A REVIEW ON NEURODEGENERATIVE DISORDERS

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ABSTRACT:

Neurodegenerative diseases are characterized by progressive loss of neurons leading to impaired motor and cognitive function, e.g., dementia. The major diseases such as Alzheimer's, Parkinson's, Huntington's, amyotrophic lateral sclerosis, prion diseases, and multiple sclerosis all share common mechanisms for disease that involve protein aggregation, mitochondrial dysfunction, oxidative damage, and neuroinflammation. These diseases represent a rising global health burden and, in the case of their worst aspects, are exacerbated by aging populations, and are predominant in Asia. Pathogenesis is the result of complex interactions between genetic, environmental, and lifestyle determinants, including viral disease and immune imbalance. Advances in technology clinical evaluation, imaging, and fluid biomarkers, notably exosomes microRNAs enhance early diagnosis and disease monitoring. Current therapy is mainly symptomatic; however, emerging approaches involving nanotechnology-based drug delivery systems, gene and RNA therapies, immunomodulation, and multi-drugs have the potential for disease modification. Preventive strategies, especially high vitamin and antioxidant containing lifestyle and nutritional interventions, are crucial in prevention and slowing the progress. Continued research and development of multimodal diagnostics, targeted treatments, and preventions are essential to address the growing burden of neurodegenerative disease globally.

KEYWORDS: Neurodegenerative diseases, Alzheimer’s disease, Parkinson’s disease, Huntington’s disease, Neuroinflammation, Protein aggregation, Mitochondrial dysfunction, Neurodegeneration mechanisms.

1.INTRODUCTION:

Neurodegenerative diseases are caused by progressive degeneration and/or death of neurons (nervous system functioning cells). This degeneration may impair body movement and brain function, leading to dementia [1]. Neurodegenerative diseases like Parkinson's disease (PD), Alzheimer's disease (AD), and Huntington's disease (HD) are increasingly thought to share similar cellular and molecular mechanism, such as protein aggregation, mitochondria

dysfunction, and inclusion body formation. It is hard for the therapy of advanced neurodegenerative diseases because the death of neurons is irreversible [2]. Neurological diseases represent the main reason of physical and intellectual disability worldwide, presently affecting about 15% of the total population. Absolute numbers of patients have significantly increased during the last 30 years. On top of that, the burden of chronic neurodegenerative conditions is expected to at least double over the next two decades [3]. The problem of population aging occurs globally, but the process in western countries is not as rapidly accelerating as in Asia. Alzheimer's report in 2015 also indicated that Asia leads with the greatest number of individuals with dementia (22.9 million) followed by the European region (10.5 million) and the American region (9.4 million). The trend is also expected to rise if proper interventions are not being carried out. Parkinson disease (PD), the second most prevalent neurodegenerative disorder after Alzheimer disease (AD), also develops more frequently with advancing age. It is more than 1.7% of the world population aged 65 years [4]. Virus-induced neurodegeneration is significant as it describes the interaction between environmental and viral factors and CNS, and implies a critical role of immune response in neurodegeneration. Activation of the immune in the CNS, invariably occurring in viral infections, immune mediated illness, and neurodegenerative disorders, is through microglia and astrocytes that form the resident immune cells of the CNS and are vital in the regulation of brain homeostasis during development, adulthood and aging [5]. Neuroinflammation is a vital component of the progression of neurodegenerative diseases, characterized by the activation of microglia, the key immune cells that form the central nervous system. Microglia, in normal physiological states, provide neuroprotection through the expression of neurotrophic factors and the preservation of an anti-inflammatory environment, thus enhancing the health and proper functioning of neurons [6].

2.CLASSIFICATION OF NEURODEGENERATIVE DISEASES:

Neurodegenerative diseases are classified based on the type of neurons affected, molecular pathology, and clinical manifestations. They are primarily categorized into disorders affecting the central nervous system, such as Alzheimer’s, Parkinson’s, Huntington’s, amyotrophic lateral sclerosis, and prion diseases.

