Recent advances in Parkinson disease

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ABSTRACT

The article reviewed various therapies other than dopamine treatment like A2a antagonists: antiparkinson medication reducing the over reactivity of substantia nigra due to loss of dopamine; Levodopa/Carbidopa Intestinal Gel: an aqueous gel containing levodopa and carbidopa; stem-cell therapies like embryonic and adult stem cell can be act through several mechanism; acupuncture: reduced the motor symptoms and other disease related factors; various antiparkinson medications like IPX066 and ND0611 are sustained release and transdermal patches which are transported to GIT through high nutrients and patches are found to be useful in increasing the concentration, half-life of levodopa, thus downs the threatening risk of PD. The future treatment for PD should be considered as they have less side-effect and better results than other treatment as they not only decrease the symptoms but also the incidences of PD. If the symptoms are diagnosed early patient should go for genetic therapy to relieve from the disease which not only reduce the progressive increase of symptoms and disease. Considering all therapies, future treatments shows the weightage in reducing the progressive increase of PD in patient. Though these treatments are proven to be effective in treatment but still more targeted tools and techniques are required which can specifically target the cause and thus lowers the graph and rating scale of PD.

Keywords: Oxidative stress, Monogenic and familial, Necropsy, TRAP, Acupuncture

Introduction

Parkinson disease (PD) is known from ancient times but their symptoms were discovered by James Parkinson under the name of ‘the shaking palsy’. In 1879, Charcot found the autonomic dysfunction as an additional feature.1 PD is a slowly progressive, age-related, second most common neurodegenerative disorder found all over the world, after Alzheimer’s disease (AD) with unknown aetiology.2 Loss of dopaminergic neuronal cells in the substantia nigra pars compacta (SNc) in the mid brain is the pathological hallmark of PD, which causes dopamine depletion in the striatum, and the presence of intracytoplasmic inclusions known as Lewy bodies in the remaining cells.3 The three “cardinal signs” of PD are resting tremor, rigidity, and bradykinesia. Postural instability, is found late in PD, is the fourth cardinal sign. There may be unresponsive of levodopa to this disorder.4 By far the most common form of parkinsonism is idiopathic, or classic,
Parkinson’s disease (PD), but for a significant minority of diagnosis — about 15% of the total — one of the Parkinson’s plus syndromes (PPS) may be present. These syndromes, also known as atypical Parkinsonism, include corticobasal degeneration, Lewy body dementia, multiple system atrophy and progressive supranuclear palsy. Each one has its own distinctive set of symptoms. Although there is currently no cure for Parkinson’s plus syndromes, researchers are making advances to better understand and manage them. It is important to note that disease and symptoms are variable in different patients; the impact of PD on functional capacities, quality of life, activities of daily living and social participation may also differ among individuals. The progressive nature of the disease will threaten the patient’s quality of life.5

Etiology

The aetiology of PD still remains unclear. Age has been identified as the major risk factor as it affects approximately 3% of the population over 66 year of age. PD mainly occurs with an increasingly elderly population. It will be encountered with greater frequency in surgical patients. So prevalence of disease is expects to be increase in the next decades as the population ages, which might ultimately results to serious health care issues globally in reference to society and health care system.6 There might be combination of genetic and environmental factors which causes PD. Genetic factors may include as genetic mutations, including alpha-synuclein (SNCA), Parkin, PINK, DJ-1 (PARK6), Leucine-rich repeat kinase 2 (LRRK2), PARK9, GBA (glucocerebrosidase), DNAJC6, SYNJ1, ATXN2, ATXN3, GCH1, DCTN1 etc.2 Environmental factors as the exposure to the environmental toxin as MPTP was identified and explained by Langston & Ballard. Other than MPTP a large number of environmental toxins such as pesticide, rotenone, paraquat, herbicide farming, rural life, industrial toxin, heavy metals, smoking and drinking tea and coffee shown to loss of dopaminergic neuronal cells and parkinsonism.3,7

Genetic factor

Several monogenic forms of the disorder and of number of genetic factors has been identified as the increasing risk to develop PD. Monogenic forms, caused by a single mutation in a dominantly or recessively inherited gene, lead to 30% of familial PD and 3%-5% of sporadic PD.8 Familial PD is caused by rarely because of highly age penetrate mutations, inherited in a Mendelian way (autosomal recessive or dominant). The disease is developed by biological effect of these mutations. Sporadic PD is a complex very common genetic variant which play a very important role alone while interaction with other genes and environmental factors, producing cumulative effect leading to the development of the disease.9 Increasing risk of PD is the result of mutation in different genes, since different protein product are related to PD. Mutations results to aggregate and deposited for the formation of Lewy bodies, hall mark of PD, cause loss in dopaminergic neuronal cells, decreasing the motor activity and muscle atrophy. An important mitochondrial PINK1 protein produced by PTEN induced kinase1. This protein deals specifically with oxidative stress containment in the mitochondria. Gene mutation in SYN and PINK1 independently lead to the onset of PD. The mutation in SYN results in imbalance of α-synuclein folding, dopaminergic neuronal and motor function loss. Mutations in PINK1 gene have different mechanism results in “leaky” mitochondria.10

