layer of fibrin. Over the coming days to weeks, a membrane encapsulates the clot, and phagocytic cells liquefy it. On CT, as the clot is resorbed (after approximately one week), the SDH will appear isodense to the brain.
- Chronic SDH is defined as one presenting more than 21 days after an injury. In chronic SDH, the hematoma is fluid in consistency. On CT, after approximately three weeks post-injury, the SDH will appear hypodense to brain tissue.

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 focal deficits. 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 t**ransient ischemic attack (**TIA) symptoms that are caused by intermittent cortical vessel compression or vascular displacement. Seizures may also be an initial presentation of SDH, especially in cases in which the SDH occurred after modest head trauma or spontaneously. The Syndrome of Inappropriate Secretion of Antidiuretic Hormone (SIADH) also can be a sequelae of SDH.

DIAGNOSIS

- CT scan is the study of choice, as it can detect both hemorrhages and bony fractures with high sensitivity. As stated, 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 will appear isodense to the brain. After three weeks, the SDH becomes 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 as emergent treatment prior to more extensive surgery. Post-operative re-accumulation of blood must be monitored for with repeat CT scans.
- Medical management consists of close monitoring and seizure prophylaxis. Mannitol may be used to reduce intracranial pressure. Patients on anticoagulants should have their coagulopathy reversed with vitamin K, fresh frozen plasma, platelets, or cryoprecipitate as needed. Anticoagulation can often be restarted in about three weeks.
- 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 with SDH with fresh clot.

PROGNOSIS

- The level of the underlying brain injury has the most prognostic significance in anticipating the degree of recovery from clinical deficits.

SAMPLE EXAM QUESTION

A 63-year-old man, in addiction treatment for chronic alcohol dependence, reports to his counselor that he has developed a headache this morning that is getting worse. It's especially severe when he coughs. He says he never has headaches and doesn't know why he would be having one now. He doesn't want to miss the afternoon groups, so he obtains ibuprofen from another patient and decides to stay in the program. Later that afternoon, he tells his counselor he is leaving because his headache continues to increase. As he is walking from her office, he stumbles and then lies down on the floor saying he feels dizzy and weak. Emergency medical services are called. In the intervening minutes before EMS arrives the patient appears confused and agitated. When examined by EMS personnel, he is not noted to have any evident head trauma but has moderate left hemiparesis. What is the most likely cause of the patient's presentation?

A. Acute subdural hematoma

B. Chronic subdural hematoma

C. Epidural hematoma

D. Myocardial infarction

E. Seizure

EXPLANATION

The rapid progression of symptoms in this case suggests either an acute epidural or acute subdural hematoma. An emergent head CT will clarify the etiology when he arrives at the hospital. Given his history - an older man with a history of chronic alcoholism and without suggestion of recent head injury– his presentation is more suggestive of an acute subdural hematoma. Persons with heavy alcohol consumption often have coagulopathies with thrombocytopenia and increased bleeding times. They are also more likely to have a history of multiple head traumas, even if only mild to moderate in intensity. The learning point of this question is that subdural hematomas are often thought of as chronic and less likely to be acute in presentation and

progression. However, the most common presentation of subdural hematomas is an acute one.

Epidural Hematoma

CASE VIGNETTE

- 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." Her level of consciousness declines on the way to the hospital. In the Emergency Department she is currently unconscious and difficult to arouse. Her Glasgow Coma Scale score is 7 (that is, she is able to open eyes to pain, make 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 operating room emergently.

BACKGROUND

- The patient developed 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 is more gradual and 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 presentation 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 (bi-convex) accumulations that are restricted by the suture lines in the skull, but not by falcine divisions. This is the opposite of subdural hematomas, which can cross suture lines but respect the boundaries of the tentorial spaces, that is, the supratentorial and infratentorial spaces. In cases of epidural hematoma, it is common to see fractures of the skull along the path of the middle meningeal artery.

TREATMENT

- Treatment consists of emergent treatment either with 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.

SAMPLE EXAM QUESTION

A 57-year-old woman strikes her head while skiing. She gets up feeling 'dizzy' and skis to the lodge to take ibuprofen for her headache and to rest. Three hours later she is poorly responsive and her husband calls EMS. Which initial intervention could be most dangerous and should be avoided?

A. IV fluids, since patient may go into acute heart failure
B. Lumbar puncture, since patient may have increased intracranial pressure
C. Thiamine given in IV fluids, since thiamine can interfere with glucose metabolism
D. Naloxone, since it may precipitate a potentially lethal opiate withdrawal
E. Oxygen by nasal cannula due to possible suppression of respiratory drive

EXPLANATION

- It is standard of care to order a head CT prior to conducting a lumbar puncture (LP). A contra-indication to an LP is evidence of increased intracranial pressure. By removing cerebrospinal fluid from the lumbar cistern, as is done in an LP, the pressure differential between the cranium and the spinal column may increase and, thus, raise the chance of brain herniation, especially a tonsillar herniation in which the cerebellar tonsils are pushed downward through the foramen magnum. The other response options, if implemented, will be completely or relatively benign.

Cortical Ischemic Stroke

CASE VIGNETTE

- 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 fluency and repetition are markedly impaired. There is no sensory neglect, acalculia, or left-right confusion. His NIH Stroke Scale (NIHSS) score is 13, indicative of moderate stroke severity. He is unable to answer questions regarding the month or his age, and he displays partial gaze palsy with gaze preference to the left, complete right 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 expressive aphasia, and mild-to-moderate dysarthria. A head CT shows blurring of the grey-white junction at the left 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 left 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 middle cerebral artery (MCA), anterior cerebral artery (ACA), or posterior cerebral artery (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 the 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 also can 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 the site of intimal tearing.
- Small-territory strokes can occur with occlusion of the end-arterioles. This is termed lacunar strokes, which are defined as strokes that damage areas of brain less than 15 mm in diameter. These lacunar strokes are strongly associated with uncontrolled hypertension, causing smooth muscle hypertrophy of the vessel walls and lipohyalinosis.
- Determining the etiology of stroke is important for deciding on appropriate therapy. Once the clot has occluded the vessel, a core of infarcted brain tissue forms. There is a 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.
  - When the frontal cortical eye field is damaged unilaterally, the eyes cannot voluntarily be moved in a direction contralateral to the lesion. And at rest, the eyes will tend to deviate towards the side of the lesion.
- Subcortical strokes have a predilection to occur in the periventricular subcortical white matter, the internal capsule, the basal ganglia, the thalamus, or the brainstem, each location producing a different syndrome. The classic lacunar stroke syndromes are the following:
  - Pure hemiplegia
  - Pure hemisensory loss
  - Mixed hemiplegia-hemisensory loss
  - Clumsy hand-dysarthria
  - Ataxic hemiparesis
- The initial weakness following a stroke is a placid paralysis. Spasticity and hyperreflexia develop later in the course of a stroke.

DIAGNOSIS

- Noncontrast head CT or brain MRI should be done within 30 minutes of patient arrival in the setting of 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 (DWI) and Apparent Diffusion Coefficient (ADC) 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 (or vascular imaging with CTA or MRA) can be checked from intravascular disease, and echocardiogram is done to evaluate for risk factors of cardiac emboli.

TREATMENT

- Treatment of acute stokes (less than 3 to 4.5 hours after onset) consists of intravenous tissue plasminogen activator (tPA). Strokes of duration greater than 3-4.5 hours but less than 6 hours can be treated with intraarterial tPA. Patients who are at risk for major bleeds (e.g., coagulopathies, recent surgery, history of intracranial bleed) are excluded from this therapy. tPA has been shown to improve function at three months, regardless of stroke type. Although tPA significantly increases the number of intracranial hemorrhages, mortality is not increased. There is growing evidence to support significant benefit to the use of intrarterial clot retrieval devices.
- Blood pressure is allowed to run high during the first 24 hours but no greater than 220/120, and then should be gradually tapered down. If tPA is to be given, BP needs to be maintained below 185/110. Hyperglycemia and hyperthermia should be avoided. Patients with stroke from cardioemboli should be maintained on anticoagulation, which can be initiated three to five days following the stroke. Patients with carotid stenosis greater than 70% 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.
- All patients with acute stroke should undergo at least a bed-side swallow evaluation, DVT prophylaxis, and PT/OT evaluation.

SAMPLE EXAM QUESTION

A 72 y.o. male is being driven home by his son from a family visit in another town. While in the car the son notices that his father's speech is garbled and 'not making much sense.' He asks his father what's going on but his father seems unconcerned and tells him to keep driving. He gets agitated when his son suggests they stop at a 'hospital along the way' so the son keeps driving to their hometown. When they reach home, the son notices that his father is weak on his right and his face is asymmetrical; he calls his father's doctor who tells the son to drive his father immediately to the nearest ER. At the ER the patient has right arm and right facial weakness sparing the forehead. He has comprehension aphasia with noticeable paraphasic errors and repetition deficits. His blood pressure is 170/105 and his symptoms started approximately 7 hours ago. The ER physician starts the patient on aspirin. Why is this patient ineligible for treatment with tissue plasminogen activator (tPA)?

