Case Report

DOI: 10.5582/irdr.2014.01005

Seizures caused by pyridoxine (vitamin B6) deficiency in adults: A case report and literature review

Yisha Tong*

Vascular Surgery Unit, Austin Hospital, University of Melbourne, Melbourne, Australia

Summary **Pyridoxine (vitamin B6) deficiency is a recognised cause of intractable seizures in neonates. However, pyridoxine deficiency related seizures in adults were rarely reported. This article reports a case of a 79 year old lady who suffered from new-onset seizures and was successfully treated with vitamin B6. The patient had chronic renal disease and weight loss due to anepithymia following a pelvic fracture. This article also reviews literatures of seizures caused by pyridoxine deficiency in adults. Seizures caused by vitamin B6 deficiency in adults may result from dietary deficiency, liver disease, pregnancy and certain medications and can be easily treated by vitamin B6 with excellent outcome. Clinicians should consider vitamin B6 deficiency as a potential aetiology of seizures, even in patients who suffer from other underlying diseases which can cause seizures.**

Keywords: Adult, literature review, pyridoxine, seizure, vitamin B6

1. Introduction

Pyridoxine (vitamin B6) deficiency is a recognised cause of intractable seizures and most reported cases of this condition are in neonates (*1,2*). Very few adult cases of pyridoxine deficiency related seizures have been reported in the English literature (*3-7*). This article reports a case of an elderly lady who suffered from new-onset seizures and was successfully treated with vitamin B6, includes a literature review of seizures caused by pyridoxine deficiency in adults.

2. Case Report

A 79 year old lady, a family member of the author, suffered from Parkinson's disease, and stage 4 chronic renal failure and was not on dialysis. She experienced a sudden onset of seizure-like attacks with upper limb jerking, head tilting back and eyeballs rolling up. She had five episodes within 24 hours. In two of the five episodes, she was responsive initially and then briefly unresponsive for one to two minutes. She had never experienced such episodes previously. Five weeks prior to the onset, the patient had fall which resulted in a pelvic fracture and she was slowly recovering at home. She lost 5 kg (from 33 kg to 28 kg) due to anepithymia during the 5 weeks.

The patient was taken to Box Hill Hospital in Melbourne by ambulance after the 5th episode. Her renal function tests showed Urea 14.6 mmol/L, Creatinine 440 umol/L and eGFR 8 mL/min/1.73m^2 which were no worse than the results of five weeks earlier (28.0, 485, 8). A brain CT scan was unremarkable. She had another episode in the Emergency Department (ED) just after the CT scan when she was observed by an ED doctor to be initially responsive, with jerking of upper limbs, and then becoming tonic and unresponsive. Her systolic blood pressure and heart rate increased to 230 mmHg and 150/min respectively during the episode. It lasted three minutes and resolved spontaneously. The conclusion of the neurologist's consultation in ED was that her seizure-like episodes were secondary to chronic kidney disease, despite a decrease in her urea level compared to test results five weeks ago. The neurologist prescribed oral clonazepam 0.25 mg twice a day, increasing to 0.5 mg if necessary.

The patient was then admitted to the renal ward of the hospital and did not experience any further episodes on the first day of the admission. She had a mild episode in the early morning of the second day in the hospital and underwent an EEG in the afternoon which was unremarkable. She was seizure free on the third day and did not receive a second dose of clonazepam

**Address correspondence to:*
Dr. Yisha Tong, Vascular Surgery Unit, Austin Hospital, 145 Studley Road, Heidelberg, Melbourne 3084, Australia.
E-mail: yisha.tong@austin.org.au

in the evening. The patient had an episode similar to the one in the ED in the afternoon on the 4th day and was given clonazepam 1mg intravenously. She was given clonazepam 0.25 mg at night for the next two days and had one episode each day. She was then given clonazepam 0.25 mg twice a day on 7th day and had one episode on that day. She had two episodes in the morning of the 8th day and the second clonazepam dose was increased from 0.25 mg to 0.5 mg after a neurology review.

