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RESEARCH REPORT

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Vitamin B6 levels do not correlate with severity of neuropathy in chronic idiopathic axonal polyneuropathy

Sarah L. Stewart[1] | Simone Thomas[1] | Erol Höke[1] | David Simpson[2] | J. Robinson Singleton[3] | Ahmet Höke[1]

[1]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

[2]Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, New York, USA

[3]Department of Neurology, University of Utah, Salt Lake City, Utah, USA

Correspondence
Ahmet Höke, MD, PhD, Department of Neurology, Johns Hopkins University School of Medicine, 855 N. Wolfe St., Suite 248, Baltimore, MD 21025, USA.
Email: ahoke@jhmi.edu

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Abstract

Pyridoxine (vitamin B6) toxicity is known to cause a length-dependent, sensory predominant axonal polyneuropathy. There is debate regarding the threshold at which intake levels can cause neurological symptoms through pyridoxine toxicity. We asked if elevated plasma vitamin B6 levels were related to outcome measures in a well-characterized cohort of patients with chronic idiopathic axonal polyneuropathy (CIAP). We included 261 patients enrolled in the Peripheral Neuropathy Research Registry who had a complete dataset including a plasma vitamin B6 value. Patients with vitamin B6 deficiency (0-4.9 μg/L) were excluded. We performed a chi-square test for independence and analyzed the logistic relation of elevated plasma B6 level to nerve conduction studies (NCS), neurological examination findings, and patient-reported symptoms controlling for age and time elapsed since neuropathy symptom onset. Plasma B6 level was not related to neuropathy severity. There was no logistic relation of elevated plasma B6 level to NCS results, examination features including toe strength, vibration sense, and deep tendon reflexes, or patient-reported numbness or pain intensity. This study suggests that moderately elevated plasma B6 levels, even in the 100 to 200 μg/L range, are not associated with significantly worse neuropathy signs or symptoms. Although standard supplementation of B6 does not appear to have a major negative affect on CIAP, this study does not directly answer whether stopping supplementation will have a beneficial effect. Very few patients in the study had vitamin B6 levels >300 μg/L, suggesting that screening for vitamin B6 toxicity may be left to the discretion of the physician.

KEYWORDS
chronic idiopathic axonal polyneuropathy, vitamin B6

1 | INTRODUCTION

Pyridoxine or vitamin B6 is a water-soluble vitamin usually considered non-toxic and critical for several cellular functions including amino acid metabolism and essential for nerve function.[1,2] When ingested, vitamin B6 is converted into its active form, pyridoxal-5-phosphate (PLP), in the liver.[3] The recommended daily amount of dietary vitamin B6 is between 1.6 and 2 mg/day for adults to maintain acceptable nutritional status.[4] Insufficient dietary intake of vitamin B6 is a well-documented cause of peripheral polyneuropathy.[5] The upper limit of acceptable intake is not clear. A dose of 500 mg/day is widely considered to be neurotoxic.[6,7] However, some studies show neurological

ABBREVIATIONS: CIAP, chronic idiopathic axonal polyneuropathy; IENFD, intra-epidermal nerve fiber density; NCS, nerve conduction studies; OR, odds ratio; PLP, pyridoxal-5-phosphate; PN, polyneuropathy; PNRR, peripheral neuropathy research registry; TNSr, total neuropathy score-reduced.

impairment at daily doses as low as 100 mg/day[7] while others report no observed adverse effects in daily dosages of 200 mg/day.[7] In all studies, toxicity only occurred through diet supplementation[8] and symptoms usually improved after daily intake was discontinued or adjusted.[6,9-13]

Patients with either vitamin B6 deficiency or overdose identified as the underlying etiology of their polyneuropathy (PN) often develop progressive numbness and clumsiness[12] and neuropathy or sensory neuronopathy.[11] Symptoms include sensory dysfunction in a stocking-glove distribution, including paresthesia, hyperesthesia, and loss of proprioception, but without weakness or central nervous involvement, and action potentials remain measurable in the larger sensory nerves.[12] There are reports of patients with sensory-motor neuropathy, demyelinating sensorimotor neuropathy, and gait abnormalities[3,14] but these symptoms seem to only appear at extremely high doses (ie, 960 mg/day).

