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Case Report

A case of drug induced dizziness in a patient on anti-Parkinson drugs

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ABSTRACT

Parkinson's disease (PD) is the second most common age-related neurodegenerative disease, exceeded only by Alzheimer's disease. Clinically, PD is characterized by resting tremor, rigidity (stiffness), bradykinesia (slowing), and gait dysfunction with postural instability. These are known as the classical or "cardinal" features of the disease. Levodopa remains the most effective symptomatic treatment for PD and the gold standard against which new therapies are compared. Levodopa is routinely administered in combination with a peripheral decarboxylase inhibitor to prevent its peripheral metabolism to dopamine and the development of nausea, vomiting, and orthostatic hypotension. The major concern with levodopa is that chronic levodopa treatment is associated with the development of motor complications, nausea and dizziness in the large majority of patients. We are here reporting a case of Syndopa plus (Levodopa+Carbidopa) induced dizziness in a 76 years old male patient on anti- parkinsonism treatment. The causality assessment was done by Naranjo scale. The causality of Syndopa plus in the case was "probable" as per Naranjo scale. The patient was managed by reducing the dose of Syndopa plus to the half of it's initial dose. The case was recorded properly in adverse drug reaction reporting form and was sent to nearby ADR (adverse drug reaction) monitoring centre.

Keywords: PD, Levodopa, Dizziness

INTRODUCTION

Parkinson's disease (PD) is the second most common age-related neurodegenerative disease, exceeded only by Alzheimer's disease (AD). Its cardinal clinical features were first described by the English physician James Parkinson in 1817. James Parkinson was a general physician who captured the essence of this condition based on a visual inspection of a mere handful of patients, several of whom he only observed walking on the street and did not formally examine. It is estimated that the number of people with PD in the most populous nations worldwide is ~5 million persons, and this number is expected to double within 20 years based on the aging of the population. The mean age of onset of PD is about 60 years, and the lifetime risk is ~3% for men and 2% for women.[1] The frequency of PD increases with age, but cases can be seen in individuals in their twenties and even younger, particularly when associated with a gene mutation. Clinically, PD is characterized by resting tremor, rigidity (stiffness), bradykinesia (slowing), and gait dysfunction with postural instability. These are known as the classical or "cardinal" features of the disease. Additional clinical features can include freezing of gait, speech difficulty, swallowing impairment, and a series of nonmotor features that include autonomic disturbances, sensory alterations, mood disorders, sleep dysfunction, cognitive impairment, and dementia.

Pathologically, the hallmark features of PD are degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc), reduced striatal dopamine, and intraneuronal proteinaceous inclusions in cell bodies and axons that stain for α-synuclein (known as Lewy bodies and Lewy neurites, collectively as Lewy pathology).

Ongoing loss of nigral dopaminergic presynaptic neurons with a reduction of about 70-80% striatal dopamine mainly

leads to clinical diagnosis due to the occurrence of the main motor symptoms and their dopaminergic response. Therapeutic approaches of non-motor features gain increasing importance in addition to motor symptoms control to improve quality of life in PD patients and their caregivers.[2] Long term treatment of this array of symptoms with various drugs causes the occurrence of short- and long-term side effects. Course of PD, expression of motor and non-motor symptoms, efficacy and tolerability of therapeutic interventions vary from one patient to another. Therefore, an individualized therapeutic regime is performed with repeated control and titration by the treating physician in close cooperation with the patient and his caregiver in clinical practice.

