

# White Paper on Neurodegenerative Disease and Related Disorders and Associated Case Study

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## Introduction

Numerous diseases have been reported to have reduced human performance and functionality. Attention should be paid to neurodegenerative disorders as it usually oppresses patients' central and peripheral nervous systems, which weakens muscles. It dramatically affects the neurons which are produced by neural stem cells (Masrori & Van Damme, 2020). Neurons usually reduce with ageing. Neurons cannot live forever, but the progressive loss of neurons, their structure, or their activities, known as neurodegeneration, is a significant health concern and a vital component of the pathogenesis of many different brain illnesses (Hampel et al., 2018). Parkinson's disease and Alzheimer's account for the maximum prevalent neurodegenerative conditions. Although several medications are currently approved for treating neurodegenerative diseases, most address symptomatology (Mathis et al., 2020). The blood-brain barrier (BBB), which prevents over 99% of entirely "external chemicals" from entering the brain, is the leading cause of this death of pathogenesis-targeting therapeutics.

Since their discovery, the targeted transport of substances into various organs, including the brain, has been accomplished with the help of nanoparticles. The primary pathophysiological alteration in most illnesses involving the brain has been identified as neurodegeneration (Armstrong & Okun, 2020). Despite modern science's constant attempts to provide a medicinal or surgical cure, the results have failed. Many older adults continue to experience clinical concerns related to Alzheimer's and dementia (Mathis et al., 2020). Despite its remarkable effectiveness, the blood-brain barrier (BBB) still poses a significant obstacle to the efficient therapy of many illnesses (Delamarre & Meissner, 2017). Alzheimer's disease is characterized by dementia common, a progressive disease characterized by mild memory loss, potentially leading to loss of communication ability. Parkinson's disorder affects the nervous system leading to stiffness with balance and coordination loss. Similarly, Amyotrophic sclerosis, a nervous system disease, affects the brain's nerve cells, thus causing loss of muscle control (Mathis et al., 2020). Even with the numerous triumphs achieved with surgeries and extremely evasive techniques, their clinical acceptance is constrained because of conflicting worries about their long-term benefits due to the possibility of damaging the blood-brain barrier.

Recently, millions of people have been affected by neurodegenerative diseases globally (Tambasco, Romoli & Calabresi, 2018). Researchers have shown that a mix of an individual's genetic makeup and environmental circumstances can contribute equally to increasing the risk for NDs, even if age is the most critical risk factor for developing all NDs (Bloem, Okun & Klein, 2021). The severity and timing of neurodegeneration also heavily depend on the local environment, despite the expression of specif-

ic genes responsible for NDs (Delamarre & Meissner, 2017). Recent research has shown that many other disorders may accompany a single neurodegenerative illness. Therefore, the severity of NDs depends purely on the nature and stage of the disease; in some cases, they may even be life-threatening (Mathis et al., 2020). These disorders thus impair numerous elements of human functioning and impede the capacity to accomplish simple and complex tasks since the brain regulates several bodily functions. While the majority of these conditions proceed without remission, some treatments aim to lessen symptoms, relieve any pain that may be present, and restore balance and mobility (Vázquez- Vélez & Zoghbi, 2021). This review comprehensively discusses the numerous NDs (Parkinson's disease, Amyotrophic lateral sclerosis, and Alzheimer's disease with the case study), their alternative treatments and the effectiveness of integrated approaches for management.

## **Parkinson's disease**

### **Introduction**

Parkinson's disease (PD) is a common neurodegenerative disease characterized by postural instability, resting tremors, and rigidity (Jankovic, & Tan, 2020). The clinical symptoms and some of the therapeutic targets have been found to alter the progressivity of this disease. Typically, early symptomatic phases of PD are when treatment decisions are made to reduce disability resulting from the earliest motor signs and symptoms, avoiding motor problems later on, and, ideally, decreasing the disease's course (Bloem, Okun & Klein, 2021). Other stages of treatment have different goals, such as managing motor problems, preventing falls, treating dementia and psychosis, and finally, delaying the damage to self-sufficiency (Jankovic, & Tan, 2020). Moreover, the reflection of medicine changes is considered highly influential during the first 3-5 years to become linked to motor problems, which can include unpredictable on-off swings and dyskinesias, as well as a shortening of the antiparkinsonian effect's duration. Tysnes & Storstein, (2017) asserts that an increasing concern with the non-motor characteristics identified in Parkinson's disease, includes pain, sleep disorders, and neuropsychiatric symptomatology.

Nevertheless, non-pharmacological treatments for this condition may include psychosocial counselling, work-related therapy, speech, and physiotherapy (Bloem, Okun & Klein, 2021). Surgical therapies have also become crucial, mainly due to subthalamic nucleus stimulation. This white paper seeks to conduct a comprehensive review of Parkinson's disease and patient case studies presented with the disease and discuss the alternative to the treatments and the effectiveness of integrated approaches to treatment (Bloem, Okun & Klein, 2021).

