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Neurodegenerative Disorder

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Abstract: Neurodegenerative disorders of the nervous system that can primarily be characterized by neuron loss. Neurodegenerative diseases such as Alzheimer, Parkinson, Huntington, Amyotrophic lateral sclerosis and Multiple sclerosis are known as Lou Gehrig's disease. The huge body of evidence disorders arise by multifactorial conditions. Alzheimer's and Parkinson's disease are most common neurodegenerative disorders. It includes generation of new neurons, the phenotypic level of essential functions: sensory & motor, and cognitive abilities. The therapeutic interventions directed toward treatment of these neurodegenerative diseases. Multiple sclerosis is treated mainly by immune-suppressors, speed of recovery from relapse and slow down the disease. The neurodegenerative diseases have some therapies like stem cell therapy, gene transfer therapy, and the multitarget directed ligands have promising to find new therapies for neurodegenerative disorders. In nanotechnology, there is a great potential for neurotherapeutic modalities. The nanomedicines administered from several routes like olfactory, oral and systemic etc. The brain there is the one or more targeting changes for the disease modifying treatment that is slow disease progression in the Alzheimer's disease, in the Amyotrophic lateral sclerosis antisense treatment in the development to reduce superoxide dismutase and the Huntington's disease are monoclonal antibody in development to block the Semaphorin 4D.

I. INTRODUCTION

Neurodegenerative diseases such as Alzheimer's (AD), Parkinson's (PD), and Huntington's diseases (HD), amyotrophic lateral sclerosis (ALS) and Multiple sclerosis (MS), thus make a characterized group of pathologies by separate etiologies with pathophysiological features and distinct morphological features.

Numerous pieces of evidence point to the multifactorial conditions that include (a) abnormal protein dynamics with impaired protein degradation and aggregation, (b) oxidative stress and free radical formation, (c) impaired bioenergetics and mitochondrial dysfunction, and (d) exposure to metal toxicity and pesticides as possible causes of these disorders [1]. Numerous molecular and cellular abnormalities are shared by neurodegenerative disorders, including protein aggregation, mitochondrial dysfunction, glutamate toxicity, calcium load, proteolytic stress, oxidative stress, neuroinflammation, and aging, resulting in neuronal death (Kiaei, 2013; Ganetal., 2018) [2]. To achieve the best results, nanotherapeutics still need to be improved despite this significant advancement. In this review, we initially describe the pathophysiology of major NDs and their current management strategies [3]. Neuroregeneration can also be defined as the progressive structural and functional recovery of the damaged nervous system over time [4]. In contrast to neuronal inclusions encountered in viral infections, when the protein is foreign, these aberrant protein aggregates are made up of native neuronal proteins and other cellular components. In many cases, the protein has an abnormal conformation with amyloid-like properties [5]. Examples of neurodegenerative diseases are Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, frontotemporal dementia and the spinocerebellar ataxias [6]. Other possible causes may include gender, poor education, endocrine conditions, oxidative stress, inflammation, stroke, hypertension, diabetes, smoking, head trauma, depression, infection, tumors, vitamin deficiencies, immune and metabolic conditions, and chemical exposure [7]. On the cellular level, research in PD focuses on protein aggregation, neurotoxicity, increased oxidative stress, excitotoxicity, mitochondrial dysfunction, and defects in the protein degradation machinery [8].

The ability of the nanomedicines to incorporate both hydrophilic and hydrophobic molecules, as well as enhanced chemical or biological substantiation, makes them extremely advantageous for the treatment and diagnostics of many neurodegenerative diseases (NDs). In addition, the nanomedicines can be administered from several routes like olfactory, oral and systemic etc. This review highlights a variety of features of nano-technological approaches involved in the treatment and prognosis of various NDs [9]. It is known that the etiology of neurodegenerative diseases is multifactorial, and there is evidence that potential external factors including life style and chemical exposures are linked with the risk of the onset of these diseases. Since the majority of AD and PD cases are found in senior populations, yet the exposure to risk factors happened years or decades before the diagnosis, it might be challenging to assess chronic exposures in retrospective investigations and link them to the onset or progression of the disease [10]. The levels of expression in the brain itself are however lacking to our knowledge [11].

