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Case Presentation
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Amlodipine: Guardian or Provocateur? Exploring Its Role in Parkinsonism

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Abstract

Drug-induced parkinsonism (DIP) is a debilitating side effect associated with several classes of medications. Amlodipine is a widely used dihydropyridine calcium channel blocker (CCB) commonly prescribed for hypertension and angina. We present a case of a 62-year-old man who underwent liver transplantation and developed parkinsonism shortly after initiation of amlodipine for hypertension. After ruling out other causes for his neurological presentation, discontinuation of amlodipine resulted in a rapid improvement of symptoms, confirming the diagnosis of DIP. This report highlights the importance of recognizing amlodipine as a potential cause of new-onset parkinsonism and underscores the need for further research to understand its effects on the dopaminergic pathway.

Keywords: Amlodipine; Parkinson's Disease; Drug-Induced Parkinsonism; Calcium Channel Blockers; Antihypertensives

Introduction

Parkinsonism, a debilitating syndrome characterized by tremors, bradykinesia, rigidity, and postural instability, is commonly seen in Parkinson's disease (PD). However, there are a number of secondary causes, including medications. Drug-induced parkinsonism (DIP) was initially reported as a complication of antipsychotics but has also been described in other classes of medications, usually with antidopaminergic effects [1].

Amlodipine is an antihypertensive and anti-anginal agent with the combined advantages of a good safety profile, gradual onset, and long duration of action. It is a calcium channel blocker (CCB) that inhibits calcium influx through L-type calcium channels, causing vasodilation and decreased peripheral resistance. Although it is a widely used drug with a well-known safety profile, its effect on the dopaminergic pathway and associated neurological effects has not been well-addressed.

This case report sheds light on a rare incidence of parkinsonism induced by amlodipine, highlighting the relation between the initiation of medication and the onset of parkinsonian symptoms. Resolution of symptoms following the discontinuation of the drug reinforced the diagnosis of DIP. This report aims to draw attention to this rare adverse effect and the possible consideration of CCBs, particularly amlodipine, as a causative factor in patients presenting with new-onset parkinsonism.

Case Presentation

A 62-year-old man with a history of end-stage liver disease due to autoimmune hepatitis was transferred for rehabilitation following a liver transplant 2 weeks ago. The patient presented with significant neurological deficits. He remained persistently and severely encephalopathic following the transplant. He was disoriented and extremely deconditioned. He had a long-standing history of hepatic encephalopathy before the transplant with fluctuating mental status, which responded to lactulose but never as severe. He also had a history of tremors without limitations to his activities. On examination, there was marked rigidity and cogwheeling in both upper and lower extremities with a pill-rolling tremor in the right hand, raising concern for DIP with superimposed delirium. There were no apparent signs of underlying neurodegenerative processes, and Wilson's disease was also ruled out. A neurology consult was sought, and the patient underwent a computed

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tomography (CT) scan of the head which revealed no acute bleed (Figure 1), followed by a magnetic resonance imaging (MRI) of the brain (Figure 2). Both showed changes consistent with moderate small vessel ischemic disease in the periventricular and subcortical white matter in the bilateral cerebral hemispheres and pons and chronic neurodegeneration. There were several recent changes in the patient's medications, and a careful review was done for drugs associated with DIP. He was started on amlodipine 12 days before the transplant for persistent hypertension. Following the transplant, the patient was started on immunosuppression with methylprednisolone and tacrolimus. He was also on trimethoprim/sulfamethoxazole for Pneumocystis pneumonia prophylaxis. In view of his altered mental status, steroids were stopped 7 days post-transplant without effect. The patient was then taken off tacrolimus, which has been implicated in DIP, after 16 days and switched to cyclosporine before transfer to rehab. Finally, amlodipine was stopped 23 days post-transplant, and the patient showed dramatic improvement within 2 days after discontinuation with almost complete resolution of parkinsonian features, with the exception of a persisting tremor.

