Relation of Parkinson's Disease to Rhabdomyolysis: an Overview

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Abstract: Parkinson's disease (PD) is neurological disorder developed due to hyposecretion of dopamine; a neurotransmitter released by nerve cells to send signals to other nerve cells. There is loss of dopamine generating cells leading to the formation of lewy bodies inside the neurons. This leads to many motor and non-motor dysfunctions. Movement of individuals is mostly affected. Levodopa treatment has been normally employed to maintain the dopamine levels to reduce symptoms of PD. However, long term use of levodopa for treatment of PD leads to levodopa-induced dyskinesias (LID) finally leading to rhabdomyolysis. Rhabdomyolysis is a life-threatening condition caused by breakdown of muscles. This may lead to many other complications and finally acute renal failure.

Keywords: Parkinson's disease, Levodopa, Dyskinesias, Myoglobin

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder of the central nervous system [1]. It was first described by James Parkinson in 1817 [2]. It is caused by the death of dopamine-producing cells present in substania nigra, a region of midbrain. The cause of this cell death due to an accumulation of a protein called a-synuclein bound to ubiquitin in the damaged cells forming lewy bodies. There is no specific diagnostic test for identifying the disorder. However, it is generally identified by the symptoms which are usually developed after about 80 % of the brain's dopamine-producing cells are lost. The major motor symptoms of PD are tremor, rigidity, slow movement, and postural instability, however; non-motor complications of the disease are depression, dementia and autonomic dysfunction. Neuropsychiatric disturbances range from mild to severe including disorders of speech, cognition, mood, behavior, and thought process. The most common cognitive deficit in affected individuals is executive dysfunction [3]. Apart from cognitive and motor symptoms, other body functions are also impaired. Sleep problems are the main features of the disease and can be worsened by medications. Other observed symptoms of PD are daytime drowsiness, disturbances in REM (Random Eye movement), disturbed sleep or insomnia.



Figure 1: Comparative images focusing *substania nigra* of PD brain and a healthy brain.

2. Development of Parkinson's Disease

Parkinson's disease is idiopathic i.e. having no specific known cause. It is both chronic and advancing in severity i.e. it persists over a long period of time and, its symptoms worsen with time. The brain cells that control the movement rely mainly on a chemical called dopamine that is manufactured in substantia nigra. The dopamine-producing cells in the substantia nigra are lost due to degeneration leading to an accumulation of α -synuclein forming lewy bodies in neurons. Distribution of the lewy bodies throughout the Parkinsonian brain varies from one individual to other. These are found in many regions, including the substantia nigra, locus ceruleus, nucleus basalis, hypothalamus, cerebral cortex, cranial nerve motor nuclei, and the central and peripheral divisions of the autonomous nervous system [4].

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Figure 2: Lewy bodies

However, it is also believed that many environmental factors are also responsible for development of PD [5, 6]. These include pesticide exposure, head injuries, and living in the country where use of pesticide or insecticides in agriculture or farming is in regular practice. The causative insecticides primarily include chlorpyrifos and organochloride herbicides such as Agent Orange, etc [7]. Continuous exposure to heavy metals also leads to high risk factors.

Traditionally PD has been considered to be a non- genetic disorder. However, recent discoveries led to the findings that there are mutations in one of several specific genes. Mutations in specific genes coding for α -synuclein (SNCA), parkin (PRKN), leucine-rich repeat kinase 2 (LRRK2 or *dardarin*), PTEN-induced putative kinase 1 (PINK1), DJ-1 and ATP13A2 have been reported to cause PD [8]. Alpha-synuclein protein being main component of lewy bodies, the role of SNCA gene is important [9]. It is likely that PD results from a combination of genetic susceptibility and exposure to one or more environmental factors that trigger the development of PD.

