CEREBRAL EDEMA, ICP, HERNIATIONS

Cerebral Edema
- Vasogenic
- Cytotoxic
- Interstitial
- Osmotic

Herniations
- Subfalcine
- Uncal
- Cerebellar

Hydrocephalus
- Communicating
- Noncommunicating
- Ex Vacuo

CEREBRAL EDEMA

Cerebral edema is defined as fluid in the brain. That fluid can be blood, CSF, water, or whatever else, so long as there is extra fluid in or around the brain space. Edema may be benign, but because it is within a closed space (the skull) edema often has affects ranging from focal deficits to death. Because fluid gets into the brain, microscopically there will be vacuolization, large wide spaces within the neuropil representing where the water is/was.

Vasogenic Edema is caused by a failure of the Blood Brain Barrier. That means blood gets into or around the brain parenchyma. In other words, you’ve got extracellular fluid that came from the vascular space. This is seen in cancer or in generalized hypoperfusion and changes made to poorly supplied arteries. This is not hemorrhage (that is another subject).

Cytotoxic Edema is what happens when neurons die. When neurons suffer an hypoxic or toxic injury, the supply of oxygen and glucose, and therefore ATP, depletes. Without ATP, the Na/K-ATPase fails, leading to electrolyte imbalances within the cell. Most significantly, water enters the cell to balance the osmolar load, and there is a significant intracellular fluid increase. Cells swell, and will eventually lyse. Because the cell bodies are most affected (they have the highest metabolic demand), the grey matter is most often affected.

Interstitial Edema is caused by the failure of the CSF-Brain Barrier. Much like Vasogenic edema, fluid from another compartment is allowed to penetrate brain parenchyma. It has all the characteristics of Vasogenic edema, except that it is CSF in the extracellular fluid. Because it is CSF, and CSF has little protein, the protein level is low in interstitial edema. This is seen in obstructive hydrocephalus where the ventricles become dilated and stretched with increasing pressure; stretched so far that they start to literally squeeze CSF out into the brain (since it cannot drain).

Osmotic Edema does not appear in Robbins. It is caused by an osmolar imbalance such as with excess water intake or hyponatremia. Fluid shifts from the hypoosmolar vasculature into the hyperosmolar brain, causing swelling.

HERNIATIONS

Herniations are a result of increased intracranial pressure, brought on by the presence of edema, a bleed, a tumor mass, or anything that increases the mean intracranial pressure above 200mmH₂O, exceeding the capacity for veins and ventricles to compress.
**Subfalcine Herniations** are caused by unilateral expansion of the cerebral hemisphere as might be seen in a thrombotic occlusion of the anterior cerebral artery. This expansion displaces the Cingulate Gyrus under the falx cerebri, compressing both the pericallosal arteries (of the corpus callosum) and the anterior cerebral artery which may lead to infarcts in their distribution.

Transtentorial also called Uncal Herniations are caused when the medial aspect of the temporal lobe goes through the free edge of the tentorium cerebelli as may be seen in an epidural hematoma. Pathological findings are as follows, listed in the order of severity (more severe Herniations progress down this list). Compression of the 3rd cranial nerve causes ipsilateral pupil dilation and eye paralysis. Compression of the posterior cerebral artery causes an infarct of visual cortex. Compression of the Contralateral Cerebral Peduncle causes ipsilateral hemiparesis relative to the Herniation, which gets a special name, “Kernohan's Notch.” Finally, hemorrhage within the midbrain and pons may result, a process known as Duret’s Hemorrhage.

Tonsil Herniation of the cerebellum through the foramen magnum is a rapidly fatal herniation seen with significant trauma to the head. This requires massive intracranial pressure increases and compression of the brainstem suppresses cardiorespiratory centers resulting in death.

**HYDROCEPHALUS**

Hydrocephalus is basically the accumulation of excessive CSF within the ventricular system. Whatever the cause, the ventricles are bigger, full of more fluid, and, depending on circumstance, may push against and compress surrounding brain parenchyma, increasing ICP. Hydrocephalus that occurs prior to the closure of the cranial vault (as in children) results in an enlarged head and normal ICP. Hydrocephalus that occurs after the closure of the cranial vault (as in adults) results in a normal head and increased ICP.

Communicating Hydrocephalus means that the ventricular system is all connected to itself. That is, it is nonobstructive hydrocephalus. The problem then is not in the flow of CSF within the ventricles, but either with its production or its exist. This can be created either by a cancer of the choroid plexus (which is unlikely) or by a problem with the arachnoid granulations. A subarachnoid hematoma or meningitis can cause a temporary failure of these granulations, thus restricting efflux of CSF. Pacchioni's Granulations which basically means agenesis of the granulations is a congenital defect that results in hydrocephalus in children, requiring shunting for draining.

Noncommunicating Hydrocephalus means that the ventricular system is blocked somewhere. That is, it is obstructive hydrocephalus. The problem is that somewhere along the way that physically blocks the movement of CSF from one ventricle to another. Since CSF is produced at a constant rate, ventricles proximal to the obstruction are enlarged. Since CSF is drained at a constant rate, ventricles distal to the obstruction are normal or shrunken. Certain areas, where the tract for CSF is small, pose high risk areas, such as the Foramen of Monroe. The thing doing the obstructing is likely to be a mass effect caused by a hematoma / bleed / tumor.

