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Review on Neurodegenerative Disorders And Its Management

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Abstract:Neurodegenerative disorders are a group of diseases that affect the central nervous system and lead to progressive loss of neurons and their functions. They include Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS), and multiple sclerosis. These disorders have a significant impact on individuals' quality of life, and they pose a considerable burden on the healthcare system. In this review, we will discuss the current management strategies for these disorders. Alzheimer's disease is the most common neurodegenerative disorder, accounting for approximately 60-70% of cases. It is characterized by the deposition of beta-amyloid and tau proteins in the brain, leading to cognitive impairment and memory loss. Currently, there are no disease-modifying therapies for Alzheimer's disease. However, the management strategies focus on improving symptoms and maintaining quality of life.Parkinson's disease is characterized by the loss of dopaminergic neurons in the substantia nigra, leading to motor symptoms such as tremors, rigidity, and bradykinesia. Levodopa is the gold standard treatment for Parkinson's disease, and it works by increasing the levels of dopamine in the brain. Other medications such as dopamine agonists, MAO-B inhibitors, and COMT inhibitors can also be used in combination with levodopa. Deep brain stimulation has been shown to be an effective treatment option for patients with advanced Parkinson's disease. Huntington's disease is a genetic disorder characterized by the progressive loss of neurons in the basal ganglia, leading to motor, cognitive, and psychiatric symptoms. There are currently no disease-modifying therapies for Huntington's disease. However, medications such as tetrabenazine and deutetrabenazine can be used to manage chorea, a common motor symptom of the disease. Non-pharmacological interventions such as speech therapy, physical therapy, and occupational therapy can also improve symptoms and quality of life.

1. INTRODUCTION

Neurodegenerative are a group of disorders that primarily affect the neurons in the brain and spinal cord, leading to progressive deterioration of these cells and ultimately resulting in various cognitive, behavioural, and motor symptoms. These diseases are typically chronic, debilitating, and ultimately fatal, and they represent a significant burden on public health worldwide.

There are many different types of neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS), and frontotemporal dementia (FTD), among others. Although each of these diseases has unique characteristics and clinical features, they share several common pathogenic mechanisms that ultimately result in neuronal death.

Despite the significant progress made in the exact causes of neurodegenerative diseases are not fully understood, but there is evidence to suggest that genetic, environmental, and lifestyle factors all play a role in their development. For example, mutations in specific genes have been linked to several neurodegenerative diseases, including the amyloid precursor protein (APP) gene in Alzheimer's disease, the alpha-synuclein gene in Parkinson's disease, and the huntingtin gene in Huntington's disease. Environmental factors such as exposure to toxins or traumatic brain injuries may also increase the risk of developing neurodegenerative diseases. Additionally, lifestyle factors such as poor diet, lack of exercise, and smoking have been linked to an increased risk of cognitive decline and dementia.

understanding the pathophysiology of neurodegenerative diseases, effective treatments for these disorders are currently lacking. The current approach to managing these diseases is largely symptomatic, with medications and therapies aimed at alleviating the various symptoms associated with the disease. For example, in Alzheimer's disease, cholinesterase inhibitors and memantine are commonly used to manage cognitive symptoms, while levodopa and dopamine agonists are used in Parkinson's disease to manage

motor symptoms. However, these medications do not modify the underlying disease process and may have limited efficacy in some patients.

Given the lack of effective treatments for neurodegenerative diseases, much research is currently focused on developing disease-modifying therapies that can slow or halt the progression of these disorders. One promising area of research is the development of therapies that target the misfolded proteins that accumulate in the brains of patients with neurodegenerative diseases. For example, several monoclonal antibodies that target beta-amyloid and tau proteins are currently being tested in clinical trials for the treatment of Alzheimer's disease. Similarly, small molecules that target alpha-synuclein are being developed for the treatment of Parkinson's disease.

inefficacy of neural stem in the Another promising area of research is the use of stem cell therapies to replace damaged or lost ne brain. For example, several clinical trials are currently underway to evaluate the safety and cell transplantation for the treatment of ALS and Parkinson's disease.[1] Neurodegenerative disorders represent a challenging unmet medical need. As the incidence of chronic neurodegenerative diseases, such as Alzheimer's and Parkinson's disease, increases with age, the expected demographic change to a more elderly population will increase considerably the socioeconomic burden of these devastating conditions. While current treatments are palliative only, with increasing understanding of the biological basis of these disorders, there is now a realistic prospect for drugs that slow, or even halt, the process of neurodegeneration. This meeting reviewed the progress made in the discovery and development of medicines to treat neurodegenerative disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD), traumatic brain injury (TBI), stroke and multiple sclerosis (MS), and considered future prospects for effective pharmacotherapy, including the possibility of slowing, or even halting, the course of neurodegenerative disorders. Jill Richardson (GlaxoSmithKline, Harlow, Essex, U.K.) set the scene for the meeting with a comprehensive overview of the incidence and prevalence of AD, PD and MS. By 2050, the prevalence of AD will have tripled, to 1.5 million patients in Italy, the United Kingdom, Spain, Germany and France combined (compared with nearly 15 million patients in the United States). In the same regions, PD is predicted to have a prevalence of 1.1 million, with MS not that far behind with 0.5 million. Recombinant interferons have been approved in many countries for treatment of relapsing-remitting MS, but, despite claims to the contrary, their ability to modify disease course has not been clearly established.[2] By contrast, no disease-modifying therapies are yet available for AD and PD. Symptomatic drugs are on the market, but they are associated with serious side effects in PD and provide only modest improvements in cognitive status in patients with probable AD. The deposition of amyloid in the brains of AD patients, as well as the strong human genetic links to amyloid pathology, has made the amyloid cascade hypothesis2 a central theme in the CNS drug discovery efforts of many pharmaceutical companies. As a consequence, several potential therapies are currently in late-stage clinical testing for AD. These include Myriad's FlurizanTM (tarenflurbil), Neurochem's AlzhemedTM (tramiprosate), Wyeth/Elan's anti-Aβ antibody bapineuzumab, Lilly's anti-Aβ antibody LY-2062430 and Lilly's γ-secretase inhibitor LY-450139. GlaxoSmithKline are working on therapies to reduce beta amyloid (Aβ) production, including inhibitors of BACE1 (β-APP cleaving enzyme-1) and have demonstrated, for the first time, in vivo Aβ-lowering efficacy in the TAST-TM transgenic mouse model with a BACE inhibitor administered via the oral route. In addition to therapies targeting amyloid deposition, GlaxoSmithKline are also seeking targets and agents to ameliorate the inflammatory response seen in the brains of AD patients. For PD, the discovery in 2004 of Leucine Rich Repeat Kinase-2 (LRRK2) as a gene responsible for autosomal dominant disease3 has stimulated research into the cellular mechanisms that result in the destruction of dopaminergic cells in PD with the promise of uncovering new targets amenable to therapeutic intervention. Current estimates suggest that LRRK2 is responsible for about 2% of all PD patients but can rise to greater than 10% in certain populations, such as Ashkenazi Jews.[3]