Vitamin and nutritional deficiencies are more prevalent in older adults[15] and many older Americans take vitamin and mineral supplements. Chronic idiopathic axonal polyneuropathy (CIAP) is a common ailment and affects approximately 15% of the population over the age of 40 in the United States.[16] Patients with polyneuropathy often supplement their diets with neurotropic vitamins, including vitamin B6. These supplements are frequently taken without physician-guidance and adverse side effects are common.[17-19] Little is known about how vitamin B6 supplementation influences the natural history of CIAP, and the supplemental dosage at which plasma pyridoxine levels start to influence disease progression. We examined plasma vitamin B6 levels in CIAP patients, using cross-sectional data from the Peripheral Neuropathy Research Registry (PNRR), to determine if vitamin B6 supplementation level influenced the features of PN.

2 | MATERIALS AND METHODS

2.1 | Study population

PNRR is a multicenter database and biorepository of well-characterized patients with distal, symmetrical polyneuropathies, sponsored by the Foundation for Peripheral Neuropathy.[20] The registry enrolls patients with diabetic PN, chemotherapy-induced PN, HIV-induced PN, and CIAP. This study was limited to those with a diagnosis of CIAP, who had negative testing for other common PN etiologies.[20]

Patients from three consortia sites (Johns Hopkins University School of Medicine, Icahn School of Medicine at Mount Sinai, and University of Utah) met the following inclusion criteria: (a) diagnosis of CIAP; (b) plasma vitamin B6 value available within the 3 years of study enrollment date; (c) no recorded history of vitamin B6 deficiency (0-4.9 μg/L); and (d) complete PNRR dataset. Two hundred sixty-one (261) patients, enrolled prior to December 31, 2020, met the inclusion criteria. We initially did analysis by normal (5-49.9 μg/L), mildly elevated (50-99.9 μg/L), elevated (100-199.9 μg/L), very elevated (200-299.9 μg/L) and extremely elevated (≥300 μg/L) vitamin B6 level, but due to the small sample in the extremely elevated group ($n = 6$), we were not able to perform meaningful analysis. For all other analyses, we divided patients by normal (5-50 μg/L) and elevated plasma vitamin B6 level (>50.0 μg/L). PNRR is approved by the Institutional Review Boards of Johns Hopkins University, Mount Sinai Medical Center, and University of Utah and all study participants provided written consent.

2.2 | PNRR data set

The data collected from each patient in the PNRR database includes: (a) neurological examination capturing muscular strength, deep tendon reflexes, sensory examination findings, gait evaluations, and Romberg test; (b) NCS evaluations of major motor and sensory nerves; (c) laboratory testing results to evaluate for common underlying etiologies for PN as recommended by the American Academy for Neurology[21]; and (d) history questionnaire that asked patients to evaluate the nature and severity of their PN symptoms, that is, pain, numbness, weakness, balance, and autonomic symptoms. The questionnaire also captured their medication intake.[20]

Vitamin B6 laboratory results were recorded as either plasma pyridoxal-5-phosphate (PLP) or total pyridoxine, with normal ranges of 5 to 50 mcg/L and 3 to 30 mcg/L, respectively, per the Mayo Clinic catalog (Test ID: B6PA).[22-24] Painful CIAP was determined by the examining physician as well as self-reported by the patient as part of the questionnaire. For analysis, we looked at the relation of vitamin B6 level on reported pain. We used the Total Neuropathy Score-reduced (TNSr)[25] as a measure of overall neuropathy severity, which includes pinprick sensibility, vibration sensibility, muscular strength, and absence of deep tendon reflexes along with degree of paresthesia extension as measured by pain and numbness (Table S2a,b). For analysis, patients were divided by TNSr categories for mild (0-5), moderate (6-9), and severe (10-16) impairment. Daily medication intake and dietary supplementation were defined by patient-reported questionnaire, and relevant laboratory testing results were recorded in the PNRR data set (ie, vitamin B12 and B6 levels, etc). Intra-epidermal nerve fiber density (IENFD) information as measured by skin biopsy was also utilized but only available for patients enrolled at Johns Hopkins University.