Hydrocephalus Ex Vacuo is a special kind of hydrocephalus. Since the skull is enclosed and there is a well maintained ICP, if something were to leave that space, something else would fill it in. In this case, if part of the brain is removed (trauma, surgery, atrophy/Alzheimer’s/dementia), the ventricles are allowed to expand to fill the gap. Intracranial pressure is normal, but the ventricles are enlarged.
DEVELOPMENTAL DISEASES AND PERINATAL TRAUMA

NEURAL TUBE DEFECTS

Anencephaly (this comes from lecture which is contradictory to Robbins Outline)
There is no normal brain. The brain initially protrudes through a defect in the cranial vault (normal brain, through the skull). Then, with mechanical injury and vascular disruption, the brain degenerates (with injury, no brain). Instead there is an area cerebrovasculosa which is the left-over brain. Because the malformation is on top of skull the eyes and face are preserved, but this is not compatible with life.

Encephalocele
“Cele” means pouch. This means there is brain protruding, in a sac, through the defect of the skull. The difference between this and anencephaly is that there is only a small portion of brain through the skull, with most of brain parenchyma developing normally. However, the intracranial portion of the brain may be malformed. This is sort of a gradation of anencephaly; large encephaloceles basically are anencephaly, and are incompatible with life, though small encephaloceles may survive.

Spina Bifida
This caused by a failure of closure of the vertebral arch. The spine has a vertebral body in front, the arch in back, and between the two structures there is the spinal canal that contains the spinal cord. In this disease, the back of the spine is defective, and the spinal cord can be exposed out the back. There are different kinds of spina bifida based on severity. In Spina Bifida Occulta the spine does not close, but the skin is intact and the cord is in the right place, with a tuft of hair above the abnormality. In Spina Bifida Meningocele the spinal cord is in the right place, but the meninges protrude and form a bulge of skin, CSF is within the exposed region. In Spina Bifida Myelomeningocele the spinal cord is raised from its seat in the spine and also protrudes and forms the bulge along with the meninges.

FOREBRAIN ABNORMALITIES

Holoprosencephaly
This is the failure of the lobes to separate. There are sporadic forms (environmental) and genetic forms (Sonic Hedge Hog on chromosome 7 and some are X-Linked). Whatever the cause, there is the absence of brain cleavage of the initially spherical brain into two lobes. There can be complete holoprosencephaly which is termed Alobar Holoprosencephaly where there is a single ventricle, small brain, and strange midline facial abnormalities (single nostril, single eye) and is incompatible with life. Semilobar Holoprosencephaly has partial separation of hemispheres, presents with a larger brain, and is a spectrum up from death to near normal function.
Polymicrogyria
Poly (many) micro (small) gyria (gyri). Therefore, there is an excessive number of small gyri. This can also be caused by environmental or genetic causes, but you so don’t have to know the genes involved. The cortex exists only of 3 cortical layers (normal is 6) which are irregularly over-folded and fused eliminating sulci. These patients have severe psychomotor retardation and seizures.

Lissencephaly/Agyria
This is a genetically produced smooth brain. There is a thick cortex with there is no sulci. If there are no sulci you cannot tell the difference between the sulci and gyri, so the brain looks smooth. There are only 4 cortical layers under the scope (normal is 6). While compatible with life, there will be severe psychomotor retardation and seizures. Caused by a deletion of chromosome 17.

Agenesis of the Corpus Callosum
This is literally the absence of the corpus callosum. The white fiber tract between the two hemispheres is replaced by adipose. This is caused by a mutation of the L1 Cell Adhesion Molecule which acts to direct neurons during migrational development. There will be psychomotor retardation, but it is possible for these patients to be relatively normal; severing the corpus callosum is a primitive neurosurgical intervention for seizures that is, except in special cases, not performed anymore.

Mega and Microencephaly
This is either big (mega) or small (micro) head and brain diseases. It is associated with fetal alcohol syndrome, chromosomes abnormalities, or HIV. It is generally caused by problems of neuronal migration. Those neurons that get trapped can be identified in the microscope as neuronal heterotopias.

POSTERIOR FOSSA

Chiari Malformation
Characterized by a small posterior fossa with the contents squished out the back end (cerebellar Herniation). Depending on the severity, these patients may be asymptomatic, but they may also present with syrinx, headache, Nausea, vomiting, etc. There are three types, but even baby robbins doesn’t care if you know them.

Dandy-Walker Malformation
Characterized by a large posterior fossa and the absence of a cerebellar vermis. Because the vermis is the roof the 4th ventricle, there is a large midline cyst filled with CSF representing

CYSTIC DISEASE
Syrinx
This is either an expansion of the central core hydromyelia or the formation of a cleft-like cavity in the inner cord (syringomyelia) following trauma to spine or in Chiari-Malformations. There is progressive loss of pain and temperature (ALS) in a cape-like fashion in the cervical vertebrae. Usually manifests itself around the 20s and 30s.
PERINATAL INJURY

The injury can be caused by any number of events including trauma, hypoxia, infection, or toxins. These diseases plague the OB/GYN field and are a source of lawsuits. Outcome of all injury is dependent on the location of the lesion. For example, if the brain stem is injured, it results in death. If the cortex is involved, then you get mental retardation. If the thalamus is involved, then the patient is left in a vegetative state.

Multicystic Encephalopathy and Periventricular Leukomalacia

These are anoxic-ischemic destruction of white matter. There will be multiple cystic cavities containing necrotic debris and macrophages. This is basically an infarct of the brain from the anoxic injury. This may result of early separation of placenta, embolic blood vessels, or even strangulation by the cord during delivery. Anything that disrupts the blood supply to the fetus will cause ME. Ulegyria is a more severe form involving deeper parts of the sulci producing mushroom-shaped sulci.

Status Marmoratus and Ulegyria

An anoxic-ischemic injury involving damage to the thalamus and basal ganglia. It produces a marbled appearance of these structures as a result of irregular patches of dense myelin mixed with gliotic zones. There is a loss of neurons, mineralization/calcification of damaged neurons, gliosis, and excessive myelin.

