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Vitamin D Levels in Children with Sleep Terror: Analytical Cross-Sectional Study

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ABSTRACT

Objective: This study aimed to investigate 25(OH) vitamin D levels in children with sleep terror compared to those in normal controls.

Materials and Methods: In this study, we enrolled 81 children diagnosed with sleep terrors and 81 normal control children of similar ages. We analyzed plasma 25(OH) vitamin D, calcium, phosphorus, alkaline phosphatase, and parathyroid hormone levels. Levels of 25(OH) vitamin D less than 20 ng/ml were interpreted as representing vitamin D deficiency, while levels of 20–30 ng/ml indicated vitamin D insufficiency.

Results: The mean serum 25(OH) vitamin D level of children with sleep terror was 23.29±10.39 ng/ml, which was significantly lower than in the control group at 29.07±8.32 ng/ml ($p<0.001$). Children with sleep terror with frequent attacks had lower 25(OH) vitamin D levels than those without frequent attacks ($p<0.001$).

Conclusion: This study demonstrated a greater prevalence of vitamin D deficiency or insufficiency among children with sleep terror. We now need further studies with larger series investigating the effect of vitamin D replacement on sleep terror.

Keywords: Children, parasomnia, sleep terrors, 25(OH) vitamin D

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INTRODUCTION

Sleep terror is one of the most frequent causes of pediatric parasomnias. It is characterized by screaming, intense fear, and crying during sleep (1). There may also be signs and symptoms due to excessive stimulation of the autonomic system, such as sweating, chills, skin redness, pupillary dilation, and tachycardia. The prevalence of sleep terror between 4- and 12-year-olds is 1%–6.5% (2). Attacks generally occur in the first one-third of nocturnal sleep. Parental efforts to calm the child generally give no response. Diagnosis can be based on American Academy of Sleep Medicine criteria (2). Many factors related to central nervous system maturation are implicated in the development of sleep terror (3). The condition has been reported in adolescent patients with migraine associated with serotonergic system dysfunction. In addition, serotonin precursors and selective serotonin reuptake inhibitors are considered to reduce the incidence of sleep terror (1). The facilitating factors may be genetic, but they may also involve physical stresses such as fever, asthma, gastroesophageal reflux, insufficient and inappropriate sleep, bladder pressure during sleep, the presence of obstructive sleep disorders, occasional limb movements, and medications (3). In addition, a relation has been reported between sleep terror and sleepwalking in the relatives of patients with nocturnal frontal lobe epilepsy (4).

Previous studies have linked vitamin D deficiency to neurological disorders such as autism, epilepsy, multiple sclerosis, depression, schizophrenia, and Alzheimer's disease (5–8). Additionally, low vitamin D levels have been described as one of the risk factors for unhealthy sleep, with a notable inverse correlation being observed between short duration and vitamin D status. Although the mechanism involved in the relation between vitamin D deficiency and sleep disorders is not yet fully understood, several possibilities have been suggested (9). Vitamin D receptors exist in many regions of the brain, including the prefrontal cortex, cingulated gyrus, thalamus, substantia nigra, hippocampus, and the hypothalamus that regulates sleep-wakefulness. Vitamin D deficiency is therefore considered to regulate the development of wakefulness symptoms widely associated with sleep disorders. In addition, there is a known relation between bone demineralization and vitamin D deficiency, and non-specific chronic pain resulting in poor sleep quality occurs in subjects with vitamin D deficiency (9). However, studies are needed to elucidate the complex link between low vitamin D levels, normal sleep, and sleep disorders. Moreover, the effects of 25(OH) vitamin D levels on children with sleep terror are unknown. This study therefore aimed to determine vitamin D levels in children with sleep terror, and to perform a comparison of vitamin D levels between children with sleep terror and normal controls.

