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Introduction into Neurodegenerative Diseases

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Abstract: ***This function of this article is to introduce the topic of neurodegenerative diseases to anyone interested into the field of neuroscience. This was done by researching through various different conditions and explaining the classifications. Afterwards, they were then explained based on the symptoms, onset, variants, and currently studied cause. Any treatment for these diseases was excluded as the research is currently in progress and is beyond the scope of this article.***

Keywords: Neurodegenerative diseases, Alzheimer's, Parkinson's, Amyotrophic Lateral Sclerosis, Spinal Muscular Atrophy, Motor Neuron Disease, Dementia

1. Introduction

1.1 Importance

There are over 600 neurodegenerative disorders, with over 50 million Americans affected each year. Each disease is differently identified and each one has their own causes and symptoms. This review article aims at introducing the subject of neuroscience to potential interested individuals by providing the basic set of knowledge in a condensed form. This is done by providing practical knowledge of the brain through the use of disorders affecting the brain and their subsequent regions. This article can be used to inform the audience and prevent any misunderstanding as false information is common in this age of information exchange. This topic (neurodegenertaive diseases) has plagued humanity since the early 1800s, and has not been fully cured. This topic is seldom discussed in medical textbooks, but is crucial in understanding the physical applications of the brain, as well as the effects of losing certain regions of the brain. This can help to better understand the brain and its functioning.

Beginning with the basic terminology and the root word 'neurodegenerative diseases', 'neuro' refers to the central nervous system (more specifically the brain and spinal cord) and the neurons within them, 'degenerative' refers to the deterioration and breaking down of cells (specifically neurons), and 'diseases' which commonly refers to a disfunctioning of regions in the body of an animal or any living being. Directly stated, it is a disease which breaks down the neurons in the spinal cord and/or the brain. In reality, there are many different classes of these diseases each one having their own causes and symptoms. This will be discussed later in the article, and will be divided based on the disease.

There are four main diseases that will be discussed: Alzheimer's disease (AD), Parkinson's disease (AD), Amyotrophic Lateral Sclerosis (ALS), and Spinal Muscular Atrophy (SMA). There are two reasons for choosing these diseases. The first is based on their size and scope. Alzheimer's and Parkinson's are the two largest diseases in the world, meaning that they are the most common and most studied. The second is the classification system present. Both ALS and SMA fall under the same category of neurons, known as Motor Neuron Disease. Similarly, Alzheimer's disease falls under Dementia. To represent these classifications, ALS and SMA were chosen. While other diseases such as Huntington's disease and Vascular dementia are present, their presence is understated and does not fit the criteria of this article

1.2 Variations and Classifications

Neurodegenerative diseases are often classified as a larger syndrome which is present. This is mainly because the variants all share similar symptoms or they affect similar regions of the brain. One example is motor neuron disease. There are over 7 variants, and while every form of this disease affects the motor neurons in the spinal cord, some affect the upper motor neurons (inhibiting fine touch), while others affect the lower motor neurons, suppressing gross movements; some affect both the upper and lower motor neurons. Along with this identification, there are also three classifications: Autosomal dominant, Autosomal recessive, and X - linked inheritance. These classifications refer to how the disease is inherited. Autosomal dominant refers to the location of the gene, being in one of the numbered (or non - sex) chromosomes. The dominant trait refers to its higher probability of causing the disease. Similarly, dominant recessive refers to the gene being in one of the numbered chromosomes, but does not mean that the individual will have the disease. They are simply a carrier of the disease. Lastly, there is X - linked inheritance, which refers to the X chromosome in men, and how in X linked recessive inheritance, only males are affected and females can become carriers. In X linked dominant inheritance, both males and females are affected however females are affected to a lesser extent [3]. In summary, diseases fall under classifications based on their symptoms and their affected regions. These can then be further classified into categories based on factors such as method of contraction or method of causation. Note, that this is generalized for any disease, not for neurodegenerative diseases alone.

