Vitamin B12 and folate levels in children with primary nocturnal enuresis

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ABSTRACT

Aims: Primary nocturnal enuresis (PNE) is associated with the maturation of the central nervous system in children. Vitamin B12 and folate are involved in the metabolism, development, and maturation of the nervous system. We examined vitamin B12, folate, and ferritin levels in children with PNE.

Methods: This retrospective study included children with and without PNE from a tertiary pediatric nephrology clinic. PNE was defined as nighttime bedwetting (≥2 nights per week) in children aged >5 years. Children with chronic diseases or neurological, psychiatric or urological abnormalities were excluded. Vitamin B12, folate, hemoglobin, hematocrit, and ferritin levels were obtained from medical health records.

Results: The study included 86 patients with PNE and 90 age- and sex-matched controls. The PNE group had lower vitamin B12 (229 vs. 264 pg/mL; p=0.001) and folate (7.9 vs. 12.4 ng/mL; p=0.001) levels than the control group. Vitamin B12 deficiency was more common in children with PNE than in controls (40.7% vs. 25.6%; p=0.037). None of the children with PNE or controls had folate deficiency. The hemoglobin, hematocrit, and ferritin levels were similar between the two groups.

Conclusions: Compared with controls, children with PNE had lower vitamin B12 and folate levels and a higher prevalence of vitamin B12 deficiency. Further studies are needed to determine whether vitamin B12 and folate supplementation can improve PNE symptoms.

Introduction

Primary nocturnal enuresis (PNE) is characterized by involuntary bedwetting during sleep in children aged >5 years without any congenital or acquired defects in the central nervous system (CNS) (1). Children with PNE have a lifelong inability to achieve continence, whereas those with secondary enuresis have experienced continence for ≥6 months (2). The exact cause of PNE remains unclear; several mechanisms have been proposed, including small bladder capacity, abnormal sleep patterns, excessive urine production during sleep, and delayed functional maturation of the CNS (3). The prevalence of PNE decreases rapidly with increasing age, which is likely associated with neuroanatomical development (4).

Vitamin B12 plays a crucial role in the maturation of peripheral nerves, optic nerves, brain tissue, and the posterior and lateral columns of the spinal cord (5). Vitamin B12 deficiency results

in the accumulation of methylmalonyl-CoA, which replaces acetyl-CoA and leads to the formation of unstable myelin. Myelin instability can cause neurological damage to the nervous system in children (5).

Folate is an essential nutrient for CNS development (6). In fact, folate deficiency during preconception and early pregnancy is a major risk factor for neural tube defects (7). The precise mechanism by which folate prevents neural tube defects is not understood but may be related to methionine and nucleotide biosynthesis (8). Mice fed a folate-poor diet exhibited impairments in the hypothalamic serotonin and dopamine systems and behavioral changes (6).

Iron plays a crucial role in early brain development and is essential for myelination and neurotransmitter function (9). Iron deficiency leads to impaired myelination, neurotransmission, synaptogenesis, and dendritogenesis, particularly during infancy (10). Ferritin, a form of iron, is not only crucial for brain

development but also plays a significant role in spinal cord development and repair (11).

Because vitamin B12, folate, and iron are involved in nervous system development and PNE is associated with delayed CNS maturation, we explored whether vitamin B12, folate, hemoglobin, hematocrit, and ferritin levels are associated with PNE.

Methods

This single-center, retrospective study included 176 children with PNE, and age- and sex-matched controls admitted to the Pediatric Nephrology Clinic of Gülhane Training and Research Hospital between November 2016 and December 2022. The medical records of children with PNE and controls were obtained from the hospital information system. This study included children with and without PNE who underwent testing for vitamin B12, folate, and ferritin levels and complete blood count on family request or physician advice during routine check-ups. Children who did not undergo the aforementioned laboratory tests or had incomplete data were excluded. PNE was diagnosed in children aged >5 years with two or more nighttime enuretic episodes per week and no daytime urinary incontinence, no history of continence lasting for >3 months, no neurological, psychiatric (e.g. autism spectrum disorder, attention deficit disorder, and hyperactivity), urological abnormalities, and no chronic diseases such as diabetes mellitus or diabetes insipidus (1). The control group included children aged >5 years who had normal blood and urine tests, no neurological, psychiatric, or urological abnormalities, no bacterial growth in urine culture, no chronic diseases, and no history of PNE.

