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Pathophysiology And Treatment Of Parkison's Disease

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Abstract
Parkinson's disease is a progressive neurodegenerative disorder of nervous system which mainly effects movement. Initial symptoms start slowly, certain times and beginning with tremor in one hand. The reasons to cause this disease are unclear. But it is caused by the dysfunction of dopaminergic neurons in the brain. Also some risk factors including elderly age, genetics and family history are mainly responsible for causing this disease. Some conditions such as tremor, rigidity and bradykinesia also may be occurred. There is no specific cure or treatment of this disease. But there are so effective pharmaceutical drugs or treatment methods that widely used in the patients who suffered with Parkinson disease. To minimize or prevent from this disease early detection and proper diagnosis and treatment should be considered. This review paper we briefly summarizes the pathophysiology and treatment of Parkinson disease.

Keywords: *Parkinson disease, dopaminergic neurons, bradykinesia, carbidopa and levodopa*

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I. Introduction:

Parkinson's disease (PD) affects over a 1 million people in the United States, one in every 100 people older than 55. [1]. Since it was first discovered by James Parkinson around two centuries, a lot about the disease has been observed, for example, the primary lesion of the disorder has been mastered and more about clinical features. However, the past years

Have started to emerge, about the progress of the disease, the possibilities of disease treatment can arise which will provide more than short-term symptomatic relief. Beginning with the Nobel Prize–winning work of Arvid Carlsson, which points to the loss of dopamine (DA) as the principal deficiency in PD and to levodopa as a mode of pharmacotherapy, recently analyzed to understand what is failing in this disorder and, more recently, how we can improve it that failure.[2] Moreover, although Parkinson on all motor system is not fully understood, it has been quite understood this disease is much complex and includes a panoply of psychiatric symptoms as well. [3].

CLINICAL SIGNS AND SYMPTOMS:
rigidity, bradykinesia (slowing of movement), and postural instability, All patients do not come up with these signs of the disease. Usually one or two patients may present with these symptoms. Often, the early sign of the Parkinson disease is stiffness or weakness, the etiological factors are often miss diagnosed [4]. However, tremor and orthostatic deficit may soon arise, prompting a reconsideration of the basis of the problem. It is very important to note, however, that the clinical evaluations for those with parkinson disorder are based on neurological examinations and medical history; examinations in laboratory test cannot be found definitively.[5] As well as neuroimaging, which is important forattaining an estimate of DA loss is not perfect and the price is much higher for diagnosis of the disease.[5] As a result, it has been estimated that a significant number of individuals diagnosed as having PD fail to show the histopathological hallmarks of the disease upon autopsy.[6] A tremor has the most features of clinical manifestations of the disorder. This may affects more than in 70% of patients. Whereas it is not required for diagnosis, the long-term absence of tremor of individuals illness should be paid more attention to other neurologic disorders which can come up with disorders of Parkinsonism, such as the corticobasal ganglionic deficit, supra nuclear palsy, multiple system atrophies and so on.[7]Rigidity is a motor sign which is usually accumulating by the evaluating doctors than the patients; it was discovered as defiance to inactive movement of the limbs. It is usually directional uniform of flexion and extension (causing pipe rigidity), but there is possibility to lay over ratcheting (rigidity of cogwheel). Bradykinesia regards slowness and in adequacy movement, for examples, loss of facial expression that may lead to a loss of facial sensibility, and cohort movements including arm swinging when walking. Bradykinesia occurs not only rigidity of the limbs; it can also be seen in treatment.[8]When the oropharynx is affected by the bradykinesia difficult swallowing can occur, which maylead to aspiration pneumonia, and life threatening complications.[9]in

The cardinal motor signs, potential dangerous may occur due to pos-tural instability which may result fractures. It is also has a slow responsiveness symptoms during levodopa treatment. Even the first in the course Tremor also has less responsiveness, moreover motormanifestations of PD is the freezing condition, also referred to as ‘‘motor block, In its most common cast, freezing occurs as a sudden inability to step forward while walking.[10].