### ***History and Epidemiology***

Parkinson, in 1817 described Parkinson's disease as a neurological syndrome, although his fragments of Parkinsonism were still in earlier descriptions. Also, the earliest reports of PD can be found in traditional Indian writings dating from 1000 BC and ancient Chinese sources. According to estimates based on healthcare utilization, incidences of Parkinson's disease range between 5 and 35 new PD cases yearly (Simon et al., 2020). Between the sixth and ninth decades of life, the incidence multiplies by 5 to 10 times (Tysnes & Storstein, 2017). Age is also seen to associate with the development of Parkinson's disease. Studies have shown that Parkinson's disease prevalently rose from less than 1% among men and women aged 45–54 to 6%, according to the meta-analysis of four North American groups (Tysnes & Storstein, 2017). In the next two decades, the prevalence of PD is predicted to more than double as the world's population ages. In addition to this rise, the societal and financial costs associated with PD will rise unless better cures, treatments, or preventative measures are found.

### ***PD Risk Factors***

#### ***Environmental factors***

Although numerous research studies have identified the environmental factors contributing to PD, most findings have yet to be deemed conclusive. Water-borne risk factors and pesticide exposure impacts have received the majority of attention (Vázquez-Vélez & Zoghbi, 2021). The Geo-Parkinson study investigated such correlations among the five European nations and discovered a high proportion of pesticides containing manganese in patients' brains during a necropsy examination (Simon et al., 2020). Hence, it is hy-

pothesized that even a little pesticide exposure can significantly raise the risk of developing PD (Simon et al., 2020). A meta-analysis of environmental risk factors for PD development shows that individuals living in rural areas and getting their water from wells are more likely to develop PD (Chen, Li & Liu, 2020). Therefore, the potentiality of developing PD is said to associate with exposure of pesticide.

### **Genetic Risk Factors**

Genetic factors are also deemed major type of risk factors leading to PD development besides environmental exposures (Marinus et al., 2018). Despite PD accounting for a slight percentage of cases, it may also give a firm and precise understanding of the underlying mechanisms (Delamarre & Meissner, 2017). Since the disease is linked to several protein products, it has been established that different genes can influence how the disease manifests (Delamarre & Meissner, 2017). SYN gene mutations are thought to speed up the beginning of the disease in both people and animals. Moreover, findings shows that these mutations can cause dopaminergic neuronal degeneration, a reduction in motor function, and muscular atrophy (Delamarre & Meissner, 2017). However, research indicates that PTEN-induced kinase produces essential PINK1 protein which is majorly associated with causing containment in oxidative stress occurring in the mitochondria (Marinus et al., 2018). Moreover, PINK1 genes cause PD in the same way that SYN genes do. However, a critical genetic component has been applied since PINK1 gene is purported to cause PD (Chen, Li & Liu, 2020). Based on these findings, it has been established that mutations in the genes SYN independently cause the beginning of PD (Chen, Li & Liu, 2020).

### **Oxidative Stress**

Oxidative stress refers to a phenomenon that causes the disparity in creation and accumulation of volatile oxygen species in tissues and cells (Delamarre & Meissner, 2017). Dopamine-producing neurons in the nigrostriatal system have been identified as the main cause of PD (Marinus et al., 2018). The role of unstable free radicals in the degeneration of nerve cells is among the triggers for PD that is gaining popularity (Chen, Li & Liu, 2020). Reactive oxidative species (ROS), often known as free radicals, are byproducts of chemical reactions that mainly occur in the mitochondria (Vázquez-Vélez & Zoghbi, 2021). The amount of ROS generated under some circumstances may surpass the capacity of the cleanup systems thus the inability to contain the disease (Vázquez-Vélez & Zoghbi, 2021). Typically, oxidative stress is the name given to this process and thus due this failure, the highly volatile oxidative types combine with other stable molecules (Delamarre & Meissner, 2017).

### **Pathophysiology**

Parkinson's disease pathophysiology involves the demise of *dopaminergic* neurons because of the changes in biological actions within the brain concerning PD (Marinus et al., 2018). Several mechanisms have been developed in response to the death of neuronal cells in PD. Diverse hypothesized causes for neuronal death in PD are available some of which include; Lewy body aggregation, and blood-brain barrier disruption (Chen, Li & Liu, 2020). One of the main factors contributing to neuronal death in Parkinson's disease is protein oligomerization (Simon et al., 2020). Alpha-synuclein is more prevalent in the brain of PD patients and due to their insolubility, it clumps and form Lewy bodies within the neurons (Simon et al., 2020).

Moreover, heat-shock proteins help in refolding proteins that are prone to aggregations because of its favorable effect on Parkinson's disease (PD) when overexpressed (Delamarre & Meissner, 2017). These findings support this process. Reduced DNA repair appear to be closely related in ways that include alpha-synuclein (Tysnes & Storstein, 2017). Alpha-ability synucleins usually facilitate in the overall DNA repair process which is known as non-homologous end joining the double-stranded DNA breaks (Tysnes & Storstein, 2017). Simon et al., 2020) asserts that Lewy bodies, forms when alpha-synuclein aggregates in the cytoplasm, lower the nucleus levels of the protein, which in turn increases DNA double-strand breaks and raise programmed cell's death within the neurons.

