

## Genetic and Degenerative Neurological Disorders – an Emphasis on Alzheimer's, the Mystery

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### Abstract

Neurologic diseases are disorders of the brain, spinal cord and nerves throughout the body. Neurological Disorders have a major emotional, mental, social and economic impact on the lives of patients, as well as their families. The incidence of age-related neurological diseases is continuously increasing primarily due to the increased life expectancy of the general population of many developed nations. One of the more prevalent and debilitating neurological disorders is Alzheimer's disease (AD). AD involves an economical and emotional cost; hence the understanding of aspects related with AD prevalence, risk factors and potential interventions are topics of significant importance for medical attention and public health.

**Keywords:** Neurological Disorders; Genetic Disorders; Leukodystrophies; Phenylketonuria; Tay-Sachs Disease; Wilson's Disease; Huntington's Disease; Multiple Sclerosis; Myasthenia Gravis; Degenerative Disorders; Parkinson's Disease; Epilepsy; Stroke; Schizophrenia; Autism; Neuropathies; Alzheimer's Disease

**Abbreviations:** PKU: Phenylketonuria; WD: Wilson disease; HD: Huntington's disease; CNS: Central Nervous System; MS: Multiple Sclerosis; MG: Myasthenia gravis; AChRs: Acetylcholine Receptors; PD: Parkinson's disease; IP: Ischemic penumbra; ASD: Autism Spectrum Disorder; DN: Diabetic neuropathy; CIDP: Chronic inflammatory demyelinating polyneuropathy; HAART: Highly Active Anti-Retroviral Therapy; DSP: Distal Symmetric Polyneuropathy; NMBAs: Neuromuscular Blocking Agents; MMSE: Mini Mental State Examination; AD: Alzheimer's disease; APP: Amyloid Precursor Protein; PS-1: Presenilin-1; PS-2: Presenilin-2; EC: Entorhinal Cortex; DGy: Dentate Gyrus; neurofibrillary tangles (NFTs); A $\beta$ : Amyloid  $\beta$ ; APOE: Apolipoprotein-E; A $\beta$ PP: Amyloid  $\beta$ -Protein Precursor; FDG-PET: Fluorodeoxyglucose-Positron Emission Tomography; MCI: Mild Cognitive Impairment

### Introduction

Neurologic diseases are disorders of the brain, spinal cord and nerves throughout the body [1]. There are more than 600 neurologic diseases. Neurological diseases are defined as an inappropriate function of the peripheral or central nervous system due to impaired electrical impulses throughout the brain or nervous system [2]. Deterioration in neurological function is accompanied by significant decrease in the global quality of life in patients [3]. Genetic disorders are the diseases caused by defects in the genes and they affect the development and functioning of the brain. Degenerative diseases are the diseases where nerve cells are damaged or die. These brain disorders can cause serious problems that affect the nervous system. Some are life-threatening. One of the more prevalent and debilitating neurological disorders is Alzheimer's disease (AD). Alzheimer's disease is a progressive neurodegenerative disease for which no cure exists.

### Genetic Disorders

A genetic disorder is a disease caused by a different form of a gene, called a variation, or a change in a gene, called a mutation. Genetic brain disorders specifically affect the development and functioning of

the brain. Many people with genetic brain disorders fail to produce enough of certain proteins that influence brain development and function. These brain disorders can cause serious problems that affect the nervous system. Some are life-threatening. Some genetic brain disorders are due to random gene mutations or mutations caused by environmental exposure. Other disorders are inherited, which means that a mutated gene or group of genes is passed down through a family. Genetic brain disorders include leukodystrophies, phenylketonuria, Tay-Sachs disease, Wilson disease, Huntington's disease and muscular dystrophy.