Oxidative stress

Free radicals have reactive oxygen and nitrogen species. Some of these substances are normally produced during metabolism like superoxide anion, hydrogen peroxide, nitric oxide, peroxynitrite, nitroxy1 and hydroxy radical. Formation of these products can be responsible for the damage of protein, DNA and lipid in cell. The brain contains a high amount of lipophilic substances, such as phospholipids and free fatty acids, which are susceptible to oxidative modifications and, as a result, are responsible for the high susceptibility of the central nervous system to the deleterious action of free radicals. Peroxidation of lipids represents a key mechanism mediating the toxicity of free
radicals on a wide range of cell organelles and functions. Formation of free radicals initiate peroxidation of the membrane lipids and lose a hydrogen atom from a methylene group, with formation of a diene; this product mediates the formation of a peroxy radical with oxygen through reaction; this peroxy radical abstracts a hydrogen atom from another lipid to form hydroperoxides, which mediates the propagation of lipid peroxidation. Oxidative damage plays a major pathogenetic role in Parkinson’s disease and represents a key to the loss of dopaminergic neurons. The high concentration of dopamine is presumed to be essential to determine the high susceptibility of dopaminergic cells to oxidative stress.11

Figure 1: Dopaminergic neuronal death.

Environmental factors

Influence of environmental factors on PD, have shown undetermined results. The focus has been on the effects of pesticide exposure and waterborne risk factors. A study demonstrated that associations in five European countries found that a large percentage of pesticides containing manganese were found in the brains of patients after a study known as “necropsy”. Therefore it was suggested that even the slight amount of pesticide exposure can greatly increase the risk of PD. Hence it shows that pesticides do in fact have an effect on the development of PD, it was limited due to its inability to determine the specific agent within the pesticide that induced this risk.10

Pesticides

Epidemiological studies proven the relation between PD and exposure of pesticides such as rotenone and paraquat. Rotenone is an inhibitor of complex I have high-affinity and is potent. In rodents, continuous accumulation of these toxic agents causes dopaminergic neuronal cell death and Lewy bodies in PD patients. Therefore, both MPTP and rotenone cause disruption of mitochondrial function and play important roles in this neurodegenerative disorder. Paraquat, a bipyridyl derivative of chemical, is most commonly used pesticides, and leads to oxidative and nitrate stress. Paraquat is chemically similar to MPP+. Exposure to this toxin leads to the development of PD. A study has revealed that exposure to a combination of both paraquat and mane, is widely used as an agricultural pesticide, exerts degeneration of dopaminergic neuronal cells in the rodent model and causes an increased incidence of PD in human. Exposure to a combination of several toxins leads to greater risk of developing PD.3

Environmental factors plays the major role for the development of PD. Results indicates that people living in rural regions using wells as their water supply have a greater risk of PD. However, environmental risks of developing PD from well water or pesticide exposure may not be mutually exclusive, since pesticides leached into the soil and then into the groundwater.10

Symptoms of PD

Motor symptoms

PD is related to motor symptoms including asymmetric onset of bradykinesia, tremors, and rigidity due to the loss of dopaminergic neuronal cells of the basal ganglia. There are four cardinal symptoms of PD are named as TRAP: Tremor at rest, Rigidity, Akinesia (or bradykinesia) and Postural instability. In addition, flexed posture and freezing (motor blocks) are also included as the features of Parkinsonism, with PD as the most common form.

Tremor

Rest tremor is the common symptom of PD. Tremors is biased, occur at a frequency between 4 and 6 Hz, and almost always in the distal part. Rest tremor involves the lips, chin, jaw and legs but, while essential tremor involves the neck/head or voice, rarely. Thus a patient who presents with head tremor represents the
essential tremor, cervical dystonia, or both, rather than PD. Characteristically, rest tremor disappears gradually with action and during sleep. Some patients also report an “internal” shaking that is not associated with a visible tremor.

Table 1: Motor symptoms.

| Motor symptoms                                      |
|-----------------------------------------------------|
| Tremor, bradykinesia, rigidity, postural instability |
| Hypomimia, dysarthria, dysphagia, sialorrhea         |
| Decreased arm swing, shuffling gait, festination difficulty arising from chair, turning in bed |
| Micrographia, cutting food, feeding, hygiene, slow activities of daily living. |

Rigidity

Rigidity is related to pain, and painful shoulder is frequent initial tidal wave of PD although it is commonly misdiagnosed as arthritis, bursitis or rotator cuff injury.