2.1. ALZHEIMER'S DISEASE:

The most prevalent neurodegenerative disease is Alzheimer's disease (AD), primarily in elderly people, leading to progressive cognitive deterioration, loss of memory, and behavioural disturbances. According to recent epidemiological evidence, millions of people worldwide are affected with the prevalence rising sharply with increasing age [2]. Classic features are progressive memory impairment, space-time disorientation, language impairment, and executive dysfunction. As the disease progresses, changes in behaviour and serious impairments in everyday functioning become evident, also posing significant burden to caregivers [7]. The most significant pathological features of AD are extracellular amyloid-beta (Aβ) plaques and intracellular neurofibrillary tangles (NFTs) made of hyperphosphorylated tau protein. Based on the amyloid hypothesis, ectopic cleavage of amyloid precursor protein results in insoluble Aβ plaques, which trigger disease progression [2,8]. AD is marked by chronic neuroinflammation, mitochondrial dysfunction, loss of synapses, oxidative stress, and cell death [2]. The accumulation of Aβ results in local inflammation and the formation of reactive oxygen species, further propagating neurodegeneration. Neuromodulation methods, including repetitive transcranial magnetic stimulation (rTMS) and deep brain stimulation (DBS), have indicated potential to improve cognitive functions and quality of life in patients with AD. Recent ones involve the coupling of neuromodulation with imaging, adaptive DBS, photo biomodulation, and nanoparticles to enable more targeted therapy [7].

2.2. PARKINSON'S DISEASE**:**

Parkinson's disease (PD) is the second most common neurodegenerative illness in the world, characterized primarily by static tremor, rigidity, bradykinesia, depression, anxiety, sleep disturbance, and cognitive impairment. Pathologically, PD is defined by progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta and nonspecific cortical shrinkage with sulcal widening and ventricular dilatation. A central feature in the middle of Parkinson's pathogenesis is accumulation of misfolded alpha-synuclein (α-Syn), resulting in the formation of Lewy bodies a process closely associated with PD progression and regarded as amyloid fold pathology [2]. Non motor complications such as sleep disorder, cognitive impairment, mood disorders, and autonomic dysfunction pervade advanced forms, contributing to the challenges of management [7]. PD's etiologic is multifactorial, involving environmental and genetic risk factors, oxidative stress, neuroinflammation, and mitochondrial dysfunction [9]. Neuromodulation therapies, particularly deep brain stimulation (DBS) for the subthalamic nucleus (STN) and globus pallidus internus (GPi), have proved exceptional for

advanced PD, ameliorating both motor and (to some extent) non motor symptoms. Other forms of neuromodulation under investigation for the treatment of PD are transcranial magnetic stimulation (TMS), which may have the benefit of enhancing gait and even some of the non-motor features. Pharmacologically, treatment remains largely symptomatic, with levodopa and dopamine agonists being the foundation of treatment. They are prescribed to replace or mimic dopamine, augmenting motor function [7].

2.3. HUNTINGTON'S DISEASE:

Huntington's disease is an autosomal dominant, progressive neurodegenerative disorder characterized by abnormal involuntary movements, psychiatric features, and mental decline. It is caused by a mutation that creates an expanded CAG repeat within the Huntington gene on chromosome 4, leading to toxic protein folding and neuronal loss, primarily within the striatum and cortex. Symptoms usually arise in middle life but extend from childhood to extreme old age, and include involuntary movements (chorea), dystonia, incoordination, mental disturbance, and behavioural change [8,10,11]. The early symptoms may be subtle, e.g., mood change or minimal involuntary movements [8]. Huntington's disease is autosomal dominant; so, each child of an affected parent has a 50% risk of inheriting the disorder [10,11]. Pathogenesis is mediated by a number of mechanisms including toxic protein aggregation, mitochondrial damage, oxidative stress, excitotoxicity, and transcriptional deregulation that lead to selective neuronal death. The major neuro transmitters involve dare GABA, dopamine, and glutamate [11]. At this time, treatment is symptomatic. Medications such as dopamine antagonists, depleting agents, benzodiazepines, glutamate antagonists, and others (such as deep brain stimulation, and for some, experimental fetal cell transplantation) are used to control the symptoms but not cure [8,10,11].

2.4. AMYOTROPHIC LATERAL SCLEROSIS:

Though the disease manifests as a rapid loss of motor function, ALS, also known as motor neuron disease or Lou Gehrig's disease, typically spares intelligence and personality [8,12]. The prognosis for ALS is bleak; most patients only live for three to five years after being diagnosed, and the prevalence is approximately 1-2 cases per 100,000 person years worldwide [8,10]. Clinical subgroups are linked to the most prevalent combinations of upper motor neuron presentation (primary lateral sclerosis), lower motor neuron presentation (progressive muscular atrophy), and bulbar presentation (progressive bulbar palsy) [8]. The symptoms include stiffness, hyporeflexia, fasciculation (muscle twitching), and progressive muscular atrophy [8].

