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Evaluation of vitamin B_6 supplementation in Wilson's disease patients treated with D-penicillamine

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ABSTRACT

Introduction Wilson's disease (WD) is a copper metabolism disorder characterised by a progressive accumulation of this metal mainly in the liver and the brain. Treatment is based on the removal of copper operated by the chelators, among which, D-penicillamine (DP) is prescribed as a first-line treatment in most situations. There is some evidence in linking the use of DP with a risk of vitamin B_6; therefore, vitamin supplementation is sometimes recommended, although non-consensually. The objective of our study was to evaluate the level of vitamin B_6 in WD patients treated with DP with and without associated supplementation.

Methodology All WD patients followed at the National Reference Centre for WD in Lyon between January 2019 and December 2020 treated with DP for more than 1 year were included and separated in two groups according to vitamin B_6 supplementation. The level of vitamin B_6 was measured by the determination of pyridoxal phosphate (PLP).

Results A total of 37 patients were included. Average age of 23.3±14.8 years, 15 patients with <18 years. Median duration of treatment was 51 (55.8) months. 15 patients were under vitamin B_6 supplementation and 22 had interrupted it for more than 1 year. The median PLP level was significantly higher in the group with supplementation, 137.2 (86.7) nmol/L vs 64.9 (30.8) nmol/ ($p<0.01$). No patient had a PLP level<35 nmol/L.

Conclusion Long-term stable WD patients under DP treatment probably do not need vitamin B_6 supplementation.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The antipyridoxine effect of D-penicillamine (DP) has been demonstrated, but there is no consensus regarding systematic vitamin B_6 supplementation.

WHAT THIS STUDY ADDS

⇒ This is the first study addressing this subject after nearly four decades. No case of vitamin B_6 deficiency was observed in the not supplemented group. Most patients in the supplemented group had higher-than-normal vitamin B_6 levels.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study provides new evidence from a real-world experience unfavourable to recommending systematic vitamin B_6 supplementation when using DP.

INTRODUCTION

Wilson's disease (WD) is a rare, autosomal recessive disorder characterised by a progressive toxic accumulation of copper, mainly in the liver and central nervous system.[1–3] This accumulation is responsible for liver damage and secondarily for neurological and psychiatric symptoms due to copper mobilisation. The disease is exceptionally symptomatic before 3 years and after 50 years.[1 4] WD progresses to cirrhosis and irreversible central nervous system damage without early diagnosis and appropriate treatment.[1–4] Treatment of WD is based on lifetime administration of either copper chelators or copper absorption inhibitors associated with a low copper diet.[1 2 5 6] D-penicillamine (DP), a copper chelator and inducer of endogeneous metallothioneins, is the first-line chelator for symptomatic WD. This drug is frequently responsible for adverse effects that require its discontinuation in up to 30% of cases.[5–7] These effects are multiple and comprise notably cutaneous (rashes), haematological (neutropenia, thrombocytopenia and lymphadenopathy), renal (proteinuria) and immunological effects.[8 9]

Vitamin B_6, or pyridoxine, is a generic term that includes a group of six chemically related compounds with a common pyridine ring. The phosphorylated derivate, known as pyridoxal 5′-phosphate (PLP), is the biologically active form of vitamin B_6 that serves as a cofactor in more than 160 different catalytic reactions, particularly in the synthesis of haem, nucleic acids, as well as lipid, carbohydrate, amino acid metabolism.[10 11]

Studies carried out more than 40 years ago demonstrated an antipyridoxine effect of DP manifested by an increase in the urinary

secretion of tryptophan metabolites without any clinical sign.[12–14] Pyridoxin deficiency has not been observed in animals or patients receiving DP,[12–15] however; few reports have found a potential link between cases of optic neuropathy and vitamin B_6 deficiency secondary to administration of DP.[16–19] Based on these studies, the European Association for the Study of the Liver (EASL) recommends routine vitamin B_6 supplementation in all patients receiving DP.[5] Some studies suggested that the supplementation may especially be needed in case of nutritional deficit and at times of growth spurts.[12 14] The paediatric recommendations for WD published by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) only indicate that there is a low level of evidence of pyridoxine deficiency associated with DP treatment and probably a high vitamin B_6 intake in a regular diet.[6]

Therefore, we aimed to assess the effect of DP on vitamin B_6 levels and evaluate the need for vitamin supplementation in the long-term treatment of WD patients with DP.

