Review Article

PARKINSON'S DISEASE: A REVIEW

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ABSTRACT

Parkinson's disease or simply Parkinson's, is a long-termdegenerative disorder of the central nervous system that mainly affects the motor system. The symptoms usually emerge slowly, and as the disease worsens, non-motor symptoms become more common, Cognitive and behavioral problems may also occur with depression, anxiety, and apathy occurring in many people with PD. While there is no cure, various treatments have been developed to help manage the symptoms of PD. Management of PD is a growing field and targets new treatment methods, as well as improvements to old ones. Pharmacological, surgical, and therapeutic treatments have allowed physicians to treat not only the main motor symptoms of PD, but target patient-specific problems as they arise.

Keywords: Neurodegeneration, Quality of life, Disease.

INTRODUCTION

Neurodegenerative diseases pose a significant threat to human health. Such illnesses, impacting people of all ages, are one of the most important medical and socio-economic issues of our time and have a major impact at professional, social and family level of patients and can lead to a complete inability to carry out any type of everyday activity. Major problem is that these disorders are normally detected late and restricting the efficacy of the treatment options.[1]

Such age-related illnesses are increasingly prevalent, partially because the population of the elderly has increased in recent years.[2] As a result of progressive neuronal degeneration and/or death. This deterioration can affect body movement and brain function, causing dementia. These diseases are one of the most important medical and socio-economic problems of our time, affecting people of all ages. Diverse disorders can include: Parkinson's disease (PD); Alzheimer's disease (AD); Amyotrophic Lateral Sclerosis (ALS); Multiple Sclerosis (MS); Huntington's disease (HD); Machado-Joseph's disease; Amyloid Polyneuropathy Family. Being the best known, Parkinson's and Alzheimer's disease.[1]

Neurodegenerative disorders are a heterogeneous group of diseases of the nervous system, including the brain, spinal cord, and peripheral nerves that have much different aetiology. Many are inherited, some are secondary to toxic or metabolic processes, but others are infected. Due to the prevalence, morbidity, and mortality of the neurodegenerative diseases, they represent significant medical, social, and financial burden on the society. These are characterized neuropathologically by disorders in relatively specific regions of the brain and particular neuron populations.[3]

PARKINSON'S DISEASE

Parkinson's disease (PD), or paralysis agitans, is a common neurodegenerative condition, which typically develops between the ages of 55 and 65 years. This disease was first named and described by James Parkinson in 1817. The progression of this disease is gradual and prolonged. It has a plausible familial incidence, although the estimates of these occurrences are low and usually sporadic. This disease is organized into two classifications: genetic and sporadic. Genetic PD follows Mendelian inheritance. Sporadic PD, which accounts for about 90% of all Parkinson's cases, is a more complex category in which the pathogenic mechanisms that underlie it are not yet fully understood. Nonetheless, it is known that the byzantine interactions of genetic and environmental influences play roles in the determination of sporadic PD. Several subtypes of PD exist. Each has its own set of causative factors and susceptibilities, pathology, and treatment courses.[4]

PD is a progressive neurological condition characterized by a wide variety of motor and non-motor symptoms that can have a variable effect on function.[5] It happens when nerve cells in the brain don't produce enough of a brain chemical called DA.[6] PD's pathological hallmark is cell loss within the substantia nigra which affects the ventral component of the par's compacta in particular. At the time of death, this area of the brain has lost 50–70 per cent of its neurons compared to the same area in unaffected persons. In the medulla oblongata / pontine tegmentum and olfactory bulb the earliest recorded pathologic changes in PD were reported.[7]

It is often inherited, although most cases do not tend to occur within families. Environmental exposure to chemicals may play a part. Symptoms slowly begin, typically on one side of the body. Later they affect both sides.[8] Cardinal Symptoms of PD (bradykinesia, resting tremor, rigidity and postural instability) manifest due to the relatively selective loss of nigrostriatal DA neurons that are important for regulating motor function.[9] there are other signs besides these four cardinal motor symptoms which are also included in the diagnosis process. The non-motor symptoms are often more stressful for the person living with Parkinson's. Non-motor symptoms such as pain, depression, memory and sleep issues can also occur and affect the person with Parkinson's day-to-day life.[10]

CLINICAL CHARACTERISTICS OF PD

The cardinal signs of PD are shaking, rigidity, slowness and deprivation of movement. The disorder leads to physical symptoms like resting tremor, rigidity on passive movement, movement slowness (bradykinesia), and movement deprivation (hyperkinesias). Both characteristics are at first unilateral, but become bilateral as the disease advances. Later, postural instability and falls, orthostatic hypotension, and dementia can develop.[11]