The patient was discharged from hospital on day 9 of admission and doctors advised the family to adjust the clonazepam dose at home. On the day of discharge, the patient had two episodes of seizure-like attacks in the hospital and two more episodes at home. She was given clonazepam 0.25 mg twice during that day. On the following day of discharge, she had five episodes within 12 hours and was given clonazepam 0.25 mg in the morning and 0.5 mg in the evening. The author reviewed the literature on seizures, and learned that vitamin B6 deficiency could be a potential cause of seizures. The patient was given vitamin B6 10 mg that night, and then four times the following day. Vitamin B6 10 mg three times a day was given thereafter. The clonazepam dose was gradually reduced and stopped 14 days post discharge. The patient has not experienced any seizure activity since vitamin B6 was introduced and has remained seizure free (Table 1).

3. Vitamin B6 and vitamin B6 deficiency

The term pyridoxine connotes the six vitamers of vitamin B6: the alcohol pyridoxine, the aldehyde pyridoxal, the amine pyridoxamine, and their respective 5'-phosphorylated esters (pyridoxine phosphate, pyridoxal phosphate and pyridoxamine phosphate) (*8*). Both pyridoxine phosphate and pyridoxamine phosphate are converted into the active cofactor pyridoxal phosphate (PLP) by pyridox(am)ine 5'-phosphate oxidase. PLP plays numerous roles in over 140 metabolic reactions making up at least 4% of all classified enzyme activities including transamination of amino acids, decarboxylation reactions, modulation of activity of asteroid hormones and regulation of gene expression (*9,10*). From a neurological perspective, pyridoxine homeostasis is important in dopaminergic, serotonergic, glutaminergic and gabaergic neurotransmission (*8*).

Vitamin B6 is widely available in animal and plant derived food, including meat, nuts and whole grain products. As such, clinical vitamin B6 deficiency states are rare (*11,12*). Nevertheless, vitamin B6 deficiency may occur in patients with inadequate dietary intake. The elderly, alcoholics, renal patients undergoing dialysis, patients with liver disease, rheumatoid arthritis, women with type 1 diabetes, and those infected with HIV have an increased risk of vitamin B6 deficiency, despite adequate dietary intakes (*13-15*). The availability of vitamin B6 in the body can be affected by certain medications such as anticonvulsants and corticosteroids (*16*). Isoniazid, a medication used in the treatment of tuberculosis, and cycloserine, penicillamine, and hydrocortisone may interfere with vitamin B6 metabolism. These medications may form a complex with vitamin B6 that is inhibitory for pyridoxal kinase, or they may positively displace PLP from binding sites (*17*). The classic clinical syndrome for vitamin B6 deficiency is a seborrhoeic dermatitis-like eruption, atrophic glossitis with ulceration, angular cheilitis, conjunctivitis, intertrigo, and neurologic symptoms of somnolence, confusion, and neuropathy.

4. Vitamin B6 deficiency and seizures

As mentioned, the active form of vitamin B6, *i.e.*, PLP – a coenzyme that is necessary for the synthesis and metabolism of amino acids, is an important cofactor for many processes including neurotransmitter formation. Specially, PLP is an essential factor in the process of

Table 1. 30 days of seizure activities and treatment in a 79 years old lady

Day	Home/Hospital	No of seizure episode(s)	Oral clonazepam (time)		Oral vitamin B6 (time)
			Morning	Evening	
Day 1	Home	4	-	-	-
Day 2	Hospital admission	2	0.25 mg	0.25 mg	-
Day 3	Hospital	1	0.25 mg	0.25 mg	-
Day 4	Hospital	0	0.25 mg	-	-
Day 5	Hospital	1	1.00 mg intravenously (5 pm)		-
Day 6	Hospital	1	0.25 mg	0.25 mg	-
Day 7	Hospital	1	0.25 mg	0.25 mg	-
Day 8	Hospital	1	0.25 mg	0.25 mg	-
Day 9	Hospital	2	0.25 mg	0.50 mg	-
Day 10	Discharged to home	4	0.25 mg	0.25 mg	-
Day 11	Home	5	0.25 mg	0.50 mg	10 mg (10 pm)
Day 12	Home	0	-	0.125 mg	10 mg × 4
Day 13	Home	0	0.125 mg	0.125 mg	10 mg × 3
Days 14-22	Home	0	-	0.125 mg	10 mg × 3
Days 23-30	Home	0	-	-	10 mg × 3

decarboxylation of glutamine into Gamma-Animobutytic Acid (GABA), a major inhibitory neurotransmitter. A deficiency of PLP leads to decreased GABA concentration in the brain, thereby increasing the risk for seizures (*18*).