Neurodegeneration has been identified as the pivotal pathophysiological change in most brain-related disorders. Regardless of the incessant efforts by modern science to create a medical or surgical solution, the outcome has not been favorable. Neurodegenerative disorders (NDs) such as Alzheimer's and dementia continue to be a clinical concern in most older people.[4] The highly effective blood–brain barrier (BBB) continues to be a real barrier towards the successful management of NDs. Despite the several successes that have been demonstrated with surgeries and highly evasive techniques, their clinical acceptance is limited due to varying concerns about their long-term benefit, owing to the potential damage to the brain barrier. As a suitable alternative for halting or reversing neurodegeneration, nanotherapeutics with the potential to cross the BBB (without damage to the barrier) have been proposed and demonstrated in many cases.[5,6]

Despite this great progress, there is a need to refine nanotherapeutics to ensure optimum outcomes. In this review, we initially describe the pathophysiology of major NDs and their current management strategies. We also discuss the role of BBB and other challenges for brain-targeted drug delivery. Further, we look at the potential role of nanotherapeutics in the fight against neurodegeneration. Finally, we discuss breakthroughs and current findings in nanotherapeutics to manage NDs and provide perspectives for future applications.[7]

1.1 Neurodegenerative Disorder

Neurons are central to the proper functioning of the human brain since they play a critical role in communication. Most neurons originate in the brain; however, neurons are present everywhere in the body . During childhood, neural stem cells produce the majority of neurons, the number of which is significantly reduced in adulthood. Although neurons are not immortal, the progressive loss of neurons, neuron structure, and/or their functions, known as neurodegeneration, is central to the pathophysiology of several brain disorders and is also a major health concern. Neurodegeneration is associated with dysfunction of the synapse, neural network, and the deposition of physiochemically altered variants of proteins in the brain.[8]

Neurodegenerative disorders affect millions of people worldwide. Although age is the single most contributing risk factor to the development of all NDs, recent findings reveal that a combination of an individual's genetic makeup and environmental factors can equally contribute to increasing the risk for NDs. Further, despite the expression of specific genes (within an individual) accountable for NDs the time and extent of neurodegeneration largely depend on their immediate environment. More recent studies reveal that multiple pathologies may underline a single neurodegenerative disorder. Thus, NDs can be very serious or even, in certain instances, life threatening; however, it solely depends on the type and stage of the disease.[9] Neurodegenerative disorders are a group of progressive neurological disorders that result from the degeneration and death of neurons in the brain and/or spinal cord. These disorders are characterized by a wide range of symptoms, including movement problems, cognitive decline, and behavioural changes, and they can have a significant impact on the quality of life of affected individuals. There are several types of neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS). These disorders can have different underlying causes, but they share common mechanisms of neuronal damage, such as protein aggregation, inflammation, and oxidative stress.

1.2 TYPES OF SOME COMMON DISEASES

- **Alzheimer's Diseases**
- **Parkinson Diseases**
- **Huntington's Diseases**
- **Amyotrophic Lateral Sclerosis (ALS)**

1.2.1 Alzheimer's Disease (AD)

The hallmark of AD The aggregation of tau and amyloid-beta (A) proteins is crucial to the progression of Alzheimer's disease is thought to be the development of A-containing plaques in the brain that are connected to hyperphosphorylated tau neurofibrillary tangles (NFTs)[10]. Plaque formation causes hippocampal circuitry to be disrupted, which results in poor long-term memory consolidation. In AD, the crucial neurotransmitter systems required for brain activities, including memory, are damaged. There is also significant neuronal loss, dysfunctional synaptic connections, and synaptic dysfunction. Selective memory impairment is perhaps the most typical clinical sign of early-stage AD. Also frequently impacted are hippocampus- and medial temporal-lobe-dependent processes, including declarative episodic memory. Finally, further clinical indications that typically show up early include executive function impairment, judgement, and problem-solving.[11].

Alzheimer's disease is a neurodegenerative disorder that affects millions of people worldwide. It is characterized by the progressive decline in cognitive and memory functions due to the accumulation of abnormal protein aggregates in the brain. Here are some articles that review recent research on Alzheimer's disease:

"The Pathophysiology of Alzheimer's Disease" by Bart De Strooper et al. (Nature, 2021) This article provides a comprehensive overview of the molecular and cellular mechanisms that underlie the development and progression of Alzheimer's disease. It discusses the role of amyloid-beta and tau proteins in the formation of plaques and tangles, as well as the involvement of glial cells and inflammation in the disease process. The authors also highlight promising therapeutic targets that could potentially slow or halt the progression of Alzheimer's disease.[12]

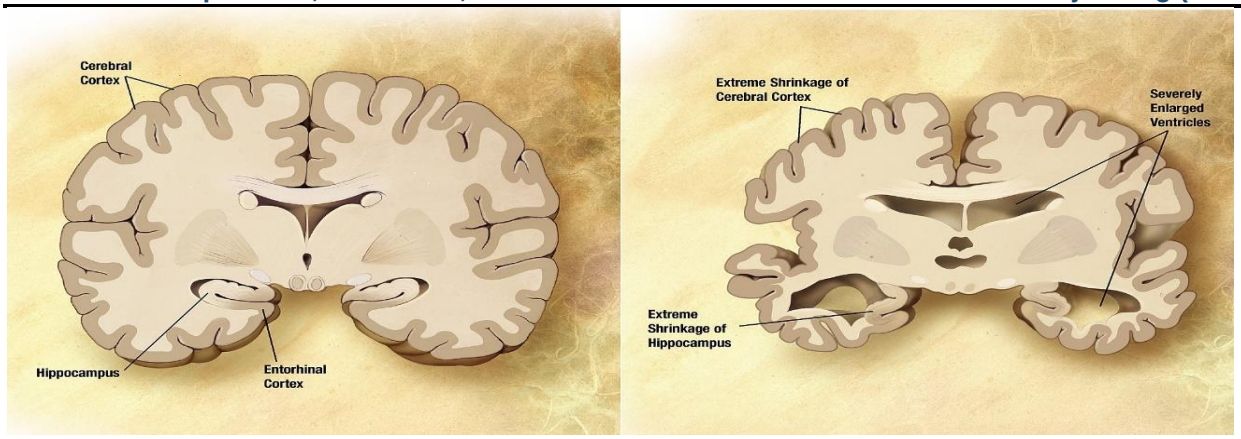

Fig:-1.1 Normal Brain **Alzheimer's Brain**

1.2.2 Parkinson's Disease [PD]

Parkinson's disease is a degenerative neurological condition that causes tremors, rigidity in the muscles, an uneven gait, and issues with balance and coordination. PD is brought on by both hereditary and non-genetic factors. Age is thought to be the main risk factor for PD Other factors that are known to affect the likelihood of developing PD include smoking, drinking too much alcohol, and being exposed to pollutants in the environment, however the precise process is yet unknown. Frontal cortical atrophy and ventricular enlargement are the main pathophysiologic factors in PD. The loss of pigmentation in the locus coeruleus and substantia nigra pars compacta (SNpc), which results from the death of dopaminergic (DA) neuromelanin-containing neurons, is the most recognisable morphological change seen in the PD brain, though.[28] The misfolding and aggregation of -synuclein, dysfunctional protein clearance systems like the ubiquitin-proteasome and autophagy-lysosome, mitochondrial dysfunction, neuroinflammation, and dysfunctional protein clearance systems are just a few of the mechanisms that have been found to be important in the progression of PD disease.