Some inflammatory markers (e.g. C-reactive protein and systemic immune inflammation index) may increase in acute otitis media (AOM) (12). Furthermore, recurrent AOM may be associated with adenotonsillar hypertrophy (ATH), which is associated with nocturnal enuresis (13). Non-steroidal anti-inflammatory drugs (NSAIDs), such as indomethacin, can be used for treating nocturnal enuresis (14). Therefore, we excluded children who were taking NSAIDs and had ATH and/or a history of recurrent AOM from both the PNE and control groups.

Hemoglobin, hematocrit, ferritin, vitamin B12, and folate levels were obtained from hospital records. The UniCel DxH 800 Hematology Analyzer (Beckman Coulter, Miami, FL, USA) was used for complete blood count analysis, and the AU680® analyzer (Beckman Coulter) was used for biochemical tests during the study period.

Vitamin B12 levels <200, 200-300, and >300 pg/mL indicate vitamin B12 deficiency, borderline vitamin B12 deficiency, and normal vitamin B12 levels, respectively (15). Folate levels <2, 2-4, and >4 ng/mL indicate folate deficiency, borderline folate deficiency, and normal folate levels, respectively (16). Ferritin levels <10 ng/mL indicated low ferritin levels (17).

The study protocol was approved by the Local Ethics Committee of the University of Health Sciences Türkiye, Gülhane Training and Research Hospital (date: 15.03.2023, decision no: 35).

Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences software (version 22; IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to test for the normality of the data distribution. Normally distributed continuous variables were compared using Student's t-test, whereas non-normally distributed continuous variables were compared using the Mann-Whitney U test. Continuous variables are presented as medians and interquartile ranges. Categorical variables were compared using the chi-square or Fisher's exact test and are presented as numbers and percentages. P values <0.05 were considered indicative of statistical significance.

Results

The study included 176 patients [median age=9 (6-14) years], including 86 children (49 boys and 37 girls) in the PNE group and 90 children (42 boys and 48 girls) in the control group. As shown in Table 1, the median age and sex were not significantly different between the groups.

The median vitamin B12 level was 229 (165-295) pg/mL in children with PNE and 264 (178-351) pg/mL in controls, with significant differences between the groups (p=0.001) (Table 1, Figure 1). The number of children with PNE with borderline vitamin B12 deficiency and vitamin B12 deficiency was 39 and 35, respectively, compared with 27 and 23, respectively, in the control group. There were statistically significant differences between the children with PNE and controls regarding the number of children with borderline vitamin B12 deficiency and vitamin B12 deficiency (p=0.034 and p=0.037, respectively) (Table 1).

The median folate level was 7.9 (6.5-10.5) ng/mL in the children with PNE group and 12.4 (9.7-15) ng/mL in the control group; the difference was statistically significant (p=0.001) (Table 1, Figure 2). The number of children with PNE with borderline folate deficiency was significantly higher than that of the controls (6 and 1, respectively; p=0.041).

There were no statistically significant differences in hemoglobin, hematocrit, or ferritin levels between the two groups (p=0.566, p=0.729, and p=0.806, respectively). Although the proportion of children with PNE with low ferritin levels was higher than that of controls, the difference was not statistically significant (15.1% and 7.8%, respectively; p=0.136) (Table 1).

A comparison of the cases and controls according to sex did not reveal any significant differences in age or hemoglobin, hematocrit, or ferritin levels (p>0.05) (Table 2).
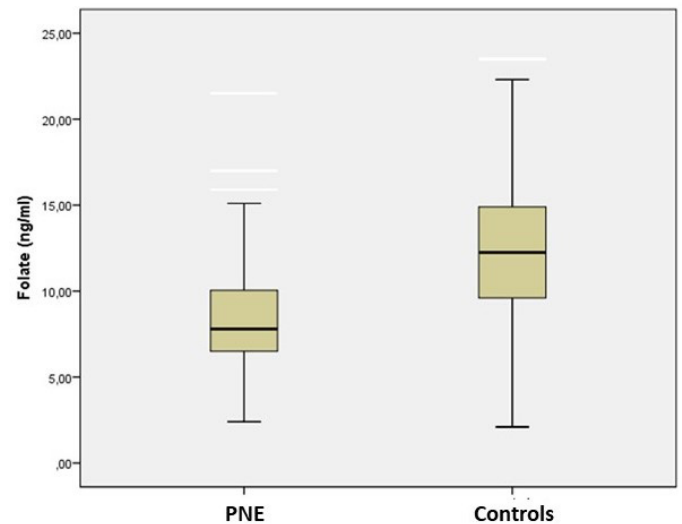
Table 1. Demographic characteristics and comparison of hemoglobin, hematocrit, vitamin B12, folate and ferritin levels

