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Original Article

Sleep disturbances and serum vitamin D levels in children with autism spectrum disorder

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Abstract: Sleep problems are among the most prevalent comorbidities experienced by children with Autism Spectrum Disorder (ASD). There is a clinical and physiological basis for a link between 25(OH)D levels and sleep disorders. In this study we aimed to investigate the frequency of sleep disorders in ASD patients and its association with 25(OH)D levels, and whether or not these frequencies changed after 25(OH)D treatment. This prospective study included 60 consecutive patients diagnosed with ASD and matched healthy controls between the ages of 4 and 10. Patients then underwent 25(OH)D replacement therapy according to their deficiency levels. Pre- and post-therapy values were compared. Sleep disturbance was detected in 78.3% of ASD patients (n = 60) and 33.3% of the control group (n = 60). When we compared the pretreatment scores of sleep disturbance between ASD and control groups (n = 60), there were significant differences in bedtime resistance, sleep anxiety, parasomnias, daytime sleepiness, sleep duration, sleep-onset delay, night wakings subscales, and total scale score ($p < 0.05$); however there were no significant differences with respect to the sleep-disordered breathing subscales ($p > 0.05$). In ASD patients, there was a significant negative correlation between serum 25(OH)D levels and the night wakings subscale ($r = -0.301$, $p = 0.019$). In control patients, there was a significant negative correlation between serum 25(OH)D levels and daytime sleepiness subscales ($r = -0.269$, $p = 0.038$). The results indicate that it may be suitable to use 25(OH)D replacement therapy in ASD patients and healthy individuals with sleep disturbances.

Keywords: Sleep disturbances, vitamin D level, children, autism spectrum disorder

Introduction

Autism spectrum disorders (ASD) are a heterogeneous group of disorders characterized by delayed and impaired social skills and abnormal patterns of behavior [1]. The prevalence of ASD in the United States is estimated to be 14.7 per 1000 school-aged children [2]. Sleep problems are among the most prevalent comorbidities experienced by children with ASD. Sleep disturbances affect approximately 40-80% of ASD patients [3]. This rate is about 25-40% for typical children [4]. The most commonly reported sleep disturbances are sleep latency, reduced sleep duration and insomnia. Other problems include daytime sleepiness, sleep apnea, parasomnias, settling difficulties, early morning wakings, and restless leg syndrome [3, 5, 6].

Vitamin D (25(OH)D) deficiency has recently been proposed to be a risk factor for ASD. Also, a link between the clinical and physiological features of 25(OH)D and sleep disorders has been proposed [5-7]. We claim that 25(OH)D has a role in both ASD and sleep disturbances and may help to improve impaired sleep in ASD patients. Here, we studied the frequency of sleep disorders in ASD patients and its association with 25(OH)D levels and observed changes after 25(OH)D treatment.

Methods

Study population

This prospective study included 60 consecutive patients diagnosed with ASD between the ages of 4 and 10 at the Kanuni Sultan Suleyman

Education and Research Hospital between April 2014 and November 2015. All children met the diagnostic criteria for Autistic Disorder according to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) [1]. The control group was composed of 60 age and sex-matched apparently healthy children. The aim of the study was to investigate the association between 25(OH)D levels and sleep disturbances. The patients who had a history of metabolic disorder, systemic inflammatory disease, obesity, and usage of antiepileptic drugs, steroids, estrogens, immune suppressors, bisphosphonates, calcium, and vitamin D were excluded. To standardize the levels of 25(OH)D, the study was conducted through April to September. The control group was chosen randomly from mentally and neurologically healthy children.

Assay of serum 25-hydroxy vitamin D

Plasma 25(OH)D concentrations were measured via radioimmunoassay using commercially available kits (DiaSorin, Inc, Stillwater, MN). Vitamin D levels were evaluated according to classification criteria of US Endocrine Society. The patients with low serum 25(OH)D concentration (> 30 ng/mL) were further divided into two subgroups: insufficient (Group A) with serum 25(OH)D concentrations between 20 to 29 ng/mL and a deficient group (Group B) with serum 25(OH)D concentrations < 20 ng/mL [8]. The A subgroup was supplemented with ergocalciferol (D2) 5000 IU daily, and the B subgroup was supplemented with ergocalciferol (D2) 50,000 IU weekly. Ergocalciferol is well absorbed from the gastrointestinal tract when taken orally and can increase serum 25(OH)D concentrations to steady state within two months [9]. Thus, oral administration was selected for its convenience in delivery and cost effectivity.