MATERIALS and METHODS

Study Design, Setting, and Participants

This research was designed as an analytical cross-sectional study with a control group and included children diagnosed with sleep terror at the Pediatric Emergency, Pediatric Neurology and Child and Adolescent Psychiatry Department. We recruited 162 children (81 children with sleep terror and 81 normal children) by convenience sampling between March 2016 and July 2018. Subjects with sleep terror were diagnosed based on the American Academy of Sleep Medicine's (AASM) 2014 International Classification of Sleep Disorders (third edition) diagnostic criteria for sleep terrors (2). Inclusion criteria were (i) absence of epileptic disease, (ii) no receipt of treatment or surgical procedure for any sleep disorder, (iii) absence of severe mental or physical disorder (such as cerebral palsy), and (iv) receipt of informed consent forms from the parents or legal guardians of all subjects. Children with abnormal neurological or physical examination, who had received steroid therapy (oral, topical, or intralesional), multivitamin supplements, immunosuppressants, or vitamin D supplements, with any acute or chronic disorder (autoimmune illness, or endocrine, renal, hepatic, gastrointestinal, and metabolic diseases), who had been hospitalized for infection in the previous month, with a disorder causing malabsorption, with a family history of osteoporosis, immobile children, and children using medications affecting bone metabolism were excluded from the study. The control group consisted of healthy children. All patients and controls were living in the same region. The city where the study was conducted lies at low altitude. Time of presentation was recorded in terms of seasons. Spring in Turkey lasts between March and May, summer between June and August, fall between September and November, and winter between December and February. We enrolled patients with similar socioeconomic levels and nutritional habits. More than five attacks per month were defined as frequent attacks.

We obtained plasma by centrifuging the collection tubes according to the manufacturer's specifications. These were then aliquoted and stored at -80°C. We determined serum calcium, phosphorus, alkaline phosphatase, serum parathyroid hormone (PTH), and 25(OH) vitamin D levels with chemiluminescence immunoassay with the Cobas 8000 modular analyzer series (Roche, Germany). The 25(OH) vitamin D levels of 20 ng/mL or less were interpreted as representing "deficiency", values between 21 and 29 ng/mL as constituting "insufficiency", and values of 30 ng/mL and above as constituting "sufficiency" (10). The PTH values were measured in all patients with low 25(OH) vitamin D levels. The PTH levels ≥65.0 ng/L were suggestive of hyperparathyroidism. Digital electroencephalograms (EEG) with 21 standard electrodes were used, and additional electrodes were employed to facilitate electrocardiogram detection. Total recording time included 3 min hyperventilation and photic stimulation from 5 to 20 Hz at the end of the recording. A certified pediatric neurologist blinded to the patient's demographic and clinical data reviewed all EEG recordings.

Statistical Analysis

Continuous variables were expressed as mean±standard deviation or median (interquartile range) values, and categorical variables as number and percentage values. Compatibility with normal distribution was confirmed using the Kolmogorov–Smirnov test. Unpaired Student t test was used to compare normally distributed variables, while the Mann–Whitney U test was used to compare non-normally distributed data. One-way ANOVA was used to compare more than two groups with normal distribution. Fisher's exact test was used for categorical variables. The results were expressed as mean±standard deviation or percentages. p values <0.05 were considered statistically significant. The SPSS version 22.0 (SPSS Inc., Chicago, IL., USA) software was used for statistical analysis.