Most neurodegenerative diseases are named based on the regions of the body that they affect and the person that discovered the disease. Two examples include Alzheimer's and Spinal muscular atrophy. Their symptoms and effects will be discussed later on in the article, but as a quick example, Alzheimer's disease was founded by Dr. Alois Alzheimer in the early 1900s and Spinal Muscular Atrophy effects the motor neurons in the spinal cord. Other diseases can have multiple names. A prime example of this is Parkinson's disease, which was discovered around 1820 by a scientist named James Parkinson. Along with the name 'Parkinson's Disease', the disease is also identified as

primary parkinsonism. The term parkinsonism refers to symptoms that are present in Parkinson's disease which will be discussed later into the article.

Along with classifications and naming, there are variants and stages of diseases, such is the case with neurodegenerative diseases. One primary example is Spinal muscular atrophy, which has 4 stages: Type I, Type II, Type III, and Type IV. Type III includes Type IIIa SMA and Type IIIb SMA. These stages are given based on age of contraction and diagnosis. Typically, the earlier the age, the earlier the stage (for someone in their teens, they may be diagnosed with Stage II SMA). Along with various stages, there is also early and late onset symptoms. This is general classifications for diseases without specificity. Early onset occurs before a certain age, and late onset occurs after a certain age. In the case of Alzheimer's disease, early onset is considered as 65 years and younger, whereas late onset is 65 years and above. The symptoms are mostly the same (in the case of Alzheimer's disease)

1.3 Terminology

Before beginning the article, some basic terminology is required in the world of neuroscience. The first concept is differential diagnosis. While a diagnosis is present to interpret potential diseases, a differential diagnosis is executed to specifically determine the disease with an exact set of tests to determine it. While the test conducted might be the same for some diseases, such as running an MRI scan, the differences in the result will lead to a diagnosis which is accurate to the present set of symptoms. One term that is present throughout diseases is atrophy. This term means that the cells in a region of the body can degenerate, and in a sense whither away. Another term is mutation. This refers to the genetic change in a cell caused by external factors such as radiation exposure, or internal causes such as errors in the replication of DNA. Certain diseases are caused by the mutation of proteins, which will be discussed later on.

2. Section 1: Alzheimer's Disease

Alzheimer's Disease is the most common neurodegenerative disease, and is also the most common form of Dementia. Roughly 60 - 80 percent of all dementia cases are Alzheimer's. Dementia is a set of symptoms which involves the loss of intellectual abilities: thinking, memory, language, and problem - solving capabilities [12]. Dementia patients also experience behavioral changes. This disease can develop into physical disabilities, such as inability to move (which means greater external assistance), paralysis, and eventually death. These are the basic symptoms of dementia. Within this categorization there are many diseases, such as Alzheimer's Dementia, Vascular Dementia, Frontotemporal Dementia, and Lewy Body Dementia which all share similar symptoms, but have varying causes. Then there are diseases which begin with separate symptoms from dementia, but in later stages result in similar cognitive and physical disabilities. These include Huntington's Disease, Creutzfeldt - Jakob disease, and Parkinson's Disease. The main cause of symptoms is the continuous loss in cortical neurons, particularly in the pyramidal cells, which are variant of neurons which is found in the cerebral cortex, hippocampus, and amygdala. It originates in the medial temporal lobe (specifically, the entorhinal cortex and hippocampus).

The main differences between the variations of Dementia disease's are the regions of the brain that are affected as well as the different causes for each one. For example, Vascular dementia can be caused by strokes carrying blood to the brain, whereas Frontotemporal dementia can be caused by the deposition of protein in the frontotemporal region (frontal and temporal lobe). This can be seen across most dementia disease's. For Alzheimer's Disease, the main causes are the deposition of β - amyloid plaque, neurofibrillary tangles caused by hyperphosphorylated tau, oxidative stress, inflammation, lipid deregulation, and genetic factors.