A. The patient's blood pressure is too high
B. The stroke symptoms started earlier than the 3-6 hour window
C. The cognitive deficits suggest that this is a subcortical stroke that will not benefit from tPA
D. The patient displays symptoms suggestive of a hemorrhagic stroke
E. It's too early in the stroke evolution to treat with tPA

EXPLANATION

- The original window for treatment with tPA was onset of stroke symptoms within 3 hours. This window was extended to 4.5 hours in 2009* for patients who meet certain criteria (age < 80 years, no anti-coagulant use regardless of INR, NIHSS <25, and no combined history of stroke and diabetes). Additionally, strokes of duration greater than 3-4.5 hours but less than 6 hours can be treated with intraarterial tPA.
- Given the history, this patient's stroke symptoms have been present for too long for the patient to be a candidate for tPA. The patient's blood pressure is below 185/100 and is thus appropriate for tPA treatment. tPA does increase risk of hemorrhagic stroke and thus a head CT is indicated prior to starting tPA. The patient's symptoms are consistent with a thromboembolic cortical stroke in the left middle cerebral artery territory, although the vignette does not present complete results from a thorough neurological evaluation.

(*del Zoppo G, Saver J, Jauch EC, et al. Expansion of the Time Window for Treatment of Acute Ischemic Stroke With Intravenous Tissue Plasminogen Activator. A Science Advisory From the American Heart Association/American Stroke Association. Stroke 2009; 40: 2945)

Brainstem Ischemic Stroke

CASE VIGNETTE

- 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 metoclopramide (Reglan). She comes to your clinic two days later, reporting continuation of these complaints without relief. You note on examination asymmetric pupils, with the left eye greater than the right by 2 mm. Both pupils are reactive. There is a slight ptosis over the left eye and 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 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.

BACKGROUND

- The patient has a brainstem stroke presenting as lateral medullary syndrome, aka Wallenberg Syndrome, caused by occlusion of the posterior inferior cerebellar artery (PICA). This is a stroke syndrome affecting the spinothalamic tract, trigeminal nucleus, vestibular system, sympathetic tracts, nucleus ambiguous, and inferior cerebellar peduncle as they converge in the lateral medulla oblongata.

PATHOLOGY

- The brainstem is subject to the same pathological mechanisms as are 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 compact 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 corticospinal 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 nucleus or tract together with corticospinal fibers leads to ipsilateral cranial nerve palsy and contralateral limb weakness. This is an example of “crossed signs,” a sign typical to brainstem infarcts.

  Sensory symptoms can be crossed as well, as seen in the case of lateral medullary syndrome. Infarcts of the cerebellar fibers lead 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 can lead to collapse of the fourth ventricle or cerebral aqueduct that, in turn, can cause life-threatening hydrocephalus.

DIAGNOSIS

- Brainstem strokes are evaluated more or less in the same manner as other strokes. Head CT often is unable to identify brainstem strokes given the large amount of bony artifact present and inadequate resolution. MRI is preferred in these cases. Magnetic resonance angiography (MRA) and computed tomographic angiography (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 the frequent presence of paralysis of oropharnygeal muscles or of depressed consciousness. Patients at high risk of aspiration should be formally evaluated with a swallow evaluation prior to onset of PO intake. Intravenous and intraarterial tPA are options for patients presenting within 3-4.5 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.

SAMPLE EXAM QUESTION

A 32-year-old woman starts birth control pills with some trepidation regarding their possible adverse effects. Two weeks later, during a visit her mother finds her "passed out" on the floor without warning. In the hospital the patient is declared to be in a coma. After 21 days her condition changes when she is noted to open her eyes and move them vertically. She does not respond to commands and presentation of noxious stimuli leads only to increased eye blinking. Her mother notices that her daughter is blinking with her left eye as if wanting to communicate with her. The mother undertakes to teach her daughter, who remains without speech or movement, an eye-blinking code. At first, the staff are skeptical, believing the mother is manufacturing her daughter's answers. The mother proceeds to teach the staff the eye-blink code and convinces the staff that her daughter is and has been fully conscious since her eyes opened. What is the most likely etiology of this patient's condition?

A. Brainstem stroke
B. Guillain-Barré syndrome
C. Myasthenia gravis
D. Multiple sclerosis
E. Westphal variant of Huntington's disease

EXPLANATION

This patient is suffering from locked-in syndrome which is a condition in which a person is fully conscious but has suffered complete paralysis of the voluntary muscles of the body and those supplied by the lower cranial nerves. Individuals are unable to speak, chew, swallow, show facial expression, breath, or move their eyes horizontally. Mechanical ventilation is usually required. Individuals with locked-in syndrome usually present in coma, which gradually lifts. Due to their inability to move or communicate, they are in danger of being considered to be in a persistent vegetative state when, in reality, they are fully conscious.

Locked-in syndrome is most often caused by a ventral brainstem stroke of the basilar artery at the level of the pons, although tumors or traumatic brain injury can be culprits. This location of stroke causes transection of the descending motor tracts, the corticospinal and corticobulbar tracts.

Since the CN III (oculomotor) nerve and nucleus are located in the midbrain, often rostral to the level of the damage, at least vertical movement is retained by the muscles supplied by this nerve. The patient is then able to partially move their eyes and to open them. (Closing of the eye is accomplished by muscles supplied by CN VII, which is usually transected. Therefore, the closing of the eyelid in locked-in syndrome is passive with gravity.) Since the patient can open one or both eyes, the patient can be trained to communicate through an eye-blink code. A best-selling book in 1997 written by a man who suffered locked-in syndrome, Jean-Dominique Bauby, describes how he developed a method of communicating through eye blinks to write his book, *The Diving Bell and the Butterfly*. The families and staff caring for individuals with locked-in syndrome sometimes use the eye blink code described in Bauby's book. With technological advances, even small eye movements can control computer-controlled devices, greatly expanding the functional capacities of these individuals. Although the majority of these individuals die within the first year, some can survive for decades.

Note that oral contraceptives, even low-estrogen pills, can double the risk of stroke in healthy women and perhaps even more in women with additional risk factors.

Hemorrhagic Stroke

CASE VIGNETTE

- 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 attending church at the time of the onset of his symptoms; he experienced a sudden severe 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 nerve function is intact, 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 operating room for craniotomy and resection. The procedure goes without complications, and 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

- There are two main types of stroke, ischemic and hemorrhagic. Hemorrhagic strokes fall into two main categories intracerebral (parenchymal) and subarachnoid (extraparenchymal). The most common source of the bleed is from a weakened blood vessel. This patient had a spontaneous hemorrhagic stroke secondary to uncontrolled hypertension.

PATHOLOGY

- Spontaneous hemorrhagic strokes account for about 15% of all strokes but for about 40% of all stroke deaths. Hemorrhagic strokes are most commonly caused by uncontrolled hypertension in the elderly and by cerebral amyloid angiopathy. However, important additional causes of hemorrhage that must be ruled out include arteriovenous malformations (AVM) and aneurysms, as they are treatable and have a high rate of recurrent bleeding if 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 strokes in typical locations as described in the following table.

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 an intracerebral hemorrhage occurs, the blood spreads between the planes of neuronal axons. The majority of expansion occurs quickly within the first hours before compression by surrounding brain tissue causes a tapenade effect, slowing further expansion. Vasogenic and cytotoxic edema occurs in the surrounding tissue, leading to tissue damage. It is believed that the neuronal injury from edema is the major cause of persistent neurologic deficit, as the stretch from the hematomatous 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 (ischemic) 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 because it increases mortality. Once inside the ventricular system, the blood can clot off normal flow of CSF, leading to increased intracranial pressure and hydrocephalus. Additionally, the blood circulating in the CSF can cause additional vessels to spasm and cause secondary ischemic strokes.

DIAGNOSIS

- Head CT is the most commonly used modality for evaluating intracranial bleeds, although MRI with T2* is now known to be 100% sensitive for acute blood. 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. Early growth of the hemorrhage is common and treatment should be instituted as soon as possible (just as in ischemic stroke).
- 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. Coagulopathies should be corrected as soon as feasible.

- 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.
- 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.
- Patients with ventricular extension should have an intraventricular catheter placed for CSF drainage and intracranial pressure (ICP) monitoring.

SAMPLE EXAM QUESTION

A 42-year-old man is at a diner with his wife when he suddenly slumps and appears lethargic. His head falls to the table and his right arm hangs to his side. EMS transports him to the hospital. His vitals are BP of 170/100, pulse of 84, glucose by finger stick is 110 and cardiac monitor shows normal sinus rhythm. Head CT discloses a left hemispheric intracranial hemorrhage of 3.5 cm diameter that is causing a 3mm falcine midline shift to the right. What is this patient's most urgently needed intervention?

A. Blood pressure control

B. Craniotomy

C. Intubation

D. IV glucose

E. Seizure prophylaxis

EXPLANATION

This patient is at risk for a subfalcine or central herniation, with the latter being more lethal. The midline shift of his falx cerebri shows that the hemorrhagic mass is exerting pressure on the surrounding brain. Craniotomy with evacuation is most clearly indicated for patients with cerebellar hemorrhages given the ease with which they can be accessed and the danger into which they place the brainstem structures. With lobar hemorrhages, as in this patient's case, the indication for surgical evacuation is less clear. However, when the hemorrhage is large, occurs in younger patients, or shows mass effect, then craniotomy with evacuation is indicated.

Status Epilepticus

CASE VIGNETTE

- 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 lorazepam x 2 doses. Her boyfriend states that she usually takes carbamazepine, but ran out of her prescription two days ago. She is given a phenytoin load of 15 mg/kg and intubated for airway protection.