PATIENTS AND METHODS

We carried out a retrospective review of medical records of WD patients treated with DP for >12 months year between January 2019 and December 2020 and followed at the national reference centre for WD in Lyon (France). Demographic, clinical and laboratory data were collected, including DP dose, vitamin B_6 supplementation and blood pyridoxine level.

Vitamin B_6 supplementation is routinely prescribed in our centre for patients at the start of DP treatment, 125 mg for children and 250 mg/week for adults. This supplementation is often later discontinued at the request of the patient or by the prescribing physician to improve adherence to the chelator treatment. Patients who discontinued vitamin supplementation for >12 months were compared with those who continued vitamin B_6 supplementation.

Vitamin B_6 level was determined by the quantification in whole blood of PLP, its biologically active form. This assay was carried out using high-performance liquid chromatography. Normal values ranged from 35.0 to 110.0 nmol/L. The quantification of PLP has been added to the routine follow-up of WD patients treated with DP since 2019.

Qualitative variables are presented as relative frequency (percentage), and as mean and SD for normally distributed quantitative variables and median (IQR) for non-normally distributed variables. Comparisons were made using the Mann-Whitney non-parametric test using SPSS software V.23.0 (IBM Corp. Armonk, NY). P<0.05 was considered significant.

This analysis was listed as a clinical practice audit, under the control of the research committee of our structure, and therefore did not require ethics approval. However, a note was sent to the institutional review board (CPP: Comités de protection des personnes) for information and approval before the publication of the results of the study.

RESULTS

Study population

A total of 37 patients were included. The mean±SD age at inclusion was 23.3±14.8 years (range: 6–63); 15 patients (40.5%) were <18 years of age. The mean±SD age at diagnosis was 9.7±5.2 years. Thirty (81.1%) patients had hepatic manifestations at diagnosis, and seven (18.9%) had neurological manifestations. The median (IQR) duration of DP treatment was 59 (21.5–162.5) months. The mean±SD dose of DP was 17.4±5.3 mg/kg/day (table 1).

Two patients had moderate undernutrition, and there was no case of pregnancy.

Vitamin B_6 supplementation

Of the 37 patients, 15 were supplemented with pyridoxine, and 22 has discontinued. There was no significant difference between these two groups in terms of mean age at inclusion, mean age at diagnosis, clinical form, mean dose of DP, median duration of treatment and mean level of transaminases and exchangeable copper (table 1).

Pyridoxal phosphate (PLP)

The median (IQR) PLP level was significantly higher in the group with supplementation (137.2 (104.9–191.6) nmol/L) than in the group without supplementation (64.9 (2.6–83.4) nmol/L, p<0.01). No patient had a PLP level<35 nmol/L, defining a biological deficit in pyridoxal; 11/15 patients (73%) in the supplemented group had a PLP level higher than normal (> 110 nmol/L), while none in the group without supplementation did so (p<0.01; table 1). No patient had any clinical signs of vitamin B_6 deficiency. No patient presented with any symptom attributable to vitamin B_6 toxicity that led to discontinuing the supplementation.

DISCUSSION

There is little published data on vitamin B_6 supplementation for patients treated with DP, and no consensus recommendation exists. Here, there was no case of vitamin B_6 deficiency defined by PLP level or clinical manifestation potentially attributable to this deficiency. Between 1963 and 1991, four cases of optic neuropathy were identified in patients treated with DP.[16–19] In three cases, this complication occurred between 13 and 30 months of treatment using dosages between 1 and 2 g per day. Only one case showed elevated urinary tryptophan metabolites indicating an antipiridoxin effect. All these patients were supplemented with variable doses of vitamin B_6 in addition to a decrease in the DP dosage or a change in chelation therapy; one patient had also received corticosteroid therapy due to the concomitant appearance of antinuclear antibodies. All of them evolved

