Pearls and Oy-sters: Vitamin B₆ deficiency presenting with new-onset epilepsy and status epilepticus in a patient with Parkinson disease

Joseph S. Modica, MD, Deana Bonno, MD, and Karlo J. Lizarraga, MD, MSc

Neurology® 2020;94:e2605-e2607. doi:10.1212/WNL.00000000000009647

Correspondence

Dr. Lizarraga
karlo.lizarraga@gmail.com

Pearls

- Pyridoxine (vitamin B₆) deficiency is a treatable cause of new-onset epilepsy and status epilepticus in patients with Parkinson disease (PD).
- Long-standing high-dose carbidopa-levodopa intake in the setting of gastroparesis or poor nutritional intake may contribute to pyridoxine deficiency in patients with PD.

Oy-sters

- Unrecognized pyridoxine deficiency in patients with PD could lead to epilepsy and status epilepticus.
- There is no evidence to support dietary avoidance of pyridoxine in patients with PD who are treated with carbidopa-levodopa.

Case report

An 83-year-old woman with hypertension, coronary artery disease, and PD developed recurring paroxysmal events consistent with multifocal motor and nonmotor epileptic seizures with and without secondary generalization. Repeated EEG studies revealed multifocal epileptiform discharges or electrographic seizures. Brain MRI and CSF studies were unremarkable.

Over the next 6 months, her epileptic seizures became progressively more frequent despite treatment with oral levetiracetam (1,000 mg twice daily, 29.45 mg/kg/d), topiramate (100 mg twice daily, 2.95 mg/kg/d), phenytoin (150 mg twice daily, 4.42 mg/kg/d), and lorazepam (0.5 mg daily). She presented to the emergency department at our institution after several recurrent seizures without return to her neurologic baseline. Despite initial administration of 2 mg IV lorazepam, the patient had 1 additional focal motor seizure requiring 2 more mg of IV lorazepam. Her levetiracetam dose was increased to 1,500 mg twice daily (44 mg/kg/d) after a loading IV dose of 1,000 mg. Clinical seizures ceased, but she required intubation for airway protection. Her health care proxy agreed to intubation despite a previous advanced directive given the potential reversibility of her current condition. Despite her antiepileptic medication levels being therapeutic, continuous video-EEG monitoring persistently showed occasional electrographic seizures and frequent multifocal epileptiform discharges (figure).

Her dopaminergic regimen for PD treatment had remained stable for the previous 2 years. Her medications included 1 tablet of carbidopa/levodopa 25/100 mg controlled release and 2 tablets of carbidopa/levodopa 25/100 mg immediate release taken together 7 times per day (2,100 mg/d), pramipexole 1.5 mg per mouth 3 times daily, and amantadine 100 mg per mouth daily. Her total

From the Department of Neurology (J.S.M., D.B., K.J.L.) and Motor Physiology and Neuromodulation Program (K.J.L.), Division of Movement Disorders and Center for Health + Technology, Department of Neurology, University of Rochester, NY.

Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

doi:10.1212/WNL.00000000000009647

Copyright © 2020 American Academy of Neurology

Neurology®

levodopa-equivalent daily dose was 2,475 mg. According to her health care proxy, the patient had developed progressively worsening symptoms consistent with gastroparesis and

unintended weight loss of 9 kg over the 6 months before seizure onset. Furthermore, the proxy reported that she had been specifically trying to avoid pyridoxine (vitamin B₆) in her diet

Figure Scalp EEG recording examples in this patient with Parkinson disease and pyridoxine deficiency causing new-onset epilepsy and status epilepticus

Frequent, independent, multifocal epileptiform discharges (arrows) are shown with maximal amplitudes on the (A and C) right frontal (Fp2 electrode), (A and C) left frontotemporal (FT9 electrode), (B and D) midline (Fz/Cz electrodes), and (B and D) right frontotemporal regions (FT10/F8 electrodes). EEG activity was recorded with scalp electrodes positioned according to the 10–20 international system. Signals from (A and B) average referential and (C and D) bipolar montages were recorded at a sample rate of 500 Hz, sensitivity of 7 µV/mm, high-frequency filter of 70 Hz, and low-frequency filter of 1 Hz. Panels A (average referential montage) and C (bipolar montage) correspond to the same time epoch. Panels B (average referential montage) and D (bipolar montage) correspond to the same time epoch.

after learning about the potential reduction of levodopa efficacy in a support group. Unfortunately, the patient and her health care proxy had not discussed this decision with any of her physicians.

Laboratory studies confirmed the suspicion of pyridoxine deficiency. She had very low serum pyridoxine (<5 nmol/L, normal 20–125 nmol/L), low serum folate (4.2 ng/mL, normal >4.6 ng/mL), normal serum vitamin B₁₂ (1,060 pg/mL, normal 232–1,245 pg/mL), and high serum homocysteine (19 µmol/L, normal 0–15 µmol/L) levels. Pyridoxine replacement was started at 20 mg/d IV with immediate improvement in her mental status, resolution of electrographic seizures, and marked reduction in the frequency of epileptiform discharges. Unfortunately, the patient did not tolerate extubation due to severe laryngeal stenosis and, along with her health care proxy, decided not to be reintubated, subsequently passing away.