2.1 Differential diagnosis and symptoms

Differential diagnosis is important when diagnosing Alzheimer's from other dementia related diseases as they all contain very similar symptoms. Most tests rely on scans and are effective in outputting a diagnosis. One diagnosis can be made from the level of Total tau (T - tau), Phosphorylated tau (P - tau), and amyloid β in the cerebrospinal fluid [17]. This liquid is present in the brain's surrounding regions and surrounds the spinal cord (and can thus be used for measuring chemical and protein values). Other scans include a PET scan of the β - amyloid deposition [22], neuroimaging techniques such as fMRI scans and computer tomographic scans [4]. Note that multiple scans and reading are taken before concluding the diagnosis. Even before the diagnosis is confirmed, assumptions can be made based on the symptoms that are already present. These symptoms include the loss of intellectual abilities, memory and learning deficits (loss of memory in later onset), and decline in cognitive functions.

2.2 Causes

As mentioned in the previous section, we discussed the definition of Alzheimer's, the variations in the different forms of Dementia, and their similarities and differences. Now, the main focus is the specific causes of Alzheimer's and it's meaning. The first main cause is the deposition of β - amyloid plaque (Aβ). This is a small piece of the larger unit called the amyloid precursor protein (APP). Although the purpose of this protein is largely unknown, the functioning is understood. It is produced within the brain cells in the neocortex, and is released through the fatty substance within the cell. It is then split into multiple smaller parts, where β - amyloid protein is produced. in relation to Aβ, it is relatively 'stickier' than the other units from the APP proteins. In the initial stages, the Aβ units create small clusters called oligomers. Multiple chains of clusters are formed are called fibrils, and multiple fibrils form β - sheets. The final stage includes the plaques which is made from multiple β - sheets, which then blocks the incoming arteries causing inflammation in the surrounding area, eventually leading to cell death [14].

The next cause is defined as the neurofibrillary tangles caused by hyper - phosphorylated tau. Neurofibrillary tangles (NFT's) are caused by increased deposition of hyper

- phosphorylated tau in the neurons [15]. The purpose of tau proteins is to maintain the integrity of microtubules. Microtubules are approximately 25 nanometers in diameter, have functions ranging from transport to structural support, and are made from the protein tubulin (which is made from smaller block called α - tubulin and β - tubulin). The presence of hyper - phosphorylated tau destabilizes the microtubules, causing defects in transportation and leading to neuronal cell death [19].

One major cause of the NFT's is oxidative stress. This variant of stress is caused by the imbalance between production and accumulation of oxygen reactive series (ROS; used to describe many reactive molecules and free radicals originating from oxygen molecules) [18]. This oxidative damage leads to the alteration of membrane properties such as fluidity, ion transport, enzyme activities, protein cross - linking, and eventually cell death [23]. Although the main effect of oxidative stress has been linked to influence on hyper - phosphorlateted tau proteins, the underlying mechanics are largely unknown.

2.3 Classifications and Stages

Although the typical stages of a degenerative disorder is present in Alzheimer's (early and late onset), there are two classification that must be discussed regarding symptoms. The first is Dementia without prominent motor sign. Alzheimer's falls under this category as the early onset symptoms are based on the decline in cognitive functions rather than physical ones. The second classification is dementia with prominent motor signs [9]. This includes frontotemporal dementia.

3. Section 2: Parkinson's Disease

Parkinson's disease is the second most common neurodegenerative disease, after Alzheimer's. This disease is characterized with the term 'Parkinsonism', which refers to the symptoms of resting tremors, instability, rigidity issues, and bradykinesia. Bradykinesia is an impairment of voluntary muscle control along with slow movements, decreased reaction time, and freezing. This develops into the inability to take care of oneself, as many task are repetitive, and the ability to perform tasks decrease over time. The set of symptoms (parkinsonism and bradykinesia) are present in Parkinson's, however, these symptoms can also be used to describe other diseases (hence the name parkinsonism). It has also been stated that a patient of Parkinson's can also deal with symptoms similar to Alzheimer's, and can even experience both Alzheimer's and Parkinson's and the same time [8]

The cause of these symptoms can be seen as the loss of neurons in the substantia nigra and the deposition of Ubiquitin proteins in the cytoplasm neurons [16]. The process of ubiquination is when a ubiquitin protein attaches to another protein which is then covalently linked to lysine residue. Once the process is over, the ubiquitin protein is attached to normal protein, which is tagged for the eradication of the protein due to its abnormalities. These include incorrect protein folding, presence of a toxic protein, and/or unusable protein. It has also been proposed that regions in the brain stem such as the vagus dorsal motor nucleus, locus coeruleus, and raphe nuclei degenerate far quicker than the substantia nigra. Both the locus coeruleus and the raphe nuclei are involved in homeostatic processes and the locus coeruleus deals with physiological responses to panic and stress along with synthesizing norepinephrine. The loss in production of norepinephrine can explain symptoms such as instability, inactivity, and fatigue [1].