PINK1 and Parkin complex is thought to be the cause of mitochondrial malfunction in Parkinson's disease because it has been demonstrated that it promotes the autophagy of mitochondria (Vázquez-Vélez & Zoghbi, 2021). The protein can build up on the surface of damaged mitochondria in addition to being routinely carried inside the mitochondrion (Marinus et al., 2018). According to Marinus et al. (2018) these genes are assumed to be altered in Parkinson's disease, restraining the interruption of injured mitochondria, resulting

to aberrant mitochondrial role and shape, and eventually cell death. However, the accumulation of mitochondrial DNA alterations has also been observed, signifying that this mechanism of neuronal death can be that susceptible with aging (Tysnes & Storstein, 2017).

### ***Clinical Features and Diagnosis***

The disease has distinctive neuropathological changes in the brain changes. Researchers have identified six neuropathological disease phases as PD stages (Tysnes & Storstein, 2017). Stage one and two of the disease according to Marinus et al. (2018). are usually the pre- symptomatic stages, in these stages the inclusion of bodies is restricted to the medulla oblongata and the olfactory anterior part of the nucleus. Substantia nigra and the forebrain nuclei are obstructed as the disease gets worsened within stages 3 and stage 4 (Vázquez-Vélez & Zoghbi, 2021). It is claimed that individuals usually begin to display clinical symptoms of the condition at this stage (Bloem, Okun & Klein, 2021). Individuals begins to show clinical signs of the illness at this point, and the process proceeds to last stage that is stages 5 stage 6 which is characterized by a wide range of clinical symptoms (Bloem, Okun & Klein, 2021). Although there may be problems in many other nervous system activities, motor disturbances typically characterize the clinical symptoms of PD (Vázquez-Vélez & Zoghbi, 2021). The dopaminergic medication may trigger or worsen some of the signs, symptoms thus can be divided into motor and non-motor symptoms (Delamarre & Meissner, 2017). A common sign can be bradykinesia, characterized by a delay at the beginning of intended actions and an advanced decrease in the speed and plenty of repetitive movements. These characteristics are prerequisites for PD diagnosis in addition to muscular rigidity and postural instability (Delamarre & Meissner, 2017).

The bradykinesia may cause an expressionless visage and reduced handwriting amplitudes (micrographia) (Bloem, Okun & Klein, 2021). A resting pill-rolling gentle of tremor of the hands is the most predominant limb tremor, affecting about 80% of people. (Tysnes & Storstein, 2017). The propensity of the thumb and index finger to come into touch and move in a rotary motion is known as “pill rolling.” Typically, the tremor involves the legs, and other types of tremors which might occur (Vázquez-Vélez & Zoghbi, 2021). Bloem, Okun & Klein, (2021) estimates that more than half of the patients have speech abnormalities like quiet or rushed talking. Dystonia is another motor sign of PD, a continuous muscular contraction characteristically conveyed by atypical postures, motions, or both (Delamarre & Meissner, 2017). Most dystonic symptoms are connected to medicinal and surgical therapy, which may occasionally be a pre-diagnostic sign in PD. For non-motor symptoms, autonomic function disturbances and cognitive, sensory, and sleep disturbances have been commonly reported (Delamarre & Meissner, 2017).

### ***Case Study***

Choosing effective therapeutic interventions for every patient with their respective diseases for decades has become an issue due to fluctuating and advanced natural conditions and the required evaluation of numerous sources with the latent application to patient supervision (Tambasco, Romoli & Calabresi, 2018). However, this section provides a case study for a PD patient and further emphasizes on current available suggestion for the pharmacological treatment of PD motor symptoms. Therefore, to ascertain alternative treatment and integrated approaches toward PD management, we will look at the case scenario below.

A 63-year-old male having a 4-year history of Parkinson’s disease had been referred to the movement disorders outpatient clinic due to deterioration of the condition. His medication consists of levodopa/benserazide 200mg/50mg. The patient started on two capsules of a proprietary blend.

No. 1, once in the morning and once at night, for three days. He then increased the dosage by one drop every three days and built up to 10 drops twice daily. No. 2, one capsule in the morning and afternoon for ten days. He then increased to two in the morning and one in the afternoon and added one sachet of proprietary blend. No.3 to his diet, one in the morning. He also started taking six drops twice daily of proprietary blend. However, after one-month, cardinal symptoms of Parkinson’s disease would be, resting tremor and muscle stiffness signifying slight decrease. In addition, his quality of sleep improved, as well as his gait. His medications have not changed.

### ***Treatment and Management of Parkinson's disease***

Medication is known as the most popular therapy for PD. The intention is to remedy the dopamine insufficiency, which is the root of the symptoms (Tambasco, Romoli & Calabresi, 2018). Pharmaceutical therapy is typically initiated as symptoms interfere with daily activities or become incapacitating (Armstrong & Okun, 2020). Several treatments may be used basing on the patient's age, reactions, and symptoms towards a particular medication. However, finding the ideal medicine combination for each patient can frequently take some time (Armstrong & Okun, 2020).

