Neurological Disorders

Causes of Brain Damage and Disease
Brain Tumors

• neoplasm or “new growth”

• a tumor is uncontrolled growth (cell division) of a mass of tissue that serves no useful purpose

• signs and symptoms

• headache, vomiting, edema of the optic disk (due to increased intracranial pressure)

• seizures and focal signs (due to irritation and compression of localized brain tissue)

• signs or symptoms may result from problems arising far from the site of the tumor - for example, if a cranial nerve on the bottom of the brain is being compressed by a tumor on the top of the brain
• brain tumors can form on any tissue in the brain, including blood vessels, endocrine cells, the pineal gland, etc.

• but neurons very rarely become cancerous because they are no longer undergoing cell division
Meningioma

History

This 65 year-old female has a 2-year history of morning headache and progressive right upper limb weakness. She woke up this morning obtunded, and did not initially respond to her husband’s cries. She screamed to her husband that she could not see anything to her right, and that her left arm and leg were very weak. At this point her husband rushed her to the nearest hospital.

(note: obtunded = mentally slowed or dulled)

Physical

The patient was remarkable for left lid ptosis, left-pupillary dilation, and failure of her left eye to constrict to light directly or consensually. Patient had bilateral lower limb weakness, with increased deep tendon reflexes on the left side, and a positive Babinski reflex on the left side. Papilledema was noted on fundoscopic exam. Visual confrontation testing revealed Homonymous hemianopia of the right side. Visual acuity was corrected to 20/20 with glasses.

(notes: left lid ptosis = drooping left eyelid
papilledema = swollen appearance at back of retina,
indicates increased pressure in the head)
Note: glioblastoma, the type of tumor that John McCain had, is a particularly aggressive form of astrocytoma.
Epilepsy
(Seizure Disorders)

(Quick overview. There is more information in the brain damage notes.)
• A seizure is an abnormal burst of high amplitude EEG spikes lasting from seconds to minutes.
• A convulsion is a violent sequence of uncontrollable muscle movements (caused by a seizure in the motor areas of the brain).

A grand mal seizure recorded from all EEG leads.
Etiology of Epilepsy

- Birth hypoxia-ischemia
- Hippocampal sclerosis
- Tumor
- Hamartoma
- Vascular
- Post traumatic
- Other: Infection, cyst, infarct, migrational disorder, tuberous sclerosis, cortical dysplasia,
Strokes

- cerebrovascular accidents or CVAs

- at one time called apoplexy

- loss of blood supply to an area of brain tissue due to:
  - cerebral hemorrhage (bleeding) - hemorrhagic stroke
  - cerebral ischemia (blockage of a blood vessel, thus depriving tissue of oxygen and glucose) - ischemic stroke
Aneurysms leading to hemorrhagic stroke

aneurysm - abnormal widening or ballooning of an artery due to a weakness in the artery wall
Aneurysm on the anterior communicating artery (angiogram)
Aneurysm at the bifurcation of the basilar artery
**Ischemic (obstructive) stroke** - due to blockage of a blood vessel by a **thrombus** or an **embolus**

Acute, involving ischemic post fossa infarction posterior inferior cerebellar artery (PICA), MRI shows absent flow in proximal left vertebral artery. (MR Angiogram (MRA)).

**infarction** - tissue death due to loss of blood supply

**thrombus** - blockage forms on the spot (e.g., fat deposit or tumor

**embolus** - travels in blood and lodges in blood vessel
• signs of a stroke - mainly focal signs

• sudden numbness, weakness, dizziness, confusion, slurring of speech, headache

• severity or extent of impairment depends upon extent of damage in the brain

• prospect for recovery - depends upon extent of tissue damage, how rapidly treatment is obtained, and the patient’s ability to pay for physical therapy
Traumatic Brain Injury

- closed-head injuries
  - contusions - bleeding detected
  - concussions - damage is more subtle
- open-head injuries
  - skull fractures
  - penetrating injuries
Closed Head Injuries

- **contusion** - damage to blood vessels causes bleeding and **hematoma** (hemato, blood; oma, mass)

- results when the brain slams against the inside of the skull (and is “bruised”)

- **concussion** - temporary impairment in consciousness due to a blow to the head (75% of traumatic brain injuries)
Contusions at the base of the frontal lobes

reflections (ignore)
Closed Head Injuries: Coup and Contrecoup Injuries
Subdural hematoma - a mass of blood forming under the dura mater

* acute SDH - sudden, rapid onset after a head trauma, may be accompanied by sudden “roaring” headache, nausea, and projectile vomiting (burst aneurysm - “thunderclap” headache but usually no vomiting)

* chronic SDH - gradual, slow onset, may be asymptomatic for several weeks
Subdural hematoma revealed at autopsy (probably of the chronic variety)
Extradural (or epidural) hematoma

* outside the dura mater

* usually after a skull fracture

* usually rapidly expanding with arterial blood
Brain injury response depends on diction

Injured kids whose parents hear the word “concussion” spend less time in the hospital, go back to school and other activities earlier, and run greater risks to their cognitive health than do kids whose parents are told their child has sustained a “brain injury.”

The study, published Monday in the journal Pediatrics, tracked 268 kids admitted to a hospital in Ontario, Canada after a head trauma. Doctors there gave one-third of them a diagnosis of “concussion,” while the rest got some variant of traumatic brain injury, sometimes shortened to TBI.

In the days following their injuries, those with a diagnosis of concussion were 1½ times as likely to be discharged from the hospital as those with a “mild TBI” diagnosis — even though there was significant overlap between the two groups in terms of the severity of their injuries. There was a 2½ times greater likelihood that the kids diagnosed with “concussion” would go back to school early.

