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The Diseased Brain: Neurodegenerative and other Diseases

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Abstract

After a brief introduction to the conundrum concerning the origin of neurodegenerative diseases, I explore in this article the multiple known diseases of the central nervous system, be they inflammatory, encephalopathic, or both, or even myelopathic to better fathom neurodegenerative disorders, in particular.

Abbreviations

ABA: Amoebic brain abscess; AD: Alexander's disease; AD; Alpers' disease; AD: Alzheimer's disease; ADD: AD dementia; ALD: Adrenoleukodystrophy; ARA: Anteretrograde amnesia; BGD: Basal ganglia diseases; CBBD: Canavan–Van Bogaert–Bertrand disease; CD: Canavan's disease; CJD: Creutzfeldt–Jakob disease; CNS: Central nervous system; CSF: Cerebrospinal fluid; CST: Cavernous sinus thrombosis; CVDD: Cerebrovascular disease dementia; DMS: Diffuse myelinoclastic sclerosis; DS: Dravet's syndrome; FAS: Foix-Alajouanine syndrome; FLD: Frontotemporal lobar degeneration; FLDD: FLD dementia; FS: Foville's syndrome; GCL: Globoid cell leukodystrophy; GD: Gaucher's disease; GHEL: Genetics, health, environment, lifestyle; GSL: Galactosylceramide lipidosis; HD: Huntington's disease; HE: Hashimoto's encephalitis; HIV: Human immunodeficiency virus; HSV: Herpes simplex virus; HTLV: Human T-lymphotropic virus; KD: Krabbe's disease; KLD: Klein-Levin disease; LBD: Lewy body dementias; LGS: Lennox-Gastaut syndrome; LS: Leigh's syndrome; MCI: Mild cognitive impairment; MGD: Millard–Gubler disease MS: Meige's syndrome; MS: Multiple sclerosis; MSA: Multiple system atrophy; NDD: Neurodegenerative diseases; NMS: Neuroleptic malignant syndrome; LS: Leigh's syndrome; MBD: Marchiafava–Bignami disease; MDDS: Mitochondrial DNA depletion syndrome; MGD: Millard–Gubler disease; MS: Morvan's syndrome; MSA: Multiple system atrophy; NDD: Neeurodegenerative diseases; NMO: Neuromyelitis optica; NMOSD: NMO spectrum

disorder; NMS: Neuroleptic malignant syndrome; OA: Osteoarthritis; OCD: Obsessive–compulsive disorder; PCA: Posterior cortical atrophy; PD: Parkinson's disease; PD: Pick's disease; PDD: PD dementia; PKAN: Pantothenate kinase-associated neurodegeneration; PPA: Primary progressive aphasia; PSP: Progressive supranuclear palsy; RLS: Restless leg syndrome; RS: Reye's syndrome; SCC: Spinal cord compressiom; SD: Schilder's disease; SD: Status dystonicus; SND: Striatonigral degeneration; SPS: Stiff person syndrome; SREAT: Steroid-responsive encephalopathy associated with autoimmune thyroiditis; SSP: Subacute sclerosing panencephalitis; ST: Spasmodic torticollis; TGA: Transient global amnesia; TIA: Transient ischemic attack; TM: Transverse myelitis; TS: Tourette's syndrome; TSP: Tropical spastic paraparesis; VM: Vascular myelopathy; WS: Weber's syndrome'; WS: West's syndrome."

Keywords

Brain pathogens; central nervous system diseases; encephalopathies; inflammatory diseases; myelopathies; neurodegenerative diseases; pathological brain.

On the origin of neurodegenerative diseases

A core neuroscience dogma is that the soma of each neuron communicates simultaneously with thousands of other neurons connected to it through the long dendrites. These dendritic trees were posited to function like electrical cables collecting signals from the connecting neurons, thus allowing electrical communications between them. Recently (October 2023), the validity of this hypothesis has been questioned by researchers at the Bar-Ilan University and the Gonda (Goldschmied) Multidisciplinary Brain Research Center in Ramat Gan, Israel.

According to the lead researcher (Prof. Ido Kanter), "...neuronal features are independent of these physiological conditions – a finding that strongly pinpoints dendrites as the segments controlling neuronal plasticity features such as the neuronal firing frequency and the stimulation threshold of the neuron." If corroborated, this finding would call for a re-examination of the origin of neurodegenerative diseases (NDD) because the origin of many neuron functions are beyond the traditional framework and must be attributed to the dendrites instead of the soma. In addition, it also questions the origin of the brain's awake-and-sleep states.

Notwithstanding the above conundrum, I will explore below the constellations of diseases of the central nervous system.

Inflammatory diseases of the central nervous system

It is not my intent to cover in great detail each of the numerous known brain diseases but rather give a synoptic overview of them so as to better fathom the neurodegenerated brain. I will begin with the diseases of the central nervous system (CNS), whether due to inflammation, encephalopathy, or both followed by diseases of the spinal cord, and those due to either/both encephalopathy or spinal cord/myelopathy, as presented below.

CNS diseases due to inflammation are encapsulated in Table 1:

Organ	Disorders/diseases
A. Brain	o Amoebic brain abscess (ABA) o Cavernous sinus thrombosis (CST) - Septic - Aseptic o Encephalitis: - Herpes viral - Lethargica

	- Limbic - Viral
B. Spinal cord	o Epidural abscess o Myelitis: - Polio - Transverse o Tropical spastic paraparesis (TSP)
C. Either/both	Acute/disseminated Myalgic o Myelitis: - Encephalomyelitis - Meningomyelitis

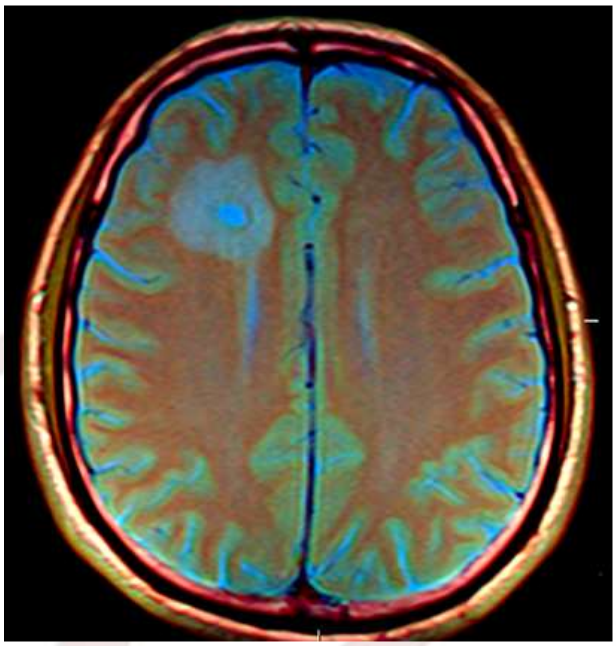
Table 1: Diseases of the central nervous system: Inflammation

A. CONCERNING THE BRAIN

- Amoebic brain abscess (ABA): This is a rare affliction caused by the anaerobic parasitic protist Entamoeba histolytica. It is difficult to diagnose and very few case reports suggest complete recovery even after the administration of appropriate treatment regimens. (Figure 1 is a copy of a brain MRI scan in an ABA patient.)

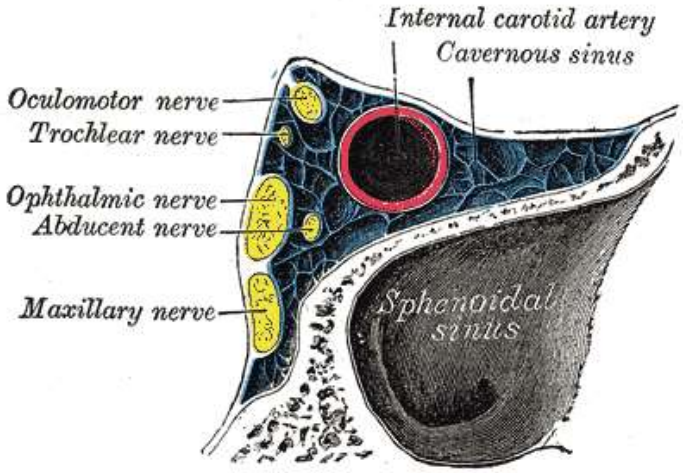
- Cavernous sinus thrombosis (CST): This is the formation of a blood clot within the cavernous sinus, which is a cavity at the base of the brain which drains deoxygenated blood from the brain back to the heart. It is a rare disorder, which can present under two forms. The cause of the most common form ("septic") is usually from a spreading infection in the nose, sinuses, ears, or teeth (Staphylococcus aureus and Streptococcus are often the associated bacteria). CST symptoms include: Decrease or loss of vision, chemosis, exophthalmos (bulging eyes), headaches, and paralysis of the cranial nerves. This infection is life-threatening and requires immediate treatment, which usually includes antibiotics and sometimes surgical drainage. The cause of the aseptic type is usually associated with trauma, dehydration, anemia, and other disorders (Figure 2).

- Encephalitis: This is an inflammation of the brain. Its severity can be variable with symptoms including reduction or alteration in consciousness, memory problems, and other symptoms (headache, fever, confusion, a stiff neck, and vomiting). Complications may include seizures, hallucinations, trouble speaking, and problems with hearing. Causes include viruses such as herpes simplex virus (HSV) and rabies virus as well as bacteria, fungi, or parasites. Other causes include autoimmune diseases and certain medications. However, in many cases, the cause remains unknown. Risk factors include a weak immune system. Diagnosis is typically based on symptoms and supported by blood tests, medical imaging, and analysis of the cerebrospinal fluid (CSF). Certain types are preventable with vaccines, antiviral medications (such as Acyclovir), anticonvulsants, and corticosteroids.



Reference: Nevit Dilmen

Figure 1: MRI scan of an amoebic brain abscess (ABA)



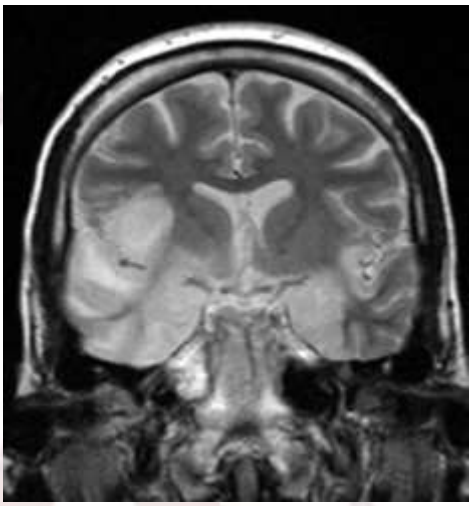
Reference: Henry Vandyke Carter and Henry Gray's Anatomy of the Human Body (Plate 571)

Figure 2: Cavernous sinus thrombosis (CST)

When it comes to brain inflammation, only encephalitis would be of concern regarding memory and cognition.

B. CONCERNING THE SPINAL CORD

- Epidural abscess: It refers to a collection of pus and infectious material located in the epidural space superficial to the dura mater which surrounds the CNS. Due to its location adjacent to the brain or the spinal cord, this abscess has the potential to cause weakness, pain, and paralysis.



Reference: Laughlin Dawes - http://www.radpod.org/2007/03/24/herpes-simplex-encephalitis/

Figure 3: MRI image of an encephalitis

- **Myelitis:** This is an inflammation of the spinal cord, which can disrupt the normal responses from the brain to the rest of the body and from the rest of the body to the brain.

  It can cause the myelin and axon to be damaged resulting in symptoms such as paralysis and sensory loss. Myelitis is classified in several categories depending on the area or the cause of the lesion; however, any inflammatory attack on the spinal cord is often referred to as transverse myelitis. (TM).

(Figure 3 is a coronal T2-weighted MR image showing high signal in the temporal lobes including hippocampal formations and parahippocampal gyrae, insulae, and right inferior frontal gyrus.)

- **Tropical spastic paraparesis (TSP):** This medical condition causes weakness, muscle spasms, and sensory disturbance by human T-lymphotropic virus resulting in paraparesis and weakness of the legs. It is most common in tropical regions, including the Caribbean. Blood transfusion products are screened for human T-lymphotropic virus 1 (HTLV-1) antibodies, as a preventive measure.

Brain encephalopathies

Table 2 lists the disorders/diseases due to brain encephalopathy whether degenerative, demyelinating, episodic/paroxysmal, cerebrospinal fluid, or due to other causes:

Characteristics	Disease category	Disorders/diseases
A. Degenerative	**A.1 Extrapyramidal & movement disorders**	o Akathisia o Athetosis o Basal ganglia disease o Blepharospasm o Chorea o Choreoathetosis o Dyskinesia o Dystonia o Epilepsy - Myoclonic o Hemiballismus o Huntington's disease (HD) o Meige's syndrome (MS) o Myoclonus - Alzheimer's disease (AD) - Gaucher's disease (GD) - Creutzfeldt–Jakob disease (CJD) - Subacute sclerosing panencephalitis (SSP) o Neuroleptic malignant syndrome (NMS) o Osteoarthritis (OA) o Parkinson's disease (PD) o Parkinsonism o Pantothenate kinase-associated neurodegeneration (PKAN) o Progressive supranuclear palsy (PSP) o Restless legs syndrome (RLS) o Spasmodic torticollis (ST) o Status dystonicus (SD) o Stiff person syndrome (SPS) o Striatonigral degeneration (SND) or multiple system atrophy (MSA) o Tauopathy o Tremor - Essential - Intentional
	A.2 Dementias	o Alzheimer's disease (AD) o Aphasia: Primary progressive (PPA) o Atrophy: Posterior cortical (PCA) o Degeneration: frontotemporal lobar (FLD) o Dementia:

		- Early onset ▪ - Frontotemporal or Pick's disease (PD) ▪ - HIV ▪ - Juvenile ▪ - Lewy body dementias (LBD) ▪ - with Lewy bodies - Late onset ◦ - Pugilistica - Vascular o Parkinson's disease (PD) o Synucleinopathies o Tauopathy o Leigh's syndrome (LS)
	A.3 Mitochondrial DNA disease	o Mitochondrial DNA depletion syndrome (MDS or MDDS) or Alpers' disease (AD)
B. Demyelinating		o Autoimmune: - Multiple sclerosis (MS) - Neuromyelitis optica (NMO) and NMO spectrum disorder (NMOSD) - Schilder's disease (SD): May include adrenoleukodystrophy (ALD) or diffuse myelinoclastic sclerosis (DMS). o Hereditary: - Alexander's disease (AD) - CAMFAK syndrome - Canavan's disease (CD) or Canavan–Van Bogaert–Bertrand disease (CBBD) - Krabbe's disease (KD) or globoid cell leukodystrophy (GCL) or galactosylceramide lipidosis (GSL) - Marchiafava–Bignami disease (MBD) - MFC - ML - Myelinolysis: central pontine - PMD - VWM
C. Episodic/ paroxysmal	**C.1 Seizure/epilepsy**	o Dravet's syndrome (DS) - Focal - Generalized o Epilepsy: - Myoclonic - Status *epilepticus* o Lennox-Gastaut syndrome (LGS) - West's syndrome (WS)
	C.2 Headache	o Migraine - Cluster - Familial - Tension
	C.3 Cerebrovascular	o ACA o Aphasia: acute o Amaurosis *fugax* o Foville's syndrome (FS)

		o MCA o Medullary: - Lateral - Medial o Millard–Gubler disease (MGD) o PCA o Stroke - Lacunar - Transient ischemic attack (TIA) o Transient global amnesia (TGA) - Anterograde amnesia o Weber's syndrome (WS)
	C.4 Sleep disorders	o Cataplexy o Circadian rythm o Insomnia - Hyper - Hypo o Klein-Levin disease (KLD) o Narcolepsy o Sleep apnea - Hypoventilation syndrome: - Congenital Central o Sleep disorder: - Advanced phase - Delayed phase - Non-24 hour wake - Jet lag
D. Cerebrospinal fluid	o Cerebral edema ◦ o Choroid plexus papilloma (CPP) ◦ o Hydrocephalus: Normal pressure (NPH) o Hyper/hypotension: Intracranial idiopathic	
E. Others	1. o Brain herniation 2. o Encephalopathy: 3. - Wernicke's (WE) - Anti-NMDA receptor - HIV encephalopathy 4. - Hashimoto's encephalopathy (HE) 5. o Reye's encephalopathy (RE)	

Table 2: Diseases of the central nervous system: Encephalopathies

A. Concerning degenerative encephalopathies

A. 1 For Extrapyramidal and movement disorders

- Akathisia: A movement disorder characterized by a subjective feeling of inner restlessness accompanied by mental distress and an inability to sit still. The most severe cases may result in aggression, violence, and/or suicidal thoughts. Akathisia is also associated with threatening behavior and physical aggression. Antipsychotic medications are a leading cause. It may also occur upon stopping antipsychotics. Diagnosis differs from restless leg syndrome (RLS) – see below - in that akathisia is not associated with sleeping although the two conditions may share symptoms in individual cases.

- Athetosis: A symptom characterized by slow, involuntary, convoluted, writhing movements of the fingers, hands, toes, and feet and in some cases, arms, legs, neck, and tongue. Lesions to the brain are most often the direct cause of the symptoms, particularly to the corpus striatum. Athetosis is often accompanied by the symptoms of cerebral palsy, as it is often a result of this physical disability.

- Basal ganglia disease (BGD): A group of physical problems caused by the failure of the basal ganglia (nuclei) to properly suppress unwanted movements or to properly prime upper motor neuron circuits to initiate motor function. (The diagram in Figure 4 illustrates the basal ganglia in red and related structures in blue within the brain.) These disorders are known as hypokinetic disorders, which can leads to the inability to suppress unwanted movements. One possible causal factor could be the natural accumulation of iron in the basal ganglia, causing neurodegeneration due to its involvement in toxic, free-radical reactions. Basal ganglia disorders can lead to other dysfunctions such as obsessive–compulsive disorder (OCD) and Tourette's syndrome (TS).

- Choreoathetosis: The occurrence of involuntary movements in a combination of chorea (irregular migrating contractions) and athetosis (twisting and writhing). It is caused by many different diseases and agents. It is a symptom of several diseases, including Lesch–Nyhan syndrome (LNS), phenylketonuria (PKU), and Huntington's disease (HD) – see below - and can be a feature of kernicterus (rapidly increasing unconjugated bilirubin that cross the blood-brain-barrier in infants). It is also a common presentation of dyskinesia as a side effect of Levodopa-Carbidopa in the treatment of Parkinson's disease (PD).

- Blepharospasm: Any abnormal contraction of the orbicularis oculi muscle. In most cases, symptoms last for a few days and then disappear without treatment, but in some cases the twitching is chronic and persistent, causing life-long challenges. In these cases, the symptoms are often severe enough to result in functional blindness.

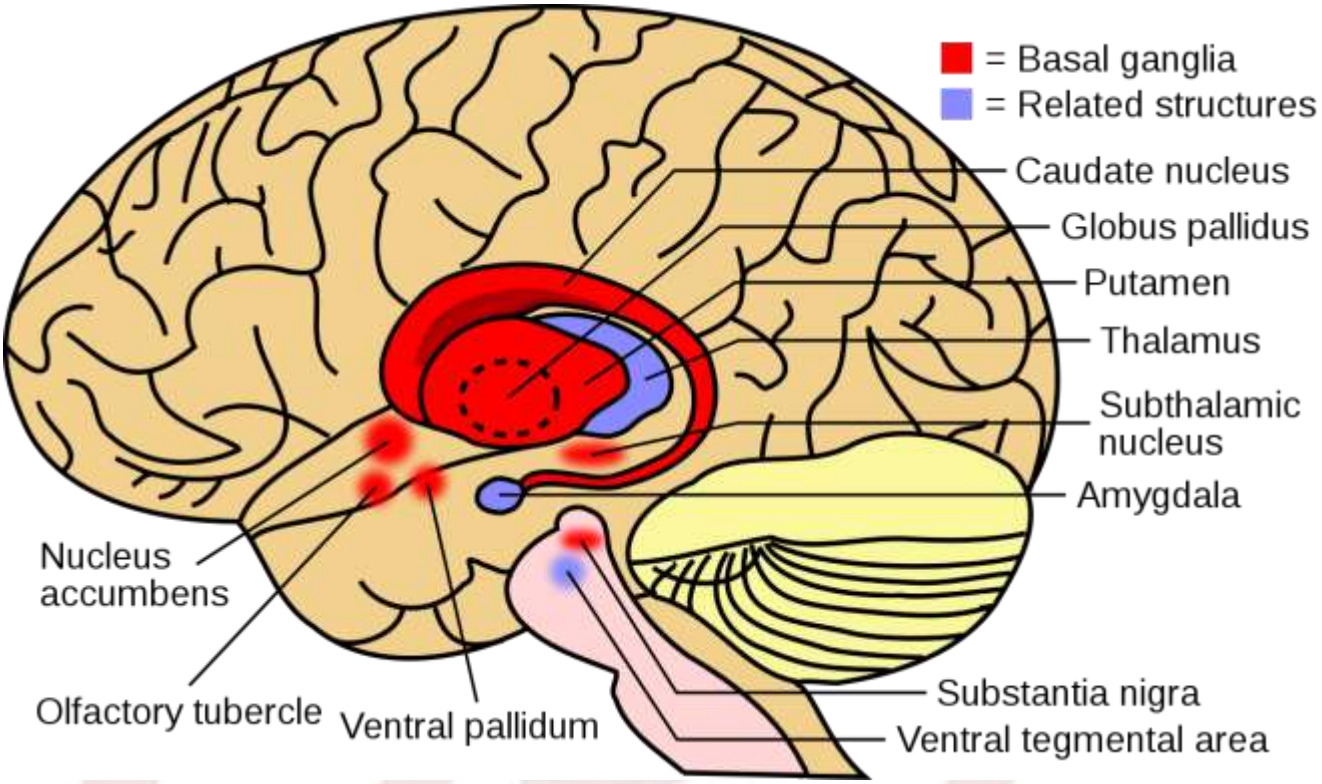


Figure 4: Diagram of the basal ganglia and related structures within the brain

- **Chorea:** An abnormal involuntary movement disorder, one of a group of neurological disorders called dyskinesias. The quick movements of the feet or hands are comparable to dancing.