	PNE (n=86)	Control (n=90)	p-value
Sex, female/male	37/49	48/42	0.184**
Age, years, median (IQR)	9 (6-13)	9 (7-13)	0.144*
Hemoglobin, g/dL, median (IQR)	13.2 (12.8-13.9)	13.3 (12.9-14.1)	0.566*
Hematocrit, %, median (IQR)	39.7 (38.1-41.2)	39.5 (37.9-41.5)	0.729*
Vitamin B12, pg/mL, median (IQR)	229 (165-295)	264 (178-351)	**0.001***
Borderline vitamin B12 deficiency, n (%)	39 (45.3)	27 (30.0)	**0.034***
Vitamin B12 deficiency, n (%)	35 (40.7)	23 (25.6)	**0.037***
Folate, ng/mL, median (IQR)	7.9 (6.5-10.5)	12.4 (9.7-15)	**0.001***
Borderline folate deficiency, n (%)	6 (6.9)	1 (1.1)	**0.041****
Folate deficiency, n (%)	0	0	1.000***
Ferritin level, ng/mL, median (IQR)	20.5 (12.2-33.4)	20.4 (14.8-32.3)	0.806*
Low ferritin level, n (%)	13 (15.1)	7 (7.8)	0.136**

*Mann-Whitney U test, **Chi-squared test, ***Fisher's exact test.
PNE: Primary nocturnal enuresis, IQR: Interquartile range
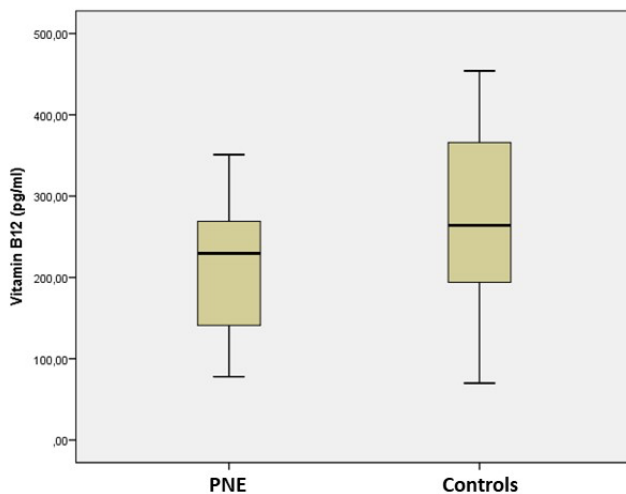
Figure 1. Boxplot diagram of serum vitamin B12 levels in PNE patients and control subjects
PNE: Primary nocturnal enuresis

Figure 2. Boxplot diagram of serum folate levels in PNE patients and control subjects
PNE: Primary nocturnal enuresis

Table 2. Comparison of demographic characteristics, hemoglobin, hematocrit, vitamin B12, folate and ferritin levels according to sex