3. Parkinson's Disease Causing Symptoms

Movement is the most affected phenomenon in PD. This leads to dysfunctions of motor nerves [10], [11]. The fundamental dysfunctions of motor symptoms includetremor, bradykinesia, rigidity, and postural instability. Among these tremors are the most commonly observed symptom of PD. In many cases tremors are not seen during onset of this disease but as the disease progresses tremors become more prominent. The type of tremors called as a rest tremors, are maximal when the limb is at resting state. These rest tremors disappear with voluntary movement and during sleep. Bradykinesia is the slowing down of movement [10]. It is caused by the brain's slowness in transmitting the necessary instructions to the appropriate parts of the body. Hindrance in performance of sequential and simultaneous movement is observed. This leads to an inability in performing day-to-day work which requires fine motor control such as writing, sewing or getting dressed. Bradykinesia affecting the facial muscles may cause the mask-like appearance as normally seen in PD. Rigidity of muscles leads to stiffness and resistance to limb movement [10]. Rigidity is also associated with joint pain. In initial phase of the disease, asymmetrical rigidity is observed which shows effects on the neck and shoulder muscles prior to the muscles of the face. Extremities and progression of this disease increases the rigidity of all muscles of whole body thereby reducing the ability to move. Postural instability leads to improper balance of the body leading to frequent falls causing bone fractures. These symptoms are observed in later stages of the disease. Neuropsychiatric disturbances also range from mild to severe. These include disorders of speech, cognition, mood, behavior, and thinking process. The cognitive disturbances include executive dysfunction including difficulties in planning, cognitive flexibility, abstract thinking, and rule acquisition, initiating appropriate actions and fluctuations in attention [3]. Behavior and mood alterations such as depression, apathy and anxiety are common in PD. Dementia is more commonly observed in PD.



4. Various stages of Parkinson's Disease

PD affects the health in five stages. Although the time for which each stage subsides varies and skipping of stages is also common. Following are the stages of PD:

Stage one: It is the onset of disorder in which patient usually experiences mild symptoms which results in inconvenience in performing day-to-day activities. These symptoms include tremors or shaking of one of the limb. During this stage change of poor posture, loss of balance, and abnormal facial expressions of the patients can be observed by friends and family.

Stage two: In this stage, patient's symptoms are bilateral, affecting both limbs and both sides of the body. The patient usually encounters problems walking or maintaining balance. Inability in performing normal physical tasks becomes more apparent.

Stage three: In this stage the symptoms are severe and include the inability to walk straight or to stand. There is a noticeable slowing of physical movements in this stage.

Stage four: This stage of the disease is accompanied by more severe symptoms of PD. Walking become limited. Rigidity of limbs and *bradykinesia* are often visible in patient. During this stage, most of the patients are incapable to perform the day-to-day tasks, and usually cannot live on their own. The tremors or shakiness lessens or become non-existent for unknown reasons during this time.

Stage five: This is the last or final stage of PD in which there is no physical movement of patient. The patient is usually unable to take care of him and may not be able to stand or walk during this stage. A patient at this stage usually requires constant (one-on-one) attention and nursing care at all the time.

5. Some Preventive measures for Parkinson's disease

Scientists have identified some preventive measures which gave evidence that caffeine consumption decreases the risk of PD (Parkinson's disease). This includes intake of coffee and caffeinated beverage. However, studies conducted by Alberto Ascherio in Harvard School of Public Health, USA, shows that this effect differs in males and females. It features that combining coffee and hormones significantly increases risk of developing PD in women [12]. The study also shows that postmenopausal women who took hormone replacement therapy (HRT) and consumed more than five cups of coffee per day (heavy coffee drinkers) are more likely to develop PD than heavy coffee drinkers who didn't take HRT [12]. Similarly estrogens have neuro-protective effects in PD and show relationship with coffee consumption [12]. Even tobacco smoking may reduce the risk of PD as compared to the non-smokers [13]. This effect is due to nicotine which acts as dopamine stimulant. Tobacco smoke contains compounds that act as MAO inhibitors (Monoamine oxidase) that also might contribute to this effect [14]. Neuronal cells are particularly vulnerable to oxidative stress which may add to development of PD. Consumption of enough antioxidants could efficiently block or retard the progress of such diseases [13]. A research by Departments of Chemistry and Food Science and Technology, Oregon State University, Corvallis, Oregon shows that Chinese beer, made up of hops (*Humulus lupulus L.*) contains large quantity of Xanthohumol (Xn), has a capability to reduce the level of oxidative stress, protecting the brain cells from further damage [15].