2.3 | Statistical analysis

Baseline characteristics were summarized using STATA descriptive statistics. We analyzed the logistic effect of normal vs elevated plasma vitamin B6 level on NCS results (peroneal motor and sural sensory nerve), neurological examination findings, and patient-reported neuropathy symptoms. T-*test* analysis was used to compare differences in means between the normal and elevated vitamin B6 groups while Chi-square test for independence was used to compare differences in expected and observed frequencies between these groups. We report adjusted odds ratios (ORs) for all tests with adjustment for age and time elapsed since the onset of symptoms (in years). For NCS analysis, the testing result from the right leg was used when available, and for

those without right leg testing, the values from the left were used. The applied normative values were as follows: Peroneal Motor Nerve Conduction Velocity > 39 m/s; Peroneal Compound Muscle Action Potential amplitude >2 mV; Sural Sensory Nerve Conduction Velocity > 39 m/s; Sural Sensory Nerve Action Potential amplitude >5 μV if patient age ≥65, >9 μV if patient age <65.

3 | RESULTS

The mean vitamin B6 level of the 261 patients included in the study was 57.7 μg/L. Vitamin B6 levels in the normal range (ie, 5-50.0 μg/L) were found for 67.8% of patients; 15.9% had slightly elevated plasma levels (50.1-99.9 μg/L), while 16.3% had a level greater than 100 μg/L (Table S1). Those with an elevated vitamin B6 level had a significantly higher mean age ($M = 63.9$, $SD = 11.8$) compared to those with a normal level ($M = 59.9$, $SD = 14.3$) $t(259) = -2.23$, $P = .027$ (Table 1). There were no significant differences in mean vitamin B6 plasma levels or percent with elevated vitamin B6 level in those taking a multivitamin compared to those not taking one (Table 2). A chi-square test of independence showed that those taking a vitamin B6 supplement were more likely to have an elevated vitamin B6 level X^2 (1, N = 261) = 8.6, $P = .003$ and had a significantly higher, $t(259) = -2.97$, $P = .003$, mean plasma B6 level ($M = 115.4$ μg/L, $SD = 116.3$ μg/L) compared to those not taking the supplement ($M = 54.7$ μg/L, $SD = 77.9$ μg/L). Similarly, chi-square test of

TABLE 1 Baseline demographics and health behaviors in patients with chronic idiopathic axonal polyneuropathy

	Overall	Normal plasma B6	Elevated plasma B6	*P*-value
Number of patients (% of all)	261 (100)	177 (67.8)	84 (32.2)	
Mean age (years ± SD)	61.2 ± 13.6	59.9 ± 14.3	63.9 ± 11.8	**.0267**[a]
Mean neuropathy duration (years ± SD)	5.8 ± 6.3	5.7 ± 6.5	5.9 ± 5.8	.8478[a]
Mean weight (kg ± SD)	84.6 ± 20.7	83.9 ± 20.9	86.2 ± 20.5	.4136[a]
Mean height (cm ± SD)	173.8 ± 10.2	173.1 ± 10.6	175.2 ± 9.1	.1356[a]
Mean BMI (kg/m^2 ± SD)	27.9 ± 5.9	27.8 ± 5.9	28.0 ± 5.7	.8755[a]
Sex				
Female (% of all)	115 (44.1)	79 (44.6)	36 (42.9)	.787[b]
Male (% of all)	146 (56.0)	98 (55.3)	48 (57.1)	
Age (categorical)				
<50 (% of all)	45 (17.2)	36 (20.3)	9 (10.7)	.133[b]
50-60 (% of all)	55 (21.1)	40 (22.6)	15 (17.9)	
60-70 (% of all)	79 (30.3)	50 (28.3)	29 (34.5)	
≥70 (% of all)	82 (31.4)	51 (28.8)	31 (36.9)	
Race				
White (% of all)	243 (93.1)	165 (93.2)	78 (92.9)	.598[b]
Black (% of all)	9 (3.5)	5 (2.8)	4 (4.8)	
Other (% of all)	9 (3.5)	7 (4.0)	2 (2.4)	
Smoking history				
Never >1 ppd (% of all)	240 (92.0)	161 (91.0)	79 (94.1)	.440[b]
Former >1 ppd (% of all)	18 (6.9)	13 (7.3)	5 (6.0)	
Current >1 ppd (% of all)	3 (1.5)	3 (1.7)	0 (0.0)	
Alcohol use				
Never >2 drinks/day (%)	224 (85.8)	151 (85.3)	73 (86.9)	.928[b]
Former >2 drinks/day (%)	21 (8.1)	15 (8.5)	6 (7.1)	
Current >2 drinks/day (%)	16 (6.1)	11 (6.2)	5 (6.0)	
Neuropathic pain				
Painful PN (% of all)	195 (74.7)	131 (74.0)	64 (76.2)	.705[b]
Painless PN (% of all)	66 (25.3)	46 (26.0)	20 (23.8)	

