REVIEW ARTICLE

Neuroprotective Potential of Nutraceuticals in Managing Neurodegenerative Disorders

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Abstract

Nutraceuticals, a broad category of food-derived products with possible health advantages, have attracted a lot of interest in the treatment of neurodegenerative diseases (NDDs), including multiple sclerosis, Parkinson's disease, and Alzheimer's disease. These disorders present considerable therapeutic challenges because of their complex etiology and limited treatment choices. They are characterized by progressive neuronal degeneration and related motor and cognitive impairments. Because of their capacity to alter different biochemical and molecular pathways linked to neurodegeneration, nutraceuticals play a crucial role in managing non-alcoholic fatty liver disease NDD. Important processes include control of protein aggregation, antioxidative stress, anti-inflammatory effects, and mitochondrial protection. Pre-clinical and clinical research have demonstrated the potential neuroprotective effects of compounds, such as omega-3 fatty acids, polyphenols (such as curcumin and resveratrol), and vitamins (such as Vitamin E and Vitamin D). Furthermore, as a supplementary strategy to traditional treatments, nutraceuticals have the ability to improve therapeutic results and halt the advancement of disease. Their accessibility, natural origin, and usually acceptable safety profile make them appealing candidates for long-term usage in the management of NDDs notwithstanding its potential, variables, including bioavailability, dose optimization, and response variability, pose challenges to the therapeutic use of nutraceuticals in NDDs. To create uniform dosages, clarify the mechanisms of action, and confirm their efficacy through well-planned clinical studies, more research is required.

Key words: Anti-inflammatory, antioxidative stress, neurodegenerative disorders, neuroprotection, nutraceuticals.

INTRODUCTION

A number of the most crippling illnesses impacting the elderly population are neurodegenerative disorders (NDDs), which include multiple sclerosis (MS), Alzheimer's disease (AD), and Parkinson's disease (PD). The progressive loss of neuronal structure and function that characterizes these illnesses causes severe deficits in motor, cognitive, and behavioral functions. Global healthcare systems face enormous problems as the frequency of non-communicable diseases (NCDs) rises in tandem with an increase in life expectancy. These illnesses have significant social and financial costs because they affect millions of people who need long-term care and assistance.[1]

Therapeutic alternatives that are successful for neurodegenerative illnesses are still scarce, despite significant research efforts. As whole, present pharmacological treatments do not target the underlying causes of neurodegeneration instead, they concentrate on symptom relief and temporary disease progression slowing. The complex combination of lifestyle, environmental, and genetic factors that contribute to various disorders makes it more challenging to create effective treatments. Important pathogenic characteristics include the

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build-up of misfolded proteins, including alpha-synuclein and beta-amyloid, oxidative stress, chronic inflammation, mitochondrial dysfunction, and excitotoxicity.[2]

There is rising interest in the possible application of nutraceuticals in the management and prevention of NCDs in light of these difficulties. Nutraceuticals are bioactive substances that come from food sources and have been proved to provide health benefits beyond basic nutrition. Examples of these substances include vitamins, minerals, polyphenols, and fatty acids. Due to their capacity to target several pathways linked to neurodegeneration, these chemicals have attracted interest and provide a more comprehensive strategy to managing disease.[3]

Natural origin, a typically good safety profile, and the possibility of long-term usage are what make nutraceuticals appealing. Neuroprotective effects have been shown in pre-clinical trials by several nutraceuticals, including omega-3 fatty acids, Vitamin E, resveratrol, and curcumin. By lowering oxidative stress, modifying inflammatory responses, improving mitochondrial function, and preventing the aggregation of neurotoxic proteins, these substances influence the body in a number of ways.

Nutraceuticals clinical translation faces numerous challenges. A significant obstacle being their bioavailability; a lot of nutraceuticals have quick metabolisms and poor absorption rates, which reduce their therapeutic potential. Furthermore, there is a great deal of variation in the way that people react to nutraceuticals, which can be attributed to a variety of factors, including lifestyle, gut microbiota composition, and genetics. Establishing uniform dosages and formulations, together with carrying out meticulous clinical trials, are crucial measures to confirm the effectiveness of nutraceuticals concerning neurodegenerative conditions.

