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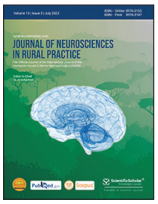

Case Series

Polyneuropathy due to Vitamin B6 hypervitaminosis: A case series and call for more education

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ABSTRACT

Polyneuropathy (PN) due to Vitamin B6 hypervitaminosis is well described in medical literature. However, only little is known about this relationship among the general population as well as under health care professionals. The following describes eight consecutively recruited patients: Seven of whom developed sensorimotor PN due to uncritical Vitamin B6 medication, and one patient who experienced a worsening of a pre-existing PN of another etiology associated with Vitamin B6. Due to the fact that Vitamin B6-induced PN is a preventable disease, we strongly advocate for increased awareness and education among the population and medical practitioners. It is crucial to understand that taking vitamin supplements is not always beneficial and can be associated with serious side effects.

Keywords: Hypervitaminosis, Polyneuropathy, Pyridoxine, Self-medication, Vitamin B6 hypervitaminosis

INTRODUCTION

Peripheral neuropathies are known to be very common diseases with a high prevalence, affecting 2–75% of the population.[1] One of the most common subtypes of peripheral neuropathy is distal symmetric polyneuropathy (PN), a diffuse length-dependent process.[2] The overall prevalence of PN in the general population is about 1–3%, increasing to roughly 7% among people older than 65 years.[3] PN can be caused by multiple conditions, with diabetes being the most common etiology, responsible for 32–53% of cases.[1,4,5] Other common causes include rheumatological diseases, paraproteinemia, chronic kidney disease, Vitamin B12 deficiency, and inherited conditions like Charcot-Marie-Tooth disease.[1,4,6,7] Toxic neuropathies are known, for example, those related to alcohol,[8] as well as in patients receiving chemotherapy or immunotherapy for cancer or inflammatory, rheumatological, or gastroenterological diseases.[9]

PN due to the toxicity of Vitamin B6 (pyridoxine) has first been described in 1983.[10] Since then, there have been repeated case reports in the literature, some of which are very impressive, involving massive intake of Vitamin B6 due to self-medication.[11] Although the literature clearly indicates that uncritical self-medication is highly problematic, cases continue to emerge in everyday medical practice, sometimes leading to serious conditions. Therefore, we describe eight patients in whom uncritical intake of Vitamin B6 led to the development or worsening of pre-existing PN.

CASE SERIES

Patients were consecutively recruited from our outpatient clinic over a period of four years. In all cases, a detailed clinical and neurological examination was conducted. Electrophysiological studies included sensory and motor nerve conduction studies, as well as electromyography (EMG). In addition, extensive laboratory analyses were performed. Tests included a complete blood cell count, thyroid, renal and liver function tests, blood glucose levels, hemoglobin A1C, immunofixation, levels of Vitamin B1, B6, B12, holotranscobalamin, and methylmalonic acid. Serum rheumatologic tests were also conducted, including extractable nuclear antigen antibodies, antinuclear antibodies, antineutrophil cytoplasmic antibodies, anti-ds-DNA antibodies, anti-cyclic citrullinated peptide antibodies, rheumatoid factor, and Burrelia burgdorferi Immunoglobulin G and Immunoglobulin M antibodies.

RESULTS

The demographics, clinical characteristics, and results of the electrophysiological examinations are summarized in Table 1.

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Table 1: Demographics, clinical characteristics, electrophysiological results, and diagnosis.