3.1 Differential Diagnosis and Symptoms

Differential diagnosis of Parkinson's is relatively simple. The first diagnosis is the simple presence check of Parkinsonism features (though this is not able to differentiate the disease). The second method is noting if the motor and other symptoms must be present before the cognitive decline seen in other major neurocognitive diseases [8]. As previously mentioned, the symptoms include rested tremors, Bradykinesia, rigidity issues, and instability. Note, that all of these symptoms fall under the category called parkinsonism.

3.2 Causes and Classifications

There are approximately five causes for Parkinson's: mutation of the gene encoding for α - synuclein protein, loss of dopamine producing neurons (neurons in the substantia nigra), oxidative stress, necrosis, and inflammation. Firstly, α - synuclein is a protein that is encoded by the SNCA gene. This protein regulates synaptic vesicle trafficking and subsequent neurotransmitter release due to the mutation of this protein, neurotransmitters such as dopamine and norepinephrine are either released in decreased amounts or is not released. This leads to decreased functionality, as seen with the lack of norepinephrine causing instability. Next, the loss of dopamine producing neurons is caused by the degradation of neurons in the substantia nigra as that region is one of the dopamine pathways, dedicated for synthesizing dopamine. Oxidative stress and inflammation have been discussed in other sections. Lastly, necrosis is a form of cell injury which results in the premature death of cells by autolysis, which is the self - destruction of cells due to their own enzymes. This could be a potential explanation for the degradation of neurons in the substantia nigra and the brain stem.

Parkinson's disease has also been classified as an α - Synucleinopathy disease [13]. This simply refers to its genetic mutation to the α - synuclein protein. There are also 2 stages to this; early and late onset, which is below and above fifty years of age respectively.

4. Section 3: Motor Neuron Disease: Amyotrophic Lateral Sclerosis

This disease is the most common form of motor neuron disease, but is generally considered rare affecting two in every one hundred people worldwide. This muscle weakness is caused by motor neurons degenerating and peripheral nerves becoming severed, causing the neuromuscular junction to destabilize. Amyotrophic lateral sclerosis in specific is a combination of upper motor and lower motor neuron dysfunction [10], along with corticospinal tract damage. This is visible through the presence of brisk

reflexes (an above average response during deep tendon reflex, resulting in faster responses than normal) and extensor plantar responses (the stroking of the sole results in the extension of the big toe and the extension of other toes [21]). Effects of ALS can be seen through the disproportionate muscle weakness, impeded speech caused by jaw jerk, tongue wasting (which is hypoglossal nerve disorder), along with the aforementioned reflexes and response. Other characteristics such as intellect and emotions are unaffected [5].

4.1 Differential diagnosis

There are two main ways of identifying ALS; the first consists of measuring asymmetrical weakness. This refers to greater strength in one side of the body rather than the other. The second is referred to as 'wasting in the limbs', which is representative of corticospinal spinal tract damage [20]. It is a combination of these two diagnoses by which ALS is detected.

4.2 Symptoms and Causes

There are 4 main symptoms: muscle weakness, breathing difficulty, loss of motor functions, and paralysis, which can eventually lead to death. The causes of these include toxic neuropathy and other immune mediated disease. 'Toxic neuropathy' refers to the ingestion of drugs and other harmful chemicals, causing damage to multiple nerves and their respective nerve endings. In rare cases, a patients with HIV can also have ALS at much later stages of HIV. This is known as HIV - associated motor neuron disease, which is a rare manifestation of ALS.