The goal of this study is to present a thorough examination of the function of nutraceuticals in the treatment of neurodegenerative diseases (NDDs). It will examine the molecular processes by which these substances have neuroprotective benefits, evaluate the available data from pre-clinical and clinical research, and go over the opportunities and problems associated with incorporating nutraceuticals into treatment plans. The purpose of this analysis is to emphasize the potential of nutraceuticals as a supplemental strategy in the battle against these debilitating diseases by bridging the gap between nutritional science and neurodegenerative research.[4]

Objectives of nutraceuticals in NDDs

Examining the potential of nutraceuticals to treat several neurodegenerative disorders, such as MS, PD, and AD [Figure 1]. The goal of the present review is to evaluate the use of nutraceuticals as alternatives to conventional medicine and to investigate their mechanisms of action, clinical efficacy, and to evaluate applications of nutraceuticals in personalized medicine and their impact on Public health.[5-7]

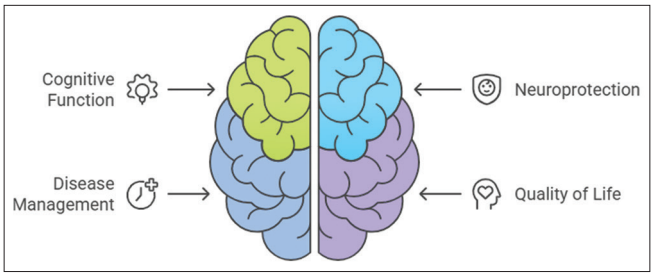

Figure 1: Objectives of nutraceuticals in neurodegenerative diseases

OVERVIEW OF NEURODEGENERATIVE DISORDERS

Key characteristics

A class of diseases known as neurodegenerative illnesses is defined by the progressive deterioration and loss of function of neurons, the nerve cells that comprise the nervous system. The cognitive, motor, and functional capacities of those with these conditions gradually deteriorate because they are usually chronic and irreversible.[8-10] The four main NDDs are amyotrophic lateral sclerosis (ALS), PD, AD, and Huntington's disease (HD).

Pathophysiology and clinical manifestations of neurodegenerative disorders

The buildup of aberrant proteins in the brain causes neuronal damage and death; clinical symptoms vary based on the type of Neurodegenerative Disorders.

AD

Characterized by the build-up of tau tangles and amyloid-beta plaques, this causes neuronal death and synaptic dysfunction, especially in the cortex and hippocampus.

Symptoms

Figure 2 the symptoms include confusion, memory loss, trouble solving problems, and ultimately the inability to carry out daily tasks.

PD

The degenerative process of dopaminergic neurons in the substantia nigra, an area of the brain critical for motor functioning, that results from the build-up of alpha-synuclein aggregation in Lewy bodies within neurons.

Symptoms

Figure 3 bradykinesia, or slowness of movement, tremors, stiff muscles, and unsteadiness in posture. Autonomic dysfunction, sadness, and sleep difficulties are examples of non-motor symptoms.

HD

Brought on by a genetic mutation that produces an aberrant Huntington protein that collects in neurons and causes atrophy throughout the brain, especially in the basal ganglia.

Symptoms

Figure 4 describes the cognitive deterioration, mental symptoms, such as melancholy and anger, and involuntary jerking or writhing motions (chorea).

ALS

Involves the degeneration of motor neurons in the brain and spinal cord, which results in atrophy and weakening of the muscles. Figure 5 Involves the degeneration of motor neurons in the brain and spinal cord, which results in atrophy and weakening of the muscles.

Symptoms

Progressive discomfort, stenosis (difficulty swallowing), dysarthria (difficulty speaking), and ultimately respiratory failure.