Note: For chi-2 analysis, the total number of patients is listed with the percentage in parenthesis. For *t*-test analysis, the mean value ± standard deviation (SD) are listed.

Bold entries denote statistical significance that is <0.05.

Abbreviation: PN, polyneuropathy.

[a]*t*-test.

[b]Chi-2 analysis.

TABLE 2 Number of patients who are taking a specific supplement with percentage taking supplement by normal or abnormal vitamin B6 plasma levels

	N (% of all)			Mean ± SD (μg/L)		
Supplement	Normal plasma B6	Elevated plasma B6	*P*-value	Not taking supplement	Taking supplement	*P*-value
Vitamin B6 supplement	4 (2.3)	9 (10.7)	**.003**$^{+}$	54.7 ± 77.9	115.4 ± 116.3	**.0081***
Unspecified B-complex	13 (7.3)	10 (11.9)	.225^{+}	57.4 ± 83.0	61.3 ± 57.7	.8250*
Vit. B6 or B-complex	17 (9.6)	17 (20.2)	**.017**$^{+}$	55.1 ± 80.3	75.1 ± 84.4	.1799*
Multivitamin	14 (7.9)	11 (13.1)	.184^{+}	55.5 ± 81.1	78.6 ± 78.3	.1754*
Vit. B6 or B-complex or Multivitamin	28 (15.8)	38 (33.3)	**.001**$^{+}$	51.9 ± 79.7	78.8 ± 82.7	**.0272***
Vitamin B12	28 (15.8)	21 (25.0)	.076^{+}	54.3 ± 76.1	72.2 ± 99.1	.1656*
Vitamin B3	3 (1.7)	1 (1.2)	.757^{+}	58.0 ± 81.5	36.4 ± 34.4	.5966*

Note: Mean plasma vitamin B6 levels in μg/L ± SD of those patients who take this specific supplement and those who do not. Statistical analysis: **t*-test, $^{+}$chi-2.
Bold entries denote statistical significance that is <0.05.

independence showed that those taking either vitamin B6 or a B-complex were more likely to have an elevated vitamin B6 level X^2 (1, N = 261) = 5.7, *P* = .017. Finally, those in a combined group taking a vitamin B6 supplement, a B-complex or a multivitamin were more likely to have an elevated plasma vitamin B6 level, X^2 (1, N = 261) = 10.4, *P* = .001, and *t*-test analysis showed higher mean plasma vitamin B6 level in those taking supplements (*M* = 78.8 μg/L, *SD* = 82.7 μg/L) compared to those not taking supplements containing pyridoxine (*M* = 51.9 μg/L, *SD* = 79.7 μg/L), *t*(259) = −3.27, *P* = .001 (Table 2).

In chi-square analysis and logistic regression modeling, controlling for age and neuropathy duration, elevated plasma vitamin B6 levels were not related to any patient-reported neuropathy sign or symptom. There was no logistic effect of elevated vitamin B6 level on nearly all NCS results including peroneal or sural velocities or amplitudes, nor on IENFD. Chi-square test for independence showed that

TABLE 3 Nerve conduction study findings for peroneal (motor) and sural (sensory) nerves and intra-epidermal nerve fiber density (IENFD) results for distal skin biopsy site