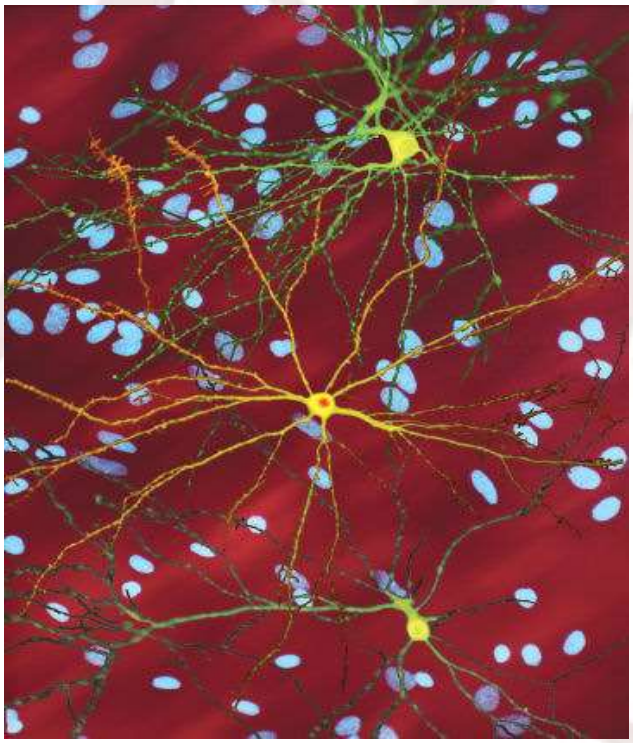
- **Dyskinesia:** Refers to a category of movement disorders that are characterized by involuntary muscle movements, including movements similar to tics or chorea and diminished voluntary movements. It can be anything from a slight tremor of the hands to an uncontrollable movement of the upper body or lower extremities.

- **Dystonia:** A neurological hyperkinetic movement disorder in which sustained or repetitive muscle contractions result in twisting and repetitive movements or abnormal fixed postures. The movements may resemble a tremor. Dystonia is often intensified or exacerbated by physical activity, and symptoms may progress into adjacent muscles. The disorder may be hereditary or caused by other factors such as birth-related or other physical trauma, infection, poisoning (e.g., lead poisoning) or reaction to pharmaceutical drugs, particularly neuroleptics, or stress.

- **Epilepsy:** A group of non-communicable neurological disorders characterized by recurrent epileptic seizures. An epileptic seizure is the clinical manifestation of an abnormal, excessive, purposeless, and synchronized electrical discharge in the brain cells called neurons. Epileptic seizures can vary from brief and nearly undetectable periods to long periods of vigorous shaking due to abnormal electrical

activity in the brain, tend to recur, and may have no immediate underlying cause. These episodes can result in physical injuries (e.g., broken bones, causing accidents). The underlying mechanism is excessive and abnormal neuronal activity in the brain cortex. The cause is unknown but may occur as the result of brain injury, stroke, brain tumors, infections of the brain, or birth defects through a process known as epileptogenesis. Known genetic mutations are directly linked to a small proportion of cases.

- **Hemiballismus (or hemiballism):** A basal ganglia syndrome resulting from damage to the subthalamic nucleus in the basal ganglia. It is a rare hyperkinetic movement disorder characterized by violent involuntary limb movements on one side of the body, which can cause significant disability. Ballismus affects both sides of the body and is much rarer. Hemiballismus differs from chorea in that the movements occur in the proximal limbs whereas in chorea the limb movements are in the distal limbs.Also in chorea the movements are more dance-like, flowing from one region to another.



Source: Steven Finkbeiner, Gladstone Institute of Neurological Disease, The Taube-Koret Center for Huntington's Disease Research, and the University of California San Francisco.

Figure 5: Mutant Huntington's disease (HD) proteins affecting neurons

- **Huntington's disease (HD) or Huntington's chorea (HC):** An incurable neurodegenerative disease that is mostly inherited. The earliest symptoms are often subtle problems with mood or mental/ psychiatric abilities. (Figure 5 is a study using a robotic microscope to show how mutant HD's protein affects neurons.) A general lack of coordination and an unsteady gait often follow. It is also a basal ganglia disease causing a hyperkinetic movement disorder known as chorea. As the disease advances, uncoordinated, involuntary body movements of chorea become more apparent. Physical abilities gradually worsen until coordinated movement becomes difficult and the person is unable to talk. Mental abilities generally decline into dementia, depression, apathy, and impulsivity at times.

- **Meige's syndrome (MS) or Brueghel's syndrome (BS) or oral facial dystonia OFD):** A type of dystonia. It is actually a combination of two forms of dystonia, blepharospasm and oromandibular dystonia (OMD). The combination of upper and lower dystonia is sometimes called cranial-cervical dystonia.

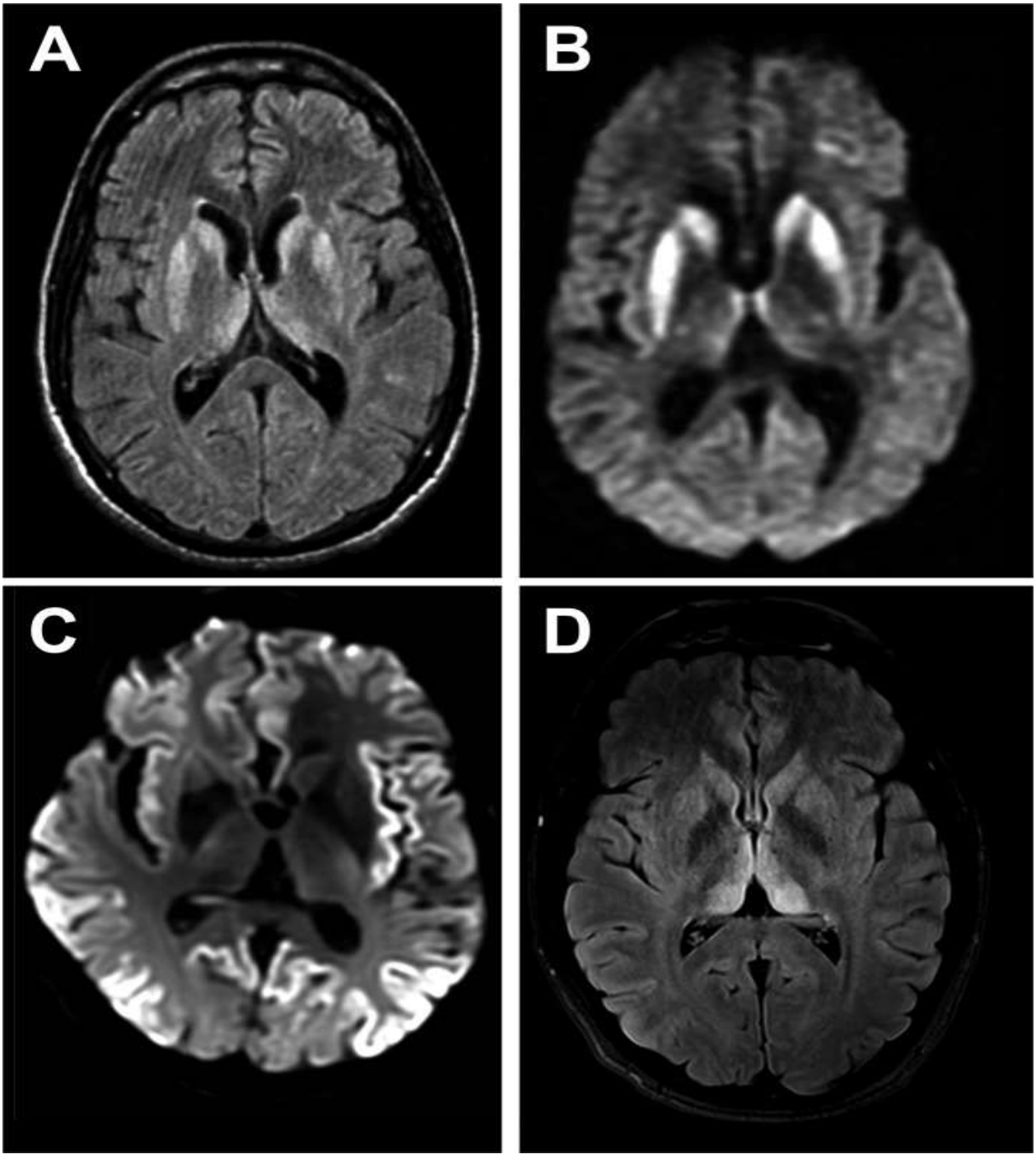
- **Myoclonus:** A brief, involuntary, irregular (lacking rhythm) twitching of a muscle, a joint, or a group of muscles, different from clonus, which is rhythmic or regular. It describes a medical sign and, generally, is not a diagnosis of a disease. These myoclonic twitches, jerks, or seizures are usually caused by sudden muscle contractions (positive myoclonus) or brief lapses of contraction (negative myoclonus). The most common circumstance under which they occur is while falling asleep (hypnic jerk). They can be a sign of various neurological disorders. They may occur alone or in sequence, in a pattern or without pattern. They may occur infrequently or many times each minute.

  Most often, myoclonus is one of several signs in a wide variety of nervous system disorders such as multiple sclerosis (MS), Parkinson's disease (PD), dystonia, cerebral palsy, Alzheimer's disease (AD), Gaucher's disease (GD), Creutzfeldt–Jakob disease (CJD), subacute sclerosing panencephalitis, serotonin toxicity, some cases of Huntington's disease, some forms of epilepsy, and occasionally in intracranial hypotension. In almost all instances in which myoclonus is caused by CNS disease, it is preceded by other symptoms; for instance, in CJD it is generally a late-stage clinical feature that appears after the patient has already started to exhibit gross neurological deficits. Anatomically, myoclonus may originate from lesions of the cortex, subcortex or spinal cord.

- **Gaucher's disease (GD):** A genetic disorder in which the enzyme glucocerebroside (a sphingolipid, also known as glucosylceramide) accumulates in cells and certain organs. The disorder is characterized by bruising, fatigue, anemia, low blood platelet count, and enlargement of the liver and spleen. The enzyme can collect in the spleen, liver, kidneys, lungs, brain, and bone marrow. Manifestations may include enlarged spleen and liver, liver malfunction, skeletal disorders or bone lesions that may be painful, severe neurological complications, swelling of lymph nodes and (occasionally) adjacent joints, distended abdomen, a brownish tint to the skin, anemia, low blood platelet count, and yellow fatty deposits on the white of the eye (sclera).

- **Creutzfeldt-Jakob disease (CJD),** also known as subacute spongiform encephalopathy or neurocognitive disorder due to prion disease. It is an invariably fatal degenerative brain disorder.

Early symptoms include memory problems, behavioral changes, poor coordination, and visual disturbances. Later symptoms include dementia, involuntary movements, blindness, weakness, and coma.



Reference: Pract Neurol - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5520355/figure/F2/

Figure 6: MRI of sporadic Creutzfeldt-Jakob disease

About 70% of people die within a year of diagnosis. CJD is caused by a type of abnormal protein known as a prion. Infectious prions are misfolded proteins that can cause normally folded proteins to also become misfolded (Figure 6).

- **Subacute sclerosing panencephalitis (SSPE)** also known as Dawson's disease (DD): It is a rare form of progressive brain inflammation caused by a persistent infection with the measles virus. The condition primarily affects children, teens, and young adults. It is almost always fatal and should not be confused with acute disseminated encephalomyelitis (ADE), which can also be caused by the measles virus, but has a very different timing and course.

- **Neuroleptic malignant syndrome (NMS):** A rare but life-threatening reaction that can occur in response to neuroleptic or antipsychotic medication. Symptoms include high fever, confusion, rigid muscles, variable blood pressure, sweating, and fast heart rate. Complications may include rhabdomyolysis, high blood potassium, kidney failure, or seizures.

- **Osteoarthritis (OA):** A type of degenerative joint disease that results from breakdown of joint cartilage and underlying bone.The most common symptoms are joint pain and stiffness. Other symptoms may include joint swelling, decreased range of motion, and, when the back is affected, weakness or numbness of the arms and legs. Causes include previous joint injury, abnormal joint or limb development, and inherited factors. OA is believed to be caused by mechanical stress on the joint and low grade inflammatory processes.

- **Parkinson's disease (PD):** A chronic degenerative disorder of the CNS that mainly affects the motor system. The symptoms usually emerge slowly, and as the disease worsens, non-motor symptoms become more common. Early symptoms are tremor, rigidity, slowness of movement, and difficulty with walking. Problems may also arise with cognition, behavior, sleep, and sensory systems. Parkinson's disease dementia becomes common in advanced stages of the disease. The motor symptoms of the disease result from the death of nerve cells in the substantia nigra, a region of the midbrain that supplies dopamine to the basal ganglia. The cause of this cell death is poorly understood, but involves the aggregation of the protein alpha-synuclein into Lewy bodies within the neurons. The cause of PD is unknown, but a combination of genetic and environmental factors are believed to play a role.

- **Parkinsonism:** A clinical syndrome characterized by tremor, bradykinesia (slowed movements), rigidity, and postural instability. It usually leads to dementia with Lewy bodies (DLB), Parkinson's disease dementia (PDD), and many other conditions. This set of symptoms occurs in a wide range of conditions and may have many causes, including neurodegenerative conditions, drugs, toxins, metabolic diseases, and other conditions than PD.

- **Pantothenatekinase-associated neurodegeneration (PKAN)** also known as Hallervorden-Spatz syndrome (HSS) is a genetic degenerative disease of the brain that can lead to parkinsonism, dystonia, dementia, and ultimately death. Neurodegeneration in PKAN is accompanied by an excess of iron that progressively builds up in the brain. (The MRI image of Figure 6.7 used a T2-weighed GRASE sequence to shows iron deposits in the basal ganglia, the so-called eye-of-the-tiger sign.) (Figure 7).

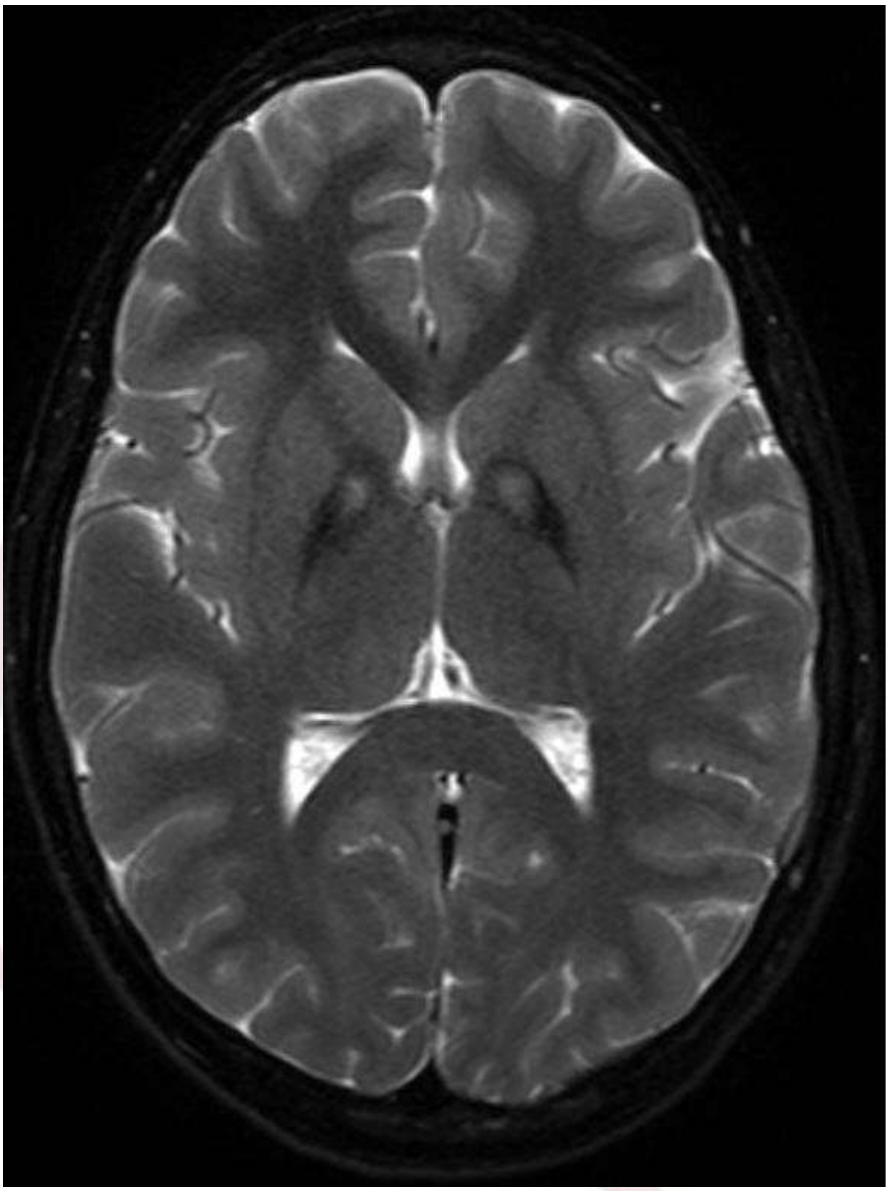
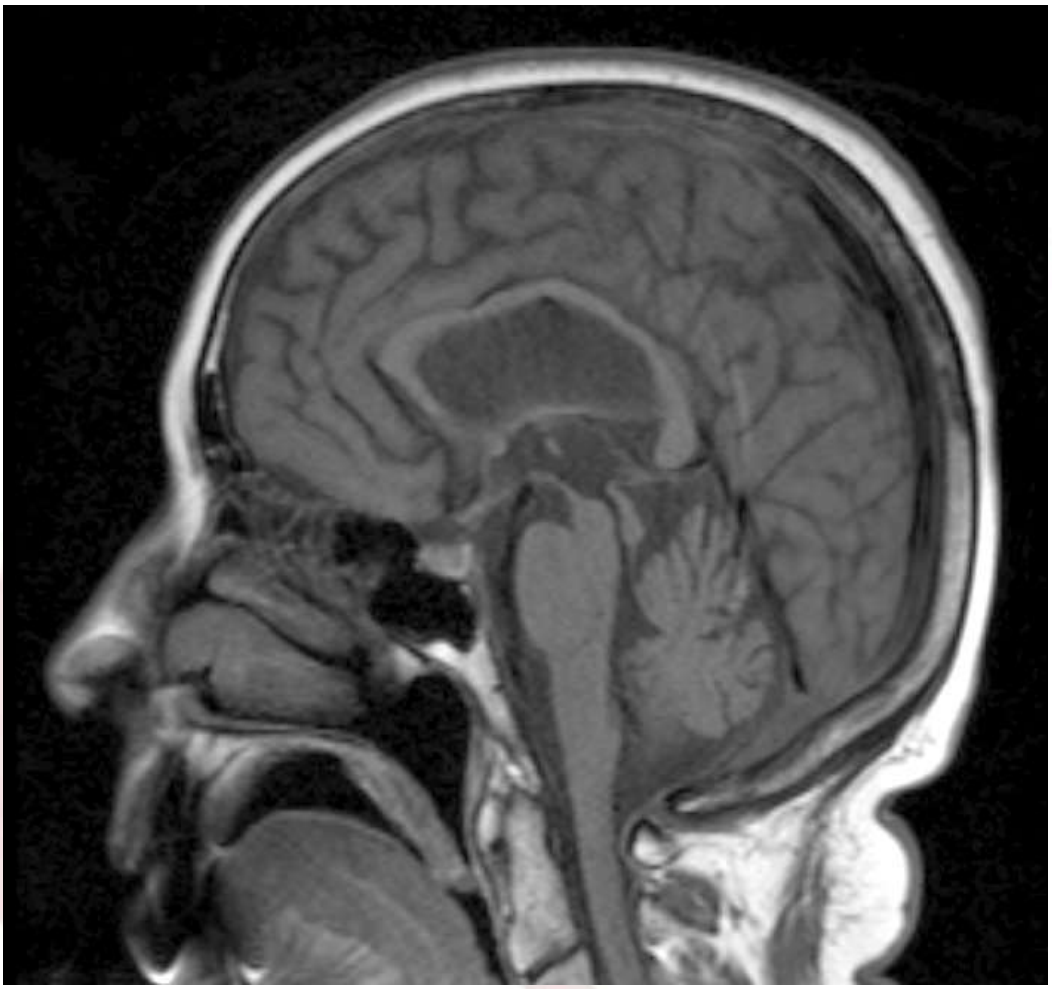


Figure 7: MRI of the pantothenate kinase-associated neurodegeneration

- **Progressive supranuclear palsy (PSP):** A late-onset neurodegenerative disease involving the gradual deterioration and death of specific volumes of the brain. The condition leads to symptoms including loss of balance, slowing of movement, difficulty moving the eyes, and cognitive impairment. PSP may be mistaken for other types of neurodegeneration such as PD, frontotemporal dementia (FTD), and Alzheimer's disease (AD). The cause of the condition is uncertain, but involves the accumulation of the tau-protein within the brain. (Figure 8 is a sagittal T1-weigted MRI image showing atrophy of the midbrain, with preservation of the volume of the pons. This appearance has been called the "penguin sign")



Reference: Laughlin Dawes – radpod.org

Figure 8: Showing atrophy of the midbrain in progressive supranuclear palsy

- **Restless legs syndrome (RLS) or Willis–Ekbom disease (WED):** Generally, a long-term disorder that causes a strong urge to move one's legs. This is often described as aching, tingling, or crawling in nature. Due to the disturbance in sleep, people with RLS may have daytime sleepiness, low energy, irritability and a depressed mood. Additionally, many have limb twitching during sleep, a condition known as periodic limb movement disorder. Risk factors for RLS include low iron levels, kidney failure, PD, diabetes mellitus, rheumatoid arthritis, pregnancy and celiac disease.

