A Review On Neurodegenerative Diseases: Types, Pathology & Recent Advancement In Neurodegenerative Treatment

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Abstract: Neurodegenerative diseases are characterised by the progressive loss of selective population of neurons thereby breaking the synaptic circuit and these diseases are rapidly increasing in prevalence. The most common neurodegenerative diseases are Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis. Often these diseases result in loss of memory, uncontrolled movements, lack of coordination, slurred speech and other body impairments. The brain is a complex organ made up of billions of cells on which we depend for proper functioning. Some of the most essential cells in the brain are called "Neurons" .These neurons communicate with each other to perform every function of the brain. .These neurons are interconnected and any miscommunication in one area can affect other activities of the brain leading to neural disordersThe death of the neurons in Alzheimer's disease is caused by the accumulation of β amyloid plaques and tau protein extracellularly. In case of Huntington's disease the expansion of CAG tri-nucleotide repeat in the huntingtin gene is the cause. This review offers a brief introduction to neurodegenerative diseases and provides an overview of its types and pathology. It also touches upon the recent advancement in the treatment of neurodegenerative diseases. In this review we have attempted to summarize the symptoms, pathology and treatment of three main neurodegenerative diseases namely; Alzheimer's disease, Parkinson's disease , Huntington's disease.

Index terms: Alzheimer's disease, β amyloid plaques, Dopaminergic neurons, Familial Alzheimer's disease (FAD), Induced pleuripotent stem cells (iPSCs), Neurofibrillary tangles (NFT), Substantia nigra.

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1 INTRODUCTION

What are neurodegenerative diseases?
Neurodegenerative disease is a collective term for a vast range of conditions which affects neurons of the human brain. Around millions of people worldwide are being affected by

neurodegenerative diseases.
Alzheimer's disease and Parkinson's disease are the most common neurodegenerative diseases found among people. It has been estimated that over 5.4 million Americans were diagnosed with Alzheimer's disease in the year 2016 and around 9, 30,000 people in the United States could be living with Parkinson's disease by 2020. Neurodegenerative diseases occur to a person when their nerve cells in the brain lose its function and eventually die. It also cause damage to the nerve cells associated with the peripheral nervous system .Existing treatments may help the patients relieve from some of the mental and physical symptoms connected with neurodegenerative diseases yet there is no any known cure for the disease or to slow down the progression of the disease. The chances of being affected by neurodegenerative disease increases with age. For example the longer the lifespan of an American the greater is the chance of him developing a neurodegenerative disease in the coming decades. This calls for a need to improve our knowledge on the causes of neurodegenerative diseases and developing newer approaches for its prevention and treatment. [1]

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Scientists think that the combination of environment and a person's gene can contribute in developing a neurodegenerative disease. This means a person may possess a gene that makes him more susceptible to a particular neurodegenerative disease. But how and when the person is severely affected depends on the exposure to environmental factors throughout one's life.Neurodegenerative diseases affects our body's activities such as movement, balance, talking, breathing and heart function .Many of these diseases are genetically transmitted. Sometimes it can also be caused due to alcoholism, a tumour, or a stroke. [2]

Neurodegenerative diseases include:
- Alzheimer's disease
- Amyotrophic lateral sclerosis
- Friedreich's ataxia
- Huntington's disease
- Lewy body disease
- Parkinson's disease
- Spinal muscular atrophy

Neurodegenerative diseases can be serious or life-threatening. It depends on the type of the disease. Most of them have no cure. Treatments may help improve symptoms, relieve pain, and increase mobility. [3] The brain is a complex organ made up of billions of cells on which we depend for proper functioning. Some of the most essential cells in the brain are called "Neurons" .These neurons communicate with each other to perform every function of the brain. .These neurons are interconnected and any miscommunication in one area can affect other activities of the brain leading to neural disorders. Such diseases affecting the brain cells and its activity are called neurodegenerative diseases. Neurodegenerative diseases pose a great threat to human lives .This disease is also increasing with the elderly population in the recent years. It includes Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis. These