TO EXPLORE THE MECHANISMS OF ACTION OF NUTRACEUTICALS

Antioxidative mechanisms

Nutraceuticals, including Vitamins E and C and polyphenols, present in berries, green tea, and wine, can counteract free radicals and lower oxidative stress, which is a major factor in brain damage in NDDs by directly scavenging reactive oxygen species and boosting the activity of endogenous antioxidant enzymes, such as catalase and superoxide dismutase, these substances shield neurons from oxidative injury.[11]

Anti-inflammatory mechanism

Numerous neurodegenerative illnesses are characterized by chronic inflammation in the brain, which is mediated by microglia activation. Curcumin, resveratrol, and omega-3 fatty acids are examples of nutraceuticals that modify inflammatory pathways by lowering the expression of inflammatory enzymes (such as COX-2 and iNOS) and inhibiting pro-inflammatory cytokines (such as TNF-α and IL-6), which reduces neuroinflammation and shield neurons from harm brought on by inflammation.

Mitochondrial protective mechanisms

In NDDs, a major factor in neuronal death is mitochondrial malfunction. Coenzyme Q10, acetyl-L-carnitine, and certain polyphenols are examples of nutraceuticals that improve mitochondrial function through lowering oxidative stress in the mitochondria, stabilizing mitochondrial membranes, and increasing adenosine triphosphate generation.[12-14] These functions promote neuronal survival, preserve mitochondrial integrity, and avert apoptosis.

TO ASSESS THE PRESENT EVIDENCE FOR NUTRACEUTICALS IN NDD MANAGEMENT

Preclinical studies

Preclinical research gives early evidence of possible neuroprotective effects of nutraceuticals, which is mostly carried out in *in vitro* systems and animal models. Research has shown that in models of Alzheimer's, Parkinson's, and HDs, substances, including curcumin, resveratrol, and omega-3 fatty acids can lower oxidative stress, suppress neuroinflammation, and prevent neuronal death.[15-17] For example, curcumin has been demonstrated in animal models of AD to decrease the production of amyloid plaques, and resveratrol has been discovered in models of PD to improve mitochondrial function and decrease neurodegeneration.

Clinical studies

Transforming pre-clinical results into effective medicines requires human subjects to participate in clinical trials.[18] With differing degrees of success, a number of nutraceuticals have been studied in clinical trials.

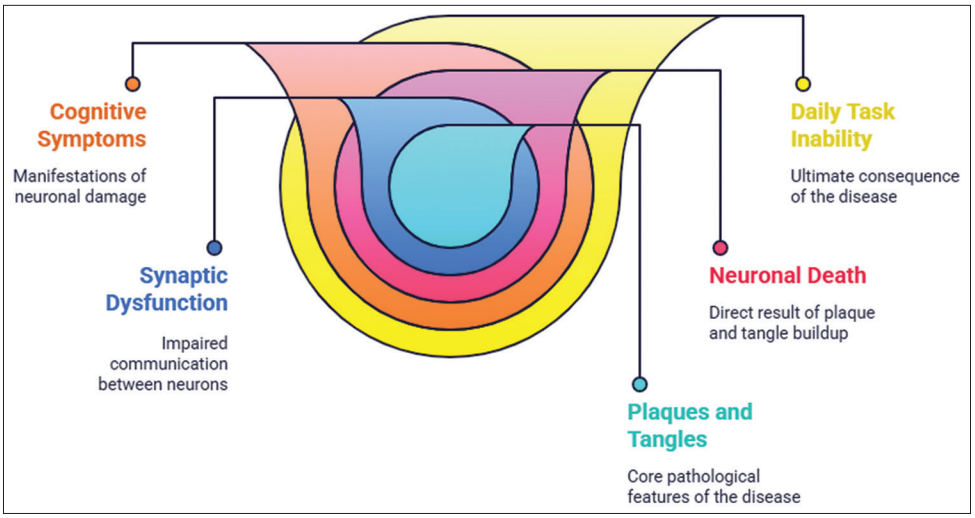

Figure 2: Progression of Alzheimer's disease progression

Curcumin

Although outcomes from clinical trials have revealed increases in cognitive function in Alzheimer's patients. The results are inconsistent, which may be the result of less bioavailability.

Omega-3 fatty acids

Numerous studies have demonstrated that omega-3 supplements may help lower the risk of cognitive decline and may even slow the early stages of AD progression.