- **Spasmodic torticollis (ST) or cervical dystonia (CD):** An extremely painful chronic neurological movement disorder causing the neck to involuntarily turn to the left, right, upwards, and/or downwards. Both agonist and

antagonist muscles contract simultaneously. Causes of the disorder are predominantly idiopathic.

- **Status dystonicus (SD):** A serious and potentially life-threatening disorder which occurs in people who have primary or secondary dystonia. Symptoms consist of widespread severe muscle contractions.

- **Stiff-person syndrome (SPS) or stiff-man syndrome (SMS):** A rare neurologic disorder of unclear cause characterized by progressive muscular rigidity and stiffness. The stiffness primarily affects the truncate muscles and is superimposed by spasms, resulting in postural deformities. Chronic pain, impaired mobility, and lumbar hyperlordosis are common symptoms.

- **Striatonigral degeneration (SND) or multiple system atrophy (MSA):** A rare neurodegenerative disorder characterized by autonomic dysfunction, tremors, slow movement, muscle rigidity, and postural instability (collectively known as parkinsonism) and ataxia. This is caused by progressive degeneration of neurons in several parts of the brain including the basal ganglia, inferior olivary nucleus, and cerebellum. It commonly manifests as orthostatic hypotension, impotence, loss of sweating, dry mouth, and urinary retention and incontinence. Palsy of the vocal cords is an important and sometimes initial clinical manifestation of the disorder. MSA often presents with some of the same symptoms as PD. MSA is distinct from multisystem proteinopathy, a more common muscle-wasting syndrome. It is also different from multiple organ dysfunction syndrome, sometimes referred to as multiple organ failure, and from multiple organ system failures, an often-fatal complication of septic shock and other severe illnesses or injuries.

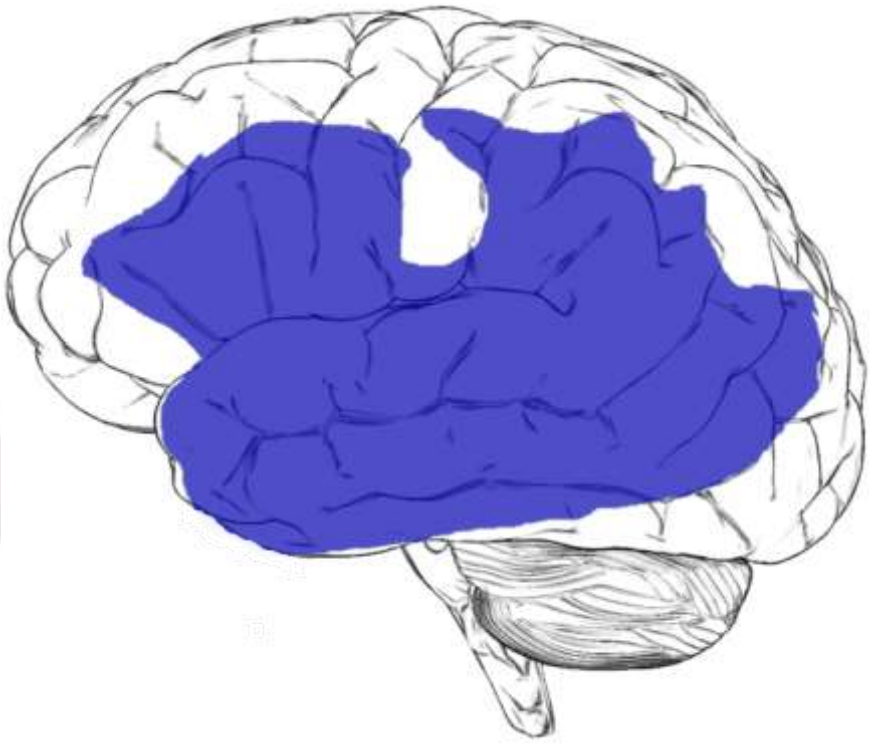
- **Tauopathy:** It belongs to a class of neurodegenerative diseases involving the aggregation of tau protein into neurofibrillary or gliofibrillary tangles in the human brain. Tangles are formed by hyperphosphorylation of the microtubule protein known as tau, causing the protein to dissociate from microtubules and form insoluble aggregates.The mechanism of tangle formation is not well understood, and whether tangles are a primary cause of AD or play a peripheral role is unknown.

- **Tremor:** An involuntary, somewhat rhythmic, muscle contraction and relaxation involving oscillations or twitching movements of one or more body parts. It is the most common of all involuntary movements and can affect the hands, arms, eyes, face, head, vocal folds, trunk, and legs. Most tremors occur in the hands. In some people, a tremor is a symptom of another neurological disorder.

A.2 For dementias

- Alzheimer's disease (AD): A neurodegenerative disease that usually starts slowly and progressively worsens. It is the cause of 60%–70% of cases of dementia. The most common early symptom is progressive memory loss and difficulty in remembering recent events. As the disease advances, symptoms can include problems with language, disorientation (including easily getting lost), mood swings, loss of motivation, self-neglect, and behavioral issues. As a person's condition declines, they often withdraw from family and society. Gradually, bodily functions are lost, ultimately leading to death. Although the speed of

progression can vary, the typical life expectancy following diagnosis is three to nine years. The cause of AD is poorly understood.



Reference: I. Henseler, F. Regenbrecht, and H. Obrig, 2014). doi: 10.1093/brain/awt374

Figure 9: Primary Progressive Aphasia

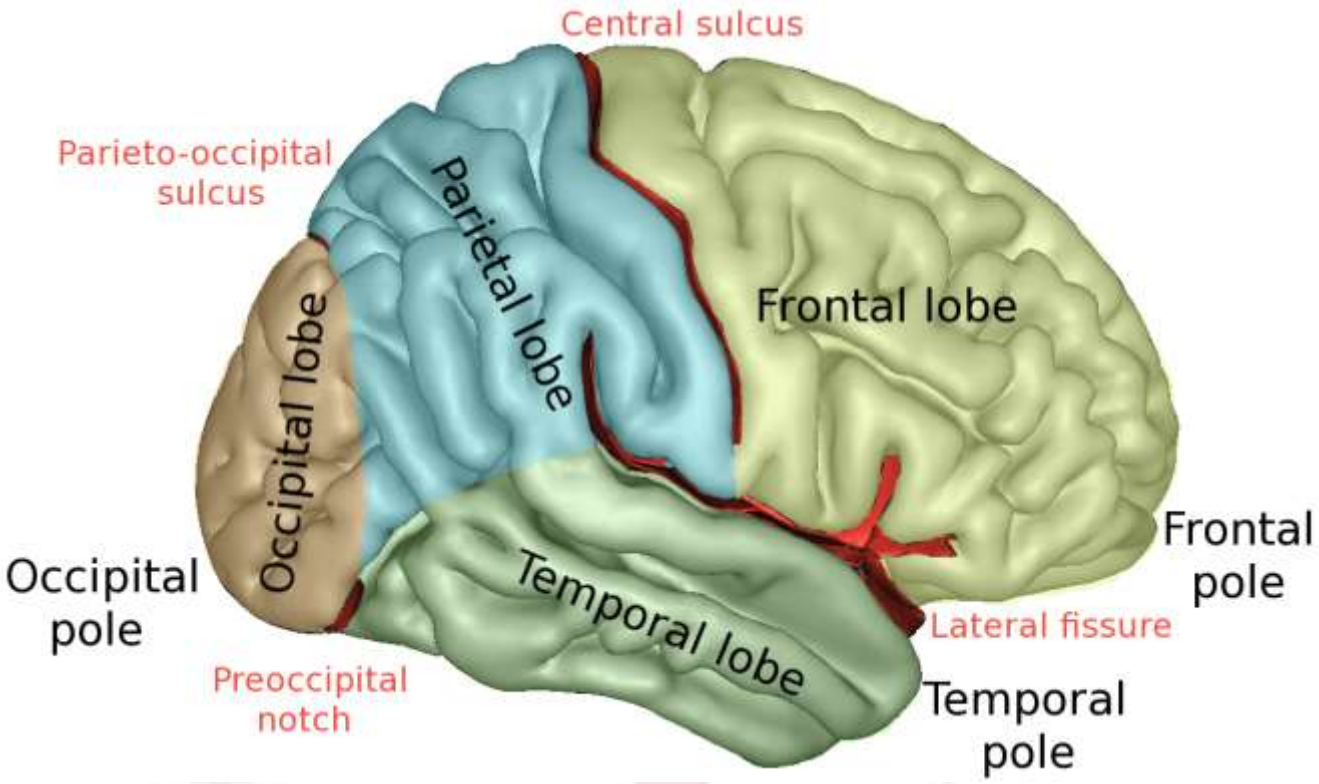
There are many environmental and genetic risk factors associated with its development. The strongest genetic risk factor is from an allele of APOE. Other risk factors include a history of head injury, clinical depression, and high blood pressure. A probable diagnosis is based on the history of the illness and cognitive testing, with medical imaging and blood tests to rule out other possible causes. Initial symptoms are often mistaken for normal brain aging. Good nutrition, physical activity, and engaging socially are known to be of benefit generally in aging, and may help in reducing the risk of cognitive decline. No current treatments can stop or reverse its progression, though some may temporarily improve symptoms.

- Primary progressive aphasia (PPA): A type of neurological syndrome in which language capabilities slowly and progressively become impaired. As with other types of aphasia, the symptoms that accompany PPA depend on what parts of the left hemisphere are significantly damaged. However, unlike most other aphasias,

- PPA results from continuous deterioration in brain tissue, which leads to early symptoms being far less detrimental than later symptoms. Those with PPA slowly lose the ability to speak, write, read, and generally comprehend language. Eventually, almost every patient becomes mute and completely loses the ability to understand both written and spoken language. Many, if not most of those with PPA experience impairment of memory, short-term memory formation and loss of executive functions. (Figure 9 shows regions of the left hemisphere that can give

rise to aphasia when damaged.)

- Posterior cortical atrophy (PCA) or Benson's syndrome (BS): A rare form of dementia which is considered a visual variant or an atypical variant of Alzheimer's disease (AD).



Reference: Sebastian023

Figure 10: Posterior cortical atrophy (PCA)

The disease causes atrophy of the posterior part of the cerebral cortex, resulting in the progressive disruption of complex visual processing. PCA usually affects people at an earlier age than typical AD cases. In rare cases, PCA can be caused by dementia with Lewy bodies (DLB) and Creutzfeldt–Jakob disease (CJD). (Figure 10 shows brain lobes, main sulci, and boundaries.

- **Frontotemporal lobar degeneration (FTLD):** A pathological process that occurs in frontotemporal dementia (FTD). It is characterized by atrophy in the frontal lobe and temporal lobe of the brain, with sparing of the parietal and occipital lobes.

- **Dementias:** The general name for a decline in cognitive abilities that impacts a person's ability to do everyday activities. This typically

involves problems with memory, thinking, and behavior. Aside from memory impairment and a disruption in thought patterns, the most described as occurring in a continuum over several stages. A diagnosis of dementia requires the observation of a change from a person's usual mental functioning and a greater cognitive decline than what is caused by normal aging. Several diseases and injuries to the brain such as a stroke can give rise to dementia. However, the most common cause is Alzheimer's disease. Dementia is listed as an acquired brain syndrome, marked by a decline in cognitive function, and is contrasted with neurodevelopmental disorders. It is also described as a spectrum of disorders with causative subtypes of dementia based on a known disorder, such as Parkinson's disease for Parkinson's disease dementia (PDD); Huntington's disease for Huntington's disease dementia (HDD); vascular disease, for vascular disease dementia (VDD); HIV infection causing HIV dementia (HIVD); frontotemporal lobar degeneration for frontotemporal dementia (FTLD); Lewy body disease for dementia with Lewy bodies (DLB); and prion diseases.

Subtypes of neurodegenerative dementias may also be based on the underlying pathology of misfolded proteins such as synucleinopathies, and tauopathies. More than one type of dementia existing together is known as mixed dementia (MD).

- **Synucleinopathies (or α-synucleinopathies):**

Neurodegenerative diseases characterized by the abnormal accumulation of aggregates of alpha-synuclein protein in neurons, nerve fibers or glial cells. There are three main types: Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy common symptoms include emotional problems, difficulties with language, and decreased motivation. The symptoms may be (MSA). Other rare disorders, such as various neuroaxonal dystrophies, also have α-synuclein pathologies. [Figure 11 illustrates the main dopaminergic pathways of the human brain: the mesocortical pathway, connecting the ventral tegmental area (VTA) with the frontal cortex; the mesolimbic pathway, connecting the VTA with the nucleus accumbens; the nigrostriatal pathway, connecting the substantia nigra with the dorsal striatum; and the tuberoinfundibular pathway, connecting hypothalamus with pituitary.]

- **Leigh syndrome (LS) or Leigh disease (LD) or subacute necrotizing encephalomyelopathy (SANE):** An inherited neurometabolic disorder that affects the CNS. Normal levels of thiamine, thiamine monophosphate, and thiamine diphosphate are commonly found, but there is a reduced or absent level of thiamine triphosphate. This is thought to be caused by a blockage in the enzyme thiamine-diphosphate kinase.

A.3 For mitochondrial DNA

- **Mitochondrial DNA depletion syndrome (MDS or MDDS) or Alper's disease (AD):** Any of a group of autosomal recessive disorders that cause a significant drop in mitochondrial DNA in affected tissues. Symptoms can be any combination of myopathic, hepatopathic, or encephalomyopathic. These syndromes affect tissue in the muscle, liver, or both the muscle and brain, respectively. The condition is typically fatal in infancy and early childhood, though some have survived to their teenage years with the myopathic variant and some have survived into adulthood with the SUCLA2

encephalomyopathic variant.

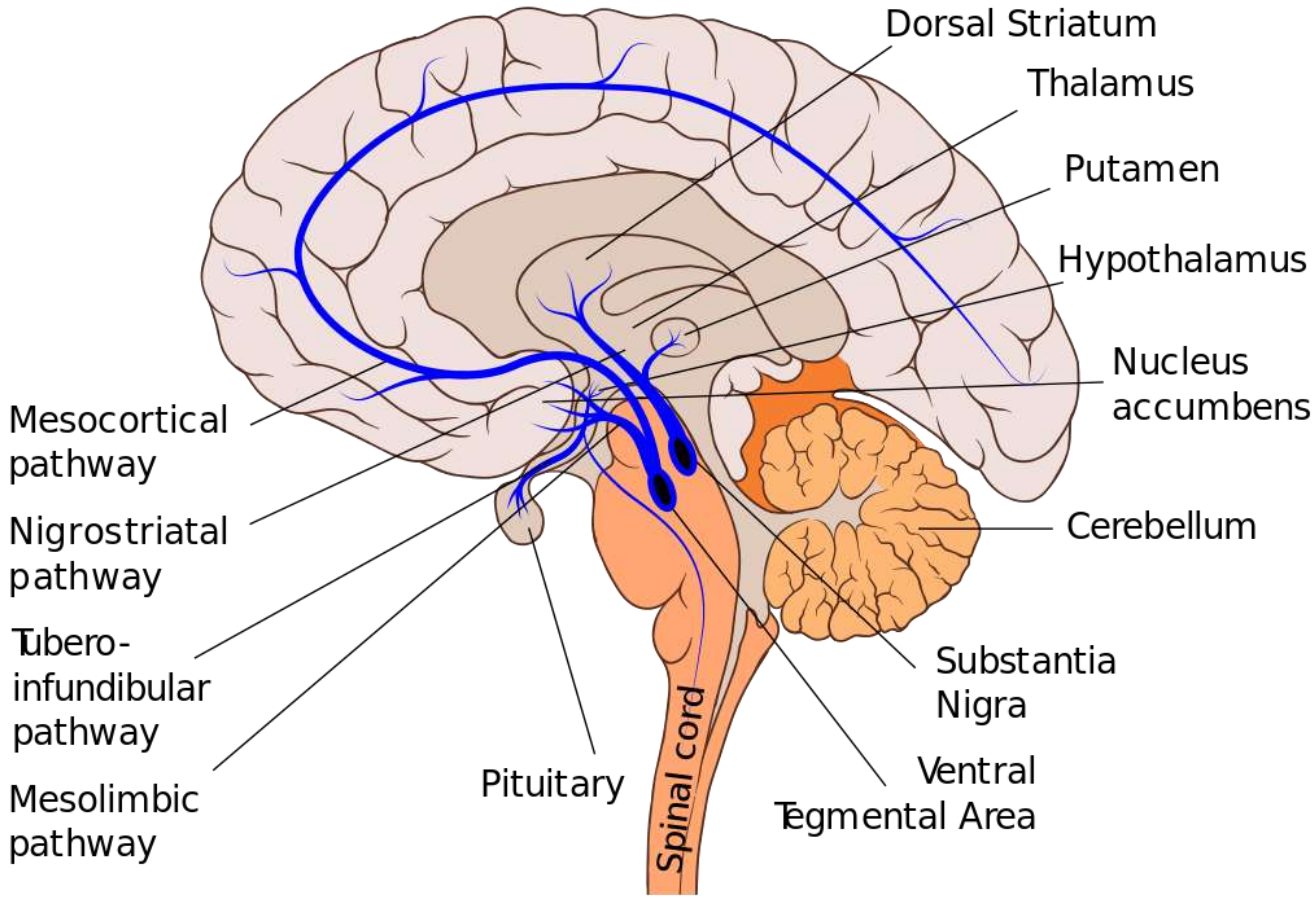
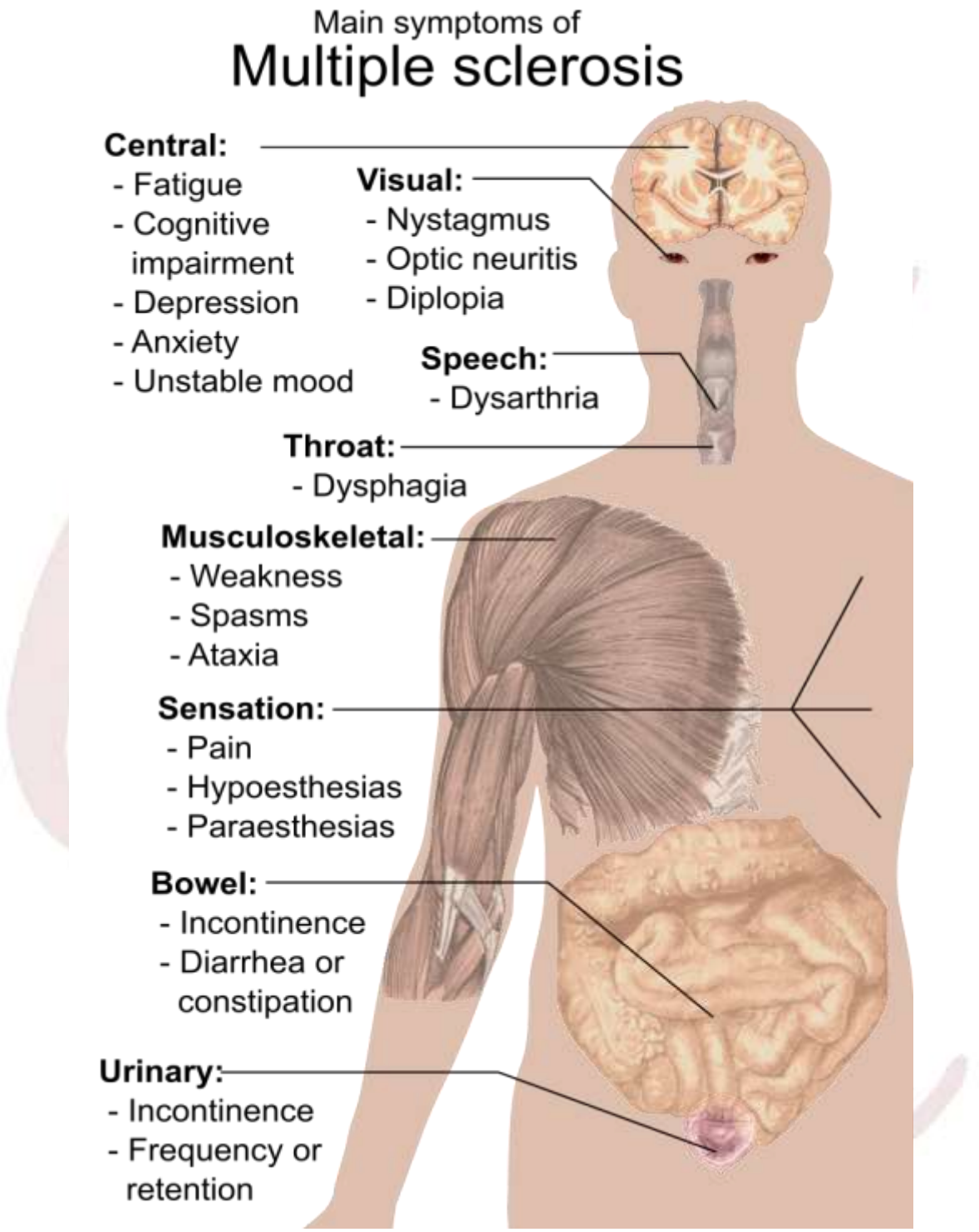