The most efficient medication for treating PD is levodopa, a precursor to dopamine in the body (Delamarre & Meissner, 2017). Levodopa is mostly inactive; dopamine is formed when levodopa is decarboxylated, which has both medicinal and harmful consequences. The drug is quickly absorbed from the small bowel after oral administration thanks to the transport mechanism for aromatic amino acids (Armstrong & Okun, 2020). After an oral dose, concentrations of drug in the blood peak within 0.5 and 2 hours later. The pH of gastric juice, the pace of stomach emptying, and the amount of time the medication is visible to the digestive intestinal mucosa all affect how quickly and how much absorption takes place (Tambasco, Romoli & Calabresi, 2018). Typically, levodopa may be less readily absorbed if food amino acids compete for absorption sites in the small bowel; thus, taking this drug with meals delays absorption as well as lowers peak plasma concentrations (Bloem, Okun & Klein, 2021). The drug is primarily decarboxylated into dopamine in the brain's striatum, in the presynaptic joints of dopaminergic neurons. The dopamine generated is what gives the medication its therapeutic impact on PD (Armstrong & Okun, 2020). Levodopa drug is often administered in clinical practice along with a peripherally acting aromatic l-amino acid decarboxylase inhibitor with poor CNS penetration, such as carbidopa (Tambasco, Romoli & Calabresi, 2018). If it is taken alone, it will substantially decarboxylated by enzymes present in the intestinal mucosa, thus only a small amount of the drug will remain intact and probably only few penetrates to the brain by less than 1%. Dopamine concentrations in the bloodstream cause nausea by activating the chemoreceptive trigger zone in the brainstem (Vázquez-Vélez & Zoghbi, 2021). The amount of initiated levodopa remaining will not be metabolized thus they are available to pass the blood- brain barrier increases with peripheral decarboxylase inhibition, lowering the likelihood of gastrointestinal side effects (Bloem, Okun & Klein, 2021). Carbidopa 25 mg/levodopa 100 mg is the dosage of carbidopa with levodopa that is most frequently recommended as a result. With this formulation, dose regimens of three or more pills daily offer most people satisfactory decarboxylase inhibition (Tambasco, Romoli & Calabresi, 2018).

In the aforementioned case study, it is seen that the major symptoms the patient presented were resting tremor, rigidity (muscle stiffness), and Bradykinesia. However, as the literature and research findings mentioned, bradykinesia and rigidity are among the typical clinical features associated with Parkinson's disease (Delamarre & Meissner, 2017). Patient experienced a spontaneous loss of movement in the case of bradykinesia. The patient experienced rigidity because of resistance to movement due to an opposing muscle. However, rigidity as a symptom comes about when the opposing muscles' delicate balance is hampered in response to the signals originating from the brain (Armstrong & Okun, 2020). Typically, tremor, as a primary symptom associated with PD, takes the arrangement of a rhythmic movement of the forefinger and the thumb. It is also seen that the patient had not changed his medication and maintained his levodopa/benserazide 200mg/50mg dose (Armstrong & Okun, 2020). Since the drug relieved the symptoms one month after administration, it proves that levodopa is an effective drug that many patients with PD can use (Tambasco, Romoli & Calabresi, 2018).

### ***Alternatives to PD Treatment and Management***

The effectiveness of levodopa drugs does not limit the inclusion of other treatment models and approaches for the disease. Due to the continued vigorous research, researchers are finding more alternative treatments that can be used to cure PD through clinical trials and drug development other than the known ones (Simon et al., 2020). Recent research findings have highlighted drugs such as Bromocriptine, Ropinirole, and pramipexole as other drugs primarily for PD symptoms (Tambasco, Romoli & Calabresi, 2018). These integrated approaches are dimmed effective in action and less associated with adverse effects. Dopamine-Receptor Agonists, unlike levodopa, have effectively treated PD since they do not require enzymatic translation to active metabolites (Armstrong & Okun, 2020).

Additionally, Dopamine-Receptor Agonists do not hinge on the functional capacities of the neurons and are thus considered a better alternative treatment for Parkinson's disease (Delamarre & Meissner, 2017). COMT inhibitors have been identified as a relatively recent class of medications for treating PD (Bloem, Okun & Klein, 2021). It is associated with the catabolism of Levodopa and dopamine. COMT produces the pharmacologically inactive substances 3-O-methyldopa (from levodopa) and 3-O-methoxy tyramine by transferring a methyl group from the donor S-adenosyl-l-methionine (from dopamine) (Bloem, Okun & Klein, 2021).

However, an AAD inhibitor, such as carbidopa, increases the quantity of levodopa, which is methylated by COMT, while decreasing dopamine production (Tambasco, Romoli & Calabresi, 2018). The main therapeutic effect of COMT inhibitors is to prevent the conversion of levodopa to 3-O-methyl-dopa in the peripheral nervous system, which prolongs the plasma half- life of levodopa and increases the proportion of each dose that reaches the central nervous system (Delamarre & Meissner, 2017). According to Tysnes & Storstein,( 2017), Selegiline, Rasagiline, and selective monoamine oxidase-B inhibitors are further PD treatment options. Selegiline is a selective MAO-B inhibitor that inhibits the enzyme irreversibly at low to moderate dosages (Tysnes & Storstein, 2017). Selegiline has been used for many years to treat the symptoms of Parkinson's disease. However, the ability of selegiline to suppress the striatal synthesis of dopamine is thought to be the basis of its effectiveness (Simon et al., 2020).