Seizures caused by vitamin B6 deficiency was first described in 1954 by Hunt *et al* (*1*). They reported a case of a newborn with pharmacoresistant seizures that eventually came under control after treatment with a multivitamin preparation and subsequently deduced that pyridoxine was the factor responsible for controlling the infant's epileptic seizures. The disorder has been known as pyridoxine-dependent seizures or pyridoxine-dependent epilepsy. Since then, more than 100 cases of neonatal pyridoxine-dependent seizures have been reported worldwide (*8,19-21*). More recently, mutations in the *ALDH7A1* gene which encodes the protein antiquitin, an aldehyde dehydrogenase that functions within the cerebral lysine catabolism pathway, were found to be responsible for the biochemical abnormalities underlying PDS (*8,22,23*).

5. Seizures caused by vitamin B6 deficiency in adults

Reported cases of vitamin B6 deficiency related seizures in adults were much less than that in neonates. Table 2 summarises cases of seizures caused by pyridoxine deficiency in adults reported in the English literature.

5.1. *Therapeutic doses of isoniazid*

Isonicotinic acid hydrazide (INH) is an effective and widely used medication in tuberculosis treatment. Severe acute neurotoxicity of INH overdose is characterised by recurrent seizures, profound metabolic acidosis, coma and even death (*24-30*). INH is thought to cause seizures by interfering with γ-aminobutyric acid synthesis. Specifically, INH inhibits glutamic acid decarboxylase by inhibiting pyridoxal 5 phosphate, a co-factor for glutamic acid decarboxylase enzyme. The consequent reduction in GABA levels increases susceptibility to seizures.

In addition to INH overdose, therapeutic doses of INH have been reported to induce seizures which were successfully treated with pyridoxine (*3,5*). It is important to be aware that possible isoniazid neurotoxicity may occur in patients with chronic renal failure or even in healthy individuals when recommended preventive doses of isoniazid are used.

5.2. *Pregnancy*

It is recognised that there is an increased demand for vitamin B6 during pregnancy which may lead to low vitamin B6 levels. Schulze-Bonhage and colleagues (*4*) reported a case of development of seizures and status epilepticus during pregnancy with low vitamin B6 levels. The patient had pyridoxine-dependent epileptic seizures during early childhood, but had been completely seizure free for 23 years with oral pyridoxine hydrochloride supplementation therapy (100 mg/day). The lack of response to antiepileptic medication and rapid improvement with parenteral administration of vitamin B6 makes a relation between low vitamin B6 levels and the development of seizures and status epilepticus highly probable. Although it is unknown whether decreased vitamin B6 levels that occur during pregnancy can precipitate seizures in otherwise healthy women with no history of epilepsy due to a disturbed metabolism of pyridoxine, pregnancy may be potential risk factor for seizures caused by vitamin B6 deficiency.

5.3. *Levodopa/carbidopa intestinal gel infusion (LCIG)*

Skodda and Müller (*7*) reported a cachectic case of seizures after the initiation of treatment with Levodopa/carbidopa intestinal gel infusion (LCIG). Vitamin B6 level in serum was markedly reduced (2.7 μg/L). The seizures ceased within 2 days of pyridoxine treatment and her serum pyridoxine level was normal (23.3 μg/L) after successful treatment. A relationship between vitamin B6 deficiency and LCIG therapy was suspected because of the chronological sequence of increasing LCIG dosage and the first manifestation of seizures although mechanisms by which how LCIG therapy might influence vitamin B6 levels are not clear. Vitamin B6 deficiency might be also aggravated by suboptimal dietary intakes in the case as her BMI was only 15.8.