Lewy bodies, aberrant cytoplasmic deposits that are immunoreactive for the protein -synuclein, and dystrophic neurites, also known as Lewy neurites, are the hallmarks of Parkinson's disease (PD) under the microscope. Lewy bodies might be phosphorylated and disseminated to different Brain areas. Protein misfolding happens in PD as well as AD, and the tau protein is the most often misfolded protein. NFT development is caused by aberrant tau protein hyperphosphorylation. There are several NFT and amyloid-beta plaques in a subset of PD patients.[29]

1.2.2.1Types Of Parkinson's Disease The types of Parkinson's disease are as follows:

- Idiopathic Parkinson's disease
- Vascular Parkinsonism
- Drug-induced parkinsonism
- Early-Onset Parkinson's
- Multiple system atrophy
- Progressive supranuclear palsy
- Dementia with Lewy bodies
- Normal-pressure hydrocephalus

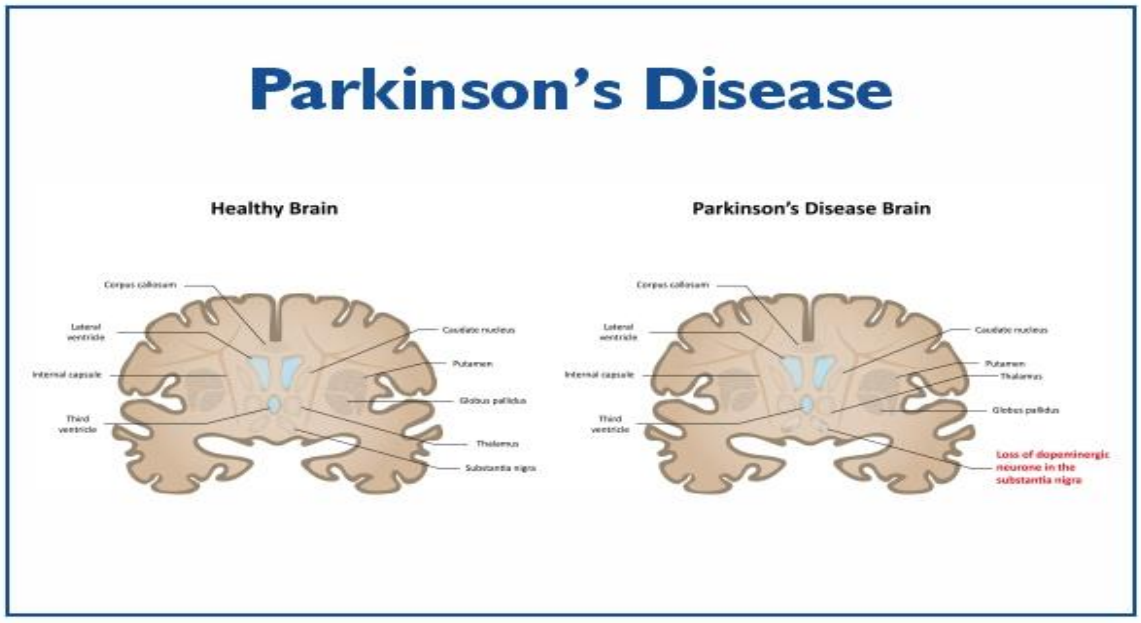

Fig:-2.3 *Parkinson's Disease Symptoms*

1.2.3 Huntington's Disease

Huntington's disease is a rare, genetic condition that results in the progressive destruction of brain nerve cells. The functional capacities of a person are significantly impacted by Huntington's disease, which typically causes mobility, cognitive, and psychological issues.

Although signs of Huntington's disease can start to manifest at any age, they frequently do so in adults in their 30s or 40s. Juvenile Huntington's disease is the term used when the disorder first manifests before the age of 20. Early-stage Huntington's disease has slightly distinct symptoms and may advance more quickly.[37]

Huntington's disease symptoms can be managed with the aid of medications. Treatments, however, are unable to stop the condition's effects on the body, mind, and behaviour.

Huntington illness is a degenerative brain condition that results in irrational behaviour, emotional issues, and loss of cognitive function (cognition). Adult-onset The most prevalent form of this ailment, Huntington disease, typically manifests in a person's thirties or forties. Irritability, depression, minor involuntary movements, poor coordination, difficulty acquiring new information, and difficulty making judgements are some of the early indications and symptoms. A common symptom of Huntington's disease is chorea, which are uncontrollable jerking or twitching motions. These motions intensify with the onset of the illness. Those who are affected could have a hard time swallowing, speaking, or walking. A deterioration in thinking and reasoning skills as well as personality changes are some symptoms of this condition. Adult-onset Huntington disease patients typically live 15 to 20 years after first showing symptoms.[38]

The juvenile type of Huntington illness, which is less prevalent, starts in childhood or adolescence. Moreover, it causes alterations in the mind and emotions as well as movement issues. Slow movements, clumsiness, frequent falls, rigidity, slurred speech, and drooling are other indicators of the juvenile form. As one's capacity for thought and reasoning deteriorates, academic achievement suffers. Between 30% and 50% of children with this syndrome experience seizures. People with juvenile Huntington disease typically live 10 to 15 years from the onset of symptoms, with the disease progressing more quickly than in adults.[39]

1.2.4 Amyotrophic Lateral Sclerosis (ALS)

ALS, also known as Lou Gehrig's disease or motor neuron disease, is a progressive condition that affects the nerve cells and spinal cord and causes paralysis and muscle weakness. Motor neurons slowly degrade before dying in ALS. When Signals that should be delivered to the brain are no longer sent because motor neurons are damaged or dead. Although more than 30 distinct genes have been linked to ALS, C9orf72, TARDBP, SOD1, and FUS mutations account for more than 70% of cases. The motor neuron degeneration seen in ALS is thought to be caused by a combination of these compromised processes. Intraneuronal protein aggregation accumulation is the ALS's pathological signature. The TAR DNA binding protein is the protein that is most frequently

found in ALS patients, but other proteins, including superoxide dismutase-1 and neurofilament, can also assemble. Yet, it is not known if protein complexes or aggregates come first or damage to neurons does.