PATHOGENIC MECHANISM:

The theory of free radical–intermediate damage which situated the degeneration of neuronal that betides in Parkinson disease, and continuing to be, the leading theory for its mechanism. The concept of free radical has been the content of many classic reviews, so it can be figured in briefly. This concept is also regarded as the oxidant stress thesis or theendogenous toxin theory. In the review, Fahn and Cohen point out that the free radical fascinating due to four facets of the neurochemistry of DA neurons and their local environment within the SN make the presumptive concept.[11]First, a main decadencepathway for DA is its oxidative deamination by monoamine oxidizes both A and B. This procedure issue in the enzymatic synthesize of H_2O_2, so long as, thus, it is not a free radical, can nevertheless react non enzymatically with ferrous or cupric ions via Fenton- type reactions to form highly reactive hydroxyl radicals. Second, DA can react non enzymatically with oxygen to cast quinones and semiquinones, with the synthesis of superoxide, hydrogen peroxide, and hydroxyl radicals. Third, the SN, especially the SN pars reticulata, which has many irons which as mentioned earlier, may in its ferrous state catalyze the setup of hydroxyl radicals from H_2O_2. Fourth, the SN containsneuromelanin formed from the auto-oxidation of DA. This auto-oxidation generates toxic quinones and reactive oxygen species.[12] The adaptability of metal ions to link in the development of reactive species of oxygen can be affected by the available of neuromelanin in the cell. The possibility that may DA neurons pass free radical– intermediated damage in PD that has got support from study by using neurotoxins (one of two) that can be performed to selectively degrade DA neurons—6-hydroxydopamine and MPTP. Oxygen for synthesis superoxide anion radical, H_2O_2, and hydroxyl radical these can be reacted by 6-OHDA.[13]Commonly cytotoxic referred It is a general cytotoxic but derives its particularity by virtue of its affinity for the high-affinity catecholamine transporters. Hence, when give in sufficiently concentrations, its actions can be subjected concerning neurons of catecholamine. in additional, it also can be defined to acting on DA neurons by pretreating animals with an inhibitor of high level-affinity norepinephrine uptake, include desipramine. Interestingly, like 6-OHDA, DA itself is a selective neurotoxin for DA neurons.It seems to be in large part because its power to oxidize reactive oxygen species production, such as dopamine quinone, that has a very high affinity for the cysteinyl residues on proteins.[13] Hence, it looks like that DA itself could bea root of oxidative stress, especially under conditions of increased DA turn over and declined antioxidant defenses. MPTP conducts through synthesis of MPP, which is particularly upholds DA neurons through the DA transporter, and the complex I activityin mitochondria is inhibited. Suppression of complex I activity not only affects with adenosine triphosphate (ATP) production, but augmented synthesis of superoxide anion radical results as well. Because of supporting directly of the demonstration by Przedborski and co-workers which transgenic mice with highly amount of cu/zn superoxide dismutase effect are constant to MPTP. The theory of free radical s of PD has also got support from studies of human postmortem brain. DNA can be damaged by free radicals, lipid, and proteins, in the cell membrane. There is proof that shows free radicals can induce alterations of every one of these classes of molecules. The evidence showsthat the amount of polyunsaturated fatty acids in the brain is insufficient. Which give amount of substrate available for lipid per oxidation and high in levels of malondialdehyde a mediated which in the lipid per oxidation process. The high level of malondialdehyde was regionally particular for the SN. It has been authenticated subsequently evidence for abnormal lipid per oxidation in PD by detecting a tenfold generate in cholesterol lipid hydroperoxide, the first detector in the lipid peroxidation procedure. DNA can also be damaged directly by Free radicals.[14]

ETIOLOGY:

Because of exposure of Parkinson's disease, some neurons in the brain slowly die. Due to lack of chemical messenger in the brain known as dopamine many symptoms and signs are caused by a loss of neurons in the brain.[15]When the amount of dopamine declines, it can cause abnormal brain activity, leading to symptoms of Parkinson's disease.[16]The etiology of Parkinson’s disease is unclearly understood till now; there are some factors which can play a role, such as.[17]

GENETIC FACTORS: it has been identified particular genetic mutations can lead to Parkinson’s disease, But these are not familiar except in some specific cases with many family members affected by Parkinson's disorder.[18]

However, it seems that the risk of Parkinson's disease can be generated by the certain gene variations. But with a relative small risk of Parkinson’s disease for each of these genetic markers. Genetic types of Parkinson’s disease are often seen in young-onset of Parkinson’s disease.[18]

For years, genetic triggers were considered improbable to participate a significant role in the mechanisms of PD.[19]Demonstrating genetics of Parkinson's disease has generated the development of the drugs for the past two decades which contributed continue to form the basis for new treatment.[20]Though Very few persons directly get Parkinson's disease from genetic mutations, the researchers studied from the biology individuals with these mutations could guide new treatment that could help to patients who suffered from this disease [21]people who suffered from genetic mutations with or with out Parkinson's disease can be underway to identify or detect the genetic revolution in Parkinson's research..