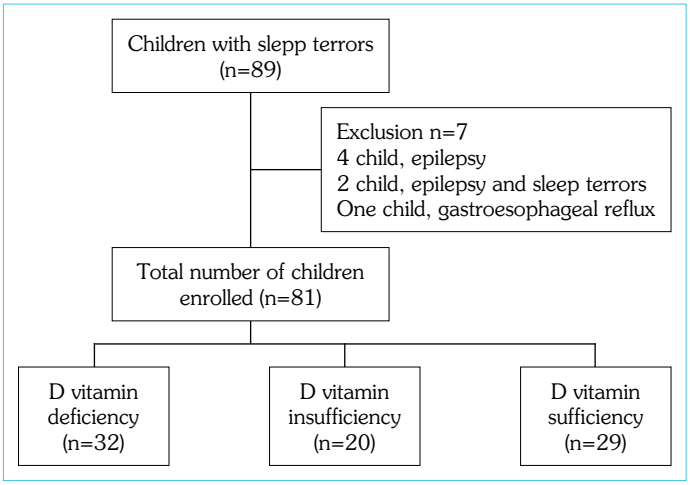

Figure 1. Flow diagram of the study

At the end of the study, mean vitamin D levels and standard deviation, together with effect size, were calculated for the two independent groups. Post-hoc power was determined at 97.2% with α=0.05 and effect size values of 0.61 for groups containing 81 participants. Power analysis was performed on G*Power version 3.1.9.2 statistical software.

RESULTS

We initially enrolled 89 patients. Four patients were subsequently excluded due to epilepsy (two with frontal lobe epilepsy, one with rolandic epilepsy, and one with occipital lobe epilepsy), two due to comorbid epilepsy (rolandic epilepsy and frontal lobe epilepsy) and sleep terror, one due to asthma, and one due to gastroesophageal reflux (GER). Finally, 81 patients (47 boys, 34 girls) were included in this study (Fig. 1). the median age was 10 years [IQR (interquartile range); 7–13 years] in the patient group and 11 years (IQR; 9–14 years) in the control group. The mean body mass index was 20.9±1.9 (18.7–24.1) in the patient group and 21.3±1.7 (18.6–24.3) in the control group (p=0.31). The mean serum 25(OH) vitamin D concentration in children with sleep terror was 23.29±10.39 ng/ml, significantly higher than in the control group, at 29.07±8.32 ng/ml (p=0.021) (Table 1). The mean serum 25(OH) vitamin D concentrations were 28.68±8.62 ng/ml in boys with sleep terror and 22.71±10.37 ng/ml in girls with sleep terror. The difference in 25(OH) vitamin D levels between boys and girls with sleep terror was statistically significant (p<0.001) (Table 2). In terms of seasonality, 19.7% (16/81) of the patients with sleep terror presented to hospital in summer,

Table 1. Comparison of Vitamin D level in patients and controls

	Patients group (n=81)		Control group (n=81)		p
	n	%	n	%	
Age	10.13±3.31		10.91±3.41		0.144
Gender					1.00
Boys	47	58	47	58	
Girls	34	42	34	42	
D vit level	23.29±10.39		29.07±8.32		0.000
D vit deficiency	32	39.5	17	21	0.010
D vit insufficiency	20	24.6	15	18.5	0.340
D vit sufficiency	29	35.8	49	60.5	0.002

D vit: Vitamin D. Values are expressed as mean±standard deviation, and as numbers with percentages

Table 2. Comparison of vitamin D level in gender

	Girls (n=34)	Boys (n=47)	p
Patient's group D vit level	19.20±10.48	26.24±9.37	0.003
Control group D vit level	26.23±9.12	31.12±7.09	0.008

D vit: Vitamin D. Values are expressed as mean±standard deviation

20.9% (17/81) in spring, 27.1% (22/81) in winter, and 33.3% (27/81) in fall. The 25(OH) vitamin D levels were not statistically significant between the patient and control groups (p=0.568 and p=0.677, respectively) (Table 3). Fifty-two (64.1%) patients with sleep terror had vitamin D deficiency or insufficiency, of whom 17.3% (9/52) also had elevated PTH levels. Thirty-two (39.5%) members of the control group had vitamin D deficiency or insufficiency, of whom 9.3% (3/32) also had increased PTH levels. A comparison between the patient and control groups with vitamin D deficiency or insufficiency revealed no statistically significant difference in PTH levels (p>0.05) (Table 4).

Patients with more than five attacks per month had statistically significant lower 25(OH) vitamin D levels than those with fewer than five attacks (p<0.001) (Table 5). Sleep terror was present in mothers only in three (3.7%) children with sleep terror, in fathers only in five (6.2%), and in siblings only in eight (9.9%). Sleep terror was present in both parents of four (4.9%) patients. Mother, father, and siblings of two (2.5%) patients were affected by sleep terror. First-degree relatives of 18 (22.2%) children had sleep terror. No patients with sleep terror had any EEG abnormality.