	Female			Male		
Parameters	PNE (n=37)	Control (n=48)	p-value	PNE (n=49)	Control (n=42)	p-value
Age, years, median (IQR)	8 (5-12)	9 (6-13)	0.065*	8 (6-11)	9 (6-12)	0.113*
Hemoglobin, g/dL, median (IQR)	12.9 (12.5-13.3)	13.0 (12.6-13.4)	0.435*	13.4 (12.8-13.8)	13.7 (13.1-16.2)	0.225*
Hematocrit, %, median (IQR)	38.8 (37.6-40.1)	38.8 (37.5-40.1)	0.645*	40.4 (38.8-42.2)	40.3 (38.1-43.1)	0.337*
Vitamin B12, pg/mL, median (IQR)	228 (137-248)	256 (186-355)	**0.004***	220 (133-285)	287 (229-420)	**0.001***
Borderline vitamin B12 deficiency, n (%)	19 (51.4)	14 (29.2)	**0.037***	20 (40.1)	13 (31.0)	0.329**
Vitamin B12 deficiency, n (%)	14 (37.8)	14 (29.2)	0.437**	21 (40.7)	9 (25.6)	**0.030***
Folate, ng/mL, median (IQR)	7.9 (5.9-10.5)	11.0 (8.8-14.7)	**0.001***	7.8 (6.6-10.2)	13.3 (10.4-15.5)	**0.001***
Borderline folate deficiency, n (%)	2 (5.4)	0 (0)	0.059***	4 (8.2)	1 (2.4)	0.228***
Folate deficiency, n (%)	0	0	1.000***	0	0	1.000***
Ferritin level, ng/mL, median (IQR)	19.2 (10.1-27.9)	18.4 (13.3-25.8)	0.946*	25.1 (14.1-34.0)	27.8 (16.0-38.1)	0.337*
Low ferritin level, n (%)	8 (21.6)	5 (10.4)	0.181**	5 (11.2)	2 (4.8)	0.442**

*Mann-Whitney U test, **Chi-squared test, ***Fisher's exact test.
PNE: Primary nocturnal enuresis, IQR: Interquartile range

Among females in the case and control groups, the vitamin B12 levels were 228 (137-248) and 256 (186-355) pg/mL, respectively, whereas among males, the levels were 220 (133-285) and 287 (229-420) pg/mL, respectively. Vitamin B12 levels were significantly different between the female and male cases and controls (p=0.004 and=0.001, respectively). Similarly, a statistically significant difference was found between the cases and controls among both males and females with folate levels ((both p=0.001). Among females in the case and control groups, the folate levels were 7.9 (5.9-10.5) and 11.0 (8.8-14.7) ng/mL, respectively, whereas the levels were 7.8 (6.6-10.2) and 13.3 (10.4-15.5) ng/mL among male cases and controls, respectively. These results suggest that serum vitamin B12 and folate levels were significantly lower in both female and male patients than in controls.

The number of female patients with borderline vitamin B12 deficiency was significantly higher in the case group than in the control group (p=0.037), whereas there was no significant difference in males (p=0.329) (Table 2). Although there were no significant differences in the number of female cases and controls with vitamin B12 deficiency (p=0.437), the number of male children with vitamin B12 deficiency was higher in the case group than in the control group (p=0.030). Finally, there were more females and males with borderline folate deficiency in the case group than in the control group, although the differences were not statistically significant (p=0.059 and p=0.228, respectively) (Table 2).

Discussion

In this study, children with PNE had significantly lower vitamin B12 and folate levels than healthy controls. The prevalence of vitamin B12 deficiency and borderline vitamin B12 deficiency was significantly higher in children with PNE than in controls. Similarly, borderline folate deficiency was significantly more common in children with PNE than in controls. Conversely, there were no significant differences between the groups in ferritin, hemoglobin, or hematocrit levels. Although the prevalence of low ferritin levels was higher in the PNE group than in the controls, the difference was not statistically significant.

Several studies have evaluated vitamin B12 and folate levels in children with PNE (18-21). However, most studies included fewer than 50 participants (18-20). Our study included 86 children with PNE, making it the second-largest study. We found that vitamin B12 and folate levels were significantly lower in the PNE group than in the controls, which is in line with most previous studies (18-20), although Keles et al. (21) did not find a significant difference in folate levels between children with and without PNE.

The lower urinary tract, including the bladder, is innervated by three types of peripheral nerves. Pelvic parasympathetic nerves, which are located at the level of the sacral spinal cord, provide sensory innervation to the bladder and relax the urethra by increasing the levels of the neurotransmitter acetylcholine (22). Lumbar sympathetic nerves inhibit contraction of the bladder body and provide sensory innervation to the bladder base and urethra by increasing the levels of the neurotransmitter norepinephrine (22). Pudendal nerves play crucial roles in opening and closing the external urethral sphincter by increasing the levels of the neurotransmitter acetylcholine (22).