ENVIRONMENTAL FACTORS:

The risk of Parkinson disease may increase by the Exposure to certain toxins or environmental factors, It has been also found that many alterations occur in the brain with individuals who suffered from Parkinson's disease, even although it's unclear the reason these changes happen.. These changes include.[22]

The presence of Lewy bodies: Bunch of particular substance in the brain which is microscopic detectors of Parkinson disease. These clumps are known as Lewy bodies, and researchers found that these Lewy bodies play a key role the etiology of Parkinson's disease.[23]

Alpha-synuclein is found within Lewy bodies. Even although multiple are seen in the lewy bodies, scientist found a significant one which is known as alpha-synuclein (a- synuclein). It has been realized that in all Lewy bodies which are a clumped form those cells can't break down easily. Currently this research can be help full to focus among the Parkinson disease.[24]

Medication is secondary form which can cause of Parkinsonism, an after effected of the disease the central nervous system infection, toxins, or vascular/metabolic disorders. Specific neurodegenerative disorders may also expose parkinsonian symptoms, these are classic parkinsonian disorders, and include degeneration of supra nuclear palsy. Progressive age is the only evidence risk factor for PD. Other risk factors which can influence progressive of PD are rural living. However, none of these factorsunequivocally has been demonstrated to cause Ipd. [25]

Risk factors

Risk factors for Parkinson's disease include:

Age: There is risky to develop to Parkinson disease in elderly age people than younger people. But from the mild age they also may be affected.[26]

Heredity: Having family history with Parkinson's disease may promote the chance that you may develop this disease. However, the risky of Parkinson's disease may not increase until you experienced family with Parkinson's disease.

Sex: Women are unlikely to develop Parkinson's disease than are men. The other things that may promote the risk of Parkinson's disease are exposure to herbicides, and pesticides.[27]

Complications

Parkinson's disease is always accompanied by other additional problems, which may be treatable such as.[28]

Thinking difficulties. Dementia may be occurred and poor thinking usually is seen,this can be occurred during elderly stages of Parkinson disease. Cognitive conditions should be treated as early as possible [29]

Depression and emotional changes. Parkinson's disease can lead to progress depression and change the mood.[30]Taking medications for depression can make possible to control other complications of Parkinson's disease. People with this disease they may also seen other emotional changes, such as anxiety, loss of motivation, and fear. Often doctors prescribe medicine to cure these symptoms.[29;30]

Swallowing problems. People with Parkinson's disease may experienced dysphasia(difficult of swallowing) as their condition develops. Because of slowed swallowing saliva may accumulate in the mouth and may lead to drooling. In late stages this disease may affect muscles in their mouth which makes chewing difficult. This can lead to poor nutrition and choking [31]

Sleep problems and sleep disorders.

Patients who suffered with Parkinson's disease may usually experienced sleepdisorder, such as waking up early, and falling asleep during the day .These patients may also have sleep behavior disorder, and rapid eye movement, treatment may help their sleep problems. Parkinson's disease may also lead to bladder problems, such as being unable to control having difficult urinating. Because of decrease digestive tract many patient with Parkinson's disease may [32] experience constipation. Due to sudden drop in your blood pressure (postural hypotension) you may experience dizzy and lightheaded. Moreover many patients with this disease experience fatigue due to loss of energy, especially later in the day.[32]

Prevention:

Due to the cause of Parkinson's disease is poorly understood; proven methods to protect the Parkinson's disease

remains a mystery.
A certain researchers have found that regular exercise programs may decrease the risk of Parkinson's disease.[33]
Some other researchers have found that individuals who drink caffeine which is found in coffee, cola, and tea get this disease unlike those who don't drink it. However, it is unclear that whether caffeine prevents for getting Parkinson's disease, or relevant in other certain ways. However, there is no authentic prove to suggest that caffeine prevents Parkinson disease.[34]

DIAGNOSIS:

There is no special test for diagnosing Parkinson's disease. Neurologist will examine Parkinson's disease according to your medical background, physical and neurological evaluations overlook your signs and symptoms. Neurologist may use a especial SPECT (single photon emission computerized tomography) scan which is known as dopamine transporter (DAT) scan to diagnose this disease.[35] Even though this can be helpful to examine the Parkinson's disease, your doctor and your symptoms will eventually determine to do exact diagnosis of this disease. Mostly patients do not need DAT scan. Neurologist may suggest laboratory examinations such as blood test or (test) to diagnose what may cause symptoms.[35;36]
MRI, PET scan, and ultrasound of the brain are also helpful to rule out other conditions that may cause Parkinson disease.[37] Not only imaging test are helpful for recognizing Parkinson's disease. According to your diagnosis, neurologist may recommend you carbidopa-levodopa (Rytary, Sinemet, others), a Parkinson's disease treatment. To show the benefit you must take enough amounts of these medications. As fewer amounts for a day or two are not dependable. The diagnosis of Parkinson's disease will always confirmed by positive improvement with this treatment. The time to diagnose Parkinson's disorder could be longer. So neurologist often recommends regular follow-up appointments to assess your situation and symptoms over time to examine this disease. Moreover, commonly the presence of bradykinesia is used for diagnosis of Parkinson's disorder and often one of the following conditions are seen: postural instability, rigidity (muscular), 4- to 6-Hz resting tremor. Differentiation of Other Causes of Parkinsonism: Ruling out of Parkinson disorder from other conditions which can cause Parkinsonism is cardinal.[38]