“Our study suggests that if a child is given a diagnosis of a concussion, the family is less likely to consider it an actual injury to the brain,” said the study’s lead author, Carol DeMatteo, an occupational therapist and childhood disability researcher.

“Concussions” not taken as seriously as “mild traumatic brain injuries.” But they do involve brain damage.
CTE = chronic traumatic encephalopathy, a degenerative brain disease resulting from repetitive brain injury.

Enhanced MRI of a patient 19 hrs. after a fall from about 6 ft., which resulted in unconsciousness and amnesia. The scan shows areas where there was damage to the meninges.

Scan showing tissue volume loss (death) after a single concussive episode. Source: Radiological Society of North America (sciencedaily.com).

Concussion and depression in retired football players.

CTE = chronic traumatic encephalopathy, a degenerative brain disease resulting from repetitive brain injury.
Chronic Traumatic Encephalopathy (CTE)

- a degenerative condition in the brain resulting from repeated head injuries (including repeated concussive episodes)
- contact sports such as football, ice hockey, pro wrestling, rugby
- symptoms usually begin to appear 8-10 yrs after an athlete experiences repeated mild TBI (although frequent subconcussive episodes may be sufficient)
- early symptoms include attention deficit disorder, confusion, disorientation, dizziness, headaches
- later symptoms include memory loss, social instability, impulsive behavior, poor judgment
- can progress to movement disorders, speech impediments, tremors, deafness, dementia
- domestic violence (including shaken baby syndrome), head banging, military veterans who were in war zones
- the pathology in the brain is similar (but not identical) to what happens in Alzheimer’s disease - frontal and temporal lobes especially hard hit
Chronic Traumatic Encephalopathy (CTE)

- professional athletes are currently the largest demographic group with CTE
- first studied in professional boxers - dementia pugilistica or “punch drunk syndrome” (1920s)
- lately, interest has centered around professional American football

Original Investigation
July 25, 2017

Clinicopathological Evaluation of Chronic Traumatic Encephalopathy in Players of American Football

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Key Points

Question  What are the neuropathological and clinical features of a case series of deceased players of American football neuropathologically diagnosed as having chronic traumatic encephalopathy (CTE)?

Findings  In a convenience sample of 202 deceased players of American football from a brain donation program, CTE was neuropathologically diagnosed in 177 players across all levels of play (87%), including 110 of 111 former National Football League players (99%).

Meaning  In a convenience sample of deceased players of American football, a high proportion showed pathological evidence of CTE, suggesting that CTE may be related to prior participation in football.
CTE At A Glance

**Full Name:** Chronic traumatic encephalopathy

**Cause:** Repetitive mild traumatic brain injury

**Who’s affected:** Athletes in contact sports such as boxing, football, ice hockey, soccer, and wrestling; military veterans; victims of domestic abuse; headbangers

**Symptoms:** Memory loss, depression, suicidal thoughts, explosive or aggressive behavior, and in some cases, trouble walking or speaking

**Pathology:** Unlike in Alzheimer’s disease, in CTE, tau protein tangles first accumulate in the brain’s cortex. What also sets CTE apart from other brain disorders is that tau collects around blood vessels (above, left) and deep in the cortical sulci (above, right) of the brain.

**Treatment:** None

**Stage I:** Hot spots of tangled tau pop up in isolated areas of the cortex (black circle).

**Stage II:** Multiple hot spots of tangled tau appear in the cortical sulci, and tau begins to migrate.

**Stage III:** Tau hot spots begin to blend with one another. Tangles appear more diffusely throughout the ridges of the brain. Tau begins to collect in the hippocampus (involved in learning and memory) and amygdala (involved in decision making and emotions).

**Stage IV:** Dense tau tangles cover the brain’s cortex and appear in most other regions, including the spinal cord.

**NOTE:** Stages proposed by Ann C. McKee, Boston University, still need to be validated by other research groups. Based on Brain 2013, DOI: 10.1093/brain/awt307.
Open Head Injuries

- skull fractures
- penetrating injuries of the head such as...
  - gunshot wounds
- etc.
Skull Fracture

Bleeding from the ears or nose and “raccoon eyes” indicate a fracture to the base of the skull.

basilar skull fractures
linear skull fractures

depressed skull fractures with underlying brain damage
An old gunshot wound
Phineas P. Gage

Horrible Accident.—As Phineas P. Gage, a foreman on the railroad in Cavendish, was yesterday engaged in tamping for a blast, the powder exploded, carrying an iron instrument through his head an inch and a fourth in circumference, and three feet and eight inches in length, which he was using at the time. The iron entered on the side of his face, shattering the upper jaw, and passing back of the left eye, and out at the top of the head.

The most singular circumstance connected with this melancholy affair is, that he was alive at two o'clock this afternoon, and in full possession of his reason, and free from pain — Ludlow, Vt., Union.

Newspaper report: Boston Post

The tamping iron was 3 feet 7 inches long and weighed 13 1/2 pounds. It was 1 1/4 inches in diameter at one end (not circumference as in the newspaper report) and tapered over a distance of about 1-foot to a diameter of 1/4 inch at the other. The tamping iron went in point first under his left cheek bone and completely out through the top of his head, landing about 25 to 30 yards behind him. Phineas was knocked over but may not have lost consciousness even though most of the front part of the left side of his brain was destroyed. Dr. John Martyn Harlow, the young physician of Cavendish, treated him with such success that he returned home to Lebanon, New Hampshire 10 weeks later.

www.deakin.edu.au/hbs/GAGEPAGE/

A common but erroneous museum exhibit.
Computer simulation of Gage’s injury
Photos of Gage’s Skull

(In the medical museum at Harvard)
“Well, here’s work enough for you, Doctor.”