PD tremor occurs at rest but decreases with voluntary activity, so it does not usually affect everyday living activities. Rigidity refers to the increased resistance (steadiness) of a patient's limbs to passive movement. Bradykinesia (slow movement), hypokinesia (reduction in amplitude of movement), and akinesia (absence of regular unconscious movement, i.e., swinging of the arm in walking) manifest as a number of symptoms, including loss of regular facial expression (hypomimia), decreased speech volume (hypophonia), drooling (failure to swallow without thinking about it), decreased size (micrography) and handwriting pace, and stepping length decreased while walking.[12]

PD patients typically develop a stooped posture and may lose normal postural reflexes, leading to falls and, sometimes, confinement to a wheelchair. Freezing, the failure to initiate a voluntary movement like walking (i.e., patients stay "stuck" to the ground while they try to move), is a common symptom of Parkinsonism. There are also numerous disorders of affect and cognition; patients may become passive or withdrawn, lacking initiative; they may sit passively unless encouraged to participate in activities. Question responses are postponed, and cognitive functions ("bradyphrenia") are slowed. Depression is normal, and dementia is significantly more common in PD, particularly in older patients.[13]

EPIDEMIOLOGY OF PD

The prevalence and incidence of PD increase with the increasing age, four common causes of Parkinsonism were Parkinson disease, drug-induced Parkinsonism, dementia with Parkinsonism and vascular Parkinsonism. Door- to-door surveys revealed higher concentrations of the disease than surveys based on reports. Varying study methodologies and differing case ascertainment methods were the most important reasons for the reported variation in incidence and prevalence of PD.[14] approximately 1–2 % of the population over 65 years suffers from PD. This figure increases to 3 % to 5 % in people over 85 years. Age-standardized incidence rates of PD in population-based studies in European countries and the USA range from 8.6 to 19.0 per 100,000 inhabitants when strict diagnostic criteria of PD are applied.

There is no homogenous and significant epidemiological data about PD from India over 60 years of age the prevalence rate was 247/100,000. There was a low prevalence rate of 27/100,000 in Bangalore, in southern India, and 16.1/100,000 in rural Bengal, in eastern India. Razdan et al., recorded a crude prevalence rate of 14.1 per 100,000 among a population of 63,645 in rural Kashmir in northern India, Bharucha et al. recorded a high crude prevalence of 328.3/100,000 among the 14,010 Parsis population living in colonies in Mumbai, Western part of India.[15] As may be anticipated, door-to-door surveys and studies using broader inclusion criteria have yielded higher prevalence and incidence figures.

AETIOLOGY OF DEVELOPING PD

Most PD cases are sporadic and idiopathic. The aetiology of PD includes both genetic and environmental influences.[16] Human epidemiological studies have included residency in a rural setting and associated exposure to herbicides and pesticides with a high risk of PD[13].Both are capable of triggering nigrostriatal cell death and tend to interfere by interacting with mitochondrial function, inducing oxidative stress, and altering proteasomal function.[16] Smoking cigarettes and drinking coffee are inversely related to the risk of developing PD.[13] Six specific genes have been identified in the past eight years causing familial PD. Mutations in α-synuclein, parkin, UCHL1, DJ1, PINK1, and LRRK2 cause PD, with a Mendelian pattern of ancestry. DJ1 and PINK1 are mitochondrial proteins, and α-synuclein and parkin over expression causes mitochondrial defects. These same proteins are involved in the response to oxidative stress and affect proteasomal function.[16]

One theory that doesn't fit neatly into a genetic or environmental category is that PD neurodegeneration can be caused by an endogenous toxin. One source of endogenous toxins may be the normal metabolism of DA, which generates harmful reactive ROS. Consistent with the endogenous toxin hypothesis reported that patients harboring specific polymorphisms in the gene encoding the xenobiotic detoxifying enzyme cytochrome P450 may be at greater risk of developing young-onset PD. In addition, iso-quinoline compounds that are toxic to dopaminergic neurons were recovered from PD brains.[13]

PATHOGENESIS OF PD

In PD pathogenesis a variety of mechanisms were involved, with α-synuclein aggregation central to the disease development. Several other mechanisms are believed to be involved, with some studies indicating irregular protein clearance, mitochondrial dysfunction and neuroinflammation play a role in the initiation and development of PD. The relationship between those paths, however, remains unclear.[17]