*Leukodystrophies* are rare diseases that affect the cells of the brain. Specifically, the diseases affect the myelin sheath, the material that surrounds and protects nerve cells. Damage to this sheath slows down or blocks messages between the brain and the rest of the body. Demyelinating diseases, or leukodystrophies, encompass a wide spectrum of inherited neurodegenerative disorders affecting the integrity of myelin in the brain and peripheral nerves [4]. *Phenylketonuria* (PKU) is a genetic disorder in which the body can't process part of a protein called phenylalanine (Phe). Phe is in almost all foods and if the Phe level gets too high, it can damage the brain and cause severe mental retardation. Phenylketonuria is the most prevalent disorder caused by an inborn error in amino acid metabolism [5]. *Tay-Sachs disease* is a rare, inherited disorder. It causes too much of a fatty substance to build up in tissues and nerve cells of the brain. This buildup destroys the nerve cells, causing mental and physical problems. Tay-Sachs disease is an autosomal recessive disease caused by a deficiency of  $\beta$ -hexosaminidase, an enzyme [6].

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*Wilson disease* (WD) is a rare inherited disorder that causes body to retain copper. Wilson disease is also known as hepatolenticular degeneration [7]. It is an autosomal recessive disorder of copper transport, resulting in copper accumulation and toxicity to the liver and brain [8]. *Huntington's disease* (HD) is an incurable, hereditary brain disorder. It is a devastating brain disorder for which there is no effective treatment. Nerve cells become damaged, causing various parts of the brain to deteriorate. The disease affects movement, behavior and cognition - the affected individuals' abilities to walk, think, reason and talk are gradually eroded to such a point that they eventually become entirely reliant on other people for their care. Huntington's disease has a major emotional, mental, social and economic impact on the lives of patients, as well as their families. It is also called Huntington's chorea. HD is a rare neurodegenerative disorder of the central nervous system [9]. It is an autosomal dominant disorder that usually begins in mid life and is characterized by involuntary movements, psychological changes and dementia [10].

*Multiple Sclerosis* (MS) is a chronic autoimmune inflammatory disorder of the central nervous system (CNS) [11]. MS is a neurological disease that occurs when the insulating material i.e., myelin around nerve cells in the central nervous system is damaged. It is caused by autoimmune reactivity of T cells towards CNS myelin components. MS progression inevitably leads to the loss of motor function, sensitive disturbances and cognitive impairment because of the immune mediated demyelination and axon degeneration. MS is one of the most common neurological disorders, which mainly affects young adults [12], and causes gradual decrease of their quality of life [13]. Infectious organisms, most likely viruses, have long been a suspect for triggering the autoimmune response in people genetically susceptible to MS [14]. *Myasthenia gravis* (MG) is an autoimmune disorder that causes weakness and fatigue of skeletal muscles [15]. Muscle weakness is caused by the blockade of neuromuscular transmission by antibodies against nicotinic acetylcholine receptors (AChRs), which are located in the post-synaptic membrane of the neuromuscular junction [16].

## Degenerative Disorders

Degenerative diseases are the diseases where nerve cells are damaged or die. *Parkinson's disease* (PD) belongs to a group of conditions called motor system disorders, which are the result of the loss of dopamine-producing brain cells. Parkinson's disease is a disorder of the brain that leads to tremors and difficulty with walking, movement, and coordination. Parkinson's disease most often develops after age 50 and sometimes occurs in younger adults. PD is a common neurodegenerative disorder with a lifetime incidence of approximately 2 percent [17]. Current concepts of the cause of Parkinson's disease (PD) suggest a role for both genetic and environmental influences [18]. *Epilepsy* is one of the seizure disorders and a serious neurological disorder that affects a wide range of people throughout the world. It is a disorder of brain characterized by unpredictable and periodic occurrence of a transient alteration of behaviour due to the disordered, synchronous and rhythmic firing of populations of brain neurons [19]. Current opinion in the treatment of epilepsy is to avoid the use of blood level determination and to rely almost exclusively on the clinical picture [20].

*Stroke* happens when blood flow to a part of the brain stops. A stroke is sometimes called a "brain attack" [21]. It is the leading cause of death and disability worldwide. Stroke rates increase dramatically in older age groups [22]. In Ischemic penumbra (IP), regions of brain tissue reduced blood flow results in hypoxia and dysfunction of physiologic function,

but not severe enough to cause irreversible damage and necrosis in an acute ischemic stroke [23]. Affective and behavioral neuropsychiatric disturbances are frequently encountered in post-stroke patients [24]. Stroke is a vascular disorder that adversely affects neurons to cause ischemic brain injury. Hyperglycemia is common in acute stroke [25]. *Schizophrenia* is a complex psychiatric disorder characterized by perceptual abnormalities including hallucinations and delusions, conceptual disorganization and cognitive impairment [26]. *Autism* is a developmental disorder. Children with Autism Spectrum Disorder are often characterized by deficits in social communication skills [27]. Autism Spectrum Disorder (ASD) cannot be diagnosed easily [28]. The developing nervous system varies in susceptibility depending on stage of development [29].