BACKGROUND

- This patient has status epilepticus (SE) secondary to missed doses of medication. SE is a life-threatening condition that classically has been defined as continuous seizure activity lasting for greater than 30 minutes, or multiple seizures without return to consciousness lasting greater than 30 minutes. There is a growing consensus supporting clinically defining SE as duration of generalized tonic-clonic seizure activity lasting longer than 5 minutes.
- Since continuous seizures become much more refractory if unabated for greater than 5 minutes, treatment for SE is initiated after 5 minutes of continuous seizure activity or after occurrence of two or more discrete seizures with incomplete recovery of consciousness.
- SE is a term reserved for generalized seizures. Prolonged focal motor seizures are called epilepsia partialis continua.

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 due to glutamate excitotoxicity. The metabolic demands of continuous, repetitive neuronal firing may also contribute to cortical damage.

CLINICAL PRESENTATION

- SE is typically associated with 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% 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 arterial blood gas (ABG) test results.
- 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 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 ascertained. 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 barbiturate 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 use 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 to a 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 use of pressor agents.
- Most patients with SE do not develop respiratory distress unless their airway is obstructed. Metabolic derangements secondary to SE consist of hyperthermia, metabolic, and respiratory acidosis. Metabolic acidosis can be observed without intervening unless profound, in which case sodium bicarbonate can be infused.

SAMPLE EXAM QUESTION

The patient is a 59 year old woman with a history of epilepsy since adolescence. Typical seizures are described as periods of behavioral arrest for 10-15 minutes that are preceded by blurred vision and fatigue. She had been treated with phenytoin for many years and averages 2 seizures per year. She had seen a neurologist many years ago and was told that her seizures were likely "stress induced." She presents currently with two generalized tonic clonic seizures and remains persistently confused and sleepy afterwards. Which medication should be ordered as first line treatment for this patient?

A. Diazepam 5mg po
B. Lorazepam 2mg IV
C. Phenytoin 1200mg IV bolus
D. Pentobarbital 500mg IV over 30 minutes
E. Propofol 100mg IV in 2 divided doses

EXPLANATION

This patient has a history apparently consistent with partial complex seizures. She presents currently in status epilepticus and needs to have her seizures aborted. First line treatment will be with a benzodiazepine, most commonly with lorazepam, given IV. Given the patient's stupor, po medications are contraindicated, although IV diazepam would be a viable treatment option. Phenytoin and propofol are

second line treatments if first line treatment fails to abort seizure activity. Note also that phenytoin needs to be given as continuous infusion with a rate no greater than 50mg/min and not as a bolus. Pentobarbital is third line treatment due to its predilection to drop blood pressure.

Note that status epilepticus, defined as a generalized tonic-clonic seizure, can have generalized or partial onset. The patient in this vignette had a partial seizure that secondarily generalized.

Partial Complex Seizure

CASE VIGNETTE

- 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 a couple of minutes before the patient collapsed into his chair. He was still lethargic and answering inappropriately when EMS arrived 15 minutes later. The patient states that he does not remember the incident nor the subsequent evaluation in the ambulance. He states that the last thing he remembers was smelling "something burning" at the time he was giving his 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 'came to' without deficits, he decided not to go to the hospital at that time. Currently, his basic chemistries and blood counts are within normal limits, and urine toxicology is negative. A head CT also is negative.

BACKGROUND

- The patient experienced 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 those caused by strokes, tumors, trauma, and infection.
- Seizures can be classified according to several different schemas. The generalized vs focal classification refers the seizure location. Epileptic activity in primary generalized seizures appears in the entire brain simultaneously and no specific inciting focus can be identified. In focal (or partial) seizures, epileptic activity starts in a single brain region. Focal seizures are further classified as being simple versus complex. Simple partial seizures involve a small brain region and are defined as seizures that do not cause changes in consciousness (that is, they are without dyscognitive features). Complex partial seizures involve larger areas of the hemisphere and are defined as causing changes in consciousness (that is, they present with dyscognitive features). Further, partial seizures – whether simple or complex – may remain localized and partial, or they can secondarily generalize to both hemispheres, thus resulting in loss of consciousness.

PATHOLOGY

- Most partial seizures in adults are acquired from focal lesions. This leads to abnormal synaptic reorganization predisposing to hypersynchronous discharges. Complex partial seizures of the mesial temporal lobe are associated with hippocampal sclerosis, 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 traumatic brain injury. It is not clear if hippocampal sclerosis is a cause or an effect of seizures.

CLINICAL PRESENTATION

- Complex partial seizures (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, intense fear, or a rising epigastric feeling. Less common auras are olfactory or gustatory hallucinations, experiences of déjà vu, and 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 amnestic for the event. Patients with CPS of the temporal lobe are at high likelihood of developing memory problems, behavior abnormalities, and depression.
- 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 generalized tonic-clonic seizures.
- Triggers for seizures include stress, sleep deprivation, and hormonal changes of the menstrual cycle.

DIAGNOSIS

- An EEG may show interictal epileptiform activity, but only 50% of EEGs are abnormal in patients presenting with a first seizure. The EEG sensitivity can be increased to nearly 90% by conducting 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 use in focal onset epilepsy. Broad spectrum medications include depakote, lamotrigine, levatiracetam, and topiramate. Narrow-spectrum medications include carbamazepine, oxcarbazepine, phenytoin, gabapentin, tiagabine, and pregabalin.
- For the treatment of complex partial seizures (CPS), head-to-head trials suggest no advantage of one medication over another. Choice of medication is based on side effect profile (see table below). Carbamazepine and 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 the start of side effects or the limit of tolerability, followed by the addition of a second agent. Patients who fail three or more agents are likely to be medically refractory to other agents as well.
- Surgical resection is an option for seizure foci that are 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. Stevens-Johnson syndrome in patients of Asian ancestry with HLA-B*1502. All patients of Asian ancestry should undergo HLA-typing prior to initiating carbamazepine.
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, gingival hyperplasia	Blood dyscrasias, conduction block, lupus-like syndrome, cerebellar atrophy
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.

SAMPLE EXAM QUESTION

The patient is a 36-year-old female reluctantly brought to the clinic by her husband. He reports that the patient has had periodic episodes of 'strange behaviors' occurring during her sleep. He describes three times in the last 3-4 months when her loud grunts and movements have awakened him from sleep. The last episode occurred last week and was 'so dramatic' that he insisted she gets evaluated despite her protestations. She says in her defense that she feels fine, doesn't remember anything, and believes her husband must be exaggerating. The husband states that after a minute of 'embarrassingly loud' grunting, while still lying on her back in bed she started moving her legs as if riding a bike. Then she rose out of bed with her eyes open, banged objects on her nightstand and clasped her hands for about a minute, and then got back into bed and fell asleep. The physician suspects a parasomnia and orders a sleep study but during the study the patient's behaviors remain normal and EEG, EKG and respiratory findings are all within normal limits. She continues to experience these episodes episodically and final is referred to a neurologist who diagnoses her with a seizure disorder. Given her presentation, which medication is not likely to be of benefit in controlling her seizures?

A. Carbamazepine
B. Ethosuximide
C. Lamotrigine
D. Pregabalin
E. Zonisamide

EXPLANATION

This patient's presentation is consistent with complex partial seizure disorder. Not uncommonly, her seizures occur during sleep. As is expected with CPS, the patient has no recollection of her seizures. CPS can present with a range of simple to complex automatisms, that is, movements and behaviors that occur during the epileptic activity. These behaviors can include movements as if the person was, for example, riding a bike or washing dishes. Or the person can actually get undressed or walk about. CPS, especially when it involves the temporal lobe, can be associated with auras.

The good news about treating CPS is that almost all anticonvulsant drugs (ACD) are effective, with the notable exception of ethosuximide whose use is limited to the treatment of absence seizures.

On a side note, many of the ACDs are associated with teratogenic risk. Since this patient is a woman of child-bearing age, she needs to be educating regarding the risk to her fetus if she were to become pregnant and the need for effective contraception.

Grand Mal Seizure

CASE VIGNETTE

- 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 she drinks 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 within normal limits. 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. 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, starting diffusely throughout the cortex simultaneously. Or seizures can be secondarily generalized, starting at a focus that propagates and spreads diffusely across both hemispheres.

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 non-specific pre-ictal sensation occurring hours prior to the onset of the seizure, and may consist in feelings of apathy, depression, or irritability. Most often, however, 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 extension of extremities and trunk. 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. As patients awake in the post-ictal stage, they remain confused for minutes to hours and remain amnestic for the event. Urinary incontinence can occur in any stage of the seizure.

DIAGNOSIS

- Diagnostic evaluation includes EEG and neuroimaging. An EEG is abnormal in 50% of patients with undergoing an initial assessment for 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 also should be investigated as the causative agent.

TREATMENT

- Patients with more than one unprovoked seizure should be started on an anticonvulsant drug (ACD). Patients with a single unprovoked seizure should be started on an ACD only if additional risk factors are present, such as, an abnormal EEG and an abnormal MRI.
- Broad-spectrum ACDs are recommended for primary generalized seizures, whereas any ACD can be used to treat focal seizures with secondary generalization. Broad spectrum ACDs that are effective for primary generalized seizures include valproate, topiramate, and lamotrigine, with levatiracetam reserved for adjunctive treatment.
- Surgical therapy is not an option for generalized seizures since no inciting seizure focus can be identified.

SAMPLE EXAM QUESTION

Question: A 37 year old male experiences a seizure that is diagnosed as a primary generalized seizure. Other than having had a febrile seizure at age 3 according to his mother, he's never had any seizure-like experiences, head trauma, periods of heavy drinking, use of other drugs or other medical conditions. Three EEGs are conducted and all are normal. A brain MRI is also normal. Which of the following anticonvulsant medications should be the patient be started on?