TREATMENT:

There is no treatment for Parkinson's disorder, but often dramatic medications mayconduct to control your signs and symptoms of this disease.[39] Surgery may consider in some later disorders. Lifestyle changes may also recommend for those who suffered from Parkinson disease by the neurologist, particularly during aerobic exercise.[40] In some times, physical therapy which high lights balance and stretching also is significant. Speech- language pathologist may help to upgrade your speech disorders. The aims of treatment are to promote quality of life and functions in order to avoid drug induced complication in people with PD.[41] Involuntary movement (bradykinesia), rigidity, abnormal posture, and tremor respond to symptomatic therapy first in the course of illness.

MEDICATIONS:

Medicine can help you to regulate disorders with tremor, walking, and movement. May help you manage problems with walking, movement and tremor.[41] . However, dopamine can't be taken directly, as it can't enter your brain. After beginning medications of Parkinson disease you may feel significant improvement of your signs and symptoms. Over time, however, the benefits of agents constantly decrease or become less consistent. You may still manage (control) your symptoms of Parkinson disease fairly well.

Medications that neurologist may recommend include:[42]

Carbidopa-levodopa. Levodopa, is the one kind of drug that is used for the treatment of Parkinson disease which has greater effect than on other anti-Parkinson agents, basically this drug passes in to the nerve cells in the brain this is converted into dopamine that acts as one kind of neurotransmitter.[43] When levodopa and carbidopa are used by the combination in early levodopa is converted into dopamine outside of the brain that decreases side effect such as nausea. Adverse effect that may cause levodopa may include lightheadedness, postural hypotension, and nausea. For a while, as your disorder develops, the advantage of levodopa may decrease and become unstable, with a tendency to wax and wane ("wearing off"). After taking greater amount of levodopa you may also seen dyskinesia (involuntary movements). And then your doctor may recommend small amount of drug to manage the side effect of the drug.[43]
Carbidopa-levodopa infusion: Duopa is a brand-name medication made up from carbidopa and levodopa. However, it's conducted via feeding tube that gives the medications in a gel form which directly passes to the small intestine.[44] This drug is used for people who suffered from highly progressive Parkinson's who still can

respond to carbidopa –levodopa, especially who have experienced more fluctuations in response.Due to Duopa is a continually infused into blood level of the two agents remain constant. Placement of the tube needs a small surgical procedure. Risk association with having the tube include the tube falling out or infections at the infusion site.[44]

Dopamine agonists: Dissimilar levodopa, the dopamine agonist does not convert agonists into dopamine. , they minimize the effect of dopamine in your brain. They are not active like levodopa in treating the signs and symptoms of the Parkinson disease. However, they can be used long time with levodopa to smooth the sometimes off-and-on effect of levodopa.[45]

Dopamine agonists include pramipexole (Mirapex), ropinirole (Requip) and rotigotine (Neupro, given as a patch). Apomorphine (Apokyn), is a short-acting injectable dopamine agonist used for quick relief. Dopamine agonist has some adverse effect which is similar to the adverse effect of carbidopa-levodopa. But the side effect that may dopamine has can include, hyper sexuality, sleepiness, compulsive behaviors, hallucinations, gambling and eating. If you're taking these medications and you behave in a way that's out of character for you, contact to your doctor.[45]

MAO B inhibitors: include selegiline (Eldepryl, Zelapar), rasagiline (Azilect) and safinamide (Xadago). These drugs help to protect breaking down dopamine in the brain by inhibiting the brain enzyme monoamine oxidase B (MAO B).[46] This enzyme metabolizes brain dopamine. Adverse effects include insomnia and nausea. When combined with carbidopa-levodopa, these drugs increase the possibility (risk) of hallucinations.

