CASE REPORT

Regressive pyridoxine-induced sensory neuronopathy in a patient with homocystinuria

Andoni Echaniz-Laguna,[1] Rachel Mourot-Cottet,[2] Esther Noel,[2] Jean-Baptiste Chanson[1]

[1]Neurologie, Hopitaux universitaires de Strasbourg, Strasbourg, France
[2]Medecine Interne, Hopitaux universitaires de Strasbourg, Strasbourg, France

Correspondence to
Dr Jean-Baptiste Chanson, jean-baptiste.chanson@chru-strasbourg.fr

Accepted 17 June 2018

SUMMARY

Pyridoxine (vitamin B6) is an essential vitamin playing a crucial role in amino acid metabolism. Pyridoxine is used for isoniazid side-effects prevention, pyridoxine-dependent epilepsy treatment and cystathionine beta-synthase deficiency (homocystinuria) treatment. However, vitamin B6 hypervitaminosis is neurotoxic and may provoke a progressive sensory neuronopathy (sensory ganglionopathy), usually when daily uptake is above 50 mg. We describe the case of a 30-year-old patient with homocystinuria who was treated with pyridoxine 1250–1750 mg/day for 20 years and developed progressive sensory neuropathy with ataxia and impaired sensation in the extremities. Electrodiagnostic testing demonstrated non-length-dependent abnormalities of sensory nerve potentials, and sensory ganglionopathy was diagnosed. Pyridoxine dosage was reduced to 500 mg/day, resulting in the disappearance of sensory symptoms and ataxia, and the normalisation of sensory nerve potentials. Our case indicates that pyridoxine-induced sensory ganglionopathy may be reversible, even after prolonged ingestion of high doses of vitamin B6 for more than 20 years.

BACKGROUND

Vitamin B6 is essential in amino acid metabolism.[1] Vitamin B6 exists in three natural forms, that is, pyridoxine, pyridoxal and pyridoxamine, with pyridoxine being the most common form used in pharmaceutical preparations and dietary supplements.[1 2] Pharmacological benefits of pyridoxine include prevention of isoniazid side-effects, treatment of pyridoxine-dependent epilepsy and treatment of cystathionine beta-synthase (CBS) deficiency (also termed homocystinuria).[2–4] Pyridoxine is also largely used as a nutritional supplement, either in isolation or more often in combination with other vitamins. However, vitamin B6 hypervitaminosis is neurotoxic and may sometimes provoke a progressive sensory neuronopathy (also termed sensory ganglionopathy) which may be irreversible.[5–8] Here, we describe a patient with CBS deficiency who developed a pyridoxine-induced reversible sensory neuronopathy after being treated with high-dose pyridoxine for 20 years.

CASE PRESENTATION

A 30-year-old female patient was addressed to our Neuromuscular Disorders Referral Centre because she presented with walking difficulties, gait disturbance and paresthesia of the extremities. She had a story of CBS deficiency diagnosed at age 10 when she developed bilateral *ectopia lentis*. Genetic analysis revealed two abnormal variants in the CBS gene, including the frequent c.833T>C variation and the less frequent c.1064C>T variation, and she self-treated herself, without medical oversight, with pyridoxine 1250 mg/day from approximately age 10 to age 20 years, and pyridoxine 1750 mg/day from approximately age 20 to age 30 years. When examined, she presented with proprioceptive ataxia and multifocal, asymmetric impaired sensation in the extremities. Strength was spared in all limbs, and tendon reflexes were unobtainable in lower limbs. Cranial nerves examination was normal, and there was no Babinski sign.

INVESTIGATIONS

Electrodiagnostic testing demonstrated abnormal sensory nerve action potentials (SNAPs) in all limbs, with upper extremity sensory nerves affected to a greater extent than lower extremity nerves (table 1). Motor nerve conduction velocities were normal in all limbs (table 1). This pattern of asymmetrical non-length-dependent SNAPs abnormalities was typical of sensory neuronopathy. As sensory neuronopathies often result in unobtainable sensory responses, the sensory neuronopathy observed in this case was considered mild.