Periventricular Leukomalacia

Caused by any insult, but primarily an anoxic-ischemic insult resulting in symmetrically effected white matter necrosis around the lateral ventricles. There is a liquifactive necrosis, gliosis, and axonal damage. The damage to the ventricles may cavitate causing cysts of CSF. Patients will have a variety of symptoms including diplegia or quadriplegia, visual disturbances, palsy, or seizures.

Germinal Matrix Hemorrhage

This is more specific for perinatal patient suffering anoxia/hypoxia injury. The germinal matrix exists only in the fetus and the neonate. The blood vessels within the germinal matrix are particularly sensitive to anoxia/hypoxia/ischemia and are vulnerable to rupture. This is seen often with prolonged complicated deliveries where the baby drops its heart rate or is caught on the cord. It is separated into four grades depending on where the hemorrhage is. If confined to the germinal matrix, it is considered grade 1. Matrix + Ventricles without dilation = grade 2. Matrix + Ventricles + Hydrocephalus = Grade 3. Matrix + Ventricles + Rupture + Brain Parenchyma = Grade 4.
Path Neuro Paragraph Style

**TRAUMA**

- Skull Fx
  - Diastatic
  - Displaced
  - Basilar
- Parenchymal Injuries
  - Concussion
  - Direct Parenchymal
  - Diffuse Axonal
- Traumatic Hemorrhage
  - Epidural
  - Subdural
  - Arachnoid
  - Intraparenchymal
- Spinal Cord

**SKULL FRACTURE**

The skull is a pretty tough piece of bone, requiring significant trauma in order to break it. A **diastatic fracture** actually crosses suture lines, and is far rarer than a fracture that does not cross suture lines. A **Displaced Skull Fracture** is a piece of skull that moves a distance greater than the thickness of the bone. Except for direct trauma (like with a hammer or piece of wood), the location of the trauma can tell you something about the patient. When **falling while conscious** there is usually occipital damage, as occurs when falling from a ladder. When **falling while unconscious** there is usually frontal damage, as occurs when passing out during a syncopal episode. A common board question is that of a **basilar skull fracture** which causes from severe occipital damage, presenting with lower cranial nerve defects, **battle sign** (bruising under the ears at the mastoid) and **raccoon eyes** (double black eyes).

**PARENCHYMAL INJURIES**

**Concussion** is a **clinical syndrome without physical findings**. It occurs with rapid deceleration, such as a football player making a tackle. It is most relevant in sports medicine. A concussion results in a transient **loss of consciousness, loss of reflexes**, and **persistent amnesia** of the event. With repeated concussions, amnesia will prolong.

**Direct Parenchymal Injury** is physical damage to the brain parenchyma. This can be in the form of a cut, or **laceration**, or, more relevant for your test, a **contusion**. Contusions occur when the brain, which is motile within the fluid of the skull, strikes the interior surface of the skull. There are two types of contusions. Say you are standing on the side walk, reading your pathology notes, and someone comes up and WHAM hits you in the front of the head with a baseball bat. The area damaged by the bat will create a **coup contusion**. The force of the blow causes the brain to be pole vaulted towards the back of your skull, where it strikes again, causing a **contracoup contusion** diametrically opposite to the initial coup injury. Old Contusions can be seen as yellow discolorations, called **plaque jaune**. The regions at greatest risk are the frontal and temporal gyri, most distant from blood supply.

**Diffuse Axonal Injury** is **loss of axons and neurons** without direct trauma. This is associated with **angular momentum**, as occurs when a patient is restrained in a vehicle and is struck from behind. The cars suffer massive direct trauma, but the people inside suffer very little. Their brains receive no direct trauma, yet they die anyway. There is **immediate depression** or **loss of consciousness** and the prognosis is relative to the duration of coma. The more axons damaged, the longer the coma, the worse the prognosis.
TRAUMATIC HEMORRHAGE

Robbins separates the four types of hemorrhage into two completely different sections. Here we present all four types of hemorrhage and will refer you back to this page when we encounter the medical hemorrhages later. Epidural and Subdural are classically traumatic hemorrhages. Subarachnoid and Intraparenchymal are classically medical hemorrhages.

Epidural Hematoma is a bleed between the skull and the dura. This space is a potential space. Most often caused by hemorrhage of the middle meningeal artery, epidural hematomas are elliptical and well contained (have a linear contour) on a CT. There is often a lucid interval prior to rapid progression to death. This is classically seen in the baseball player who takes a ball to the side of the head (the temporal region). You encountered this in both Anatomy and in Neuro.

Subdural Hematoma is a bleed between the dura and the arachnoid. Bleeding into this real space is caused by the tearing of bridging veins. As an individual ages the brain atrophies. This atrophy is accompanied by a loss of brain mass. The brain shrinks, but the veins stay the same size. This stretches those veins, making them more prone to rupture. Thus, subdural hematomas occur more often in the elderly or the demented. The hematoma gets right up to brain, but does not show up between sulci as the arachnoid layer keeps the bleed separate from the pial surface.

Subarachnoid Hematomas are more medical than traumatic, though they can also be traumatic. They are caused by a rupture of a berry or saccular aneurysm, common in the circle of Willis. The hemorrhage is between the arachnoid and pia, so the blood enters the sulci on CT. The bleed commonly occurs at the base of the brain (where the circle of Willis is). Because blood is a direct irritant to parenchymal tissue, patients complain of the Worst Headache Of Their life. Aneurysms are associated with autosomal dominant polycystic kidney disease, coarctation of the aorta, and Marfan’s. The adventitia is continuous while the media and intima are absent at the neck of the aneurysm.