Amyotrophic Lateral Sclerosis (ALS), also known as Lou Gehrig's disease, is a neurodegenerative disorder that affects nerve cells in the brain and spinal cord, resulting in progressive muscle weakness, atrophy, and eventual paralysis.[49]

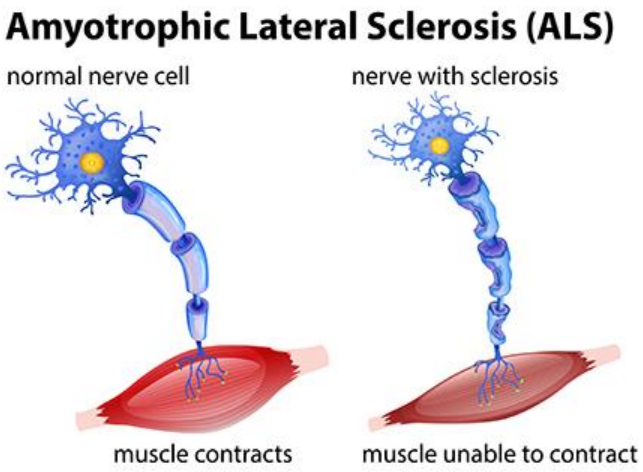

Fig2.5:- Amyotrophic Lateral Sclerosis

1.2.4.1Types of Amyotrophic Lateral Sclerosis

The two main types are:

- ***Spondaic*:** This type can affect anyone. It accounts for 90-95% of U.S. cases.
- ***Familial***: This type is inherited through genetic changes passed down in families. If a parent has familial ALS, each child has a 50% chance of developing it, too. If you have this type of ALS, your care team may suggest genetic counselling.

2.1 PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASES

Alzheimer's disease (AD) is a long-term neurodegenerative condition that impairs proper brain function. The loss of cognitive abilities, such as memory, language, judgement, and conduct, occurs gradually. Although the precise origin of AD is still unknown, there are a number of important pathophysiological changes that take place in the brain that support the onset and development of the condition.[13]

Amyloid beta plaques: The development of aberrant protein deposits in the brain known as amyloid beta (A) plaques is one of the characteristics of AD. These plaques are created by the aggregation of misfolded and clumped A peptides, which are produced from the amyloid precursor protein, a bigger protein (APP). A plaque buildup impairs regular neural communication and may cause neuronal death.

Neurofibrillary tangles: These aberrant tau protein aggregates that produce neurofibrillary tangles are another sign of Alzheimer's disease (AD). When tau is hyperphosphorylated in AD, it creates tangled formations that interfere with normal cellular function and cause neuronal death. Tau is normally involved in maintaining the structure of neuronal cells.[14]

Neuroinflammation: When A plaques and neurofibrillary tangles build up in the brain, an immunological response is triggered, which results in long-term inflammation of the brain. Inflammation has been linked to neuronal injury and disease progression.

Dysfunction of the synapses that connect neurons and allow them to interact with one another are gradually lost as AD worsens. It is believed that this synaptic disruption has a significant role in the cognitive deterioration seen in AD.[15]

Deficits in several important neurotransmitters, including acetylcholine, dopamine, and serotonin, are also linked to AD. The cognitive and behavioral signs of AD are influenced by these deficiencies.

Genetics: Although the majority of instances of AD are sporadic, there are hereditary variables that can raise the risk of contracting the illness. The amyloid precursor protein (APP), presenilin-1 (PSEN1), and presenilin-2 (PSEN2) genes are just a few of the genes that have been linked to inherited forms of AD[16]

The pathophysiology of AD is generally complicated and multifaceted, comprising a number of biological processes that eventually result in the progressive loss of cognitive function and neuronal death.[17]

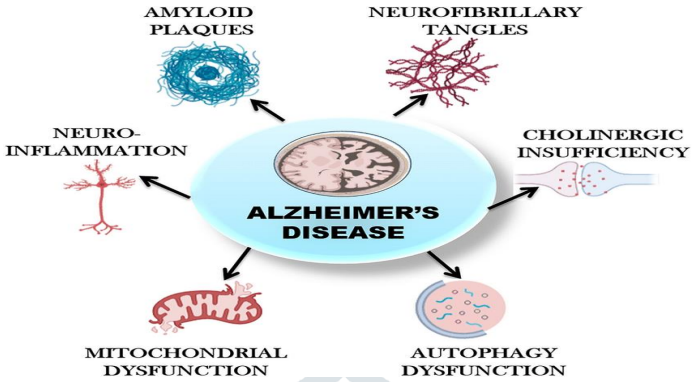

Fig:-2.1 Pathophysiology of Alzheimer's disease

2.1.1 Symptoms*-The primary sign of Alzheimer's disease is memory loss. Early warning indications include having trouble recalling previous conversations or occurrences. But as the illness worsens, memory declines and additional symptoms appear.*

A person with the illness may initially be aware of experiencing memory loss and clear-headedness issues. A friend or family member may become more aware of the problems as the symptoms worsen.

Alzheimer's disease-related brain alterations result in increasing problems with:[18]

2.1.1.1Memory

Everyone occasionally experiences memory loss, but Alzheimer's disease-related memory loss is persistent and worsens over time. Memory loss gradually impairs one's capacity to carry out daily tasks at home or at work.

Alzheimer's disease sufferers may

- Repeat questions and phrases again.
- Don't think about meetings, events, or conversations.
- Items are frequently misplaced and placed in odd places.
- Become lost in areas they used to be familiar with.
- Over time, people lose the names of their loved ones and commonplace items.
- have difficulty expressing ideas, describing things, or participating in conversations.[19]

2.1.1.2Thinking and Reasoning

Concentration and thinking problems are brought on by Alzheimer's disease, especially when it comes to abstract ideas like numbers.

Managing multiple tasks at once is very challenging. To handle money, keep chequebooks balanced, and make on-time payments on bills may be difficult. A person with Alzheimer's disease may eventually lose the ability to comprehend and use numbers.[20]

2.1.1.3 Making judgments and decisions

Alzheimer's disease causes a decline in the ability to make sensible decisions and judgments in everyday situations. For example, a person may make poor choices in social settings or wear clothes for the wrong type of weather. It may become harder for someone to respond to everyday problems. For example, the person may not know how to handle food burning on the stove or decisions when driving[21]

2.1.1.4 Changes in personality and behaviour

Brain changes that occur in Alzheimer's disease can affect moods and behaviors. Problems may include the following:

- Depression.
- Loss of interest in activities.
- Social withdrawal.
- Mood swings.
- Distrust in others.
- Anger or aggression.
- Changes in sleeping habits.
- Wandering.
- Loss of inhibitions.
- Delusions, such as believing something has been stolen.[22]

2.1.2 Causes

It is unclear what causes Alzheimer's disease exactly. But, brain proteins don't work normally on a fundamental level. This interferes with the function of brain cells, commonly known as neurons, and sets off a chain of events. Damaged neurons stop communicating with one another. They pass away in time.