α-synuclein misfolding and aggregation

Native α-synuclein in the brain is mostly unfolded without a defined tertiary structure, although in aqueous solutions it can be present in stable tetramers that resist aggregation. Upon interaction with negatively charged lipids, such as the phospholipids forming cell membranes, α-synuclein folds through its N- terminal it's α helical structures. In PD, α-synuclein adopts an amyloid-like structure that is β-sheet-rich and susceptible to aggregation. In addition, the misfolded α-synuclein is found as 5–10 nm long filaments within LBs. Several conformation changes mechanisms have been proposed that lead to abnormal α -synuclein aggregation, including serine 129 phosphorylation, ubiquitination, and C-truncation. Consequently, numerous species of α-synuclein are present in the PD brain, including unfolded monomers, soluble oligomers, protofibrils and high molecular weight insoluble fibrils.

Recent studies in rodents suggested that the most neurotoxic α-synuclein species is the early oligomeric form, instead of the mature insoluble fibrils. The raised toxicity of these oligomers, as opposed to the fibrillary α-synuclein, was validated in cell-based assays. The α-synuclein oligomeric species are capable of "seeding" and accelerating irregular protein aggregation and Danzer et al. (2011) proposed that this may be the mechanism influencing the distribution of α-synuclein pathology in the brain.[17]

LrrK2 (PARK8): This is an extensive gene consisting of 51 exons. Today, more than 80 mutations in this gene is linked with PD accounting for 10% familial PD and significant number of sporadic PD. LrrK2 is mainly associated with formation of LB and aggregation of tau protein which causes improper functioning of neurons.

Vps35 (PARK17): A mutation D620N in this gene cause late onset, autosomal dominant PD. The average age of disease initiation is around 51 years, with high levels of tremors, bradykinesia and posturalinstability.

Parkin (PARK2): This gene has a part to play in the proteasome process. Mutation causes loss of its function which is ubiquitination of protein by E3 ubiquitin ligase. These causes toxic build up proteins. Neuronal formation of these has a key function to play in PD pathogenesis.

Pink1 (PARK6): Homozygous missense mutation G309D and homozygous nonsense mutation W437X in this gene were detected to cause PD. Patients with PINK1 mutations have an early onset of PD, with slow progression and with often atypical features such as dystonia, anxiety and depression.

Dj-1 (PARK7): This gene is protective against oxidative stresses. More than ten mutations have been described in this gene that can cause autosomal recessive juvenile Parkinson's. However, PD caused by mutations in this gene is rare and very few patients have been reported.[18]

Mitochondrial dysfunction

Mitochondrial dysfunction is tightly associated with PD pathogenesis. The clear proof of mitochondrial dysfunction in PD came from brain samples of patients with PD. In SN of Parkinson disease patients, mitochondrial complex I activity is greatly reduced. In addition, PD patients had reported a high level of mitochondrial DNA deletion in SN neurons, indicating a role of mitochondrial dysfunction in PD. Furthermore, decreases of peroxisome proliferator-activated receptor gamma co activator 1-alpha (PGC-1α, a co-activator important for mitochondrial gene expressions) and PGC-1αregulated mitochondrial genes were observed in DA neurons in PD. These data indicate that PD brain has defects

in mitochondrial function and biogenesis. The direct association of mitochondrial dysfunction with PD resulted from the discovery of 1-methyl-4- phenyl-1,2,5, 6-tetrahydropyridine (MPTP), a neurotoxin that causes PD indications in patients with drug abuse in the year 1983. Soon, the neurotoxicity of MPTP was confirmed in primate and rodent model.[19]

Oxidative stress

Oxidative stress contributes to the cascade in PD which leads to DA cell degeneration. However, oxidative stress is closely related to other degenerative process elements, such as mitochondrial dysfunction, excitotoxicity, toxicity to nitric oxide, and inflammation. Therefore, it is difficult to decide whether oxidative stress induces these events or is a result of them. Oxidative damage to lipids, proteins and DNA occurs in PD, and oxidative toxic products such as 4-hydroxynonenal (HNE) may react with proteins to impair the viability of cells.