Resveratrol

There is a need for more thorough research; however, clinical trials, including Alzheimer's patients have showed some promise, especially in stabilizing biomarkers of disease progression.

Coenzyme Q10

Although findings from clinical trials on PD have been mixed and high doses are frequently needed, some neuroprotective effects have been found.

Meta-analyses and systematic reviews

A more comprehensive knowledge of the general effectiveness of nutraceuticals in managing NDD is offered by meta-analyses and systematic reviews of clinical trials. In addition to highlighting the need for more thorough, extensive clinical trials to establish these effects, these evaluations frequently highlight the potential advantages of nutraceuticals, such as enhanced cognitive function and delayed disease development.

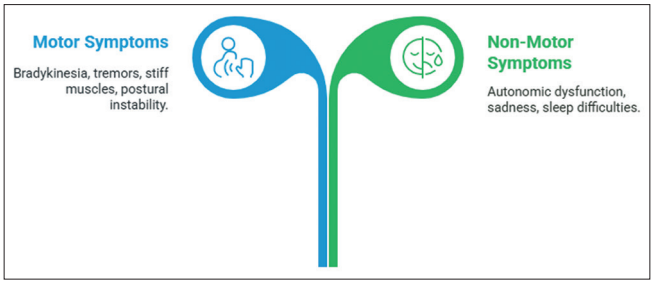

Figure 3: Unveiling Parkinson's disease

TO IDENTIFY THE CHALLENGES IN THE CLINICAL USE OF NUTRACEUTICALS

Bioavailability

The rate and extent at which the active ingredients are absorbed and used by the body is known as bioavailability, and it represents one of the major obstacles in the clinical application of nutraceuticals.[19] Numerous nutraceuticals, including resveratrol and curcumin, have low bioavailability due to their restricted absorption in the gastrointestinal tract, fast metabolism, and low solubility in water. Advanced delivery methods, such as liposomes, nanoparticles, or co-administration with bioenhancers, such as piperine, are needed to increase bioavailability.

Dosing

Determining ideal dosage for nutraceuticals is an additional difficulty due lack of defined dose standards, in contrast to pharmaceutical medications that go through extensive dosing trials. The right dose depends on the kind of nutraceutical, the illness being treated, and the patient. Furthermore, to produce therapeutic results, substantial doses could be necessary, which could be unfeasible or result in adverse effects.