In people with early or mild PD, selegiline is typically well tolerated. Selegiline may exacerbate levodopa therapy's negative motor and cognitive consequences in patients with more severe PD or underlying cognitive impairment (Bloem, Okun & Klein, 2021). Amphetamine and methamphetamine are two of the selegiline metabolites which can have adverse side effects, including anxiety and insomnia. Rasagiline is a monoamine oxidase-B (MAO-B) inhibitor that also inhibits dopamine breakdown without producing unfavorable byproducts (Vázquez-Vélez & Zoghbi, 2021). Tablets containing rasagiline are recommended for treating PD symptoms and signs, both as initial therapy without the addition of treatment for moderate PD (Delamarre & Meissner, 2017). It may be helpful as a supplement for levodopa users with dose-related fluctuations and dyskinesias. Amantadine, an antiviral agent that is also used to treat influenza A, is a different therapy option that can be used. It also functions as an antiparkinsonian (Tambasco, Romoli & Calabresi, 2018). It is the first line antidyskinetic qualities have been linked to its effects on NMDA receptors, even though memantine, an NMDA receptor antagonist that is closely related, does not appear to have the same effect.

In addition to symptoms' regulation of PD through clinical treatments, it would be advantageous to develop other therapies which, when combined, modify the process of degeneration that governs PD. Current research strategies are based on mechanical approaches such as energy metabolism, oxidative stress, environmental triggers, excitotoxicity, and detections related to the genetics of PD (Armstrong & Okun, 2020). The approaches also seek to address PD by assessing and ascertaining various risk factors associated with PD. For example, it would be more effective to manage PD when medical practitioners can seek to address ecological risk factors such as contact to toxic chemicals and pesticides (Tysnes & Storstein, 2017), Also, integrated approaches to address psychological factors such as stress through counseling are imperative to provide prevention against PD. More discoveries are coming up to offer a genetic solution if an individual has an inherited PD gene (Vázquez-Vélez & Zoghbi, 2021). Finally, observing a healthy and balanced diet is another measure that can be implemented to prevent physiological issues and cases of oxidative stress, which may accelerate the likelihood of developing PD (Bloem, Okun & Klein, 2021). Adopting these alternatives offers great betterment because they contain and manage them instead of treating them. Ideally, preventing a disease occurrence is termed more cost-effective than treatment (Armstrong & Okun, 2020). Also, since individuals will be prevented from developing the disease, there will be fewer reported cases of PD susceptibility for the future generation.

## **Amyotrophic Lateral Sclerosis**

### **Introduction**

Amyotrophic Lateral Sclerosis (ALS) refers to classic neurodegenerative condition which involves gradual degenerations of the motor neurons in the brain and spinal cord. Though it involves numerous levels of functional entities that alternate in different directions before convergence of the functional defining ALS disease development, tracing the evolving nature of ALS highlights critical measurement of individual variances which underpins this form of ailment (Masrori & Van Damme, 2020). ALS may begin as a single entity



and develop into a complex disease. However, nothing is known about how these disparate elements ultimately function together to define the course of ALS (Masrori & Van Damme, 2020). Many theories have been put out; however, there hasn't been any agreement between the opposing philosophical camps.

### ***History and Epidemiology***

Most ALS cases are sporadic linked by cortical and spinal motor neuron degeneration (Longinetti & Fang, 2019). Baseball player Lou Gehrig was identified with ALS in 1939 by a French neurologist Jean-Martin Charcot originally described the condition in 1869. It resulted to a widespread awareness of the condition in the country (Masrori & Van Damme, 2020). It is sometimes referred to as Charcot disease after Jean-Martin Charcot, who first described it, and motor neuron disease (MND) since it was considered as one among the five diseases that often affect cells in the motor neurons (Mathis et al., 2020).

In the 1990s, about 1.5 and 2.7 documented ALS cases in Europe and North America. Current research has demonstrated that the disease frequency did not show any growth for the past ten years, as the prevalence rate is still remains at 2.7/100,000, and the prevalence of ALS was 0.32/100,000 of 2008 (Goutman et al., 2022). Whereas some research has demonstrated a balance in the ratio, many investigations have revealed an increase in the risk among the males to be higher than that of females (Goutman et al., 2022). Nonetheless, 64 years old accounts as the median age through which ALS begins, with a range of 50 to 65 years. Just 5% of the cases begin before the age of 30 (Mathis et al., 2020). The prevalence of this condition is particularly prominent in elderly individuals 80 years of age and older, and data suggests that the increase is due to variations in care.