Measure of sleep patterns and sleep problems

To assess sleep habits and disorders, the short version of the Children's Sleep Habits Questionnaire (CSHQ) was given to the parents of the children aged between 4-10 years [10]. CSHQ was sequentially performed on the first day of the study and the 3rd day after 25(OH)D replacement. The CSHQ consists of 33 sleep-disturbance topics and 3 items asking for information about bedtime, morning waking time, and daily total sleep duration. Parents are asked to recall their child's sleep patterns over a recent routine week. Each item is rated on a three-point scale: 1 = rarely (0-1 time/week); 2 = sometimes (2-4 times/week); 3 = usually (5-7 times/week) [10]. A higher score reflects more disturbed sleep behavior. Needing a parent in the room to sleep and being afraid of sleeping alone are present in both bedtime resistance and sleep anxiety subscales. The 33 sleep-disturbance items are conceptually grouped into eight subscales: bedtime resistance (6 items), sleep-onset delay (1 item), sleep duration (3 items), sleep anxiety (4 items), night waking (3 items), parasomnias (7 items), sleep-disordered breathing (3 items), and daytime sleepiness (8 items). These subscales yielded a total sleep disturbance score ranging from 33 to 99 with a clinical cutoff score of ≥ 41 [10]. With permission of the original author, the CSHQ was translated into Turkish and was used in a previous study in our community. The validity and the reliability of the Turkish version of the CSHQ were studied in 1749 elementary school children. The Cronbach alpha coefficient was determined as 0.78, and the test-retest correlation coefficient was 0.81 [11]. There were statistically significant relationships between all behavioral and emotional parameters and the presence of sleep problems. The CSHQ is a parent proxy-report and is a valid and reliable instrument for assessing sleep habits and screening for possible sleep problems in Turkish children.

Procedure

Initially, the 25(OH)D vitamin levels were analyzed and CSHQ were performed in the ASD and the control group. Patients were given 25(OH)D replacement therapy according to their deficiency level. After a 3-month follow up, the 25(OH)D levels and CSHQ scores were reassessed. Pre- and post-therapy values were compared.

Statistical analyses

The results were analyzed by the Statistical Package for the Social Sciences 15. The parametric data were presented as a mean and standard deviation (SD). The student's t-test was used to compare the parametric data, and the Mann-Whitney U-test was used for comparison of non-parametric data. Qualitative variables were compared by a Chi-squared test. Spearman's rho correlation coefficient 'r' was

Table 1. 25(OH)D status of the studied children

	ASD		Control	
n = 60	Pretreatment	Posttreatment	Pretreatment	Posttreatment
25(OH)D deficiency (< 10 ng/mL)	14 (23.3%)	-	14 (23.3%)	-
25(OH)D insufficiency (10 to 30 ng/mL)	27 (45%)	7 (11.7%)	23 (38.3%)	4 (6.7%)
25(OH)D sufficiency (> 30 ng/mL)	19 (31.7%)	53 (88.3%)	23 (38.3%)	56 (93.3%)
25(OH)D Mean (ng/mL)	25.58 ± 10.31	37.27 ± 6.51	25.35 ± 9.92	37.15 ± 6.78

Table 2. Comparisons of CSHQ total scores for the ASD and control groups

	ASD		Control	
Total score	Pretreatment	Posttreatment	Pretreatment	Posttreatment
All groups	n = 60		n = 60	
< 41	13 (21.7%)	17 (28.3%)	40 (66.7%)	52 (86.7%)
≥ 41	47 (78.3%)	43 (71.7%)	20 (33.3%)	8 (13.3%)
25(OH)D < 30 ng/mL groups	n = 41		n = 37	
< 41	8 (19.5%)	13 (31.7%)	23 (62.2%)	32 (86.5%)
≥ 41	33 (80.5%)	28 (68.3%)	14 (37.8%)	5 (13.5%)