diseases vary in their pathophysiology - with some affecting cognitive response, memory, or the person's ability to move and speak. Neurodegenerative diseases can run in families and are hereditary or can occur in sporadic conditions. Alzheimer's disease is identified by the abnormal accumulation of amyloid- β plaques and tau protein extracellularly leading to the formation of intra-neuronal NFT (Neurofibrillary tangles) in the regions of the brain causing dementia in elderly individuals, cognitive abnormalities and intellectual disabilities. Parkinson's disease is characterized by the death of the neurons in a part of the brain known as "substantia nigra". This region of the brain contains large number of neurons which releases a substance called 'Dopamine'. By releasing dopamine, the neurons can communicate with movement-producing parts of the brain. Thus death of neurons in the substantia nigra cause stumbling and shaking in the people with Parkinson's disease.   Huntington's disease is also another neurodegenerative disease which affects the basal ganglia and causes movement problems. It is a genetic illness which means that if either parent has the disease, the children are most likely to develop the disease. It is caused by the abnormal protein build up in the brain resulting in movement disorder. Another neurodegenerative disease is the Amyotrophic lateral sclerosis(ALS) which is also known as motor neuron disease is characterized by the degeneration of both upper and lower motor neurons leading to the weakening of muscles and eventually result in paralysis. The exact pathology of this disease is not yet understood thoroughly but defects of RNA processing and protein clearance may be the cause. Thus this review gives an insight to the understanding of neurodegenerative diseases and it also touches upon its pathophysiology and the molecular aspects of the diseases. It also deals with the recent advancement in the treatment of neurodegenerative diseases thus providing a view on how to address the existing challenges in treating neurodegenerative diseases. [4]

2 ALZHEIMER'S DISEASE (AD)

Alzheimer's disease (AD) is an irreversible progressive disease that destroys the memory and other important mental functions such as thinking skills. Although it has been described as dementia (a collective term used to describe various symptoms of cognitive decline, forgetfulness) [5]. This is mostly affected in old age. It is the most common neurodegenerative syndromes where in human more than 80% of the elderly people are suffering from AD worldwide [6, 7]. It is a crucial challenge to solve this problematic topic about AD, that includes origin, causes, treatment, early and accurate diagnosis method. [8-10]. The AD is been clinically categorized based on age, Early-Onset AD (early 60's) and Late-Onset AD (late 60's) [11].AD is a very compound disease that is caused by combination of age, genetic and environmental factors that has the chance to trigger the risk of getting an AD [12]. Patients who tend to have Down Syndrome develop the risk of developing the pathological factors of AD over the age of 30years then, the chromosome 21 has a risk factor of developing AD, as the code of the gene for amyloid β precursor protein (βAPP) [13].

Pathology of Alzheimer's Disease (AD)

Among all types of the neurodegenerative discords the AD has aroused a lot of interest in the last few years. The primary risk factors of AD are aging, family history and genetics. Statistically 10% of the people above 65 years may be affected by AD and 50% of the people above 85 years are very likely to be affected by AD.Some of the main features of AD are formation of abnormal clumps (amyloid plaques) tangled bundle of fibres (neurofibrillary or tau).It is recommended to characterize the exact pathology of AD and analyze their strength and weakness as it was predicted that a new AD case will occur for every 30 sec in 2050[14-16]. Therefore the most fundamental work that has to be done is to characterize the precise pathology of AD even though they are still unclear and are caused by many different factors the two most significant traits that cause AD have been recommended which are Aβ, tau protein entanglement and familia of AD

Amyloid beta (Aβ)