No.	Sex	Age	Reason for admission	Sensory clinical feature	Paresis	Reflexes	Sensory NCS	Motor NCS	EMG	Diagnosis
1.	m	78	Known PN	Vibration sense ll 0/8, ul 5/8; symmetric distal sensory loss	None	PTR +/+, ATR +/+	No SNAP	No CMAP	Chronic neurogenic	Sensorimotor PN in uremia/ ckd and B6 hypervitaminosis
2.	m	84	Limb tremor	Vibration sense ll 4/8, ul 4/8	None	PTR +/+, ATR +/+	No SNAP	Reduced CMAP, reduced NCV	Chronic neurogenic	Sensorimotor PN in B6 hypervitaminosis
3.	f	79	Susp. PN	Vibration sense ll 2/8, ul 4/8, atactic gait	None	ATR -/-	No SNAP	No CMAP	Chronic neurogenic	Sensorimotor PN in B6 hypervitaminosis
4.	m	86	Known PN	Vibration sense ll 0/8, ul 8/8	None	PTR -/-, ATR -/-	No SNAP	Normal	Not performed	Sensorimotor PN in B6 hypervitaminosis
5.	f	79	Feet dysesthesia	Vibration sense ll 4/8, ul 8/8, symmetric distal sensory loss	None	PTR -/-, ATR -/-	Reduced SNAP	Normal	Chronic neurogenic	Sensorimotor PN in B6 hypervitaminosis
6.	m	83	Feet dysesthesia	Vibration sense ll 3/8, ul 8/8	None	PTR -/-, ATR -/-	No SNAP	Normal	Acute and chronic neurogenic	Sensorimotor PN in B6 hypervitaminosis
7.	m	70	Non-spec. dizziness	Vibration sense ll 8/8, ul 8/8, symmetric distal sensory loss	None	ATR -/-	no SNAP	Normal	Normal	Sensorimotor PN in B6 hypervitaminosis
8.	f	82	Feet dysesthesia; Susp. PN	Vibration sense ll 4/8, ul 8/8	None	PTR -/-, ATR -/-	reduced SNAP	Normal	Normal	Sensorimotor PN in B6 hypervitaminosis

m: Male, f: Female, NCS: Nerve conduction studies, EMG: Electromyography, PN: Polyneuropathy, Susp.: Suspected, Non-spec.: Non-specific, ll: Lower limbs, ul: Upper limbs; PTR: Patellar tendon reflex, ATE: Achilles tendon reflex, SNAP: Sensory nerve action potential, CMAP: Compound motor nerve action potential, CKD: Chronic kidney disease, NCV: Nerve conduction velocity, ATR: Achilles tendon reflex.

There were three female and five male patients with a mean age of 80, 13 years, range 70–86 years. One patient (no. 2) presented for evaluation of an unspecific tremor of upper and lower limbs while patient no. 7 presented with non-specific dizziness. All other patients were either known to have PN, requiring further clarification of the cause or were suspected of having PN. Clinically, all patients revealed sensory deficits, with a reduction or loss of vibration sense. Symmetric distal sensory loss was found in three cases, and one patient presented atactic gait.

Regarding the motor system, no paresis was observed in any of the patients, though reduced deep tendon reflexes were noted in some cases. Sensory nerve conduction studies showed/revealed a complete loss of sensory nerve action potential (SNAP) in seven patients and a reduced SNAP in one, indicating axonal affection/involvement. Motor nerve conduction examinations were normal in five patients. In two patients (no. 1 and 3), no compound motor nerve action potential (CMAP) was detected, while patient no. 2 showed reduced CMAP and nerve conduction velocity, indicating a mixed axonal-demyelinating disturbance. EMG was normal in two patients and not performed in one. In five patients, a chronic neurogenic pattern with highly polyphasic potentials of increased amplitude was found. In patient no. 6, additional

acute neurogenic changes with fibrillation potentials and positive sharp waves were observed.

Based on the clinical and electrophysiological results, all patients were diagnosed with sensorimotor PN.

Laboratory workup revealed increased Vitamin B6 levels in all patients, along with abnormalities in Vitamins B12 and B1, methylmalonic acid, and holotranscobalamin in some cases. Serum blood levels are detailed in Table 2.

All patients reported either self-medication or prescriptions from health care professionals for over-the-counter vitamin and polyvitamin preparations.

There were no other causes of PN in any of the patients except no. 1, who had known PN due to uremia in chronic kidney disease. Family history was unremarkable in all patients, with no evidence of inherited PN.

Patients no. 1, 6, and 8 are particularly interesting in our opinion; therefore, they are presented in more detail:

Patient 1

A 78-year-old male patient has suffered from uremia due to chronic kidney disease for 30 years and has been receiving dialysis three times a week for the past 10 years. He has been diagnosed with PN for 15 years, with no identified cause other than uremia. He presented himself to the outpatient clinic to obtain a further opinion on whether there was another therapeutic approach to his PN other than consistent dialysis. Clinically, he showed typical features of PN, and electrophysiologically no SNAPs or CMAPs were detected. Diagnostic workup revealed a Vitamin B6 level of 373,6 µg/L (normal range 3.6–18.0 µg/L) and a Vitamin B12 level >6000 pg/mL (normal range 87–883 pg/mL). Creatinine clearance was decreased. When discussing the elevated vitamin levels, the patient stated that his dialysis doctor had recommended a high-dose Vitamin B complex preparation, because B vitamins "are generally good for the nerves." The patient was informed about the toxic effects of hypervitaminosis and the intake was discontinued. After a period of 12 months, his vibration sense in the lower limbs improved to 3–4/8 and in the upper limbs to 6–7/8.