Table 3. Comparisons of CSHQ scale scores and total sleep time for the ASD and control groups tedavi öncesi (Pretreatment)

n = 60	ASD	Control	p
Total score	51,92 ± 9.76	41.67 ± 4.66	< 0.001
Bedtime resistance	11.13 ± 2.72	7.50 ± 1.20	< 0.001
Sleep-onset delay	2.25 ± 0.77	1.78 ± 0.87	0.02
Sleep duration	5.50 ± 1.03	4.35 ± 0.88	< 0.001
Sleep anxiety	7.57 ± 2.76	4.53 ± 0.91	< 0.001
Night wakings	5.27 ± 1.67	3.93 ± 1.29	< 0.001
Parasomnias	9.90 ± 2.72	8.22 ± 1.64	< 0.001
Sleep-disordered breathing	3.70 ± 1.41	3.58 ± 0.91	0.59
Daytime sleepiness	10.90 ± 2.63	9.67 ± 1.70	0.03
Total sleep time	8.10 ± 0.97	9.24 ± 0.89	< 0.001

used to determine the relationship between different variables. For all these tests, a probability (p) of < 0.05 was considered significant.

This study was approved by the ethics committee of the Kanuni Sultan Suleyman Education and Research Hospital. The study was conducted according to the Helsinki Declaration. Parents of these children provided informed consent and were enrolled in the protocol to begin study procedures.

Results

Sample characteristics

The study included 44 males (73.3%) and 16 (26.7%) females out of 60 ASD patients. The average patient age was 7.10 ± 1.50 years. The control group included 60 healthy children, 39 males (65%) and 21 (35%) females. The average age of the control group was 6.93 ± 1.59 years. There were no significant differences between the ASD and control groups with respect to age (P = 0.568).

25(OH)D level

Nineteen out of 60 ASD patients (31.7%) had normal values and 41 had low values (68.3%) of serum 25(OH) vitamin D values before the treatment. However, 23 of the controls had normal (38.3%) and 37 of the controls had lower than normal 25(OH)D serum levels (61.7%). The median 25(OH)D concentration in the ASD and controls were 25.58 ± 10.31 ng/mL and 25.35 ± 9.92 ng/mL (p = 0.900), respectively. After treatment, 53 out of 60 ASD patients reached normal values of 25(OH)D serum levels (88.3%). In 7 patients, the levels were still below normal (11.7%). In the control cohort, serum 25(OH)D levels were in the normal range in 56 of them (93.3%) and lower than normal in four of them (6.7%). The median 25(OH)D concentrations in the ASD group was 37.27 ± 6.51 ng/ml and 37.15 ± 6.78 ng/mL in the control group (p = 0.924) (**Table 1**).

Table 4. The CSHQ scale scores and total sleep time according to 25(OH)D levels

CSHQ	ASD		p	Control		p
n	41	19		37	23	
Dvit	< 30 ng/mL	≥ 30 ng/mL		< 30 ng/mL	≥ 30 ng/mL	
Total score	52.05 ± 8.24	51.63 ± 12.70	0.879	42.00 ± 4.78	41.13 ± 4.51	0.487
Bedtime resistance	11.24 ± 2.49	10.89 ± 3.21	0.647	7.38 ± 1.01	7.70 ± 1.46	0.324
Sleep-onset delay	2.32 ± 0.79	2.11 ± 0.74	0.328	1.86 ± 0.89	1.65 ± 0.83	0.359
Sleep duration	5.41 ± 0.92	5.68 ± 1.25	0.352	4.41 ± 0.98	4.26 ± 0.69	0.541
Sleep anxiety	7.73 ± 2.59	7.21 ± 3.15	0.502	4.41 ± 0.80	4.74 ± 1.05	0.170
Night wakings	5.59 ± 1.61	4.58 ± 1.61	0.028	4.11 ± 1.39	3.65 ± 1.07	0.184
Parasomnias	9.80 ± 2.52	10.11 ± 3.18	0.695	8.51 ± 1.76	7.74 ± 1.32	0.075
Sleep-disordered breathing	3.63 ± 0.73	3.84 ± 2.29	0.598	3.59 ± 0.90	3.57 ± 0.95	0.904
Daytime sleepiness	10.44 ± 1.84	11.89 ± 3.70	0.045	9.89 ± 1.85	9.30 ± 1.40	0.197
Total sleep time	8.16 ± 0.89	7.97 ± 1.12	0.497	9.11 ± 0.89	9.45 ± 0.86	0.904