Most often, according to scientists, Alzheimer's disease results from a confluence of hereditary, dietary, and environmental variables that have an ongoing negative impact on the brain. Only 1% of cases of Alzheimer's are brought on by certain genetic alterations that virtually always result in the disease. In these situations, the illness typically manifests in middle age.[23]

Years before the first symptoms appear, the disease starts to develop. The memory-controlling part of the brain is where the damage most frequently begins. Some parts of the brain experience a somewhat predictable pattern of neuron loss. The brain has greatly decreased in size by the disease's advanced stages. Two proteins are the focus of current research into the origins of Alzheimer's disease:

- ***Plaques***. The protein beta-amyloid is a piece of a bigger protein. These pieces appear to be harmful to neurons and disrupt brain cell communication when they group together. These aggregates combine with other cellular waste to form bigger deposits known as amyloid plaques.
- ***Tangles.*** The internal support and transportation system used by brain cells to convey nutrition and other necessary components includes tau proteins. Neurofibrillary tangles are formations made up of tau proteins that alter shape and organize in Alzheimer's disease. The tangles damage cells and interfere with the transport system.[24]

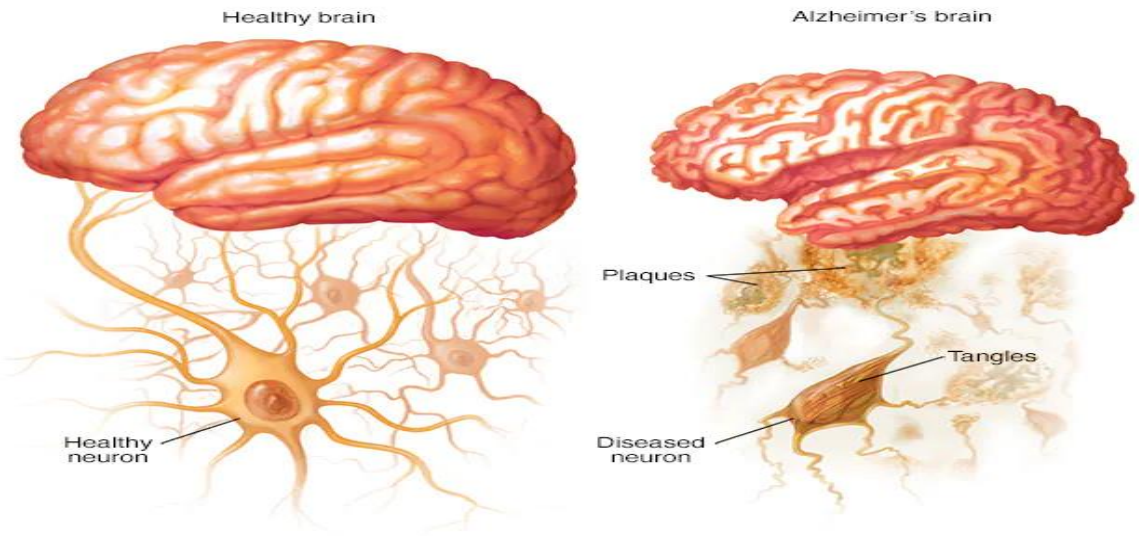

Fig:-2.2 Healthy brain and brain with Alzheimer's disease

2.1.3 Prevention

There is no cure for Alzheimer's disease. A few risk factors related to lifestyle can be changed, though
There is evidence that preventative measures for cardiovascular disease may help lower the risk of dementia.

- To lead a heart-healthy lifestyle and maybe lower your chances of dementia:
- Regularly moving around.
- Consume a diet rich in fresh fruits and vegetables, nutritious oils, and meals low in saturated fat, like a Mediterranean diet.
- To control high blood pressure, diabetes, and high cholesterol, adhere to the recommended course of treatment.
- Ask your doctor for advice on quitting smoking if you currently do so.

Making lifestyle modifications helped persons at risk of dementia's cognitive deterioration, according to a big, lengthy study conducted in Finland. Individual and group sessions focused on food, exercise, and social activities were given to research participants.[25]
Those at risk for dementia received coaching sessions on food, exercise, and other lifestyle improvements in a different Australian trial. After one, two, and three years, they outperformed others who didn't receive coaching in cognitive tests.[26]
A lower incidence of Alzheimer's disease and maintained cognitive abilities later in life are both associated with maintaining mental and social engagement, according to other studies. Attending social gatherings, reading, dancing, playing board games, and making art are all examples of this.[27]

2.2. PATHOPHYSIOLOGY OF PARKINSON'S DISEASES

A neurodegenerative condition with a focus on the motor system, Parkinson's disease. The loss of dopaminergic neurons in the substantia nigra, a part of the brain that regulates movement, is the primary sign of Parkinson's disease. Dopamine levels in the brain fall as a result of the loss of these neurons, which ultimately causes the movement symptoms of Parkinson's disease.[30]

Regarding the fundamental pathophysiology of Parkinson's disease, various theories exist. The "protein aggregation theory" is one of the most well-known ideas, and it contends that the buildup of aberrant proteins in the brain is a critical factor in the progression of the illness.

Two specific proteins, tau and alpha-synuclein, have been linked to the onset of Parkinson's disease. The abundance of the protein alpha-synuclein in the brain is hypothesised to play a role in the control of dopamine release. Alpha-synuclein is thought to aggregate

abnormally into "Lewy bodies" in people with Parkinson's disease, which are found in their brains. It is believed that these Lewy bodies are toxic to neurons and interfere with regular cellular functions, ultimately causing cell death.[31]

Another protein that has been linked to the progression of Parkinson's disease is tau. Microtubule stabilisation, which is essential for preserving the structural integrity of neurons, is a normal function of tau.

Parkinson's disease is a neurodegenerative disorder that affects the central nervous system. The hallmark of Parkinson's disease is the death of dopamine-producing neurons in the substantia nigra region of the brain, which leads to a deficiency of dopamine in the brain. Dopamine is a neurotransmitter that plays a critical role in regulating movement, emotions, and motivation.[32]

The exact cause of Parkinson's disease is not fully understood, but it is thought to be a combination of genetic and environmental factors. Some studies have suggested that exposure to toxins such as pesticides and herbicides may increase the risk of developing Parkinson's disease.[33]