Aβ are primarily produced by neuron which are secreted in the extracellular region of the brain as a soluble ingredient which is said to accumulate voluntarily that acts as an trademark of AD where it causes the aggregation of aβ to form insoluble amyloid fibrils. [17,18].By non amyloidogenic pathway, the APP is cleaved via αsecretase which is tend to occur in between Lys687 and Leu688 and release the soluble N-terminal fragments of sAPPalpha. The other membrane bound C-terminal regions are cleaved by a secretase named γsecretase, which leads to the production of amyloidogenic peptide of A (1-40) and Aβ (1-42) [17, 10]. The most common encountering Aβ that undergoes the process in senile plaques and provides small "nidi" to commence amyloid fibril formation rapidly which leads to the nucleated polymerizaion of Aβ amyloidegenesis is A (1-42) compared to the other.[21]. Aβ polymerisation also takes place during the metastable intermediates of the nucleated conformational conversions [21, 22]. The effect if A (1-40) and Aβ (1-42) was demonstrated on the SH-SYSY cell line for the time dependent increase of the aggregation of Aβ (1-42) where the concentration of Aβ; although it was not correct in the case of Aβ (1-40)[18]. During the In vitro experiments evaluated that the required concentration of Aβ's spontaneous aggregation is of the range µM. The Aβ concentration for spontaneous aggregation may increase up to three or four orders in the extracellular space in vivo .Respective mechanisms in response to the increased Aβ concentration were put forward, which includes macromolecular crowding, membrane association, specific interaction with protein complexes or chaperones, particular covalent modification and intermolecular hydrogen bonding [18, 23,24] .The number of Aβ deposits are not well correlated with the degree of cognitive impairment[25,26].
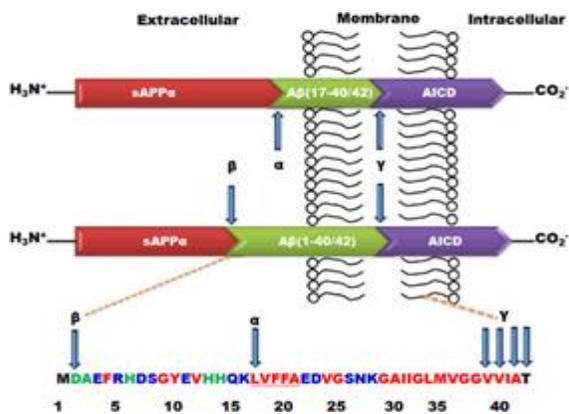
Fig. 1. (Top) Schematic representation of cleavage of APP by α-, β- and γ-secretases. Alpha-secretase releases soluble fragment (sAPP α) followed by cleavage of γ-secretase to produce either Aβ (17–40) or a β (17–42) and APP intracellular domain (AICD) subsequently.

Tau protein

Tau being the most significant microtubule associated protein (MAP) that is present in a normal mature neuron. The two neuronal MAPs are MAP1 and MAP2. Where it is of the form six molecular isoforms in the human brain [27]. The isoforms are coded by a single gene on chromosome 17 which are generated by alternative splicing of its pre-mRNA [28].The microtubule assembly promoting the activity of tau, which is a phosphoprotein that is regulated by its degree of phosphorylation. In a normal adult (human) brain tau contains 2–3 moles phosphate/mole of tau protein. Hyper phosphorylation of tau depresses this biological activity of tau which leads to Alzheimer disease (AD) where in brain the tau is ~three to four-fold more hyper phosphorylated than the normal adult brain tau and in this hyper phosphorylated state it is polymerized into paired helical filaments ([PHF) admixed with straight filaments (SF) forming neurofibrillary tangles [29] The reason by which the tau protein is non-functional is on discussion. Abnormal posttranslational modifications are suggested to be the main cause of this failure [30,31].For the optimal function of tau protein to occur normal phoshorylation has to take place, whereas due to the hyperphosphorylated state results tau to lose its biological activity[32]. In a normal mature neuron, tubulin is present as tenfold of tau, thus practically all tau protein are microtubule bounded in the cell [33, 34]. The neurons affected in AD, abnormally phosphorylated cytosolic tau (AD P-tau) which neither binds to tubulin nor advances the microtubule assembly [35-37].But the protein inhibits the assembly and disrupts the microtubule organization. The AD P-tau also removes the other two major neuronal MAPs, MAP1 and MAP2, from microtubule lattice.

Diagnostic Criteria

The standard criteria for the clinical diagnosis of the Alzheimer's were developed by the National Institute of Neurological and communicative disorders and stroke [38]. Based on this the Alzheimer's disease are classified as into three diagnostic categories: which are definite Alzheimer's disease, probable Alzheimer's disease and possible Alzheimer's disease. The definite Alzheimer's disease id generally diagnosed by getting the conformation for histopathologic of clinical features by postmoretem examination [39].In general for probable Alzheimer's disease the clinical diagnosis include onset between the ages of 40 and 90; which has no disturbance of consciousness; establishment of clinical examination and standardized assessment of mental status, which is supplemented by neuropsychological testes. The clinical diagnosis for the possible Alzheimer's disease is same as that of the probable Alzheimer's disease except that is only for a single progressive severe cognitive deficit is identified and treated [40].

