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Neurodegenerative Disorders: An Overview

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ABSTRACT
As a group of diseases that are affecting an increasing number of individuals each year, neurodegenerative disorders are steadily making their way to the top of the list of global health concerns. It is even more troubling given that there is currently no recognized cure for them. Patients with these illnesses experience memory and cognitive dysfunction, which in turn impacts their motor skills. This overview briefly describes the prevalence, neuropathology, signs and symptoms, risk factors implicated, potential biomarkers, and current therapeutic approaches for several neurodegenerative illnesses. The complications associated with neurodegenerative illnesses today are highlighted in the final remark, along with some prospective solutions.
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INTRODUCTION

Neurodegeneration is the progressive loss of the structure and function of neurons over time, resulting in memory loss, poor motor coordination, and impaired cognitive functioning.Neurodegeneration manifests itself as different neurodegenerative disorders (NDD). These neurodegenerative disorders contribute to substantial mortality and morbidity, especially among the elderly, worldwide. Alzheimer's disease, Parkinson's disease, dementia, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, ataxia, multiple system atrophy, motor neuron disease, Lou Gehrig's disease, and progressive supranuclear palsy are some of the most common and fatal NDD, with Alzheimer's disease and Parkinson's syndrome being the two most common and fatal.The pathogenesis, etiology, genetics, and biochemistry of NDD are being studied by researchers. Genetic anomalies, pathogens, and environmental variables are usually the underlying causes of NDDs, but sometimes the cause remains unidentified. Neurodegenerative disorders range in severity from mild to potentially fatal, depending on the particular disorder[1, 2]. Different NDDs show a variety of pathophysiology, ranging from the deposition of amyloid proteins to the formation of Lewy bodies. Ageing is considered one of the greatest risk factors in most NDDs.

Genetics, epigenetics, protein misfolding, intracellular mechanisms, and programmed cell death are the main types of the underlying mechanisms of NDD. Huntington disease is brought on by genetic anomalies, such as the CAG repeat in mutant Huntington genes. Neurodegeneration is also influenced by certain epigenetic alterations in genes. Protein accumulation, which is caused by protein misfolding and results in proteins such as -synuclein, tau, and -amyloid, is one of the main causes of many NDDs. Neurodegeneration events are sometimes triggered by several intracellular pathways that result in decreased protein degradation of toxic protein assembly, membrane damage by -synuclein protein, DNA damage from oxidative stress, mitochondrial dysfunction, and axonal damage.Infections and injuries result in programmed cell death, such as apoptosis, autophagy, and cytoplasmic cell death, which is enhanced in neurodegenerative illnesses. Cellular malfunction and the death of neurons are the results of a complicated web of relationships between these pathways. While some of them are more common to all NDDs, such as neuro-inflammation, free radical generation, oxidative stress, and mitochondrial dysfunction, others are more specific to a particular disorder[3, 4].The present NDD therapies are effective enough to simply enhance motor abilities. Drugs that address the underlying causes of the condition and stop the progression of neurodegeneration are currently lacking. A comprehensive understanding of these disorders' underlying mechanisms is required in order to devise the most

effective and precise methods of treatment for NDD. In this overview, a few neurodegenerative diseases are briefly described.

Parkinson's disease (PD)- is another neurodegenerative disorder that is characterized by a deficit of dopaminergic neurons in the substantia nigra of the brain. The pathologic feature of PD is the existence of Lewy bodies, which are neuronal inclusions primarily composed of synuclein protein assemblies.These protein aggregations are linked to the death of dopaminergic neurons. Dopaminergic neurons function to produce and release dopamine, a neurotransmitter, and their degeneration has a direct impact on cognitive functions and motor skills. The symptoms of PD include both motor (bradykinesia, stiffness, and tremors) and non-motor signs (loss of smell, sleep disturbances, psychiatric disorders, and cognitive impairment) that can be either rapidly manifested or gradually prevalent over time[5, 6]. More than any other neurological condition, PD is leading to an increase in disability and death worldwide. In the last 25 years, PD incidence has doubled. Over 8.5 million people worldwide had PD, according to estimations from 2019. According to recent estimates, PD caused 329 000 deaths and 5.8 million disability-adjusted life years in 2019.Ageing is one of the risk factors for PD, although younger people can also be impacted. In contrast to women, men are more affected. Numerous studies have demonstrated that environmental elements, such as pesticides, air pollution, and industrial solvents, may accumulate heavy metals in Substantia nigra and raise the risk of developing PD. Furthermore, genetic factors also pose risk factors for PD and is associated with mutations in multiple genes, including α-syn, LRRK2, PINK1, Parkin, DJ-1, VPS35, and GBA1.4.Because there is a symbolic lag between maiden vandalization of dopaminergic neurons and the realization of clinical symptoms, PD is rarely diagnosed in its early stages. Finding accurate and reliable biomarkers that can differentiate PD from other diseases, track its development, or indicate a good response to a therapy is crucial. There are four basic categories of PD biomarkers:clinical, imaging, biochemical, and genetic. Some of the potential biomarkers of PD are GFAP, 8-OH-2'-deoxyguanosine, D#R and α-syn among other neurochemical biomarkers. MicroRNAs have also emerged as potential biomarkers alongside their potential diagnostic and therapeutic applications.None of the treatments appear to have a direct impact on the progression of PD. However, initial motor problems are often augmented by dopamine-based therapy, and for nonmotor symptoms, nondopaminergic treatments are necessary, like cholinesterase inhibitors for cognition and selective serotonin reuptake inhibitors for mental disorders [7, 8].Advanced therapeutics are applied, especially therapies like levodopa-carbidopa enteral suspension or deep brain stimulation that are favourable and helpful for those people who may survive and sustain obstacles like withering symptoms and operative impairment when a medication dose wears off, medication-resistant tremor, and dyskinesias. Pharmacological therapies are enriched by rehabilitation, remedial treatment, exercise, and palliative care [5–9].