### ***ALS-associated risk factors***

Exposure to environmental toxins, agriculture chemicals, dust/fibers/fumes, heavy metals, solvents, diet, and physical activity have been associated with developing ALS in patients according to the previous epidemiology (Obrador et al., 2020). Individuals prone to smoking are at higher risk for ALS through inflammation, oxidative stress, and neurotoxicity caused by the heavy metals present in the cigarette (Obrador et al., 2020). Similarly, people engaged in more physical activities are at risk for ALS than the general population. Genetic profiles promoting physical fitness hold a proportional correlation between ALS and physical activity (Mahoney et al., 2021). In other words, a genetic profile altered by exogenous factors which promote physical fitness increases an individual's susceptibility to ALS. However, the results from the beneficial vascular risk profile in patients and their relatives have been found to have supported this concept (Mathis et al., 2020). Researchers have conveyed an abridged frequency that corresponds to coronary heart disease which increases the risk to ALS due to physical fitness (Obrador et al., 2020). Additionally, age is another factor associated with ALS where the risk increases with age. Thus, the disease is common among people of age 40-60 years. However, as age progresses, it is observed that men are more slightly are risk of developing ALS than women (Andrew et al., 2021). In another research conducted, findings showed genetic factors as one of the common risk factors accelerating ALS (Andrew et al., 2021). Of the samples collected, it was observed that those presented with ALS symptoms had a medical history of inherited ALS.

### ***Pathophysiology***

The degeneration and the demise of upper and lower motor neurons, the reactive gliosis replacement of dead neurons accounts as the hallmarks of ALS (Lian et al., 2019). Spinal motor neurons have a regressive axonal damage characterized with secondary myelin pallor which greatly rise with aging (Dorst, Ludolph & Huebers, 2018). Although they affect the entire spinal cord, these alterations are more pronounced in the brainstem and upper spinal cord. The motor strip shows abnormal immunoreactivity to GFAP (Lian et al., 2019). The ALS motor cortex generally exhibits the astrocytic gliosis within the deeper levels at the gray matter and the parts of subcortical white matter (Dorst, Ludolph & Huebers, 2018). The lysosomal marker CD68 also demonstrated that microglia activation and active macrophages account for most of the glial reply at the spinal tracts.

ALS affects spinal motor neurons and the brainstem motor neurons. From the autopsy of ALS patients, it can be detected that the loss of motor neurons and atrophic motor neurons alters the general cell's mechanism (Soriani & Desnuelle, 2017). As a result, the

ventral roots are slimmed due to the loss of large myelinated fibers within the motor nerves hence denervating the atrophy of the affected muscles (Dorst, Ludolph & Huebers, 2018). ALS impacts both brainstem motor neurons and ventral horn spinal motor neurons. Motor neuron loss and atrophic motor neurons with a basophilic appearance are seen during autopsies of ALS patients, pointing to a programmed cell process (Lian et al., 2019). The motor neurons' ventral roots thinning and loss of their big myelinated fibers cause denervation atrophy with signs of re-innervation in the affected muscles. In addition to the normal clinical symptoms of the disease, ALS causes spongiform alterations in the neocortex accompanied by neuronal loss in the amygdale, hippocampus, and frontal (Soriani & Desnuelle, 2017). The non-motor ALS pathological findings include the demyelination of the posterior columns and the decreased myelinated sensory fibers density (Soriani & Desnuelle, 2017).

### ***Clinical Features and Diagnosis***

Manifestations of the phenotypical ALS are categorized into four typical groups: PMA with pure LMN involvement, and limb-onset ALS, and PLS with pure UMN involvement (Mathis et al., 2020). These categories are defined by amalgamation of limb motor neuron (LMN) and the upper motor neuron (UMN). However, the union between UMN and LMN impairment affects the brainstem and several spinal cord innervation sites thus accounting for the primary clinical hallmark of ALS (Obrador et al., 2020). In a study, Limb-onset ALS is seen as the main kind, 70% cases were reflected among patients where 25% had a bulbar onset, and the remaining 5% had respiratory involvement (Obrador et al., 2020). Patients with ALS suffer distal or proximal localized muscle weakness in both their upper and lower limbs (Dorst, Ludolph & Huebers, 2018). Asymmetrical initial symptoms that progress to generalized weakness and muscular atrophy are typical. Most patients experience spasticity, which impairs manual dexterity and walking, as well as bulbar and respiratory symptoms (Dorst, Ludolph & Huebers, 2018). Symptoms such as emotional lability with excessive yawning have been detected in many patients. Only 5% of individuals with respiratory impairment typically exhibit severe limb or bulbar symptoms (Soriani & Desnuelle, 2017). Some individuals, however, exhibit respiratory failure that corresponds to type 2. Type 2 respiratory failure is well known as the nocturnal hypoventilation, characterized by orthopnea, dyspnea, anorexia, disturbed sleep, morning headaches, poor attention, and prickliness in mood swings (Lian et al., 2019). In the early stages of limb-onset ALS, muscular atrophy is typically found in some parts of forearms, shoulders, hands, proximal thigh, and sometimes it may extend to the foot muscles down the lower limbs (Lian et al., 2019).

### ***Treatment and management***

Treatment for ALS can help to reverse the damage of the disease or prevent symptoms. However, the Food and Drug Administration has approved three medicines which can be used for treating this disease. Riluzole drug has been examined to reduce severe ALS, it is administered orally with an effectiveness of three to six months (Soriani & Desnuelle, 2017). Despite its effectiveness, Riluzole is associated with adverse effects such alterations in liver function, nausea, and dizziness. Edaravone is another drug of choice which is administered through the vein in the arm or as a pill orally (Obrador et al., 2020). These medicinal drugs are given daily for two weeks in a month according to research and that it helps in reducing ALS symptoms (Lian et al., 2019). Sodium phenylbutyrate and taurursodiol as recently approved medicine helps to restore or enhance the motor activities in ALS patients. In addition to the clinical treatment for ALS, other approaches for management have been deployed (Dorst, Ludolph & Huebers, 2018). For instance, inclusion of different therapies such as occupational, physical and psychological therapies all together are essential in lessening associated symptoms of ALS. Additionally, nutritional and social support can encompass as they are termed as effective preventive approaches.