Most PD cases occur sporadically (~85–90%)[1] and are of unknown cause. Gene mutations are the only known causes of PD. Twin studies performed several decades ago suggested that environmental factors might play an important role in patients with an age of onset ≥50 years, with genetic factors being more important in younger-onset patients. However, the demonstration of later-onset genetic variants (e.g., LRRK2 and GBA) argues against the emphasis on environmental factors, even in individuals >50 years of age. The environmental hypothesis received some support in the 1980s with the demonstration that MPTP (1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine), a by-product of the illicit manufacture of a heroin-like drug, caused a PD syndrome in addicts in northern California. MPTP is transported into the central nervous system, where it is oxidized to form MPP^+, a mitochondrial toxin that is selectively taken up by, and damages, dopamine neurons, but typically without the formation of Lewy bodies. Importantly, MPTP or MPTP-like compounds have not been linked to sporadic PD.

Levodopa/carbidopa is mainstay of PD pharmacotherapy. As PD progresses, there is a decrease in intrasynaptic dopamine concentrations and patients require exogenous dopamine to relieve symptoms.[3] Dopamine cannot cross the blood brain barrier (BBB) because it is a polar molecule.[3] Levodopa enters the CNS where it is converted into dopamine by the aromatic amino acid decarboxylase enzyme (AADC). If levodopa is administered without carbidopa, only 1% of the dose reaches the CNS. Carbidopa decreases the peripheral metabolism of levodopa by inhibiting AADC, allowing up to 10% of the levodopa dose to reach the CNS.[3,4] Approximately three-quarters of patients on levodopa experience orthostatic hypotension (OH).[5,6] Carbidopa can result in OH by inhibiting L-amino acid decarboxylase, the enzyme that decarboxylates dihydroxyphenylserine to norepinephrine (NE). This results in impaired NE formation which can produce a vasodilatory effect. Levodopa and carbidopa also cause OH through the activation of dopamine receptors which results in vasodilation.

Dizziness is a common complaint which affects about 30% of people over the age of 65 years. Dizziness includes sensations such as faintness, light headedness, vertigo and imbalance.[7] For constituting the balance system, sensory inputs, integrating system or effector organs must be intact. Alterations in functions of one of these systems cause the dizziness or vertigo. Sensory inputs accepted from vestibular apparatus, visual system, and proprioceptive system pass into the central nervous system and are integrated by activity of cerebellum, extrapyramidal system, limbic system and cerebral cortex.[8] Causes of dizziness are neurootologic problems, general medical problems (cardiovascular disorders, drugs), cervical vertigo and multi- sensory dizziness syndrome.[8] The most common diagnosis reported in referred patients is peripheral vestibular disease.[7]

Here we are reporting a case of drug induced dizziness in a patient on anti-parkinson drugs.

CASE REPORT

A 76 years old male patient on anti-parkinson drugs treatment for 3 months came to Neurology department, Patna Medical College and Hospital, Patna on 11/12/2022 with complains of dizziness. His MRI report at the striatal level showed putaminal atrophy, putaminal hypointensity, and a putaminal hyperintense rim as showed in figure 1. He was on anti-parkinson drugs namely tab. Syndopa plus (Levodopa+ Carbidopa), 125 mg; tab. Pramipex, 0.25 mg and tab. Pacitane, 2 mg for 3 months. The neurologist with the help of other clinical departments tried to find out the cause of dizziness. He finally concluded that the dizziness was due to orthostatic hypotension. He managed the patient by reducing the dose of tab. Syndopa plus to half of it's initial dose. The complain of the patient diminished gradually. The causality assessment was done by Naranjo scale. The causality of Syndopa plus in the case was "probable" as per Naranjo scale. Score as per Naranjo scale was 6.

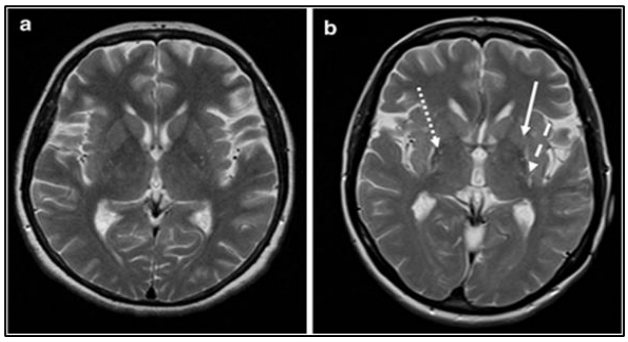

Figure 1 (A and B): Axial T2- weighted MRI at the striatal level in a patient with idiopathic Parkinson disease. Putaminal atrophy (arrow), putaminal hypointensity (dotted arrow), and a putaminal hyperintense rim (dashed arrow).