			N (% abnormal testing result)			
Nerve	N	Mean ± SD	Normal plasma B6	Elevated plasma B6	*P*-value	Odds ratio adjusted
Peroneal motor nerve						
MNCV R (m/s)	188	35.9 ± 15.8	39 (30.7)	23 (37.7)	.339	1.00
MNCV L (m/s)	142	33.7 ± 17.6	34 (35.4)	20 (43.5)	.354	1.00
MNCV R or L[a] (m/s)	237	37.3 ± 15.1	43 (26.4)	27 (36.5)	.114	1.00
CMAP R (μV)	191	3.2 ± 2.6	41 (31.8)	26 (41.9)	.169	1.00
CMAP L (μV)	144	2.6 ± 2.4	38 (38.8)	26 (56.2)	**.046**	**1.01[a] (0.020)**
CMAP R or L[a] (μV)	237	3.4 ± 2.6	44 (27.0)	28 (37.8)	.093	1.00
Sural sensory nerve						
SNCV R (m/s)	198	30.9 ± 21.3	53 (37.9)	21 (36.2)	.827	1.00
SNCV L (m/s)	174	29.8 ± 21.1	49 (40.2)	24 (46.2)	.464	1.00
SNCV R or L[a] (m/s)	232	32.4 ± 20.7	56 (34.4)	25 (36.2)	.784	1.00
SNAP R (μV)	199	9.4 ± 10.7	68 (48.2)	28 (48.3)	.995	1.00
SNAP L (μV)	175	8.3 ± 9.6	63 (51.6)	28 (52.8)	.885	1.00
SNAP R or L[a] (μV)	233	10.2 ± 10.6	70 (42.7)	31 (44.9)	.752	1.00
Skin biopsy						
Distal site (fiber density)	153	6.8 ± 7.6	59 (55.7)	23 (48.9)	.442	1.00

Note: The table lists the total number of patients (N) with this information available, the mean testing result (for all patients with information available) and the percentages of patients with abnormal testing results in those with normal and abnormal vitamin B6 levels. *P*-values were done using chi-2 test for independence and odds ratio analysis was done as logistics regression controlling for age and duration of PN and unadjusted.
Bold entries denote statistical significance that is <0.05.
[a]Right leg testing results were used for analysis for those patients who had both right and left leg testing done.

TABLE 4 Physical exam findings, total neuropathy score-reduced (TNSr) findings and patient-reported paresthesia evaluations

		N (% abnormal testing)			
N = 261	**N with testing done**	**Normal plasma B6**	**Abnormal plasma B6**	***P*-value**	**Odds ratio (adjusted)**
Muscular strength					
Finger weakness R	261	17 (9.6)	8 (9.5)	.983	1.00 (0.993-1.005)
Finger weakness L	261	20 (11.3)	10 (11.9)	.886	1.00 (0.996-1.005)
Ankle dorsiflexion R	261	16 (9.0)	6 (7.1)	.606	0.99 (0.979-1.002)
Ankle dorsiflexion L	261	17 (9.6)	6 (7.1)	.512	1.00 (0.989-1.004)
Ankle plantarflexion R[a]	237	8 (4.7)	6 (8.8)	.227	1.00 (0.990-1.008)
Ankle plantarflexion L[a]	237	7 (4.1)	6 (8.8)	.152	1.00 (1.000-1.008)
Toe dorsiflexion R	260	31 (17.6)	18 (21.4)	.462	1.00 (0.997-1.005)
Toe dorsiflexion L	260	28 (15.9)	17 (20.2)	.388	1.00 (0.997-1.005)
Toe plantarflexion R	260	25 (14.2)	13 (15.5)	.786	1.00 (0.993-1.003)
Toe plantarflexion L	260	25 (14.2)	14 (16.7)	.603	1.00 (0.996-1.004)
Deep tendon reflexes					
Patella R	261	33 (18.6)	15 (17.9)	.878	1.00 (0.995-1.004)
Patella L	261	33 (18.6)	15 (17.9)	.878	1.00 (0.995-1.004)
Achilles R	260	91 (51.7)	47 (56.0)	.521	1.00 (0.996-1.003)
Achilles L	260	89 (50.6)	47 (56.0)	.416	1.00 (0.997-1.003)
Vibration (Rydel-Fork)					
Ankle vibration R	254	47 (27.2)	25 (30.9)	.542	1.00 (0.996-1.004)
Ankle vibration L	254	51 (29.5)	22 (27.2)	.703	1.00 (0.997-1.005)
Toe vibration R	261	104 (58.8)	57 (67.9)	.158	1.00 (0.997-1.004)
Toe vibration L	261	104 (58.8)	59 (70.2)	.074	1.00 (0.996-1.004)
Joint position					
Toe R	260	49 (27.8)	23 (27.4)	.938	1.00 (0.995-1.003)
Toe L	260	46 (26.1)	24 (28.6)	.679	1.00 (0.997-1.004)
Gait evaluations					
Gait	261	32 (18.1)	16 (19.1)	.850	1.00 (0.995-1.003)
Tandem gait	258	41 (23.6)	26 (31.0)	.205	1.00 (0.997-1.004)
Romberg	260	21 (11.9)	13 (15.5)	.428	1.00 (0.993-1.005)
Toe walk	259	15 (8.5)	9 (10.8)	.548	1.00 (0.991-1.005)
Heel walk	269	20 (11.4)	13 (15.7)	.333	1.00 (0.996-1.006)
TNSr[a] (N = 236, mean TNSr score: 7.3 ± 2.6)					
Mild (0-5)	85	63 (38.4)	21 (31.4)	.561	
Moderate (6-9)	86	58 (35.4)	25 (37.3)		
Severe (10-16)	65	43 (26.2)	21 (31.3)		
Patient-reported paresthesia					
Neuropathic pain		126 (71.2)	66 (78.6)	.206	1.00 (0.982-1.011)
No pain (0)		51 (28.8)	18 (21.4)	.120	Pain scale 0-10 N = 192 (pain) Mean intensity: 5.7 ± 2.6
Low (1-3)		27 (15.3)	23 (27.4)		
Moderate (4-6)		41 (23.2)	17 (20.2)		
High (7-10)		58 (32.8)	26 (31.0)		
Patient-reported numbness (%)	261	151 (85.3)	69 (82.1)	.511	1.00 (0.995-1.002)