Huntington Disease (HD)- is a fatal neurodegenerative disease that is hereditary and autosomal dominant. It is caused by a mutation in the huntingtin gene (HTT), which is located on the short arm of chromosome 4 at position 16.3;The mutation leads to the amplification of CAG repeats in the gene. Mutant HTT (mHTT) affects transcription, obstructs immunological and mitochondrial function, and undergoes atypical post-translational modification[10]. Neuronal migration, maturation, and cell division of the neural progenitor are all affected by the mutant HTT (mHTT). There is indication that the mHTT RNA is deleterious, and somatic CAG repeat expansion in susceptible cells promotes the disease's progression at the DNA level. Striatal GABAergic neurons are the ones most susceptible to the presence of mHTT, while significant neuronal malfunction and death also take place in the cerebral cortex. The disease is characterized by abnormalities in the motor system (such as chorea), cognitive functions, emotions, behaviour, involuntary movements, dementia, and delusions. Loss of weight, sleep issues, and autonomic problems are secondary symptoms[11, 12]. The onset of these signs andsymptoms is observed between the ages of 35 and 50 years; however, symptoms appear as early as 20 years in a very small proportion of people.The frequency of HD is 2.7 instances per 100,000 people globally, however, it varies significantly regionallydepending on the allele frequency among the population. Asian and African populations have much lower rates of HD than those in western Europe, North America, and Australia[11-13].

Genetic moderators, CAG triplet repeat length, and its instability in the huntingtin gene were classified as risk factors for the onset of HD.CAG repeat length is the most crucial risk factor out of these. Genetic, ethnic, medical history, and environmental risk factors have all been investigated for HD progression. The progression of HD seems to be most significantly influenced by genetic variables among these. The potential biomarkers for treatment and diagnosis of HD are being investigated. They are clinical (accelerated tap interval, grip force, HD-CAB); imaging (caudate volume, fractional anisotropy, mean diffusivity, thalamic FDG activity, putaminal N-acetyleaspartate, putaminal myoinositol); electrophysiological (cortical activity);neurofilament, Clusterin, and 24-hydroxycholesterol (biochemical); pharmacodynamics (mutant huntingtin levels) etc. Existing treatment for HD still

prioritizes symptom management. Drugs that lessen dopaminergic neurotransmission can treat chorea, the most noticeable symptom, along with some psychiatric symptoms. Many additional symptoms, sadly, do not improve with the available therapies. A disease-modifying medication based on molecular models has not yet been identified with much effectiveness. A new gene silencing method, however, might offer a breakthrough in the fight against this terrible illness[14, 15].

Alzheimer's disease (AD)-is defined by chronic neuronal damage that results in early moderate and later significant losses in cognitive abilities, including signs like disorientation or memory lapses. A less prevalent manifestation of AD is non-amnestic cognitive impairment, which often manifests as pronounced amnestic cognitive impairment. The hallmarks of its neuropathology are amyloid- (A) peptide extracellular deposition forming amyloid plaques and intraneuronal neurofibrillary tangles (NFT) composed of aggregated hyper- and aberrant phosphorylation of tau protein. In addition to these abnormalities, persistent neuroinflammatory processes with considerable microglial and astrocyte activation take place, which aggravate the condition. AD is the most prevalent type of dementia, accounting for 60–70% of cases. The incidence of the disease is rising as the population ages; the predicted prevalence for those aged 65 to 74 is 3%, for those aged 75 to 84 is 17%, and for those aged >85 is 32%[16, 17].