Bradykinesia

Bradykinesia refers to slowness of movement. It is one of the three characteristic symptoms of Parkinson's disease (tremor and rigidity are the other two). In other words, a person having Parkinson’s shows the symptoms of Bradykinesia. This slowness of movement occurs when a person with Parkinson's is starts with the routine work. These works include daily life activities like getting dressed, making a sandwich, buttoning a shirt, using utensils or getting to a doctor’s appointment. Bradykinesia also can cause someone with Parkinson's to shuffle more than walk, and to use slow, short steps. Finally, this problem lead to soft speech and soft talk that's difficult for others to understand.

Non-motor symptoms

Before diagnosis, non-dopaminergic and non-motor symptoms are sometimes present and almost unavoidably emerge with disease manifestation. Non-motor symptoms overrule the advanced Parkinson's disease and contribute to severe disability, impaired quality of life, and threaten life. In contrast for the dopaminergic symptoms of the disease, treatment is available, non-motor symptoms are poorly identified and inadequately treated. However, attention is focused on the identification and valuation of non-motor symptoms, which forms the basis of improved treatments. Some non-motor symptoms, includes depression, constipation, pain, genitourinary problems, and sleep disorders, can be improved with present treatments. Other non-motor symptoms can be more refractory and need the introduction of novel non-dopaminergic drugs.\(^\text{13}\)

Depression

Depression is a very common in patients with PD as well as with other disease. In the brains of PD patient’s complex interactions between nor epinephrine, serotonin and dopamine systems are interrupted. The mechanism is still not cleared. It has been shown that decreased concentrations of 5-HT, a serotonin metabolite, in the cerebrospinal fluid and reduced cortical 5-HT1A receptor binds in PD. New diagnosis of PD patients revealed another form of depression known as Reactive depression and others with more advanced disease are losing independence and control because of changes in motor functioning and feelings of helplessness.

Psychosis and hallucination

Hallucination occurs, frequently in the initial stages of PD. Psychosis and visual hallucination is common, due to disease manifestation and medical illnesses dose-dependent adverse effects of anti-PD medications may occur. Factors including advancing age, presence of dementia, and polypharmacy.\(^\text{14}\)

Sleep disorders

Sleep disturbances like excessive sleepiness, insomnia or sleep attacks contribute to the pharmacological therapy for PD. Some clinicians believe that these are features which are crucial part of the disease. An observation revealed that rapid eye movement sleep behavior disorder, occurring in approximately one-third of patients yelling, swearing, grabbing,
punching, kicking, jumping and other activities, violently and potentially injurious motor activity. Insomnia, is frequent (50% prevalence), and highly variable among patients. The sleep disorders and abnormalities observed in patients with PD may possibly be related to a 50% loss of hypo cretin (orexin) neurons. Although excessive daytime sleepiness may contribute to fatigue, this common symptom is also seen in PD.12

**Diagnosis**

Diagnosis of PD is based on aetiology is difficult because of no single cause of PD. Like both genetic and environmental factors involved in pathogenesis of PD. However, monogenic causes of PD are for only a minority case. A study has revealed that earlier PD was diagnosed from pathological confirmation on autopsy of Lewy body where accuracy was 82% while in neurological diagnosis accuracy rate was higher and found to be at 91%. Thus, diagnosis of PD nowadays is based predominantly on the clinical features.15 Furthermore the diagnosis of Parkinson’s disease is also based on the presence of the cardinal features of bradykinesia and tremor. It is done by taking the careful history and physical examination. There are no definitive tests or imaging studies that confirm the diagnosis. Magnetic resonance imaging of the brain or other tests may be appropriate in some patients, particularly those with prominent gait abnormalities, to exclude other conditions, but are seldom necessary in a typical case.16

**Treatment**

The treatment of patients with PD realizes that disease progress slowly and treatment varies with persons over years. Patients with PD require experienced and compassionate healthcare providers for proper management and effective treatment, care taker should determine the appropriate medications, regular exercise, a healthy diet, social engagement and cognitive activities, counselling and other therapies. The mainstay of PD pharmacotherapy continues to be palliative or symptomatic, involving replacement of the DA deficiency in striatum.17

**Monoamine oxide inhibitors**

Selegiline a monoamine oxidase inhibitor is also used to treat Parkinson's disease. The mechanism of Selegiline is to prolong the action of dopamine in the striatum. A study has shown that Selegiline not only improves the symptoms of Parkinson's disease but also retards disease progression and exert a neuroprotective effect. A report suggest that, when Selegiline is given in combination with L-DOPA there was 60% increase in mortality compared with L-DOPA treatment alone. Analysis trials of selegiline for selegiline-treated patients didn’t confirm an excess of deaths and a recent case-controlled study reported higher mortality in Parkinson's disease patients compared with age-matched controls, but that mortality increment was not occur by taking selegiline.1