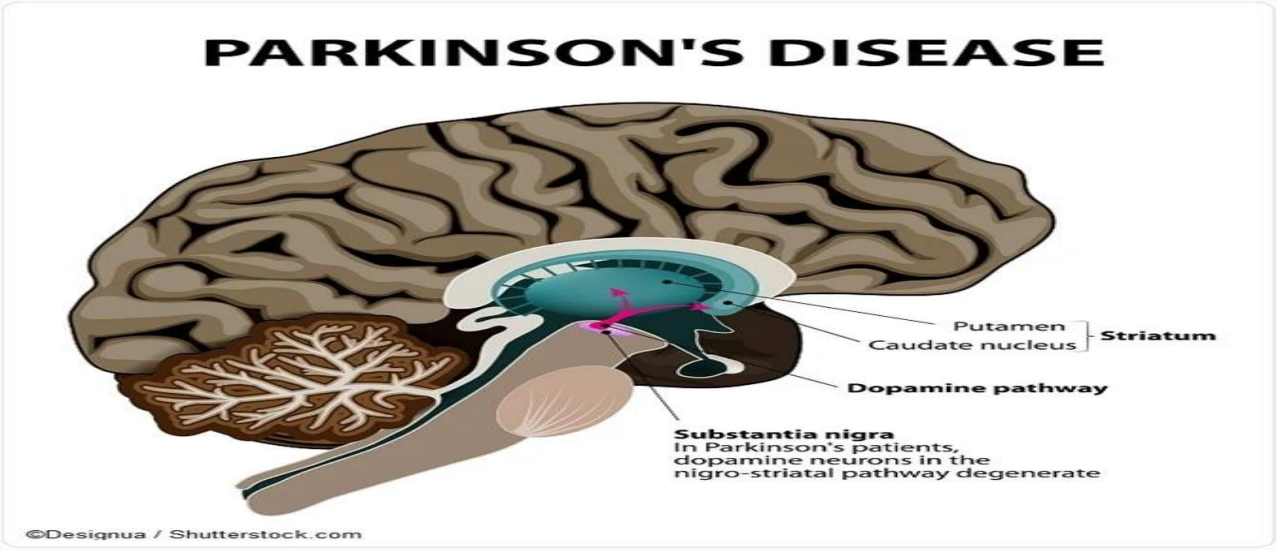

Fig:-3.1 ***Parkinson's disease and loss of neurons***

2.2.1 Parkinson's Disease Symptoms

Parkinson's disease symptoms appear slowly. They usually begin with a tremor in one hand and a sensation of rigidity throughout the body. Other symptoms emerge over time, and some people develop dementia.

The following are some early indications of Parkinson's disease:

- Tremors involving movement change.
- Impaired coordination and balance might lead a person to drop objects or fall over.
- The inability to smell
- When walking, a person's gait changes, and they lean forward slightly or stumble.
- Changes in the nerves that control facial muscles induce fixed facial expressions.
- A tremor in the voice or a weaker tone
- Handwriting is more cramped and smaller
- Sleep disturbances caused by restless legs and other factors
- Symptoms of movement may begin on one side of the body and spread to the other.

2.2.2 Other common symptoms include:

- Mood changes, including depression
- Chewing and swallowing problems,
- Fatigue
- Constipation
- Skin conditions
- Dementia, delusions, and hallucinations are all things that can happen over time.



Fig:-2.4 Parkinson's Disease Symptoms

2.2.3Causes

Parkinson's disease is a neurological condition brought on by alterations in the brain. Scientists have found a few variations, although it is unknown what the cause is. It is a complicated illness that has various effects on individuals. According to a study, this illness affects over 10 million people worldwide each year. Parkinson's disease is thought to include a genetic component and environmental influences, although the specific cause is yet unknown. According to data, the condition may be caused by genetic changes in the alpha-synuclein gene, for instance. Moreover, in people with certain genetic predispositions, exposure to certain poisons like MPTP or manganese may result in Parkinsonian symptoms.[34]

2.2.4 Diagnosis and Treatment

At any stage of the disease, but particularly at the beginning, diagnosis is difficult. A particular test cannot provide a diagnosis. Most likely, periodic physical and neurological examinations will be done to monitor changes in reflexes, coordination, muscular strength, and mental function. Clinical indicators are used by doctors to make a diagnosis.[35]

Major factors include

- Blood test

  Blood tests can help the doctor rule out other causes of parkinsonism, such as multiple system atrophy or corticobasal degeneration, even though they cannot diagnose Parkinson's disease.
- genetic analysis
- Magnetic resonance imaging using DaTscan (MRI)

2.2.5 Treatment

Although there is no known cure for Parkinson's disease, medication can help people manage their symptoms. The following are the Parkinson's disease therapy options:

2.2.6 Medications

Several drugs are used to treat Parkinson's disease.

- Levodopa and carbidopa are tremor-controlling medications that are combined with other medications to lessen tremors.
- Trembling can be momentarily controlled by benzodiazepines, also referred to as tranquillizers.

- Moreover, beta-blockers may be used to treat specific disease symptoms, such as elevated blood pressure.
- Primidone is an anti-seizure medication that can aid those with tremors that don't react to beta-blockers.
- Botulinum toxin, also referred to as Botox, is able to treat the majority of tremors.[36]

2.3 Pathophysiology of Huntington's diseases.

Huntington's disease (HD) is a rare genetic disorder that is characterized by the degeneration of certain nerve cells in the brain. HD is caused by a mutation in the huntingtin gene, which leads to the production of an abnormal form of the huntingtin protein. This protein accumulates in the brain, leading to the destruction of certain nerve cells, particularly those in the basal ganglia.

The basal ganglia are a group of structures in the brain that are responsible for controlling movement and coordination. As the huntingtin protein accumulates in these cells, they begin to malfunction and eventually die, leading to the characteristic motor symptoms of HD. These symptoms include involuntary movements, such as chorea (jerky, dance-like movements), as well as difficulties with balance and coordination.[40]

Huntington's disease (HD) is a neurodegenerative disorder caused by an inherited mutation in the huntingtin (HTT) gene. The mutation results in the production of an abnormal form of the huntingtin protein, which is toxic to brain cells.

The pathophysiology of HD involves the progressive loss of neurons in the striatum, a region of the brain that is responsible for controlling movement and cognition. The striatum is primarily composed of two types of neurons: medium spiny neurons (MSNs) that use the neurotransmitter gamma-aminobutyric acid (GABA), and interneurons that use the neurotransmitter acetylcholine.[41]

Huntington's disease (HD) is a neurodegenerative disorder characterized by a progressive loss of neurons in specific areas of the brain. The disease is caused by a mutation in the huntingtin (HTT) gene, which leads to the production of an abnormal form of the huntingtin protein.

Protein Aggregation: The abnormal huntingtin protein accumulates in the brain cells, leading to the formation of aggregates, known as inclusion bodies. These inclusion bodies disrupt cellular function, leading to cell death.[42]

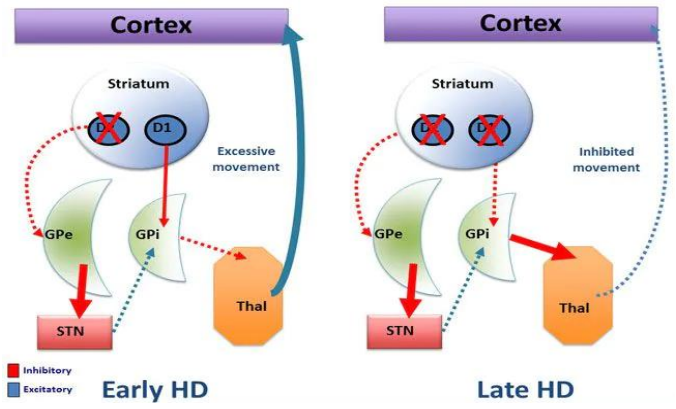

Fig:-4.1 Pathophysiology of Huntington's disease

2.3.1 Symptoms

Movement, cognitive, and psychological impairments are frequently brought on by Huntington's disease, and its indications and symptoms can range greatly. It substantially differs from person to person which symptoms start to manifest initially. While some symptoms may be more prominent or have a bigger impact on functionality than others, this might alter during the course of the illness.