DIFFERENTIAL DIAGNOSIS

Sensory neuronopathies are a rare, heterogeneous group of neuropathies caused by primary degeneration of the dorsal root ganglion and trigeminal ganglion sensory neurons and their central and peripheral sensory projections.[8] The diagnosis of a sensory neuronopathy is of crucial importance, as there is a limited differential diagnosis, including toxic neuronopathies and infectious, immune mediated, paraneoplastic and inherited disorders.[8] In the case presented here, there was no evidence of alcohol use, Sjögren syndrome, paraneoplastic disorder, HIV infection, Friedreich ataxia and *POLG* gene-related mitochondrial disease, and pyridoxine hypervitaminosis was considered the most likely culprit for the neuropathy.

TREATMENT

As recommended in the recent international guidelines for the diagnosis and management of CBS deficiency, pyridoxine dosage was reduced to 500 mg/day.[3]

To cite: Echaniz-Laguna A, Mourot-Cottet R, Noel E, *et al*. *BMJ Case Rep* Published Online First: [*please include* Day Month Year]. doi:10.1136/bcr-2018-225059

Table 1 Nerve conduction studies

	Pyridoxine treatment		Median motor		Tibial motor		Median sensory		Sural sensory		MAC sensory	
			Amp	CV	Amp	CV	Amp	CV	Amp	CV	Amp	CV
Normal values			>5.6	>49	>5.9	>44	>7.5	>48	>3.5	>45	>17.7	>60
Age 30 years	**1250–1750 mg/day for 20** years	Right	17.9	61	30.4	45	**3.7**	56	**3.4**	**37**	**NR**	**NR**
		Left	16.9	59	32.4	44	**3.1**	52	**2.1**	**42**	**NR**	**NR**
Age 31 years	**500 mg/day for 1** year	Right	16.6	63	34.2	44	8.3	52	9.3	52	**15.2**	**55**
		Left	16.7	58	34.6	46	8.6	52	**3.4**	**45**	**12.2**	**52**
Age 34 years	**500 mg/day for 4** years	Right	18.6	63	35.0	48	8.7	61	9.7	52	19.2	62
		Left	17.5	64	32.8	47	8.6	57	5.5	49	19	**60**

Abnormal values are in bold. Motor in mV and sensory in µV.
Amp: amplitude, CV: conduction velocity (in m/s); MAC: medial antebrachial cutaneous; NR: no response.

OUTCOME AND FOLLOW-UP

The effect was beneficial as sensory symptoms and ataxia progressively disappeared in the two following years. Electrodiagnostic testing performed 1 year after the first examination demonstrated normal SNAPs except in the medial antebrachial cutaneous nerve (table 1), and electrodiagnostic testing performed 4 years after the first examination demonstrated normal SNAPs in all limbs (table 1).

DISCUSSION

The first cases of pyridoxine-induced neuronopathy were reported in the 1980s.[9] Schaumburg *et al* reported seven patients who had taken high-dose pyridoxine (over 2 g/day) for several months and developed severe sensory ataxia as a result of large-fibre involvement.[9] However, several patients with muscle weakness and motor involvement have also been reported.[6 7] Toxicity is dose dependent and symptom onset usually occurs several months or years after high-dose pyridoxine is introduced.[5–11] Neuronopathies have been described with relatively low vitamin B6 dosages, and reviews have set the minimum risk dosage at approximately 50 mg/day.[10 11] Pyridoxine discontinuation improves symptoms in the majority of patients, but residual symptoms may persist in some cases.[6 7]

Pyridoxine has been used for treating pyridoxine-responsive CBS deficiency (homocystinuria) for several decades.[3–5] Treatment aims to lower the plasma total homocysteine concentration to a safe level while maintaining normal nutrition, including normal concentrations of methionine and other essential amino acids. In pyridoxine-responsive patients the target for plasma total homocysteine is <50 µmol/L, and for long-term treatment, the pyridoxine dose should be the lowest that achieves the biochemical target (plasma total homocysteine <50 µmol/L). The recently published guidelines for the diagnosis and management of CBS deficiency recommend using pyridoxine doses up to 10 mg/kg/day and avoiding doses above 500 mg/day.[3]