Intraparenchymal Hemorrhage is definitely a medical disease. This is a bleed inside the brain. Most often caused by hypertensive changes in vasculature, leading them prone to rupture, it occurs most often in the caudate and putamen. There are always focal lesions associated with the hemorrhage, but mass effects or penetration into the ventricles are possible.

SPINAL CORD

Trauma to the spinal cord produces defects dependent on the region affected. Remember that all sensory and motor at the level of trauma is lost. DCMLS crosses at the pyramidal decussion, so proprioception and vibratory sense is lost ipsilateral to injury. ALS crosses immediately, so pain and temperature are lost on the contralateral side to injury. Motor tracts cross at the pyramidal decussion, so upper motor neurons are lost ipsilateral to the site of the lesion. Neurons at the level of injury die first. General degeneration of the axons and neurons of ascending and descending tracts die eventually. Upper motor neuron lesions result in hypreflexia and babinski sign. Lower Motor Neuron lesions result in areflexia and atrophy.
GENERALITIES

The brain weighs only 1% of the entire body weight, yet consumes 15% of cardiac output and 20% of the O₂. Thusly it is a highly metabolic structure with limited stores of energy and oxygen. Therefore, even small alterations in perfusion cause devastating effects on the brain. Moreover, the brain is unable to regenerate, so the damage is permanent. Finally, the brain autoregulates its own blood pressure, maintaining a constant perfusion over a range of blood pressures from 60mmHg to over 200mmHg. Outside those ranges there is either hypoperfusion or such a large pressure that vessels “blow out.”

GLOBAL CEREBRAL ISCHEMIA

Caused by a general hypoperfusion, also called shock or low-flow states. This is where there is not enough pressure to get the blood to the brain. Depending on how bad the hypoperfusion is (gun shot with blood loss versus total cardiac arrest without CPR for 10 minutes) will determine the severity of the symptoms. Both time and pressure determine outcome. There are certain areas of the brain that are more vulnerable to ischemia/hypoxia. These are the Hippocampus CA1 / Sommer’s Sector, the Purkinje neurons of the cerebellum and the pyramidal neurons of the cortex.

FOCAL CEREBRAL ISCHEMIA

Thrombotic infarcts are caused by occlusion of a vessel, often by atherosclerosis. Hypertension and diabetes play an obvious causative role in the exacerbation of atherosclerosis, and, like heart disease, obesity and smoking increase the risk of thrombotic events. Occlusion of a vessel leads to loss of function to sites distal to the occlusion. Pale or nonhemorrhagic infarcts are characteristic of thrombosis without reperfusion. Thrombosis is treated with thrombolytics, which provides reperfusion and resolution of the clot. Thrombosis with reperfusion can lead to a hemorrhagic infarct. Thrombotic infarcts affect the extracerebral carotid circulation (aka, larger vessels)

Embolic infarcts most often affect the intracerebral carotid circulation (most often the middle cerebral artery). Emboli can come from any number of sources. They may be iatrogenic (introduction of plastic or air during catheterization), from venous circulation (with R→L shunt), from an infected valve (endocarditis), but are most frequently a complication of Atrial Fibrillation. A special type of embolus, called shower embolis, is seen after bone fractures and produces multiple tiny infarcts. Embolic infarcts are classically a hemorrhagic infarction (do not confuse this with intracranial hemorrhage)
HEMORRHAGE WAS DISCUSSED IN THE LAST SECTION, TRAUMA

VASCULAR MALFORMATIONS

AV Malformations are a tangled web of arteries connected to veins without an intervening capillary bed. Because there is no high resistance vessels (arterioles and capillaries), the structure is high flow. High flow means turbulence and the risk for hemorrhage (subarachnoid and Intraparenchymal). Because there is a nest of unusual blood vessels that essentially invades the brain, and because they are often found in cortex, they often present with seizures. These are fully developed blood vessels with thick walls.

Cavernous Hemangiomas are low flow clusters of thin walled vessels without any intervening brain parenchyma. They are a genetic disease, autosomal dominantly acquired that are often multiple. Like AV malformations, they cause seizures and hemorrhage. They are often found in the brainstem and cerebellum.

Capillary Telangiectasias are low flow clusters of thin walled vessels with intervening brain parenchyma. These are essentially cavernous hemangiomas found in the pons. Unlike Cavernous Hemangiomas, these are clinically silent and are incidental on autopsy.

Venous Hemangiomas are asymptomatic, thin-walled somewhat dilated venous channels. They are disorganized in the brain, and are an incidental finding at autopsy.

HYPERTENSIVE CHANGES

Lacunar Infarcts occur when HTN affects the blood vessels of the basal ganglia and white matter developing arteriolar sclerosis. The penetrating arteries to these structures are tiny and are easily occluded. Lacunar infarcts are small, multiple, cavitary lesions throughout internal structures (thalamus, internal capsule, caudate, pons)

Slit Hemorrhage is the other side of Lacunar Infarct. The arteriolar sclerotic changes make the blood vessels more prone to rupture. This is essentially an Intraparenchymal hemorrhage that is really small, leaving behind slit like cavities where the hemorrhage was.

Hypertensive Encephalopathy is “screwy brain” caused by hypertension. An acute, massively elevated blood pressure can cause cerebral dysfunction, headache, confusion, vomiting or coma. This is a medical emergency as it is unlikely to resolve. This is the acute form of encephalopathy. However, hypertension may lead to vascular dementia, an atrophy of cortical mass presenting with diffuse focal infarcts with nonlocalizing symptoms. Basically, hypertension leads to multiple tiny infarcts that, when summed, cause widespread loss of cortex, leading to dementia without any specific loss of function.

