B₆ and Bleeding: A Case Report of a Novel Vitamin Toxicity

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abstract
Pyridox(am)ine-5-phosphate oxidase deficiency is an inborn error of vitamin B₆ metabolism that is characterized by neonatal seizures, requiring lifelong therapy with pyridoxal-5-phosphate. We present the first case of a patient with pyridox(am)ine-5-phosphate oxidase deficiency and mild hemophilia A, whose bleeding symptoms were exacerbated by the vitamin B₆ therapy essential for his epileptic disorder. This report expands the spectrum of known vitamin B₆ toxicity and demonstrates a need for vigilance in monitoring for bleeding symptoms in patients requiring pyridoxine or pyridoxal-5-phosphate supplementation.

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Pyridoxine and pyridoxal-5-phosphate (PLP), the biologically active form of pyridoxine, are vitamin B₆ vitamers that have been used to treat a variety of disorders. They are the primary treatments for pyridoxine-dependent epilepsy caused by antiquitin deficiency and pyridox(am)ine-5-phosphate oxidase (PNPO) deficiency, respectively. These vitamers are generally well tolerated, with the most common reported side effect being peripheral neuropathy, usually occurring with higher doses.¹ Although the results of laboratory studies have revealed that PLP²⁻⁴ can impair normal platelet function, bleeding has not been reported clinically. Here we present a case of a pediatric patient with epilepsy secondary to PNPO deficiency and mild hemophilia A who has been treated with PLP since infancy. Consistent with a mild factor deficiency, he had minimal bleeding symptoms until 4 years of age when he developed recurrent spontaneous hemarthroses. The onset of these symptoms coincided with an increase in his PLP dosing for seizure control, and further laboratory evaluation revealed abnormal platelet aggregation studies consistent with PLP toxicity.

CASE PRESENTATION

The patient is an 8-year-old boy of Mexican heritage who was born at term after an unremarkable prenatal course but developed seizures shortly after birth that were refractory to multiple antiseizure medications, including phenobarbital, fosphenytoin, levetiracetam, zonisamide, and clobazam. After an extensive metabolic and genetic evaluation, he was diagnosed with PLP-dependent epilepsy at 1 month of age on the basis of a low PLP level in his cerebrospinal fluid and subsequent targeted gene sequencing that demonstrated a novel homozygous point mutation (c.673C>T, p.R225C) in the *PNPO* gene. This mutation results in a cysteine for arginine substitution in a highly conserved region of the PNPO protein and was predicted to be disease-causing on the basis of in silico analysis and the patient's cerebrospinal fluid results. He was started on therapy with PLP supplementation (initially 30 mg/kg per day divided every 8 hours, 110 mg/day). He had multiple admissions for seizures during early infancy and childhood, with various adjustments to his antiseizure medications and a continued increase in the dose of his

PLP, ultimately up to a dose of 150 mg 7 times per day (total daily dose of 1050 mg or 43 mg/kg per day) by 4 years of age. By the time of his last PLP dose increase, he was on dual therapy of topiramate and PLP for his epilepsy.

During his initial neonatal course, he was noted to have a persistently prolonged activated partial thromboplastin time (aPTT) of 48 to 55 seconds (normal 26.8–37.1 seconds). He had no bleeding symptoms in the early neonatal period other than a brief episode of hematochezia that was thought to be due to milk protein allergy; it was resolved after discontinuation of cow's milk protein exposure. Because of persistence of the prolonged aPTT past infancy, the diagnosis of hemophilia A was made at age 32 months on the basis of low factor VIII activity levels (14%) and a mixing study that corrected the aPTT (suggesting a factor deficiency). He otherwise had a reassuring evaluation, including normal prothrombin time, fibrinogen, platelet count, von Willebrand antigen and activity, factor IX activity, and negative testing for von Willebrand disease type 2N (a mild hemophilia mimicker).

Throughout infancy and early toddlerhood, the child had minimal to no bleeding symptoms, including no epistaxis, gum bleeding, or hematuria. In fact, before the diagnosis of hemophilia, the patient already had several surgical procedures, including gastrostomy tube placement, myringotomy tube placement, and vagus nerve stimulator placement without any major bleeding symptoms. However, around the time he turned 4 years, the patient started to have an increase in bleeding symptoms. Between 4 and 7 years of age (first starting 6 months after his PLP dose was increased), he had 3 knee hemarthroses requiring factor VIII infusion. All occurred spontaneously

without any preceding trauma. He also had a lingual hematoma requiring hospitalization and factor VIII infusion and an increase in several other minor bleeding symptoms requiring antifibrinolytic therapy.