Table 4. Laboratory findings of subjects between patients and controls groups

	Patients group (n=81)	Control group (n=81)	p
Ca (mg/dl)	9.6±0.5 (n=81)	9.8±0.3 (n=81)	0.144
P (mg/dl)	4.5±0.5 (n=81)	4.6±0.5 (n=81)	0.578
ALP (U/L)	175.2±74.3 (n=81)	210±89.3 (n=81)	0.421
PTH (pg/mL)	51±30.2 (n=51)	47.4±26.4 (n=32)	0.321
D vit level (ng/mL)	23.2±10.3 (n=81)	29.0±8.3 (n=81)	0.021

Ca: Calcium; P: Phosphorus; ALP: Alkaline phosphatase; PTH: Parathyroid hormone. Values are expressed as mean±standard deviation

Table 5. Correlation of vitamin D level with number of ST attack

	Patients group (n=81)		Control group (n=81)		p
	n	%	n	%	
D vit level	26.39±11.85		18.53±8.03		0.001
D vit deficiency	13	38.3	19	59.4	0.003
D vit insufficiency	16	32.7	4	12.5	0.040
D vit sufficiency	20	40.8	9	28.1	0.244

D vit: Vitamin D; ST: Sleep terror. Values are expressed as mean±standard deviation, and as numbers with percentages

DISCUSSION

In our study, levels of 25(OH) vitamin D were lower in patients with sleep terror compared to those in the healthy controls. Previous studies of sleep disorders have revealed a higher incidence of reduced 25(OH) vitamin D levels among individuals with a short sleep duration, or with poor sleep quality and efficiency (11). In patients with sleep disorders, inverse correlation has been reported between vitamin D levels and sleep scale [ESS (Epworth Sleepiness Scale)] scores (5). The ESS scores were significantly higher in the vitamin D deficiency subgroup. Similarly, in another study, as vitamin D levels decreased, severity of symptoms in 120 children with obstructive sleep apnea (OSA) worsened compared to that in normal children (12). Moreover, lower 25(OH) vitamin D levels were determined in non-obese children with OSA compared to the non-obese control group (13). In our study, since there were insufficient numbers of overweight and obese children in the patient group, we had no means of establishing a link between 25(OH) vitamin D levels and obesity. Manios et al. (14) reported that vitamin D deficiency in healthy children was more common in winter

Table 3. Vitamin D levels according to season in patient and control group

	Spring	Summer	Fall	Winter	p
Patient's group D vit level (ng/mL)	25.38±10.29	24.72±11.63	22.96±9.03	21.02±11.26	0.568
Control group	31.03±9.09	29.33±9.83	27.83±7.71	28.83±7.71	0.677

D vit: Vitamin D. Values are expressed as mean±standard deviation

and spring. However, that study revealed no significant seasonal difference in the prevalence of vitamin D deficiency between obese and non-obese children (14). Another study reported no seasonal difference between vitamin D levels in obese and non-obese children with OSA (13). Our study results were in accordance with that study. Sex appears to be another factor that affects vitamin D status. However, while some studies have reported lower vitamin D levels in men, others have determined lower levels in women (10, 15, 16). Our female patients with sleep terror had lower vitamin D levels than male patients. A total of 49 (60.5%) children in the control group had sufficient vitamin D vitamin levels, while 52 (64.1%) of the children with sleep terror had vitamin D deficiency or insufficiency. Our scan of the previous literature revealed no previous studies reporting lower vitamin D levels in children with sleep terror compared to healthy children. Thus, our study of sleep terror is original from that perspective.