Increased risk of intracranial Hemorrhage and Focal Cerebral Ischemia. Hypertension increased risk for both types of stroke, occlusive/thrombotic and hemorrhagic.
Multiple Sclerosis is an autoimmune disease characterized by symptoms that are separated in space and in time. The typical symptoms are optic neuritis (vision loss), Internuclear Ophthalmoplegia (involvement of the MLF tract), and various peripheral motor and sensory defects. It is a disease of demyelination of white matter that follows a relapsing and remitting course. It is a fairly common disease, occurring in 1 out of every 1000 people, with women being twice as likely as men. There are well circumscribed plaques on MRI and on gross where there is active demyelination. While uncertain, the thought is an autoimmune attack on a protein in myelin. These plaques occur in random assortment over the spinal cord and brain. The most obvious site is Periventricular graying where the white matter looks like gray matter (because the myelin is lost). The pathognomonic finding is increased monoclonal IgG in the CSF.

Guillan-Barre syndrome is an autoimmune disease characterized by ascending paralysis following an infection or vaccination. It is usually nonfatal, though death may result from diaphragmatic paralysis. It is thought to be caused by autoimmune reaction to the GM1 ganglioside, which is revealed on immunofluorescence. There should be an elevated protein with normal glucose.

Acute Disseminating Encephalomyelitis is a post-viral demyelinating disease that presents with headache, lethargy and coma. There is almost a full recovery in those that survive, but the mortality is 20%. Pathology is poorly understood as this disease is after the infection has cleared. There is greyish discoloration of white matter without hemorrhage. Occurs in adolescents and kids.

Acute Necrotizing Hemorrhagic Encephalomyelitis is ADEM + hemorrhage. It is a fulminant version that is highly fatal. Occurs in kids and adolescents.

METABOLISM

Central Pontine Myelinolysis is an often fatal disease that results in fatal Quadraparesis. It is caused by aggressive correction of hyponatremia. It is also seen in alcoholics or other hyperosmolar states. While not totally understood, the hyperosmolar state causes bilateral, symmetrical demyelination of the basis ponti resulting in death.
Subacute Combined Degeneration also called B12 Deficiency is seen in strict vegans and pernicious anemia. B12 comes from animal products and requires intrinsic factor to be absorbed. Vegans don’t eat meat and in pernicious anemia there is an antibody to intrinsic factor. B12 stores take decades to deplete but when they are gone it produces a syndrome characterized by loss of vibrational sense and proprioception followed by spastic paralysis that is irreversible. The classic picture is a spinal cord cut in section with the top half of the spinal cord missing its myelin. It can be easily mistaken (on picture alone) for tabes dorsalis.

LEUKODYSTROPHIES

Metachromatic Leukodystrophy is an autosomal recessive disease caused by a deficiency in arylsulfatase that causes a toxic accumulation of sulfatide in oligodendrocytes, which kills them. Death of oligodendrocytes = loss of myelin. It is a progressive peripheral neuropathy that often involves blindness and psychomotor retardation. On gross, there is a marbled appearance.

Adrenoleukodystrophy is an X-linked mutation of a protein found on peroxisome membranes called ALD. Without ALD, VLCFA (very long chain fatty acids) accumulates in the cell and is toxic. This is characterized by adrenal insufficiency that begins in childhood with neurologic manifestations (behavior, vision, spasticity, ataxia) occurring later. Death is within a few years from onset of symptoms. There is diffuse myelin loss with lipid-laden macrophages accompanied by white matter atrophy. Electron microscopy shows trilamellar membranes with VLCFA-cholesterol esters

Krabbe’s Disease is an autosomal recessive disease caused by a deficiency in β-Cerebrogalactosidase. This deficiency causes an accumulation of psychosine, a metabolite formed as beta-galactoside accumulates. Psychosine is an abnormal product of a normal substrate that is toxic. It causes globoid proliferation that is sudan positive causing cerebral atrophy and discoloration of the gray matter. It may present with seizures, retardation, vision problems, limb weakness, dementia, and ultimately, death.
DEGENERATIVE DISEASES

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Alzheimer’s

The pathogenesis is not completely understood at this time. We do know that there are two proteins that are abnormal: Aβ is the component of senile plaques and Tau is the component of neurofibrillary tangles. Aβ is 40 amino acid peptide, a cleavage product of Amyloid Precursor Protein, a normal transmembrane protein in neurons and glia. The normal processing of APP is by α-secretase and γ-secretase. The abnormal cleavage product Aβ is made from the aberrant action of β-secretase and the normal action of γ-secretase. Aβ is insoluble and forms aggregates in the interstitium, called plaques, which are directly cytotoxic via free radicals and destroy neurons and glia. Tau is a microtubule associated protein (MAP) that holds microtubules together, the substance of axons. When tau is hyperphosphorylated it dissociates from microtubules (leading to their collapse) and form aggregates within neurons. The axons fall apart and tau aggregates form, which are called neurofibrillary tangles. The genetics behind Alzheimer’s is complicated, and also not fully understood. There is a link to trisomy 21 (down syndrome) which has a higher incidence of younger onset Alzheimer’s; the APP gene is found on chromosome 21, which is thusly duplicated. The Presenelin Gene is responsible for secretase activity, mutations in Presenelin (particularly Presenelin 1) affect which secretase (α or β) gets used. Presenelin 1 and 2 genes are found on chromosome 14 and 1, respectively. Finally, there is an interaction with the ApoE gene that shows a higher incidence of Alzheimer’s when homozygous for ApoE4. The typical Alzheimer’s patient is one with progressive loss of cognitive function. Short-term memory goes first, followed by long-term memory, loss of language functionality, depression, and eventual dementia. With degeneration of cortical mass, hydrocephalus ex vacuo can often be seen. Under the microscope, you will see Neurofibrillary tangels, Senile Plaques, and Hirano Bodies. Plaques may stain positive with Congo Red, indicative of Amyloid deposition (makes sense since APP is amyloid precursor protein). Treated with Anticholinesterase inhibitors that slow, but do not stop, disease progression.