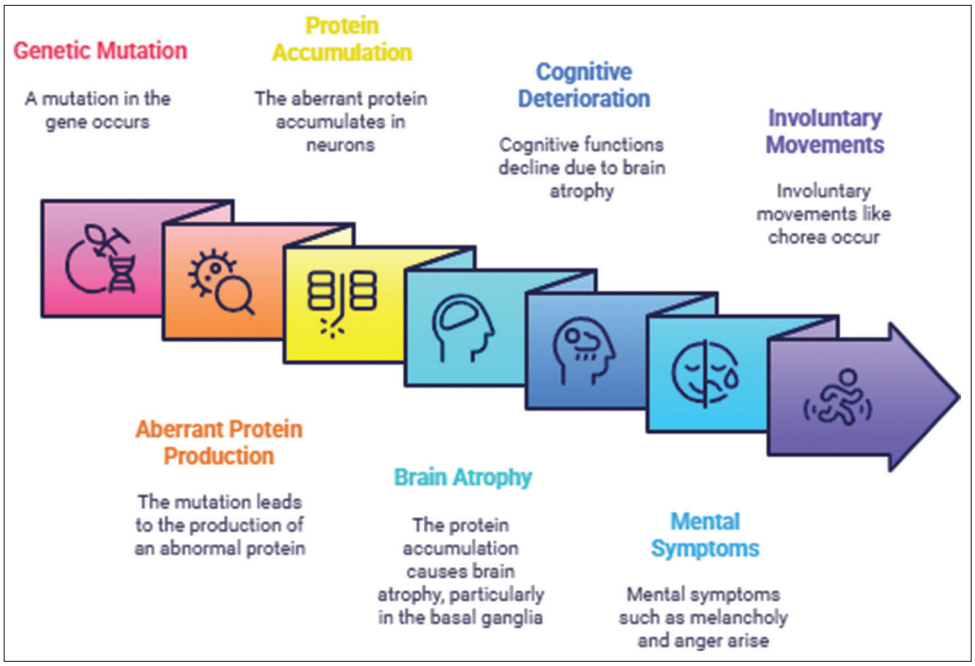

Figure 4: Huntington's disease development

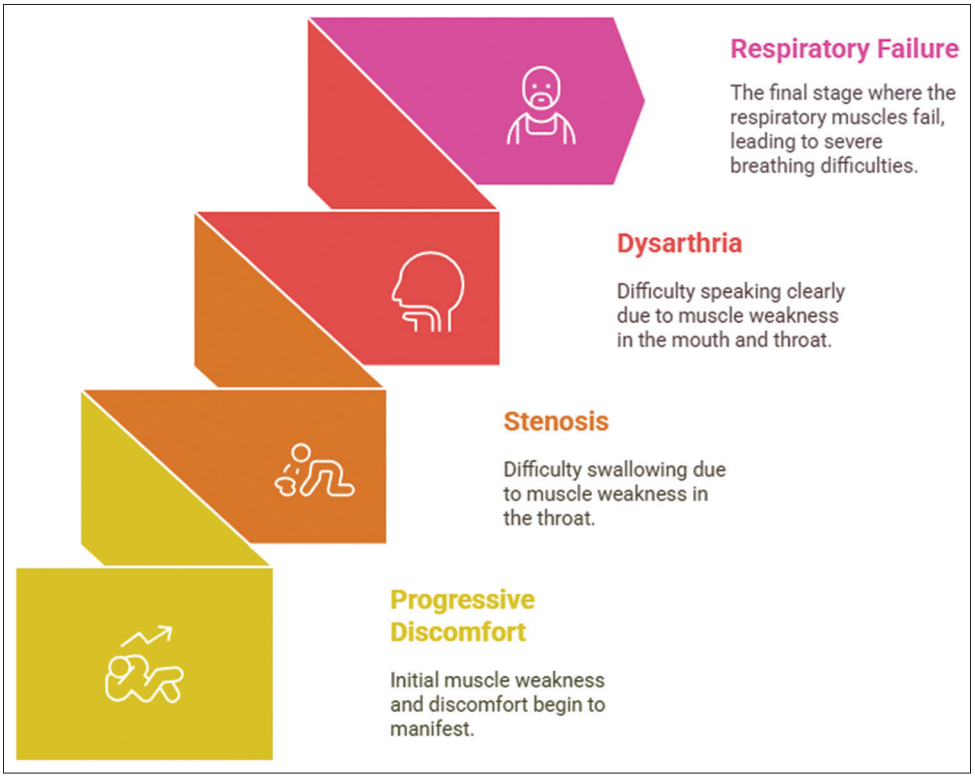

Figure 5: Progression of amyotrophic lateral sclerosis symptoms

Individual variability

Genetic variations, age, sex, food, gut microbiota, and general health can all have a substantial impact on how beneficial nutraceuticals are for a given person. It is difficult to forecast results and standardize treatment regimens because of this diversity, which also influence how an individual metabolizes and reacts to a nutraceutical. Although they are currently lacking, personalized methods to the use of nutraceuticals that take genetic and metabolic factors into consideration are necessary.

Standardized formulations

Clinical usage of nutraceuticals is severely hampered by the absence of standardized formulations. Adverse patient outcomes and inconsistent clinical trial results might arise from variations in the potency, quality, and purity of nutraceutical products. Standardization is necessary to guarantee that patients receive doses of active substances that are dependable and repeatable. The issue at hand requires the reinforcement of regulatory frameworks and quality control procedures.

Need for further clinical research

There is currently no clinical evidence to support the use of nutraceuticals in the treatment of neurodegenerative illnesses, despite encouraging pre-clinical research. Large-scale, more thorough clinical trials are required to determine the safety, effectiveness, and best use of nutraceuticals in a range of patient populations. Long-term effects and any interactions between conventional drugs and nutraceuticals should be investigated in this kind of research.