Table 5. The CSHQ scale scores and total sleep time according to low 25(OH)D levels

CSHQ	ASD (n = 41)		p	Control (n = 37)		p
	Pretreatment	Posttreatment		Pretreatment	Posttreatment	
Dvit	19.68 ± 6.22	37.26 ± 7.34	< 0.001	19.21 ± 7.35	39.13 ± 7.74	< 0.001
Total score	52.05 ± 8.24	46.43 ± 8.04	< 0.001	42.00 ± 4.78	37.56 ± 2.80	< 0.001
Bedtime resistance	11.24 ± 2.49	10.17 ± 2.66	0.015	7.38 ± 1.01	7.21 ± 0.75	0.136
Sleep-onset delay	2.32 ± 0.79	1.82 ± 0.80	0.002	1.86 ± 0.89	1.08 ± 0.36	< 0.001
Sleep duration	5.41 ± 0.92	4.70 ± 0.95	0.001	4.41 ± 0.98	4.18 ± 0.90	0.044
Sleep anxiety	7.73 ± 2.59	6.78 ± 2.35	0.016	4.41 ± 0.80	4.05 ± 0.47	0.001
Night wakings	5.59 ± 1.61	4.24 ± 1.59	< 0.001	4.11 ± 1.39	3.32 ± 0.62	< 0.001
Parasomnias	9.80 ± 2.52	8.75 ± 1.84	< 0.001	8.51 ± 1.76	7.16 ± 0.44	< 0.001
Sleep-disordered Breathing	3.63 ± 0.73	3.41 ± 059	0.027	3.59 ± 0.90	3.40 ± 0.76	0.017
Daytime sleepiness	10.44 ± 1.84	10.17 ± 1.93	0.175	9.89 ± 1.85	9.21 ± 1.08	0.016
Total sleep time	8.16 ± 0.89	8.63 ± 0.85	< 0.001	9.11 ± 0.89	9.29 ± 0.89	0.037

Comparisons of CSHQ scale scores

Comparisons of CSHQ scale scores for the ASD and control groups are shown in **Tables 2** and **3**. We found sleep disturbance in 78.3% of ASD patients (n = 60) and 33.3% of the control group (n = 60). Sleep disturbance rates were 80.5% (n = 41) in low 25(OH) vitamin D (< 30 ng/mL) ASD group and 37.8% (n = 37) low 25(OH) vitamin D low control group.

When we compared pretreatment scores of sleep disturbance between ASD and control groups (n = 60), there were significant differences in bedtime resistance, sleep anxiety, parasomnias, daytime sleepiness, sleep duration, sleep-onset delay, night wakings subscales and total scale score ($p < 0.05$). However, no significant differences with respect to sleep-disordered breathing subscales were found ($p > 0.05$) (**Table 3**).

Sleep time patterns

The pretreatment mean total sleep time of the ASD group was 8.10 ± 0.97 hours. The mean total sleep time of the control group was 9.24 ± 0.89 hours. There was a significant difference between the ASD and control groups with respect to total sleep time ($p \leq 0.001$) (**Table 3**). After treatment, the mean total sleep time of the ASD group was 8.58 ± 0.96 hours and the mean total sleep time of the control group was 9.38 ± 0.88 hours. There was a significant difference between the ASD and control groups with respect to total sleep time ($p \leq 0.001$) (**Table 3**). There were no significant differences in total sleep time between 25(OH)D deficient and non-deficient subgroups of either the ASD or control groups ($p = 0.497$ and $p = 0.904$, respectively) (**Table 4**).