Pharmacological Approaches

The pharmacological treatment for Alzheimer's are generally advised only for those patient only who have been diagnosed with mild to moderate disease. For development of the current pharmacologic approaches neurobiological features have supported the study of accumulation of amyloid and the reduction in acetylcholine and possible impairments in immune and inflammatory mechanisms of the drugs [41].

Acetylcholinesterase Inhibitors

It is considered as the well-developed approach that aims to correct the deficit if acetylcholine that is associated to the Alzheimer's disease. The acetylcholinesterase consist of first and second generation compounds such as physostigmine, tacrine, donepezil, metrifonate and rivastgmie. Considered to be the most successful drugs that enhance the transmission of acetylcholine.

Estraogen

Epidemiologic studies have proposed that replacement in women estragon therapy may significantly hold up the on-set of Alzheimer's disease which also lowers the risk of developing it [42, 43]. Small clinical trials have shown that treatment with estragon improved cognition in the patients [44, 45]. The estragon has ability to behave as both antioxidant and anti-inflammatory agent which explain its association with a reduction in risk [46-48]. American Association for Geriatric Psychiatry and the American Geriatrics Society, highlights that cholinesterase inhibitors are the mainstay of pharmacological treatment of patient that has Alzheimer's disease [49].

3 PARKINSON'S DISEASE (PD)

Parkinson's disease is the most common age related neurodegenerative disease next to Alzheimer's [50]. Parkinson disease usually develops between the age group of 55 and 65 years and occurs in 1%–2% of people over the age of 60 years which rises to 3.5% at age 85–89 years [51]. Dementia is a frequent problem experienced by the patient in advanced stages of Parkinson disease (PD) where in the pre-dementia stages of cognitive includes mild cognitive impairment (MCI). PD can primarily defined as a movement disorder, with the typical symptoms of resting tremor, rigidity, bradykinesia and postural instability and pathologically can be characterised as degeneration of nigrostriatal dopaminergic neurons and the presence of Lewy bodies (misfolded α-syncline) in the surviving neurons [52]. In addition to the pathological characters are dopamine-related motor symptoms, Where PD is increasingly recognized as a heterogeneous multisystem

disorder involving other neurotransmitter systems, such as the serotonergic, noradrenergic and cholinergic circuits. Thus, a wide variety of nonmotor symptoms (NMS) are linked with these neurotransmitters which are commonly observed in patients with PD [53]. In 2011, the estimated number of people in Canada with Parkinson disease had reached 85, 200. By 2031, the projected number of people with this disease will double [54].

Pathology of Parkinson's Disease
Dr.Parkinson did not know what was the underlying pathology of the shaking palsy was (PD).Where in 1893 a theory that was supported by all which first suggested by Bloq and Marinesco [55]. In 1912, a different Friedrich Heinrich Lewy identified the cellular inclusion bodies present in patients with Paralysis agitans, in 1919 Constantin Tretiakoff put together the two separate pathologies since both were observed in patients with PD [56]. Parkinson disease involves multiple motor and nonmotor neural circuits majorly characterised into two (a) premature selective loss of dopamine neurons; (b) the accumulation of Lewy bodies, composed of α-synuclein that misfolded and accumulate in multiple of the patients [57].With the help of pathology understandings over the years there is a stepwise degeneration of neurons where each affected site leads to specific symptoms of the Parkinson's disease. Based on the pathological studies it is evident that 30-70% cell loss in the substantia nigra that is observed when the motor symptoms are highly evident [58]. For better understanding they are organised in a table format [57]

Stage	Sites affected by Lewy bodies	Major symptoms
I	Dorsal motor nucleus of the vagus nerve and olfactory tract	Constipation, anosmia
II	Locus coeruleus and subcoeruleus complex	Sleep and mood dysfunction
III	Substantia nigra	Motor symptoms of Parkinson disease
IV–VI	Cortical involvement	Dementia, psychosis