Note: Statistical analysis was done using chi-2 test for independence and odds ratios were adjusted for age and years of PN symptoms.
[a]Were only available for patients enrolled at Johns Hopkins University.

those with an elevated plasma B6 level were more likely to have an abnormal left peroneal CMAP amplitude, X^2 (1, N = 144) = 3.99, $P = .046$ but no other relation was seen for other peroneal or sural results (Table 3). Logistic regression showed no relation of elevated vitamin B6 level on exam features including ankle and toe strength, vibration sense, deep tendon reflexes, pinprick border, or gait abnormality. There was no logistic effect of vitamin B6 level on TNSr category (mild, moderate, and severe impairment). There were no differences in frequency or severity of patient-reported pain, pain types (ie, sharp, hot, or deep pain), or numbness (Table 4).

4 | DISCUSSION

Previous studies were foremost concerned with vitamin B6-induced neuropathy - focusing on both deficiency as well as overdose-induced PN - but less is known about how vitamin B6 plasma levels may modulate neuropathy symptoms in those with a diagnosis of otherwise idiopathic PN. In this analysis, we studied the relation of vitamin B6 level on neuropathy severity and symptoms to see if patient with higher vitamin B6 levels experienced more severe impairment. Our results suggest that B6 supplementation often elevates B6 levels into the abnormal range. However, few patients taking vitamin B6 supplementation achieve extremely elevated vitamin B6 levels, and mild to moderate elevation of vitamin B6 is not related to worse neuropathy symptoms. Commonly available multivitamins have 1.7 to 2 mg of B6 (100%-113% of daily requirement) and most B-complex or single B6 supplements have 2 to 6 mg of B6. This may explain why patients taking B6 supplements or multivitamins do not achieve very high levels of Plasma B6 levels unless they take "megavitamin" supplements, which may have 100 mg or more of B6.

In our sample, there were no significant differences in symptom severity with increasing vitamin B6 levels in those with CIAP. Most prior studies on the effect of vitamin B6 overdoses were conducted with small cohorts and focused on extremely high doses. For instance, in seven patients taking extremely high doses (4000-6000 mg/day) of vitamin B6, all developed progressive numbness and clumsiness[12] and in 16 patients taking doses ranging from 100 to 3500 mg/day, all had symmetric distal sensory loss (absent or reduced SNAP).[11] Even at a dose of 50 to 300 mg/day, 40% of premenstrual patients with plasma vitamin B6 levels above normal (3-18 ng/mL) developed PN.[9] Most CIAP patients experienced sensory symptoms, including 23.0% of patients exhibiting small fiber neuropathy, 62.5% experiencing reduced vibratory sensation in the toes, and 84.3% of patients reporting numbness. However, neither the presence nor severity of these features varied significantly by vitamin B6 level.