A. Lamotrigine
B. Levatiracetam
C. None
D. Topiramate
E. Valproic acid

EXPLANATION

This patient presents with a single unprovoked seizure. He has no additional risk factors. Thus his risk of recurrence of seizure is only approximately 15% and he should not be started on an anticonvulsant medication at this time.

Multiple Sclerosis

CASE VIGNETTE

- 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, and 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 pathogenic 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 proteins, including myelin basic protein and myelin-associated glycoprotein, leading to activation of the complement pathway leading to demyelination and cytolysis. Macrophages and microglial cells may play a role as well. The inciting autoimmune event also remains a mystery, as it is thought to occur due to a combination of environmental and genetic factors.
- 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 so-called "shadow plaques."
- MS prevalence incrementally increases the further away the region is from the equator, supporting an environmental factor. Also, 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. Caucasians are affected at higher rates than other demographic groups. Onset typically occurs in the first to third decades of life.
- The course of MS falls into four different categories: relapsing-remitting MS (RRMS), primary-progressive MS (PPMS), secondary-progressive MS (SPMS), and progressive-relapsing MS. Each disease course can be mild, moderate or severe.
- The relapsing-remitting MS course is seen in 85% of MS patients. In this form, MS manifests in acute relapses or "flares" of neurologic disability that resolve without treatment over a period of weeks, leaving no or partial remaining disability. Over time, however, flares leave increasing neurologic deficits, which may eventually lead to severe disability. In a majority of relapsing-remitting MS patients, the flares eventually disappear and disability progresses at a steady rate without obvious acute declines. This is called secondary progressive MS.

- Approximately 10-15% of MS patients have a "primary progressive" course, in which disability progresses insidiously without acute flares.
- The progressive-relapsing MS course is least common and is characterized by a progressive course from the beginning and intermittent relapses or flares.
- Patients may present with an isolated first clinical event, often optic neuritis. This single event is termed a clinically isolated syndrome (CIS).
- 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 can lead to loss of sensation, strength, urinary dysfunction, and sexual dysfunction. Cerebellar ataxia, eye movement abnormalities (especially intranuclear opthalmoplegia [INO]), 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 after 15 years. Spasticity, neurogenic bladder, and neuropathic pain become increasingly difficult to treat. Eventually, death occurs from complications of immobility.

DIAGNOSIS

- 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.

TREATMENT

- Treatment for MS falls into three categories. Treatment for acute relapses or flares, treatment that is disease-modifying and that is taken long term, and symptomatic treatment.
- Treatment of acute MS flare is typically with high dose corticosteroids with an oral taper. Plasmapheresis is also available for patients who do not adequately respond or cannot tolerate steroids.
- Disease-modifying treatments reduce relapses and disease progression and should be started early in the disease. Many experts advocate treating CIS, that is, the clinically isolated syndrome. FDA approved medications are for the relapsing forms of MS, including for relapsing-remitting MS, secondary progressive MS, and progressive-relapsing MS. (There are no proven therapies for primary progressive MS.) These medications for relapsing forms of MS, now totaling 12, are available in oral, injectable or infusible forms.
  - Interferons, which have been shown to reduce clinical and radiologic relapses, most likely reducing progression to disability as well. There are three interferon treatments on the market at present (Avenox - IFN-Beta1a, Betaseron - IFN Beta1b, and Plegridy -Peg IFN-Beta1a) that have been shown to decrease frequency of MS attacks.
  - Glatiramer acetate (Copaxone) is a random polymer of four amino acids (glutamic acid, lysine, alanine, and tyrosine) that are found in myelin basic protein and that may work as a decoy for the immune system. Glatiramer acetates has been shown to decrease clinical and radiologic evidence of attacks.
  - Natalizumab is a humanized monoclonal antibody is approved as monotherapy and has shown good effectiveness. It is, however, associated with development of progressive

multifocal leukoencephalopathy (PML), a quickly progressive lethal condition due to viral infection. Natalizumab was temporarily withdrawn from the market but is not available by special prescription.

- Two medications are used to treat aggressive MS: cyclophosphamide and mitoxantrone.
- No medications are approved for use in primary progressive MS (PPMS). The current disease-modifying agents work by reducing inflammation. PPMS, however, is characterized not by inflammation but by direct neuronal injury. Only symptomatic treatment is available for PPMS.
- 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.

SAMPLE EXAM QUESTION

A 39-year-old male executive recently was playing soccer with his son. He noticed that he felt extreme fatigue within a short period of time and that his gait felt unsteady. When being evaluated he is able to recall a steady progression of this and other symptoms that began about 2-3 years ago. He reports some episodes of urinary incontinence, some sexual difficulties, and increasing levels of fatigue on minimal exertion and weakness when climbing stairs and when lifting. On MRI, he has a single lesion in his brain consistent with MS and two such lesions in his spinal cord. Which of the following disease-modifying agents are approved to treat this patient's condition?

A. Interferon Beta1a
B. Interferon Beta1b
C. Mitoxantrone
D. Natalizumab
E. None
F. Peginterferon Beta1a

EXPLANATION

This patient presents with symptoms consistent with primary progressive multiple sclerosis. He also meets MRI criteria for PPMS with one MS lesion in the brain and two in the spinal cord. No disease-modifying agent is approved for treatment of PPMS. This fact is not because the approved agents for relapsing forms of MS have not been studied in PPMS but rather because they have not shown efficacy when studied. PPMS appears to have a different pathology characterized by less inflammation – the main target of the current disease-modifying medications – and more direct damage to and destruction of neurons. Several new agents are currently being investigated for PPMS.

Amyotrophic Lateral Sclerosis

CASE VIGNETTE

- 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 having tripped once going up the stairs, feeling that his right leg "wouldn't get up high enough." 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 respiratory failure five years later.

BACKGROUND

- The patient has amyotrophic lateral sclerosis (ALS), previously known as Lou Gehrig's Disease. ALS is also sometimes termed motor neuron disease although it is not the only motor neuron disease but is the most common one. ALS is a neurodegenerative disease affecting both the upper and lower motor neurons, leading to progressive muscle wasting and spasticity.

PATHOLOGY

- The disease process of ALS selectively targets motor neurons, leading to motor neuron death in the motor cortex, leading to upper motor neuron signs, and anterior horns of the spinal cord, leading to lower motor neuron signs. Multiple mechanisms have been proposed in the pathogenesis of ALS, which 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. CD4 and CD8 cells have been seen in the anterior horns of the spinal cord, suggesting an immune mechanism, but immunomodulator 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.
- Genetic factors have been identified in some cases of ALS. A mutation in the SOD1 gene, whose product is an antioxidative enzyme, is seen in 20% of familial ALS. Also, a mutation on chromosome 9 leads to familial ALS associated with frontotemporal dementia.

CLINICAL PRESENTATION

- ALS is an unremittingly progressive disease leading to immobility and death on average within 3 years, although some individuals, such as the astrophysicist Stephen Hawkins, may live much longer. Patients with prominent bulbar symptoms have worse prognosis and are at risk for early respiratory failure.
- ALS presents as a combination of upper motor neuron signs of spasticity, hyperreflexia, positive Babinski sign and of lower motor neuron signs of fasciculations and muscle atrophy. Weakness is commonly the first complaint, and is usually asymmetric. Although limbs are commonly affected first, bulbar symptoms affecting the head and face may be the presenting symptoms in some cases. Common bulbar symptoms include dysarthria, dysphagia, tongue atrophy and tongue fasciculations. Sensory complaints are inconsistent with ALS, although patients will sometimes report subjective sensations of muscle cramps and tightness. Bladder, bowel and sexual function is unaffected. There is high prevalence of cognitive impairment in ALS patients, with 5-20% progressing to dementia. As mentioned, familial ALS is associated with frontotemporal dementia via a mutation of a gene on chromosome 9.

DIAGNOSIS

- Diagnosis of ALS is based on clinical findings and electrophysiologic criteria. Electromyography (EMG) shows a denervation pattern 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 intravenous immunoglobulin (IVIG). The EMG findings in multifocal motor neuropathy are unique with multiple conduction blocks seen on the motor nerve conduction study. A serum GM1 ganglioside is also diagnostic for multifocal motor neuropathy.

TREATMENT

- Riluzole (Rilutek) is a glutamate antagonist that prolongs survival by two to three months and, in select patients, may delay tracheostomy and ventilator-dependence, but that otherwise does not improve function or quality of life. Treatment is usually palliative. Long-term mechanical ventilation and artificial feeding can prolong life but at the cost of living in total immobility and of a 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 involving the nerve process, either the axon or the myelin sheath. The sensory equivalent of motor neuronopathy is a ganglionopathy.

SAMPLE EXAM QUESTION

A 38-year-old baseball player develops weakness in his throwing arm. Friends notice that his voice is nasal and slurred. As the weeks pass, his weakness spreads to other limbs. On exam he has a Babinski reflex, rigidity, and brisk reflexes. Also, his muscles appear atrophied and fasciculations are seen. Sensation is intact. He dies 2 years later of aspiration pneumonia after his swallow and gag reflexes became impaired. Which of the following medications is approved for treatment for this patient's condition?

A. Levodopa-carbidopa

B. Riluzole

C. Ropinirole

D. Tetrabenazine

E. Sodium oxybate

EXPLANATION

This clinical vignette is a synopsis of the course of illness experienced by Lou Gehrig, a famous American baseball player who played on the Yankees in 1923-1939, and who died of ALS in 1941.