Muscle weakness leading to respiratory failure is the most common cause of death [10]. Riluzole is the only approved drug that modestly extends survival by reducing damage to motor neurons. Supportive care and symptom management are crucial as the disease progresses [10].

2.5. PRION DISEASE:

Prion diseases, also known as transmissible spongiform encephalopathies, are invariably fatal neurodegenerative conditions caused by proteinaceous infectious particles without nucleic acids, referred to as prions, that cause abnormally folded endogenous prion proteins in the brain. These are characterized by accumulation and aggregation of misfolded prion proteins (PrPSc), resulting in neuronal tissue loss and spongiform changes in the central nervous system. The best-known human prion disease is Creutzfeldt Jakob Disease (CJD), an aggressive disorder with rapid progression and typically fatal within months, with mental decline, behavioural changes, involuntary movements, and marked neurologic impairment. CJD occurs in sporadic, familial, or acquired (iatrogenic) forms, and a variant form (vCJD) has been associated with ingestion of contaminated beef (bovine spongiform encephalopathy). As yet, there is no effective treatment for prion diseases, and knowledge of their pathogenesis gives important insights into other neurodegenerative conditions with prion like mechanisms such as Alzheimer's, Parkinson's and Huntington's disease [13].

2.6. MULTIPLE SCLEROSIS:

Multiple sclerosis (MS) is a chronic neurodegenerative condition defined by autoimmune mediated demyelination and inflammation within the central nervous system that leads to neuronal injury and lesions or plaques formation. MS presents with heterogeneous clinical symptoms, such as fatigue, depression, tremor, vision impairment, motor and sensory impairment, and cognitive impairment in approximately 50% of patients. The course of the disease is variable with relapsing remitting and progressive presentations, and MRI demonstrates dynamic lesions with brain atrophy of both white and grey matter [8]. Natural antioxidant polyphenols are promising candidates for modulating neuroinflammation and oxidative stress in MS and other neurodegenerative diseases and thus may be therapeutic agents [6].

3.RISK FACTOR:

Neurodegenerative diseases have several risk factors, including aging, genetic susceptibility, exposure to metals, pesticides, head injury, vascular disease, infection, and lifestyle [12,16]. Aging is the greatest risk factor for all major neurodegenerative diseases. The incidence of disease like Alzheimer's and Parkinson's rises exponentially with age [4,16]. Genetic influences have an important role. For instance, mutations in Amyloid Precursor Protein (APP), Presenilin ½ Gene (PSEN1/2), and the Apolipoprotein E(APOE4) allele are recognized risk factors for Alzheimer's disease [12,14,16]. Lifestyle risk factors of physical inactivity, smoking, excessive alcohol intake, poor diet, and lack of mental activity raise risk [16,20]. Risk factors for atheroma associated with vascular risk include hypertension, diabetes, stroke, and high cholesterol and are linked with raised neurodegenerative risk, especially for dementia [4,16]. High variability of blood pressure and midlife hypertension are particular risk factors that are modifiable for both Parkinson's disease and dementia [4]. Environment: heavy metal exposure (aluminium, manganese, lead, mercury, copper, iron, zinc) are repeatedly but inconsistently associated with greater risk, particularly in the case of occupational exposures (e.g., manufacturers, welders, miners) [12,17,19]. Pesticides, solvents, arc welding fumes (e.g., manganese), and electromagnetic fields exposure at work may increase risk. For example, farmers, welders, hairstylists, and solvent exposed individuals have increased chances of disease [12,17,19]. Air pollution and airborne toxins are contributors through direct and indirect pathways. Ultra fine particles, diesel exhaust, volatile organic compounds, and occupational industrial exposures (nano plastics) alter neuronal function, particularly in highly exposed workers [17,19]. Epigenetic modifications, such as DNA methylation and non-coding RNA changes, are suggested as mechanisms through which environmental risk factors hasten neurodegeneration [19]. Traumatic brain injury and cumulative microtrauma are significant for particular forms (e.g., chronic traumatic encephalopathy), prevalent in some occupations and military service [16,17]. Work related neuropathies, due to chronic nerve compression, repetitive strain, stretch, vibration, and awkward posture, are recognized as risk factors particularly for occupationally caused motor neuron diseases and neuropathies [15,17,19]. Decreased physical activity is independently associated with greater risk of dementia and Alzheimer's disease. Meta analysis demonstrates high activity decreases risk by ~45%, but it is unknown what the optimal dose of activity is unclear [20]. Infections (bacterial, viral, fungal), notably in immune compromised persons, are speculated to elevate risk, although strong human evidence is still scarce [12,16]. Educational attainment, social class, and occupational status are indirect modifiers. Lower educational attainment is linked with