The theory is that degeneration of the substantia nigra was primary to the syndrome which cemented by 2 additional discoveries, the first by Arvid Carlsson on the role of dopamine in the brain and the second by Oleh Hornykiewicz, who exhibited that the largest group of dopaminergic neurons are found in the subtantia nigra with their terminals in the caudate nucleus [59]. Moderate to severe loss of the pigmented dopamine neurons in the substantia nigra is found in all patients with clinical PD and forms 1 of 2 pathological mark required for a absolute

diagnosis [60]. The swift advance in research techniques through the past 20 years has determined that there is not a single cause but several causes all leading to the common preferential early loss of dopaminergic neurons [61]. The two most obvious cause are the numerous different genes involved (autosomal dominant, autosomal recessive, and risk genes) and some environmental factors (hydrocarbon exposure, less coffee intake and cigarette smoking, constipation, reduced physical activity) [62]. These differentiated etiologies impact on various cellular pathways that merge to cause dysfunction and then the death of the specific dopaminergic neurons that cause PD—these include protein misfolding and aggregation, disruption of autophagic catabolism, endoplasmic reticulum stress, mitochondrial dysfunction, and/or the loss of calcium homeostasis—and for an individual the balance between these pathways vary greatly. The second diagnostic marker of idiopathic PD is the presence of misfolded protein in the form of Lewy bodies in at least the brain stem. [60] In sum, the following 2 cellular pathologies are consistently found in patients with idiopathic PD: loss of dopaminergic neurons in the ventrolateral region of the SN and LP in the brain stem. The therapy aims to replace dopamine with dopaminergic medications and modulate the dysfunctional circuit. Cognitive dysfunction, mood disorders and impulse control disorders are related to deficits of dopamine outside the basal ganglia or in serotonergic and noradrenergic systems [63, 64].

Diagnostic Criteria
At present the diagnosis for PD at clinical level are based on the features from pathological examination over the time for the past 20 years on the response of dopamine agents and development of motor functions [63]. Early Parkinson's disease was difficult for primary care physicians to diagnose since the early symptoms were hard to recognise for a decade or two [64]. Motor manifestations of the disorder start of asymmetrically, and generally include a resting tremor, a soft voice (hypophonia), masked facies (initially presenting as reduced blink rate), small handwriting (micrographia), stiffness (rigidity), slowness of movements (bradykinesia), common symptom is resting tremor, usually affecting one upper limb, although 20% of patients does not have it; 30% may first present with tremor in a lower extremity [65, 66].

Treatment
Levodopa has been used clinically for half a century, but its mechanism among the patient with PD is still not fully understood. The traditional notion that the amino acid acts mainly as a dopamine precursor (by being decarboxylated into dopamine and then replenishing the deficient neurotransmitter in the striatum) has been challenged because this presumed mechanism does not explain the loss of the long duration response, the advancment of dyskinesias, and other clinical-pharmacologic effects [67]. Dopaminergic medications are the anchor of symptomatic therapy for motor symptoms in PD [68,69].

4 HUNTINGTON'S DISEASE (HD)
Huntington's diseases is a rare neurodegenerative disorder that is characterized by unwanted choreatic movements and affects the person's physical and mental stability and

the symptoms include unsteady movements, slurred speech and significant weight loss. The symptoms begins to appear in the mean age of 30-50 but in some cases it starts to appear before the age of 20 and if it occurs it may lead to difficulty in reading. This disease mainly affects basal ganglia –the part of the brain which is responsible for regulating movement and behaviour. It is an autosomal dominant genetic condition. It is caused by the genetic mutation involving the expansion of trinucleotide CAG repeats in the Huntingtin gene. If the CAG repeat is longer, then the onset of the disease is earlier. [70, 71]

Symptoms and pathology

The symptoms of the Huntington's disease consists of motor, cognitive and psychiatric disturbances: 1. The motor symptoms and signs: It includes unwanted movements and involuntary actions and it is often associated with fingers and toes and also in facial muscles. Choreatic movements exists all the time when the patient is awake. It can lead to continuous movements of facial muscles such a lifting an eyebrow, an eye being closed and the tongue protruding out while the head is bent. 2. Behaviour and psychiatric symptoms and signs: Psychiatric symptoms are likely to occur in the early onset of the disease, often it occurs prior to the development of the motor symptoms. Irritability is the first sign and it occurs at all stages of the disease. Psychosis may appear in the later stages of the disease and it is often accompanied with cognitive decline. 3. Cognitive symptoms: It is said to be the other main sign of Huntington's disease and can occur even before the first motor symptoms tend to appear. In normal conditions the cognitive and the motor behaviour is well planned and directed to do the exact task what is required but the patients with HD are devoid of this ability. Memory becomes impaired and there is a severe retardation of all psychomotor processes. [73]