*Neuropathies* are the damages that occur to a single nerve or nerve group, which results in loss of movement, sensation, or other functions of the nervous system. There are many types of Neuropathies. Neuropathy is one of the major complications of diabetes and affects the patients' quality of life [30]. Diabetic neuropathy (DN) is a chronic diabetes complication and is known to be heterogeneous regarding symptoms, pattern of neurologic involvement, pathologic alterations, underlying mechanisms and progression in time [31]. Chronic inflammatory demyelinating polyneuropathy (CIDP) is considered to be an autoimmune disorder of the peripheral nervous system [32]. Colitis is an extremely complex illness involving multiple levels of interaction between the neural, immune, and endocrine systems [33]. The use of some dideoxynucleotide analogues in Highly Active Anti-Retroviral Therapy (HAART) in AIDS patients may also lead to distal symmetric polyneuropathy (DSP) [34]. Postoperative residual paralysis remains a common occurrence following the use of neuromuscular blocking agents (NMBAs) [35]. Neurologic complications associated with spinal anesthesia can cause direct neural tissue damage [36].

There is a fast development in the various diagnostic and treatment methods for neurological disorders. Mini mental state examination (MMSE) is widely used as a brief objective assessment of cognitive function and as a measure of changes in cognitive status [37]. The excitability of the nerve can be measured by nervous conduction velocity [38]. A growing interest in the use of adult stem cells for the treatment of several neurological disorders has been developed over the last few years [39]. Neural plasticity, also known as brain plasticity or cortical plasticity refers to the structural and functional reorganization ability of brain and nervous system as a result of input from the environment [40].

## Alzheimer's disease, The Mystery

Alzheimer's disease (AD) is a form of dementia in which patients develop neurodegeneration and complete loss of cognitive abilities and die prematurely [41]. Apart from loss of memory and cognitive abilities in Alzheimer's patients, even the personalities may change dramatically [42]. Alzheimer's disease is characterized by a widespread functional disturbance of the human brain [43]. Alzheimer disease (AD) has been considered as the Century's disease. AD is a degenerative disease that is progressive loss of nervous cells. At a neuropsychological level, it affects different cognitive processes as memory, language, praxis, gnosis and executive functions. Functionality and quality of life are also affected in people with AD [44]. Alzheimer's disease (AD) is a genetically heterogeneous and insidiously progressive form of dementia in which more than 50 genetic loci are involved. Therefore, AD may represent a common phenotype that results from various genetic and environmental influences [45].

It is now understood that genetic factors play a crucial role in the risk of developing Alzheimer's disease (AD). Rare mutations in at least 3 genes are responsible for early-onset familial AD [46]. Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder that in a minority of cases (familial AD), is due to a specific mutation in one of the following three genes: *app*, *ps-1* and *ps-2* [47]. Missense mutations in amyloid precursor protein (APP), PS-1 (presenilin-1 situated on chromosome 14), PS-2 (presenilin-2 situated on chromosome 1) genes alter the proteolysis of APP and increase the generation of A $\beta$ 42 (amyloid  $\beta$ -42). There is an urgent need for biomarkers to diagnose neurodegenerative disorders early in like AD, when therapy is likely to be most effective, and to monitor responses of patients to new therapies [48]. Two important AD targets are the hubs of the memory-encoding machinery, the entorhinal cortex (EC) and the hippocampal dentate gyrus (DGy) granule cells [49].