EXPLORING THE POTENTIAL OF NUTRACEUTICALS AS ADJUNCTIVE THERAPIES

Synergistic effects with pharmacological treatments

In neurodegenerative illnesses, nutraceuticals and traditional medications can boost therapeutic outcomes. In individuals with AD, for instance, it has been demonstrated that taking omega-3 fatty acids in addition to antidepressants improves mood and cognitive performance more than taking antidepressants by themselves. In a similar vein, coenzyme Q10 may improve mitochondrial activity and lower oxidative stress when used with levodopa to treat PD. This could improve motor symptoms and halt the illness's progression.[20]

Reduction of side effects

Improved patient tolerance and treatment compliance may result from using nutraceuticals to lessen the negative effects of prescription drugs. For example, long-term use of neuroprotective medications might cause oxidative damage, but certain nutraceuticals, such as Vitamin E and curcumin, have antioxidant qualities that can guard against it. Moreover, gastrointestinal adverse effects associated with non-steroidal anti-inflammatory medicines can be lessened by nutraceuticals having anti-inflammatory qualities, such as resveratrol.[21]

Enhancement of neuroprotective effects

Complex pathologies, such as as oxidative stress, inflammation, and mitochondrial dysfunction are present in many NDDs. Broad-spectrum nutraceuticals can address numerous disease pathways at once, complementing pharmaceutical therapy. For instance, combining antioxidants, such as polyphenols or mitochondrial protectors, such as acetyl-L-carnitine, with standard cholinesterase inhibitors used to treat AD may improve neuroprotection and decrease cognitive decline more effectively than using the medications alone.[22]

Improvement in quality of life

Patients with neurodegenerative illnesses may have an overall higher quality of life if their treatment regimens include nutraceuticals. Better cognitive performance, emotional stabilization, and physical well-being can be achieved with nutraceuticals by correcting dietary deficiencies and enhancing overall brain health. For instance, omega-3 fatty acids have been linked to decrease depressed symptoms and enhanced mood, both of which are prevalent in NDDs, such as MS and PD.[23]

Potential for disease modification

Nutraceuticals have the ability to influence the course of neurodegenerative illnesses, whereas many traditional treatments are symptomatic. For instance, in AD models, curcumin and resveratrol have demonstrated promise in lowering the production of amyloid plaque and tau protein aggregation, indicating they may be able to slow or change the course of the disease. These nutraceuticals may be used as adjuvant therapy to enhance present symptom-focused treatments, offering a more all-encompassing approach to illness care.[24]

TO PROVIDE RECOMMENDATIONS FOR FUTURE RESEARCH

Large-scale clinical trials

Large-scale randomized controlled trials are desperately needed to assess the safety and effectiveness of nutraceuticals in NDDs. Even while early research has showed promise, many of the studies have been constrained by small sample sizes, brief study periods, or uneven methodology. To evaluate the generalizability of findings, future research should concentrate on.[25]

Development of optimized nutraceutical formulations

To fully realize the therapeutic potential of nutraceuticals, it is imperative to enhance their stability and bioavailability. Creating cutting-edge delivery methods (such as liposomal encapsulation and nanoparticles) to improve the efficacy and absorption of nutraceuticals should be the main emphasis of research.[26] Standardizing formulas to guarantee uniformity in terms of safety, potency, and quality across various goods.

Mechanistic studies

To precisely understand the molecular and cellular mechanisms by which nutraceuticals achieve their neuroprotective benefits, more research is required. This involves figuring out which particular biochemical pathways, such as those that lessen oxidative stress, inflammation, and mitochondrial dysfunction, are targeted by various nutraceuticals.[27]

Integration into comprehensive treatment strategies

Nutraceuticals should be incorporated into more comprehensive, empirically supported therapy plans to reach their full potential in the management of neurodegenerative illnesses.