Pick’s Disease

This is an Alzheimer’s-like disease that must be differentiated from Alzheimer’s clinically. It is a type of neurodegenerative disease that is involved in the frontotemporal region and is another examples of tau pathology. We already know from the Alzheimer’s discussion that Tau is a MAP. It binds to and stabilized microtubules in a phosphorylated state within axons. In a hyperphosphorylated state, tau dissociates from the microtubules and forms tangles. This will not present with plaques, nor will there be any genetic predisposition for Alzheimer’s. Likewise, there is significantly more language involvement associated with the Dementia, and less impact on memory. Robbin’s, Lange, and Xiong use the term “Knife-Blade Atrophy” but no one actually explained what that means; look for it as a buzzword. This shows grossly similar features to Alzheimer’s. Microscopically there will be neuronal loss, astrocytosis, and a spongiosis form of the parenchyma. But the important finding is the Pick Cells containing Pick Bodies. Pick Cells are the definitive means to differentiate Picks and Alzheimer’s.
Parkinson’s Disease

This is a degenerative disease of the disease of the nigrostriatal dopaminergic system characterized by the mask-like face (diminished expression) slowed movements and pill-rolling tremor. Dopamine is the neurotransmitter of the substantia nigra neurons that stimulates movement. In this disease, these neurons, and therefore their excitatory signal, are lost, and movement cannot be initiated. There is a link to both the α-synuclein gene as well as the parkin gene, though no definitive link has been reached. What we do know is that there are inclusions of α-synuclein in those neurons of substantia nigra neurons called Lewy Bodies which predispose the substantia nigra to immune degradation. The loss of neurons causes an increased pallor of substantia nigra and locus ceruleus on gross. Because this is a problem of loss of dopamine, L-DOPA replacement therapy is first line. This does not stop disease progression, however, and deep brain stimulation is now the final step. We are working on implantation of fetal mesenchymal tissue to regenerate the substantia nigra.

Huntington’s

This is a degenerative disease of the caudate and putamen caused by an autosomal dominant inheritance of a trinucleotide repeat (CAG) in the Huntington gene (chromosome 4) which results in chorea and dementia and which demonstrates anticipation. The caudate and putamen are considered “striate neurons,” inhibitory GABA producing neurons to the Globus Pallidus. With degeneration of striate neurons, there is no inhibitory signal to Globus Pallidus. The Globus Pallidus is inhibitory to the subthalamic nucleus. Now, the Globus Pallidus is allowed to have unrestrained activity, which is unrestrained inhibition of the subthalamic nucleus. The subthalamic nucleus normally inhibits movement. Now, with unrestrained inhibition of the subthalamic nucleus, there is no inhibitory signal on movement, so we get unrestrained movement, termed chorea. Spastic Muscle Movements are characteristic of the disease, followed by memory loss and dementia. Death occurs with 10-15 years of disease onset. The disease is autosomal dominant because the presence of CAG repeats initiates the disease. Normal CAG repeat is 50 or less, the disease can have thousands of repeats. While Autosomal Dominant, Huntington's also demonstrates anticipation which is defined as the generation of additional repeats during gametogenesis. Basically, this disease gets worse with each generation, and, as the repeats get greater in number, the onset and severity of disease increases. Currently there is no treatment. Severe cases will show total brain atrophy; hydrocephalus ex vacuo is common.

Freidrich’s Ataxia

Like Huntington’s this is a disease of trinucleotide repeats, but is autosomal recessive. There is an expansion of the FXN gene in chromosome 9 consisting of a GAA repeat. FXN codes for a mitochondrial matrix protein, frataxin, involved in ion homeostasis. Because the defect is in the mitochondria, the clinical picture is not only from the neurologic system, but from other organ systems including spinal ataxia (have unstable gait and difficulty reaching out to an object) though cardiomyopathy, diabetes, and other organ system involvement can be found. There will be atrophy of peripheral nerves, dorsal roots, posterior columns, and cerebellar peduncles from the degeneration of neurons and axons able to be seen in both gross and micro. Occurs in early childhood, wheelchair bound by age 5.
Ataxia-Telangiectasia

This is an **autosomal recessive** mutation of a gene that regulates the cell cycle, resulting in **ataxia** and **vascular dilation and proliferation**. These patients have a mutation in a gene that regulates the cell cycle that results in defective DNA repair. This is a poorly characterized disease pathogenetically, but they do show ataxia, peripherally neuropathy, vasodilation, and immunodeficiency (particularly B-cell). There is a cerebellar degeneration as well as degeneration of the substantia nigra, dorsal columns, and various, seemingly random association of cortical brain structures.

Amyotrophic Lateral Sclerosis (ALS)

There are two forms: the sporadic and familial. Sporadic ALS is caused by **TDP-42 deposition** in neurons. Familial ALS is an **autosomal dominant** mutation of **superoxide dismutase** gene on chromosome 21, which produces a toxic protein from the mutated superoxide dismutase. This is a disease of both the **upper** and **lower motor neurons**. If there is primarily lower motor neuron involvement there is **muscle weakness** (early) and eventual **atrophy** with **areflexia**. If there is upper motor neuron involvement, there will be **spasticity**, **hyporeflexia**, and **babinski signs**. If the patient lives long enough, atrophy and paralysis dominate. In the final stages of the disease, **dementia** is possible. **Death** occurs within **5 years** from **diaphragmatic paralysis**.