There were statistically significant differences in the pretreatment and posttreatment total

Table 6. Correlation between serum 25(OH)D levels and CSHQ scale scores

		r	p
Total sleep time	ASD	-0.230	0.862
	Control	0.199	0.128
Total score	ASD	-0.054	0.684
	Control	-0.214	0.100
Bedtime resistance	ASD	-0.126	0.336
	Control	0.012	0.927
Sleep-onset delay	ASD	-0.082	0.531
	Control	-0.064	0.627
Sleep duration	ASD	0.026	0.842
	Control	-0.218	0.094
Sleep anxiety	ASD	-0.188	0.149
	Control	0.097	0.460
Night wakings	ASD	-0.301	0.019
	Control	-0.221	0.089
Parasomnias	ASD	0.096	0.464
	Control	-0.231	0.076
Sleep-disordered breathing	ASD	0.105	0.426
	Control	-0.072	0.584
Daytime sleepiness	ASD	0.190	0.146
	Control	-0.269	0.038

sleep time between 25(OH)D deficient ASD and control groups ($p \leq 0.001$, $P = 0.037$) (**Table 5**). No correlation between 25(OH)D levels and total sleep time was detected (**Table 6**).

The effect of 25(OH)D levels on CSHQ scale scores

When both the ASD and the control groups with or without 25(OH)D deficiencies were compared, a significant difference in night wakings and daytime sleepiness subscales was found between the 25(OH)D deficient and non-deficient patients with ASD ($p < 0.05$). There were no significant differences in bedtime resistance, sleep anxiety, parasomnias, sleep duration, sleep-onset delay, sleep-disordered breathing subscales and total scale score ($p > 0.05$). In the control group, there was no significant difference for CSHQ subscale scores and the total score ($p > 0.05$) (**Table 4**).

The ASD patients and the controls with 25(OH)D deficiency prior to treatment in the start of the study were compared via pre- and post-treatment CSHQ scale scores. In the ASD group ($n = 41$), there was no significant difference in daytime sleepiness subscales ($p = 0.175$) between pre- and post-treatment periods. However, there were significant differences in bedtime resistance, sleep anxiety, night wakings, parasomnias, sleep duration, sleep-onset delay, sleep-disordered breathing subscales and total scale score ($p \leq 0.05$). In the control group ($n = 37$), there was no significant difference in bedtime resistance subscales ($p = 0.136$) between pre- and post-treatment periods. However there were significant differences in sleep anxiety, night wakings, parasomnias, sleep duration, sleep-onset delay, sleep-disordered breathing, daytime sleepiness subscales and total scale score ($p \leq 0.05$) (**Table 5**).

Correlation between serum 25(OH)D levels and CSHQ scale scores

As shown in **Table 6**, ASD patients show a significant negative correlation between serum 25(OH)D levels and night waking ($r = -0.301$, $p = 0.019$). In the control group, there was a significant negative correlation between serum 25(OH)D levels and daytime sleepiness subscale ($r = -0.269$, $p = 0.038$) (**Table 6**).

Discussion

The 25(OH)D levels were found to be low (≤ 30 ng/mL) in 68.3% of ASD patients and 61.7% of the controls. The 25(OH)D levels tends to be lower in the ASD group versus a healthy population [12]. In our study, the percentage of low 25(OH)D levels was higher in ASD patients compared to the control group, but no statistical significance was observed between the mean 25(OH)D levels. Moreover, Molloy et al [12] found no difference between the mean 25(OH)D levels of healthy and ASD groups similar to our study. The 25(OH)D levels did not improve in 11.7% of ASD patients and 6.7% of controls after the treatment (**Table 1**). This may indicate poorer accommodation to treatment, a tendency to spend much more time in the dark, and a rejection of drugs by the ASD patients. Sleep disturbance was overall higher in the ASD group relative to controls (**Table 2**). Our results agree with those of a previous study that showed a high prevalence of sleep disturbances in children with ASD. After treatment, the improvement in total CSHQ levels (< 41) was higher in the control group with respect to the study group. This might be due to the mean scores of the control group being close to the cut-off level as well as the mean scores of the ASD patients being much above the CSHQ cut-off level.

