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Single Case – General Neurology

Refractory Seizures Secondary to Vitamin B6 Deficiency in Parkinson Disease: The Role of Carbidopa-Levodopa

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Abstract
Carbidopa-levodopa has been used for more than 50 years in the treatment of Parkinson disease (PD) and other movement disorders. Pyridoxal 5′-phosphate (PLP), an active form of vitamin B6 (pyridoxine), is involved in the decarboxylation of levodopa to dopamine; carbidopa, which is combined with levodopa to reduce peripheral levodopa conversion and minimize peripheral dopamine side effects, binds irreversibly with PLP. As a result, carbidopa-levodopa may cause vitamin B6 deficiency and associated sequelae, including seizures, especially in high doses. A 78-year-old gentleman with a 6-year history of PD on carbidopa-levodopa therapy and recent weight loss presented with new-onset myoclonus and focal to bilateral tonic-clonic seizures. Workup for vascular, infectious, malignant, metabolic, and autoimmune causes of seizure was unrevealing. The folate level was critically low at <2.20 ng/dL. Video EEG studies showed moderate cerebral dysfunction and seizures with diffuse onsets. Several anti-seizure medications (ASMs) were unsuccessfully tried, so empiric treatment with high-dose steroids was initiated eventually alongside intravenous vitamin B6 therapy. Following introduction of these interventions, the patient had no further epileptic events. The vitamin B6 level came back as undetectable at <1 µg/dL. The patient was discharged to a rehabilitation center for improved strength and function. At the time of writing, he remained on two ASMs as well as IV B6 supplementation. Vitamin B6 is a required cofactor in the decarboxylation of levodopa to dopamine, and high levodopa dosages may cause B6 deficiency; in addition, carbidopa binds B6

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irreversibly. We recommend screening of vitamin B6 levels in PD patients, especially those requiring high or increasing doses of carbidopa-levodopa and those with poor nutrition.

Introduction

Pyridoxine deficiency is a well-established cause of seizures in neonatal and pediatric populations [1, 2]. It may also cause seizures in adults [3, 4]. Pyridoxal 5′-phosphate (PLP), an active form of vitamin B6 (pyridoxine), is a cofactor in over 100 enzymatic reactions, including decarboxylation of levodopa to dopamine by dopa-decarboxylase [5]. For treatment of movement disorders, levodopa is combined with carbidopa, a peripheral dopa-decarboxylase blocker, to reduce peripheral levodopa conversion and thus minimize peripheral dopamine side effects and increase central levodopa, which, unlike dopamine, crosses the blood-brain barrier. Carbidopa also binds irreversibly with PLP and may cause vitamin B6 deficiency and associated sequelae, especially in high doses [6, 7].

Case Presentation

A 78-year-old gentleman with a 6-year history of Parkinson disease (PD) on carbidopa-levodopa, rivastigmine patch, and selegiline presented with new-onset myoclonus and focal to bilateral tonic-clonic seizures. Five months prior, he began experiencing a more rapid progression of his PD symptoms and an overall decline in functional status notable for worsening off periods, depression, and anorexia. His response to treatment with carbidopa-levodopa grew less robust despite increasing dosages.

Workup for vascular, infectious, malignant, and metabolic causes of seizure, including CT head without contrast, MRI brain with and without contrast, chest X-ray, CT chest, abdomen and pelvis, urinalysis, white blood cell count, thiamine level, acetaminophen level, and salicylate level, was unrevealing. The following additional lab studies were also unremarkable: TSH, RPR, B12, HIV, SPEP/UPEP, ANA, anti-TPO, anti-thyroglobulin, and NH3. The folate level was critically low at <2.20 ng/dL. Video EEG studies showed moderate cerebral dysfunction and seizures with diffuse onsets. CSF initially showed no white blood cells, normal protein, and normal glucose levels. CSF from a second sample, 4 days later, showed mild pleocytosis in the setting of a traumatic tap with normal protein and glucose. Over the course of his hospitalization, he required three concurrent anti-seizure medications (ASMs), which were added incrementally in the setting of ongoing seizures.

As our leading diagnosis was an autoimmune or paraneoplastic condition, empiric treatment with high-dose steroids was initiated while we awaited full CSF results, and folate was repleted intravenously. In addition, in light of his anorexia and carbidopa-levodopa treatment history, pyridoxine deficiency was also considered as a possible etiology, and intravenous B6 was initiated. Following introduction of these interventions, the patient had no further epileptic events.

Serum and CSF autoimmune and paraneoplastic panel results were returned in the weeks following patient's presentation and were negative. The vitamin B6 level came back as undetectable at <1 μg/dL.

The patient was discharged to a rehabilitation center for improved strength and function. At the time of writing, he remained on two ASMs as well as IV B6 supplementation.