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TUMORS

Astrocytomas: Glioblastoma Multiforme + Pilocytic Astrocytoma Oligodendrocytoma
Ependymoma Meningioma Medulloblastoma Schwanomma Craniopharyngioma

Tumors, like Degenerative Diseases, is a massive section in Robbins. We have chosen to include only the higher yield diseases found in BRS, Rapid Review, Kaplan, and Baby Robbins. There were over 20 tumors (40 with subtypes) to learn, far more than the two hours it got in lecture (presentation and cases).

Let’s start with epidemiology. **Half of all tumors** of the CNS are metastatic, usually occurring in the grey-white junction. The other half are **primary malignant tumors**, accounting for only 2-3% of Cancer Related Deaths each year (so they are rare). The two that are most important to know are meningiomas and glioblastoma multiforme.

Clinically, when you have a cancer in your brain, you will get a headache worse in the morning and late at night, seizures, and focal symptoms from a mass effect. Because tumors grow in a limited space, they compress local structures, causing an increased intracranial pressure, herniations, and obstructive / noncommunicating hydrocephalus.

A **primary tumor will kill the patient before metastasizing** so will always be found as a single mass within the brain. A **secondary, metastatic tumor** in the brain will present with **multiple small nodules** distributed randomly throughout the brain. Because tumors of the brain kill the patient prior to metastasis, malignancy is a bit more challenging (since metastasis is the primary manner in which grade is determined), and relies more on **invasiveness, anaplasia**, and being **poorly circumscribed**.

**Astrocytoma** is derived from astrocytes. These tumors stain with a marker called GFP, a marker for glial cells. When you look an astrocyte, they have ill-defined borders. There are two kinds, fibrillay and pilocytic. **Fibrillary Astrocytomas** are based on grade, where grading is important for both prognosis and treatment. Grades are determined by atypia, mitosis, necrosis, and vascular endothelial hyperplasia. The lower the grade, the less malignant the tumor. Grades 1-2 are well differentiated. Grade 2 is anaplastic. The one you must absolutely know is grade 4, also called glioblastoma multiforme (super high-yield cancer). It is the **most common CNS primary malignancy**, and the **most lethal** (death within 1 year of diagnosis). Usually occurring with the **white matter**, it often **crosses the corpus callosum**. It is **poorly demarcated**, are difficult to resect, and produces a **ring enhancing lesion** on MRI. There is marked nuclear atypia, multiple mitoses, central necrosis, and vascular endothelial hyperplasia. A characteristic finding under the microscope is **pseudopalisading necrosis**: hyperchromatic nuclei line up around the central area of necrosis. Blood vessels proliferate so much that it looks like a glomerulus, giving rise to glomeruloid formations. A pilocytic astrocytoma is a **benign astrocytoma** occurring in kids. As a general rule, primary malignant tumors occur below the tentorium cerebelli in kids and above for adults. So, you will look for this lesion below the tentorium, within the **posterior fossa**. They have a characteristic appearance on gross, CT, and MRI, which tend to be **cystic mass with a mural nodule** on the edge of the cyst. Under the scope you will see **spindle shaped astrocytes** that are often rich in Rosenthal fibers within astrocytes.

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Oligodendroglioma is a cancer of oligodendrocytes, commonly occurring in adults. This is also a white matter lesion that manifests with seizures. This is identified by histology, demonstrating a fried-egg appearance (major buzzword for this block) created by a central nucleus with a region of clearing around the nucleus. The blood vessels, which is typically not a classic image, have a prominent capillary network in a “chicken-wire pattern.” These are slow-growing tumors that allow long survival (5-10 years), though often recur after resection.

Ependymomas are the tumors of the ependymal cells that line the ventricular spaces. In kids, ependymomas are commonly seen in the 4th ventricle (kids = posterior fossa) while in adults, ependymomas are commonly seen in the lateral ventricles (adults = anterior fossa). These are well-circumscribed papillary tumors growing inside the ventricle. A characteristic histologic finding is ependymal rosettes, cells that are organized around a central lumen. These tend to present with obstructive hydrocephalus, recur after resection, and can degenerate into high-grade tumors.

Meningiomas are one of the most common tumors occurring in adults, and are highly Board-Relevant. It originates from meningotheial cells of the arachnoid. It is usually adults who get it, women more often than men, and it is a tumor attached to the dura in the subdural space. This does not invade the brain but pushes in on the brain, generating focal symptoms and seizures. Since it does not invade, complete resection is curative. Under the microscope, you will see spindle shaped cells forming a whirling pattern. In the center of the whorl is a dark purple nodule of calcification that tends to form layers, called psammoma bodies (“p” is silent).

Primitive Neuroectodermal Tumors (PNET) are highly undifferentiated tumors originating from a primordial neural source. Their name depends on the location. Retinoblastoma (found in the retina) was a tumor already discussed in pathology while medulloblastoma (found growing inside the CSF, starting in the cerebellum, potentially embolizing to the spinal cord) was talked about in our Neuro Pathology Block. All PNETs share some characteristics: (1) they develop in children, (2) they are highly aggressive but respond to chemo (don’t give retinoblastoma radiation!), (3) have round, blue tumor cells.