From the response options, only riluzole is indicated for the treatment of ALS and may prolong life by a period of 2-3 months and that may delay need for a tracheostomy. Riluzole is a neuroprotective drug that blocks glutamatergic neurotransmission in the CNS.

Ropinirole is a dopamine agonist indicated for restless leg syndrome. Tetrabenazine is a monoamine depleter that reduces hyperkinetic movements and is indicated for the treatment of Huntington's disease. Sodium oxybate, also known as gamma-hydroxy-butyric acid (GHB), is a powerful CNS depressant indicated for the treatment of narcolepsy.

Guillain-Barre Syndrome

CASE VIGNETTE

- 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), also known as 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 may be associated with recent Campylobacter jejuni gastroenteritis, cytomegalovirus (CMV), or Epstein-Bar virus (EBV) infection. Symptoms of GBS begin two to four weeks after the inciting 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 the myelin component of the nerve leads to sensitization against the 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 to the underlying axons. Axonal damage is a negative prognostic factor for motor recovery, given the incomplete nature of axonal repair.
- 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. The Miller-Fisher variant is a syndrome of acute ophthalmoplegia, ataxia, and areflexia which spreads to produce a more diffuse polyneuropathy. 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.

CLINICAL PRESENTATION

- Motor symptoms are the predominant finding and classically begin distally with an ascending paralysis. In practice, weakness may sometimes begin proximally and spread distally as the disease attacks nerve roots prior to distal processes. Lower extremities are often involved first. 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 abnormities are a common but relatively minor component of the presentation, often consisting of pain, tingling, and numbness. Areflexia is such an important feature that 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, 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

- Electromyography (EMG) and CSF analysis are the cornerstones of diagnostic testing. However, results may not turn positive 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 are 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, a condition termed 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 infection 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 intravenous immunoglobulin (IVIG) or plasmapheresis, typically for five days. It is thought that these interventions have similar levels of efficacy. Although GBS 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.

SAMPLE EXAM QUESTION

Guillain-Barre syndrome is most consistent with which of the following clinical presentations?

A. Equal severity of motor and sensory symptoms
B. Upper and lower motor signs with spared sensation
C. Prominent urinary incontinence and impotence
D. Peripheral neuropathy affecting predominantly motor nerves
E. Optic neuritis with blindness in one eye

EXPLANATION

Guillain-Barre Syndrome is a polyradiculoneuropathy which means it involves both the nerve roots of the spinal nerves and the peripheral nerves. As such, the presentation is consistent with lower motor neuron disease. GBS affects motor nerve function more prominently than sensory function, although sensory nerves are also affected. In GBS; as in most neuropathies other than diabetic neuropathy; bowel, bladder, and sexual function are preserved. GBS, however, does impair function of the phrenic and intercostal nerves and, thus, can lead to respiratory insufficiency or failure.

Myasthenia Gravis

CASE VIGNETTE

- 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, her pupils are equally round and reactive. There is bilateral ptosis with her eyelids touching 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 reduced at level of 1+ 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 downward drift. As part of your work-up, 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 voluntary muscles, including the limbs and bulbar muscles.

PATHOLOGY

- MG is secondary to the production of autoantibodies against the postsynaptic nicotinic acetylcholine receptors (AChR). These autoantibodies block binding of the 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 from thymoma or hyperplasia. Of those with myasthenia, 10%-15% have thymomas and, conversely, 40% of patients with thymomas develop MG. The thymus produces autosensitive 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 deficits produced by dysfunction of cranial nerves 3, 4, 6 in any combination, as well as be caused by intranuclear or supranuclear lesions. In some patients, MG symptoms will be confined to the ocular muscles, a condition which is termed ocular MG.
- Most patients will go on to develop further symptoms, however, developing a generalized form of MG. Limb weakness and fatigability can be presenting symptoms. The weakness of MG tends to be worst at the end of the day and improves with rest. Dysarthria and dysphagia are particularly concerning as they predispose to aspiration pneumonia and respiratory failure.
- Cardiac and smooth muscles are not affected in MG due to differing antigenicity from skeletal muscle.
- Myasthenic crisis is defined as respiratory weakness and is a medical emergency. Weakness of neck flexion and extension, dyspnea on exertion, and inability to count from 1 to 20 in a single breath are signs of concern for impending respiratory distress. Fatal respiratory dysfunction can develop as quickly as several hours in a myasthenic crisis. Metabolic derangements, infectious agents, emotional stress, hot environment, fever, and other factors can trigger myasthenic crisis.
- Since MG is a chronic disease that can progress to myasthenic crisis in a matter of hours, days, or weeks, long-term treatment and close monitoring are indicated. Patient and family education are crucial so that an impending myasthenic crisis is recognized.

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, blocking and modulating antibodies. Binding antibodies are the most common, and thus are useful for an initial screen. Blocking antibodies are found in only 1% of patients who are negative for binding antibodies. Modulating antibody may be more sensitive in patients with ocular MG.
- A small number of patients are AChR antibody seronegative. Most of these cases have anti-MuSK antibodies directed against muscle specific kinase.
- EMG with repetitive nerve stimulation shows a pattern of electrical decrement, with decrements greater than 10% being diagnostic. This abnormality is secondary to decreased binding of ACh to AChR during maximal contraction. Single fiber EMG can be performed, with increased jitter being 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 evaluate 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 either as monotherapy or in conjunction with steroids to decrease the burden of chronic steroid use. Azathioprine and mycophenolate mofetil are reasonable first choices as

steroid-sparing agents. Cyclosporin and cyclophosphamide are reserved for refractory cases.

- Thymectomy is a safe and effective therapy for MG, leading to remission of MG in up to 50% of patients when performed in conjunction with continued use of 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, nor in elderly patients older than 65 years of age due to associated surgical risks.
- Myasthenic crises should be treated with intravenous immune globulin (IVIG) or with plasmaphoresis. High dose steroids are contraindicated because of 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 H20 are indications for intubation, respectively.

SAMPLE EXAM QUESTION

A 37-year-old female presents to clinic with complaints of double vision and easy fatigability that has been becoming more prominent in the last few months. What precipitated her clinic appointment was that after she developed an upper respiratory infection last week, she has had increasing problems speaking and swallowing, and feels short of breath. Vitals are blood pressure 140/86, respirations 32, temperature 99.3. On exam, lungs sounds are clear. Oxygen saturation on room air as measured by pulse oximetry is 88%. What is your next clinical step?

Order labs for anti-acetylcholine receptor antibodies

A. Refer to a neurologist
B. Admit to the ICU
C. Order edrophonium
D. Order single fiber EMG

EXPLANATION

This patient's history is consistent with Myasthenia Gravis. She presents in a myasthenic crisis, defined as respiratory failure. Pulse oximetry normal oxygen saturation is
95%-100%. Since myasthenic crisis is a medical emergency that can have a lethal outcome, admission to the ICU and respiratory support are emergently indicated.

Duchenne Muscular Dystrophy

CASE VIGNETTE

- A 3-year-old boy presents to your clinic with gait difficulty. He is the offspring from a nonconsanguineous marriage and had an unremarkable childbirth. His APGAR scores were 8 and 10 at birth, and he had no difficulties with feeding. At 1 year of age, he was able to sit without support and to crawl, and he said his first word. He began walking at 22 months.
- His parents are concerned now because he frequently falls seemingly without provocation. At this point, he remains unable to walk up stairs and 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 towards the center of gravity with each step, resulting in a "waddling" gait. In addition, to maintain balance, he arches slightly backwards and stands on his tip-toes. When asked to stand up from a supine position, he rolls over until prone, elevates himself on his elbows and knees, and then uses his hands to push up off his extended legs 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 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 same syndrome.

BACKGROUND

- The patient has Duchenne Muscular Dystrophy (DMD), an X-linked recessive inherited myopathy caused by mutations of the dystrophin gene. The disease is characterized by weakness and progressive muscle degeneration.
- DMD is the most common out of nine types of muscular dystrophies, occurring in 1 in 3,500 male births. It also can rarely occur in girls. It is also one of the most common lethal genetic diseases.

PATHOLOGY

- The dystrophin 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.
- DMD carriers are females who have a normal dystrophin gene on one X chromosome and an abnormal dystrophin gene on the other X chromosome. Thus, their one normal gene protects them from the disease process and symptom development. Males, with a single X chromosome, have no normal gene to protect them and, thus, develop the disease. Rarely a female carrier may have attenuated symptoms of DMD. Additionally, female carriers may be symptomatic for elevated CK levels.
- DMD shares a clinical spectrum with Becker Muscular Dystrophy, of which DMD is the more severe form of this disease. Becker Muscular Dystrophy is caused by the same gene and protein defect as DMD.

CLINICAL PRESENTATION

- Patients with DMD present with progressive proximal muscular weakness, typically with symptom onset between ages 2 and 3 years. Symptoms may not be recognizable until the boy 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 (that is, increased forward curvature of the lumbar spine). The tip-toe walking develops as a mechanism to balance on the center of gravity, and precedes weakness of the anterior tibialis muscle.

- Gower's sign is the classical finding in DMD and is conducted by instructing the child to lie in a supine position then to get 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 that are extended at the knees to reach a standing position. Calf enlargement, called pseudohypertrophy, is another typical feature, with the enlarged calves appearing as "inverted Champaign bottles."
- 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. Starting with the pelvis, and the proximal legs and arms, weakness progresses to the distal extremities, trunk and neck. 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 mid-20's.
- Of note, patients with DMD who are exposed to halothane anesthetics are at risk for developing malignant hyperthermia.