increased dementia risk [4,16]. Psychosocial risk factors such as early life stress and depression are also linked with greater risk. Vitamin deficiency (e.g., vitamin D) and endocrine/hormonal disorders have been suggested among risk factors [12,16]. Interactions between the environment and genes are important: frequently, the risk is established by combinations of factors rather than single factors [12,14]. Olfactory dysfunction has been identified as an early biomarker and potentially associated with exposure to neurotoxic environmental agents [18].

4.PATHOPHYSIOLOGY:

Neurodegenerative diseases present progressive loss of neuronal structure and function within the central nervous system (CNS), which usually happens among older individuals in the form of Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS), and frontotemporal dementia [5,21]. The pathophysiology of these diseases is multifarious, usually entailing mechanisms such as protein misfolding and aggregation, oxidative stress, mitochondrial impairment, neuroinflammation, cytoskeletal dysfunction, and energy metabolism disturbances [21,22,23]. A key unifying factor in several neurodegenerative disorders is atypical aggregation of certain proteins (amyloid-β in Alzheimer's, α-synuclein in Parkinson's, tau in tauopathies, TDP-43 or SOD1 in ALS), into insoluble intraneuronal or extracellular aggregates, which interfere with neuronal viability and function These aggregated proteins may disrupt important cellular functions, such as axonal transport, integrity of synapses, protein degradation pathways(ubiquitin proteasome system, autophagy lysosomal degradation), and induce cellular toxicity through oligomer and fibril formation [21,22,25]. Oxidative stress, which results from imbalance between the production of reactive oxygen species (ROS) and antioxidant defences, is prevalent in neurodegenerative diseases, inducing lipid, protein, and DNA damage [21,22,23]. ROS are generated during mitochondrial impairment and chronic inflammation, which worsen with aging [23]. Mitochondrial impairment, induced by genetic and environmental insults, disrupts ATP production and raises oxidative stress, which impair neuron survival and function, particularly in high demand brain areas [21,22,23]. Neuroinflammation, initiated by chronic glial cell activation (microglia and astrocytes), is a major driver of neurodegeneration. These glial cells, in response to protein aggregates or peripheral insults, release cytokines, chemokines, and ROS, amplifying neuronal damage [5,22,26]. Inflammasomes, particularly NLRP3, play a pathogenic role in mediating neuroinflammation in the brain and periphery, including the gut; their overactivation leads to production of pro-inflammatory cytokines (e.g., IL-1β) and can be influenced by changes in gut microbiota composition [22,26]. Disruption of the blood-brain barrier (BBB), observed in

many neurodegenerative diseases and acute insults (such as viral infections), allows peripheral immune cells and inflammatory mediators to enter the CNS, exacerbating inflammation and neuronal injury [5,24]. In certain diseases, such as Alzheimer's, the abnormal post translational modification of tau (hyperphosphorylation, truncation, glycation, etc.) results in loss of its normal stabilizing effect on microtubules and induces toxicity, neuronal dysfunction, and spread of pathology across brain regions, in part through prion- like mechanisms [21,22,25]. The gut brain axis, including the microbiota inflammasome brain connection, is increasingly recognized in pathogenesis, with alterations in gut microbiota contributing to systemic and CNS inflammation via signalling pathways such as NLRP3 activation and affecting disease onset and progression [22,24,26]. Many of these disruptive cellular and molecular events result in loss of synaptic connections, impaired neurotransmission, and ultimately, selective neuronal death (by apoptosis or necrosis), which manifest as the clinical syndromes of dementia, motor impairment, or other neurological deficits [5,22,25]. Neurodegenerative pathophysiology is also influenced by systemic factors such as aging, metabolic syndromes, vascular injury, and potentially viral infections and immune dysregulation (e.g., as in the context of long COVID or peripheral immune activation) [5,24,26].