Schwannomas are tumors of Schwann cells and are derived from neural crest cells. They are most often found on the 8th cranial nerve, where they are termed acoustic neuromas, manifesting as hearing loss and tinnitus. Under histology there are spindle shaped cells with areas of hypercellularity (Antoni A) and hypocellularity (Antoni B) with regions of Verocay Bodies (parallel rows of cancer cells). These tumors have the S-100 marker. These tumors respond well to resection.

Craniopharyngioma usually arises of rests of odontogenic epithelium right next to the pituitary. You probably know this better as remnants of Rathke’s Pouch. These are cystic lesions usually occurring in kids. Since they are next to the pituitary, they may impinge on the optic chiasm, creating bilateral hemianopsia. Good news is that these are benign, but may recur after resection.

CNS Lymphoma is typically a B cell proliferation within the CNS, a non-Hodgkin’s Lymphoma. This is most often associated with Immunocompromise such as in AIDS patients. The Epstein Barr Virus is commonly implicated. So, if you question/vignette has a tumor and has AIDS, its probably CNS Lymphoma.
Epilepsy is a disease of the brain in a patient who has had at least one seizure and has a cerebral predisposition to have another. You can see these predispositions on EEG or even MRI. Seizures do not equal epilepsy (an OD of cocaine can cause a seizure, but there is nothing in the brain that says that patient will have another one).

Seizure is a clinical neurological event characterized by a change in behavior, sensation, or cognition associated with hypersynchronous cerebral discharge (large spike EEG).

Status Epilepticus is one long seizure or a series of seizures without regaining consciousness that lasts greater than 20 minutes. Any seizure that lasts more than 5 minutes should be treated as status. Most seizures are 3 minutes max. If it lasts for 5 minutes the chances that it will progress to status is exponentially increased. Status causes permanent brain damage.

Generalized Seizures have complete brain involvement. There is a loss of consciousness. This loss of consciousness may be so brief that the patient cannot even tell it happened. The typical seizure that we all think about is the tonic-clonic seizure where the patient starts rigid for a second, then goes into constant spastic episodes jerking all over the place as depicted on TV. There can be clonic or tonic seizures on their own, such as kids that must wear football helmets (they get tone for a brief instant, tighten up, lose consciousness, and fall over). Absence Seizures are clinically significant and difficult to pick up. These are the “bad kids” that “don’t pay attention” in school. The seizure is brief, without a post-ictal state, with maintenance of posture that lasts only 2-3 seconds. These patients suffer “jumping sentence syndrome” where the teacher will be talking about one thing, then suddenly be at the other end of the room talking about something else. Myoclonic Seizures are rapid jerking movements, sort of like when you are awakened from almost-sleep because you pictured yourself trip and fall. You weren’t quite asleep yet, but you weren’t fully awake, then your leg kicks or your arm jerks? Yeah, imagine that, but not asleep.

Partial Seizures have incomplete brain involvement. There is no complete loss of consciousness, though there is a grade of “preservation.” Simple Partial Seizures are localized to only a very small region of the brain. In fact, a surface EEG may not even detect the seizure, nor will the patient necessarily be aware of...
it. Classic examples are déjà vu, olfactory/auditory/visual hallucinations, and auras. However, if you placed deep brain electrodes you would detect some change. These are capable of spreading to become complex partial or even generalized seizures. Complex Partial Seizures do have a change in consciousness but not a loss. These are usually characterized by automatisms (lip smacking, staring spells, button playing). These last 30 seconds and up to two minutes. There is amnesia of the event.

Post-ictal is a state after a complex partial or after a generalized seizure characterized by confusion, sleepiness, and/or headache. They basically are coming out of their loss of consciousness and going into recovery. If you look at the EEG, you will see a generalized slowing of the background. This is caused by an innate brain mechanism to turn off the seizures (mechanism to be determined). If they do not come out of the post-ictal state prior to engaging in another seizure, we still consider that status.

Types of Epilepsy

There are not just different types of seizures, but also different types of epilepsy. Do not get confused, and do not think that seizures are epilepsy. The type of epilepsy is actually quite important. The type of epilepsy determines the treatment and prognosis of the disease.

Type 1 Epilepsy is idiopathic generalized epilepsy. Current research indicates that they are probably genetic involving problems with the receptors or channels. These are usually generalized onset and produce Absence seizures, Juvenile Myoclonic Epilepsy, and GTC seizures upon awakening. Absence we already talked about. JME is a seizure you get in the morning, with myoclonus, usually following sleep deprivation and alcohol use. GTC Seizures are JME, only without the myoclonus. Diseases are generally well controlled, but they usually never go away (Absence is best at 50% decrease after puberty).

Type 2 Epilepsy is idiopathic focal epilepsy. This is also probably genetic, but right now remains unknown. Benign Rolando Epilepsy is a childhood seizure disorder that goes away by age 17. It has a characteristic EEG with centrotemporal spikes. The typical history is night time twitching, usually confined to one side of the body, and it may digress into generalized seizures.

Type 3 Epilepsy is the generalized onset structural lesions that are the catastrophic epilepsies of childhood. They are either general or multifocal structural abnormalities. They are commonly associated with mental retardation (thus the name catastrophic). Examples, that you do not have to know for the Board’s or Tulane’s Exam, but you should be aware of, are West’s Syndrome, Lennox-Gastaut. Very poor prognosis.

Type 4 Epilepsy is the focal onset structural lesions that are the most common adult-onset epilepsy. These are frontal lobe structural lesions (most common), temporal lobe structural lesions (next common), then other diseases we have already learned about (cavernous hemangiomas, AV malformations, tumors, etc.). These are the obvious structural lesions that we think about when we do imaging in our course. 66% will be controlled by seizure medications.

Treatments include meds from the pharm section, vagal nerve stimulation (for unknown reasons), and resection of epileptic area.