DIAGNOSIS

- Creatine kinase (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.
- DMD 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 production of the dystrophin protein. Dystrophin levels less than 5% of normal are diagnostic of DMD. (Decreased amounts of dystrophin higher than 5% are a diagnostic of Becker Muscular Dystrophy.)
- Electromyography confirms that weakness is caused by degeneration of muscle tissue rather than by nerve damage.
- Once the diagnosis has been made, serial transthoracic echocardiograms should be checked annually to evaluate the patient's cardiac status.
- Once a patient has been identified with DMD, female members of the family must be screened for carrier status.

TREATMENT

- There is no cure for DMD. However, corticosteroids have been shown to slow the progression of disability. They can prolong ambulation for years, but do not affect overall outcome. The use of steroid medications must be tempered by chance of adverse effects associated with chronic use. Steroids are believed to work via membrane stabilizing effects rather than through 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 at the end-stage of the disease.

NOTE ON BECKER'S MUSCULAR DYSTROPHY

- Becker's Muscular Dystrophy is 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.

SAMPLE EXAM QUESTION

A 30-month-old boy is brought to your clinic by parents concerned about his 'problems walking.' He had a normal birth and met developmental motor and cognitive milestones through his second year of life other than having a delay in walking – he only took his first step at 16 months of age. Now, his gait has not progressed. He does not run or jump and his gait is slow and unsteady. As you observe the boy in your office you note a "waddling" gait with toe walking. You ask him to lie down on his back on the floor and the get up as fast as he can. The boy rolls onto his stomach, and while keeping his legs locked at the knees uses his arms to 'walk up' into a standing position. You know you will order genetic tests to confirm your suspicion but know that results will not be available for about 10 days. Which of the following routine lab tests can you order that would help in establishing the diagnosis today?

A. Complete blood count

B. Creatine kinase

C. Erythrocyte sedimentation rate

D. Parathyroid hormone

E. Serum calcium

EXPLANATION

Duchenne muscular dystrophy is characterized by extremely high serum creatine kinase (CK) levels. Although high CK levels are non-specific, indicating the likely destruction of muscle tissue from whatever cause, they can distinguish a muscular etiology from CNS and peripheral nerve etiologies. Because of its wide availability and rapid results, CK levels are usually obtained early in the diagnostic process. The definitive test for DMD is genetic testing.

Glioblastoma

CASE VIGNETTE

- 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 reveals a right frontal mass. Follow up of an MRI with and without infusion demonstrates a heterogenously enhancing lesion in the frontal lobe with surrounding edema. The patient undergoes a craniotomy with complete radiographic tumor resection. Pathology demonstrates a dense collection of cells which stain for glial fibrillary acidic protein (GFAP) on immunohistochemistry. Both pseudopalisading necrosis and endothelial proliferation are present.

BACKGROUND

- The patient has a CNS malignancy consistent with glioblastoma, also known as grade IV astrocytoma and as glioblastoma multiforme (GBM).
- Approximately 18,000 individuals are diagnosed annually in the US with glioblastoma.

PATHOLOGY

- Glioblastoma has no clear environmental etiologic factors, except for prior history of ionizing radiation. Histologically, the two cardinal features (only one is necessary for the diagnosis) are pseudopalisading necrosis, and endothelial proliferation. Astrocytic tumors, including glioblastoma, as well as ependymal tumors are typically positive for GFAP. Oligodendroglial tumors, however, are typically negative for GFAP.

CLINICAL PRESENTATION

- Glioblastoma is the most common glioma. 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, a finding consistent with increased intracranial pressure. 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 study 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 obtained via a craniotomy or stereotactic biopsy.

TREATMENT

- Treatment of glioblastoma is multi-modal. Treatment begins with surgery (maximum safe surgical resection), followed by radiation therapy with concomitant chemotherapy, followed by adjuvant chemotherapy (temozolomide). There are multiple therapeutic options if individuals' tumors progress while being treated with a particular regimen.
- For recurrent/progressive glioblastoma the FDA has approved a medication bevacizumab (an anti-VEGF antibody) and a somatic treatment called Tumor Treatment Fields (TTFields).
- TTFields, which goes by the commercial name Optune, kills dividing cells by creating alternating, "wave-like" electric fields called Tumor Treating Fields (TTFields) that travel through the brain and interfere with mitosis (cell division), thus preventing cancer cells from dividing. TTFields are delivered by removable transducer arrays that are placed on the scalp.

PROGNOSIS

- The mean survival with surgery and radiation is 12.1 months and with surgery/radiation/ chemotherapy is 14-20 months. Some patients can survive for much longer. Favorable prognostic factors include young age, good performance status, and extensive resection.

NOTES

- Note that the following names refer to the same tumor: glioblastoma, glioblastoma multiforme, GBM, and grade IV astrocytoma.
- Primary brain tumors are classified as follows:
  - Gliomas
    - Astrocytomas (glioblastoma is a Grade IV astrocytoma)
    - Oligodendrogliomas
  - Primitive neuroectodermal tumors (PNET)
    - Medulloblastoma
    - Ependymoblastoma
    - Pineoblastoma
  - Meningiomomas
  - Pituitary tumors
  - Pineal tumors
  - Choroid plexus tumors
- When diagnosing a CNS malignancy, it is important to distinguish between primary brain tumors (which begin in the brain) from metastatic brain tumors that spread to the brain from other organs. Metastatic brain tumors and abscesses (infections) often appear as multiple ring-enhancing lesions on CT and MRI. Patients with metastatic cancer will often have lesions that can be localized elsewhere in the body or have high-risk histories which include smoking and recent weight loss that occurs without dieting. Patients with CNS abscesses will often present with fever, a preceding invasive surgical procedure, or a recent infection.

SAMPLE EXAM QUESTION

A 69-year-old woman presents with an eight week history initially of fatigue and irritability that progressed to weakness in the right upper extremity and dysarthria. MRI of the brain with and without contrast shows a left fronto-temporal parenchymal lesion enhanced with contrast, and with surrounding edema. Craniotomy is performed to obtain tissue for biopsy. Pathology demonstrates a dense collection of cells which stain for glial fibrillary acidic protein on immunohistochemistry. Pseudopalisading necrosis is present. What is the patient's most likely diagnosis?

A. Astrocytoma Grade II
B. Glioblastoma
C. Medulloblastoma
D. Meningioma
E. Metastatic lung cancer

EXPLANATION

This patient's history is consistent with a rapidly progressing tumor or tumors. MRI shows that the tumor is parenchymal. Immunochemistry is positive for glial fibrillary acidic protein (GFAP) which is present in astrocytomas. Presence of necrosis places the astrocytoma at Grade IV, according to the WHO classification system, which means it is a glioblastoma.

Astrocytoma

CASE VIGNETTE

- 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.
- Astrocytomas are the most common primary brain tumors. However, grade IV astrocytomas (also known as glioblastomas) are the most common astrocytoma. Only about 1500 individuals with a grade II astrocytoma are diagnosed each year in the US.
- Astrocytomas are graded from I to IV based on how quickly the cancer cells are reproducing and what kind pathological evidence they provide of their reproduction: Grade IV astrocytomas are the most aggressive tumors. Grade III astrocytomas, also known as anaplastic astrocytomas, have an intermediate rate of reproduction. And grade I and II astrocytomas have the slowest rate of reproduction.

PATHOLOGY

- Grade II astrocytomas are the lowest grade of astrocytoma that is infiltrating. They 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 presence of significant mitoses, which define grade III astrocytomas, and they lack the necrosis and endothelial proliferation which define grade IV astrocytomas.

- Note in passing that low grade astrocytomas, that is grade I and II astrocytomas, are subdivided into three groups: pilocytic astrocytomas, pleomorphic xanthoastrocytomas, and diffuse astrocytomas.

CLINICAL PRESENTATION

- Clinically, lower grade (i.e. grade II) astrocytomas is seen in slightly younger patients. Oftentimes patients have a longer history of symptoms. Location of the tumor determines specific neurological symptoms.
- All patients with brain tumors may have headaches which often are worse upon first awakening or with a Valsalva maneuver. Also, all patients may develop seizures of focal onset with the possibility of becoming secondarily generalized.

DIAGNOSIS

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

TREATMENT

- In certain scenarios these lesions are followed radiographically without intervention. In most cases, however, the largest safe surgical resection is performed, although in most cases, especially in the diffuse form, total tumor resection is impossible.
- There is growing data to support earlier treatment and, in "high-risk" low grade gliomas, multi-modality therapy with radiation and chemotherapy at diagnosis is recommended.

PROGNOSIS

- The median survival for a grade II astrocytoma is about 5 years. Those patients with two or fewer prognostic factors were deemed low risk, and their median overall survival time was 7.7 years. Patients with three or more prognostic factors were judged to be high risk, and their median overall survival time was 3.2 years.
- Grade II astrocytomas can progress to become grade III (anaplastic astrocytoma) and grade IV (glioblastoma) tumors.

SAMPLE EXAM QUESTION

A 26-year-male is at work when his coworkers observe his left arm moving. The movement spreads and the patient falls to the ground unconscious with his entire body shaking. At the ER he is loaded with phenytoin. Head CT discloses a right frontal tumor with diffuse boundaries. He is subsequently diagnosed with a grade II astrocytoma. He asks you his approximate life expectancy. What do you tell him?