5.DIAGNOSIS:

Diagnosis of neurodegenerative diseases (NDDs) is crucial for timely intervention to slow disease progression and improve patient outcomes [27]. Diagnosis is often challenging due to subtle onset of symptoms and overlap with other conditions [8,27]. Biomarkers, both fluid based and imaging based, play a key role in differentiating NDDs, tracking progression, and classifying disease subtypes [22,28].

5.1 Clinical Diagnosis:

- Clinical diagnosis commonly relies on detailed neurological history, cognitive and motor assessments, and observation of progression patterns [22,28].
- For dementias, specific criteria exist, but clinical diagnosis in early phases is difficult, as symptoms are often misattributed to normal aging [8].
- Motor symptoms, psychiatric features, or sensory complaints are essential clinical clues for disorders such as Parkinson's disease, ALS, and multiple sclerosis [8].

5.2 Imaging Modalities

- Magnetic Resonance Imaging (MRI): Widely used for structural assessment and to exclude other causes. MRI can reveal brain atrophy patterns, especially in Alzheimer's disease (AD), detect demyelination in MS, and distinguish some movement disorders [8,28].
- Computed Tomography (CT): Used mainly to exclude other pathologies; less sensitive than MRI for parenchymal changes [8].
- Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT): Essential for detecting functional changes e.g., cerebral glucose metabolism (FDG-PET), regional blood flow (SPECT), and receptor binding [8,28].
    - PET and SPECT have high sensitivity for early detection of cognitive impairment and can help distinguish AD from frontotemporal dementia and other syndromes [8].
    - Amyloid PET and tau PET tracers offer in vivo visualization of hallmark retinopathies in AD [22,28].
- Advanced modalities: Volumetric MRI, diffusion tensor imaging, and neuromelanin sensitive imaging improve diagnostic accuracy for subtypes and early stages, but interpretation requires expertise [28].

5.3 Fluid Biomarkers:

- Cerebrospinal Fluid (CSF) Biomarkers:
    - Measurement of amyloid beta (Aβ42), total tau (t-tau), and phosphorylated tau (p-tau) in CSF is core to AD diagnosis [28].
    - Abnormal CSF protein profiles may be used to identify prion diseases (e.g., real time quaking-induced conversion (RT-QuIC) assay for Creutzfeldt-Jakob disease) [22,28].
    - Neurofilament light chain (NfL) in CSF or plasma indicates neurodegeneration but is not disease-specific [28].
- Blood Biomarkers: Aβ42/40 ratio, plasma p-tau, NfL, and others are under validation or early use for non-invasive diagnosis and screening [28].

Emerging Biomarker Technologies:

- Exosomal microRNAs: Electrochemical biosensors detecting exosomal miRNA (e.g., miR-21, miR-34a, miR-107 for AD; miR-195, miR-153, miR-133b for PD) show promise for early, minimally invasive diagnosis [27].
- Panels of fluid and imaging biomarkers, analyzed with machine learning, enable patient stratification, monitoring disease progression, and might facilitate earlier intervention [22,30].
- Disease-specific microbiota profiling, metabolic markers, and advanced omics approaches are emerging as adjunct diagnostic tools for research and clinical translation [29].

5.4 Disease-Specific Diagnosis:

- Alzheimer's Disease (AD):
  - Clinical: Progressive memory loss, cognitive impairment, often confirmed by neuropsychological testing and exclusion of alternate causes [8].
  - Imaging: MRI for hippocampal atrophy, PET/SPECT for glucose hypometabolism and Aβ/tau pathology, SPECT for perfusion mapping [8].
  - Fluid: CSF Aβ42 (decreased), CSF t-tau and p-tau (increased), plasma Aβ42/40, and plasma p-tau [28].
- Parkinson's Disease (PD):
  - Clinical: Resting tremor, bradykinesia, rigidity, supported by Presynaptic Dopamine Transporters (DAT) imaging [8].
  - Imaging: DAT, SPECT/PET is a gold standard for dopaminergic neuron loss visualization [8].
  - Fluid: No highly specific routine biomarkers; some research into α-synuclein and exosomal miRNAs [27].
- Amyotrophic Lateral Sclerosis (ALS):
  - Clinical: Combination of upper and lower motor neuron signs; exclusion of mimic syndromes [8]

- Imaging: MRI for spinal tract changes, PET for regional glucose hypometabolism [8]
- Fluid: Elevated NfL and other markers of neural injury [28].

➢ Multiple Sclerosis (MS):

- Clinical: Disseminated CNS demyelination, with relapsing or progressive course; neuroimaging is essential [8].
- Imaging: MRI is the mainstay, showing demyelinating plaques. PET and SPECT can show functional changes [8].