6. Levodopa Treatment

There is no cure for PD at present. Now a day a treatment is aimed at reducing the symptoms. The medication employed helps in elevation of dopamine level. Medication with dopamine alone is ineffective because it is restricted by the blood brain barrier. Levadopa, the metabolic precursor of dopamine is the most commonly prescribed medication for treatment of PD [14]. Levodopa is converted into dopamine in the dopaminergic neurons by DOPA decarboxylase. The newly formed dopamine replaces the missing dopaminein brain cells improving control of movements [14]. This reaction occurs both in the peripheral circulation and in the central nervous system and also in brain after levodopa has crossed the blood brain barrier. However, activation of peripheral dopamine receptors causes nausea and vomiting. Carbidopa is added to the levodopa to prevent the breakdown of levodopa before it enters the brain. Carbidopa does not cross the blood-brain barrier and does not affect the metabolism of levodopa in the central nervous system [14]. The incidence of levodopa-induced nausea and vomiting is reduced with the combination carbidopa-levodopa, than with levodopa alone. In many patients, this reduction in nausea and vomiting will permit more rapid dosage titration. Addition of carbidopa also allows lower doses of levodopa to be used for treatment.



Figure 3: Levodopa



Figure 4: Changes in levodopa response associated with progression of PD

7. Levodopa Induced Dyskinesias

High levodopa dose increases the risk of development of levodopa-induced dyskinesias (LID) [16]. Dyskinesias is a condition with unintended, involuntary and uncontrollable movements. LID does not appear in initial stages of



Figure 5: Schematic representation of sequence of events leading to levodopa-induced dyskinesias (LID).

The pathological process of LID is incompletely understood. It is known that dopamergic (or dopaminergic) therapy leads to dyskinesias and there is a time lag between the start of treatment and the emergence of LID. Some peripheral and central mechanisms have been proposed. Development of LID may be due to reduced capacity to maintain the pH of the intact neurons, dietary proteins, role of D3 receptors, and the role of glutamate receptors. The pulsatile stimulation of the postsynaptic receptors, which is due to intermittent administration of levodopa leads to downstream changes in proteins and genes, leading alterations in striatal output which promotes dyskinesias [18]. Over activity of glutamatergic systems (using N-methyl-D aspartate (NMDA) receptors) in the basal ganglia has been observed in patients with LID [19]. Both dopamine and NMDA receptors are expressed along the dendritic spines of striatal medium sized γ -aminobutyric acid (GABA)-ergic neurons. Alterations in cell signals in striatal dopaminergic medium spiny neurons are brought by chronic intermittent stimulation of normally tonically active dopaminergic receptors [16]. This causes potentiation of the GABA-ergic efferents, particularly, glutamate receptors of the NMDA subtype. Genetic abnormalities sometimes result in dopaminergic and non-dopaminergic receptor dependent transmission eventually leading to LID. Fos- and Fos-related proteins (FRA) are also induced in the striatal neurons by excessive glutamatergic inputs [16]. FRAs bind to different transcription factors such as Jun-D, forming activator protein-1AP-1 complexes in nucleus and produce abnormal proteins, including encephalin and NMDA receptors. Many case studies have revealed that levodopa-induced dyskinesias lead to rhabdomyolysis which in turn leads to acute renal failure [20].