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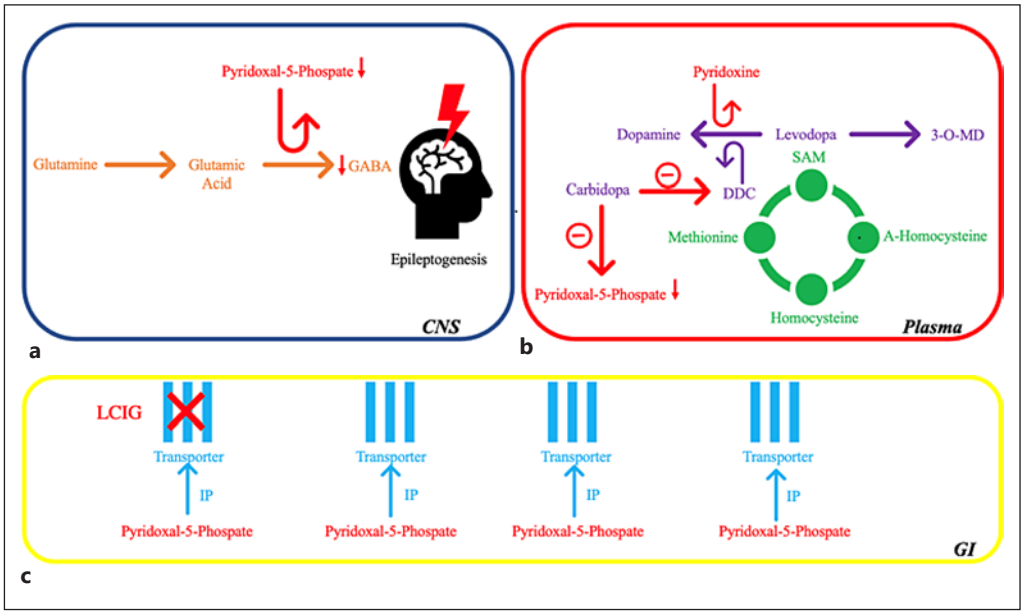

Fig. 1. Proposed mechanism of pyridoxine induced seizures [1, 6, 7, 9, 10]. **a** B6 deficiency decreases GABA synthesis causing epileptogenesis. **b** Carbidopa binds to PLP irreversibly, blocking peripheral levodopa decarboxylation. **c** IPs hydrolyze pyridoxine's phosphate group for absorption; LCIG may inhibit the absorption of water-soluble vitamins such as pyridoxine. GABA, gamma-aminobutyric acid; CNS, central nervous system; 3-O-MD, 3-O-methyldopa; DDC, dopamine decarboxylase; SAM, S-adenosyl-methionine; A-Homocysteine, adenosylhomocysteine; LCIG, levodopa-carbidopa intestine gel; IP, intestinal phosphatase; GI, gastrointestinal; ⊖, inhibition; ↓, deficiency.

Discussion/Conclusion

With a wide range of mechanisms, deficiencies or excesses of multiple vitamins and other nutrients have been linked to cortical hyper excitability and seizures [8]. An active form of vitamin B6, PLP is a nearly ubiquitous coenzyme with wide-ranging synthetic, developmental, and modulatory functions. With regard to seizures, its role in the formation of gamma-aminobutyric acid (GABA) is of particular relevance as reduced GABA-mediated inhibition causes epilepsy in both humans and animals [6].

Our patient presented with new-onset refractory seizures after 5 months of weight loss and functional decline despite increasing doses of carbidopa-levodopa. Seizure cessation was achieved only after the addition of a third ASM, initiation of a 5-day course of high-dose steroids, and intravenous vitamin B6 repletion. Given noninflammatory findings on spinal tap, negative CSF/serum autoimmune/paraneoplastic antibodies, and unrevealing imaging studies, we concluded that this patient's epileptic events had been secondary to depletion of vitamin B6 in the setting of relatively high doses of carbidopa-levodopa (shown in Fig. 1a).

The mechanism of B6 deficiency in patients treated with carbidopa-levodopa is not fully elucidated, although studies have demonstrated an inverse relationship between dosages of both levodopa and carbidopa and B6 levels [7]. Vitamin B6 is a required cofactor in the decarboxylation of levodopa to dopamine and high levodopa dosages may cause B6 deficiency. Considered even more important is carbidopa, which binds B6 irreversibly (shown in Fig. 1b).

Prior reports of B6-related seizures on carbidopa-levodopa therapy have included patients on levodopa-carbidopa intestinal gel, which may inhibit the absorption of water-soluble

vitamins, or patients on hemodialysis [9, 11] (shown in Fig. 1c). In our patient, as well as in another recently reported case, anorexia with poor nutrition played an important role [10].

We suspect that this patient's vitamin B6 reserves fell below a clinically significant threshold around the time that his response to carbidopa-levodopa decreased, prompting increasing doses of medication (>1,200 mg of levodopa daily with >300 mg of carbidopa). This may have provoked a vicious cycle in which his parkinsonian symptoms caused anorexia, thus resulting in further nutritional deficiencies. In addition to seizures, B6 deficiency can lead to depression, peripheral neuropathy, skin rashes, and other systemic manifestations.

As noted above, at the time of presentation, this patient's folate level was also critically low. Folate deficiency is a well-established cause of depression, cognitive impairment, and peripheral neuropathy; but to our knowledge, an association between low folate and seizures in adult patients has not been reported. Even so, many inherited disorders of folate transport and metabolism are known to cause epilepsy, and it is therefore possible that this patient's folate deficiency also contributed to his presentation [12].

Although the evidence for weaning ASMs after new-onset status epilepticus is scarce, the current recommendation is discontinuation of medications after 2 years of seizure freedom [13]. A single center retrospective study found no association between the etiology of status epilepticus, elderly age, or use of multiple ASMs as predictors of seizure recurrence after weaning of ASM [14]. Nomograms are available for clinicians to identify predictors of seizure recurrence and long-term seizure outcomes, including the absence of epileptiform activity on EEG prior to withdrawal of the medications [15].

Despite growing evidence supporting carbidopa-levodopa-associated vitamin B6 deficiency and its critical import, clinical documentation is sparse, suggesting under-recognition. We recommend screening of vitamin B6 levels, especially in patients requiring high and increasing doses of carbidopa-levodopa and in those with poor nutrition.

Statement of Ethics

In compliance with ethical standards, written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. Ethical approval is not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

The authors declare that they have no competing interests.

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Author Contributions

Adina Wise, Hernan Nicolas Lemus, and Susan Bressman: substantial contributions to the conception or design of the work, drafting the work or revising it critically for important intellectual content, and final approval of the version to be published. Madeline Fields and Matthew

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Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to Adina Wise, author, adina.wise@mountsinai.org.

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