A. A few months
B. One to two year
C. About five years
D. Ten to twenty years
E. His tumor is benign and he will have a normal life expectancy

EXPLANATION

Grade II astrocytomas are divided into three subgroups, each of which is associated with somewhat different life expectancies. Overall, the median life expectancy is about 5 years, depending on whether the patient is low or high risk, which is based on number of risk factors.

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, ependymoma, 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 in younger patients, hemispheric in older patients). They can grow into the forth 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. Substantial residual disease post-operatively and evidence of CSF dissemination both negatively impact prognosis.

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. Ependymomas can also arise there. They often appear to arise from the linings of the 4th ventricle.

Migraine Headache

CASE VIGNETTE

- A 22 year old woman presents to clinic with a 2 year history of recurrent headaches (3-4 per year) that have been gradually increasing in frequency and intensity. She describes them as a throbbing pain that starts in the right frontal part of her head, steadily increasing over about an hour, and spreading towards the back to encompass her entire head. Once the pain starts it last for 'at least a day' and is accompanied by nausea and occasionally with emesis. She avoids eating for the duration of the pain. Also, she notes that head movement and bright light make her headache worse. As soon as she can she gets home and lies in bed in a darkened quiet room. She gets up only to use the bathroom and even that movement makes her headache 'excruciating.'
- She notes that she can tell when the headache is coming on because she begins seeing patterns of colorful lights in both eyes about an hour before the onset of the pain.
- She is concerned because she misses work when she has the migraine and fears losing her job.

BACKGROUND

- This patient is suffering from migraine with aura (formerly called classic migraine). Migraines can occur with or without auras, and with and without neurological deficits. Migraines are more common in women, often beginning in adolescence or early adulthood. Vulnerability to migraines is inherited and they tend to run in families. Due to their disabling nature, patients are at risk for psychosocial consequences such as loss of a job due to work absence.

PATHOLOGY

- The pathophysiologic mechanisms of migraines remain unclear. Migraines are now considered to be neurovascular events that result in depression of brain function and metabolism, and in decreases in regional cerebral blood flow, a condition called oligemia. Some theories give primacy to changes occurring in the brain and others to changes occurring in blood vessels and with blood flow. For example, the depolarization theory states that a wave of electrical depolarization spreads across the brain, leading to release of inflammatory substances that irritate the cranial nerve roots. And the vascular theory is based on the finding that blood vessels initially dilate leading to hyperemia, followed by spasm and constriction leading to oligemia. These vascular changes begin in the posterior part of the brain and spread forward. A third theory focuses on low serotonin levels which leads to dilation and swelling of blood vessels and to pain.
- Individuals have a certain level of susceptibility to migraines: the higher the susceptibility, the lower the threshold and the more frequent the migraine. Attacks start when environmental and internal triggers pass the individual's threshold, initiating the series of pathophysiological changes that culminate in the migraine.

CLINICAL PRESENTATION

- Some patients experience a prodromal phase of vague neurovegetative and affective symptoms that begin 24 hours before pain onset. The next phase is the aura phase characterized by several neurological symptoms. This phase is followed

by the headache that can last up to three days. This phase is followed by the resolution phase characterized by fatigue and deep sleep. Some patients will even have slight recurrences in pain in the subsequent days.

- Migraine with aura is characterized by presence of an aura that usually precedes the migraine pain. Visual symptoms are the most common aura but sometimes sensory or motor symptoms or a combination of symptoms occur. Visual symptoms may be positive, that is, presenting with visual stimuli such as patterns of flashing lights or, conversely, may be negative symptoms, that is, presenting with partial visual loss.
- The headache of migraine usually starts as localized pain at the front of the head on either side that then generalizes to the rest of the head. The intensity of pain increases over 1-2 hours and reaches a maximum of moderate to severe pain. Once started the migraine lasts from between 4 and 72 hours.
- Migraine headaches are exacerbated by movement, even by routine movements such as walking or climbing stairs. Photophobia and phonophobia are common, leading patients to want to lie down in a darkened and quiet room. Nausea and vomiting also may be prominent.
- Physical features may include vital sign changes such as tachycardia or bradycardia, hypertension or hypotension. Additional signs include cranial or cervical nerve tenderness, conjunctival injection, and signs of Horner syndrome: ptosis and miosis on ipsilateral to the headache.
- Complicated migraine can occur and is defined by presence of hemiparesis and/or hemianesthesia.

TREATMENT

- Migraine treatment falls into two categories: abortive (acute) treatment of current migraine symptoms and preventive (prophylactic) treatment.
- Abortive treatment
  - Background
    - For abortive treatment there are two migraine-specific medication classes, triptans (serotonin 5-HT_{1D} agonists) and ergot alkaloids. Additional non-migraine-specific medication types are included in the algorithms.
  - For moderate pain
    - NSAID
    - Isometheptene
    - Triptan (serotonin 5-HT_{1D} agonist): sumatriptan, rizatriptan, naratriptan, zolmitriptan, eletriptan, almotriptan, frovatriptan
  - For severe pain
    - Triptan
    - Dihydroergotamine or ergotamine
  - For extreme pain
    - Dihydroergotamine IV
    - Opioid
  - When nausea / emesis present
    - Dopamine antagonist (anti-emetic): metoclopramide, domperidone, promethazine, and others
- Preventive treatment
  - Background
  - Preventive treatment is indicated for patients who have ≥ 2 migraines per month or duration of pain is > 24 hours or complicated migraine with neurologic deficits.
  - Preventive medications fall into several classes
    - Anticonvulsants: valproate, gabapentin, topiramate
    - Tricyclic Antidepressants: imipramine, amitriptyline, nortriptyline, doxepin
    - Serotonin 5-HT2 antagonists: methysergide
    - ACE inhibitors: lisinopril, candesartan
    - Beta-blockers: propranolol, atenolol, metoprolol, nadolol, timolol
    - Calcium channel blockers: diltiazam, verapamil, nifedipine

- Patient education
  - Patients need to be counseled regarding their increased risk of stroke. Given this increased risk, they should avoid use of oral contraceptives or smoke, which are additional stroke risk factors.

SAMPLE EXAM QUESTION

A 27-year-old female presents the emergency department with complaints of an extreme headache. She was diagnosed with migraine with aura three years ago. Since her attacks occur only 4 times a year on average, she does not take any 'anti-migraine medications' in between attacks. She just deplaned from a 12 hour flight from Tokyo. Her pain began 3 hours ago and is 'excruciating.' Which of the following medications would be most appropriate for treating her current migraine attack?

A. Dihydroergotamine
B. Metoclopramide
C. Naproxin
D. Nifedipine
E. Valproic acid

EXPLANATION

This patient is in the midst of a migraine attack with severe to extreme level of pain. Treating her with an ergot medication is most appropriate. Dihydroergotamine (DHE) is an ergot derivative that is available as a nasal spray or by IV injection.

Metoclopramide may be indicated as adjunctive treatment, especially if nausea or vomiting is present. Naproxen, an NSAID, is indicated for acute migraine attacks but use is usually limited to mild to moderate pain. Nifedipine and Valproic acid are indicated as preventive or prophylactic treatment only.

Cluster Headache

CASE VIGNETTE

- The patient is a 27-year-old male who presents to the ER with his sister with complaints of new onset of severe unilateral periorbital pain. He had an attack yesterday while camping alone. The pain was so severe he thought he was going to die from 'a stroke or maybe one of those aneurysms.' Since he couldn't drive himself from the campground, he lay down 'accepting of whatever was going to happen next.' After about 30 minutes the pain resolved and felt he was getting back to his normal self. He then drove home. This morning he had another attack and called his sister to drive him to the hospital. He reports that the eye in pain tears up and his nose on that side begins to run. On exam, the patient is a fit well developed male in acute distress from pain. His right eye's conjunctiva is injected, right forehead shows perspiration, his right eyelid shows ptosis and right pupil is miotic. Rest of physical and neurological exam is normal.

BACKGROUND

- The patient is suffering from cluster headache, one of a number of headaches in the category of trigeminal autonomic cephalgias. Cluster headaches are further divided into episodic and chronic types based on duration and frequency of symptoms.
- Cluster headaches occur more commonly in men with onset most commonly between the ages of 20 and 40 years.

PATHOLOGY

- The pathophysiology is not well understood. It involves defective function of the posterior hypothalamic gray matter, which controls the circadian rhythm, and causes the cascade of pathophysiologic changes that lead to symptoms. Cluster headaches are proximately triggered by central disinhibition of the trigeminal nociceptive pathways (causing pain) and autonomic pathways (causing the associated autonomic changes).

CLINICAL PRESENTATION

- Cluster headaches present with unilateral periorbital pain of severe intensity – sometimes called 'suicide headaches' because of their intensity. They last from 15 to 180 minutes, occur at the same time each day, and are accompanied by ipsilateral autonomic signs: miosis, ptosis, lacrimation, conjunctival injection, nasal congestion and rhinorrhea, eyelid edema and ptosis, forehead and facial perspiration and swelling.
- Chronic cluster headache is defined by occurrence of at least one cluster period that lasts at least one year with either no remission or a remission shorter than one month.
- Episodic cluster headache is defined by occurrence of at least two cluster periods that last at least one week but less than one year, with remission between clusters of at least one month.
- A cluster is defined as a headache occurring at least every other day and up to 8 times a day.