2.3.2 Movement Disorder

Huntington's disease-related movement disorders can affect both voluntary and involuntary motions, resulting in symptoms like:

- uncontrollable jerking or writhing motions (chorea)
- issues with the muscles, such as stiffness or contracture (dystonia)
- Unusual or slow eye movements
- gait, posture, and balance issues
- difficulty swallowing or speaking

A person's capacity to work, carry out everyday activities, communicate, and maintain independence may be more negatively impacted by impairments in voluntary movements than by impairments in involuntary movements.[43]

2.3.3Cognitive Disorder

The following cognitive problems are frequently linked to Huntington's disease:

- difficulty planning, ranking, or concentrating on tasks
- rigidity or a propensity to persist in a single idea, conduct, or action (perseveration)
- Impulsivity, which can lead to irrational behaviour, tantrums, and sexual promiscuity
- lack of self-awareness regarding one's own actions and skills
- Slowness when thinking or "finding" words Trouble picking up new knowledge.[44]

2.3.4 Psychiatric Disorder

Depression is the psychiatric illness most frequently linked to Huntington's disease. This isn't only a reaction to the Huntington's disease diagnosis. Instead, brain damage and subsequent alterations in brain function appear to be the source of depression. Some warning signs and symptoms include:

- feeling irritable, depressed, or uninterested
- Social isolation
- Insomnia
- fatigue and energy decline
- frequently having thoughts of suicide or death

Other prevalent psychiatric conditions include:

- Obsessive-compulsive disorder is characterised by persistent, bothersome thoughts and obsessive actions.
- Mania, which can result in hyperactivity, impulsive conduct, high moods, and exaggerated self-esteem
- A illness known as bipolar disorder that causes recurrent episodes of mania and depression
- In addition to the aforementioned conditions, Huntington's disease patients frequently lose weight.[45]

2.3.5 Symptoms of Juvenile Huntington's disease

Younger individuals may experience a different onset and course of Huntington's disease than adults. The following issues frequently surface early in the course of the disease:

- Behavioral alterations
- difficulty concentrating
- rapid, considerable decline in student performance overall
- behavioural issues
- muscles that are tense and tight that impact gait (especially in young children minor involuntary movements, such as tremors falling down a lot or being clumsy

2.3.6 Causes

An hereditary variation in a single gene is the root cause of Huntington's disease. A person just requires one copy of the unusual gene to acquire Huntington's disease because it is an autosomal dominant disorder.

Every gene, with the exception of those on the sex chromosomes, is inherited twice, once from each parent. Either the healthy copy of the gene or the nontypical copy could be inherited from a parent with an abnormal gene. Hence, there is a 50% probability that each child in the family will inherit the gene responsible for the genetic condition.[46]

2.3.7 Complications

The functional capacities of a person steadily deteriorate after the onset of Huntington's disease. The duration and rate of illness progression vary. Usually, it takes between 10 and 30 years from the onset of symptoms to death. In most cases, juvenile Huntington's disease causes death 10 years after the onset of symptoms.

The risk of suicide may be increased by the clinical depression linked to Huntington's disease. According to several studies, the risk of suicide is highest before a diagnosis is established and during the later stages of the illness, when the patient begins to lose their independence.

A person with Huntington's disease eventually needs assistance with all everyday tasks and caring for themselves. By the end of the illness, the patient will probably be bedridden and mute.

Common causes of death include:

Pneumonia or other infections

Injuries related to falls

Complications related to the inability to swallow [47]

2.3.8 Prevention

It seems sense that people who have a known family history of Huntington's disease worry about perhaps passing the gene to their future offspring. These individuals might think about genetic testing and family planning choices.

It can be beneficial to consult with a genetic counsellor if a parent who is at risk is thinking about genetic testing. A genetic counsellor will talk about the possible hazards of a test result showing a parent will get the illness. Couples will also have to decide whether they want to start a family or explore other options, like prenatal gene testing or in vitro fertilisation using donated sperm or eggs.

In vitro fertilisation and preimplantation genetic testing are additional options for couples. In this procedure, the eggs are taken out of the ovaries and fertilised in a lab using the father's sperm. Only those embryos that test negative for the Huntington gene are implanted in the mother's uterus after being tested for the existence of the gene.[48]

2.4 PATHOPHYSIOLOGY OF AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a progressive neurodegenerative disease that affects the motor neurons in the brain and spinal cord. The exact cause of ALS is still unknown, but it is believed to involve a complex interplay between genetic and environmental factors.

The pathophysiology of ALS involves the progressive degeneration of both upper motor neurons (UMN) and lower motor neurons (LMN). The UMN are responsible for transmitting signals from the brain to the spinal cord, while the LMN transmit signals from the spinal cord to the muscles.[50]

In ALS, the degeneration of the UMN leads to muscle spasticity and weakness, while the degeneration of the LMN leads to muscle atrophy and fasciculations (muscle twitches). The progressive loss of motor neurons eventually leads to paralysis, respiratory failure, and ultimately, death.

There are several pathological features associated with ALS, including the accumulation of misfolded proteins, oxidative stress, mitochondrial dysfunction, and neuroinflammation. One of the most well-known pathological features of ALS is the presence of intracellular inclusions called "protein aggregates" that contain abnormal forms of proteins such as superoxide dismutase 1 (SOD1) and TAR DNA-binding protein 43 (TDP-43).

The exact mechanism by which these pathological features lead to the degeneration of motor neurons is not fully understood, but it is believed that they contribute to the formation of toxic aggregates and disrupt cellular processes that are necessary for neuronal survival.

Overall, the pathophysiology of ALS is complex and involves multiple cellular and molecular pathways. While there is currently no cure for ALS, understanding the underlying mechanisms of the disease is crucial for the development of effective treatments that can slow or halt its progression.Protein Misfolding: In ALS, there is an accumulation of abnormal protein aggregates in the motor neurons, particularly in the cytoplasm and nuclei of affected cells. These aggregates may interfere with cellular functions and lead to cell death.[51]

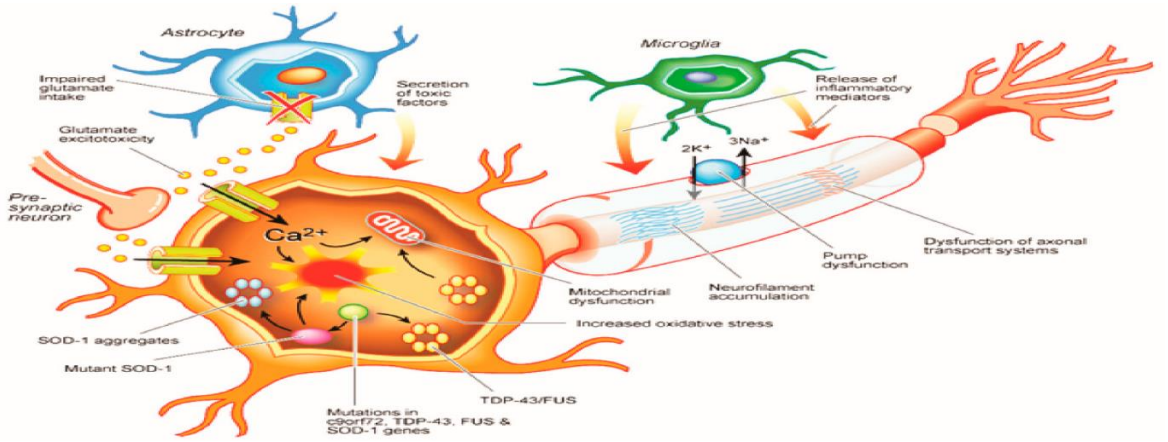

Fig:-5.1 PATHOPHYSIOLOGY OF AMYOTROPHIC LATERAL SCLEROSIS

2.4.1 SYMPTOMS

Depending on which neurons are impacted, ALS signs and symptoms differ widely from person to person. Often, it starts out with muscle weakness and gradually spreads and grows worse. Some warning signs and symptoms include:

- walking or carrying out regular tasks with difficulty
- Falling and tripping
- a weakened ankle, foot, or leg
- Hand clumsiness or weakness
- Speech slurring or swallowing issues
- twitching and cramping in your arms, shoulders, and tongue muscles
- sobbing, laughing, or yawning without cause
- Behavioral and cognitive changes

ALS frequently develops in the hands, feet, or limbs before spreading to other areas of the body. Your muscles become progressively weaker as the disease worsens and more nerve cells are lost. This eventually has an impact on breathing, speaking, chewing, and swallowing.

In the early stages of ALS, there is typically little discomfort, and pain is rare in the later stages. Typically, ALS does not impair your senses or bladder control.[52]

2.4.2 CAUSES

The nerve cells that regulate voluntary muscular movements like walking and talking are impacted by ALS (motor neurons). The motor neurons steadily degrade and eventually die as a result of ALS. The brain, spinal cord, and all the muscles in the body are connected by motor neurons. Motor neurons that have suffered damage stop communicating with the muscles, which prevents the muscles from working. In 5% to 10% of cases, ALS is hereditary. The reason of the remaining cases is unknown. Researchers are still looking at potential ALS causes. The majority of ideas focus on the intricate interplay between hereditary and environmental influences.[53]



Fig2.6:- Causes of Amyotrophic Lateral Sclerosis

2.4.3 Risk Factor

the following are recognised ALS risk factors

- ***Heredity***. Between five and ten percent of those who have ALS inherited it (familial ALS). Most adults with familial ALS have a 50/50 probability of passing the disease along to their children.
- ***Age***. The risk of developing ALS rises with age, peaking between the ages of 40 and 60.
- ***Sex***. Men are slightly more likely than women to develop ALS before the age of 65. Beyond age 70, the sex difference is no longer present.
- ***Genetics***. Those with familial ALS and certain people with noninherited ALS have several genetic changes in common, according to some research that looked at the complete human genome. Certain genetic variants may increase a person's risk of developing ALS.
  The following environmental factors could cause ALS.
  The following environmental factors could cause ALS.
- ***Smoking***. The only known environmental risk factor for ALS is smoking. Women appear to be most at risk, especially after menopause.
- ***exposure to environmental toxins***. According to some data, exposure to lead or other toxins at work or home may contribute to the development of ALS. Many studies have been conducted, however no one substance or chemical has consistently been linked to ALS.

- ***a military career***. According to studies, those who have served in the military are more likely to get ALS. It's unclear what aspect of military service could cause ALS to manifest. It might involve being exposed to specific metals or chemicals, suffering from physical harm, contracting a virus, or working out vigorously

2.4.4 Diagnosis

Early diagnosis of amyotrophic lateral sclerosis is challenging since it can resemble other neurological conditions. Testing to rule out alternative conditions may involve:

- ***Electromyogram (EMG).*** A needle electrode is inserted into several muscles by your doctor through your skin. The test analyses your muscles' electrical activity both during contractions and at rest.
  EMG abnormalities in the muscles can aid in the diagnosis or exclusion of ALS. Moreover, an EMG can direct your exercise treatment.
- ***Nerve conduction study***. The capacity of your nerves to activate muscles in various parts of your body is measured in this study. This examination can reveal whether you have certain muscle or nerve illnesses or nerve damage.
- ***MRI***. A magnetic field and radio waves are used in an MRI to create precise images of your brain and spinal cord. An MRI can detect malignancies in the spinal cord, herniated discs in the neck, and other diseases that could be the source of your symptoms.
- ***Blood and urine test***. Your doctor may be able to rule out more potential causes of your symptoms and signs by having samples of your blood and urine examined in a lab.

2.4.5 Treatment

Although there is no cure for amyotrophic lateral sclerosis, there are treatments that can delay the symptoms' progression, stop complications, and increase your comfort and independence.

Medications: Some Medication prescribed by Doctor:

- ***Riluzole (Rilutek, Exservan, Tiglutik kit) (Rilutek, Exservan, Tiglutik kit)***. When taken orally, this medication can extend life by three to six months. It may have adverse consequences such alterations in liver function, nausea, and dizziness. While you're taking the medication, your doctor will keep an eye on your blood counts and liver health.
- ***Edaravone (Radicava) (Radicava).*** This medication, which can be taken orally as a pill or delivered intravenously, might lessen the deterioration in daily functioning. Its impact on life expectancy is still unknown. Bruising, headaches, and shortness of breath are some of possible side effects. Two weeks out of every month, this medication is administered daily.

- **5. CONCLUTION**

Neurodegenerative disorders are a group of progressive neurological disorders that affect the neurons and other components of the nervous system, leading to a range of symptoms and impairments. These disorders are caused by the progressive loss of neurons and other brain cells, leading to a decline in cognitive, motor, and sensory functions.

Some of the most common neurodegenerative disorders include Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS). Each of these disorders has unique symptoms, causes, and treatment options.

Alzheimer's disease is a progressive disorder characterized by the accumulation of amyloid-beta protein in the brain, leading to the death of neurons and the progressive deterioration of cognitive function. There is currently no cure for Alzheimer's disease, but there are treatments that can slow its progression and improve symptoms.

Parkinson's disease is a progressive disorder caused by the loss of dopamine-producing neurons in the brain. This loss leads to motor symptoms such as tremors, stiffness, and difficulty with movement. Treatment options for Parkinson's disease include medications, surgery, and lifestyle changes.

Huntington's disease is a genetic disorder that causes the progressive deterioration of neurons in the brain. It leads to a range of symptoms, including cognitive, motor, and psychiatric symptoms. There is currently no cure for Huntington's disease, but there are treatments available to manage symptoms.

ALS is a progressive disorder that affects the motor neurons in the brain and spinal cord, leading to muscle weakness and atrophy. There is currently no cure for ALS, but there are treatments available to manage symptoms and improve quality of life.

In conclusion, neurodegenerative disorders are a group of progressive neurological disorders that affect the neurons and other components of the nervous system. These disorders have unique symptoms, causes, and treatment options, and there is currently no cure for most of them. However, research into these disorders is ongoing, and new treatments and therapies are being developed to improve the lives of those living with these conditions.

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