Our results are slightly different than a study that found that patients with CIAP were more likely to take vitamin B6 supplements but had similar vitamin B6 levels compared to healthy controls.[26] We saw that those taking certain supplements did have significantly higher vitamin B6 levels but did not have corresponding worse symptoms. Although elevated plasma B6 level was related to a higher chance of having an abnormal left peroneal CMAP result, other NCS associations were not noted. Further analysis showed that patients with concurrent lumbar stenosis or radiculopathy were slightly more likely to have elevated vitamin B6 levels (although this difference did not reach statistical significance), and this may have impacted NCS results on the left side. It has been suggested to include vitamin B6 toxicity in the differential diagnosis of sensory or sensorimotor polyneuropathy with particular symptoms of numbness, burning pain, balance difficulties, and weakness,[27] but our study suggests that moderately elevated vitamin B6 plasma levels are not a contributing factor in regard to PN symptoms or severity.

Our study offers a unique perspective on vitamin B6 and neuropathy as we examined outcomes in CIAP patients taking low dose supplementation, rather than more regimented clinical trials or high dose prescribed doses. One major limitation in this study was that we used cross-sectional data so we could not consider changes in patient symptoms before, during, and after vitamin supplementation. Vitamin B6 laboratory testing results were only available for a subset of patients enrolled in PNRR, suggesting the potential for acquisition bias in our sample. Finally, we did not have an exact dosage or duration of supplementation for every patient, so we could not look at the effect of dose or cumulative exposure on symptomology and had to use plasma vitamin B6 level as a proxy.

Overall, our study suggests that taking vitamin B6 supplementation has no significant effect on neuropathy symptoms in patients who have already developed neuropathy. Elevated plasma vitamin B6 levels, even in the 100 to 200 ug/L range, were not associated with significantly worse neuropathy signs or symptoms. Although patients taking multivitamins or a pooled group taking vitamin B6, B-complex, or multivitamin were more likely to have an abnormally elevated vitamin B6 level, these patients were not more likely to have more severe signs and symptoms of neuropathy. This suggests that standard supplementation of B6 does not appear to have a major negative affect on CIAP, but this study does not directly answer whether stopping them will have a beneficial effect. In our sample, very few patients (2.3%) had vitamin B6 levels >300 μg/L. Because the prevalence of extremely elevated vitamin B6 levels was low even in idiopathic neuropathy patients taking supplementation, pyridoxine testing may be left to the discretion of the physician.

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CONFLICT OF INTERESTS

The study was supported by the Foundation for Peripheral Neuropathy (FPN) and Dr. Hoke is the chair of the Scientific Advisory Board of

the FPN. The officers of the FPN did not have any role in conducting the study or writing the manuscript. The authors do not report any other relevant conflicts of interest.

DATA AVAILABILITY STATEMENT

The deidentified study data from the Peripheral Neuropathy Research Registry used in this study can be requested from the corresponding author.