➢ Huntington's Disease:

- Clinical: Genetic testing is confirmatory; diagnosis suspected on the basis of motor and cognitive symptoms and family history [8].
- Imaging: PET can detect striatal glucose hypometabolism years before clinical onset [8].

5.5 Integrated, Multimodal Diagnosis and Personalized Approaches:

➢ Combining clinical evaluation, imaging, and fluid biomarkers increases diagnostic specificity and sensitivity [8,22].

➢ Future diagnosis is moving toward integrated panels (e.g., omics, microbiome, exosomes, imaging) and machine learning models for early detection, subtyping, and personalized therapy [22,30].

6.TREATMENT:

Novel Drug Therapies in Neurodegenerative Disorders:

The blood-brain barrier (BBB) markedly hinders drug delivery to the brain, making new drug delivery systems like carbon nanotubes (CNTs) and exosomes promising to improve therapeutic efficacy, target specificity, and brain penetration for treating neurodegenerative disorders [10,31]. CNTs, with high surface area and chemical versatility, and the capability to penetrate the BBB, have been developed into nano scaled structures that can deliver and release therapeutic payloads directly to targeted neuronal cells in Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD). Functionalized CNTs (e.g., PEGylated or neurotrophic factor coated) enhance neuro growth, promote neurodegeneration, and function as vehicles for gene therapy, with therapeutic

delivery and neuronal nurturing potential in models of PD, HD, and brain injuring. Dual targeted CNTs and other nanotechnology-based systems demonstrate high anti-glioma activity and encouraging results against brain tumours and neuroinflammation. Surface functionalized CNTs are more biocompatible and have lower cytotoxicity, essential for the translation of such systems into clinical environments [10]. Exosomes naturally occurring, nano-sized vesicles can be used to encapsulate proteins, mRNA, microRNA, and drugs, and cross the BBB efficiently to act as effective drug carriers for NDs. Targeted delivery of small-molecule drugs(e.g., baicalin, curcumin, quercetin), gene and RNA based therapies, has been made possible with engineered exosomes and has found success in delivering therapies directly to brain tissues in animal models, leading to decreased neuronal apoptosis, inhibited neuroinflammation, enhanced synaptic plasticity, and functional recovery in ischemic stroke, AD, and PD. Gene and RNA therapies by exosomes, including miRNA and siRNA delivery, regulate neurodegeneration pathways and increase neuronal survival in numerous ND models. Targeting ligand modification of exosomes further enhances site-directed delivery and efficiency [31]. Gene based therapies like antisense oligonucleotides (ASOs), CRISPR/Cas9 editing, and viral vector-mediated gene addition/silencing are under advanced preclinical and clinical trials for familial ALS, HD, and AD. These represent precise targeting of disease-causing mutations, modulation of pathogenic proteins (e.g., tau, APP, SOD1, HTT), and delivery of neurotrophic factors for neuronal rescue [32]. Flavonoid based drugs, because of their pleiotropic activity (antioxidant, anti -inflammatory, anti-apoptotic), are under development, sometimes in nanocarrier formulations for increased bioavailability, to target multiple ND pathologies like protein aggregation, synaptic dysfunction, and mitochondrial damage in AD, PD, HD, and ALS [33,34]. Flavonoid nano formulations (e.g., quercetin, EGCG, baicalin) delivered into exosomes or nanoparticles produce enhanced cognitive benefits, neuroprotection, and diminished plaque/tangle pathology in animal models versus free drug [31,33]. Animal and human trials indicate that early and ongoing supplementations of such compounds may be of benefit to prevention and adjunct treatment [33,34]. Multifunctional drugs novel molecules targeting several pathogenic processes (e.g., amyloid/tau interaction, redox status, neuroinflammation) are under active investigation and have potential in preclinical models. Such drugs can provide better disease modifying potential and symptomatic relief than single target agents [35]. Immunotherapies such as monoclonal antibodies against misfolded proteins (Aβ, tau, α-synuclein), active vaccines, and immune modulatory drugs are another field of new drug development in NDs and some are in late-stage clinical trials. Despite ongoing challenges (e.g., penetration through BBB, risk of

inflammation), antibody-based treatments have demonstrated potential to decrease pathological load in animal models and mild cognitive benefit in early-stage patients [36].