8. What is Rhabdomyolysis?

Rhabdomyolysis is a condition which ends up in death because of failure of kidney. It is due to the breakdown of

damaged myocytes. The damaged myocytes after necrosis are released in the blood stream causing renal failure. In rhabdomyolysis elevated levels of serum creatine kinase lactate dehydrogenase, glutamic-oxaloacetic (CK), transaminase, and aldolase; the heme pigment myoglobin; electrolytes, such as potassium and phosphate; and nitrogen containing bases such as purines are normally observed [21, 22]. It could be generalized, or ii may involve specific groups of muscles [23]. The classic triad of symptoms includes weakness, tea-coloured urine and loss of proper muscle contraction with unbearable pain. Life threatening complications such as acute renal failure because of dysfunction of renal tubule filtrations capacity, change of cardiac rhythm, heart failure, increased potassium level, decrease in calcium level and intravascular coagulation, thereby requiring positive management for all these factors.

treatment. Sometimes, it is seen that many patients who have

been prescribed high dose levodopa therapy do not develop dyskinesias. Genetic factors could play a role in occurrence

of dyskinesias. Certain types of dopamine receptor genes

have been associated with a reduced the risk of developing

peak-dose dyskinesias [17].

9. Development of Rhabdomyolysis

There are many reasons for development rhabdomyolysis varying from person to person. Muscular damage, higher than normal exercise, tetanus, Crush syndrome, arterial thrombosis, hypokalemia, hypocalcaemia, increase in body temperature, auto antibody induced muscular cell damage etc, are some of the major reasons of development of rhabdomyolysis [24, 25]. Various formulations of HMG-CoA reductase inhibitors such as drug gemfibrozil cause accumulation of fibrates disturbing the glomerulus infiltration [21]. Consumption of many drugs and toxins simultaneously also leads to this disorder [26, 27], employment of neuromuscular blocking agents in malignant hyperthermia also leads to rhabdomyolysis, prescription of levodopa and carbidopa together for treatment of PD, that too at elevated doses leads to the development of rhabdomyolysis.



Figure 6: Muscle fiber necrosis



Figure 7: Tea coloured urine, a characteristic of rhabdomyolysis.

Muscles contain large amount of myoglobin which carry large amount oxygen. When muscle injury occurs, the released myoglobin binds with other proteins and gets precipitated in glomerular filtrate, causing obstruction in renal tubular epithelium. Intrinsic muscle enzyme deficiencies are generally inherited. This deficiency may lead to rhabdomyolysis due to dysfunction of renal tubules [26-28].

10. Symptoms of Rhabdomyolysis

Rhabdomyolysis includes a classic triad of symptoms that involves weakness, muscle pain and tea-coloured urine. Release of the components of muscle tissue into the bloodstream causes electrolyte disturbances, causing nausea, vomiting, confusion, coma or abnormal heart rate and rhythm. Damage to the kidneys may give rise to decreased or absent urine production, usually within 12 to 24 hours after the initial muscle damage [22]. Rhabdomyolysis is always accompanied with rise in creatine kinase (CK) [23]. There is also high level of potassium in the blood which may lead to an irregular heartbeat or cardiac arrest and kidney damage.

11. Diagnosis of Rhabdomyolysis

Rhabdomyolysis can be diagnosed in patients reporting with high creatine kinase in blood than the normal level. The half life of myoglobin is very short; hence its estimation in blood or urine is difficult for diagnosis of rhabdomyolysis. Various types of urine analysis can identify presence of myoglobin in urine [21]. Increased levels of LDH [26], high levels of potassium ions may also tend to be a feature of severe rhabdomyolysis [23].

12. Changes in Cellular metabolism due to Rhabdomyolysis

Sarcoplasmic influx of sodium, chloride, and water increases due to stretching or exhaustive work of muscle cells resulting into cell swelling and auto destruction [21]. There is an exchange of sodium with calcium inside the cell. Presence of free calcium ions inside the cells helps to maintain cytoplasmic calcium related functions to normal. In addition, calcim activates phospholipase A_2 , as well as vasoactive molecules and proteases leading to free oxygen radicals [29]. Damaged muscles are attacked by activated neutrophils that amplify the damage by releasing proteases and free super oxide radicals, resulting into an inflammatory, self-sustaining myolytic reaction, rather than pure necrosis [25, 30].