ORCID

Ahmet Höke https://orcid.org/0000-0003-1215-3373

REFERENCES

1. Eliot AC, Kirsch JF. Pyridoxal phosphate enzymes: mechanistic, structural, and evolutionary considerations. *Annu Rev Biochem*. 2004;73:383-415.
2. Percudani R, Peracchi A. The B6 database: a tool for the description and classification of vitamin B6-dependent enzymatic activities and of the corresponding protein families. *BMC Bioinformatics*. 2009;10:273.
3. Ghavanini AA, Kimpinski K. Revisiting the evidence for neuropathy caused by pyridoxine deficiency and excess. *J Clin Neuromuscul Dis*. 2014;16:25-31.
4. Palmer S. Recommended dietary allowances, tenth edition. *Eur J Clin Nutr*. 1990;44(Suppl 2):13-21.
5. Hammond N, Wang Y, Dimachkie MM, Barohn RJ. Nutritional neuropathies. *Neurol Clin*. 2013;31:477-489.
6. Berger A, Schaumburg HH. More on neuropathy from pyridoxine abuse. *N Engl J Med*. 1984;311:986-987.
7. Institute of Medicine (US) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes and its Panel on Folate, Other B Vitamins, and Choline. *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B(6), Folate, Vitamin B(12), Pantothenic Acid, Biotin, and Choline*. Washington, DC: National Academies Press (US); 1998.
8. Hemminger A, Wills BK. *Vitamin B6 Toxicity*. [Updated 2021 Apr 19]. In: StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; 2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554500/
9. Dalton K. Pyridoxine overdose in premenstrual syndrome. *Lancet*. 1985;1:1168-1169.
10. Friedman MA, Resnick JS, Baer RL. Subepidermal vesicular dermatosis and sensory peripheral neuropathy caused by pyridoxine abuse. *J Am Acad Dermatol*. 1986;14:915-917.
11. Parry GJ, Bredesen DE. Sensory neuropathy with low-dose pyridoxine. *Neurology*. 1985;35:1466-1468.
12. Schaumburg H, Kaplan J, Windebank A, et al. Sensory neuropathy from pyridoxine abuse. A new megavitamin syndrome. *N Engl J Med*. 1983;309:445-448.
13. Waterston JA, Gilligan BS. Pyridoxine neuropathy. *Med J Aust*. 1987;146:640-642.
14. Gdynia HJ, Muller T, Sperfeld AD, et al. Severe sensorimotor neuropathy after intake of highest dosages of vitamin B6. *Neuromuscul Disord*. 2008;18:156-158.
15. Hamfelt A. Age variation of vitamin B6 metabolism in man. *Clin Chim Acta*. 1964;10:48-54.
16. Gregg EW, Sorlie P, Paulose-Ram R, et al. Prevalence of lower-extremity disease in the U.S. adult population ≥40 years of age with and without diabetes: 1999–2000 national health and nutrition examination survey. *Diabetes Care*. 2004;27(7):1591-1597.
17. Achari M, Haider M, Mohammed Z. Vitamin B6 (pyridoxine) toxicity and OTC supplements (5222). *Neurology*. 2021;96(Suppl 15):5222.
18. Silva CD, D'Cruz DP. Pyridoxine toxicity courtesy of your local health food store. *Ann Rheum Dis*. 2006;65:1666-1667.
19. Timbo BB, Ross MP, McCarthy PV, Lin CT. Dietary supplements in a national survey: prevalence of use and reports of adverse events. *J Am Diet Assoc*. 2006;106:1966-1974.
20. Thomas S, Ajroud-Driss S, Dimachkie MM, et al. Peripheral neuropathy research registry: a prospective cohort. *J Peripher Nerv Syst*. 2019;24:39-47.
21. England JD, Gronseth GS, Franklin G, et al. Practice parameter: evaluation of distal symmetric polyneuropathy: role of laboratory and genetic testing (an evidence-based review). Report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of physical medicine and rehabilitation. *Neurology*. 2009;72:185-192.
22. Burtis CA, Ashwood ER, Bruns DE. *Tietz Textbook of Clinical Chemistry and Molecular Diagnostics*. 4th ed. St. Louis: Elsevier Saunders; 2006.
23. Henry JB, McPherson RA, Pincus MR. *Henry's Clinical Diagnosis and Management by Laboratory Methods*. 22nd ed. Philadelphia, PA: Elsevier Saunders; 2011.
24. Wallach JB. *Interpretation of Diagnostic Tests*. 6th ed. New York, NY: Little, Brown; 1996.
25. Lavoie Smith EM, Cohen JA, Pett MA, Beck SL. The validity of neuropathy and neuropathic pain measures in patients with cancer receiving taxanes and platinums. *Oncol Nurs Forum*. 2011;38:133-142.
26. Visser NA, Notermans NC, Degen LA, de Kruijk JR, van den Berg LH, Vrancken AF. Chronic idiopathic axonal polyneuropathy and vitamin B6: a controlled population-based study. *J Peripher Nerv Syst*. 2014;19:136-144.
27. Scott K, Zeris S, Kothari MJ. Elevated B6 levels and peripheral neuropathies. *Electromyogr Clin Neurophysiol*. 2008;48:219-223.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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