7.PREVENTION:

7.1 Role of Nutrition and Diet in Prevention:

Adequate nutrition is one of the principal modifiable variables in the prevention of neurodegenerative disease because a healthy diet can reduce risk factors and slow the progression of disease by lessening oxidative stress and inflammation. Both animal and human research indicate that a diet with adequate intake of vitamins B, D, E, C, K, and A is protective for the nervous system and cognitive functions. Diet, lifestyle, and environmental factors like smoking, physical inactivity, and inappropriate diet also are associated with increased risk of disease; their modification along with dietary changes is essential to prevent disease. A balanced, healthy diet (with antioxidant sources, vitamins, and minerals) promotes brain health through the elimination of oxidative stress and neuroinflammation, which are both key in the pathogenesis of neurodegenerative diseases [37,38].

7.2 Specific Vitamins in Prevention:

Water-Soluble Vitamins:

B Vitamins (B1, B2, B3, B6, B7, B9, B12):

These play a critical role in neuronal health and preventing brain atrophy, as well as in lowering oxidative stress and homocysteine (a recognized neurotoxin). Thiamine (B1) supplementation is linked with enhanced cognition and neuroprotection. Proper intake of B2 (riboflavin), B3 (niacin), B6 (pyridoxine), folate (B9), and B12 are all linked with reduced risk deficiencies cause elevated homocysteine and oxidative stress, both of which speed up neurodegeneration [37,38]. Research indicates that combined supplementation with B6, B12, and folate reduces homocysteine and decelerates cognitive impairment [37].

Vitamin C:

Vitamin C is an effective antioxidant, destroying free radicals in the brain, as well as aiding in collagen formation for vascular well-being. Pre-clinical and clinical evidence indicates elevated levels of vitamin C consumption correlate with reduced progression of Alzheimer's disease, presumably through actions on amyloid metabolism and inflammation [37,38].

Fat-Soluble Vitamins:

Vitamin D:

Plays a significant neuroprotective function by controlling neuroinflammation, promoting neuronal differentiation, and inhibiting amyloid plaque accumulation in the brain. Vitamin D deficiency is associated with higher risks and accelerated development of conditions such as Alzheimer's, multiple sclerosis, and Parkinson's; supplementation can mitigate these risks [37,38]. Clinical trials demonstrate that supplementation can enhance cognitive function and decrease biomarkers of neurodegeneration [37].

Vitamin E:

Vitamin E, particularly its alpha tocopherol component, is crucial for neuronal protection from oxidative stress, minimizing inflammation, and maintaining synaptic plasticity. Increased dietary intake and supplementation with vitamin E were associated with a diminished rate of cognitive decline in Alzheimer's and lower risk in Parkinson's disease. A few studies have indicated that the combination of vitamin E and C provides greater antioxidative properties and aids in prevention [37,38].

Vitamin A:

Retinoic acid (Vitamin A) plays a key role in synaptic plasticity, memory, and cognitive function; deficiency disrupts neuroplasticity and cognitive function. Adequate intake is linked to lower beta amyloid deposition and cognitive function; high intake, though, is toxic [37,38].

Vitamin K:

Current research associate’s greater levels of vitamin K2 with lower risk and severity of dementia and improved memory function. It is due to antioxidant defence, sphingolipid metabolism, and inhibiting inflammation that it has a neuroprotective action [37,38].

CONCLUSION:

Neurodegenerative illnesses are a growing global health problem with irreversible neuronal dysfunction leading to cognitive decline, motor dysfunction, and significant morbidity. The review suggests that while the pathogenesis of such disorders is multifactorial and intricate from protein misfolding, mitochondrial disruption, oxidative stress, neuroinflammation, and genetic and environmental risk factors, advances in clarifying these mechanisms have aided diagnostic as well as therapeutic strategies. Early identification using clinical assessment,

imaging, and fluid biomarkers, combined with novel technologies like exosomes microRNA quantitation, is crucial to improve outcome. Palliation of the symptoms is the current treatment, but new methods like nanotechnology-based drug delivery, gene and RNA therapy, immunomodulation, and multi mechanism drugs hold hope for modifying the disease. Moreover, the review emphasizes the core position of preventive interventions, particularly lifestyle and nutritional modifications, in reducing the incidence and course of disease. Finally, the article refers to the need for continued investigation of converged multimodal diagnostics and new therapeutics, as well as greater emphasis on prevention, to counter the growing weight of neurodegenerative disease among elderly populations.

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