There has long been evidence of a genetic risk factor for sleep terror (3, 17). A history of sleep terror in first-degree relatives was present in 22.2% of our patients, which suggests a strong relationship between the condition and genetic factors. In one case series, rhythmic theta and delta activity was not identified as a characteristic capable of differentiating nocturnal frontal lobe epilepsy from parasomnias (16). Sleep terror is typically incorrectly interpreted as nocturnal frontal lobe epilepsy in particular at differential diagnosis. Some seizures are mistaken for non-epileptic events due to being characterized by short-lived stereotypic movement and bizarre automatism, and also due to occurring in sleep. The relationship between epilepsy and sleep terror is complex. Epileptic disease may cause parasomnia through sleep disorders (3). Four patients with sleep terror were excluded from this study due to epilepsy. Two patients had both epilepsy and sleep terror. All patients with sleep terror should undergo EEG testing, detailed history taking and physical examination; and differential diagnosis should include epilepsy, gastroesophageal reflux, and asthma attacks.

Low vitamin D levels may cause myalgia as a result of aromatase-inhibitor deficiency, immune modulation due to macrophage maturation and cytotoxic activity, cardiovascular disease due to hypertension, and sleepiness due to increase in substances such as TNF-a and IL-1 (18). Vitamin D deficiency is more prevalent among populations with sleep-disorder-related symptoms. It may also lead or contribute to frequently observed sleep disorder symptoms such as chronic nonspecific pain, a lower subjective sleep quality, or insufficient wakefulness (5). However, previous studies have not fully clarified the association between sleep terror and vitamin D deficiency. We detected a higher rate of vitamin D deficiency among children with sleep terror than in the controls.

The low number of patients and the fact that therapeutic doses of vitamin D were not investigated in these patients limited our study. In addition, a study with a different design, such as being randomized controlled, and with larger numbers of children might have been designed. The data for a two-year period were collected from the children in our study. However, we were only able to identify 81 children with sleep terror. Moreover, since there were no previous similar studies, we did not consider a randomized study or one revealing the effect of vitamin D in therapeutic doses on sleep terror. Another limitation is that although vitamin D deficiency is defined as <30 ng/mL by the US Endocrine Society Clinical Practice Guideline, different results might be obtained for various 25(OH) vitamin D cut-off points. Interestingly, one report involving a large series of patients concluded that maintaining 25(OH) vitamin D levels at 60–80 ng/ml led to improvement in several sleep disorders. However, no similar benefit was obtained at vitamin D levels below 50 ng/ml or above 80 ng/ml (19, 20). The variability of the cut-off levels may have affected our results. Body mass indexes were similar between our patient and control groups, and no subjects were overweight or obese. We were therefore unable to relate obesity to sleep terror and vitamin D levels.

CONCLUSIONS

In our study population, children with sleep terror had lower vitamin D levels than the control group. This suggests that children with sleep terror should be assessed in terms of vitamin D deficiency or insufficiency. Future larger sample studies are now needed to reveal the pathogenic role of hypovitaminosis D as a potential risk factor for sleep terror. Studies investigating the effect on sleep terror of vitamin D replacement therapy are also needed.

Ethics Committee Approval: The Ethics Committee of Kahramanmaraş Sütçü İmam University provided the ethics committee approval for this study (06.12.2017-2017/20).

Informed Consent: Written informed consent was obtained from all participants in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Conceived and designed the experiments or case: AKÖ, OG. Performed the experiments or case: OG. Analyzed the data: AKÖ, OG. Wrote the paper: AKÖ, OG. All authors have read and approved the final manuscript.