A prodromal stage of mild cognitive impairment (MCI), a syndromic designation that does not always imply dementia, precedes the clinical symptoms of Alzheimer's disease as the underlying aetiology. Together, the presymptomatic and prodromal phases comprise pre-manifest Huntington's disease [12].

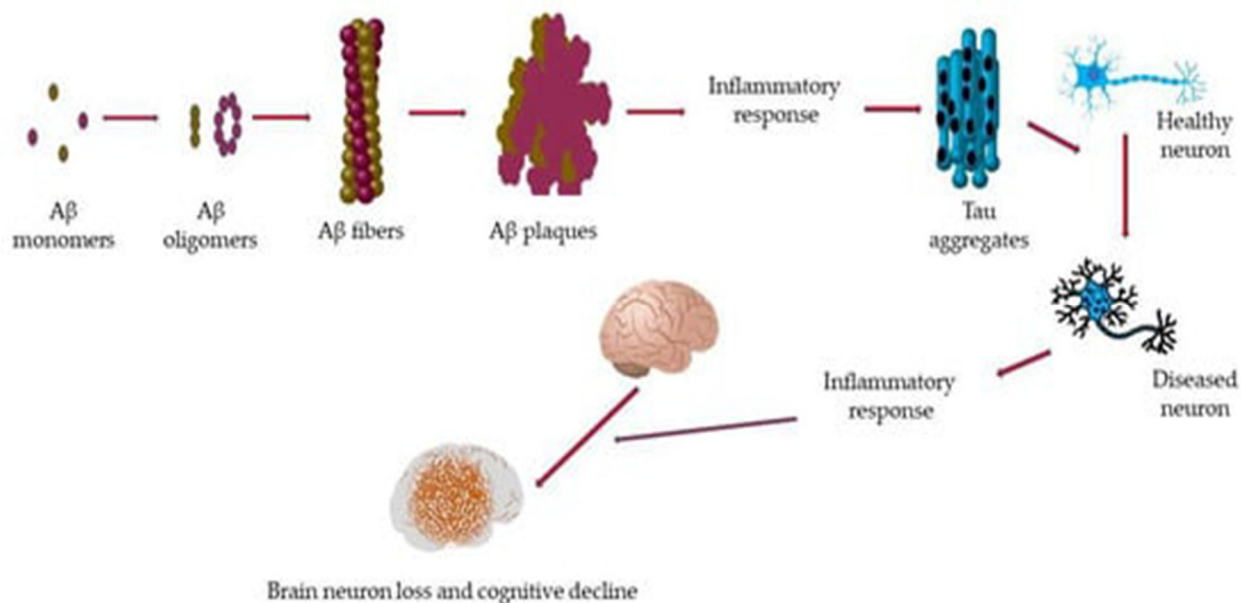


Figure 1. Path of neurodegeneration leading to cognitive impairment. Amyloid-beta (A) monomers aggregate to create oligomers with different structural compositions. The oligomers then combine to create A fibres, which subsequently rearrange to create A plaques. Plaque development causes an inflammatory reaction that results in the creation of tau aggregates, which turns healthy neurons into sick neurons. More damaged neurons cause another inflammatory reaction, which further reduces the number of healthy neurons, thus impairing brain function and contributing to cognitive decline [3].