## **Alzheimer's disease**

### **Introduction**

Alzheimer's disease (AD) accounts to about 80% of cases of late-life cognitive dysfunction caused by degenerative condition of the brain. There is a widespread notion that dementia only occurs as a normal byproduct of aging (Weller & Budson, 2018). Dementia, however, affects the cognitive brain processes of perception, memory, thought, and language, severely limiting the capability to carry out daily functions (Burke et al., 2018). Even while dementia is not a definite result of aging, the risk of having it rises dramatically with



age. Dementia and Alzheimer's disease are the primary causes of illness related to mortality in the old people, adding to the burden of non-communicable diseases worldwide (Weller & Budson, 2018).

### ***History and Epidemiology***

Neuronal cell death causes Alzheimer's, the dying cells sets on in the entorhinal cortex in the hippocampus (Juźwik et al., 2019). The disease was first identified in 1901 when German doctor Alois Alzheimer saw patient Auguste D. Oskar Fischer, a psychiatrist, and neuropathologist evaluated 12 instances of dementia simultaneously and gathered more clinical signs and symptoms and neuropathological evidence of the condition (Olivari et al., 2023). Later, in 1990, Levy and Frangione identified mutation as the root cause of amyloid protein buildup in the walls of the cerebral vessels in AD patients, which resulted in hemorrhages in the brain and early death (Juźwik et al., 2019). Since then, research on AD has advanced as scientists now look for the most efficient alternative and comprehensive treatment for the condition.

Epidemiological data on AD shows that the disease primarily affects older people. Alzheimer's illness usually affects old people due to their characteristic weak immune, globally the prevalence reported accounts to about 24 million (Eratne et al., 2018). It is therefore expected to rise heavily by the year 2050. It was estimated that 4.5 million Americans aging 65 and older were affected by clinical Alzheimer's disease in 2011 (Lane, Hardy & Schott, 2018). After the age of 65, the prevalence of Alzheimer's disease duos with five-year interval with less than 1% increase before age 65 and about 6% per year after age 85 (Hampel et al., 2018). The World Health Organization (WHO) estimates that there are presently 35.6 million individuals living with dementia worldwide, this figure is expected increase every 20 years to reach 115.4 million by 2050 (Liguori et al., 2019). Also, it is anticipated that over 5 million Americans had AD in 2013; by 2050, that number is expected to triple. Over \$225 billion was spent on Alzheimer's patients in the United States in 2010 (Armstrong, 2019). According to the Centers for Disease Control and Prevention (CDC), AD is said to be the 6th leading disease that causes death. Even though much time, money, and effort are being put into understanding the pathophysiology and effective care for Alzheimer's and other forms of dementia, initial disease diagnosis is still a significant challenge (Caruso et al., 2019). Through delaying of AD and other forms of dementia within a year, it is expected that by 2050, less than nine million cases will be accounted for which suggestively reduces the disease's burden.

### ***Risk factors***

Alzheimer's disease is accompanied by various menace factors ranging from environmental, physiological, and genetic factors, which are suggested as common causes of AD and other dementias (Hampel et al., 2018). However, other risk factors include; diabetes and heart disease, can also accelerate prevalence and incidence of AD. Conversely, a recent cohort study has demonstrated that gout disease can potentially reduce the risk of developing the disease.

### ***Genetic risk factors***

Based on family history of dementia, intermittent mutations in genes impacts the amyloid within the brain. Apolipoprotein E are among the commonly identified genetic factors associated with AD (Caruso et al., 2019). Evidence shows that the risk of developing AD from a family history of dementia varies depending on the kind of familial link, the phase of the illness starts (Hampel et al., 2018). A person's chance of having AD rises by 10–30% if they have a first-degree relative who has dementia (Armstrong, 2019). Moreover, in the case of two or more persons are affected with the late-onset AD risk will be higher as compared to the overall population. The biggest genetic risk factor for late-onset AD is APOE (Lane, Hardy & Schott, 2018). Thus those persons carrying one or both e4 alleles is considered to have a 2- to 3-fold higher chance of acquiring Alzheimer's disease than non-carriers. Race, gender, and vascular risk factors alters the association's strength.

### ***Physiological risk factor***

Stress, age, gender, hypertension, and coronary disease are all physiological risk factors for AD. Researchers have discovered more about the association between stress and AD, which indicates that psychological stress is a major risk factor for AD (Weller & Budson, 2018). Age-related cognitive loss may be sped up by the persistent stress linked to elevated cortisol levels (Burke et al., 2018). In another study, it is evident that glucocorticoids are typically released in reaction to stress (Weller & Budson, 2018). Regarding age, research findings show that AD progresses with age, where the disease is primarily prevalent in older people (Caruso et al., 2019). However, several studies demonstrate gender, in addition to age, also has an imperative role as a risk factor for developing AD, suggesting that the prevalence of AD is more common among women than men (Eratne et al., 2018). However, inconsistencies have been observed in studies related to the incidence of AD between males and females, incidence of AD studies conducted in the United States shows no significant difference between men and women (Weller & Budson, 2018).