-- Phineas Gage; September 13th, 1848.
A portrait of Gage with the tamping iron discovered in 2009.
THE WORLD'S WONDER

PHINEAS P. GAGE,
A native of LEBANON, N. H., wouls announce to the citizens of CONN.,
that on
Tuesday Evening,
AT
RUMFORD HALL,
He will exhibit to them, in his own person, one of the
Greatest Wonders of the World!

Nothing less than a Man who has had a
Huge Iron Bar, which he will Exhibit,
Forced through his Head from chin to crown; has had, in fact,
HIS BRAINS BLOWN OUT!

Partially, and who is still living, breathing, and in full possession of his health and faculties. It is a case unparalleled in the annals of Surgery, and has excited the astonishment of the most eminent members of the Medical Faculty in the country. On the 15th of September, 1848, Mr. GAGE was engaged in blasting a rock, in Cavendish, Vt., on the line of the Rutland and Burlington Railroad, when a premature explosion took place, which forced an
IRON BAR!
Three Feet seven Inches long, one Inch and a quarter in diameter, and weighing thirteen Pounds and a quarter, which he was using to tamp down the charge, completely
THROUGH HIS HEAD!

And high into the air, falling a distance of some rods from the victim, besmeared with his blood and brains. The Bar in question, which Mr. GAGE will exhibit, entered on the outside of the lower jaw, half way from the chin to the angle, passing obliquely upwards under the zygomatic process of the upper jaw, back of the left eye, which it forced out, and came out at the top of the Head, near the centre of the back part of the frontal bone. This is one of the most interesting and
WONDERFUL CASES

In the annals of Surgery, such cases heretofore always terminating fatally.

He has since been examined by a large number of the most accomplished Medical Men in the State, and appears to be in as fine a state of health, and with all the faculties of the brain, as they have ever seen them. The President of the Board of Directors of the Medical College of Vermont, Dr. BRADBURY, has been Examined by several of the celebrated Medical Men of the Country, and the report of the President, Dr. McCudden, is that Mr. GAGE is in fine health.

TICKETS, 12 1/2 Cents; To be had at the Door.
• most of what we think we know about the psychological effects on Gage of his injury cannot be verified

• the “American crowbar case” - first case to suggest that brain damage could result in changes in personality and complex behavior

• Gage died May 21, 1860, in San Francisco

• Gage’s doctor didn’t publish details of Gage’s mental changes until 1868 (20 years after the original injury)
Neurotoxins
Heavy Metal Poisoning

lead poisoning symptoms
* tingling in hands and feet
* abdominal pain
* constipation
* headache
* irritability
* memory problems
* sterility

mechanisms of action
* interferes with calcium, iron, and zinc in the body
* creates free radicals that damage membranes and interferes with DNA transcription
* demyelination of neurons
* many others
* gets into the brain and neurons by hijacking calcium transporters
Carbon Monoxide Poisoning

Hemoglobin carries oxygen and carbon dioxide

Carbon monoxide binds very tightly to hemoglobin

Oxygen and carbon dioxide can no longer be carried
MPTP

Nature Reviews Neuroscience 4, 365-375 (2003); doi:10.1038/nrn1100
TARGETING PROGRAMMED CELL DEATH IN NEURODEGENERATIVE DISEASES
15.16 ABNORMAL BRAIN DEVELOPMENT ASSOCIATED WITH FETAL ALCOHOL SYNDROME A brain from an FAS infant (left) compared to a brain from a normal infant of the same age (right). The FAS brain shows microcephaly, cerebral cortical gyri, and the presence of a sheet of ectopic (abnormally migrated) glia over the surface of the left hemisphere. (Courtesy of S. Clarren.)
Effect of Alcoholism on the Adult Brain

Women

Men

More makes less. MRI scans of the brains of alcoholic men and women and controls show striking differences in brain shrinkage (female alcoholic, top left; male alcoholic, bottom left; controls, right).
Heavy Drinking in College Students Is Associated with Accelerated Gray Matter Volumetric Decline over a 2 Year Period

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Background: Heavy and/or harmful alcohol use while in college is a perennial and significant public health issue. Despite the plethora of cross-sectional research suggesting deleterious effects of alcohol on the brain, there is a lack of literature investigating the longitudinal effects of alcohol consumption on the adolescent brain. We aim to probe the longitudinal effects of college drinking on gray matter change in students during this crucial neurodevelopmental period.

Methods: Data were derived from the longitudinal Brain and Alcohol Research in College Students (BARCS) study of whom a subset underwent brain MRI scans at two time points 24 months apart. Students were young adults with a mean age at baseline of about 18.5 years. Based on drinking metrics assessed at both baseline and followup, subjects were classified as sustained abstainers/light drinkers (N = 45) or sustained heavy drinkers (N = 84) based on criteria established in prior literature. Gray matter volumetric change (GMV-c) maps were derived using the longitudinal DARTEL pipeline as implemented in SPM12. GMV-c maps were then subjected to a 1-sample and 2-sample t-test in SPM12 to determine within- and between-group GMV-c differences in drinking groups. Supplementary between-group differences were also computed at baseline only.