Figure 11: Illustrating the dopamine pathways throughout the brain



Source: Mikael Haggstrom

Figure 12: Main symptoms of multiple sclerosis

B. Concerning Demyelinating Encephalopathies

Autoimmune - Multiple sclerosis (MS) or multiple cerebrospinal sclerosis (MCSS):

The most common demyelinating disease in which the insulating covers of nerve cells in the brain and spinal cord are damaged. This damage disrupts the ability of parts of the nervous system to transmit signals, resulting in a range of signs and symptoms, including physical, mental, and sometimes psychiatric problems. Specific symptoms can include double vision, visual loss, muscle weakness, and trouble with sensation or coordination. MS takes several forms, with new symptoms either occurring in isolated attacks (relapsing forms) or building up over time (progressive forms). While the cause is unclear, the underlying mechanism is thought to be either destruction by the immune system or failure of the myelin-producing cells. Proposed causes for this include genetics and environmental factors, such as viral infections. No cure for MS is known. MS is the most common immune-mediated disorder affecting the CNS. (Figure 12 above schematically describes the main symptoms of MS. Note the cognitive impairment.)

- **Autoimmune - Neuromyelitis optica (NMO) and NMO spectrum disorders (NMOSD):** Autoimmune diseases characterized by acute inflammation of the optic nerve: optic neuritis (ON) and spinal cord (myelitis). Episodes of ON and myelitis can be simultaneous or successive. A relapsing disease course is common, especially in untreated patients.The etiology remains unknown (idiopathic NMO). NMO can be similar to MS in clinical and radiological presentation, and MS may very rarely present with an NMO-like phenotype. However, NMO is not related to MS in the vast majority of cases and differs from MS substantially in terms of pathogenesis, clinical presentation, magnetic resonance imaging, cerebrospinal fluid findings, disease course, and prognosis.

- **Autoimmune - Schilder's disease (SD):** May refer to two different diseases– Adrenoleukodystrophy (ALD) and diffuse myelinoclastic sclerosis (DMS).

  (a) ALD: A disease linked to the X chromosome. It is a result of fatty acid buildup caused by failure of peroxisomal fatty acid beta oxidation which results in the accumulation of very long chain fatty acids in tissues throughout the body. The most severely affected tissues are the myelin in the CNS, the adrenal cortex, and the Leydig cells in the testes.

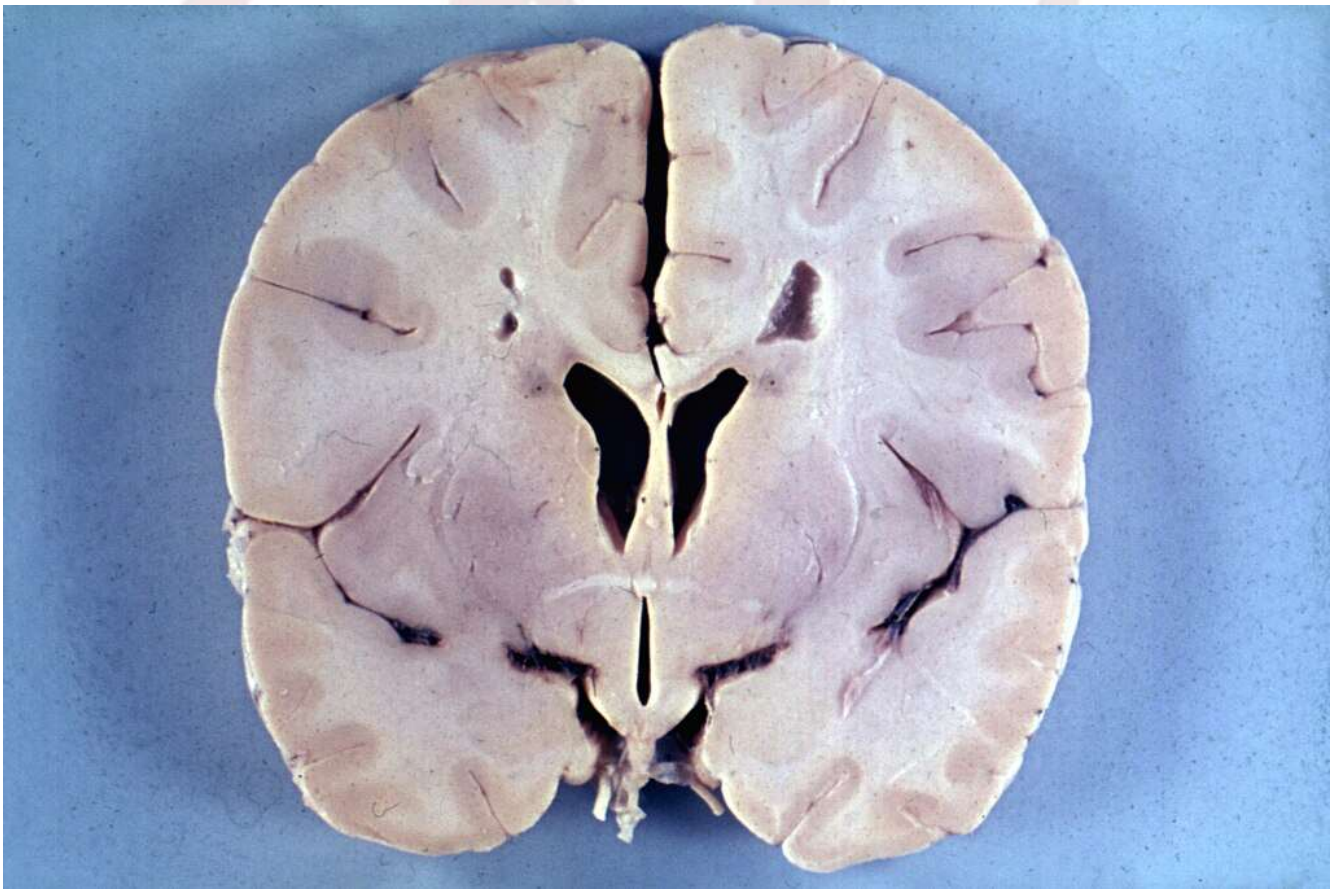
  (b) DMS: A very infrequent neurodegenerative disease that presents clinically as pseudotumoral demyelinating lesions, making its diagnosis difficult. It is considered one of the borderline forms of MS. Other diseases in this group are:

- **Balo concentric sclerosis (BCS) also formerly known as leuko-encephalitis periaxialis concentrica (LEPC):** BCS is a disease in which the white matter of the brain appears damaged in concentric layers, leaving the axis cylinder intact. It is a demyelinating disease similar to standard MS, but with the particularity that the demyelinated tissues form concentric layers. The concentric ring appearance is not specific to Baló's MS. Concentric lesions have also been reported in patients with neuromyelitis optica, standard MS, progressive multifocal leukoencephalopathy, cerebral autosomal dominant arteriopathy with subcortical infarcts, leukoencephalopathy,

concomitant active hepatitis C and human herpes virus 6.

- **Marburg multiple sclerosis (MMS) or acute fulminant multiple sclerosis (AFMS):** MMS is considered one of the MS borderline diseases, which is a collection of diseases classified by some as MS variants and by others as different diseases. Other diseases in this group are neuromyelitis optica (NMO), Balo concentric sclerosis (BCS), and Schilder's disease (SD), and for some as tumefactive multiple sclerosis (TMS).

- **Hereditary - Alexander's disease (AD):** A very rare autosomal dominant leukodystrophy, which is a neurological condition caused by anomalies in the myelin which protects nerve fibers in the brain. The most common type is the infantile form that usually begins during the first two years of life. Symptoms include mental and physical developmental delays, followed by the loss of developmental milestones, an abnormal increase in head size and seizures. Adult-onset forms of AD are less common than the juvenile ones.



Reference: Marvin 101

Figure 13: Neuropathology of Alexander's disease

The symptoms sometimes mimic those of PD or MS, or may present primarily as a psychiatric disorder. AD is a progressive and often fatal disease. Neuropathology of Alexander's disease. (Figure 13 is an archival image of the brain of a 4-year-old boy showing macroencephaly and periventricular demyelinization as noted by the brownish discoloration around the cerebral ventricles.)

- **Hereditary - CAMFAK (or CAMAK syndrome):** (The aconym "CAMFAK" comes from the first letters of the characteristic findings of the disease: cataracts, microcephaly, failure to thrive, and kyphoscoliosis.) A rare inherited neurologic disease, characterized by peripheral and central demyelination of nerves, similar to that seen in Cockayne's syndrome. The disease may occur with or without failure to thrive and arthrogryposis. Severe intellectual deficit and death within the first decade are typical.

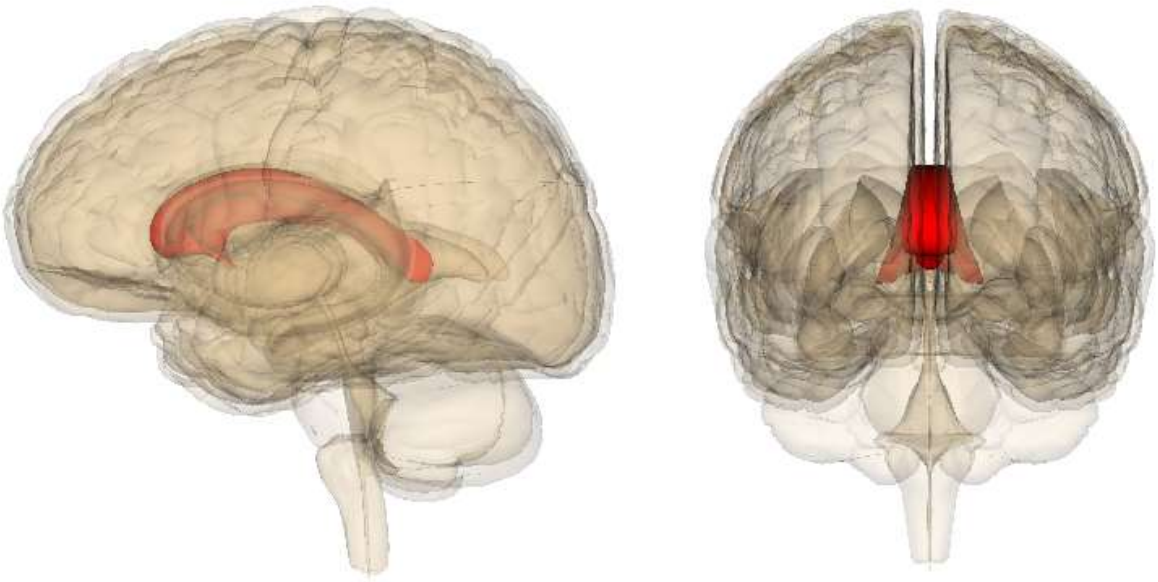
- **Cockayne's syndrome (CS) or Neill-Dingwall syndrome (NDS):** A rare and fatal autosomal recessive neurodegenerative disorder characterized by growth failure, impaired development of the nervous system, abnormal sensitivity to sunlight (photosensitivity), eye disorders and premature aging. Problems with any or all of the internal organs are possible. It is associated with a group of disorders called leukodystrophies, which are conditions characterized by degradation of neurological white matter. There are two primary types of Cockayne syndrome: Cockayne syndrome type A (CSA), arising from mutations in the ERCC8 gene, and Cockayne syndrome type B (CSB), resulting from mutations in the ERCC6 gene. It result in death within the first or second decade of life.

- **Hereditary − Canavan's disease (CD) or Canavan–Van Bogaert–Bertrand (CBBD) disease:** A rare and fatal autosomal recessive degenerative disease that causes progressive damage to nerve cells and loss of white matter in the brain. It is one of the most common degenerative cerebral diseases of infancy. It is caused by a deficiency of the enzyme aminoacylase 2 and is one of a group of genetic diseases referred to as leukodystrophies. It is characterized by degeneration of myelin in the phospholipid layer insulating the axon of a neuron and is associated with a gene located on human chromosome 17. Symptoms of the most common (and most serious) form of CD typically appear in early infancy usually between the first three to six months of age. CD then progresses rapidly from that stage, with typical cases involving intellectual disability, loss of previously acquired motor skills, feeding difficulties, abnormal muscle tone (i.e., initial floppiness - hypotonia - that may eventually translate into spasticity), poor head control, and megalocephaly (abnormally enlarged head). Paralysis, blindness, or seizures may also occur.

- **Hereditary - Krabbe's disease (KD) or globoid cell leukodystrophy (GCL) or galactosylceramide lipidosis (GSL):** A rare and often fatal lysosomal storage disease that results in progressive damage to the nervous system. KD involves dysfunctional metabolism of sphingolipids and is inherited in an autosomal recessive pattern. The buildup of unmetabolized lipids adversely affects the growth of the nerve's protective myelin sheath (the covering that insulates many nerves) resulting in demyelination and severe progressive degeneration of motor skills. As part of a group of disorders known as leukodystrophies, KD results from the imperfect growth and development of myelin.

- **Hereditary - Marchiafava–Bignami disease (MBD):** A progressive neurological disease of alcohol use disorder, characterized by corpus callosum demyelination and necrosis and subsequent atrophy. Here, the middle two-thirds of the corpus callosum becomes necrotic. It is

very difficult to diagnose and there is no specific treatment (Figure 14).



Source: Anatomography maintained by Life Science Databases (LSDB)

Figure 14: Corpus callosum in Marchiafava–Bignami disease (MBD)

- **Hereditary – Myelinolysis - central pontine (MCP):** A neurological condition involving severe damage to the myelin sheath of nerve cells in the pons (an area of the brainstem). It is predominately iatrogenic (treatment-induced), and is characterized by acute paralysis, dysphagia (difficulty swallowing), dysarthria (difficulty speaking), and other neurological symptoms. It was described as a disease of alcoholics and malnutrition. It is distinct from demyelinating conditions such as multiple sclerosis and other neuroinflammatory disorders. Central pontine myelinolysis, and osmotic demyelination syndrome, present most commonly as a complication of treatment of patients with profound hyponatremia (low sodium), which can result from a varied spectrum of conditions, based on different mechanisms. It occurs as a consequence of a rapid rise in serum tonicity following treatment in individuals with chronic, severe hyponatremia who have made intracellular adaptations to the prevailing hypotonicity.

C. CONCERNING EPISODIC/PAROXYSMAL ENCEPHALOPATHIES

C.1 Seizures, Epilepsy

- **Dravet's syndrome (DS) previously known as severe myoclonic epilepsy of infancy (SMEI):** An autosomal dominant genetic disorder which causes a catastrophic form of epilepsy. It is characterized by prolonged febrile and non-febrile seizures within the first year of a child's life. The disease progresses to other seizure types like myoclonic and partial seizures, psychomotor delay, and ataxia. It is characterized by cognitive impairment, behavioral disorders, and motor deficits. Behavioral deficits often include hyperactivity and impulsiveness, and in more rare cases, autistic-like behaviors. DS is also associated with sleep disorders including somnolence and insomnia. The associated seizures become worse as the patient ages. Children with DS typically experience a lagged development of language and motor skills, hyperactivity and sleep difficulties, chronic infection, growth and balance issues, and difficulty relating to others.

- **Epilepsy:** A group of non-communicable neurological disorders characterized by recurrent epileptic seizures. (An epileptic seizure is the clinical manifestation of an abnormal, excessive, purposeless and synchronized electrical discharge in the brain cells called neurons.) Epileptic seizures can vary from brief and nearly undetectable periods to long periods of vigorous shaking due to abnormal electrical activity in the brain. These episodes can result in physical injuries, either directly such as broken bones or through causing accidents. Seizures tend to recur and may have no immediate underlying cause. The cause of epilepsy is unknown (cryptogenic); some cases occur as the result of brain injury, stroke, brain tumors, infections of the brain, or birth defects through a process known as epileptogenesis. Known genetic mutations are directly linked to a small proportion of cases.

- **Lennox-Gastaut syndrome (LGS):** A complex, rare, and severe childhood-onset epilepsy. It is characterized by multiple and concurrent seizure types including tonic seizure, cognitive dysfunction, and abnormal aspect on electroencephalogram (EEG) such as slow spike waves. Typically, it presents in children aged 3–5 years and most of the time persists into adulthood with slight changes in the electroclinical phenotype. It has been associated with perinatal injuries, congenital infections, brain malformations, brain tumors, genetic disorders such as tuberous sclerosis and several gene mutations. Sometimes, LGS is observed after infantile epileptic spasm syndrome formerly called West's syndrome (WS).

C.2 Headaches

- **Migraine:** A genetically-influenced complex neurological disorder characterized by episodes of moderate-to-severe headache, most often unilateral, and generally associated with nausea and light and sound sensitivity. Other characterizing symptoms may include vomiting, cognitive dysfunction, allodynia, and dizziness. Exacerbation of headache symptoms during physical activity is another distinguishing feature.Up to one-third of migraine sufferers experience 'aura': a premonitory period of sensory disturbance widely accepted to be caused by cortical spreading depression at the

onset of a migraine attack. Although primarily considered to be a headache disorder, migraine is highly heterogenous neurological disease in its clinical presentation and is better thought of as a spectrum disease rather than a distinct clinical entity.The currently accepted theory suggests that multiple primary neuronal impairments lead to a series of intracranial and extracranial changes, triggering a physiological cascade that leads to migraine symptomatology. Migraine is associated with psychiatric disorders (major depression, bipolar disorder, anxiety disorders, and obsessive–compulsive disorder).