5.4. *Dietary deficiency of vitamin B6*

The case of new onset of seizures described in this report was successfully treated with small doses of pyridoxine (40 mg for 24 h and then 30 mg daily). A hypothesis for this case is that the patient had insufficient dietary intake due to anepithymia following the fall and pelvic fracture which was evident by weight loss (from 33 kg to 28 kg within 5 weeks). Insufficient dietary intakes may cause vitamin B6 deficiency which subsequently induces seizures. Gerlach and colleagues (*6*) reported three cases of refractory seizures consequent to vitamin B6 deficiency which may be aggravated by alcoholism or liver disease (*31-35*). Low PLP concentration in those patients may occur over time owing to a dietary deficiency coupled with intact aldehyde oxidase activity.

6. Conclusion

Seizures caused by vitamin B6 deficiency in adults are rarely reported and may be underdiagnosed and underreported. This condition may result from dietary deficiency, liver disease, pregnancy and certain medications and can be easily treated by vitamin B6

Table 2. Reported cases of seizures related to pyridoxine deficiency in adults

Author/s (year)	Age (Gender)	Medical history prior to seizures	Failed seizure treatment	Pyridoxine Pre (Post) pyridoxine treatment	Pyridoxine (Vitamin B6) treatment and response
Asnis DS, *et al* (*3*) (1993)	66 (F)	• Oral administration of isoniazid 300 mg/day for 4 days following PPD test positive • Just began peritoneal dialysis training program	–	–	Oral pyridoxine 50 mg/day: Seizure ceased within 24 hours
Schulze-Bonhage A, *et al* (*4*) (2004)	30 (F)	• History of early childhood pyridoxine-dependent epileptic seizures • Seizure free for 23 years with oral pyridoxine hydrochloride 100 mg per day • Status epilepticus during week 14 of pregnancy	Days 1 and 2: parenteral phenytoin 750 mg/day Days 3 and 4: parenteral phenytoin 500 mg/day and phenobarbitone 450 mg/day→ continuous benzodiazepine infusion (bolus of 4 mg and subsequent infusion rate of 1 mg/h)	PLP(pyridoxal 5'-phosphate): 2.96 ng/mL* (19 ng/mL) *Normal range: 4.3-17.5 ng/mL)	Parenteral pyridoxine hydrochloride 100 mg/day for a week and oral pyridoxine 100 mg/day: Disappearance of epileptic discharges on the first EEG recording obtained 3 days after intravenous administration of pyridoxine and regained consciousness after antiepileptic drug was tapered off
Vasu and Saluja (*5*) (2006)	45 (F)	• Isonicotinic acid hydrazide 300 mg/day for 2 months after being found to be PPD positive	Intravenous diazepam 5 mg, lorazepam 4 mg and fosphenytoin 1200 mg	–	Intravenous pyridoxine 5 g: Seizure ceased
Gerlach, *et al* (*6*) (2011)	54 (M)	• Advanced alcoholic cirrhosis and encephalopathy • Hepatic transplantation • Intolerance of enteral nutrition	Intravenous phenytoin 1000 mg followed by intravenous phenytoin 100 mg every 8 hours and then intravenous phenyton 350mg every 24 hours	PLP: 2 mcg/L* (6 mcg/L) *Normal range: 5-50 mcg/L)	Intravenous pyridoxine 200 mg every 24 hours: Seizures ceased within 2 days Oral pyridoxine 100 mg daily: Seizure free
	59 (M)	• End-stage renal disease and intermittent hemodialysis • Hepatitis C • Gastroesophageal reflux disease • Evacuation of subdural hematoma	Intravenous fosphenyotoin 1000 mg followed by intravenous phenytoin 100 mg every 8 hours and enteral levetiracetam 250 mg every 12 hours then levetiracetam 500 mg every 12 hours via nasogastric tube Phenobarbital 600 mg x 2 then enteral phenobarbital 20 mg twice daily	PLP: 3 mcg/L* (5 mcg/L) *Normal range: 5-50 mcg/L)	Intravenous pyridoxine 100 mg twice daily: Seizures ceased following day Oral Pyridoxine 100 mg daily: Seizure free
	78 (M)	• Intraventricular hemorrhage • History of alcoholism	Intravenous phenytoin 1000 mg followed by intravenous phenytoin 100 mg every 8 hours	PLP: 4 mcg/L* (26 mcg/L) *Normal range: 5-50 mcg/L)	Intravenous pyridoxine 100mg every 12 hours: Seizures ceased within 24 hours Oral Pyridoxine 100 mg daily: Seizure free
Skodda and Müller (*7*) (2013)	74 (F)	• Parkinson's disease treated with Levodopa/carbidopa intestinal gel infusion for 3 month • Cachectic (BMI = 15.8)	Levetiracetam (500 mg/day) and lorazepam (2 mg/day) Intravenous lorazepam 0.5-1.0 mg Levetiracetam (maximum daily dose of 4000 mg) successively supplemented by lorazepam (maximum daily dose of 4 mg) and phenytoin (from 1500 mg/day to 400 mg/day)	Pyridoxine: 2.7 µg/l* (23.3 µg/L) *Normal range: 5-30 µg/L)	Pyridoxine 100 mg twice daily: Seizures ceased within 2 days
Tong (current)	79 (F)	• Stage 4 chronic renal disease • Weight loss (from 33 kg to 28 kg in 5 weeks) due to anepithymia following a fall and pelvic fracture	Oral clonazepam 0.25 mg - 0.75 mg/daily	–	Oral pyridoxine 50 mg for 24 hours and then 30 mg daily: seizures ceased within 24 hours and remained seizure free since