Discussion

Amlodipine is a widely used third-generation dihydropyridine calcium channel antagonist with unique physicochemical properties. With a pKa value of 8.7, amlodipine is mainly in its ionized form at physiological pH and circulates bound to plasma proteins. Its distinctive pharmacokinetic profile is marked by nearly complete absorption, delayed peak plasma levels, high bioavailability, and slow hepatic metabolism. This profile offers clinical benefits such as a gradual onset and prolonged duration of action, accounting for minimal reflex tachycardia and reduced vasodilator side effects compared to first- and second-generation CCBs. It does not easily penetrate the blood-brain barrier and is considered a peripherally acting CCB. Uniquely, amlodipine also exhibits antioxidant activity at a cellular level, unlike other CCBs [2].

While some published reports suggest neuroprotective roles of CCBs in neurodegenerative diseases like PD, contradictory evidence exists regarding their association with parkinsonism. DIP or worsening of previously diagnosed PD has been documented primarily in medications with antidopaminergic effects, notably central dopaminergic antagonists, and to a lesser extent with antidepressants, CCBs, peripheral dopaminergic antagonists, and H1 antihistamines. An initial peak in drug-induced or -worsened parkinsonism symptoms was reported within 3 months of starting the medication in a majority of patients, though a second smaller peak at 12 months was noticed in 20% of the patients, mostly in those using CCBs [1]. While the precise mechanism of amlodipine's effect on the dopaminergic system remains unclear, studies on other CCBs suggest a reduction in dopamine neurotransmission both in vitro and in vivo [3]. The pathogenic mechanism may involve both presynaptic factors, like loss of tyrosine hydroxylase, and postsynaptic factors, such as blocking of striatal dopaminergic receptors [3]. These symptoms typically reverse upon discontinuation of the drug, though rarely some patients exposed to certain CCBs like flunarizine and cinnarizine do not fully recover [4].

The cellular pathogenesis of neurodegeneration in PD involves protein accumulation, mitochondrial dysfunction, oxidative and nitrative stress, neurotransmitter excitotoxicity, and inflammation. L-type calcium channels located on the plasma membrane of dopaminergic neurons are responsible for the extracellular to intracellular calcium flux that plays a part in generating autonomous pace making signals in substantia nigra pars compacta. The Cav 1.3 isoform in particular has been implicated in the calcium influx and oxidative stress of dopaminergic neurons. The neuroprotective effect of dihydropyridine CCBs may be explained by their preferential binding to and inhibition of Cav1.3 L-type calcium channels at therapeutic concentrations [5]. In animal models of PD, treatment with dihydropyridine CCBs was found to reduce toxin-induced loss of substantia nigra dopaminergic cells and to protect against toxin-induced motor deficits [6]. The neuroprotective association of both dihydropyridine and non-dihydropyridine CCBs in PD was corroborated in several large-scale studies [7]. A prospective study in patients with hypertension using centrally-acting dihydropyridine CCBs such as felodipine and nifedipine showed dose-dependent decreased risk of PD, hinting at a potential protective effect. Despite amlodipine's limited blood-brain barrier penetrance, this study also showed a decreased association between higher cumulative amlodipine use and incidence of PD [8].

The patient recently began taking immunosuppressants including steroids, tacrolimus and cyclosporine, which are also reported to exert both potential neuroprotective and neurotoxic effects through various mechanisms. Evidence indicates that the neuroprotective effect may be due to the inhibition of T-cell mediated inflammation and neuronal cell death [9]. However, there are reports of tacrolimus- and cyclosporine-induced neurotoxicity, which may be attributed to the inhibition of calcineurin in the central nervous system [10-12]. These medications are unlikely to be the cause of DIP in this case, given the timing of the onset and resolution of parkinsonian symptoms.

Conclusion

Amlodipine is a dihydropyridine CCB characterized by distinctive pharmacokinetic properties and decreased blood-brain barrier penetrance. Its effect on parkinsonism is not well understood and a review of literature shows contradictory reports of both neuroprotective effect and worsening of parkinsonian symptoms. DIP secondary to amlodipine use may be explained by the anti-dopaminergic activity of CCBs. This adverse effect, while rare, has to be considered in a patient with new-onset parkinsonian symptoms as it is reversed after discontinuation of the drug. More research on the unique pharmacological profile of amlodipine is warranted to better elucidate its effect on the dopaminergic pathway in the central nervous system.

Ethical Statement

This case report was conducted in accordance with the principles of the Declaration of Helsinki. Patient consent for participation and publication (including the use of clinical details and images) was obtained. All identifying information has been removed to protect patient anonymity.

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