The mechanism of vitamin B6 toxicity is unknown. One commonly reported hypothesis is that the toxic levels of B6 may affect other B vitamin levels and provoke axonal damage.[8] Animal models show increased neurofilament synthesis, microtubule-neurofilament dissociation and large sensory neuron degeneration in the dorsal root ganglion of animals with pyridoxine-induced neuronopathy.[8] Interestingly, recent in vitro studies have shown that pyridoxine competitively inhibits the active pyridoxal-5′-phosphate enzymes and increases the expression of proapoptotic proteins Bax and caspase-8.[12] Paradoxically, high concentrations of vitamin B6 result in decreased vitamin B6 function, with vitamin B6 deficiency and vitamin B6 toxicity provoking similar symptoms.[12]

The case reported here demonstrates that pyridoxine-induced sensory ganglionopathy may be completely reversible, even after prolonged ingestion of vitamin B6 for more than 20 years.

Learning points

- Pyridoxine (vitamin B6) is an essential vitamin playing a crucial role in amino acid metabolism.
- Pyridoxine is used for the treatment of isoniazid side-effects, pyridoxine-dependent epilepsy and cystathionine beta-synthase deficiency (homocystinuria).
- Physicians should be aware that vitamin B6 hypervitaminosis is neurotoxic.
- Pyridoxine uptake above 50 mg/day may provoke a progressive sensory neuronopathy with ataxia and impaired sensation in the extremities.
- Pyridoxine-linked neuropathy may be reversible, even after prolonged ingestion of vitamin B6 for more than 20 years.

Contributors AE-L was responsible for the conception and design and drafting the article. RM-C, EN and J-BC were responsible for the acquisition, analysis and interpretation of data and revising it critically for important intellectual content. All authors contributed to the final approval of the version published and agreed to be accountable for the article and to ensure that all questions regarding the accuracy or integrity of the article are investigated and resolved.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests J-BC reports hospitality fees from LFB laboratories, CSL-Behring, Biogen, Grifols.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Ink SL, Henderson LM. Vitamin B6 metabolism. *Annu Rev Nutr* 1984;4:455–70.
2 Bender DA. Non-nutritional uses of vitamin B6. *Br J Nutr* 1999;81:7–20.
3 Morris AA, Kožich V, Santra S, *et al*. Guidelines for the diagnosis and management of cystathionine beta-synthase deficiency. *J Inherit Metab Dis* 2017;40:49–74.
4 Kruger WD. Cystathionine β-synthase deficiency: of mice and men. *Mol Genet Metab* 2017;121:199–205.
5 Ludolph AC, Masur H, Oberwittler C, *et al*. Sensory neuropathy and vitamin B6 treatment in homocystinuria. *Eur J Pediatr* 1993;152:271.
6 Kulkantrakorn K. Pyridoxine-induced sensory ataxic neuronopathy and neuropathy: revisited. *Neurol Sci* 2014;35:1827–30.
7 Gdynia HJ, Müller T, Sperfeld AD, *et al*. Severe sensorimotor neuropathy after intake of highest dosages of vitamin B6. *Neuromuscul Disord* 2008;18:156–8.
8 Kuntzer T, Antoine JC, Steck AJ. Clinical features and pathophysiological basis of sensory neuronopathies (ganglionopathies). *Muscle Nerve* 2004;30:255–68.

9 Schaumburg H, Kaplan J, Windebank A, *et al*. Sensory neuropathy from pyridoxine abuse. A new megavitamin syndrome. *N Engl J Med* 1983;309:445–8.
10 van Hunsel F, van de Koppel S, van Puijenbroek E, *et al*. Vitamin B_6 in health supplements and neuropathy: case series assessment of spontaneously reported cases. *Drug Saf* 2018.
11 Ghavanini AA, Kimpinski K. Revisiting the evidence for neuropathy caused by pyridoxine deficiency and excess. *J Clin Neuromuscul Dis* 2014;16:25–31.
12 Vrolijk MF, Opperhuizen A, Jansen E, *et al*. The vitamin B6 paradox: supplementation with high concentrations of pyridoxine leads to decreased vitamin B6 function. *Toxicol In Vitro* 2017;44:206–12.