Table 1 Demographic, clinical and laboratory characteristics

	Total	Supp. B_6 vit.	No suppl. B_6 vit.	
	n=37	n=15	n=22	P value
Sex M, n (%)	22 (59.5)	8 (53.3)	14 (63.6)	
Age at inclusion*	23.3±14.8	19.0±11.6	26.3±16.3	
Age at diagnosis*	9.7±5.2	10.0±4.4	9.5±5.8	
<18 years, n (%)	15 (40)	8 (53)	7 (32)	
Hepatic manifestations	30 (81)	11 (73)	19 (86)	
Neurological manifestations	7 (19%)	4 (27%)	3 (14%)	
Dose DP (mg)*	948.6±369.2	830±334.8	1029.5±376.9	
Dose (mg/kg)*	17.4±5.3	16.3±4.4	18.1±5.8	
Duration of treatment in months†	59 (21.5–162.5)	51 (22.3–78.1)	78.2 (21.1–224.7)	
PLP level (nmol/L)†	81.8 (61.9–117.4)	137.2 (104.9–191.6)	64.9 (52.6–83.4)	p<0.05
PLP<35 (nmol/L), n (%)	0	0	0	
PLP>110 (nmol/L), n (%)	11 (30)	11 (73)	0	p<0.05
Hb (g/L)*	14.1±1.5	14.0±1.5	14.1±1.6	
WBC (G/L)*	6.4±1.5	5.8±1.4	6.8±1.8	
Platelets (G/L)*	256.7±104.4	238.2±125.8	269.3±87.0	
ALT (U/L)*	46.9±33.8	41.5±32.8	50.6±34.7	
Elevated ALT, n (%)	11 (30)	5 (33)	6 (27)	
ASAT (U/L)*	34.5±10.9	32.6±11.5	50.6±34.7	
Elevated AST, n (%)	10 (27)	3 (20)	7 (32)	
GGT (U/L)*	36.9 (21.1)	33.1±21.7	39.5±20.7	
Elevated GGT, n (%)	16.0 (43)	6 (40)	10.0 (45)	
Alkaline phosphatase (U/L)*	158.0±119.4	175.2±120.8	147.4±120.2	
Exchangeable copper (umol/L)*	0.8±1.7	1.2±0.9	0.6±0.5	

*Mean±SD.
†Median (IQR).
DP, D-penicillamine; PLP, pyridoxal phosphate.

into full vision recovery. Attributing these complications to the antipyridoxine effect of DP remains challenging to prove, considering that in one case, optic neuropathy appeared in the first weeks of treatment using DP in low doses; in another case, a vitamin B_6 supplementation was prescribed concomitantly.

In the supplemented group, more than three-quarters of patients had above-normal PLP levels, but we did not find any neurological manifestation that could be attributed to vitamin B_6 overdose; however, patients were assessed only by clinical neurological examination without a dedicated electrophysiology study. Multiple publications have described a link between the occurrence of peripheral neuropathy and vitamin B_6 overdose.[20] In most published cases, this complication appears with large doses of vitamin B_6 (2–6 g/d)[21]; but also with 50–600 mg/day dosages over several months to several years.[20]

All the patients included in this study received DP for a relatively long time, about 4 years on average, so these results should not be extrapolated to patients in the initial phases of treatment.

Without an established toxicity threshold, it is recommended not to exceed 25–50 mg/day of vitamin B_6.[22 23] Due to the ubiquity of vitamin B_6 in common animal and plant foods, the need for vitamin B_6 is generally satisfied. Supplementation may be necessary in exceptional cases (malnutrition and pregnancy). Our cohort only had two cases of moderate undernutrition and no pregnancy.

This study has many limitations: the retrospective and descriptive design, the small number of patients, the absence of a dietary evaluation and the predominance of chronic patients with long-term DP treatment.

Vitamin B_6 level assessment or monitoring of clinical symptoms of vitamin toxicity are not routinely recommended during WD follow-up. However, we recommend thoroughly assessing both until more firm evidence is available.

CONCLUSION

No signs of vitamin B_6 deficiency were found in a group of long-term stable WD patients treated with DP who did not receive vitamin supplementation. Prospective studies are required to help determine if routine vitamin B_6 supplementation needs to be routinely recommended.

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