Because of potential risk that may occur, these drugs are not usually used in combination with many antidepressants or certain narcotics but rare reactions. Talk to your doctor before taking any additional medications with an MAO B inhibitor.

Catechol O-methyltransferase (COMT) inhibitors: Entacapone (Comtan) is a primary medication from this class. And slighty prolongs the effect of levodopa therapy by blocking an enzyme that breaks down dopamine. Adverse effect of this medication include an increased risk of dyskinesia (involuntary movement)), due to promoted adverse effect of levodopa other side effect can occur such as diarrhea or other increased levodopa adverse effect. Tolcapone (Tasmar) is another form of COMT inhibitor which is rarely prescribed because of a risk of serious liver injury and liver failure.[47]

Anticholinergics. These type of medications have been used for many years to manage (help control) tremor which is caused by the Parkinson's disease. Several types of anticholinergic are available, such as benzatropine (Cogentin) or trihexyphenidyl. However, their benefits are usually offset by adverse effects such as confusion, loss of memory hallucinations, constipation, impaired urination and dry mouth.[48]

Amantadine. Because of early-stage of Parkinson's disorder Doctors may prescribe amantadine alone to provide short-term relief of symptoms of mild. Early-stage Parkinson's disease, It may also combined with carbidopa-levodopa medications in the later stages of Parkinson's disease to regulate control dyskinesia (involuntary movements)caused by carbidopa-levodopa. Adverse effect that may induce amantadine are include, hallucination, ankle swelling, and purple mottling of the skin. Surgical procedures:[49]

Deep brain stimulation Due to deep brain stimulation (DBS) implantation of electrodes is performed by surgeons into a specific region in the brain. In deep brain stimulation (DBS), surgeons implant electrodes into a specific part of your brain. There are some electrodes that are located at the chest which impulses to the brain that minimizes thesign and symptoms of Parkinson disease.

Some risks conditions such as infections; stroke or brain hemorrhage may be occurred due to surgery. Some patients who suffered with DBS or having complications because of stimulation doctors should be diagnosed about this.

The individuals who suffered with advanced Parkinson disease can be offered by the Deep brain stimulation those have unstable effect of levodopa. With the help of medication in DBS dyskinesia, tremor, rigidity as well as improvement of slowing movement can be reduced

BDS is used to help lack of regularity and fluctuating effects to levodopa and managing dyskinesia which cannot be cured with medications. DBS is not useful for conditions which does not effect to levodopa medications. However, DBS can control the tremor evenly that cannot effect to levodopa.

In spite of DBS, Parkinson disease can be beneficiary for decreasing signs and symptoms of this disease. It can be prevented from the improvement of Parkinson disease.[50]

Physiotherapy

Patients with Parkinson's disease are advised Exercise programs. There are some evidences that mobility and speech problems can develop with rehabilitation. Muscle stiffness and joint pain can be reduced by a physiotherapist though manipulation and exercise. The main goal of physiotherapist is to make movement easier. Physiotherapist also tries to decrease level of fitness and control thing for you. Physical exercise can be

beneficiary to sustain and improve life quality, gait speech, strength, flexibility, and mobility. When exercise programs are accomplished under the control of physiotherapist,there can be more development in daily living activity, mental and emotional function, and quality of life.[51]

Regular exercise can be helpful patients with Parkinson's disease to improve their flexibility and mobility. The effect of exercise on disease improvement is poorly understood, but it may participate improvement of body strength and flexibility. Exercise can improve body balance as well. Helping patients to decrease gait problems, and can improve strengthen muscles so that individuals may swallow better and speak. Exercise improves physical activity and social well being, such as exercise machines, swimming, gardening, and calisthenics could be more beneficiary.

Many patients who suffered with Parkinson's disease have experienced dysphasia (difficult of swallowing) and speech problems.[51]

A language and speech therapist may often help you to manage these problems through swallowing exercise and speaking, or by giving assistive technology. The goal of occupational therapy is to improve health and quality of life by helping patients who suffered from the disease in order to take part daily live activity as possible.

Diet therapy

For certain patients who suffered with Parkinson's disease, dietary changes can be helpful for improvement signs and symptoms of this disease. This change may include: taking high amount of fiber in the diet and drinking sufficient water to prevent constipation, consuming high amount of salt in the food and eating less, taking food frequently to avoid the problems that may cause low blood pressure (hypotension), such as dizziness. While there no an evidence that specific food is beneficiary, however, healthy diet can improve overall well-being for patients who suffered with this disease just like everyone else. Eating a diet with high amount of fiber can and drinking more fluid can help alleviate constipation. A diet rich in protein, however, may reduce the absorption of levodopa.[52]

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