Patient 6

The 83-year-old male, accompanied by his spouse of the same age, presented with progressive dysesthesia in his feet for 3 years. During the anamnesis, it was noticeable that the patient hardly spoke; instead, his extremely talkative wife, who expressed racing thoughts and a "flight of ideas," answered all questions. She seemed obsessed and completely absorbed by the belief that her husband suffered from various psychological issues, particularly severe depression and listlessness. For this reason, she has been treating her husband with multiple vitamin preparations and trace elements for 10 years. Clinically and electrophysiologically, he showed signs of sensorimotor PN. Laboratory workup revealed a Vitamin B6 level of 98,1 µg/l and a Vitamin B12 level of 948 pg/mL.

His wife only reluctantly stopped the medication. At a follow-up check 12 months later, his vitamin levels were normal, but his symptoms had not improved.

During the psychiatric examination, the patient appeared completely unremarkable both at initial contact and follow-up, but he did exhibit a dependent personality structure.

Table 2: Serum levels of Vitamin B6, B12, B1, methylmalonic acid, and holotranscobalamin.

No.	Vitamin B6	Vitamin B12	Methylmalonic acid	Holotrascobalamin	Vitamin B1	Cause of hypervitaminosis reported by patient
1.	**373.6**	**>6000**	**65**	**>256**	**527.3**	B-Polyvitamin medication in uremic PN
2.	**73.9**	**4995**		**>256**	79.3	B-Polyvitamin self-medication in unclear tremor
3.	**80.6**	599			83.5	B-Polyvitamin self-medication for general strengthening
4.	**159.4**	455		100,1	79	B-Polyvitamin medication by an alternative practitioner
5.	**35.6**	422	19,9	68,3	43.6	B-Polyvitamin self-medication for general strengthening
6.	**98.1**	**948**		128	62	Polyvitamin and trace elements self-medication by patients' spouses for general strengthening
7.	**53.2**	653	20,2	128	46.5	B-Polyvitamin self-medication for general strengthening
8.	**>200**	749		**232,3**	**95.1**	B-Polyvitamin medication by general practitioner

Reference values: Vitamin B6: 3.6–18.0 µg/L, Vitamin B12: 87–883 pg/mL, Methylmalonic acid: 9–32 µg/L, Holotrascobalamin: 50–165 pmol/L, Vitamin B1 (Norm 28–85 g/L), PNP: Polyneuropathy, >: Not higher measurable. Pathological values are in bold letters.

Patient 8

An 82-year-old female patient presented with dysesthesia in her feet for many years. Professionally, the patient held a doctorate in economics and was highly educated and intellectually engaged. Her personal history included elevated lipoprotein (a), osteoarthritis, and degenerative spine disease which caused severe episodes of lower back pain. In this regard, the patient underwent several lumbar infiltrations with local anesthetics and steroids. Clinically, she exhibited features of sensorimotor PN. Electrophysiological examinations demonstrated/revealed reduced SNAPs, but normal CMAPs and EMG. The patient's family doctor was commissioned to carry out the laboratory test for differential diagnosis of PN. The patient stated that the Vitamin B6 level was only measured reluctantly. According to the family doctor's office, such an examination is not routinely performed, and they lack experience with it.

Her Vitamin B6 level was elevated up to >200 µg/L (beyond measurable limits). The patient stated that she had been taking a polyvitamin preparation (which contains 10 mg of Vitamin B6) for the past 13 years, recommended by her family doctor for general strengthening following an anaphylactic reaction.

After being carefully informed about the toxicity of Vitamin B6, she was very dismayed at how little these facts were known among the public and medical professionals.

DISCUSSION

In this report, we detailed the cases of eight consecutively recruited patients who were seen at our outpatient clinic and were diagnosed with PN. One patient had known PN caused by uremia in chronic kidney disease. In all patients, laboratory diagnostic workup revealed elevated levels of Vitamin B6. As no other causes for PN were identified, patient no. 2–8 were diagnosed with PN due to Vitamin B6 hypervitaminosis. The sensory symptoms of our patient with PN in uremia improved after the withdrawal of Vitamin B6, suggesting that hypervitaminosis might have contributed to his symptoms and possibly worsened his uremic PN.