DISCUSSION

Since its introduction in the late 1960s, levodopa has been the mainstay of therapy for PD. Experiments in the late

1950s by Carlsson and colleagues demonstrated that blocking dopamine uptake with reserpine caused rabbits to become parkinsonian; this could be reversed with the dopamine precursor, levodopa. Subsequently, Hornykiewicz demonstrated a dopamine deficiency in the striatum of PD patients and suggested the potential benefit of dopamine replacement therapy. Dopamine does not cross the blood-brain barrier (BBB), so clinical trials were initiated with levodopa, the precursor of dopamine. Studies over the course of the next decade confirmed the value of levodopa and revolutionized the treatment of PD.

Levodopa is routinely administered in combination with a peripheral decarboxylase inhibitor to prevent its peripheral metabolism to dopamine and the development of nausea, vomiting, and orthostatic hypotension due to activation of dopamine receptors in the area postrema (the nausea and vomiting center) that are not protected by the BBB. In the United States, levodopa is combined with the decarboxylase inhibitor carbidopa (Sinemet), whereas in many other countries it is combined with benserazide (Madopar). Levodopa plus a decarboxylase inhibitor is also available in a methylated formulation, a controlled-release formulation (Sinemet CR or Madopar HP) and in combination with a catechol-O- methyltransferase (COMT) inhibitor (Stalevo). A long-acting formulation of levodopa (Rytary) and a levodopa carbidopa intestinal gel that is administered by continuous intraintestinal infusion via an implanted jejunal tube are also now available. An inhaled form of levodopa that is rapidly and reliably absorbed through the pulmonary alveoli has recently been approved as an on-demand therapy for the treatment of individual "off " episodes.

Levodopa remains the most effective symptomatic treatment for PD and the gold standard against which new therapies are compared. No current medical or surgical treatment provides antiparkinsonian benefits superior to what can be achieved with levodopa. Levodopa benefits the classic motor features of PD, prolongs independence and employability, improves quality of life, and increases life span. Indeed, levodopa also benefits some "nondopaminergic" features such as anxiety, depression, and sweating. Almost all PD patients experience improvement, and failure to respond to an adequate trial of levodopa should cause the diagnosis to be questioned.

There are important limitations of levodopa therapy. Acute dopaminergic side effects include nausea, vomiting, and orthostatic hypotension. These are usually transient and can generally be avoided by starting with low doses and gradual titration. If they persist, they can be treated with additional doses of a peripheral decarboxylase inhibitor (e.g., carbidopa), administering with food, or adding a peripheral dopamine-blocking agent such as domperidone (not available in the United States). As the disease continues to progress, features such as falling, freezing, autonomic dysfunction, sleep disorders, and dementia may emerge that are not adequately controlled by levodopa. Indeed, these nondopaminergic features (especially falls and dementia) are the primary source of disability and the main reason for hospitalization and nursing home placement for patients with advanced PD in the levodopa era.

Medications used to treat PD, including Levodopa[9], may result in orthostatic hypotension (OH). Dopamine agonists can markedly reduce blood pressure, and precipitous changes can occur even with the first dose.[10] Dopamine agonists lower blood pressure primarily by venous and arterial dilation through inhibition of the sympathetic nervous system.[11] Because apomorphine hydrochloride and bromocriptine mesylate decrease blood pressure in normotensive and hypertensive subjects, dopamine agonists have been used in the treatment of high blood pressure.[12,13] In PD, OH has been a well- recognised adverse effect of all available dopamine agonists, including bromocriptine, pergolide mesylate, and the newer agents, pramipexole dihydrochloride and ropinirole hydrochloride.[14,15]

In the present case, the possible causes of dizziness are discussed one by one.