4.3 Classifications

Motor neuron disease can be classified into 3 categories: mixed upper and lower motor neuron syndrome (this include ALS), pure upper motor neuron syndrome, and pure lower motor neuron syndrome. Any damage to upper motor neurons results in inability to operate at finer levels of touch and interaction, whereas damage to lower motor neurons leads to inability to operate gross movements such as walking. Mixed upper and lower motor neuron damage results in decreased ability to operate at finer and grosser movement, however this is disproportionate.

5. Section 4: Motor Neuron Disease: Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) is an autosomal, recessive neurodegenerative disease, which affects the spinal cord, causing symmetrical proximal muscle weakness. This is brought about through the degeneration of the α motor neurons in the ventral horn of the spinal cord. The α motor neurons are somatic neurons that innervate the skeletal muscle. This degeneration is caused by the deletion or alteration of the survival motor neuron 1 gene (abbreviated to SMN_1) [11].

5.1 Differential Diagnosis and Symptoms

There are 3 main methods to differentially diagnosing SMA. The first is by taking a reading and checking the presence of congenital myopathy [7]. This is a reading of a rare muscle disease after birth (congenital), which could hint at the presence of SMA. The next includes metabolic myopathies, similar to congenital myopathies, where a disease affects the rate of metabolism. These patients lack enzymes contributing to production of energy in the body, preventing muscle contraction. Next is the presence of non - neuromuscular conditions, referring to other conditions that lie outside the neuromuscular junction. This includes scoliosis (curvature of the spine) as one of the symptoms of SMA.

The symptoms include muscle weakness, muscle atrophy, lack of deep tendon reflexes (opposite to brisk reflex), and rapid impulsive muscle reflexes (trembling). In this context, atrophy is the degradation of muscular tissue and cells due to the decreased usage in said muscles.

5.2 Causes and Classifications

The main cause is the modification of the gene SMN_1 in chromosome 5. It is largely unknown what the function of the SMN gene is, however, it has been identified that the SMN gene consists of the SMN_1 and SMN_2 parts. IN patients with SMA, there is a distinct absence of the SMN_1 gene. Normally, 70 - 75 (percent) of the SMA protein is made of SMN_1 gene, where the other 25 (percent) is made from SMN_2. Whereas, in SMA patients, there is no SMN_1 gene found. However, if there is an increased presence of the SMN_2 gene, then the effects are slightly mitigated (but not completely).

There are 4 classifications for SMA: Type I, Type II, Type III, and Type IV. Type III includes Type IIIa SMA and Type IIIb SMA [2]. The only difference is mainly the age of the patient. For Type I, over 60 percent of patients with SMA have this stage, which occurs at birth up til and infants first 6 months. Type II appears between a patients age of 6 to 18 months old. Patients are capable of sitting without any support but may have difficulty walking. Type III occurs after 18 months of age, and the patients can walk independently with some difficulties. However, after a few years, they lose the ability to walk entirely. Lastly, Type IV occurs in early adulthood (after the age of 21 years). Symptoms include weakened legs, tremors, and mild breathing problems. The life expectancy remains the same [6]. There is also a Type 0, where the patient is less than a month old.

6. Conclusion

Although these diseases are dangerous in their own merit, there are many potential solutions, ranging from medication to specific therapies for rehabilitation. Note that treatment and solutions to these diseases have not been discussed for two main reasons. The first being that this review article is not intended to be used as any guide for treatment, rather for educational purposes and for understanding the mechanics of these diseases in greater detail. The second is that the mechanics of treatments and medications are out of the

scope of this article in terms of difficulty as their interactions with the body and the nervous system are intricate and complicated. The main purpose of this article, as previously stated, is to introduce the subject of neuroscience to potential interested individuals, along with providing the basic set of knowledge on a vast topic in a condensed form.