PN caused by Vitamin B6 hypervitaminosis has been known since 1983 when Schaumburg *et al*. described sensory neuropathies in mannequins who took 3–5 g of Vitamin B6 to enhance their skin color.[10] Since this initial description, there have been only a few other case reports.[12-14] Initially assumed to cause purely sensory neuropathy by means of ganglionopathy,[15] motor involvement was first described by Gdynia *et al*. in 2008.[11] They described a case of severe Vitamin B6 abuse in a patient, who calculated his daily metabolic demands with a pendulum. The ingestion of 9, 6 g Vitamin B6 per day led to a severe sensorimotor PN. Since then, the relationship between excessive Vitamin B6 intakes and the development of motor symptoms in B6-related PN has been well established.

All our patients exhibited clinical and/or electrophysiological involvement of motor nerves, confirming this finding. Examining Vitamin B6 levels in Table 2, we found striking that even slightly elevated serum levels can affect the motor system.

In 2002, a daily dose of 300–450 mg of pyridoxine was considered safe in healthy adults of normal weight.[11,16] By 2023, the European food safety authority (EFSA) Panel on Nutrition, Novel Foods, and Food Allergens established the tolerable upper intake level (UIL) of Vitamin B6 at 12 mg per day for adults including pregnant and lactating women. UILs for infants and children were derived by the EFSA Panel from adults UIL using allometric scaling: 2.2–2.5 mg/day (4–11 months), 3.2–4.5 mg/day (1–6 years), and 6.1–10.7 mg/day (7–17 years).[17]

Our female patient (no. 8) was highly educated and kept very accurate records of her illnesses and medications. She took 10 mg of Vitamin B6 daily for 13 years and developed PN, contradicting EFSA Panel recommendations, so we cannot endorse their recommendations.

Our cases of sensorimotor PN due to Vitamin B6 hypervitaminosis complement those described in the literature. It was very striking to us, that this specific cause of PN plays a significant role in clinical practice and should not be underestimated; yet, it remains poorly recognized. In addition, we found that self-medication is a major issue.

To the best of our knowledge, all reported cases of Vitamin B6 hypervitaminosis described in the literature are caused by self-medication or inadequate prescription of Vitamin B6 or polyvitamin preparations by healthcare professionals. No cases of hypervitaminosis due to incorrect food intake, other diseases or medications have been reported. Vitamin B6 is present in numerous over-the-counter drugs and supplements. Self-medication is defined as the selection and use of medicines by individuals to treat self-recognized or self-diagnosed conditions or symptoms.[18] While appropriate self-medication offers benefits, we believe that the risks outweigh them, including incorrect self-diagnosis, potential delays in seeking medical advice, infrequent but possibly severe adverse reactions, drug interactions, incorrect manner of administration, incorrect dosage, incorrect choice of therapy, masking of severe disease, and dependence and abuse.[18] All of our patients practiced self-medication uncritically or in good faith. None of those patients were aware that vitamin overdoses could cause diseases. Two patients received vitamin prescriptions from physicians and in one case from an alternative practitioner.

Apparently, there is very little awareness of this problem among the general public and medical professionals alike. The guidelines of the German Society for Neurology

mention that high doses of Vitamin B6 (>2 g/day) can cause toxic PN. However, the guideline only provides a standard recommendation for determining blood levels of Vitamins B1, B6, and B12, when alcoholism or a malabsorption syndrome is suspected.[19] In our opinion, in this way, cases can be overlooked where the intake of high doses is not evident in the anamnesis.

In a highly respected review by Mirian *et al*. regarding the diagnosis and management of PN, Vitamin B6 is considered a "common medication associated with PN." This work also mentions the recommendations of the practice guideline of the American Neurological Society for high-yield screening laboratory tests in distal symmetric PN, a determination of Vitamin B6 is not specifically recommended here.[20]

CONCLUSION

Given that Vitamin B6-induced PN is a serious but preventable condition, we strongly advocate for increasing public awareness. It is important to understand that taking vitamin supplements is not always beneficial and can be associated with serious side effects. Healthcare professionals, especially family doctors, must be adequately educated about the diagnosis and treatment of PN. Therefore, we recommend that the condition of PN due to Vitamin B6 hypervitaminosis should be mentioned with more emphasis in the diagnostic guidelines. Furthermore, in our opinion, the analysis of Vitamin B6 blood levels should be standard in all patients with polyneuropathies.

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Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent.

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