Discussion

Pyridoxine deficiency is thought to cause epilepsy due to decreased production of gamma-aminobutyric acid, the main inhibitory neurotransmitter in the brain. Pyridoxine deficiency is a well-known etiology of intractable epileptic seizures and status epilepticus in neonates and children. However, it has rarely been reported and may be underdiagnosed as a cause of epileptic seizures in adults.^{1,2}

Pyridoxine is required as a cofactor for the metabolism of levodopa into dopamine and can theoretically be depleted by excessive amounts of levodopa.³ In fact, a dose-dependent association has been reported in which levodopa-equivalent daily doses of ≥2,000 mg result in pyridoxine deficiency in virtually all patients, regardless of the levodopa formulation and route of administration.⁴ Indeed, the prevalence of peripheral neuropathy associated with reduced levels of vitamins B₆ and B₁₂ is higher in patients treated with oral (30.2%) or intestinal (42.1%) formulations of levodopa compared to people of a similar age (8%–10%).⁵

For unknown reasons, the 1% prevalence of epilepsy in non-institutionalized elderly people increases to 8.3% in those who live with PD in nursing homes.⁶ High-dose carbidopa-levodopa treatment as a jejunal gel infusion has previously been reported to cause marked pyridoxine deficiency and epileptic seizures that resolved after pyridoxine supplementation in 1 patient with PD.⁷ The patient we report developed new-onset treatment-resistant multifocal epilepsy and status epilepticus due to multifactorial pyridoxine deficiency, including treatment with oral levodopa. She was consistently taking levodopa-equivalent daily doses >2,000 mg/d for at least 2 years in the setting of poor nutritional intake, weight loss, and avoidance of supplementary

dietary pyridoxine. Although early research suggested that pyridoxine might accelerate the metabolism and reduce the effectiveness of levodopa in the treatment of PD,⁸ further studies suggested that carbidopa prevented this theoretical reduction of levodopa effects and recommended against dietary avoidance of pyridoxine.^{9–11} Moreover, vitamin B₆ and B₁₂ supplementation has been recommended for patients with PD who have peripheral neuropathy symptoms or supportive biochemical alterations.⁵ Timely recognition and treatment of pyridoxine deficiency could prevent new-onset epileptic seizures and status epilepticus in patients with PD treated with high-dose levodopa.

Study funding

No targeted funding reported.

Disclosure

The authors report no disclosures relevant to the manuscript. Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures.

Appendix Authors

Name	Location	Contribution
Joseph S. Modica, MD	University of Rochester, NY	Acquired and interpreted the data, drafted and revised the manuscript for intellectual content
Deana Bonno, MD	University of Rochester, NY	Acquired and interpreted the data, drafted and revised the manuscript for intellectual content
Karlo J. Lizarraza, MD, MSc	University of Rochester, NY	Acquired and interpreted the data, drafted and revised the manuscript for intellectual content

References

1. Tong Y. Seizures caused by pyridoxine (vitamin B₆) deficiency in adults: a case report and literature review. *Intractable Rare Dis Res* 2014;3:52–56.
2. Plecko B, Stöckler S. Vitamin B₆ dependent seizures. *Can J Neurol Sci* 2009;36(suppl 2):S73–S77.
3. Sourkes TL. Dopa decarboxylase: substrates, coenzyme, inhibitors. *Pharmacol Rev* 1966;18:53–60.
4. Loens S, Chorbazhieva E, Kleimann A, Dressler D, Schrader C. Effects of levodopa/carbidopa intestinal gel versus oral levodopa/carbidopa on B vitamin levels and neuropathy. *Brain Behav* 2017;7:e00698.
5. Romagnolo A, Merola A, Artusi CA, Rizzone MG, Zibetti M, Lopiano L. Levodopa-induced neuropathy: a systematic review. *Mov Disord Clin Pract* 2018;6:96–103.
6. Birnbaum AK, Leppik IE, Svensden K, Eberly LE. Prevalence of epilepsy/seizures as a comorbidity of neurologic disorders in nursing homes. *Neurology* 2017;88:750–757.
7. Skodda S, Müller T. Refractory epileptic seizures due to vitamin B₆ deficiency in a patient with Parkinson's disease under duodopa therapy. *J Neural Transm* 2013;120:315–318.
8. Leon AS, Spiegel HE, Thomas G, Abrams WB. Pyridoxine antagonism of levodopa in parkinsonism. *JAMA* 1971;218:1924–1927.
9. Yahr MD, Duvoisin RC. Pyridoxine and levodopa in the treatment of Parkinsonism. *JAMA* 1972;220:861. Letter.
10. Mars H. Levodopa, carbidopa, and pyridoxine in Parkinson disease: metabolic interactions. *Arch Neurol* 1974;30:444–447.
11. Pinder RM, Brogden RN, Sawyer PR, Speight TM, Avery GS. Levodopa and decarboxylase inhibitors: a review of their clinical pharmacology and use in the treatment of parkinsonism. *Drugs* 1976;11:329–377.

Neurology®

Pearls and Oy-sters: Vitamin B₆ deficiency presenting with new-onset epilepsy and status epilepticus in a patient with Parkinson disease

Joseph S. Modica, Deana Bonno and Karlo J. Lizarraga

Neurology 2020;94:e2605-e2607 Published Online before print May 28, 2020

DOI 10.1212/WNL.0000000000009647

This information is current as of May 28, 2020

Updated Information & Services	including high resolution figures, can be found at: http://n.neurology.org/content/94/24/e2605.full
References	This article cites 11 articles, 2 of which you can access for free at: http://n.neurology.org/content/94/24/e2605.full#ref-list-1
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): Nutritional http://n.neurology.org/cgi/collection/nutritional Parkinson's disease/Parkinsonism http://n.neurology.org/cgi/collection/parkinsons_disease_parkinsonism Status epilepticus http://n.neurology.org/cgi/collection/status_epilepticus
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.neurology.org/about/about_the_journal#permissions
Reprints	Information about ordering reprints can be found online: http://n.neurology.org/subscribers/advertise

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2020 American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.