NEURODEGENERATIVE DISORDERS

Overview of neurodegenerative disorders

Neurodegenerative disorders

The progressive deterioration and loss of function of neurons, the specialized cells that make up the nervous system, is the hallmark of a set of illnesses known as neurodegenerative disorders. As a result of these illnesses, neurons that are impacted gradually suffer damage or are killed, which results in a loss in cognitive, motor, and functional capacities. Neurodegenerative illnesses, in contrast to acute neurological problems, usually progress slowly over time, are frequently chronic, and have no recognized treatment.[28]

KEY CHARACTERISTICS OF NEURODEGENERATIVE DISORDERS INCLUDE

Progressive neuronal loss

One of the main characteristics of NDDs is the progressive loss of neurons in particular brain or spinal cord regions. Disability increases as a result of this loss, which causes a slow deterioration in neurological abilities.[29-32]

Chronic nature

The majority of NDDs is chronic and deteriorate over time, with symptoms getting worse as the illness worsens.

Diverse symptoms

The particular illness and the areas of the brain that are affected determine the symptoms. Cognitive decline, memory loss, physical impairment, and behavioral or personality abnormalities are common symptoms.

Complex etiology

A combination of genetic, environmental, and behavioral variables can contribute to the exact causes of neurodegenerative illnesses, which are frequently complicated and multivariate.

Examples of neurodegenerative disorders

AD

Brain tangles and amyloid-beta plaques, as well as memory loss and cognitive impairment, are characteristic.

PD

Caused by the death of dopaminergic neurons in the substantia nigra, and characterized by tremors, bradykinesia (slowness of movement), and rigidity.

HD

Involves increasing motor dysfunction and cognitive deterioration as a result of hunting in protein mutation accumulation.

ALS

Features gradual atrophy and muscle weakness brought on by the loss of motor neurons in the spinal cord and brain.

TREATMENT APPROACHES

Early treatments

Supportive care

In the past, supportive care, which aimed to control symptoms and enhance quality of life, was the only available treatment for neurodegenerative illnesses.[33] Occupational therapy, physical therapy, various herbal therapies, and supportive interventions were used as early forms of treatment.

PHARMACOLOGICAL DEVELOPMENTS

Symptomatic treatments

The 20th-century witnessed the creation of pharmaceutical therapies meant to reduce symptoms. For instance, levodopa became a vital component in the treatment of PD symptoms, while cholinesterase inhibitors, such as donepezil, were introduced to improve cognitive performance in patients with AD.[34]

Disease-modifying research

The goal of more recent research has been to create disease-modifying treatments that go after the fundamental causes of neurodegeneration. This includes medications for PD and neuroprotective treatments for AD that try to lower the buildup of amyloid-beta in the brain.

CLASSIFICATION OF NEURODEGENERATIVE DISORDERS

AD

Key characteristics

Prevalence

With AD accounting for 60–80% of dementia cases, it is the most prevalent type of dementia.

Onset

Normally appears in late life, after the age of sixty-five, while varieties with an earlier onset may appear earlier.

Progression

A progressive deterioration in cognitive abilities, impacting language, thinking, and memory, is the hallmark of AD.

Pathophysiology

Amyloid plaques

Amyloid-beta plaque buildup in the brain is a defining feature of AD. These plaques are made up of amyloid-beta peptide clusters that obstruct neuronal transmission and cause inflammatory reactions.

Neurofibrillary tangles

The presence of intracellular aggregations of hyperphosphorylated tau protein, known as neurofibrillary tangles, is another distinguishing feature. Microtubule stability and neuronal function are compromised by these tangles.

Neurodegeneration

Particularly in the cortex and hippocampus, the co-occurrence of tau tangles with amyloid plaques results in extensive nerve loss and atrophy.

Clinical manifestations

Cognitive decline

Language difficulties and memory loss are among the early symptoms.[35] Patients have severe deficits in executive function, problem-solving, and spatial orientation as the disease worsens.

Behavioral changes

Behavior abnormalities, mood fluctuations, and personality changes are possible in patients.

Functional impairment

As the condition progresses, people need help with everyday tasks, including eating, dressing, and maintaining personal hygiene.

PD

Key characteristics

Prevalence

PD is the second most common neurodegenerative disorder, affecting approximately 1% of people over the age of 60.