C.3 Cerebrovascular diseases

- **Aphasia (see also above primary progressive aphasia, PPA):** Aphasia is related to the individual's language cognition. In aphasia, a person may be unable to comprehend or unable to formulate language because of damage to specific brain regions. It can be due to stroke, head trauma, epilepsy, brain tumors, brain damage and brain infections, or neurodegenerative diseases (such as dementias). In the case of progressive aphasia, the four aspects of communication (spoken language production and comprehension, and written language production and comprehension) must have significantly declined over a short period of time. Impairments in any of these aspects can impact on functional communication. Intelligence, however, is unaffected. Aphasia also affects visual language such as sign language. In contrast, the use of formulaic expressions in everyday communication is often preserved. One prevalent deficit in the aphasias is a difficulty in finding the correct word (anomia).

- **Amaurosis fugax:** A painless temporary loss of vision in one or both eyes that appears as a "black curtain coming down vertically into the field of vision, monocular blindness, dimming, fogging, or blurring. Total or sectorial vision loss typically lasts only a few seconds, but may last minutes or even hours. Duration depends on the cause of the vision loss. Obscured vision due to papilledema may last only seconds, while a severely atherosclerotic carotid artery may be associated with a duration of one to ten minutes.

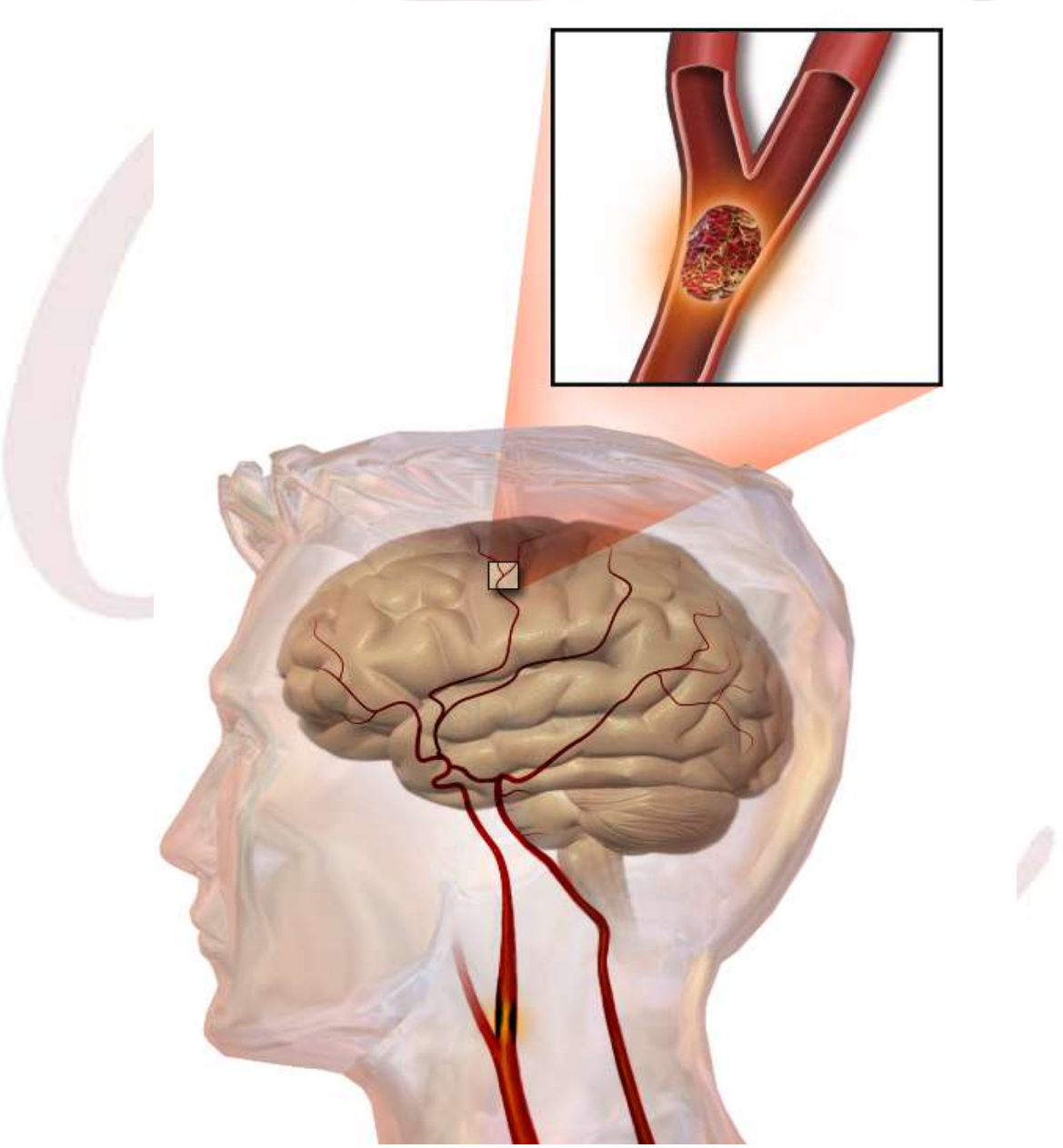
- **Foville's syndrome (FS):** It is caused by the blockage of the perforating branches of the basilar artery in the region of the brainstem known as the pons. It is most frequently due to lesions such as vascular disease and tumors involving the dorsal pons.

- **Stroke:** A medical condition in which poor blood flow to the brain causes cell death. There are two main types: ischemic (due to lack of blood flow) or hemorrhagic (due to bleeding). Both cause parts of the brain to stop functioning properly. Signs and symptoms may include an inability to move or feel on one side of the body, problems understanding or speaking, dizziness, or loss of vision to one side. They often appear soon after the stroke has occurred. If symptoms last less than one or two hours, the stroke is a 'transient ischemic attack' (TIA), also called a 'mini-stroke'.

  A hemorrhagic stroke may also be associated with a severe headache. The symptoms of a stroke can be permanent. Long-term complications may include pneumonia and loss of bladder control. Bleeding may occur due to a ruptured brain aneurysm. The biggest risk factor for stroke is high blood pressure. Other risk factors include high blood cholesterol, tobacco smoking, obesity, diabetes mellitus, a previous TIA, end-stage kidney disease, and

atrial fibrillation. (Figure 15 illustrates an embolic stroke showing a blockage lodged in a blood vessel.)

- **Transient global amnesia (TGA):** A neurological disorder whose key defining characteristic is a temporary but almost total disruption of short-term memory with a range of problems accessing older memories. A person in a state of TGA exhibits no other signs of impaired cognitive functioning but recalls only the last few moments of consciousness, as well as possibly a few deeply encoded facts of the individual's past, such as their childhood, family, or home perhaps. Both TGA and anterograde amnesia (ARA) deal with disruptions of short-term memory.



Reference: Blausen Medical Communications

Figure 15: Illustration of embolic stroke showing blockage lodged in blood vessel

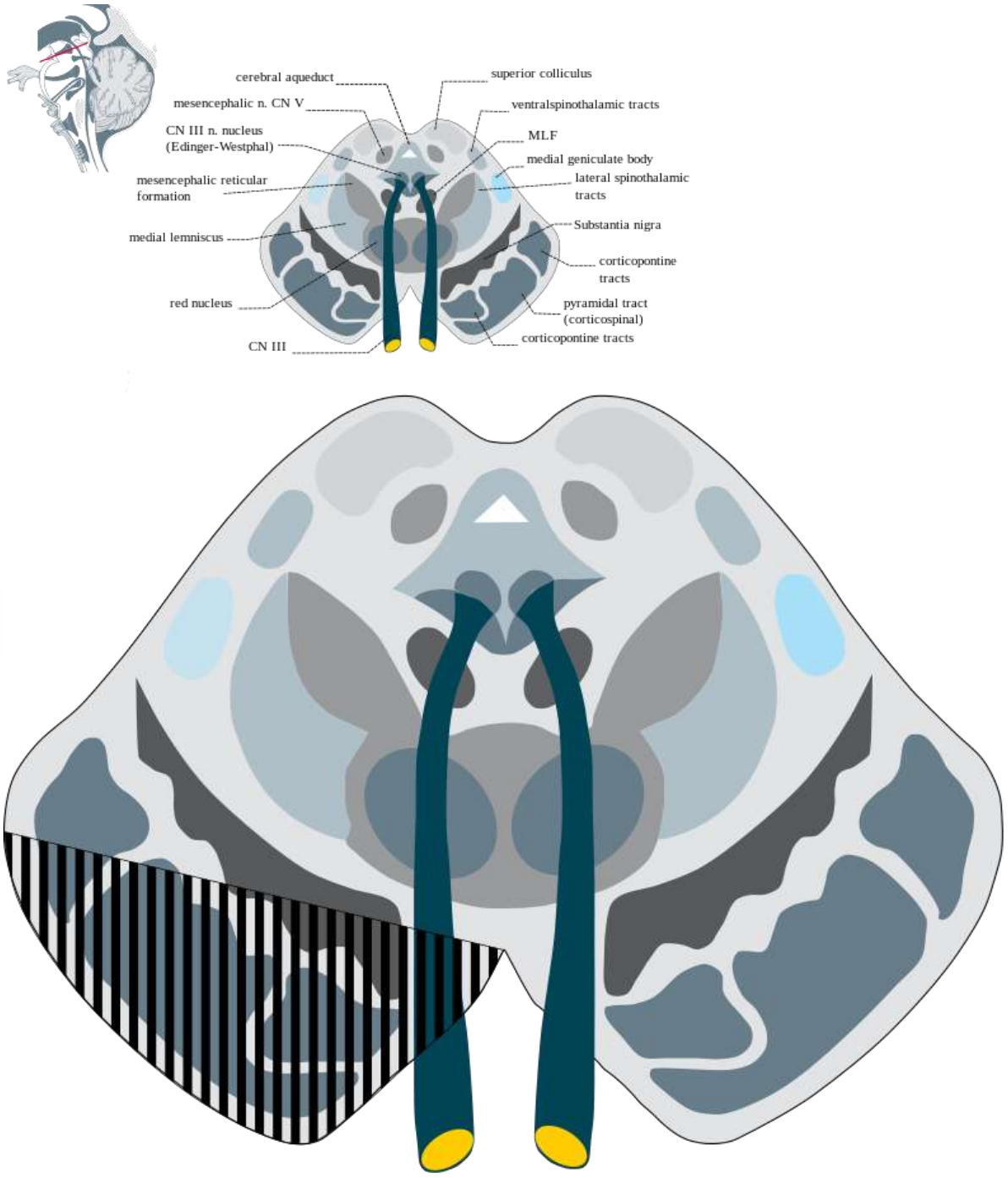


Figure 16: Illustrating Weber's syndrome

- **Weber's syndrome (WS) also known as midbrain stroke syndrome (MSS) or superior alternating hemiplegia (SAH):** A form of stroke that affects the medial portion of the midbrain. It involves oculomotor fascicles in the interpeduncular cisterns and cerebral peduncle so it characterizes the presence of an ipsilateral lower motor neuron type oculomotor nerve palsy and contralateral hemiparesis or hemiplegia (Figure 16).

C.4 Sleep disorders

- **Cataplexy:** A sudden and transient episode of muscle weakness accompanied by full conscious awareness. It is, typically triggered by emotions such as laughing, crying, or terror. It is caused by an autoimmune destruction of hypothalamic neurons that produce the neuropeptide hypocretin (also called orexin), which regulates arousal and has a role in stabilization of the transition between wake and sleep states. Cataplexy without narcolepsy is rare and the cause is unknown.

- **Narcolepsy:** A chronic neurological syndrome of hypothalamic disorder that involves a decreased ability to regulate sleep–wake cycles.

  Symptoms often include periods of excessive daytime sleepiness and brief involuntary sleep episodes, vivid hallucinations or an inability to move (sleep paralysis) while falling asleep or waking up. Narcolepsy paired with cataplexy is an autoimmune disorder. There are two main characteristics of narcolepsy: excessive daytime sleepiness and abnormal REM sleep. A person with narcolepsy is likely to become drowsy or fall asleep, often at inappropriate or undesired times and places, or just be very tired throughout the day.

- **Sleep apnea (SA):** A sleep disorder in which pauses in breathing or periods of shallow breathing during sleep occur more often than normal. SA may be either obstructive sleep apnea (OSA), the most common form in which breathing is interrupted by a blockage of air flow, or central sleep apnea (CSA) in which regular unconscious breath simply stops, or a combination of the two. OSA has four key contributors (a narrow, crowded, or collapsible upper airway; an ineffective pharyngeal dilator muscle function during sleep; airway narrowing during sleep; and unstable control of breathing).

  It is often a chronic condition. Episodes of hypoxemia (drop in the percentage of oxygen in the circulation to a lower than normal level) and hypercapnia (concentration of carbon dioxide higher than normal level) will trigger additional effects on the body. Further, if the level of blood oxygen goes low enough for long enough, brain damage and even death can occur. A systemic disorder, sleep apnea is associated with a wide array of effects, including increased risk of car accidents, hypertension, cardiovascular disease, myocardial infarction, stroke, atrial fibrillation, insulin resistance, higher incidence of cancer, and neurodegeneration.

  Alzheimer's disease (AD) and severe obstructive sleep apnea are connected because there is an increase in the protein beta-amyloid as well as white-matter damage. AD in this case comes from the lack of proper rest or poorer sleep efficiency resulting in neurodegeneration. Having sleep apnea in mid-life brings a higher likelihood of developing AD in older age, and if one has AD then one is also more likely to have

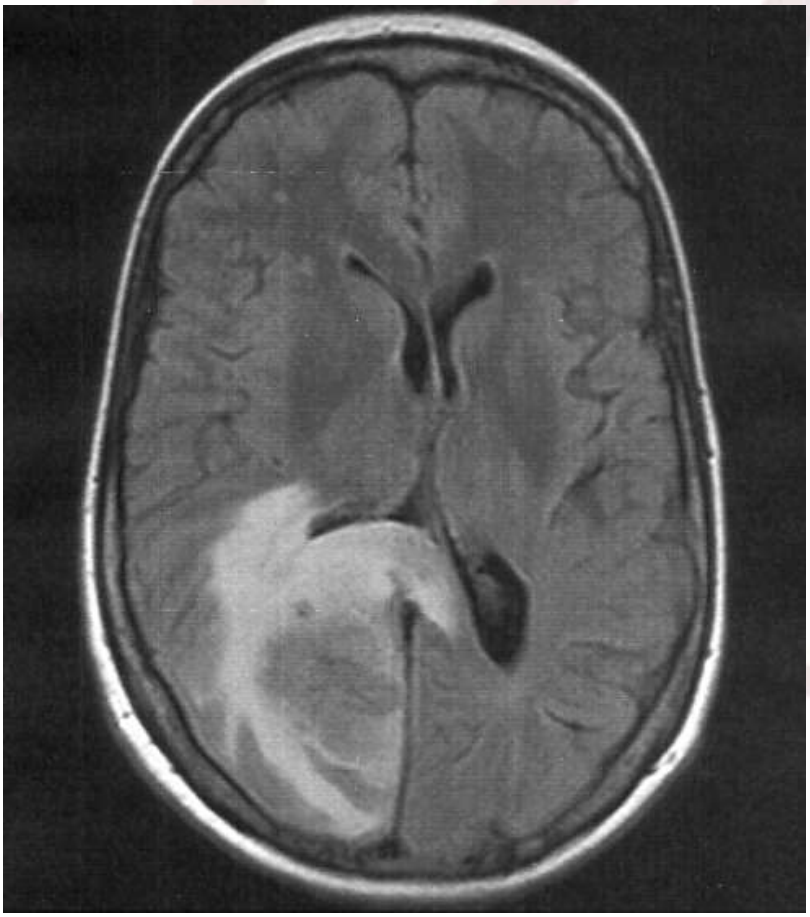
sleep apnea.

- **Hypoventilation (or respiratory depression) syndrome (RDS):** It occurs when ventilation is inadequate to perform needed respiratory gas exchange. It causes an increased concentration of carbon dioxide (hypercapnia) and respiratory acidosis. Hypoventilation is not synonymous with respiratory arrest, in which breathing ceases entirely and death occurs within minutes due to hypoxia and leads rapidly into complete anoxia, however, both are medical emergencies.

  Hypoventilation can be considered a precursor to hypoxia and its lethality is attributed to hypoxia with carbon dioxide toxicity.

D. Concerning Cerebrospinal Fluid Diseases

- Cerebral edema (CE): The excess accumulation of fluid (edema) in the intracellular or extracellular spaces of the brain. This typically causes impaired nerve function and increased pressure within the skull, and can eventually lead to direct compression of brain tissue and blood vessels. Symptoms vary based on the location and extent of edema and generally include headaches, nausea, vomiting, seizures, drowsiness, visual disturbances, dizziness, and in severe cases, coma and death.



Reference: Dragher01

Figure 17: MRI image of a brain metastasis with accompanying edema

CE is commonly seen in a variety of brain injuries including: Ischemic stroke; subarachnoid hemorrhage; traumatic brain injury (TBI); subdural, epidural, or intracerebral hematoma; hydrocephalus; brain cancer; brain infections; low blood sodium levels; and acute liver failure. CE is a major cause of brain damage and contributes significantly to the mortality of ischemic strokes and TBIs. (Figure 17 is a skull MRI (T2 flair) scan of a brain metastasis with accompanying edema.)

- Choroid plexus papilloma (CPP): A rare benign neuroepithelial intraventricular lesion found in the choroid plexus. It leads to increased cerebrospinal fluid production, thus causing increased intracranial pressure and hydrocephalus. CPP occurs in the lateral ventricles of children and in the fourth ventricle of adults. This is unlike most other pediatric tumors and adult tumors, in which the locations of the tumors is reversed. In children, brain tumors are usually found in the infratentorial region and in adults, brain tumors are usually found in the supratentorial space. The relationship is reversed for choroid plexus papillomas (Figure 18).

- Normal pressure hydrocephalus (NPH): A condition in which an accumulation of cerebrospinal fluid (CSF) occurs within the brain. This typically causes increased pressure inside the skull. Older people may have headaches, double vision, poor balance, urinary incontinence, personality changes, or mental impairment. In babies, it may be seen as a rapid increase in head size. Other symptoms may include vomiting, sleepiness, seizures, and downward pointing of the eyes. The four types of hydrocephalus are communicating, non-communicating, ex vacuo, and normal pressure. Hydrocephalus can occur due to birth defects or be acquired later in life. Causes include meningitis, brain tumors, traumatic brain injury, intraventricular hemorrhage, and subarachnoid hemorrhage. (Figure 19 is a brain-CT scan with hydrocphalus.)

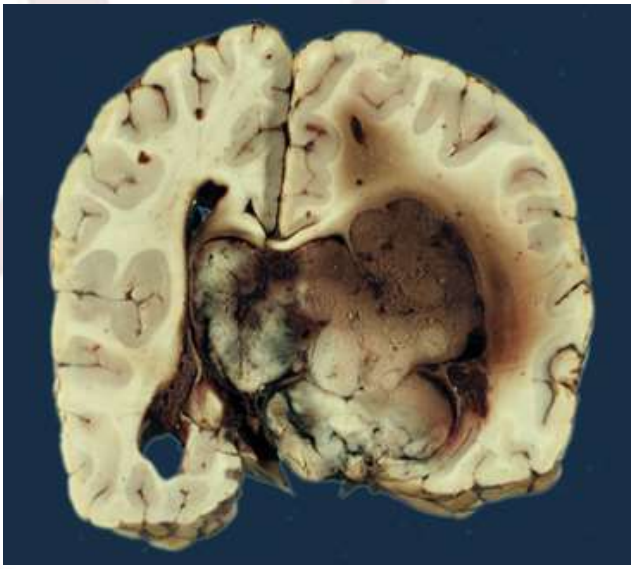
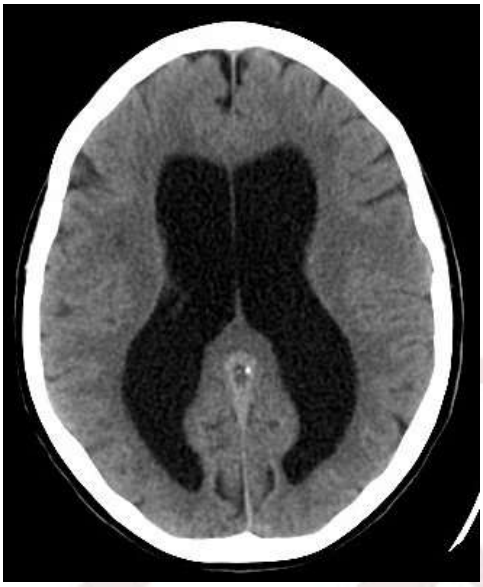


Figure 18: Choroid plexus papilloma



Reference: Lucien Monfils

Figure 19: CT scan of the brain with hydrocephalus

E. CONCERNING OTHER DISEASES

- Brain herniation: A potentially deadly side effect of very high pressure within the skull that occurs when a part of the brain is squeezed across structures within the skull. The brain can shift across such structures as the falx cerebri, the tentorium cerebelli, and even through the foramen magnum (the hole in the base of the skull through which the spinal cord connects with the brain).