Results: Within-group analysis revealed significant decline in GMV in both groups across the 2 year followup period. However, tissue loss in the sustained heavy drinking group was more significant, larger per region, and more widespread across regions compared to abstainers/light drinkers. Between-group analysis confirmed the above and showed a greater rate of GMV-c in the heavy drinking group in several brain regions encompassing inferior/medial frontal gyrus, parahippocampus, and anterior cingulate. Supplementary analyses suggest that some of the frontal differences existed at baseline and progressively worsened.
Summary of Neurotoxins

- **ion channel inhibitors** - tetrodotoxin, conotoxins, various toxins derived from algae and bacteria
- **inhibitors of neurotransmitter release** - botulinum toxin, tetanus toxin
- **neurotransmitter receptor blockers** - bungarotoxin (from snake venom), curare
- **irreversible neurotransmitter receptor stimulators and substances inducing neurotransmitter release** - black widow spider venom, anatoxin ("Very Fast Death Factor") produced by cyanobacteria
- **substances that attack the cytoskeleton** - arsenic
- **substances that interfere with or "hijack" calcium transport** - lead
- **blood-brain barrier inhibitors** - aluminum, mercury
- **substances with multiple effects** - alcohol
Developmental Disorders

- brain damage caused by toxic chemicals such as heavy metals and alcohol
- effect of neglect
- genetic disorders
  - phenylketonuria (PKU) - one of 100 or more metabolic disorders that can affect brain development
  - Tay-Sachs disease
  - Down syndrome
The child on the right was raised in an orphanage in Eastern Europe.
• PKU - an **autosomal recessive** trait
  • both parents must be carriers of the recessive allele
  • the abnormal allele is part of the gene that codes for the enzyme phenylalanine hydroxylase
  • if this enzyme is abnormal, phenylalanine accumulates in the body and is converted to substances that damage the developing brain (by preventing normal myelinization)
• PKU (cont.)

Phenylketonuria (PKU)

Dietary Protein
Tissue Protein
Phenylalanine
Phenylpyruvate
Phenylketonuria (PKU)

Phenylalanine Hydroxylase
Tyrosine

Tetrahydrobiopterin
Dihydrobiopterin
Oxidation
Protein Synthesis
Catecholamines
Thyroxine
Melanin

Phenylalanine hydroxylase

myelin sheath
• PKU (cont.)

• abnormal brain development can be prevented by restricting phenylalanine in the diet while the brain is developing
PKU (cont.) - if left untreated...

Phenylketonuria (PKU): Clinical findings

- Severe brain damage, progressive motor-mental retardation
- Spasticity
- Paralysis
- Convulsions
- Self-mutilation
- Light colored skin and eye (yellow hair, blue eyes; tyrosine deficiency)
- Mouse-like odor in urine and sweat.
• Tay-Sachs disease

• due to a mutation of the HEXA gene on chromosome 15

• there are several unrelated mutations of this gene

• a person who inherits two of them will have Tay Sachs - autosomal recessive trait
• Tay-Sachs (cont.)

• HEXA mutations are rare and are seen frequently only in certain genetically isolated populations

• Ashkenazi Jewish people - first discovered

• Cajuns of southern Louisiana

• French Canadians in SE Quebec
• Tay-Sachs (cont.)
  • a cherry red spot on the retina is diagnostic
  • occurs most often in infants - infantile Tay-Sachs disease (there are other forms in juveniles and adults that are much rarer)
  • symptoms begin to occur after about 6 months of normal development
  • abnormal startle reaction to loud noises, listlessness, muscle stiffness
  • progressing to blindness, deafness, paralysis, and usually death by the age of 4
• Tay-Sachs (cont.)

• due to an inability to biodegrade and dispose of waste gangliosides (named because they were first discovered in certain cells of the nervous system)

• components of the cell membrane involved in signaling

• as the waste accumulates, the cells swell, and eventually the entire brain swells

• there is no treatment for Tay-Sachs
• Down syndrome - a congenital (not inherited) genetic abnormality in which chromosome 21 is tripled (trisomy 21)
• results in abnormal brain development and retardation
• in adults the brain undergoes a degenerative disorder similar to that in Alzheimer’s disease

Tim Harris
* born with Down syndrome
* owns and operates his own restaurant
• Down syndrome (continued)

• 6000 births/year in U.S.
• life expectancy 50-60 years in developed countries with proper health care
• average adult IQ=50, but even in high functioning Down cases, cognitive decline is almost inevitable by age 60, leading eventually to dementia
• other medical problems
  • congenital heart disease: 40%
  • sterility (males): nearly 100%
  • speech problems (stuttering, etc.): 50%
  • hearing and vision disorders: >50%
• findings in the brain (MRI or autopsy)
  • enlarged ventricles and lower overall brain volume
  • smaller left amygdala and hippocampus
  • amyloid plaques in nearly 100% of cases by age 40
• mechanism behind neurological problems - ???
Degenerative Diseases

Absence of substantia nigra in a Parkinsonian brain
Spongiform Encephalopathy
(a once almost unheard of brain disease--until the 1990s)
The spongy state is typically observed in the deep part of the cerebral cortex (LFB-HE, high power). Spongiform encephalopathy represents a histological feature of prion disease.
- mad cow disease (bovine spongiform encephalopathy)
- due to a change in the way cattle feed was rendered in Great Britain in the 1970s, infective agents from sheep and cattle tissue found their way into cattle feed
- the result was a “new” spongiform encephalopathy in beef cattle that was probably transmitted from sheep (1980s)
- eventually, it was shown to be transmissible to humans (new variant Creutzfeldt-Jakob disease or vCJD, 1990s)
• prion diseases

• the prion or “protein only” hypothesis is now widely accepted (the “slow virus” hypothesis is no longer popular)

• a prion is an abnormally shaped protein (see the Brain Eater video for details)

• Creutzfeldt-Jakob Disease (CJD) is the best known one

  • jerky movements, hallucinations, mutism, blindness, dementia

• others: variant-CJD, Kuru, fatal familial insomnia
Prion diseases of humans and animals