Alzheimer's disease is a progressive neurodegenerative disorder characterized by deposition of amyloid plaques composed of aggregated amyloid beta plaques, and neurofibrillary tangles composed of hyperphosphorylated tau that leads to synaptic defects resulting in neuritic dystrophy and neuronal death. Dementia-associated neuropsychiatric symptoms, such as depression and apathy, are core features of Alzheimer's disease (AD). Pathological hallmarks of AD include senile plaques, neurofibrillary tangles (NFTs), and neurodegeneration. Alzheimer's disease (AD) is characterized by progressive cognitive impairment as a consequence of extensive neuronal loss. Almost all patients diagnosed with AD develop dementia-associated neuropsychiatric symptoms at some stage during their disease. A $\beta$  peptides are produced from amyloid precursor protein (APP) by combination cleavages with  $\beta$ -secretase and  $\gamma$ -secretase. The accumulation of A $\beta$  in brain is a primary event driving other AD pathogenesis, such as NFTs formations and neuronal loss (amyloid cascade hypothesis) [50].

The number of people affected by dementia is becoming a public and socioeconomic concern in many countries all over the world. The most significant susceptibility gene for AD is the apolipoprotein-E (APOE) gene [51]. The deposition and aggregation of amyloid  $\beta$  (A $\beta$ ) peptides are hallmarks of Alzheimer's disease (AD). The most important genetic risk factor for late-onset AD was identified as the APO $\epsilon$ 4 allele [52].

Oxidative stress has been implicated in mechanisms leading to neuronal cell injury in various pathological states of the brain. Many studies suggest that oxidative damage is one of the factors in the neuronal death underlying the loss of cognition. Nutritional status in older adults also plays an important risk factor for the cause of AD. It could also result from acceleration of the normal ageing process in brain regions particularly sensitive to free radical damage. Antioxidants could, therefore, play an important role in preventing the deleterious actions of free radicals in brains. Most of the antioxidants measured were lower in the AD patients compared to the controls [53].

There are strong connections among mitochondria, aging, and Alzheimer's disease (AD) [54]. It has been suggested that mitochondrial dysfunction is relevant to Alzheimer disease (AD) and some mitochondrial haplogroups could be related to the risk of AD [45]. Cognitive decline most commonly associated with Alzheimer's dementia can also result from other conditions including cerebral ischemia or brain trauma. One of the more prevalent and debilitating neurological disorders is Alzheimer's disease (AD). AD is the leading cause of dementia among the elderly and is characterized by the presence of amyloid plaques, extensive neuronal death and shrinkage of the brain [55].

Altered levels of amyloid  $\beta$ -protein precursor (A $\beta$ PP) and/or amyloid beta (A $\beta$ ) are characteristic of Alzheimer's disease (AD). These proteins serve as valuable blood-based biomarkers for assessing disease severity and pharmacological efficacy. The dysregulated expression of A $\beta$ PP (Amyloid  $\beta$ -protein precursor) and its proteolytic products has been implicated in the pathology of AD. A $\beta$  senile plaques are found in brain autopsy tissue from individuals with Alzheimer's disease [56]. AD patients were shown to have lower serum A $\beta$  levels compared with control subjects [57]. A progressive reduction in neuronal activity, as indexed by fluorodeoxyglucose-positron emission tomography (FDG-PET) scan analysis, is an early characteristic of Alzheimer's disease (AD) that is correlated with cognitive decline and highly predictive of conversion from mild cognitive impairment (MCI) to AD [58].

Developing new therapies for Alzheimer's disease (AD) is critically important to avoid the impending public health disaster imposed by this common disorder. Biomarkers play an increasingly important role in AD drug development [59]. The development of targeted drug delivery will improve therapeutic efficacy through reductions in drug dosing intervals, and diminished toxicities [60]. Alzheimer's disease is a progressive neurodegenerative disease for which no cure exists. There is a substantial need for new therapies that offer improved symptomatic benefit and disease-slowng capabilities [61].

## Conclusion

The neurological disorders have a greater effect on the quality of life. Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder which doesn't have a cure. Alzheimer's is a progressive disease, where dementia symptoms gradually worsen over a number of years. Although current Alzheimer's treatments cannot stop Alzheimer's from progressing, they can temporarily slow the worsening of dementia symptoms and improve quality of life for those with Alzheimer's and their caregivers. Today, there is a worldwide effort under way to find better ways to treat the disease, delay its onset, and prevent it from developing.

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