**Alternate therapy**

Other than L-dopa treatment and MAO-inhibitors, few different therapies are used to treat PD like catechol-O-methyl transferase (COMT) inhibitors, dopamine agonists, anticholinergic agents, and amantadine. The dopamine agonist provides stimulate the dopamine receptor during the wearing off period. Another approach is to use catechol-O-methyl transferase (COMT) inhibitors, results in increase the bioavailability of dopamine by breakdown of its in periphery. Anticholinergic drugs such as benzhexol may be useful in early disease to treat tremor and have limited efficacy and many side-effects.1,16

**Surgical therapy**

Surgery for PD is becoming increasingly available as new techniques of electrical stimulation have been developed and the physiology of basal ganglia has been attained. The location of the stereotaxic target is the other critical factor that needs to be individualized for each patient. For controlling tremor the thalamus, particularly the ventral intermediate nucleus, considered to be the most successful target, but bradykinesia is not eliminated by this target; so stereotaxic thalamotomy is not proven to be a good choice today. Expert team of neurosurgeon performed surgery at targeted
specialty centres for patients with PD, to monitor the target of operating procedure and to program the stimulators of procedure a neurophysiologist and a neurologist is needed.\(^{18}\)

**Stem cell therapy**

Stem cell technologies are therapeutic and current clinical option which is widely used to investigate and treat neurodegenerative diseases. Various stem cell therapies are in pipeline and are develop to treat neurodegenerative diseases, in which embryonic stem cells (ESCs), mesenchymal stem cells (MSCs), neural stem cells (NSCs) and induced pluripotent stem cells (iPSCs) are the most common tools for regenerating the brain cells. Dopaminergic (DA) neural cells in the substantia nigra pars compacta are lost in PD. Stem cell-based therapies can be beneficial by acting through several mechanisms such as cell replacement, trophic actions, mediating remyelination and modulation of inflammation.\(^{2}\)

**Acupuncture therapy**

Acupuncture therapies are also now used as an alternative treatment for PD and are proven to be effective. A report has shown that 63% of patients in Korea and 25% patient in Singapore with PD use acupuncture as a complimentary therapy which treats well but did not alleviate the symptoms of PD. If the treatment is follows in a manner like applying acupuncture on body or scalp acupoints for 1 hour twice per week in patients with disease improves the sleep and rest but not symptoms. Functional magnetic resonance imaging studies shown that if acupuncture is applied to the Yanglinquan (GB34) acupoints stimulates the portions of putamen and primary motor cortex and improves motor function. Furthermore, this therapy leads to improves glucose metabolism, hemispheric regional blood flow in brain. Hence, acupuncture plays a vital role for patients with PD in reducing the intellectual decline. However research and reports are in pipeline for more betterment.\(^{19}\)

**Future treatments for Parkinson’s disease**

Researchers have designed new formulations and drugs for the treatment of PD. Earlier therapies treat few symptoms and few remains unprotect able results in partial treatment, bradykinesia and tremor are the factors would not disappear even after treatment. So high effective treatment for bradykinesia and tremor is required. These future treatments reduce disability and discomfort from bradykinesia and make the physicians free to use dopaminergic therapies more liberally. These treatments include:\(^{20}\)

- A2a Antagonists (Istradefylline, Preladenant, SYN115).

Adenosine 2a (A2a) receptor antagonists is a nondopaminergic medications which are under trials to the effects in improving signs and symptoms of PD. They provide potential benefits over dopaminergic therapy and medications and may reduce the dopaminergic side effects. These medications are used in different models to see the various effects.

**Levodopa formulations**

- Levodopa/Carbidopa Intestinal Gel (LCIG; Duodopa)

**PRODRUG**

- XP21279—a sustained-release levodopa prodrug.

**Other antiparkinsonian medications**

- IPX066 extended-release oral formulation of Carbidopa/ levodopa.
- Cogane (PMY50028)
- ND0611 Carbidopa subcutaneous patch
- Safinamide
- Fipamezole

**Gene therapy**

- CERE-120 (AAV2-NRTN)
- Glutamic Acid Decarboxylase (GAD) Gene Transfer

**Discussion**

I reviewed the article which includes the full description of PD along with its treatment and other treatment technologies and medications which shows the better results when comparing
to traditional medication or treatment. Earlier dopamine therapy found to have various side-effects and was not shown the appropriate results of decreasing the slope of PD which is been modified by combination with other drugs and found to have increase outcomes.

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