- Scrapie in sheep and goats
- Transmissible mink encephalopathy
- Chronic wasting disease in deer & elk
- Bovine spongiform encephalopathy
- Feline spongiform encephalopathy
- Kuru
- Creutzfeldt-Jakob disease
- Gerstmann-Straussler-Scheinker disease
- Fatal familial insomnia
- Variant Creutzfeldt-Jakob disease
• prion diseases
  • the prion protein (PrP) - a normal protein that we all have (a membrane protein, exact function still unknown)
  • abnormal folding of the protein renders it “contagious” to normal prion proteins
  • since the infective agent does not contain genetic material, it cannot be “killed” by normal sterilization or disinfectants or antibiotics or antivirals
  • all known prion diseases affect the structure of the brain - all are incurable
A Delicacy in St. Louis
Parkinson’s Disease

• one of the most common neurodegenerative disorders

• Parkinson’s disease and Alzheimer’s disease are the two most common neurodegenerative diseases in the elderly

• caused by degeneration in the nigrostriatal dopamine system, which originates in the substantia nigra of the mesencephalon

• most cases are of unknown origin (idiopathic), but probably environmental
there are two (three) dopamine systems in the brain

the nigrostriatal system originates in the substantia nigra of the midbrain and terminates in the striatum (caudate nuc. and putamen) of the telencephalon
PET scan showing diminished DA in striatum

Normal

Parkinson's Disease
• symptoms (signs)
  • motor impairment (primarily)
    • tremor and rigidity
    • resting tremor in the hands
    • “pill rolling”
  • masklike face
  • stooped posture, short, shuffling gait, with freezing
  • difficulty initiating voluntary movements
• standard treatment is with l-dopa
• a precursor of dopamine in the brain
• this eventually stops working when the number of DA neurons remaining is low
• side effects
  • hallucinations
  • abnormal choreiform and athetotic movements, which are uncontrollable
• various surgical procedures have also been tried - lesions in the globus pallidus
Other Causes of Tremor

Resting tremor occurs when the muscle is relaxed, such as when the hands are resting on the lap. With this disorder, a person’s hands, arms, or legs may shake even when they are at rest. Often, the tremor only affects the hand or fingers. This type of tremor is often seen in people with Parkinson’s disease and is called a “pillrolling” tremor because the circular finger and hand movements resemble rolling of small objects or pills in the hand.

Action tremor occurs with the voluntary movement of a muscle. Most types of tremor are considered action tremor. There are several sub-classifications of action tremor, many of which overlap.

- **Postural tremor** occurs when a person maintains a position against gravity, such as holding the arms outstretched.
- **Kinetic** tremor is associated with any voluntary movement, such as moving the wrists up and down or closing and opening the eyes.
- **Intention tremor** is produced with purposeful movement toward a target, such as lifting a finger to touch the nose. Typically the tremor will become worse as an individual gets closer to their target.

![Tremor Flowchart](https://via.placeholder.com/150)
Essential Tremor Test
7 Oct 2019

Left Hand

Right Hand
Huntington’s Disease

• genetic in origin - autosomal dominant

• symptoms begin to appear in middle age
  • fidgetiness at first

• evolving into uncontrollable jerky limb movements - choreiform movements

• progressive dementia - loss of cognitive functions (memory, thinking, language, judgment)

• death - it is always fatal and there is no cure (although there is a test!)
inheritance pattern is different from that of recessive disorders like PKU.

Most famous case was no doubt folk singer Woodie Guthrie, whose famous son was __________? (one of five children, two affected)
Folk-Singer Guthrie Dies

15-Year-Old Illness Finally Kills Him

NEW YORK (AP) — Balladeer Woody Guthrie, America’s folk poet of the downtrodden, their singing, guitar-playing apostle of self-esteem, died Tuesday, foredoomed 15 years ago by an encroaching illness that robbed him of his voice. He was 55.

“[I] want to thank you for making this world a beautiful place,” an unidentified admirer once wrote him. “Your songs make people think about the good that is within them.” Many persons heard Guthrie’s songs without ever knowing his name. Among those who have recorded them are Bing Crosby, Harry Belafonte, Frank Sinatra and Peter, Paul and Mary. He wrote more than 1,000 of them, the best known being “This Land Is Your Land.”

“I hate a song that makes you think you’re not any good,” Guthrie said. “I hate a song that makes you think that you are just born to lose, no good to nobody, no good for nothing. I am out to fight those kinds of songs to my very last breath of air and my last drop of blood. I am out to sing the songs that make you take pride in yourself and in your work.”

GIVEN AWARD

In 1966, Interior Secretary Stewart L. Udall presented Guthrie with a federal government award and called him a poet of the American landscape.

For the past 15 years, Guthrie had been slowly, hopelessly dying of an hereditary disease called Huntington’s chorea, an affliction that progressively destroyed his muscular coordination. The disease had killed his mother.

The end came at Creedmoor State Hospital in Queens, where Guthrie had lost the voice that was more fervid than faultless.

The short, lean Guthrie, with weather worn, unsmiling face and wiry, bushy hair, was born in Okemah, Okla., one of five children. As a boy, he sang and performed jigs for pennies in the streets. He dropped out of school in the 10th grade.

In his teens, he struck out on his own, traveling, working at odd jobs, playing the harmonica in barber shops and pool halls. An uncle taught him the guitar, and he played and sang at country dances, rodeos and carnivals.

TENDER SONGS

It was during this period that Guthrie began making up his own songs, which evidenced tenderness, humor and an affinity for the working class.