There is compelling evidence that nitric oxide reacts with superoxide to create peroxynitrite, and eventually leads to hydroxyl radical production. As a guide to dopaminergic cell death in PD, altered ubiquitination and degradation of proteins have been inferred recently. Oxidative stress can directly affect these processes, and oxidative damage products, such as HNE, can damage the 26S proteasome. Impairment of proteasomal activity also results in free radical production and oxidative stress. Oxidative stress happens in idiopathic PD and products of oxidative damage interfere with cellular function, but these are only part of a cascade, so that they cannot be separated from other events like dopaminergic cell death.[20]

Inflammation

Inflammatory processes have also been implicated in the pathophysiology of PD with increased levels of inflammatory mediators (interleukins and TNF-α) found. These stimulate the activation of microglial cells and increase nitric oxide (NO) production. These further increases oxidative stress and exacerbate cellular damage.[21]

Excitotoxicity

Excessive glutaminergic stimulation acting on N-methyl-D-aspartate (NMDA) receptors can damage cells via activation of a number of enzyme systems.70 Stimulation is mediated by calcium ion influx. Excessive influx is prevented by maintenance of a normal membrane potential. This, in turn, relies on mitochondrial ATP production and may be deficient in PD. Physiological levels of glutamate may therefore be toxic in PD.[21]

TREATMENT OF PD

Though the exact cause of Parkinson's disease has not been identified, treatment discoveries have been progressive. There is no known cure for the disease, so treatments seek to manage symptoms rather than prevent or slow the progression of the disease. Treatments can vary from drugs, surgeries, therapy, or a combination of different treatments. They must also be adjusted throughout the course of the disease, as some common treatments, such as L-DOPA loses effectiveness over time. Treatment of PD using available drugs has positive symptomatic effects; however, there are no disease-modifying or neuroprotective therapies available to slow the progression of the disease. Therefore, treatment begins at the discretion of the patient and the physician when symptoms begin to impair function or provide social embarrassment. No one drug is more beneficial than the other for initial treatment, but instead the disease itself must be looked at in terms of severity and time of onset. PD is a disease that affects multiple neural pathways in the brain. While L-DOPA may treat motor problems caused by low dopamine levels, it will not treat motor problems caused by low acetylcholine levels in other pathways. Additionally, each sub type responds differently to drugs. It is up to the discretion of the doctor to choose a plan that works for an individual patient based on responsiveness and symptoms.[4]

SUPPORTIVE THERAPIES

There are many medications that can make surviving with Parkinson's disease simpler, and can help with day-to-day symptoms. Speech therapy, Physiotherapy Occupational therapy Medication.

Pharmaceutical treatment

These methods focus on many ways of restoring the balance of dopamine and other neurotransmitters: three primary types of treatment are widely used. They are levodopa, dopamine agonists, and monoamine oxidase-B (MAO-B).

Levodopa: Most people with Parkinson's disease will eventually need to have a medication called levodopa. Levodopa is processed by the brain's nerve cells and converted into the chemical dopamine that is used to send signals between the parts of the brain and the nerves that regulate motion. Increasing the dopamine levels with levodopa usually improves movement issues.[22]

Dopamine agonists: These act as a dopamine replacement in the brain, and have a similar but milder effect compared to levodopa. These are used to treat early Parkinson's disease as they are less likely than levodopa to induce involuntary movements (dyskinesias).[23]

Monoamine oxidase-B inhibitors: MAO-B inhibitors, including selegiline and rasagiline, are another alternative to levodopa for treating early Parkinson's disease. These inhibit the action of dopamine-destroying brain chemicals. These can be used with dopamine or levodopa agonists. MAO-B inhibitors can cause a wide range of side effects, including nausea, headache and abdominal pain.[22]

SURGERY

The three most common forms of surgery for PD are

Thalamotomy: To relieve certain symptoms of tremor, the surgeon makes a lesion (cut) on part of the brain.

Pallidotomy: The surgeon makes a lesion on a different part of the brain to alleviate dyskinesia (wriggling movements).

Deep brain stimulation: Electronic deep-brain stimulator is placed in the brain to control specific symptoms. This is connected to one or two fine wires placed under the skin and inserted precisely into specific areas in brain. A tiny electric current is produced from the pulse generator, which runs through the wire and stimulates the part of your brain affected by PD. The electrical impulse creates a lesion, which blocks abnormal nerve signals and reduces the targeted symptom.[24]

CONCLUSION

Parkinson's disease is one of the most common neurodegenerative diseases affecting the aging population and is associated with an increased morbidity and mortality. Awareness of the disease manifestations, the treatments, and the progressive long-term course of the disease is necessary for the optimal management of the cases. Tremendous progress has been made in understanding the neuropathology of PD and its progression throughout the nervous system. However, none of these treatments is curative. PD remains a progressive disorder that eventually causes severe disability due to the increasing severity of treatment-resistant motor problems and non-motor symptoms. Modifying factors that lead to the disease progression and in further delaying its disability are the key unmet needs to be addressed by the current and future research efforts.

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