with excellent outcome. Clinicians should consider vitamin B6 deficiency as a possible aetiology in patients presenting with seizures, even in those who suffer from other underlying disease which can cause seizures.

Acknowledgements

The author would like to thank Associate Professor Brian Chambers, Senior Neurologist of Department of Neurosciences, Austin Hospital for his comments and suggestions.

References

1. Hunt AD Jr, Stokes J Jr, McCrory WW, Stroud HH. Pyridoxine dependency: Report of a case of intractable

convulsions in an infant controlled by pyridoxine. Pediatrics. 1954; 13:140-145.
2. Baxter P. Pyridoxine dependent and pyridoxine responsive seizures. In: Baxter P, ed. Vitamin Responsive Conditions in Paediatric Neurology. London: MacKeith Press, 2001:109-165.
3. Asnis DS, Bhat JG, Melchert AF. Reversible seizures and mental status changes in a dialysis patient on isoniazid preventive therapy. Ann Pharmacother. 1993; 27:444-446.
4. Schulze-Bonhage A, Kurthen M, Walger P, Elger CE. Pharmacorefractory status epilepticus due to low vitamin B6 levels during pregnancy. Epilepsia. 2004; 45:81-84.
5. Tajender V, Saluja J. INH induced status epilepticus: Response to pyridoxine. Indian J Chest Dis Allied Sci. 2006; 48:205-206.
6. Gerlach AT, Thomas S, Stawicki SP, Whitmill ML, Steinberg SM, Cook CH. Vitamin B6 deficiency: A potential cause of refractory seizures in adults. J Parenter Enter Nutr. 2011; 35:272-275.
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. Gospe SM Jr. Neonatal Vitamin-responsive Epileptic Encephalopathies. Chang Gung Med J. 2010; 33:1-12.
9. Bender DA. Vitamin B6. Nutritional Biochemistry of the Vitamins (2nd ed). Cambridge: Cambridge University Press, 2003:232-269.
10. Percudani R, Peracchi A. A genomic overview of pyridoxal-phosphate-dependent enzymes. EMBO Rep. 2003; 4:850-854.
11. Gospe SM Jr. Pyridoxine-dependent seizures: New genetic and biochemical clues to help with diagnosis and treatment. Curr Opin Neurol. 2006; 19:148-153.
12. Wang HS, Kuo MF. Vitamin B6 related epilepsy during childhood. Chang Gung Med J. 2007; 30:396-401.
13. Bowman BA, Russell RM. Present Knowledge in Nutrition (9th Ed). Washington, DC: ILSI Press; 2006; 273.
14. Rall LC, Meydani SN. Vitamin B6 and immune competence. Nutrition Reviews. 1993; 51:217-225.
15. Massé PG, Boudreau J, Tranchant CC, Ouellette R, Ericson KL. Type 1 diabetes impairs vitamin B6 metabolism at an early stage of women's adulthood. Appl Physiol Nutr Metab. 2012; 37:167-175.
16. Sauberlich H. Vitamins – how much is for keeps? Nutr Today. 1987; 22:20-28.
17. Bhagavan HN. Interraction between vitamin B6 and drugs. In Reynolds RD, Leklem JE. Vitamin B6: Its role in health and disease. New York: Liss. 1985: 401-415.