During the depression, Guth-

Times-Picayune (New Orleans) reported his death on 3 Oct 1967.
• finding in the brain - extensive degeneration in the caudate nucleus and putamen

• later progressing into the neocortex
Multiple Sclerosis

an autoimmune demyelinating disease

sclerosis - hardening of tissue
Multiple Sclerosis - Symptoms

• numbness or weakness in one or more limbs, typically occurring on one side of the body at a time
• partial or complete loss of vision, typically in one eye at a time, often with pain upon eye movement
• prolonged double vision
• tingling or pain
• electric shock sensations that may occur with certain neck movements
• tremor, lack of coordination, unsteady gait
• slurred speech
• fatigue
• dizziness
• bowel and bladder problems
Multiple Sclerosis

- most common in northern latitudes - one of the most common neurological diseases north of about 45 degrees latitude

- relapsing-remitting disease course (most people)
  - remissions can last months or years

- 60-70% of these cases will eventually become steadily progressive - secondary progressive MS

- in a minority of cases there is a gradual onset and steady progression - primary progressive MS
Main symptoms of
Multiple sclerosis

Central:
- Fatigue
- Cognitive impairment
- Depression
- Anxiety
- Unstable mood

Visual:
- Nystagmus
- Optic neuritis
- Diplopia

Speech:
- Dysarthria

Throat:
- Dysphagia

Musculoskeletal:
- Weakness
- Spasms
- Ataxia

Sensation:
- Pain
- Hypoesthesias
- Paraesthesias

Bowel:
- Incontinence
- Diarrhea or constipation

Urinary:
- Incontinence
- Frequency or retention
Multiple Sclerosis

- cause - unknown other than that it is an autoimmune disease that attacks myelin in the CNS
- risk factors
  - can occur at any age
  - women are about 2X as likely to develop MS as men
  - family history of MS
  - race - northern Europeans are at highest risk
  - climate - more common in temperate climates
  - cigarette smoking increases the risk of a relapse
Amyotrophic Lateral Sclerosis (ALS)

- Lou Gehrig’s disease
- strikes motor neurons in the spinal cord and cranial nerves (aka, motor neuron disease)
- symptoms - spasticity, exaggerated stretch reflexes, progressive weakness, muscle atrophy, fasciculations, death (within 5-10 yrs)
- is this an upper motor neuron or lower motor neuron disease?
- 10% of cases are genetic, 90% are sporadic (idiopathic)
- it is unclear whether head injuries (such as multiple concussions) are a risk factor
Another famous case is the physicist Stephen Hawking, who was diagnosed in 1963 at the age of 21. At that time, he was given 2-3 years to live.

* first diagnosis is more typically around age 60 (40-70)
* usual lifespan after diagnosis is 3-5 years
* usual cause of death is respiratory failure
Alzheimer’s Disease
Alzheimer’s Disease

- most common cause of dementia (loss of cognitive abilities) in the elderly (70-80%), BUT NOT THE ONLY ONE!

- occurs (estimated) in 10% of people over 65 and 50% of people over 85

- there has been discussion of the fact that AD behaves like a prion disease, but...

  - you CANNOT get AD from an afflicted relative

  - CJD is sometimes mistaken for AD
Alzheimer’s Disease

• there is no definitive test for this disease, and there is no treatment (yet)

• usually strikes in people over 70, but there is also an early onset form that may occur as young as 40 and is probably genetic in origin

• a history of strokes as well as other forms of brain damage such as concussions is the leading risk factor (aside from age)
Alzheimer’s Disease

- progressive degenerative disease progressing generally as follows:
  - depression - often unrecognized as a sign
  - cognitive decline, esp. memory
  - deterioration of speech
  - personality changes
  - motor impairment
  - death
Alzheimer’s Disease

- findings in the brain
- general cell loss throughout the cortex - up to 1/3 of brain weight may be lost!

PET scans showing glucose utilization
Alzheimer’s Disease

- **neurofibrillary tangles** - intracellular, due to degeneration of microtubules resulting in tangled clumps of tau protein
Alzheimer's Science Shocked by Discovery That Key Protein Behaves Like an Infection

Alzheimer's disease may spread though the brain like an infection, a new study has found. Most scientists agree that tau proteins are one of the main causes of Alzheimer's and now, for first time, researchers observed the protein in real-time as it spread throughout neurons in the brain. The finding may fundamentally change how we think about Alzheimer's disease, and in turn affect how we treat the disorder as well.

The findings published online in the journal, Brain appear to support the theory of transneuronal spread, IFL Science reported. Tau proteins normally aid in brain function, but can become defective or collapse and then form tangles, which may lead to the onset of Alzheimer's. The transneuronal spread theory suggests that the proteins spread just like an infection and areas with the largest build-up of proteins will then pass these on to the surrounding connections. While this idea has been shown in mice, this is the first time researchers have seen it happening in human brains.
Alzheimer’s Disease

- **amyloid plaques** - extracellular debris of dying cells mixed with amyloid protein
- these are not unique to AD but also occur in other disorders, such as Down syndrome, and even during normal aging
Alzheimer’s Disease - Myths

- Alzheimer’s disease is not fatal - false
- only old people get Alzheimer’s disease - false (there is an early onset form that appears to be hereditary)
- drinking out of aluminum cans or cooking in aluminum pots can cause Alzheimer’s - false (this was one of those 1970s scares, and it didn’t even require social media to spread!)
- aspartame causes memory loss - there is no credible evidence of this
- flu shots increase the risk of Alzheimer’s disease - the evidence from credible studies actually suggests that flu shots and other vaccinations decrease the risk of AD
- silver dental fillings increase the risk of Alzheimer’s disease - there is no credible evidence of this
- the progression of Alzheimer’s disease can be stopped - not at this time (but see video--they’re working on it!)
Other Dementias