Pathology

Normal HTT gene is essential for the development of the brain, the HTT knock-out mice embryos have shown major abnormalities in the development of central nervous system and they tend to die shortly after birth. It is also said that HTT is expressed in the brain during the entire course of development and plays a key role in neural stability and survival. The classic theory of HD pathology is that mutant HTT (mHTT) results in gain -of – function toxicity that is responsible for neural damage. The loss of function of normal HTT is also an important mechanism in the disease. Moreover, mHTT is known to cause impairments in several stages of striatal development. The etiologic dogma of HD is that the development of the disease lies within the toxic effects of the mutant huntingtin that is encoded by mHTT. It gets accumulated in the cells and is said to be toxic resulting in degeneration. This mutant neuronal circuit however remains relatively functional with subtle abnormalities known as the 'mutant steady state'. Later the maturation and aging process combined with the toxic effects of the mutant huntingtin eventually leads the faulty circuit towards degeneration. The diagrammatic representation is given below. [74, 75]

Diagnosis and treatment

The diagnosis is carried out on the basis of clinical symptoms and signs in a person with a parent with proven HD. First, it is mandatory to get the precise history of the person with the symptoms and then the detailed family history. When all the necessary details are obtained the diagnosis is very simple. The most commonly followed strategy is the DNA determination which counts the number of CAG repeats on the HD gene. The clinical symptoms are the motor and the psychiatric changes. These symptoms along with the family history is sufficient for diagnosis. For any diagnosis it is necessary to get the consent from the patient, it is because if a person is given a diagnosis of HD, then many people around the patient may be confronted with an increased risk of Huntington's disease.[76]

Treatment

Even though the pathogenesis of HD is not clearly resolved and the exact cure still remains undiscovered, many therapeutic options are available for treating the signs and symptoms. On the other hand very little information is available regarding the drug and dosage prescribed for signs and symptoms. Therefore treatment with the drugs is individualized and is based on expert opinion. Pharmacological interventions are designed to address the hyperkinetic movement disorders associated with HD such as chorea, ballism and myoclonus. An American Academy of Neurology Guidelines publication was recently released which recommends the use of tetrabenazine (TBZ), amantadine or riluzole for chorea treatment. Cochrane review concluded that TBZ shows greater efficacy in controlling chorea.TBZ is the only drug for HD that is approved by the US Food and Drug Administration, indicated for the treatment of chorea associated with HD. It works by reversibly inhibiting the central vascular monoamine transporter type 2, TBZ selectively depletes dopamine than norepinephrine. The efficacy of TBZ as an antichoreic drug was demonstrated in a double-blind, placebo-controlled trial conducted by the Huntington group study. Other medications for treating chorea include dopamine antagonists, benzodiazepines and glutamate antagonists. The dopamine antagonists are the most commonly prescribed agents for the management of chorea and psychosis in patients with HD. The N- methyl D-aspartate-amantadine antagonist in controlled trials has significantly shown to reduce chorea in patients with HD. Benzodiazepines are also frequently used in patients with HD to treat chorea and anxiety. [77,78]

5 AMYOTROPHIC LATERAL SCLEROSIS

Recent advancement in neurodegenerative research
Induced pluripotent stem cells application in neurodegenerative disease: stem cells are the cells which has the self-renewal ability and generates differentiated functional cell types that are derived from embryo and various sources of postnatal animals. Pleuripotent cells are the cells that have the ability to create different cell types of the body in an identical behaviour as embryonic stem cells. Induced pleuripotent cells (iPSCs) are the cells which can be genetically reprogrammed to an embryonic stem cell-like state via transcription factors and express genes such that these adult cells can maintain the characteristics of embryonic stem cells. iPSCs can be used to monitor the specific mutations of neurodegenerative disease due to