II. TYPES OF NEURODEGENERATIVE DISORDER

A. Alzheimer's Disease [AD]

Alzheimer disease is perhaps the prototypical degenerative disease affecting the central nervous system[7]. The accumulation of amyloid-beta (A β) and tau proteins is crucial to the progression of Alzheimer's disease (AD), according to more current research on the illness's aetiology. The formation of A β -containing plaques within the brain, linked with neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau, has been identified as the classical feature of AD[3]. The neuropathology of AD is a mixed proteinopathy that includes the presence of both A β deposits in the parenchyma as amyloid or senile plaques, as well as neuronal tau inclusions(i.e.,NFTs)[5]. It is commonly acknowledged that glial cells have a role in the development of AD. It has been shown that, besides neuronal loss, reactive astrocytes and activated microglial cells can be associated with amyloid plaques and neurofibrillary AD-like rats showed differential expression of NMDA receptor subunit tangles [8].

In case of CA1 neurons, the gene expression studies of (NR1, NR2B) in the CA1 and CA3 regions. During prolonged glutamate stimulation, calcium influx was higher in CA1 compared to CA3, and a substantial amount of calcium is sequestered in CA1 mitochondria[2]. Alzheimer's disease is the major form of dementia in elderly and possibly contributes to 60–70% of cases. It is a progressive, disabling and irreversible disease (Goedert and Spillantini, 2006). There are two recognized forms of AD. The first is referred to be familial or of early onset (EOAD), and it is strongly linked to particular gene mutations in the amyloid precursor protein (APP), presenilin (PSEN) 1, and 2 genes, both related to the amyloid beta (A β) peptide synthesis[10].

Alzheimer's disease leads to onward loss or deterioration of neurons of cortical and hippocampal leads to memory and cognitive dysfunction [9]. Prior to recently, the diagnosis of "probable Alzheimer's disease" or "Alzheimer's disease dementia" was made on the basis of the typical clinical symptoms of progressive impairments in two or more distinct cognitive areas, including memory, executive, language and visuospatial functions, resulting in impairment in daily function, with supporting neuroimaging and CSF biomarkers, the diagnosis of MCI is made on the basis of demonstrable cognitive impairment in at least one component of cognition and a patient's, informant's, or clinician's description of a deterioration in when available.

The absence of significant functional impairment, Significant work has been done to characterize the early features of mild Alzheimer's disease including MCI (and even pre-MCI)[12].

B. Parkinson's Disease [PD]

Parkinson disease is unique from AD in that it is characterized by abnormalities of motor control, as opposed to intellectual and personality changes[7]. In addition, several other factors, such as excessive caffeine intake, smoking, and exposure to environmental toxins, are known to modulate the risk of development of PD[3].

The presence of calbindin in midbrain DA neurons suggests being a marker to distinguish DA neurons with higher susceptibility to neurodegeneration in PD[2]. In PD, this significant cell loss results in dysfunction of the nigrostriatal pathway, culminating in decreased dopamine concentration within the striatum, and consequently, the cardinal motor symptoms [3]. SNc dopamine (DA) neurons exhibit elevated rates of oxidative phosphorylation, showing a three fold increase in ATP production and ROS generation in SNc compared to VTA neurons [2]. PD lead a progressive loss of neurons of specific areas of brain approximately 1–2% of the population of age ≤ 65 years is affected from PD disorder in the world[9]. The lifetime risk for PD is estimated to be 2 and 1.3% for men and women, respectively, and between 3.7 and 4.4% for “parkinsonism,” a term used to characterize other clinical conditions characterized by akinesia and rigidity that do not meet clinical or pathologic criteria for idiopathic PD (Elbaz et al. 2002)[7].

Parkinson's disease-related neurodegeneration generally starts outside the dopaminergic motor areas (in the olfactory bulb/nucleus, lower brainstem, and peripheral autonomic system), most markers are non-motor[12].

C. Huntington's Disease [HD]

Progressive motor abnormalities, behavioural problems, and cognitive deterioration are all hallmarks of HD, a hereditary neurodegenerative condition that runs in the autosomal dominant family. The cause of the disease is accepted as a CAG repeat expansion in the huntingtin gene, resulting in a long stretch of polyglutamine (PolyQ) in the encoded protein, huntingtin (Htt)[8].