  Herniation can be caused by a number of factors that cause a mass effect and increase intracranial pressure (ICP): these include traumatic brain injury (TBI), intracranial hemorrhage, or brain tumor.

  Herniation can also occur in the absence of high ICP when mass lesions such as hematomas occur at the borders of brain compartments. In such cases local pressure is increased at the place where the herniation occurs, but this pressure is not transmitted to the rest of the brain, and therefore does not register as an increase in ICP.

  Because herniation puts extreme pressure on parts of the brain and thereby cuts off the blood supply to various parts of the brain, it is often fatal. (Figure 20 is an MRI image showing injury due to brain herniation in a patient with choriocarcinoma.)

- Encephalopathy: Any disorder or disease of the brain, especially chronic degenerative conditions. It does not refer to a single disease, but rather to a syndrome of overall brain dysfunction. It has many possible organic and inorganic causes.

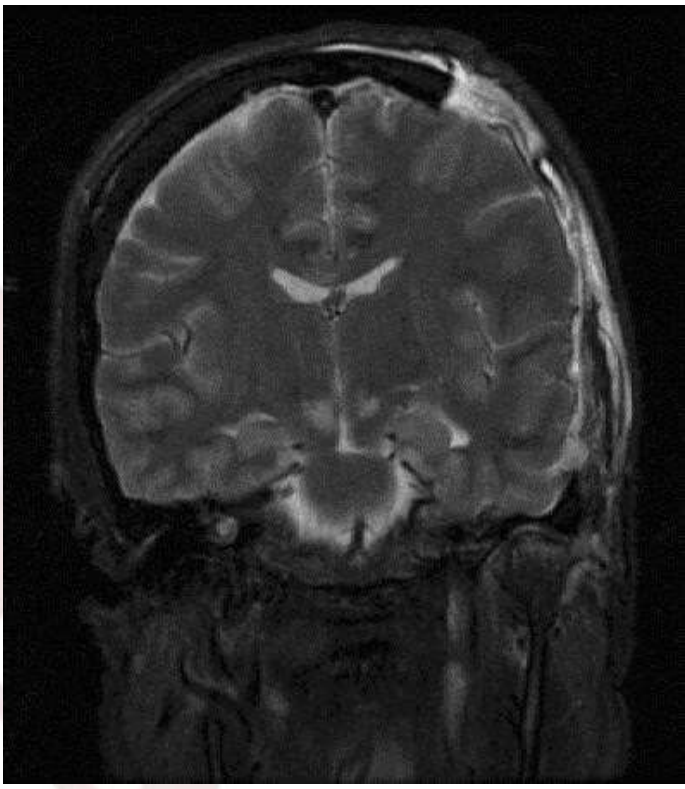
  The hallmark of encephalopathy is an altered mental state or delirium. Characteristic of the altered mental state is impairment of the cognition, attention, orientation, sleep–wake cycle and consciousness.

  An altered state of consciousness may range from failure of selective attention to drowsiness. Hypervigilance may be present; with or without: cognitive deficits, headache, epileptic seizures, myoclonus (involuntary twitching of a muscle or group of muscles) or asterixis ("flapping tremor" of the hand when wrist is extended).

  Depending on the type and severity of encephalopathy, common neurological symptoms are loss of cognitive function, subtle personality changes, and an inability to concentrate.

  Other neurological signs may include dysarthria, hyponimia, problems with movements (they can be clumsy or slow), ataxia, tremor. Other neurological signs may include involuntary

grasping and sucking motions, nystagmus (rapid, involuntary eye movement), jactitation (restlessness while in bed), and respiratory abnormalities such as Cheyne-Stokes respiration (cyclic waxing and waning of tidal volume), apneustic respirations and post-hypercapnic apnea. Focal neurological deficits are less common.



Reference: Rocque BG, Başkaya MK (2008). "Spontaneous acute subdural hematoma as an initial presentation of choriocarcinoma: A case report". J Med Case Reports 2:211. doi:10.1186/1752-1947-2-211.

Figure 20: Coronal MRI showing brain herniation injury

- **Wernicke's encephalitis (WE):** It can co-occur with Korsakoff's alcoholic syndrome, characterized by amnestic-confabulatory syndrome: retrograde amnesia, anterograde amnesia, confabulations (invented memories), poor recall, and disorientation.

  ◦ **Anti-NMDA receptor encephalitis:** The most common autoimmune encephalitis. It can cause paranoid and grandiose delusions, agitation, hallucinations (visual and auditory), bizarre behavior, fear, short-term memory loss, and confusion.

  ◦ **HIV encephalopathy:** It can lead to dementia.

  ◦ **Hashimoto's encephalitis (HE):** A steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT). It is a neurological condition characterized by

encephalopathy, thyroid autoimmunity, and good clinical response to corticosteroids. It is associated with Hashimoto's thyroiditis.

- **Reye's syndrome (RS):** A rapidly worsening brain disease. Symptoms may include vomiting, personality changes, confusion, seizures, and loss of consciousness. While liver toxicity typically occurs in the syndrome, jaundice usually does not. The cause is unknown.

Spinal Cord Myelopathies

Diseases of the central nervous system due to the spinal cord are charted in Table 3.

Organ	Disorders/diseases
Spinal cord/Myelopathy	• o Foix-Alajouanine syndrome (FAS) • o Morvan's syndrome (MS) • o Spinal cord compressiom (SCC) • o Syringobulbia • o Syringomyelia • o Vascular myelopathy (VM)

Table 3: Diseases of the central nervous system: Spinal cord

- **Morvan's syndrome (MS) or fibrillary chorea (FC) (in French: la chorée fibrillaire):**

  A rare, life-threatening autoimmune disease describing patients with multiple, irregular contractions of the long muscles, cramping, weakness, pruritus, hyperhidrosis, insomnia, and delirium. This rare disorder is characterized by severe insomnia, amounting to no less than complete lack of sleep (agrypnia) for weeks or months in a row, and associated with autonomic alterations consisting of profuse perspiration with characteristic skin miliaria (also known as sweat rash), tachycardia, increased body temperature, and hypertension. Patients display a remarkable hallucinatory behavior, and peculiar motor disturbances, which are best described as neuromyotonic discharges. The association of the disease with thymoma, tumor, autoimmune diseases, and autoantibodies suggests an autoimmune or paraneoplastic etiology. Besides an immune-mediated etiology, it is also believed to occur in gold, mercury, or manganese poisoning.

- **Spinal cord compressiom (SCC):** A form of myelopathy in which the spinal cord is compressed. Causes can be bone fragments from a vertebral fracture, a tumor, abscess, ruptured intervertebral disc or other lesion.

- **Syringobulbia:** A medical condition in which syrinxes, or fluid-filled cavities, affect the brainstem (usually the lower brainstem). The exact cause is often unknown, but may be linked to a widening of the central canal of the spinal cord. This may affect one or more cranial nerves, resulting in various kinds of facial palsies. Sensory and motor nerve pathways may be affected by interruption or compression of nerves.

- **Syringomyelia:** A generic term referring to a disorder in which a cyst or cavity (called syrinx) forms within the spinal cord. This cyst can expand and elongate over time, destroying the spinal cord. The damage may result in loss of feeling, paralysis, weakness, and stiffness in the back, shoulders, and extremities. Syringomyelia may also cause a loss of the ability to feel extremes of hot or cold, especially in the hands. It may also lead to a cape-like bilateral loss of pain and temperature sensation along the upper chest and arms.

- **Vascular myelopathy (VM):** Refers to an abnormality of the spinal cord in regard to its blood supply. The blood supply is complicated and supplied by two major vessel groups: the posterior spinal arteries and the anterior spinal arteries; both arteries running the entire length of the spinal cord and receiving anastomotic (conjoined) vessels in many places. The anterior spinal artery has a less efficient supply of blood and is therefore more susceptible to vascular disease. Whilst atherosclerosis of spinal arteries is rare, necrosis (death of tissue) in the anterior artery can be caused by disease in vessels originating from the segmental arteries such as atheroma (arterial wall swelling) or aortic dissection (a tear in the aorta).

- **Foix-Alajouanine syndrome (FAS) or subacute ascending necrotizing myelitis (SANM):** A disease caused by an arteriovenous malformation of the spinal cord. Most cases involve dural arteriovenous malformations that present in the lower thoracic or lumbar spinal cord. Patients can present with symptoms indicating spinal cord involvement such as (paralysis of arms and legs, numbness and loss of sensation and sphincter dysfunction) and disseminated nerve cell death in the spinal cord.

Encephalopathies or/and Myelopathies

CNS diseases that are either or both encephalopathy and spinal cord/myelopathy are summarized in Table 4:

Characteristic	Disease category	Diseases
Degenerative	**A. Ataxia**	o Ataxia telangectasia (AT) o Friedreich's ataxia (FA)
	B. Motor Neuron Diseases (MND)	*LMN only:* ◦ o Atrophy: ◦ - Progressive muscular (PMA) ◦ - Spinal Muscular (SMA) ◦ - Congenital Distal Spinal Muscular (cdSMA) ◦ - DSMA1 ◦ - SMA-LED ◦ - SMA-PCH ◦ - SMA-PME ◦ - SMAX1 ◦ - SMAX2

		◦ o Distal hereditary motor neuropathies *UMN only:* ◦ o Palsy: ◦ - Progressive bulbar (PBP) ◦ - Fazio-Lande infantile (IFLP) ◦ - Pseudobulbar (PBP) ◦ o Paraplegia: ◦ - Hereditary spastic (HSP) ◦ o Sclerosis: Primary lateral ▪ *Both LMN, UMN:* ▪ o Amyotrophic lateral sclerosis (ALS)

Table 4: Diseases of the central nervous system: Either/both encephalopathy, spinal cord/myelopathy

Degenerative

A. CONCERNING ATAXIA

- Ataxia telangectasia (AT) or ataxia–telangiectasia syndrome (ATS) or Louis–Barre syndrome (LBS): A rare, neurodegenerative, autosomal recessive disease causing severe disability. Ataxia refers to poor coordination and telangiectasia to small dilated blood vessels, both of which are hallmarks of the disease.

  It impairs certain areas of the brain including the cerebellum, causing difficulty with movement and coordination. It weakens the immune system, causing a predisposition to infection. Lastly, it prevents repair of broken DNA, increasing the risk of cancer.

- Friedreich's ataxia (FA): An autosomal-recessive genetic disease that causes difficulty walking, a loss of coordination in the arms and legs, and impaired speech that worsens over time.

  Many develop hypertrophic cardiomyopathy and require a mobility aid. As the disease progresses, some affected people lose their sight and hearing. Other complications may include scoliosis and diabetes mellitus.

B. CONCERNING MOTOR NEUROSN DISEASES (MND)

Atrophies

- **Progressive muscular atrophy (PMA) or Duchesne–Aran disease (DAD) or Duchesne –Aran muscular atrophy (DAMA):** A disorder characterized by the degeneration of lower motor neurons, resulting in generalized, progressive loss of muscle function. This is to be contrasted with amyotrophic lateral sclerosis (ALS), the most common MND, which affects

both the upper and lower motor neurons, or primary lateral sclerosis (PLS), another MND, which affects only the upper motor neurons. The distinction is important because PMA is associated with a better prognosis than ALS.

- **Spinal muscular atrophy (SMA):** A genetically and clinically heterogeneous group of rare debilitating disorders characterized by the degeneration of lower motor neurons (neuronal cells situated in the anterior horn of the spinal cord) and subsequent atrophy (wasting) of various muscle groups in the body.

- **Congenital distal spinal muscular atrophy (cdSMA):** A hereditary condition characterized by muscle wasting (atrophy), particularly of distal muscles in legs and hands, and by early-onset contractures (permanent shortening of a muscle or joint) of the hip, knee, and ankle. The condition is a result of a loss of anterior horn cells localized to lumbar and cervical regions of the spinal cord early in infancy, which in turn is caused by a mutation of the TRPV4 gene. The disorder is inherited in an autosomal dominant manner.

Neuropathies

- **Distal hereditary motor neuropathies (dHMN):** A genetically and clinically heterogeneous group of motor neuron diseases that result from genetic mutations in various genes and are characterized by degeneration and loss of motor neuron cells in the anterior horn of the spinal cord and subsequent muscle atrophy.

- **Palsy:** A medical term referring to various types of paralysis or paresis, often accompanied by weakness and the loss of feeling and uncontrolled body movements such as shaking.

Specific kinds of palsy include:

- Bell's palsy: Partial facial paralysis.
- Bulbar palsy: Impairment of cranial nerves.
- Cerebral palsy: A neural disorder caused by intracranial lesions.
- Conjugate gaze palsy: A disorder affecting the ability to move the eyes.
- Erb's palsy (or brachial palsy): It involves paralysis of an arm.
- Fazio-Lande infantile palsy.
- Spinal muscular atrophy (or wasting palsy).
- Progressive supranuclear palsy: A degenerative disease.
- Squatter's palsy: A bilateral peroneal nerve palsy that may be triggered by sustained squatting.
- Third nerve palsy: Involves the cranial nerve III.

Paraplegia

- Hereditary spastic paraplegia (HSP) or hereditary spastic paraparesis (HSP), or familial spastic paraplegia (FSP), or French settlement disease (FSD), or Strumpell disease (SD), or Strumpell-Lorrain disease. (SLD): A group of inherited diseases whose main feature is a progressive gait disorder. The disease presents with progressive stiffness (spasticity) and contraction in the lower limbs. It is different from cerebral palsy.

- Primary lateral sclerosis (PLS): A very rare neuromuscular disease characterized by progressive muscle weakness in the voluntary muscles. It belongs to a group of disorders known as motor neuron diseases (MND, discussed earlier) which develop when the nerve cells that control voluntary muscle movement degenerate and die, causing weakness in the muscles they control. It only affects upper motor neurons with no evidence of the degeneration of spinal motor neurons or muscle wasting (amyotrophy) that occurs in

amyotrophic lateral sclerosis (ALS).

- Amyotrophic lateral sclerosis (ALS) also known as Lou Gehrig's disease: A rare neurodegenerative disease that results in the progressive loss of motor neurons that control voluntary muscles. It is the most common form of the motor neuron diseases. Around half of people with ALS develop at least mild difficulties with thinking and behavior, and about 15% develop frontotemporal dementia. Motor neuron loss continues until the abilities to eat, speak, move, or, lastly, breathe are lost.

In an earlier article in this Journal, I discuss the presence of pathogens in the brain.

Conclusions and take-aways

- The core neuroscience dogma stating that the soma of each neuron communicates simultaneously with thousands of other neurons connected to it has been questioned and rather attributed to dendrites.

- **Pathologies due to inflammation, include:**

◦ Encephalopathy: Degenerative, demyelinating, episodic/paroxysmal, cerebrospinal fluid, and other causes.

◦ Spinal cord/myelopathy, and/or

◦ Degenerative encephalopathy and spinal cord/myelopathy.

- **The severity of encephalitis vary with symptoms including reduction or alteration in consciousness and memory problems.**

- Among the central nervous system's diseases due to encephalopathies, one must distinguish between:

◦ **Degenerative diseases, including:**

▪ Extrapyramidal & movement disorders: Particularly Huntington's disease; myoclonus (Alzheimer's disease, Creutzfeldt-Jakob disease); Parkinson's disease and parkinsonism; panthotenate kinase-associated degeneration; and progressive supranuclear palsy.

▪ Dementias: Including Alzheimer's disease; primary progressive aphasia; posterior cortical atrophy; frontotemporal lobar degeneration, and the various dementias (early onset; frontotemporal; HIV; juvenile; Lewy bodies; late onset; pugilistica; and vascular); Parkinson's disease; synucleinopathies; and tauopathy.

▪ Seizures/epilepsy: Dravet's syndrome; Lennox-Gastaud syndrome.

◦ Demyelinating diseases, including:

▪ Multiple sclerosis; and

▪ Canavan's disease.

◦ Episodic paroxysmal diseases, including:

▪ Seizures;

▪ Cerebrovascular diseases (acute aphasia; stroke; transcranial global amnesia and anteretrograde)

▪ Sleep disorders, especially sleep apnea.

◦ Other related diseases including the encephalopathies of:

▪ Wernicke's;

▪ Anti-MDS receptor; and

▪ HIV.

- Among the central nervous system's neurodegenerative diseases are:

◦ Motor neuron diseases, including particularly:

▪ Amyotrophic lateral sclerosis.

References

1. Bredesen DE, Rao RV, and Mehlen P (2006). "Cell death in the nervous system". Nature 443(7113): 796–802. doi:10.1038/nature05293.
2. Brody DL and Holtzman DM (2008). "Active and passive immunotherapy for neurodegenerative disorders". Annual Review of Neuroscience 31:175–93. doi:10.1146/annurev.neuro.31.060407.125529.
3. Camandola S and Mattson MP (June 2017). "Brain metabolism in health, aging, and neurodegeneration". The EMBO Journal 36(11):1474–92. doi:10.15252/embj.201695810.
4. De Vos KJ, Grierson AJ, Ackerley S, and Miller CC (2008). "Role of axonal transport in neurodegenerative diseases". Annual Review of Neuroscience 31:151–73. doi:10.1146/annurev.neuro.31.061307.090711.
5. Erkkinen MG, Kim M-O, and Geschwind MD (2018). "Clinical neurology and epidemiology of the major neurodegenerative diseases". Cold Spring Harbor Perspectives in Biology 10(4):20. doi:10.1101/cshperspect.a033118.
6. Fymat AL (2018a). "Regulating the brain's autoimmune system: The end of all neurological disorders?" Journal of Current Opinions in Neurological Science 2(3):475-9.
7. Fymat AL (2018b). "Harnessing the immune system to treat cancers and neurodegenerative diseases", Journal of Clinical Research in Neurology 1(1):1-14.
8. Fymat AL (2019). "From The Heart To The Brain: My Collected Works in Medical Science Research (2016- 2018), Tellwell Talent Publishers, pp 580, 1 February 2019. ISBN: 978-0-2288-0910-4 (Hardcover); 978-0-2288-0575-5 (Paperback).
9. Fymat AL (2023). "The aging brain: Structural, biochemical, neuropsychological and genetic changes", Journal of Neurology and Psychology Research XXX
10. Jeppesen DK, Bohr VA, and Stevnsner T (2011). "DNA repair deficiency in neurodegeneration". Progress in Neurobiology 94(2):166–200. doi:10.1016/j.pneurobio.2011.04.013.
11. Kanter I et al. (2023); "Neuronal plasticity features are independent of neuronal holding membrane potential", Physica A.
12. Lin MT and Beal MF (2006). "Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases". Nature 443 (7113):787–95. doi:10.1038/nature05292.
13. Liu Z, Zhou T, Ziegler AC, Dimitrion P, and Zuo L (2017)."Oxidative stress in neurodegenerative diseases: From molecular mechanisms to clinical applications". Oxidative Medicine and Cellular Longevity 2017: 2525967. doi:10.1155/2017/2525967.
14. Lobsiger CS and Cleveland DW (November 2007). "Glial cells as intrinsic components of non-cell- autonomous neurodegenerative disease". Nature Neuroscience 10(11):1355–60. doi:10.1038/nn1988.
15. Madabhushi R, Pan L, and Tsai LH (2014). "DNA damage and its links to neurodegeneration". Neuron 83(2):266–82. doi:10.1016/j.neuron.2014.06.034.
16. Maynard S, Fang EF, Scheibye-Knudsen M, Croteau DL, and Bohr VA (2015). "DNA damage, DNA repair, aging, and neurodegeneration". Cold Spring Harbor Perspectives in Medicine 5 (10):a025130. doi:10.1101/cshperspect.a025130.
17. Nabais MF, Laws SM, Lin T, Vallerga CL, Armstrong NJ, Blair IP, Kwok JB, Mather KA, Mellick GD, Sachdev PS, and Wallace L (2021). "Meta-analysis of genome-wide DNA methylation identifies shared associations across neurodegenerative disorders". Genome Biology 22(1):90. doi:10.1186/s13059-021-02275-5.
18. Pereira TMC, Côco LZ Ton AMM, Meyrelles SS, Campos-Toimil M, Campagnaro BP, and

Vasquez EC (2021). "The emerging scenario of the gut-brain axis: The therapeutic actions of the new actor Kefir against neurodegenerative diseases".Antioxidants 10(11):1845. doi:10.3390/antiox10111845.