18. Kluger G, Blank R, Paul K, Paschke E, Jansen E, Jakobs C, Wörle H, Plecko B. Pyridoxine-dependent epilepsy: Normal outcome in a patient with late diagnosis after prolonged status epilepticus causing cortical blindness. Neuropediatrics. 2008; 39:276-279.
19. Baxter P. Epidemiology of pyridoxine dependent and pyridoxine responsive seizures in the UK. Arch Dis Child. 1999; 81:431-433.
20. Been JV, Bok LA, Andriessen P, Renier WO. Epidemiology of pyridoxine dependent seizures in the Netherlands. Arch Dis Child. 2005; 90:1293-1296.
21. Basura GJ, Hagland SP, Wiltse AM, Gospe SM Jr. Clinical features and the management of pyridoxine-dependent and pyridoxine-responsive seizures: Review of 63 North American cases submitted to a patient registry. Eur J Pediatr. 2009; 168:697-704.
22. Mills PB, Struys E, Jakobs C, Plecko B, Baxter P, Baumgartner M, Willemsen MA, Omran H, Tacke U, Uhlenberg B, Weschke B, Clayton PT. Mutations in antiquitin in individuals with pyridoxine-dependent seizures. Nat Med. 2006; 12:307-309.
23. Plecko B, Paul K, Paschke E, *et al*. Biochemical and molecular characterization of 18 patients with pyridoxine-dependent epilepsy and mutations of the antiquitin (*ALDH7A1*) gene. Hum Mutat. 2007; 28:19-26.
24. Coyer JR, Nicholson DP. Isoniazid-induced convulsions. South Med J. 1976; 69:294-297.
25. Wason S, Lacouture PG, Lovejoy FH Jr. Single high-dose pyridoxine treatment for isoniazid overdose. JAMA. 1981; 246:1102-1104.
26. Yarbrough BE, Wood JP. Isoniazid overdose treated with high-dose pyridoxine. Ann Emerg Med. 1983; 12:303-305.
27. Bredemann JA, Krechel SW, Eggers GW Jr. Treatment of refractory seizures in massive isoniazid overdose. Anesth Analg. 1990; 71:554-557.
28. Cash JM, Zawada ET Jr. Isoniazid overdose-Successful treatment with pyridoxine and hemodialysis. West J Med. 1991; 155:644-646.
29. Alvarez FG, Guntupalli KK. Isoniazid overdose: Four case reports and review of the literature. Intensive Care Med. 1995; 21:641-644.
30. Desai VA, Agarwal SB. Isoniazid Toxicity. JIACM 2004; 5: 83-85.
31. Ohgi N, Hirayama C. Vitamin B6 status in cirrhotic patients in relation to apoenzyme of serum alanine aminotransferase. Clin Biochem. 1988; 21:367-370.
32. Henderson JM, Scott SS, Merrill AH, Hollins B, Kutner MH. Vitamin B6 repletion in cirrhosis with oral pyridoxine: Failure to improve amino acid metabolism. Hepatology. 1989; 9:582-588.
33. Merrill AH Jr, Henderson JM. Vitamin B6 metabolism by human liver. Ann N Y Acad Sci. 1990; 585:110-117.
34. Brussaard JH, Löwik MR, van den Berg H, Brants HA, Bemelmans W. Dietary and other determinants of Vitamin B6 parameters. Eur J Clin Nutr. 1997; 51:S39-S45.
35. Glória L, Cravo M, Camilo ME, Resende M, Cardoso JN, Oliveira AG, Leitão CN, Mira FC. Nutritional deficiencies in chronic alcoholics: Relation to dietary intake and alcohol consumption. Am J Gastroenterol. 1997; 92:485-489.

(Received February 19, 2014; Accepted March 15, 2014)