For vestibulospinal system; Romberg test, Unterberger's tests, Tandem gait test, and gait test were applied by the neurologist. For vestibulo-ocular function; nystagmus, gaze abnormalities, oculocephalic test, doll's eye maneuver, head impulse test, Hallpike test, past-pointing test were done. Complete otological examinations were made by otoneurologist. The patient in the case was normal on vestibulospinal, vestibulo-ocular and otological examinations.

Routine blood biochemistry tests, complete blood count, thyroid function tests and cranial computed tomography were performed for the patient and all the results were normal.

The patient was investigated with colour Doppler ultrasonography for vertebral artery insufficiency and gave the normal result.

The patient underwent a direct radiographic evaluation of cervical region. Planes were taken anterior-posterior and lateral view. Loss of disc height, with subsequent loss of cervical lordosis, presence of anterior osteophytes and posterior osteophytes, reduced space between vertebrae of neck were determined by radiologist. The radiologist noted normal radiographies of the cervical region. In addition, for evaluation of vestibular nerve, audiometric tests were done and gave the normal results.

Electrocardiography of the patient was evaluated for cardiac arrhythmia. Blood pressure and heart rate were recorded using flat manometer instrument. Blood pressure was first measured after a 15-minute rest in a supine position. Patient was then asked to spontaneously stand up and blood pressure was recorded after three minutes. A decrease ≥20 mm Hg in systolic blood pressure, ≥10 mm Hg in diastolic blood pressure and, an increase ≥30 beats

per minute in peripheral artery pulses were chosen as the criterion for orthostatic hypotension. In the present patient there was 24 mm Hg decrease in systolic blood pressure, 14 mm Hg decrease in diastolic blood pressure and increase of 32 beats per minute in peripheral artery pulses after 3 minutes of standing. Thus, we can safely say that the dizziness in the patient was due to orthostatic hypotension.

The treatment of OH in PD includes non- pharmacological as well as pharmacological measures to stabilize blood pressure. Non-pharmacological therapies include eliminating or decreasing medications that cause OH, increased consumption of salt and fluids, smaller but more frequent meals, avoidance of alcoholic beverages, and use of elastic Jobst stockings to increase venous return of blood to the heart. Since these conservative measures may be effective in patients who have only mild dysfunction, pharmacological agents are usually necessary to improve the patient's symptoms. The number of medications available is extensive and diverse, each with an associated profile of potential adverse effects, supine hypertension being the most common. Frequently used drugs in the treatment of OH include mineralocorticoids (fludrocortisone), sympathomimetics (ephedrine and phenylpropanolamine), direct vasoconstrictors (midodrine hydrochloride), prostaglandin synthetase inhibitors (indomethacin) and prohemopoietic agents (erythropoietin). In present case, the patient was managed with non- pharmacological therapy by reducing the dose of Syndopa plus to half of it's initial dose. The initial dose was 125 mg, TDS and now the dose was reduced to half. Then the complain of dizziness was diminished gradually.

CONCLUSION

Dizziness is a common complaint in PD patients. This dizziness is mainly due to orthostatic hypotension (OH), but a high proportion of dizzy PD patients without OH are seen in the clinical setting. Even they do not show postural instability and ataxia. One study reported that non-specific dizziness was seen in 29.7% of patients in the early stage of PD. It is the second most common type of dizziness after orthostatic hypotension. Dizziness has also been reported to be a prodromal symptom of PD. PD patients report frequent dizziness at least 5 years before diagnosis. In patients of PD, dizziness may be managed by pharmacological or non- pharmacological therapies. In our case the patient was managed non- pharmacologically by reducing dose of Syndopa plus to half of it's initial dose.

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