Onset

Although there may be early-onset types, symptoms usually start to show after the age of 60.[36]

Progression

PD is typified by increasing motor symptoms that can also impair non-motor abilities.

Pathophysiology

Dopaminergic neuron loss

A major characteristic of PD is the destruction of dopaminergic neurons in the substantia nigra, a crucial area of the basal ganglia. Dopamine is a neurotransmitter that is essential for coordinating movement, and this causes a deficit in it.[37]

Lewy bodies

Lewy bodies, which are intracellular inclusions made of clumped alpha-synuclein protein, are another distinguishing feature. The malfunction and death of neurons are facilitated by these inclusions.

Clinical manifestations

Motor symptoms

Tremor (resting tremor), Bradykinesia (slowness of movement), rigidity (stiffness of the muscles), and postural instability (difficulties with balance) are the hallmarks of PD.

Non-motor symptoms

Non-motor symptoms that include mental problems (such as anxiety and sadness), sleep difficulties, and autonomic

dysfunction (such as constipation and orthostatic hypotension) can also be experienced by patients.

HD

Key characteristics

Prevalence

A rare hereditary condition called HD affects 5–10 persons worldwide for every 100,000 people.

Onset

The typical age range for symptoms to manifest is between 30 and 50, while younger variants can manifest sooner.

Progression

Progressive motor, cognitive, and mental symptoms are hallmarks of HD.

Pathophysiology

Genetic mutation

An enlarged CAG repeat in the Huntington protein is the result of a mutation in the HTT gene that causes HD. A poisonous protein is produced as a result of this mutation, and it builds up in neurons.

Neuronal degeneration

Selective neuronal death results from the build-up of mutant huntingtin protein, primarily in the striatum (a region of the basal ganglia) and, to a lesser degree, in the cortex.

Clinical manifestations

Motor symptoms

Dystonia, or muscle contractions, chorea, or involuntary, erratic movements, and issues with motor coordination are the hallmarks of HD. Deterioration of motor control over time results in severe impairment.

Cognitive symptoms

Progressive cognitive deterioration affects the patients, causing issues with memory, problem-solving, and executive function.[38,39]

Psychiatric symptoms

Anxiety, anger, and depression are typical mental health symptoms.

ALS

Key characteristics

Prevalence

ALS affects 2–5 persons/100,000.

Onset

Typically, symptoms start in middle adulthood, between the ages of 55 and 65.

Progression

Muscle weakness and atrophy result from the progressive loss of motor neurons in the brain and spinal cord, which is the hallmark of ALS.

Pathophysiology

Motor neuron degeneration

Both lower motor neurons (found in the brain stem and spinal cord) and upper motor neurons (found in the cortex) degenerate in ALS. Atrophy, spasticity, and muscular weakening are the outcomes of this.

Protein aggregates

In ALS patients, abnormal protein aggregates, such as TDP-43 and SOD1 are frequently seen, and they play a role in the destruction of neurons.

Clinical manifestations

Motor symptoms

Muscle twitching, cramping, and weakness are among the early symptoms. As the illness worsens, patients have extreme muscular weakness and have trouble breathing, swallowing, speaking, and speaking.

Cognitive and behavioral changes

Along with motor symptoms, some individuals may also experience behavioral and cognitive abnormalities, though these are less severe.

CONCLUSION

Nutraceuticals possess a great deal of promise for treating NDDs, offering further advantages through anti-inflammatory, anti-oxidant, and neuroprotective processes. Certain substances, such as Vitamin D, curcumin, and omega-3 fatty acids, have demonstrated promise in symptom relief and brain health maintenance. However, the data supporting their effectiveness are frequently sparse and inconsistent, with conflicting findings from clinical trials. Their use is complicated by factors, such as bioavailability, inconsistent product quality, and regulatory considerations. Notwithstanding these difficulties, nutraceuticals can be beneficial when included in all-encompassing therapy programs that are customized to meet the wants of certain patients. To elucidate their mechanisms, improve dosages, and validate long-term safety and efficacy, more research is necessary. Their use will be further increased by improved standardization and quality control, which will ultimately lead to improved management of neurodegenerative disorders.

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