References

[1] American Psychiatric Association et al. *Diagnostic and statistical manual of mental disorders (DSM - 5®)*. American Psychiatric Pub, 2013.
[2] Mariana Baioni and Celia Ambiel. Spinal muscular atrophy: Diagnosis, treatment and future prospects. *Jornal de pediatria*, 86: 261–70, 08 2010. doi: 10.2223/JPED.1988. URL https: //doi. org/10.1590/ S0021 - 75572010000400004.
[3] Marina Basta and Ashish M Pandya. Genetics, x - linked inheritance.2020.
[4] Anto´nio Bastos - Leite and Ph Scheltens. *MRI and the Differential Diagnosis of Dementia*, pages 261–271.10 2009. ISBN 978 - 0 - 19 - 532887 - 5. doi: 10.1093/acprof: oso/9780195328875.003.0016.
[5] Rebecca C Brown, Alan H Lockwood, and Babasaheb R Sonawane. Neurodegenerative diseases: an overview of environmental risk factors. *Environmental health perspectives*, 113 (9): 1250–1256, 2005.
[6] Kyra Y Chen. Spinal muscular atrophy - the disease and its treatments. *Archives of Community Medicine and Public Health*, 7 (2): 138–141, 2021.
[7] Adele D'Amico, Eugenio Mercuri, Francesco D Tiziano, and Enrico Bertini. Spinal muscular atrophy. *Orphanet journal of rare diseases*, 6 (1): 1–10, 2011.
[8] Fifth Edition et al. Diagnostic and statistical manual of mental disorders. *Am Psychiatric Assoc*, 21, 2013.
[9] David S Geldmacher and Peter J Whitehouse. Differential diagnosis of alzheimer's disease. *Neurology*, 48 (5 Suppl 6): 2S–9S, 1997.
[10] Majid Ghasemi. Amyotrophic lateral sclerosis mimic syndromes. *Iranian journal of neurology*, 15 (2): 85, 2016.
[11] Stephen J Kolb and John T Kissel. Spinal muscular atrophy. *Neurologic clinics*, 33 (4): 831–846, 2015.
[12] Igor O Korolev. Alzheimer's disease: a clinical and basic science review. *Medical Student Research Journal*, 4 (1): 24–33, 2014.
[13] Gabor G Kovacs. Molecular pathological classification of neurodegenerative diseases: turning towards precision medicine. *International journal of molecular sciences*, 17 (2): 189, 2016.
[14] Hyoung - gon Lee, Xiongwei Zhu, Akihiko Nunomura, George Perry, and Mark A Smith. Amyloid beta: the alternate hypothesis. *Current Alzheimer Research*, 3 (1): 75–80, 2006.
[15] M Paul Murphy and Harry LeVine III. Alzheimer's disease and the amyloid - β peptide. *Journal of Alzheimer's disease*, 19 (1): 311–323, 2010.
[16] Robert L Nussbaum and Christopher E Ellis. Alzheimer's disease and parkinson's disease. *New england journal of medicine*, 348 (14): 1356–1364, 2003.
[17] Maria Paraskevaidi, Camilo LM Morais, Ka´ssio MG Lima, Julie S Snowden, Jennifer A Saxon, Anna MT Richardson, Matthew Jones, David MA Mann, David Allsop, Pierre L Martin - Hirsch, et al. Differential diagnosis of alzheimer's disease using spectrochemical analysis of blood. *Proceedings of the National Academy of Sciences*, 114 (38): E7929–E7938, 2017.
[18] Gabriele Pizzino, Natasha Irrera, Mariapaola Cucinotta, Giovanni Pallio, Federica Mannino, Vincenzo Arcoraci, Francesco Squadrito, Domenica Altavilla, and Alessandra Bitto. Oxidative stress: harms and benefits for human health. *Oxidative medicine and cellular longevity*, 2017, 2017.
[19] Renata Santos, Anne - Laure Bulteau, and Cla´udio M Gomes. Neurodegeneration, neurogenesis, and oxidative stress 2015. *Oxidative medicine and cellular longevity*, 2016, 2016.
[20] Kevin Talbot. Motor neurone disease. *Postgraduate medical journal*, 78 (923): 513–519, 2002.
[21] H Kenneth Walker. The plantar reflex. *Clinical Methods: The History, Physical, and Laboratory Examinations.3rd edition*, 1990.
[22] Jason Weller and Andrew Budson. Current understanding of alzheimer's disease diagnosis and treatment. *F1000Research*, 7, 2018.
[23] Zhengyuan Xia, Yanfang Chen, Qian Fan, Mengzhou Xue, and Ke - xuan Liu. Oxidative stress - mediated reperfusion injury 2014, 2015.