- Lewy body dementia
  - associated with abnormal deposits in the brain of a protein called alpha-synuclein (Lewy bodies)
  - Lewy bodies are intracellular clumps of protein occurring in the cortex, limbic system, basal ganglia, and brainstem
  - also occur in Parkinson’s disease
- usually in people age 50 or older (but occasionally in younger people)
  - impaired cognition
  - sleep disorders (REM sleep behavior disorder)
  - visual hallucinations
  - problems with attention
  - rigidity and problems with walking and movement
  - effects in the autonomic nervous system - heart and gastrointestinal
  - mood changes such as depression and apathy
- progressive - lasting 5-8 years until death (on average, but 2-20 range)
- no cure
- Parkinson’s disease dementia is diagnosed when Parkinsonian symptoms occur well before the onset of the dementia
Other Dementias

- Fronto-temporal dementia
  - half a dozen different forms - originally called Pick’s disease, but that term is now reserved for one specific form
  - exact symptoms depend upon which form is occurring - but all are associated with degeneration in the frontal and temporal lobes
  - often difficult to differentiate from Alzheimer’s disease early on
  - onset is usually in middle to late adulthood (45-65) then progresses to death in 2-15 years - there is no cure

- common symptoms
  - changes in personal and social behavior (loss of social awareness, poor impulse control)
  - emotional changes such as apathy and blunting of emotions
  - various forms of aphasia (language disorders)
  - compulsions
  - changes in eating behavior such as binge eating and eating inedible objects, cravings for sweets and carbohydrates are common
  - changes in executive functions (judgment, planning)
  - deficits in short-term memory
  - long-term memory, perception, and spatial skills are usually spared
  - there is evidence of genetic predisposition - particularly strong in some forms of the disorder
Infections

- **meningitis** - an infection (or inflammation) of the meninges
- **encephalitis** - an infection (or inflammation) of the brain tissue
Meningitis - infection of the meninges

- college students living in dorms are at increased risk

GEORGIA

CDC issues warning on meningitis at colleges

ATLANTA | College freshmen living in dorms should be told about the risks of contracting meningitis, and a vaccine should be made available to those who want it, the government said Thursday.

The recommendation was issued by the Centers for Disease Control and Prevention.

The rate of meningitis among college students living in dormitories is about 4.6 per 100,000, higher than that of any age group other than children younger than 2. Still, the rate for college students falls under the threshold for a mandatory vaccination campaign, of 10 per 100,000.
CDC reports meningitis outbreak grows; 14 dead

BY LAURAN NEERGAARD
AND MIKE STOBBE
The Associated Press

WASHINGTON | Federal health
officials have tracked down
12,000 of the roughly 14,000
people who may have received
contaminated steroid shots in
the nation’s growing meningitis
outbreak, warning Thursday
that patients will need to keep
watch for symptoms of the
deadly infection for months.

“We know that we are not
out of the woods yet,” Dr. J.
Todd Weber of the Centers for
Disease Control and Preven-
tion said as the death toll
reached 14.

Of the 170 people sickened in
the outbreak, all but one have a
rare fungal form of meningitis
after receiving suspect steroid
shots for back pain, the CDC
said. The other case is an ankle
infection discovered in Michi-
gan; steroid shots also can be
given to treat aching knees,
shoulders or other joints.

Meningitis is considered
a medical emergency.
• can be due to infection by bacteria, viruses, fungi, or any other infectious organism

• signs

• headache, nausea, fever

• stiff neck - from a protective reflex

• confusion, altered consciousness, malaise (a feeling of general discomfort), convulsions, loss of consciousness, death
• viral meningitis - usually not as serious as...
• bacterial meningitis

Pneumococcal Meningitis:

Retraction of dura reveals leptomeninges which are edematous and have multiple small hemorrhagic foci (red) note greenish pus covering brain.
• bacterial meningitis may result from
  • a middle ear infection that spreads into the brain - probably most common source
  • bacteria that enter through an open head injury
  • an embolism of bacterial debris that arrives in the brain from elsewhere in the body (such as might result from use of contaminated hypodermic needles)
Encephalitis - infection of the brain tissue

Saint Louis Encephalitis
Disease caused by a mosquito transmitted virus.
**Incubation:** period usually 5-10 days.
**Symptoms:**
Fever, severe headache, nausea, and stiff neck.
Severe cases may include vomiting, disorientation and paralysis.
**Diagnosis:** By physician using acute phase serum or cerebral spinal fluid.
**Treatment:** There is no specific treatment for infection. Supportive care is important (contacting your physician, fluids, electrolytes, managing fever, etc.).
**Mosquito vector:**
- Encephalitis Mosquito (*Culex tarsalis*)
- Little House Mosquito (*Culex pipiens*)
- Southern House Mosquito (*Culex pipiens quinquefasciatus*)

Culex pipiens (also carries West Nile virus)
• encephalitis is usually (but not always) viral
• *pantropic* viral encephalitis - brain is not the primary site of infection (the virus travels from elsewhere in the body)
• mumps
• herpes simplex - lives in the trigeminal nerve ganglia and sometimes travels outwards and causes fever blisters (or cold sores) around the mouth, but rarely can also go the other way into the brain, and can cause extensive damage in the frontal and temporal lobes
• AIDS - 75% of people who die from AIDS show accompanying brain damage (1989 study)
• encephalitis (cont.)
  • neurotropic viral encephalitis - a viral infection that targets CNS tissue particularly
  • poliomyelitis ("polio") - virus targets the motor neurons in the ventral horns of the spinal cord and sometimes travels into the brain (polioencephalitis) and targets motor neurons there as well
  • rabies - a viral infection of the brain transmitted in the saliva from the bite of an infected animal (one of the most feared diseases in human history)
Viral infections - polio

Infiltration and congestion of anterior horns

Selective sites in brain in polioencephalitis:
1. Precentral gyrus
2. Hypothalamus
3. Reticular formation
4. Quadrigeminate bodies
5. Cerebellar roof nuclei
MUSCLES COMMONLY WEAKENED BY POLIO

- Shoulder muscles
- Muscles behind arm (weakness straightening arm)
- Back muscles (either side of backbone)
- Thumb muscles
- Muscles that straighten or bend hip, or that spread or close legs
- Muscles that straighten knee
- Muscles that lift foot
- Contractures causing tight cords
Central nervous system

Risk factors for polio include lack of immunization

POLIO HAS RETURNED to AMERICA!