The most common sleep disturbances in the ASD group were delayed sleep-onset and insomnia in the study conducted by Sikora et al [13]. In addition, irregular sleep-wake patterns, early morning awakenings, decreased total sleep time and poor sleep routines were the least common features [13]. Our results showed that the ASD group (n = 60) had significantly higher scores in bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, night wakings, parasomnias, daytime sleepiness, and global sleep disturbance (CSHQ total score) relative to the control group (**Table 3**). Only the mean scores of sleep-disordered breathing were not different between the two groups.

The effect of 25(OH)D levels on sleep parameters is presented in **Table 4**. The ASD and control groups were subclassified according to 25(OH)D levels in each group. We found that only night wakings and daytime sleepiness scores were affected in the ASD group. The 25(OH)D levels were not effective on the CSHQ scores of total and of the other subscales in both ASD and control patients. There was negative correlation of 25(OH)D levels with night wakings subscales in the ASD patients ($r = -0.301$, $p = 0.019$) and with daytime sleepiness subscales in the controls ($r = -0.269$, $p = 0.038$). This suggests a relationship between 25(OH)D levels and these two subscales (**Table 6**). Previous studies showed that low levels of 25(OH)D generated daytime sleepiness through the central inflammatory mediators (TNF-a and IL-1) [14]. Similarly, McCarty et al [15] showed that serum 25(OH)D level was inversely associated with daytime sleepiness in adults.

Low levels of 25(OH)D caused obstructive sleep apnea via myopathy, chronic rhinitis and tonsils hypertrophy-this results in sleep-disordered breathing [16]. However 25(OH)D levels did not affect sleep-disordered breathing in ASD patients and controls in the current study (**Tables 4**, **6**). However, the scores of sleep-disordered breathing were decreased after 25(OH)D treatment (**Table 5**). Polysomnography is a gold standard in sleep-disordered breathing. The main limitation of the current study is that the assessment of pediatric sleep and symptoms were done by parents who could over- or under-estimate sleep and symptom severity. The total CSHQ scores as well as subscales were significantly lower in both ASD and control group with 25(OH)D deficiency and after treatment. The replacement therapy did not change daytime sleepiness in ASD and bedtime resistance scores in the control group (**Table 5**). The CSHQ scores of total and subscales (except night waking and daytime sleepiness in ASD group) were not affected by the low or normal levels of 25(OH)D in both groups (**Table 4**). However, there was a significant decrease in the scores with replacement (**Table 5**) therapy indicating that there is no direct relation between 25(OH)D levels and clinical response. However, no has yet studied this association in a pediatric population. The results raised a question about the use of 25(OH)D including in normal patients with sleep disorders.

The total sleep time was shown to be lower in the ASD group with respect to the controls. Similar to Humphreys et al [17], we found that total sleep time was lower in the ASD group versus the controls (**Table 3**). Kim et al [18] found a positive correlation between total sleep time and 25(OH)D levels in a geriatric population. These results suggest that inadequate sleep duration may be associated with lower vitamin D levels in the elderly. This study did not confirm these results because no correlation was found between total sleep time and 25(OH)D levels similar to the study by Shiue et al (**Table 4**). [19] Interestingly, after replacement therapy, the total sleep duration was improved (**Table 5**). However, Grandner et al [20] did not show a significant association between 25(OH)D intake and sleep duration.

In conclusion, sleep problems are common in this group of children with ASD. This study failed to find an association between serum 25(OH)D levels and total CSHQ among ASD and controls. The association between serum 25(OH)D levels and night wakings/daytime sleepiness scores were especially remarkable. This significant improvement was observed after treatment via the total CSHQ levels in both ASD and control groups. The results indicate that 25(OH)D replacement therapy can be used in both ASD patients and healthy individuals with sleep disturbances.

Disclosure of conflict of interest

None.

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