Because of the increase in bleeding symptoms, which is highly unusual for mild hemophilia, additional testing was done; the results revealed that the patient had abnormal platelet aggregation studies with decreased response to adenosine diphosphate (ADP), ristocetin, and arachidonic acid. His liver function tests at time of these events were normal, ruling out synthetic liver dysfunction as a cause for the bleeding. A review of the literature confirmed that high doses of PLP have been shown to interfere with normal platelet function. The patient's laboratory abnormalities were consistent with the PLP toxicity as documented in previous studies.^{2–6} Unfortunately, this patient's seizure symptoms were so severe so as to not allow decrease or discontinuation of PLP. Increased spontaneous joint bleeding was addressed with modification of activity, judicious use of antifibrinolytic agents, and education about the need for urgent factor VIII infusion in the setting of any bleeding symptoms. Prophylactic factor VIII infusion was considered but at this time thought to not be warranted.

DISCUSSION

We report the first case, to our knowledge, of a patient with PNPO deficiency who required high doses of PLP for seizure control and in whom PLP therapy exacerbated symptoms of the patient's other rare genetic disorder, mild hemophilia A. The lack of severe bleeding normally seen in patients with mild hemophilia depends on the relatively intact state of the remainder of the coagulation system, namely other clotting factors,

normal endothelium, fibrinogen, and platelet function. We hypothesize that the combination of decreased factor VIII activity and impaired platelet function from exogenous PLP administration (as confirmed by the laboratory evaluation) contributed to a more severe bleeding phenotype.

Pyridoxine toxicity is rare but can cause peripheral sensory neuropathy with ataxia and loss of balance.⁷ Subtle symptoms such as paresthesia and muscle weakness have also been reported in those taking doses as low as 10 mg/kg per day.^{8,9} There have also been several reports of liver toxicity with prolonged high-dosage use of PLP,^{10,11} but overall pyridoxine and PLP supplementation are generally well tolerated.^{7,8,10,12} To our knowledge, no bleeding symptoms have been reported in those taking either pyridoxine or PLP.

There are a number of inborn errors of metabolism that can cause epileptic encephalopathy and that respond to 1 or more forms of vitamin B₆.¹³ One such disorder is PNPO deficiency, which is inherited in an autosomal recessive fashion and that presents as an intractable neonatal epileptic encephalopathy.¹⁴ It is a rare pyridoxine-responsive epileptic encephalopathy with <50 cases reported in the literature.^{14–16} PNPO is required for the conversion of pyridoxine (vitamin B₆) to its active coenzyme form, PLP. PLP is required for the function of many essential enzymes in amino acid metabolism, neurotransmitter synthesis, and glycogen catabolism.^{5,7,12} Control of seizures in PNPO deficiency often requires lifelong supplementation with high doses of PLP, although some patients may also respond to pyridoxine therapy.¹⁷

Hemophilia A is a rare X-linked recessive bleeding disorder characterized by reduced presence and activity of coagulation factor VIII. The incidence of hemophilia A in the United States is ~1 in 5000

male births,¹⁸ and typical bleeding symptoms include recurrent joint bleeding leading to chronic hemarthroses and debilitating arthropathy. Hemophilia A is subcategorized on the basis of severity, with severe hemophilia in those with <1% factor VIII activity, moderate hemophilia in those with 1% to 5% factor VIII activity, and mild hemophilia in those with 5% to 40% factor VIII activity. Bleeding in mild hemophilia patients tends to be infrequent, and these patients rarely have spontaneous hemarthroses or develop arthropathy.^{18,19} Patients with mild hemophilia generally only require intervention when bleeding develops because of trauma or a surgical procedure, in contrast to patients with severe hemophilia who have spontaneous joint bleeding and require lifelong factor VIII infusion for bleeding prophylaxis.

The authors of in vitro studies have demonstrated an inhibitory effect of PLP on platelet function, but no bleeding symptoms have been reported with its clinical use.² PLP was first shown in the 1970s to be efficient at inhibiting platelet aggregation to ADP, collagen, and thrombin.³ It has also been shown to prolong bleeding time and to significantly inhibit platelet aggregation to ADP and epinephrine on platelet aggregation in human subjects.^{2,5} Suggested mechanisms for this inhibition include PLP's inhibition of released ADP² and/or direct interactions with ristocetin or factor VIII ristocetin cofactor or adenylyl cyclase.^{4,6} Conceivably, high doses of PLP could exacerbate a bleeding phenotype in a patient with a bleeding disorder, which appears to have occurred in our patient.

CONCLUSIONS

We report a novel side effect of increased bleeding secondary

to platelet dysfunction caused by therapy with PLP, the active metabolite of vitamin B₆. Clinicians should be aware of the potential adverse effect of high doses of pyridoxine or PLP, either in patients who require it for a certain disease state or in those with accidental ingestion. Our experience supports increased vigilance for this rare side effect of vitamin B₆ therapy, especially in patients already at risk for spontaneous bleeding.

ABBREVIATIONS

ADP: adenosine diphosphate
aPTT: activated partial thromboplastin time
PLP: pyridoxal-5-phosphate
PNPO: pyridox(am)ine-5-phosphate oxidase

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