### ***Environmental factors***

Apart from genetic and psychological factors, current studies have sparked interest in investigating toxicity exposure to environment as the primary potential risk factors accounting for AD increase (Hampel et al., 2018). Smoke, pesticides, and air pollution are the examples of such potential factors within the environment. Exposure to air pollution and pesticides can accelerate the likelihood of developing coronary and heart-related health conditions, possibly increasing the risk of AD (Weller & Budson, 2018).

### ***Pathophysiology***

Alzheimer's disease is primarily build up by neurofibrillary tangles and the aberrant neurotic plaque. Such plaques are usually spherical microscopic lesions having an extended axonal tail with an extracellular amyloid beta-peptide core (Lane, Hardy & Schott, 2018). Alpha, beta, and gamma-secretases work as proteases to cleave the beta-amyloid peptide from APP, amyloid precursor protein is a transmembrane protein that produces the beta-amyloid peptide (APP) (Caruso et al., 2019). Typically, alpha- or beta-secretase will cleave APP, and the resulting minute pieces are not harmful to neurons (Hampel et al., 2018). Rising in the beta-amyloid 42 leads to the aggregation amyloid which probably harms neurons. Amyloid buildup usually surrounds within the body parts including cerebral, meningeal, and gray matter arteries (Lane, Hardy & Schott, 2018). Multifocal gray matter deposits combine to produce plaques, which are milliary structures (Caruso et al., 2019). Hyper-phosphorylation of tau occurs since there is an aggregation of extracellular beta-amyloid causing the formation of tau aggregates, it is frequently seen in the cerebral cortex.

### ***Clinical features and diagnosis***

An asymptomatic period is experienced from the beginning of biochemical changes within the brain and the appearance of clinically related symptoms of AD (Juźwik et al., 2019). Research findings report memory impairment as a common hallmark of AD. The deterioration of other cognitive functions encompasses a memory decline (Weller & Budson, 2018). However, symptoms develop progressively with initial symptoms of AD include; executive dysfunction and visuospatial abnormalities, behavioral changes and language deficit are usually symptoms which appears in the later stages of the disease (Juźwik et al., 2019). Diagnostic and Statistical Manual (DSM) states that clinical assessment of AD has reflected the significant cognitive impairment within the cognitive areas like complex attention, memory, executive function, language, and perceptual-motor function (Armstrong, 2019).

### ***Treatment and Management***

There are now various pharmacologic therapies used to treat AD. For people with moderate to severe AD, melamine is one of the therapies which function as a non-competitive N-methyl-D-aspartate receptor antagonist (Weller & Budson, 2018). The second type involves giving patients with mild, severe AD inhibitors such as donepezil, galantamine, and rivastigmine to medicate them (Lane, Hardy & Schott, 2018). For people who choose alternative therapy, there are several possibilities besides these two programs. Examples include the nutritional supplement huperzine A, which has been shown to improve daily activities and memory (Hampel et al., 2018). Inhibitors and interventions for the main risk variables are used in the majority of standard AD treatments. BACE 1 successfully serves

as an AD intervention by limiting the rate of A production. Researchers like Weller and Budson (2018) consider the use of unproven non-steroid anti-inflammatory medications and omega-3 fatty acids, such as fish oil, in the management of risk factors. According to Weller and Budson (2018), these supplements have been shown to have cardiovascular advantages over the past ten years, and two randomized control trials have shown that fish oil can help memory and thinking in MCI patients. The tiny sample size used in these investigations was their lone drawback.

## Conclusion

PD is indeed a neurodegenerative movement disorder; its management is very challenging owing from the changing phenomenology leading to long duration (Vázquez-Vélez & Zoghbi, 2021). The case study shows that PD is a condition associated with older patients who may experience rigidity, tremor, and bradykinesia symptoms (Tysnes & Storstein, 2017). It has been demonstrated that as many other alternatives are essential in the treatment and management of PD, levodopa remains the most effective drug that can be used. The key root to the successful management of patients with PD is based on the available treatment evidence (Tysnes & Storstein, 2017). Amyotrophic Lateral Sclerosis (ALS) is a classic neurodegenerative condition where motor neurons in the brain and spinal cord gradually degenerate (Obrador et al., 2020). Though it involves numerous levels of functional entities that alternate in different directions before convergent functionally defining ALS disease development, the constantly evolving nature of ALS highlights a critical dimension of individual variances that underpin this ailment (Lane, Hardy & Schott, 2018). AD is one of the most prevalent types of dementia, mainly present in older people. According to the literature, the condition is designated as one among the neurodegenerative sicknesses that is progressive and incurable (Caruso et al., 2019). Its prevalence rises sharply from time to time with advancing age and the absence of effective treatments. An in-depth discussion has been given on AD's psychological, emotional, and biological elements, symptoms, and diagnosis (Caruso et al., 2019). It has been established that controlling risk factors and using inhibitors are the most prevalent therapies for the disease.

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