The National Immunization for Polio Prevention in Infants and Toddlers Campaign

Nearly one million U.S. children are not vaccinated against POLIO.

Join the "NIPP IT" Campaign and vaccinate your children against POLIO at:

- 2 Months
- 4 Months
- 6 - 18 Months
- Booster at 4 years

Don't wait to VACCINATE!

PostPolioInfo.com

Join the "NIPP IT" CAMPAIGN
Another illness that no longer steals lives, thanks to vaccines, is polio. This 1955 photo of an emergency polio ward at Haynes Memorial Hospital in Boston, where patients whose illness had affected their respiratory systems were kept in "iron lungs," depicts the days when polio was still rampant. Boston's polio epidemic hit a high of 480 cases that summer.
Jonas Salk and the Salk vaccine - Time Magazine cover, March 29, 1954
In man, the premonitory symptoms are malaise, headache, anxiety, depression, insomnia, restlessness, delusions, hypersensitivity of the skin, and excessive salivation. During this stage there are alternating periods of rage and calmness. Convulsions may be brought on by so slight a stimulus as breath exhaled on the back of the neck. In the paralytic stage, which may start 24 to 48 hours after onset of symptoms, there are spasms of the larynx and pharynx; the patient’s thirst increases, yet any attempt at drinking causes clenching of the jaws (hydrophobia). The entire body is seized with tonic contractions. Finally, convulsions become more intense, and death results from respiratory paralysis.

(Description of rabies in humans from Netter)
6. Virus enters salivary glands and other organs of victim.
5. Virus reaches brain and causes fatal encephalitis.
4. Virus ascends spinal cord.
3. Virus moves up peripheral nervous system to CNS.
2. Virus replicates in muscle near bite.
1. Virus enters tissue from saliva of biting animal.
• encephalitis (cont.)

• the “latest” viral scourge (it was when I made this slide!)

  • **Eastern equine encephalitis** is a mosquito-borne virus that causes a rare, potentially fatal disease and seems to be spreading across the US.

  • There have been 12 human cases of the virus and two deaths so far this season. It's also killed horses across the U.S. and been found in mosquitoes in several states and in Canada.
Severe Infection

The first possible way is that the virus may have the capacity to enter the brain and cause a severe and sudden infection. Cases reported in China and Japan found the virus’s genetic material in spinal fluid, and a case in Florida found viral particles in brain cells. This might occur due to the virus entering the bloodstream or nerve endings. The loss of smell that occurs in some patients with COVID-19 could indicate that the virus entered through the olfactory bulb, which is located right above the nose and communicates information about smell to the brain.

Immune System in Overdrive

A second possibility is that the immune system goes into overdrive in an attempt to fight COVID-19, producing a “maladaptive” inflammatory response that may cause much of the tissue and organ damage seen in this disease — perhaps more than the virus itself.

Chaos in the Body

The third theory is that all of the physiological changes induced in the body by COVID-19 — ranging from high fevers to low oxygen levels to multiple organ failures — contribute to, or account for, brain dysfunction, such as the delirium or coma seen in many of the severe COVID-19 patients.

Blood-Clotting Abnormalities

The fourth way COVID-19 might affect the brain has to do with the tendency for these patients to suffer a stroke. The blood-clotting system in patients with the illness is highly abnormal, with clots much more likely to occur in these patients than in others. Clots can form in veins deep inside the body or in the lungs, where they can cut off blood flow. A stroke could occur if a blood clot were to block or narrow arteries leading to the brain.

COVID-19

Encephalitis

- Confusion
- Loss of consciousness
- Seizures
- Stroke
- Loss of smell and taste
- Headaches
- Trouble focusing
- Changes in behavior

• encephalitis (cont.)
  • an example of bacterial encephalitis (caused by *Treponema pallidum*, a spirochete)
  • syphilis (an STD) - after 10-20 years the bacteria can attack the CNS (although mental signs can appear much sooner)
  • *tabes dorsalis* - sensory and motor problems resulting from infection attacking the spinal cord, esp. the dorsal columns
  • *general paresis* - insanity and dementia resulting from infection attacking the brain
tabes dorsalis - a demyelinating disease
• encephalitis (cont.) - syphilis
  • tabes dorsalis
    • demyelination, particularly of the dorsal columns in the spinal cord
    • paresthesias - shooting and burning pains, pricking sensations, and formication
  • diminished tactile sensation
  • locomotor ataxia - due to proprioceptive loss
• encephalitis (cont.) - syphilis

• **general paresis**
  • initially considered a “psychiatric disorder”
  • psychotic symptoms of sudden and dramatic onset
  • Argyll Robertson pupils - constrict when patient focuses on a near object but not when exposed to bright light

• diagnostic of neurosyphilis

• clearly involves damage to cranial nerve III, but exact nature of this damage is still unclear
Other “infestations” of the brain!

Tapeworm cysts in the brain
General Effects of Brain Damage

- Central Fissure
- Motor cortex
- Somatosensory cortex
- Sensation and touch
- Body movement and coordination
- Frontal lobe
- Parietal lobe
- Occipital lobe
- Temporal lobe
- Planning and consciousness
- Speech
- Hearing
- Body position
- Vision
- Lateral fissure