their ability to differentiate into neural cell types or neural organoids.[79,80] In recent decades, researches have used iPSCs in creating disease models from patients with genetic and neuronal defects and by creating successful disease models, iPSCs have made a promising platform for studying the disease development , examining pathophysiology and testing the therapeutic agents. Alzheimer's disease is the most common neurodegenerative disease that is caused by the extracellular accumulation of plaques of amyloid-β peptides and neurofibrillary tangles formed by the tau protein. Familial Alzheimer's disease (FAD) occurs as a result of autosomal dominant mutation in amyloid precursor protein (APP) gene and in the presenilin genes (PSEN1 and PSEN2). iPSCs models were derived from patients with specific mutations in PSEN1 and PSEN2 or APP genes. Along with this Aβ40, Aβ42 and Aβ42/40 peptide ratios are used as markers to indicate the pathological characteristics in these models. Extending the culture periods in the in vitro study of neurogenesis helps in the easy observation of action potential patterns and synaptic activity. Immune rejection in the treatment of AD can be avoided by using iPSCs based regenerative medicine and it involves gene correction and iPSCs-derived neuronal transplantation. [81,82] Parkinson's disease is the second most common neurodegenerative disease that is marked by the gradual loss of dopaminergic neurons (DAn) in the substantia nigra pars compacta (SNpc). It is caused by the mutation in number of genes such as SNCA, LRRK and PINK. L-dopa is a precursor of dopamine which can regulate the levels of dopamine in the brain based on dopaminergic transmission. It was found that in a PD rat model, the motor function was improved by using ESC-derived dopaminergic progenitors. However, ESCs or iPSCs are not implemented in clinical trials till now.Huntington's disease is another neurodegenerative disease caused by the expansion of CAG tri-nucleotide repeats in the Huntington (HTT) gene. The conversion of HD-IPSCs into GABAergic striatal neurons was carried out in a grafted rat after the transplantation of HD-iPSC derived neural precursors. This study exhibited the expression of several pathological markers of HD, with the iPSCs showing higher response to proteasome inhibition.[83] Peptide based therapeutics for treatment of ND: Bioactive peptides have an active contribution in various biological functions and mainly in human health. Peptides as therapeutics are successfully used in disease management. In 1974, rDNA technology paved way for the production of therapeutic peptides on an industrial scale. These peptides have a number of therapeutic effects such as antimicrobial, antioxidant and antithrombotic effect. Here are some examples of natural peptides; Carnosine, Defensins Cathelicidin, Dermcidin and Hepcidin. [84]

Peptide Inhibitors for ND

- QBP1: It is a peptide inhibitor for the treatment of polyglutamine neurodegenerative disease.
- P110: Drp1 is found to be an essential regulator of mitochondrial fission. Under stress, Drp1 is activated and translocated to mitochondria leading to excessive mitochondrial fission and dopaminergic neural death. A study by Emily Filichia et al. have shown that Drp1 is potentially inhibited by peptide inhibitor P110 leading to the stable preservation of dopaminergic neurons.

- NAP: NAPVSIPQ is derived from activity dependent neuroprotective protein (ADNP), which is a neuroprotective peptide. It is known to protect axonal transport, inhibit apoptosis and increase microtubule stability. These effects of NAP are used in the treatment of Parkinson's disease.
- VIP: Vasoactive intestinal peptides play a neuroprotective role in major NDs like Alzheimer's disease, Huntington's disease and Parkinson's disease.
- β- Sheet breaking peptides: Aβ aggregation is the most common characteristic feature of AD and the treatment of AD involves breaking up of Aβ structure. β-sheet breakers are short peptides that can destabilize Aβ conformers thus preventing amyloid formation and suppressing the toxicity induced by Aβ aggregation.[85,86]
- Nanoemulsion (NE) in the treatment of Parkinson's disease: Nanoemulsions are set of dispersed particles that are commonly used as vehicles for formulating pharmaceutical preparations and are used in drug therapy for NDs. NE is known for its extended drug delivery from nose to brain via olfactory region. Researchers have modified them with mucoadhesive NE (MNE) for the treatment of Parkinson's disease. An example is the work done by Mustafa et al in which they formulated NE loaded with Ropinirole. MNE loaded holds a promising perspective in intranasal drug delivery and is used in the treatment of PD because of its ability to produce DA by stimulating DA receptor. [87]

6 CONCLUSIONS

Neurodegenerative disease are in an expanding medical crisis taking an enormous personal and financial tool on those affected and their families. The problem is exacerbated by the lack of routine diagnostic tools for identifying patients early enough in their course of treatment. Effectiveness of therapeutic approaches requires concurrent progress in developing specific and sensitive diagnostic tools. These challenges are considerable as are the costs to the millions of patients affected by this disease. Given the rising prevalence and mortality of neurodegenerative disease couples with growing total healthcare costs, there continues to be a sense of urgency in the medical community to develop effective means for early diagnosis and successful treatment of the disease.

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