Certain vitamin deficiencies are involved in the pathogenesis of some diseases; for example, vitamin D deficiency is involved in the pathogenesis of celiac disease (23). Similarly, vitamin B12 deficiency is primarily associated with impaired neurotransmitter production, myelin damage, subacute combined degeneration of the spinal cord, polyneuritis, neuropathy, myelopathy, optic nerve atrophy, and cognitive dysfunction (24). The main cause of neuronal demyelination is reduced levels of S-adenosylmethionine (SAM), a universal methyl donor (5). Vitamin B12 deficiency plays a crucial role in SAM synthesis, and SAM plays important roles in the nervous system, including myelination and neurotransmitter synthesis (5). Myelinated Aδ-afferent fibers participate in the normal micturition reflex (25). In cases of vitamin B12 deficiency, these Aδ-afferent fibers also undergo demyelination (26).

Folate has crucial functions in the nervous system, including multiple CNS methylation reactions (27). Folate deficiency can lead to subacute combined spinal cord degeneration (28). It enters the nervous system in the form of methyl folate (27). Methyl folate donates its methyl group via SAM (7). Mouse studies have shown that folate contributes to myelination by promoting oligodendrocyte survival and differentiation (29).

Therefore, both vitamin B12 and folate are involved in the regulation of myelination of nerves that innervate the urinary system and promote neurotransmitter synthesis for normal micturition (24,29).

In our study, vitamin B12 and folate levels were significantly lower in the PNE group than in the controls. The prevalence of borderline vitamin B12 deficiency was significantly lower in females than in males. Margalit et al. (30) also found a higher rate of vitamin B12 deficiency in males than in females and attributed this difference to genetic variations rather than dietary habits or estrogen. In the present study, although only six children with PNE had borderline folate deficiency, it was more common in males than in females, which is consistent with previous studies (31).

Although several case reports have described improvements in enuresis in adults with vitamin B12 supplementation (32,33), limited evidence exists for children (34). In an 18-year-old autistic patient, oral vitamin B12 supplementation administered to improve psychobehavioral status also improved nocturnal enuresis (34). Furthermore, the same patient experienced a recurrence of enuresis after discontinuation of supplements.

Kurabayashi et al. (32) and Lindenbaum et al. (33) showed that vitamin B12 supplementation improved urinary incontinence in adults. Conversely, Campellone et al. (35) found no improvement in vitamin B12 deficiency-related neurogenic bladder dysfunction after intramuscular vitamin B12 administration. Although the aforementioned evidence is useful, the patients in previous studies were much older than our study population and did not have PNE.

PNE is more common in patients with anemias, including sickle cell disease and thalassemia major (36). However, the increased incidence of these diseases was not associated with nephropathy or hypostenuria, which may be due to anemia, but rather to factors such as younger age and positive family history in the general population (36,37). We observed no statistically significant differences in ferritin levels between children with PNE and controls, which is in agreement with previous studies (19,21). Moreover, there were no significant differences between the children with PNE and controls regarding the prevalence of anemia or in the hemoglobin or hematocrit levels. Therefore, iron deficiency may not play a role in the etiopathogenesis of PNE.

Study Limitations

Our study had several limitations. First, this was a retrospective study. Second, we did not analyze serum methylmalonic acid or homocysteine levels, which are more sensitive indicators of vitamin B12 or folate deficiency, particularly in patients with borderline levels. Third, we did not evaluate the history of iron deficiency anemia during infancy, which can be related to PNE because of the role of iron in myelination and neurotransmitter functions. Fourth, the study had a small sample size, which may have been insufficient to determine the role of vitamin B12, folate, and ferritin levels in the etiopathogenesis of PNE.

Conclusion

Children with PNE had lower vitamin B12 and folate levels than controls. No significant differences were observed in the hemoglobin, hematocrit, or ferritin levels between children with PNE and controls. Further studies are needed to determine whether vitamin B12 and folate deficiencies contribute to the etiopathogenesis of PNE and to establish whether vitamin B12 and/or folate supplementation can improve PNE in children.

Acknowledgments

Ethics

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