A greater The striatum was shown to contain mitochondrial mass, and when compared to other areas of the brain, large mtDNA losses were seen in HD transgenic mice reduced ROS-scavenging activity[2].

D. Amyotrophic Lateral Sclerosis [ALS]

Cortical motor neurons and spinal cord's anterior horn cells degenerate in ALS, commonly known as Lou Gehrig's illness or Charcot's disease. This leads to muscle atrophy, loss of muscle control, and death resulting from respiratory failure, generally within 3-5 years of diagnosis [8]. The National Institute of Neurological Disorders and Stroke reports that only 5–10% of all ALS cases can be traced to genetics, particularly to a mutation related to the superoxide dismutase 1 enzyme. This leaves the vast majority of cases without a known etiology [7].

Amyotrophic lateral sclerosis (ALS), which causes deadly neurodegeneration, affects between 1 and 10,000 people annually. The signet of this disorder includes paralysis of voluntary muscles from the selective death of motor neurons in the brain and spinal cord[9]. 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 gradually degrade before dying in ALS. Signals that should be conveyed to the brain are no longer provided when motor neurons are killed or injured.. Although over 30 different genes have been associated with ALS, mutations in four main genes (C9orf72, TARDBP, SOD1, and FUS) account for greater than 70% of ALS cases.

These four genes encode for proteins involved in major motor function aspects such as DNA repair, homeostasis, mitochondrial function, and glial cell function [3]. This might be due to increased level of ROS, which in turn impairs both mitochondrial functionality and protein degradation, there by inhibiting the cargo activity [2].

E. Multiple Sclerosis [MS]

Multiple sclerosis (MS) is an autoinflammatory disease of the CNS characterized by white matter lesions. Although the main cause of dysfunctions is due to inflammatory processes in CNS, disease progression and especially irreversible neurological disability are associated with axonal loss[11].

Aquatherapy has been especially beneficial in patients with MS due to the reduction in the risk of falls in water[12]. It is also known that increasing cAMP levels reduces inflammatory cellular responses[11]. used an aquatherapy program to evaluate fatigue and health-related quality of life in MS[12].

1) Causes And Consequences of Neurodegeneration

While each neurodegenerative illness affects a different part of the brain and has its own individual phenotypic features, such as the progressive loss of sensory-motor and cognitive abilities, they all have a common cellular and molecular genesis. If we have a thorough understanding of the current commonalities, then we can analyse the parallels between these ailments critically and give the opportunity for therapeutic improvements that could treat several of these diseases at once between these disorders offers the potential for therapeutic advancements, which could tackle many of these diseases simultaneously if we clearly understand the commonalities existing between various neurodegenerative disorders. In this regard, neurodegeneration can be observed at several levels of neural circuitry, ranging from disturbance of intracellular protein molecules to intercellular disturbance of tissue and overall systems [1].

2) Therapies for Neurodegenerative Diseases

Promising emerging treatments for neurodegenerative diseases include stem cell therapy, gene transfer therapy, multitarget directed ligands (MTDLs), nanotechnology, and medicinal chemistry. By replacing damaged cells, stem cells can restore damaged nerve tissue. Additionally, they provide neuroprotection or foster conditions that encourage the growth of new endogenous cells. Nanotechnology-based treatment. The development of neurotherapeutic methods to prevent and treat the neuropathology of AD and PD has shown to offer considerable potential in nanotechnology. Therapy involving gene transfer. There are now a number of in vivo gene therapy methods being tested for neurodegenerative illnesses in both animal models and early human clinical trials. Strategies for the Treatment of Neurodegenerative Diseases Based on Medicinal Chemistry. Analogs, prodrugs, and codrugs are examples of techniques based on medicinal chemistry. [1]

3) Current Treatment Paradigm

Current approaches to treating neurodegenerative disorders only affect a small portion of the population and concentrate on symptomatic alleviation, with no attempt to slow the course of the disease. As a result, those affected either become permanently disabled or pass away. Presently, the Food and Drug Administration (FDA) has approved acetylcholine esterase inhibitors [Donepezil (Aricept), Rivastigmine (Exelon)], to be used as palliative treatment (see Figure 1 for action in different brain regions)[4].