19. Rubinsztein DC (2006). "The roles of intracellular protein-degradation pathways in neurodegeneration" Nature 443(7113):780–6. doi:10.1038/nature05291.
20. Singh A, Kukreti R, Saso L, and Kukreti S (2019). "Oxidative stress: A key modulator in neurodegenerative diseases". Molecules 24(8):1583. doi:10.3390/molecules24081583.
21. Stephenson J, Nutma E, van der Valk P, and Amor S (2018). "Inflammation in CNS neurodegenerative diseases". Immunology 154(2):204–19. doi:10.1111/imm.12922.
22. Thompson LM (2008). "Neurodegeneration: A question of balance". Nature 452(7188):707–8. doi:10.1038/452707a.
23. Vila M and Przedborski S (2003). "Targeting programmed cell death in neurodegenerative diseases". Nature Reviews-Neuroscience 4(5):365–75. doi:10.1038/nrn1100.
24. Wang H, Dharmalingam P, Vasquez V, Mitra J, Boldogh I, Rao KS et al. (2017). "Chronic oxidative damage together with genome repair deficiency in the neurons is a double whammy for neurodegeneration: Is damage response signaling a potential therapeutic target?". Mechanisms of Ageing and Development161 (Pt A):163–76. doi:10.1016/j.mad.2016.09.005.

Alzheimer's disease:

25. Archer MC, Hall PH, and Morgan JC (2017). "Accuracy of clinical diagnosis of Alzheimer's disease in Alzheimer's disease centers". Alzheimer's & Dementia 13(7S Part 16): P800–1. doi:10.1016/j.jalz.2017.06.1086.
26. Birks J (2006). "Cholinesterase inhibitors for Alzheimer's disease". The Cochrane Database of Systematic Reviews (1): CD005593. doi:10.1002/14651858.CD005593.
27. Brookmeyer R, Johnson E, Ziegler‐Graham K, and Arrighi HM (2007). "Forecasting the global burden of Alzheimer's disease". Alzheimer's Dement 3:186–91.
28. Chen Y, Zhou K, Wang R, Liu Y, Kwak YD, Ma T et al. (2009). "Antidiabetic drug metformin (Glucophage(R)) increases biogenesis of Alzheimer's amyloid peptides via up‐regulating BACE1 transcription". Proc Natl Acad Sci USA 106:3907–12.
29. Commission de la transparence (2012). "Drugs for Alzheimer's disease: best avoided. No therapeutic advantage". Prescrire International. 21(128):150.
30. Cummings JL (2002). "Alzheimer's disease". J. Amer. Med. Assoc. 287(18):2335-8. doi:10.1001/jama.287.18.2335.
31. Davis P, Morris J et al. (1991). "The distribution of tangles, plaques, and related immunohistochemical markers in healthy aging and Alzheimer's disease". Neurobiology of Aging 12(4):295–312. doi:10.1016/0197-4580(91)90006-6.
32. Delrieu J, Ousset PJ, Caillaud C, and Vellas B (2012). "'Clinical trials in Alzheimer's disease': immunotherapy approaches". Journal of Neurochemistry 120(Suppl 1):186–93. doi:10.1111/j.1471-4159.2011.07458.x.
33. Duthie A, Chew D, and Soiza RL (2011). Non‐psychiatric comorbidity associated with Alzheimer's disease". Q J Med 104:913–20.
34. Fymat AL (2017a). "Alzheimer's disease: A review", Journal of Current Opinions in Neurological Science 2(2);415-36.
35. Fymat AL (2018a). "Alzheimer's disease: Prevention, delay, minimization and reversal", Journal of Clinical Research in Neurology 1(1):1-16.
36. Fymat AL (2018b). "Is Alzheimer's an autoimmune disease gone rogue?", Journal of

Clinical Research in Neurology 2(1):1-4.

37. Fymat AL (2018c). “Is Alzheimer's a runaway autoimmune disease? And how to cure it?” Proceedings of the European Union Academy of Sciences, 2018 Newsletter, pages 379-83.
38. Fymat AL (2019). “Alzhei … Who? Demystifying The Disease And What You Can Do About It”, Tellwell Talent Publishers, pp 236. ISBN: 978-0-2288-2420-6 (Hardcover); 978-0-2288- 2419-0 (Paperback).
39. Fymat AL (2020a). “Is Alzheimer's an autoimmune disease gone rogue? The role of brain immunotherapy”, Journal of Clinical Research in Neurology 3(2):1-3.
40. Fymat AL (2020b). “Alzheimer's: What do we know about the disease and what can be done about it?”. EC Journal of Psychology & Psychiatry 9(11):69-74.
41. Fymat AL (2020c). “Alzheimer's: Will there ever be a cure?” Journal of Clinical Psychiatry and Neuroscience 3(4):1-5.
42. Fymat AL (2022a). “Alzheimer's disease: A path to a cure”, Journal of Neurology and Psychology Research 3(1):1-15. https://researchnovelty.com/articles.php?journal_id=5.
43. Fymat AL (2022b). “Alzheimer's disease: A path to a cure”, Current Opinions in Neurological Science 3(1):1-16.
44. Gosche KM, Mortimer JA, Smith CD, Markesbery WR, and Snowdon DA(2002). "Hippocampal volume as an index of Alzheimer neuropathology: Findings from the Nun Study". Neurology 58(10): 1476–82. doi:10.1212/WNL.58.10.1476.
45. Graff BJ, Harrison SL, Payne SJ, and El-Bouri WK (2023). "Regional cerebral blood flow changes in healthy aging and Alzheimer's disease: A narrative review". Cerebrovascular Diseases 52(1):11–20. doi:10.1159/000524797.
46. Hyman BT, Phelps CH, Beach TG, Bigio EH, Cairns NJ, Carrillo MC, Dickson DW, Duyckaerts C, Frosch MP, Masliah E, Mirra SS, Nelson PT, Schneider JA, Thal DR, and Thies B (2012). "National Institute on Aging–Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease". Alzheimer's & Dementia 8(1):1–13. doi:10.1016/j.jalz.2011.10.007.
47. Karlawish JH, Klocinski JL, Merz J, Clark CM, and Asch DA (2000). “Caregivers’ preferences for the treatment of patients with Alzheimer's disease”. Neurology 55:1008–14.
48. Keohane K and Balfe M (2019). "The Nun Study and Alzheimer's disease: Quality of vocation as a potential protective factor?". Dementia. 18(5):1651–62. doi:10.1177/1471301217725186.
49. Krivanek TJ, Gale SA, McFeeley BM, Nicastri CM, and Daffner KR (2021). "Promoting successful cognitive aging: A ten-year update". Journal of Alzheimer's Disease 81(3):871–920. doi:10.3233/JAD-201462.
50. Larson EB, Shadlen MF, Wang L, McCormick WC, Bowen JD, Teri L et al. (2004). “Survival after initial diagnosis of Alzheimer's disease”. Ann Intern Med 140:501–9+I526.
51. Lock MM (2013). “The Alzheimer conundrum: Entanglements of dementia and aging”. Princeton. ISBN 978-1-4008-4846-1.
52. McCormick WC, Kukull WA, van Belle G, Bowen JD, Teri L, and Larson EB (1994). “Symptom patterns and comorbidity in the early stages of Alzheimer's disease”. J Am Geriatr Soc 42:517–21.
53. Montine TJ, Phelps CH, Beach TG, Bigio EH, Cairns NJ, Dickson DW, Duyckaerts C, Frosch MP, Masliah E, Mirra SS, Nelson PT, Schneider JA, Thal D, Trojanowski JQ, and Vinters HV (2012). "National Institute on Aging–Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: A practical approach".

Acta Neuropathologica 123(1):1–11. doi:10.1007/s00401-011-0910-3.

54. Moore BA (1995). "Study of Nuns turns up clues to brain aging and Alzheimer's disease". Public Health Reports 110(4):508.
55. Nicolazzo JA and Mehta DC (2010).Transport of drugs across the blood‐brain barrier in Alzheimer's disease". Ther Deliv 1:595–611.
56. Pini L, Pievani M, Bocchetta M, Altomare D, Bosco P, Cavedo E, Galluzzi S, Marizzoni M, Frisoni GB (2016). "Brain atrophy in Alzheimer's Disease and aging". Ageing Research Reviews 30:25–48. doi:10.1016/j.arr.2016.01.002.
57. Reisberg B, Borenstein J, Salob SP, and Ferris SH (1987).“Behavioral symptoms in Alzheimer's disease: Phenomenology and treatment”. J Clin Psychiatry 48:9–15.
58. Sauer A (2017). "What Nuns are teaching us about Alzheimer's". Alzheimers.net.
59. Schenk D, Basi GS, and Pangalos MN (2012). "Treatment strategies targeting amyloid β-protein". Cold Spring Harbor Perspectives in Medicine 2(9): a006387. doi:10.1101/cshperspect.a006387.
60. Sirts K, Piguet O, and, Johnson M (2017). "Idea density for predicting Alzheimer's disease from transcribed speech". arXiv:1706.04473.
61. Snowdon DA (1997). "Aging and Alzheimer's disease: Lessons from the Nun Study". The Gerontologist 37(2):150–6. doi:10.1093/geront/37.2.150.
62. Snowdon DA, Kemper SJ, Mortimer JA, Greiner LH, Wekstein DR, and Markesbery WR (1996). "Linguistic ability in early life and cognitive function and Alzheimer's disease in late life: Findings from the Nun Study". JAMA 275(7):528–32. doi:10.1001/jama.1996.03530310034029.
63. Stewart WF, Kawas C, Corrada M, and Metter EJ (1997). “Risk of Alzheimer's disease and duration of NSAID use”. Neurology 48:626–32.
64. Svob S, Dubravka K, Konjevod M, Sagud M, Nikolac PM, Nedic EG, Vuic B, Simic G, Vukic V, Mimica N, and Pivac N (2021). "Personalizing the care and treatment of Alzheimer's disease: An overview". Pharmacogenomics and Personalized Medicine 14:631–53. doi:10.2147/PGPM.S284615.
65. Tiraboschi P, Hansen LA, Thal LJ, and Corey-Bloom J (2004). "The importance of neuritic plaques and tangles to the development and evolution of AD". Neurology 62(11):1984–9. doi:10.1212/01.WNL.0000129697.01779.0A.
66. Turner PR, O'Connor K, Tate WP, and Abraham WC (2003). "Roles of amyloid precursor protein and its fragments in regulating neural activity, plasticity and memory". Progress in Neurobiology 70(1):1–32. doi:10.1016/S0301-0082(03)00089-3.
67. Veld in t' BA, Ruitenberg A, Hofman A, Launer LJ, van Duijn CM, Stijnen T et al. (2001). “Nonsteroidal anti-inflammatory drugs and the risk of Alzheimer's disease”. N Engl J Med 345:1515–21.
68. Wenk GL (2003). "Neuropathologic changes in Alzheimer's disease". The Journal of Clinical Psychiatry 64(Suppl 9):7–10.

Creutzeldt-Jakob disease:

69. (U.S.) National Institute of Neurological Disorders and Stroke (2022). “Creutzfeldt-Jakob Disease Fact Sheet “.
Mayo Clinic (2022). “Creutzfeldt-Jakob disease - Symptoms and causes".

Dementia:

70. Alzheimer's Association (2022). “What Is dementia? https://www.alz.org/alzheimers-dementia/what-is- dementia
71. American Speech Language Hearing

Association. “Dementia-Signs and symptoms”.

72. Annear MJ, Toye C, McInerney F, Eccleston C, Tranter B, Elliott KE, and Robinson A (2015). “What should we know about dementia in the 21st century? A Delphi consensus study”. BMC Geriatr.15:5. doi: 10.1186/s12877-015-0008-1.
73. Ayalon L, Bachner YG, Dwolatzky T, and Heinik J (2012). ″Preferences for end‐of‐life treatment: Concordance between older adults with dementia or mild cognitive impairment and their spouses. Int Psychogeriatr 24:1798–804.
74. Bains J, Birks J and Dening T (2002). In Dening T, ed. "Antidepressants For Treating Depression in Dementia". The Cochrane Database of Systematic Reviews (4):CD003944. doi:10.1002/14651858.CD003944.
75. Barclay, TR; Brasure, M; Nelson, VA and Kane, RL (2018). "Pharmacologic interventions to prevent cognitive decline, mild cognitive impairment, and clinical Alzheimer-type dementia: A systematic review", Annals of Internal Medicine 168(1):39–51. doi:10.7326/M17-1529.
76. Bergh S, Selbaek G, and Engedal K (2012). “Discontinuation of antidepressants in people with dementia and neuropsychiatric symptoms (DESEP study): double blind, randomized, parallel group, placebo controlled trial”. Br Med J 344:12.
77. Boustani M, Peterson B, Hanson L, Harris R, and Lohr KN (2003). “Screening for dementia in primary care: a summary of the evidence for the U.S. Preventive Services Task Force”, Annals of Internal Medicine 138(11):927–37. doi:10.7326/0003-4819-138-11-200306030-00015.
78. British Dental Association (2017). "Can poor oral health lead to dementia?", British Dental Journal 223(11):840. doi:10.1038/sj.bdj.2017.1064.
79. Budson AE and O’Connor MK (2017). “Seven steps to managing your memory: What’s normal, what’s not, and what to do about It”, New York: Oxford University Press.
80. Budson AE and Solomon PR (2021). “Memory loss, Alzheimer’s disease, and dementia: A practical guide for clinicians”, 3rd Edition, Philadelphia: Elsevier, Inc.
81. Bunn F, Burn AM, Goodman C, Rait G, Norton S, Robinson L et al. (2014). “Comorbidity and dementia: A scoping review of the literature”. BMC Med 192.
82. Burns A and Iliffe S (2009). "Dementia". British Medical J 338: b75. doi:10.1136/bmj.b75.
83. Burns A, Cohen-Mansfield J, Cooper C, Fox N, Gitlin LN, Howard R, Kales HC, Larson EB, Ritchie K, Rockwood K, Sampson EL, Samus Q, Schneider LS, Selbæk G, Teri L and Mukadam N (2017). "Dementia prevention, intervention, and care", Lancet 390 (10113): 2673– 2734. doi:10.1016/S0140-6736(17)31363-6.
84. Butler M, McCreedy E, Nelson VA, Desai P, Ratner E, Fink HA, Hemmy LS, McCarten JR, Barclay TR, Brasure M, Davila H, and Kane RL (2018). "Does Cognitive Training Prevent Cognitive Decline: A Systematic Review". Annals of Internal Medicine 168(1):63–8. doi:10.7326/M17-1531.
85. (U.S.) Centers for Disease Control and Prevention (CDC&P) (2022). “Dementia risk reduction”. https://www.cdc.gov/aging/publications/features/dementia-risk-reduction-june-2022/index.html.
86. Cerejeira J, Lagarto L, and Mukaetova-Ladinska EB (2012). “Behavioral and psychological symptoms of dementia”, Frontiers in Neurology. 3: 73. doi:10.3389/fneur.2012.00073.
87. Chang‐Quan H, Hui W, Chao‐Min W, Zheng‐Rong W, Jun‐Wen G, Yong‐Hong L

et al. (2011). "The association of antihypertensive medication use with risk of cognitive decline and dementia: A meta‐analysis of longitudinal studies". Int J Clin Pract 65:1295–305.

88. Clionsky E and Clionsky M (2023). "Dementia prevention: Using your head to save your brain", Johns Hopkins Press, Baltimore, 276 pages.

89. Creavin ST, Wisniewski S, Noel-Storr AH, Trevelyan CM, Hampton T, Rayment D et al. (2016). "Mini-Mental State Examination (MMSE) for the detection of dementia in clinically unevaluated people aged 65 and over in community and primary care populations". The Cochrane Database of Systematic Reviews(1):CD011145. doi:10.1002/14651858.CD011145.pub2.

90. Cullen B, O'Neill B, Evans JJ, Coen RF, and Lawlor BA (2007). "A review of screening tests for cognitive impairment", Journal of Neurology, Neurosurgery, and Psychiatry 78(8):790–9. doi:10.1136/jnnp.2006.095414.

91. (U.S.) Department of Health and Human Services (DHHS) (2022). "Can I prevent dementia? https://www.alzheimers.gov/life-with-dementia/can-i-prevent-dementia.

92. Dougall NJ, Bruggink S, and Ebmeier KP (2004). "Systematic review of the diagnostic accuracy of 99mTc-HMPAO-SPECT in dementia", The American Journal of Geriatric Psychiatry 12(6):554-70. doi:10.1176/appi.ajgp.12.6.554.

93. European Association for Palliative Care. "White Paper defining optimal palliative care in older people with dementia; A Delphi study".

94. Fink, HA, Jutkowitz E, McCarten JR, Hemmy LS, Butler M, Davila H Ratner E, Calvert C, Lampit A, Hallock H, and Valenzuela M (2014). "Computerized cognitive training in cognitively healthy older adults: A systematic review and meta-analysis of effect modifiers". PLoS Medicine 11(11):e1001756. doi:10.1371/journal.pmed.1001756.

95. Fink HA, Jutkowitz E, McCarten JR, Hemmy LS, Butler M, Davila H, Ratner E, Calvert C, Barclay TR, Brasure M, Nelson VA, and Kane RL (2018). "Pharmacologic interventions to prevent cognitive decline, mild cognitive impairment, and clinical Alzheimer-type Dementia: A systematic review", Annals of Internal Medicine 168(1):39–51. doi:10.7326/M17-1529.

96. (U.S.) Food and Drug Administration (2014). "Information for Healthcare Professionals: Conventional Antipsychotics". fda.gov. 2008-06-16.

97. Fymat AL (2018a). "Dementia treatment: Where do we stand?", Journal of Current Opinions in Neurological Science 3(1):1-3. 599.603.

98. Fymat AL (2019a). "On dementia and other cognitive disorders", Journal of Clinical Research in Neurology 2(1):1-14.

99. Fymat AL (2019b). "Dementia: A review", Journal of Clinical Psychiatry and Neuroscience 1(3):27-34.

100. Fymat AL (2019c). "Dementia with Lewy bodies: A review", Journal of Current Opinions in Neurological Science 4(1);15-32.

101. Fymat AL (2019d). "Our two interacting brains: Etiologic modulations of neurodegenerative and gastroenteric diseases", Journal of Current Opinions in Neurological Science 4(2):50-4.

102. Fymat AL (2019e). "What do we know about Lewy body dementias?" Journal of Psychiatry and Psychotherapy (Editorial) 2(1)-013:1-4. doi:10.31579/JPP.2019/018.

103. Fymat AL (2020a). "Dementia: Should we reorient our approach to treatment?" EC Journal of Psychology & Psychiatry 9(12):1-3.

104. Fymat AL (2020b). "Dementia: What is its causal etiology?" International Journal of Neuropsychology and Behavioral Sciences 1(1):19-22.

105. Fymat AL (2020c). “Dementia: Fending Off The Menacing Disease... And What You Can Do About It”, Tellwell Talent Publishers, pp 488. ISBN: 978-0-2288-4146-3 (Hardcover); 978-0-2288-4145-6 (Paperback).

106. Fymat AL (2021). “On potentially reversible forms of dementia”, Journal of Current Opinions in Neurological Science 6(1):101-8.

107. Fymat AL (2022). “Dementia: Eliminating its potentially reversible forms”. Proc. European Union Academy of Sciences. Pages 270-7.

108. Gleason OC (2003). “Delirium”, American Family Physician. 67(5): 1027–34.

109. Glind van de EMM, van Enst WA, van Munster BC, Olde RMG, Scheltens P, Scholten RJ et al. (2013).“Pharmacological treatment of dementia: A scoping review of systematic reviews”. Dement Geriatr Cogn Disord 36:211–8.

110. Hall CB, Lipton RB, Sliwinski M, Katz MJ, Derby CA, and Verghese J (2009). "Cognitive activities delay onset of memory decline in persons who develop dementia". Neurology 73(5):356–61. doi:10.1212/wnl.0b013e3181b04ae3.