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REFERENCES

1. Fialho LM, Pinho RS, Lin J, Minett TS, Vitalle MS, Fisberg M, et al. Sleep terrors antecedent is common in adolescents with migraine. Arq Neuropsiquiatr 2013; 71(2): 83–6. [CrossRef]
2. International Classification of Sleep Disorders. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014. p. 230-9.
3. Mason TB 2nd, Pack AI. Sleep terrors in childhood. J Pediatr 2005; 147(3): 388–92. [CrossRef]
4. Bisulli F, Vignatelli L, Naldi I, Licchetta L, Provini F, Plazzi G, et al. Increased frequency of arousal parasomnias in families with nocturnal frontal lobe epilepsy: a common mechanism? Epilepsia 2010; 51(9): 1852–60. [CrossRef]
5. McCarty DE, Chesson AL Jr, Jain SK, Marino AA. The link between vitamin D metabolism and sleep medicine. Sleep Med Rev 2014; 18(4): 311–9. [CrossRef]
6. Donmez A, Orun E, Sonmez FM. Vitamin D status in children with headache: A case-control study. Clin Nutr ESPEN 2018; 23: 222–7.
7. Xia W, Zhou Y, Sun C, Wang J, Wu L. A preliminary study on nutritional status and intake in Chinese children with autism. Eur J Pediatr 2010; 169(10): 1201–6. [CrossRef]
8. Yildiz EP, Poyrazoglu Ş, Bektas G, Kardelen AD, Aydinli N. Potential risk factors for vitamin D levels in medium- and long-term use of

antiepileptic drugs in childhood. Acta Neurol Belg 2017; 117(2): 447–53. [CrossRef]
9. Gao Q, Kou T, Zhuang B, Ren Y, Dong X, Wang Q. The Association between Vitamin D Deficiency and Sleep Disorders: A Systematic Review and Meta-Analysis. Nutrients 2018; 10(10): E1395. [CrossRef]
10. Hagenau T, Vest R, Gissel TN, Poulsen CS, Erlandsen M, Mosekilde L, et al. Global vitamin D levels in relation to age, gender, skin pigmentation and latitude: an ecologic meta-regression analysis. Osteoporos Int 2009; 20(1): 133–40. [CrossRef]
11. Kim JH, Chang JH, Kim DY, Kang JW. Association between self-reported sleep duration and serum vitamin D level in elderly Korean adults. J Am Geriatr Soc 2014; 62(12): 2327–32. [CrossRef]
12. Ozgurhan G, Vehapoglu A, Vermezoglu O, Temiz RN, Guney A, Hacihamdioglu B. Risk assessment of obstructive sleep apnea syndrome in pediatric patients with vitamin D deficiency: A questionnaire-based study. Medicine (Baltimore) 2016; 95(39): e4632. [CrossRef]
13. Kheirandish-Gozal L, Peris E, Gozal D. Vitamin D levels and obstructive sleep apnoea in children. Sleep Med 2014; 15(4): 459–63.
14. Manios Y, Moschonis G, Hulshof T, Bourhis AS, Hull GLJ, Dowling KG, et al. Prevalence of vitamin D deficiency and insufficiency among schoolchildren in Greece: the role of sex, degree of urbanisation and seasonality. Br J Nutr 2017; 118(7): 550–8. [CrossRef]
15. Crescioli C, Minisola S. Vitamin D: Autoimmunity and Gender. Curr Med Chem 2017; 24(24): 2671–86. [CrossRef]
16. Williams SG, Correa D, Lesage S, Lettieri C. Electroencephalographic hypersynchrony in a child with night terrors. Sleep Breath 2013; 17(2): 465–7. [CrossRef]
17. Nguyen BH, Pérusse D, Paquet J, Petit D, Boivin M, Tremblay RE, et al. Sleep terrors in children: a prospective study of twins. Pediatrics 2008; 122(6): e1164–7. [CrossRef]
18. Bellia A, Garcovich C, D'Adamo M, Lombardo M, Tesauro M, Donadel G, et al. Serum 25-hydroxyvitamin D levels are inversely associated with systemic inflammation in severe obese subjects. Intern Emerg Med 2013; 8(1): 33–40. [CrossRef]
19. Gominak SC, Stumpf WE. The world epidemic of sleep disorders is linked to vitamin D deficiency. Med Hypotheses 2012; 79(2): 132–5.
20. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an endocrine society clinical practice guideline. J Clin Endocrin Metab 2011; 96(7): 1911–30. [CrossRef]