13. Complications of rhabdomyolysis

Complications of rhabdomyolysis can be classified into two different stages i.e. early and late. Early complications include hyperkalemia, hypocalcemia, cardiac arrhythmia and cardiac arrest. Approximately 25% of patients with rhabdomyolysis suffer from hepatic dysfunction [31]. Injured muscle release of proteolytic enzymes damaging hepatic cells leading to inflammation of liver. The late symptoms include acute renal failure and diffused intravascular coagulation. The mortality rate of about 20% is generally observed in patients with rhabdomyolysis complicated with acute renal impairment [23]. There is a correlation between CK levels and acute renal failure (ARF). During ARF, the levels of CK may reach to 16,000 units/L [32]. Serum creatinine level is more (up to 2.5 mg/dL) in myoglobinuric renal failure patients per day [220 µmol/ L]) as compared to causes of ARF.

14. Acute renal failure in Rhabdomyolysis

The pathophysiologic mechanism of ARF includes renal vasoconstriction, intraluminal cast formation, and direct heme-protein induced cytotoxicity [29]. Myoglobin is filtered through the glomerular basement membrane while water is progressively reabsorbed in the tubules. Thus, the concentration of myoglobin rises proportionally, until it precipitates and causes obstructive cast formation. This process is favored by decrease in tubular flow and increased water reabsorption due to dehydration and renal vasoconstriction [29]. High rate in generation and excretion of uric acid leads to tubular obstruction by uric acid casts. Low pH of tubular urine due to acidosis favors precipitation of myoglobin and uric acid. The breakdown of intratubular myglobin release produces free radicals and enhances ischemic damage [29]. Lipid peroxidation also initiates the free radical formation, [33] which can be stopped by providing alkaline conditions by stabilizing the reactive ferryl-myoglobin complex.

15. General Treatment for Rhabdomyolysis

usually recover completely Patients can from rhabdomyolysis if the syndrome is recognized and treated promptly at an early stage. The main aim of treating rhabdomyolysis is preserving renal function. In the necrotic muscle tissues up to 12 L of fluid (usually isotonic saline 0.9% weight per volume sodium chloride solution) may be sequestered, thereby preventing to hypovolemia, which is one of cause of renal failure in patients with rhabdomyolysis [34]. In victims of crush syndrome, it is recommended to administer intravenous fluids even before they are extracted from collapsed structures. High rates of IV fluid administration should be used at least until the CK level decreases to or below 1,000 units per L. The main objective behind this treatment is to alkalinize urine to a pH of greater than 6.5, thereby decreasing the toxicity of myoglobin to the tubules which enhances the flushing of myoglobin casts from renal tubules by means of osmotic diuresis. However, if oliguria is established despite initial generous hydration with normal saline, these measures should not be employed.

Mannitol and bicarbonate are commonly employed following the initial recovery with saline. Mannitol is made from mannose sugar in a reduced form, and it can be used as a protective drug due to the associated diuresis that minimizes intratubular heme pigment deposition in kidney [29, 35, 36]. Mannitol minimizes the cell injury as it acts as free- radical scavenger [34]. Furthermore, mannitol acts as a renal vasodilator and reduces the blood viscosity [30, 37]. The use of fully prescribed drug mannitol remains controversial because it reduces the α - *synuclein* level in brain, and it was proved in several experimental animal models.

16. Conclusion

Parkinson's disease is a degenerative and progressive disorder which does not have complete cure till date. The most effective treatment practiced by physicians is levodopa treatment which reduces the symptoms of PD. Levodopa is used in combination with carbidopa to reduce side effects of levodopa. It is observed that in the initial phase of PD the requirement of levodopa is less but as the disease progresses the quantity of drug requirement also increases. Continuous intake of high concentration of levodopa leads to levodopainduced dyskinesias (LID) causing involuntary muscle movements. Further studies prove that LID leads to rhabomyolysis which is a life threatening disorder, because muscle breakdown results into ARF. To avoid these complications authors suggest that levodopa should be prescribed at low doses. Owing to such complications, there is a need to make available of more effective treatment for PD, than levodopa treatment alone, which may not lead to such complications.

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