DIAGNOSIS

- Diagnosis is primarily clinical since the presentation is so specific for cluster headache.
- Neuroimaging is not indicated in diagnosis unless patient presents with 'red flag' signs: presence of neurological deficits, signs that suggest a pituitary mass, sudden change in headache features.

TREATMENT

- Abortive treatment: first line treatment is supplemental oxygen with either a triptan or dihydroergotamine
  - List of triptans (serotonin 5-HT_{1D} agonists): sumatriptan, rizatriptan, naratriptan, zolmitriptan, eletriptan, almotriptan, frovatriptan
  - Oxygen parameters: 100% via nonrebreather face mask at 8-15 L per minute for 10 to 20 minutes
  - Second line treatments: intranasal lidocaine or capsaicin, or opioid
- Preventive treatment
  - First line treatment: calcium channel blockers, especially verapamil at doses up to 240mg qd which, because they can trigger atrioventricular block, may require monitoring with periodic EKGs.
  - Second line treatment: steroids, dihydroergotamine, valproic acid, topiramate, lithium, nerve blocks
  - Patient education: avoidance of triggers such as vasodilators such as alcohol and nitroglycerin, histamine, and smoking.

SAMPLE EXAM QUESTION

A 24-year-old male presents to morning clinic. He was diagnosed last year with cluster headache, episodic type. After no headaches for five months, he experienced a new headache yesterday evening. Last year he was on 'prevention treatment' but doesn't remember what it was. He wants to get back on it now. Which of the following medications would be most appropriate for this patient right now?

A. Dihydroergotamine

B. Naratriptan

C. Oxygen through non-rebreather mask

D. Sumaptriptan

E. Verapamil

EXPLANATION

This patient requires prophylactic treatment. The first line treatment is with a calcium channel blocker, in particular verapamil at higher doses. Sumatriptan and Naratriptan are both triptans and are indicated for acute or abortive treatment. Dehydroergotamine is indicated as first line abortive treatment and as second line preventive treatment. Thus, verapamil takes precedence. Supplemental oxygen is indicated as first line abortive treatment.

Tension Headache

CASE VIGNETTE

- A 37 year old female in treatment for generalized anxiety disorder reports a chronic headache that is really starting to "drive [her] crazy!" She describes it as of moderate intensity, occurring bilaterally, feels like a tightness or 'vice grip around the head,' and not changed by either lying down or doing physical activities like walking up stairs. She has it 'every day' for the last few weeks. Each time it lasts for about 2-3 hours each time. She denies nausea or episodes of vomiting, or experiencing photophobia or phonophobia in conjunction with the headaches.

BACKGROUND

- This patient is experiencing frequent episodic tension-type headaches. Tension headaches are the most common type of primary headache, accounting for about 90% of all headaches. They are divided into infrequent episodic, frequent episodic and chronic. Further, each type is further divided in headaches associated with pericranial tenderness and those not associated with pericranial tenderness.
- Tension headaches occur more frequently in women but are common in both genders.
- The International Headache Society (IHS) has retired the term tension headache because it implies that the etiology primary etiology of pain is muscle tension which is not borne out by research as being a prominent component in the pathogenesis of these headaches. Therefore, the IHS has renamed these headaches as tension-type headaches, or TTH.

CLINICAL PRESENTATION

- TTHs present with bilateral pain that is described as a non-pulsating tightness or 'vice-like' pain. It is not associated with nausea or vomiting but it can be associated with photophobia or phonophobia.
- Infrequent episodic TTH, defined as headaches occurring on less than one day a month, affect almost everyone. These headaches tend to have little impact on the individual and usually no medical attention is required. Usually the individual either does not treat it or treats it with over-the-counter analgesics.
- Frequent episodic TTH, defined as headaches that occur more frequently than on one day a month and up to 14 days a month. These headaches are more impactful on the individual and many of them do seek medical consultation. Also, frequent episodic TTH often co-exists with migraines without aura. Patients should be educating on distinguishing these two headache types because confusing TTH for a migraine may incorrectly lead to a conclusion of failure of migraine treatment.
- Chronic TTH is defined as occurring at least on 15 days per month.
- Pericranial tenderness, when present, occurs interictally and often in more severe form during the headache. Tenderness to palpation may occur in the following muscles: frontal, temporal, masseter, pterygoid, sternocleidomastoid, splenius and trapezius muscles. The tenderness is rated on severity and summed across muscles to yield a pericranial tenderness score.

PATHOLOGY

- The exact pathophysiology of TTH is unknown. The episodic forms of TTH likely involve peripheral pain mechanisms while the chronic form likely involves central mechanisms.
- Well known precipitating factors for TTH include stress, eyestrain, insomnia or sleep deprivation, remaining in an uncomfortable position for extended periods of time, hunger, and dehydration.

DIAGNOSIS

- Individuals who present with presumed TTH should receive a physical and neurological exam as well as receive routine lab work to rule out other causes of headache, such as for instance, hypertension. Also, focal neurological signs should be evaluated for and excluded.
- Further, because of the association of some forms of TTH with migraine, a migraine history also should be obtained.
- Recall that TTH can occur with photophobia or phonophobia, but not with nausea or vomiting.

- The clinician should remember to inquire about and examine for pericranial tenderness.
- Neuroimaging is unnecessary when the presentation is classic in presentation and when no other medical or neurological signs are present.

TREATMENT

- Treatment for TTH includes medications and non-medication interventions.
- First line medications are aspirin, acetaminophen and the NSAIDS such as ibuprofen, naproxen, indomethacin, and ketorolac. Second line medications are the opioids, which should be prescribed with caution.
- Non-medicinal interventions include hot and cold packs, trigger point injections and nerve blocks, relaxation exercises, improved posture, better sitting and working environment, and lifestyle changes that lead to more balanced and regularly spaced meals, adequate levels of hydration, and better rest and sleep.

SAMPLE EXAM QUESTION

A 26-year-old female presents to clinic with complaints of "I have tension headaches but yesterday I've developed this headache that's killing me. It's right around my right eye. Also, I see halos when I look out from my right eye. I've taken ibuprofen 400mg which usually helps but it hasn't helped this time. I didn't want to take more on my own." You obtain a history that is consistent of a 2 year history of partially controlled frequent episodic tension-type headaches. Otherwise, the patient has no other medical conditions and denies any psychiatric difficulties. She reports that due to seasonal allergies she's been taken diphenhydramine pills. On physical exam you note a mid-dilated nonreactive right pupil and right conjunctival injection. Your next step is which of the following?

A. Order a head CT
B. Prescribe an increased dose of ibuprofen for the next two days
C. Prescribe prednisone
D. Prescribe sumatriptan
E. Send patient to the emergency department

EXPLANATION

The patient's presentation is consistent with acute angle-closure glaucoma, which is a medical emergency because it can permanently damage the eye and lead to blindness.

Any medication or drug of abuse that causes pupillary dilation (mydriasis) in a susceptible individual can trigger acute angle-closure glaucoma. Drug classes include: antihistamines; anticholinergics; antidepressants including tricyclic antidepressants, monoamine oxidase inhibitors, and bupropion; sympathomimetics including amphetamine, cocaine, and ecstasy; and antipsychotics with anticholinergic effects.

Although the patient states that she has tension-type headaches, the current headache differs from her usual headache in intensity and location. Also, it is associated with additional signs and symptoms: the

patient sees a halo out of right eye, her pupil is fixed in mid-position and her conjunctiva is injected.

Brain Death

CASE VIGNETTE

- 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
- Criteria for Determination of Brain Death (for the diagnosis of brain death, these criteria must be fulfilled):
  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 reflex present
     d. Apnea Test
        vi. Preoxygenate the patient to PO2 of >200 and PCO2 <40
        vii. Hold ventilations for 8 minutes
        viii. Abort test if respiratory movements seen, systolic Bp<90mmHg, significant desaturation or cardiac arrhythmia
        ix. Draw ABG
        x. => Test positive if PC02 >60 mmHg or 20 mmHg 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 99hexamehtlyporplyeneamine 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. Patient must have temp > 36.5.
  3. Tone must be flaccid, with absent reflexes in extremities.
     a. 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.

SAMPLE EXAM QUESTION

A 72-year-old male suffered a cardiopulmonary arrest during hip replacement surgery. He remains on a respirator. Three days later, he remains unresponsive to verbal and painful stimuli. Muscle tone is flaccid with absent muscle reflexes, pupils are in mid-position and unreactive to light, and eyes do not move in their sockets to the 'doll's eye procedure' or to 'cold calorics'. Corneal and gag reflexes are absent. Vital signs are blood pressure is 170/90, respirations on respirator are 16, and temperature is 97.4F. Lab tests disclose normal CBC and metabolic results. Head CT shows no masses or hemorrhages. What do you tell the family?

A. The patient is brain dead
B. The patient is in a neurovegetative state
C. The patient is comatose
D. The patient cannot be diagnosed with brain death without a Technetium scan
E. The patient's body temperature is too low to confirm brain death

EXPLANATION

The criteria for brain death exclude establishing brain death when the patient has reduced body temperature. Such a scenario, of a cold patient, is unlikely to occur in a hospital. The requirement that you cannot be 'cold and dead' is to guard against establishing death when the patient has been brought to a hospital following exposure to cold air or water temperature, since lower body temperature can reduce metabolic rate and responsiveness to almost nothing. Some combination of Technetium scan, EEG, and cerebral angiogram are obtained in almost all cases although they are considered optional and not required to formally establish brain death.

1. TOC