Genetics account for almost 70% of the chance of acquiring AD. However, acquired variables like diabetes, hypertension, obesity, dyslipidemia, and cerebrovascular disorders raise the chance of AD development. Aside from these, environmental factors including food, brain injury, and ageing also have an impact on AD. To improve the diagnosis and therapy of AD, the use of biomarkers plays a major role. Current AD biomarkers include CSF markers of amyloid (A) plaque buildup, such as A42 and the A42/A40 ratio, and CSF markers of tau, a key component of neurofibrillary tangles, such as phosphorylated tau and truncated tau. Some potential blood biomarkers of AD include amyloid plaques (Aβ42/Aβ40, Aβ40/Aβ42), tau proteins (T-tau), and neurofilament light chain (NfL, Plasma)

For patients with AD, there are currently only memantine and cholinesterase inhibitors available as types of drug treatment. Both raise memory and alertness, but neither affects how long AD dementia will last or how it will grow overall. The only therapies that have been shown to reduce the risk of AD and potentially prevent overall cognitive decline are lifestyle changes like diet and exercise, which are first-line guidelines for all people, irrespective of brain performance. The primary targets for prospective treatments are the pathological traits connected to AD, Aβ and p-tau. The drugs aiming for these targets are currently in the early phases of clinical trials[18, 19].

DEMENTIA- is a common neurodegenerative disorder that entails a decline in cognitive functions as a result of the biological process of ageing. Memory, reasoning, attention, comprehension, processing, learning ability, language, and judgement are all impacted. Approximately 10 million new cases of dementia are diagnosed each year, and there are already over 55 million people who suffer from the condition worldwide. Besides being a substantial contributor to impairment and dependency among older folks worldwide, dementia is presently the seventh greatest death cause among all diseases. Dementia can be caused by a number of conditions and traumas, such as AD, stroke, infections such as HIV, or even nutritional deficiencies, that either directly or indirectly impact the brain[1-3]. The most prominent type of dementia, which accounts for 60–70% of cases, is AD. Vascular dementia, dementia with Lewy bodies, and a number of illnesses that cause frontotemporal dementia is some of the other prominent kinds. The neuropathologic features of dementia vary according to its subtypes. Vascular dementia features endothelial dysfunction, atherosclerosis, small vessel disease, ischemia, and hemorrhage. Amyloid plaques, p-tau and neurofibrillary tangles, amyloid precursor proteins, and amyloid precursor protein are all found in AD.Lewy body dementia is characterized by the presence of -synuclein, Lewy bodies, amyloid plaques, p-tau, and neurofibrillary tangles.Frontotemporal dementia features TDP-43, fused in sarcoma, and p-tau inclusions. Some of these subtypes share the same neuropathological features.

Ageing is the primary risk factor for dementia, as it is for most other NDDs; however, this does not imply that dementia is only a disease of the elderly.Young-onset dementia may be defined as the symptoms developing at the age of 65, which accounts for up to 9% of cases. According to the studies, staying physically and mentally active, quitting smoking, abstaining from alcohol use, managing one's weight, eating a well-balanced nutritious diet, and maintaining normal blood pressure, cholesterol, and blood sugar levels all help people lower their risk of cognitive decline and dementia. Depression, social exclusion, low academic success, cognitive inactivity, and pollution are also risk factors for dementia[1-4].Dementia cannot currently be cured by any medication. Although many new treatments are being

researched in various phases of clinical trials, the anti-dementia medications and disease-modifying therapeutics developed to date have inadequate effectiveness and are mostly designated for AD.

CONCLUSION

Researchers have faced several challenges as a result of neurodegenerative diseases, which are quickly on the rise and are the seventh biggest cause of mortality worldwide. Effective therapies for neurodegenerative illnesses are desperately needed on a global scale. The development of early detection methods and efficient treatments for these disorders faces enormous difficulties due to the intricate nature of the molecular pathways behind neurodegeneration. Furthermore, it is extremely difficult to diagnose neurodegenerative diseases in their early stages due to their latent signs and symptoms. As a result, the disorders become incurable due to the inevitable progression of neuronal death. However, the advancement of technology offers hope for potential strategies to improve disease detection and treatment approaches. The use of artificial intelligence (AI) and machine learning (ML) holds promising possibilities in the realms of early diagnosis, prognosis, and therapeutic developments. Stem cells and stem cell therapy have a wide spectrum of applications when it comes to neurodegenerative disorders. In vitro modelling and the development of therapeutic approaches are made possible by the ability of patient-derived induced pluripotent stem cells (iPSCs) to differentiate into disease-relevant neurons. Further, the healthy cells manipulated by genome editing can be transplanted into the patient to stimulate the regeneration of neurons and glial cells. The combination of stem cell technology with genome editing, organoid engineering, and other technologies will undoubtedly hasten the creation of new treatments for human neurodegenerative illnesses, with the potential to ultimately use cell replacement therapy to treat these debilitating conditions. Once strategies to overcome the current challenges are discovered, the future appears promising for treating incurable diseases.

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