111. Harris D. (2009). “Withholding and withdrawing life sustaining treatment in advanced dementia: How and when to make these difficult decisions”. Geriatr Aging 12:403–7.

112. Herr K, Karp JF, and Weiner DK (2007). "Pain in persons with dementia: complex, common, and challenging", The Journal of Pain 8(5):373–8. doi:10.1016/j.jpain.2007.03.003.

113. Hoffmann F, van den Bussche H, Wiese B, Schön G, Koller D, Eisele M et al. (2011). “Impact of geriatric comorbidity and polypharmacy on cholinesterase inhibitors prescribing in dementia”. BMC Psychiatry 11.

114. Iadecola C (2013). “The pathobiology of vascular dementia”, Neuron. 80 (4): 844-66. doi:10.1016/j.neuron.2013.10.008.

115. Jick H, Zornberg GL, Jick SS, Seshadri S, and Drachman DA (2000). “Statins and the risk of dementia”. Lancet 356:1627–31.

116. Jorm AF (2004). "The Informant Questionnaire on cognitive decline in the elderly (IQCODE): a review", International Psychogeriatrics 16(3):275-93. doi:10.1017/S1041610204000390.

117. Karlawish JH and Clark CM (2003). "Diagnostic evaluation of elderly patients with mild memory problems", Annals of Internal Medicine 138(5):411–9. doi:10.7326/0003-4819-138-5- 200303040-00011.

118. Kunik ME, Snow AL, Molinari VA, Menke TJ, Souchek J, Sullivan G et al. (2003). “Health care utilization in dementia patients with psychiatric comorbidity”. Gerontologist 43:86–91.

119. Lüders S and Schrader J (2015). “Dementia and hypertension”. Dtsch Med Wochenschr 140:1599–603.

120. Langa KM and Levine DA (2014). "The diagnosis and management of mild cognitive impairment: a clinical review", JAMA 312(23):2551-61. doi:10.1001/jama.2014.13806.

121. Laver K, Cumming RG, Dyer SM, Agar MR, Anstey KJ, Beattie E et al. (2016). “Clinical practice guidelines for dementia in Australia”. Med J Aust 204.

122. Lee AY (2011). "Vascular dementia". Chonnam Medical Journal. 47 (2): 66-71. doi:10.4068/cmj.2011.47.2.66.

123. Liao JN, Chao TF, Liu CJ, Wang KL, Chen SJ, Tuan TC et al. (2015). ″Risk and prediction of dementia in patients with atrial fibrillation - A nationwide population - based cohort study″. Int J Cardiol 199:25–30.

124. Lin JS, O'Connor E, Rossom RC, Perdue LA, and Eckstrom E (2013). "Screening for cognitive impairment in older adults: A systematic review for the U.S. Preventive Services Task Force". Annals of Internal

Medicine 159(9):601–12. doi:10.7326/0003-4819-159-9-201311050- 00730.

125. Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, Ballard C, Banerjee S,

126. Kavirajan H, and Schneider LS (2007). "Efficacy and adverse effects of cholinesterase inhibitors and memantine in vascular dementia: a meta-analysis of randomized controlled trials", The Lancet. Neurology. 6 (9): 782–92. doi:10.1016/s1474-4422(07)70195-3.

127. Livingston G et al. (2020). "Dementia prevention, intervention, and care". The Lancet. doi.org/10.1016/S0140-6736(20)30367-6.

128. Lleó A, Greenberg SM, and Growdon JH (2006). "Current pharmacotherapy for Alzheimer's disease". Annual Review of Medicine. 57 (1): 513-33. doi:10.1146/annurev.med.57.121304.131442.

129. Lolk A and Gulmann NC (2006). "Psychopharmacological treatment of behavioral and psychological symptoms in dementia". Ugeskrift for Laeger (in Danish) 168(40):3429–32.

130. Loy CT, Schofield PR, Turner AM, and Kwok JB (2014). "Genetics of dementia", Lancet 383 (9919):828–40. doi:10.1016/s0140-6736(13)60630-3.

131. Lyketsos CG, Steinberg M, Tschanz JT, Norton MC, Steffens DC, Breitner JC et al. (2000). "Mental and behavioral disturbances in dementia: Findings from the Cache County Study on memory in aging". Am J Psychiatry 157:708–14.

132. Malouf R and Grimley EJ (2008). "Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people". The Cochrane Database of Systematic Reviews (4): CD004514. doi:10.1002/14651858.CD004514.pub2.

133. McCleery J, Cohen DA, and Sharpley AL (2016). "Pharmacotherapies for sleep disturbances in dementia". The Cochrane Database of Systematic Reviews. 11 (11):CD009178. doi:10.1002/14651858.CD009178.pub3.

134. McGuinness B, Craig D, Bullock R, Malouf R, and Passmore P (2014). "Statins for the treatment of dementia". The Cochrane Database of Systematic Reviews. 7 (7):CD007514. doi:10.1002/14651858.CD007514.pub3.

135. MD Guidelines (2009). "Dementia definition", Reed Group.

136. Melis RJ, Marengoni A, Rizzuto D, Teerenstra S, Kivipelto M, Angleman SB et al. (2013).The influence of multimorbidity on clinical progression of dementia in a population‐based cohort."PLoS One 8:e84014.

137. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, and Chertkow H (2005). "The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment", Journal of the American Geriatrics Society 53(4):695– 9. doi:10.1111/j.1532-5415.2005.53221.x.

138. (U.S.) National Institute on Aging (NIA), U.S. Department of Health and Human Services (2021)."What is dementia?" https://www.nia.nih.gov/health/what-is-dementia.

139. (U.S.) National Institute on Aging (2022). "Reducing your risk of dementia". https://order.nia.nih.gov/sites/default/files/2022-05/dementia-risk-tip-sheet.pdf.

140. (U.K.) National Institute for Clinical Excellence (NICE) (2014). "Dementia overview", pathways.nice.org.uk.

141. (U.S.) National Library of Medicine (NLM) (2015). "Dementia", MedlinePlus (14 May).

142. Ott A, Stolk RP, Van Harskamp F, Pols HA, Hofman A, Breteler MM et al. (1999). "Diabetes mellitus and the risk of

dementia: The Rotterdam Study". Neurology 53:1937–42.

143. Page A, Potter K, Clifford R, McLachlan A, and Etherton‐Beer C (2015). "Prescribing for Australians living with dementia: study protocol using the Delphi technique". BMJ Open 5:e008048.

144. Page AT, Potter K, Clifford R, McLachlan AJ, and Etherton-Beer C (2016). "Medication appropriateness tool for co-morbid health conditions in dementia: consensus recommendations from a multi-disciplinary expert panel", Internal Medicine Journal. 46 (10): 1189-97. doi:10.1111/imj.13215.

145. Page AT, Clifford RM, Potter K, Seubert L, McLachlan AJ, Hill X, King S, Clark V, Ryan C, Parekh N, and Etherton-Beer CD (2017). "Exploring the enablers and barriers to implementing the Medication Appropriateness Tool for Co-morbid Health conditions during Dementia (MATCH-D) criteria in Australia: A qualitative study". BMJ Open 7(8):e017906. doi: 10.1136/bmjopen- 2017-017906.

146. Parsons C, Hughes CM, Passmore AP, and Lapane KL (2010). "Withholding, discontinuing and withdrawing medications in dementia patients at the end of life: A neglected problem in the disadvantaged dying?" Drugs Aging 27:435–9.

147. Reeve E, Simon Bell J, and Hilmer SN (2016). "Barriers to optimizing prescribing and deprescribing in older adults with dementia: A narrative review". Curr Clin Pharmacol 10:168–77.

148. Rolinski M, Fox C, Maidment I, and McShane R (2012). "Cholinesterase inhibitors for dementia with Lewy bodies, Parkinson's disease dementia and cognitive impairment in Parkinson's disease", The Cochrane Database of Systematic Reviews. 3 (3): CD006504. doi:10.1002/14651858.CD006504.pub2.

149. Rosenbloom MH, Smith S, Akdal G, and Geschwind MD (2009). "Immunologically mediated dementias". Current Neurology and Neuroscience Reports (Review) 9(5):359–67. doi:10.1007/s11910-009-0053-2.

150. Sadock BJ and Sadock VA (2008). "Delirium, Dementia, and Amnestic and Other Cognitive Disorders and Mental Disorders Due to a General Medical Condition", Kaplan & Sadock's Concise Textbook of Clinical Psychiatry (3rd ed.). Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins. p. 52. ISBN 978-0-7817-8746-8.

151. Şahin CE (2014). "Management of Behavioral and Psychological Symptoms of Dementia". Noro psikiyatri arsivi. 51(4):303–12. doi:10.5152/npa.2014.7405.

152. Schneider LS, Dagerman KS, and Insel P (2005). "Risk of death with atypical antipsychotic drug treatment for dementia: Meta‐analysis of randomized placebo‐controlled trials". JAMA 294:1934–43.

153. Schofield P (2005). "Dementia associated with toxic causes and autoimmune disease". International Psychogeriatrics (Review). 17 Suppl 1:S129–47. doi:10.1017/s1041610205001997.

154. Schubert CC, Boustani M, Callahan CM, Perkins AJ, Carney CP, Fox C et al. (2006). "Comorbidity profile of dementia patients in primary care: Are they sicker?" J Am Geriatr Soc 54:104–9.

155. Seitz DP, Gill SS, Herrmann N, Brisbin S, Rapoport MJ, Rines J et al. (2013).Pharmacological treatments for neuropsychiatric symptoms of dementia in long‐term care: A systematic review". Int Psychogeriatr 25:185–203.

156. Shega J, Emanuel L, Vargish L, Levine SK, Bursch H, Sampson EL, Ritchie CW, Lai R, Raven PW, and Blanchard MR (2005). "A systematic review of the scientific evidence for

the efficacy of a palliative care approach in advanced dementia", International Psychogeriatrics 17(1): 31–40.

157. Shub D and Kunik ME (2009). "Psychiatric Comorbidity in Persons With Dementia: Assessment and Treatment Strategies". Psychiatric Times 26(4).

158. Smith T, Maidment I, Hebding J, Madzima T, Cheater F, Cross J et al. (2014). "Systematic review investigating the reporting of co-morbidities and medication in randomized controlled trials of people with dementia". Ageing 43:868–72.

159. Snowdon DA (2003). "Healthy aging and dementia: Findings from the Nun Study". Annals of Internal Medicine 139(5 Part_2):450–4. doi:10.7326/0003-4819-139-5_Part_2-200309021- 00014.

160. Stein PS, Desrosiers M, Donegan SJ, Yepes JF, and Kryscio RJ (2007). "Tooth loss, dementia, and neuropathology in the Nun Study". The Journal of the American Dental Association 138(10):1314–22. doi:10.14219/jada.archive.2007.0046.

161. Taghizadeh-Larsson A, and Osterholm JH (2014)." How are decisions on care services for people with dementia made and experienced? A systematic review and qualitative synthesis of recent empirical findings". Int Psychogeriatr 26:1849–62.

162. Teng EL and Chui HC (1987). "The Modified Mini-Mental State (3MS) examination". The Journal of Clinical Psychiatry 48(8):314–8.

163. Umphred D (2012). Neurological rehabilitation (6th ed.). St. Louis, Mo.: Elsevier Mosby. p.838. ISBN 978-0-323-07586-2.

164. Weitzel T, Robinson S, Barnes MR, Berry TA, Holmes JM, Mercer S et al. (2011). "The special needs of the hospitalized patient with dementia", Medsurg Nursing 20(1):13–8, quiz 19.

165. Welsh TJ, Gladman JR, and Gordon AL (2014). "The treatment of hypertension in people with dementia: A systematic review of observational studies". BMC Geriatr 14.

166. Wolfson C, Wolfson DB, Asgharian M, M'Lan CE, Østbye T, Rockwood K et al. (2001). "Areevaluation of the duration of survival after the onset of dementia". N Engl J Med 344:1111–6

167. Woods B, O'Philbin L, Farrell EM, Spector AE, and and Orrell M (2018). "Reminiscence therapy for dementia". Cochrane Database Syst Rev. 3: CD001120.pub3. doi:10.1002/14651858.

168. World Health Organization (2012). "Dementia Fact Sheet N0. 362" (April 2012).

169. World Health Organization (2021). "Global status report on the public health response to dementia" ISBN 978-92-4-003324-5.

Epilepsy:

170. Fymat AL (2017a). "Epilepsy: A review", J of Current Opinions on Neurological Science 1(5):240-54.

171. Fymat AL (2017b). "Neurological disorders and the blood brain barrier: 1. Epilepsy", J of Current Opinions on Neurological Science 1(6):277-93.

172. Fymat AL (2022). "Epilepsy: The Electrical Storm In The Brain", Tellwell Talent Publishers, pp 412. ISBN-978-0-2288-8203-9 (Hardcover); 978-0-2288-8203-9;978-0-2288-8202-2 (Paperback). https://portal.tellwell.ca/Tellwell/design/187051.

173. Fymat AL (2023). "Epilepsy: Surgical and non-surgical management and treatment", Current Opinions in Neurological Science 8(1):1-26.

Huntington's disease:

174. Barnat M, Capizzi M, Aparicio E, Boluda S,

Wennagel D, Kacher R, Kassem R, Lenoir S, Agasse F, Braz BY, and Liu J-P (2020). "Huntington's disease alters human neurodevelopment".Science 369(6505):787–93.
doi:10.1126/science.aax3338. ISSN 0036-8075.

175. Labbadia J and Morimoto RI (2013). "Huntington's disease: Underlying molecular mechanisms and emerging concepts". Trends in Biochemical Sciences 38(8):378–85. doi:10.1016/j.tibs.2013.05.003.

176. Purves DE, Sánchez AM, Mejía-Toiber J, and Massieu L (2008). "Excitotoxic neuronal death and the pathogenesis of Huntington's disease". Archives of Medical Research 39(3):265–76. doi:10.1016/j.arcmed.2007.11.011.

Lyme disease:

177. Fymat AL (2020). "Lyme Disease: The Dreadful Invader, Evader, and Imitator… And What You Can Do About It", Tellwell Talent Publishers, pp 278. ISBN: 978-0-2288-3198-3 (Hardcover); 978-0-2288-3199-0 (Paperback).

178. Fymat AL (2023a). "Lyme disease neurological implications: I. Symptomatology and etiology". Neurology and Psychology Research Journal 5(2):1-24.

179. Fymat AL (2023b). "Lyme disease neurological implications: II. Diagnostic methodology". Neurology and Psychology Research Journal 5(2):1-26.

180. Fymat AL (2023c). "Lyme disease neurological implications: III. Neuroborreliosis and other diseases transmitted by the Lyme tick vector". Neurology and Psychology Research Journal 5(2):1-26.

181. Fymat AL (2023d). "Lyme disease neurological implications: IV. Symptoms management, treatment, and human vaccine development". Neurology and Psychology Research Journal 5(2):1-32.

Multiple sclerosis:

182. Fymat AL (2023a). "Multiple Sclerosis: The Progressive Demyelinating Autoimmune Disease", Tellwell Talent Publishers pp 504. ISBN: 978-0-2288-9292-2 (Hardcover); 978-0-2288-3(Paperback). https://portal.tellwell.ca/Tellwell/Design/212669.

183. Fymat AL (2023b). "Multiple sclerosis: I. Symptomatology and etiology", Journal of Neurology and Psychology Research 4(2):1-46. https://researchnovelty.com/articles.php?journal_id=5.

184. Fymat AL (2023c). "Multiple sclerosis: II. Diagnosis and symptoms management", Journal of Neurology and Psychology Research 4(2):1-21. https://researchnovelty.com/articles.php?journal_id=5.

185. Fymat AL (2023d). "Multiple sclerosis: III. Treatment and prognosis", Journal of Neurology and Psychology Research 4(2):1-46. https://researchnovelty.com/articles.php?journal_id=5.

186. Irvine KA and Blakemore WF (2008). "Remyelination protects axons from demyelination-associated axon degeneration". Brain 131(6):1464–77. doi:10.1093/brain/awn080.

187. Kaufman DM and Milstein MJ (2013). Kaufman DM and Milstein MJ (eds.), "Chapter 15 - Multiple Sclerosis", Kaufman's Clinical neurology for psychiatrists (Seventh Edition), Philadelphia: W.B. Saunders, pp. 329–49, ISBN 978-0-7234-3748-2.

188. (U.S.) National Institute of Neurological Disorders and Stroke (2020). "Multiple sclerosis: Hope through research".

189. Stys PK and Tsutsui S (2019). "Recent advances in understanding multiple sclerosis". F1000Research 8:2100. doi:10.12688/f1000research.20906.1.

190. Multiple system atrophy:

191. Fymat AL (2023a). "Multiple System aArophy: The Chronic, Progressive, Neurodegenerative Synucleopathic Disease", Tellwell Talent Publishers, pp. 302. ISBN: 978-0-2288-9493-8 (Hardcover); 978-0-2288-9492-1 (Paperback). https://portal.tellwell.ca/Tellwell/Design/256783.

192. Fymat AL (2023b). "Multiple system atrophy: Symptoms management and treatment", Journal of Neurology and Psychology Research 4(1):1-37.

Parkinson's disease:

193. Crossman AR (2000). "Functional anatomy of movement disorders". Journal of Anatomy 196(Pt 4) (4):519–25. doi:10.1046/j.1469-7580.2000.19640519.x.

194. Elbaz A, Carcaillon L, Kab S, and Moisan F (2016). "Epidemiology of Parkinson's disease". Revue Neurologique 172(1):14–26. doi:10.1016/j.neurol.2015.09.012.

195. Fymat AL (2017a). "Parkinson's disease and other movement disorders: A review", Journal of Current Opinions in Neurological Science 2(1):316-43.

196. Fymat AL (2017b). "Neurological disorders and the blood-brain barrier: 2. Parkinson's disease and other movement disorders", Journal of Current Opinions in Neurological Science 2(1)362-83.

197. Fymat AL (2018). "Blood-brain barrier permeability and neurological diseases", Journal of Current Opinions in Neurological Science (Editorial) 2(2):411-14.

198. Fymat AL (2019). "Viruses in the brain...? Any connections to Parkinson's and other neurodegenerative diseases?" Proceedings of the European Union Academy of Sciences, 2019 Newsletter, pages 249-52.

199. Fymat AL (2020a). "Recent research developments in Parkinson's disease", Current Opinions in Neurological Science 5(1):12-30.

200. Fymat AL (2020b). "Parkinson's: What is known about the disease and what can be done about it?" Journal of Clinical Research in Neurology 3(2):1-12.

201. Fymat, AL (2020c). "Parkin.. ss..oo..nn: Elucidating The Disease... And What You Can Do About It", Tellwell Talent Publishers, pp 258, 6 April 2020. ISBN: 978-0-2288-2874-7 (Hardcover); 978-0-2228-2875-4 (Paperback).

202. Hill-Burns EM, Debelius JW, Morton JT, Wissemann WT, Lewis MR, Wallen ZD, Peddada SD, Factor SA, Molho E, ZabetianCP, and Knight R (2017). "Parkinson's disease and Parkinson's disease medications have distinct signatures of the gut microbiome: PD,Medications, and Gut Microbiome". Movement Disorders 32(5):739–49. doi:10.1002/mds.26942.

Tourette's syndrome:

203. Fymat AL (2023a). "Tourette: The Self-Under-Siege Neurodevelopmental And Neuropsychiatric Motor Syndrome", Tellwell Talent Publishers pp. 466. ISBN: 978-1-7794-1027-6 (Hardcover); 978-1-7794-1026-6 (Paperback). https://portal.tellwell.ca/Tellwell/Design/256783.

204. Fymat AL (2023b). "Tourette's syndrome: I. Symptomatology and etiology", Journal of Neurology and Psychology Research 5(1):1-34. https://researchnovelty.com/articles.php?journa

l_id=5.

Neurology and Psychology Research 5(1):1-39.

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205. Fymat AL (2023c). "Tourette's syndrome: II. Diagnosis and symptoms management", Journal of Neurology and Psychology Research 5(1):1-27. https://researchnovelty.com/articles.php?journal_id=5.

206. Fymat AL (2023d). "Tourette's syndrome: III. Treatment and prognosis", Journal of Neurology and Psychology Research 5(1):1-39. https://researchnovelty.com/articles.php?journal_id=5.

207. Fymat AL (2023e). "Tourette's syndrome: IV. Research and latest updates", Journal of Neurology and Psychology Research 5(1):1-12. https://researchnovelty.com/articles.php?journal_id=5.

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