MS is treated with many immuno-suppressers, which help to speed up recovery from relapse and slow down the progression of the disease. Prednisone is used to treat inflammation and prevent MS relapses. Ocrelizumab is used to treat primary progressive MS, while a few other medications, such as beta-interferon (immunomodulatory) and Ocrelizumab (neutralising), are used to treat recurrence re-emitting MS. glatiramer acetate, alemtuzumab and mitoxantrone (immuno-suppressor), Tysabri, and natalizumab, which provoke immune cells to enter into the brain[4].

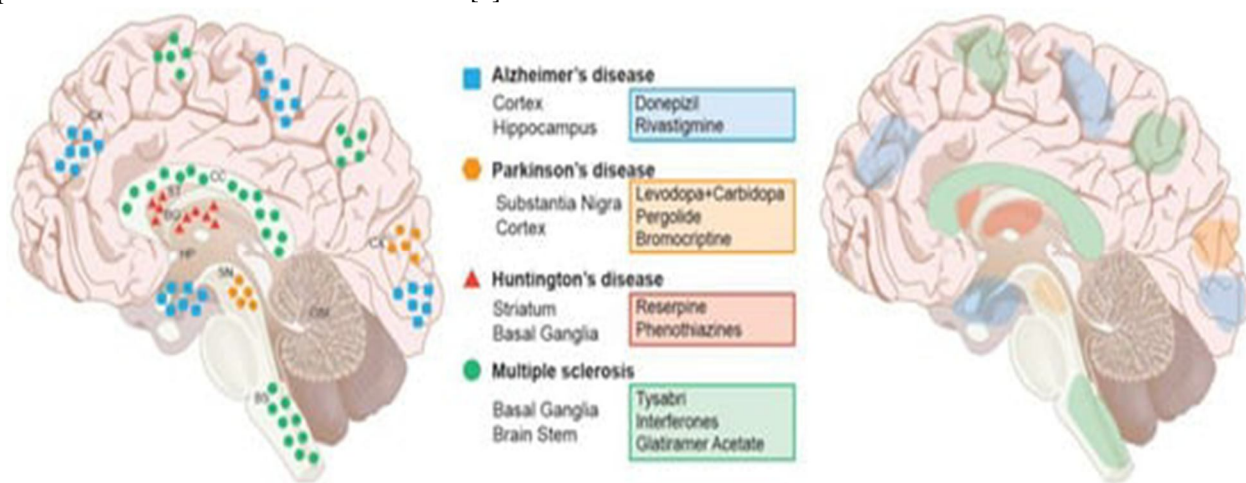


Figure 2 . Major neurodegenerative illnesses, the areas they affect, and the current treatments. In the left panel, typical regions of the brain are coloured to depict brain illnesses. Right panel: existing pharmaceutical treatments and the brain regions they affect. The following terms are abbreviations: Basal ganglion (BG), Brain Stem (BS), Cerebellum (Crbl), Corpus callosum (CC), Cortex (Cx), Hippocampus (Hp), Striatum (St), and Substantia Nigra (SN)[4].

III. CONCLUSION

In the present review, we discuss the types of neurodegenerative disorder, the recent achievements in the fields of AD, PD, HD, ALS, and MS neurodegenerative diseases appear to share several common multifactorial degenerative processes. Alzheimer's disease pathophysiology have the accumulation of amyloid-beta. In the Parkinson's disease the current therapies center on the oral administration of L-dopa and dopamine and on deep-brain the sub thalamic nucleus is stimulated. HD transgenic mice reduced ROS-scavenging activity. The ALS prevention with the study of pre-symptomatic disease in individuals at genetic risk for ALS. Stem cells are capable for repairing/preparing new in injured nervous tissue by replacing damaged of a cell.

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