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Sleep Quality in Children with Iron Deficiency Anemia

Demir Eksikliği Anemisi Olan Çocuklarda Uyku Kalitesi

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ABSTRACT

Objective: Iron deficiency is the most common cause of anemia in our country as well as all over the world. In this study, it was aimed to evaluate the subjective sleep quality of patients with iron deficiency anemia in childhood.

Materials and Methods: One hundred thirty patients diagnosed with iron deficiency anemia and 110 healthy individuals, gender and age-matched, who applied to the Pediatrics clinic between April 2022 and September 2022, were included in the study. All participants were requested to fill out three forms: a socio-demographic form (age, gender, income level), hemogram laboratory findings and The Pittsburg Sleep Quality Index (PSQI) measures subjective sleep quality, was applied, and the data were analyzed.

Results: Total PSQI score was 6.56±3.51 in patients, and 4.36±2.34 in controls. There was a difference between the study and control groups in terms of low hemoglobin, hematocrit, mean erythrocyte volume (MCV) and mean erythrocyte hemoglobin concentration (MCHC) values and decreased sleep quality.

Conclusion: Iron deficiency anemia is a significant public health problem that adversely affects sleep quality in childhood.

Keywords: Childhood, iron deficiency anemia, sleep quality

ÖZ

Amaç: Tüm dünyada olduğu gibi ülkemizde de aneminin en sık sebebi demir eksikliğidir. Bu çalışmada çocukluk çağında demir eksikliği anemisi saptanan hastalarda subjektif uyku kalitesinin değerlendirilmesi amaçlanmıştır.

Materyal ve Metot: Nisan 2022-Eylül 2022 tarihleri arasında Pediatri kliniğine başvuran yaşları ve cinsiyetleri eşleşmiş 130 demir eksikliği anemisi tanısı alan hasta ve 110 sağlıklı birey çalışmaya dahil edildi. Tüm katılımcılara yaş, cinsiyet, gelir düzeyleri gibi sosyodemografik bilgileri, hemogram laboratuvar bulguları ve subjektif uyku kalitesini ölçen Pittsburg Uyku Kalitesi İndeksi (PUKİ) ölçeğini içeren 3 formdan oluşan anket uygulandı. Veriler analiz edildi.

Bulgular: Hasta grubun toplam PUKİ puanı 6,56±3,51 kontrol grubun 4,36±2,34 idi. Düşük olan hemoglobin, hematokrit, ortalama eritrosit hacmi (MCV) ve ortalama eritrosit hemoglobin konsantrasyonu (MCHC) değerleri ile azalmış uyku kalitesi açısından çalışma ve kontrol grubu arasında fark saptanmıştır.

Sonuç: Önemli bir halk sağlığı sorunu olan demir eksikliği anemisi çocukluk çağında uyku kalitesini kötü yönde etkilemektedir.

Anahtar Kelimeler: Çocukluk çağı, demir eksikliği anemisi, uyku kalitesi

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INTRODUCTION

Iron deficiency anemia (IDA) develops when the negative iron balance due to hemoglobin synthesis, chronic blood loss, increased iron requirement, and malabsorption cannot be compensated from the stores.[1] As in the whole world, the most common cause of anemia in our country is iron deficiency, and it is more common in women than men.[2] More than 30% of patients admitted to the emergency department in developed countries are anemic, and this rate is much higher in developing countries.[3,4] Symptoms such as loss of appetite, fatigue, pallor, lethargy, headache, tinnitus, cognitive and intellectual dysfunction can be seen in iron deficiency anemia. Iron plays a crucial role in monoamine metabolism in the brain, responsible for mood and cognitive functions. Apathy, irritability, lack of attention and depressive temperament develop due to impaired monoamine oxidase.[5]

Sleep is biological, physiological, periodic, and reversible changes in consciousness and behavior, allowing the body to rest physically and renew itself.[6] Sleep problems are seen in 30-33% of the population. This rate is higher in the elderly, adolescents, pregnant women, and those with psychiatric disorders and learning difficulties. Many studies have shown female gender, stress, depression, anxiety, physical illness, and alcohol or substance use in the etiology of sleep disorders.[6,7] The balance of serotonin, noradrenaline and dopamine neurotransmitters plays a role in sleep neurophysiology.[5,8] The enzymatic balance disrupted in iron deficiency adversely affects sleep quality.[9]

In this study, it was aimed to evaluate the subjective sleep quality of patients with IDA in childhood.

MATERIALS AND METHODS

***Ethics Committee Approval*:** This prospective and cross-sectional study was conducted in the Pediatrics Clinic of Samsun Training and Research Hospital between April 2022 and September 2022. Ethics committee approval was obtained from the Ethics Committee of Samsun Training and Research Hospital (Date: 26.2.2022, decision no:2022/3/1), and conducted by the Declaration of Helsinki.

Design, Participants, and Setting: A total of 130 patients aged 12-18 years were diagnosed with IDA and 110 healthy individuals matched by gender and age were included in the study. It was confirmed that the patients had no accompanying neurological or endocrinological disease. Since anemia parameters vary according to age and gender until the age of 12, hemoglobin level is below 13 mg/dL in boys, below 12 mg/dL in girls, transferrin saturation rate is below15%, and ferritin level is below 15 ng/ml, those were considered IDA. The control group consisted of healthy volunteers. Individuals who were similar to the group diagnosed with IDA in terms of age and gender were invited to the study. Informed consent was obtained from the participants and their parents. Patients with chronic disease or regular medication were excluded from the study.

Instruments: A questionnaire including sociodemographic information such as age, gender, income level, hemogram laboratory findings, and the Pittsburg Sleep Quality Index (PSQI) scale, which measures subjective sleep quality, was administered face-to-face to the participants.[10] PSQI is a 19-item test that evaluates seven subgroups: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping pills, and daytime dysfunction. There is an evaluation table in which each subgroup is scored between 0-3 points, with a maximum of 21 points. High scores are associated with poor sleep quality. A total score of 6 or more indicates impaired sleep quality. The Turkish version was developed by Ağargün et al.[11]

Statistical Analysis: SPSS 25.0 (Statistical Package for the Social Sciences, Version 25.0, Chicago, USA) statistical program was used for statistical analysis. Continuous variables were given as mean± Standard deviation (SD), and categorical variables as percentages. The independent sample t-test was used to compare the data of patients and healthy individuals. The chi-square (x2) test was used to compare the data presented as a percentage. Pearson correlation coefficient was used for correlation analysis. P<0.05 was considered statistically significant in all data.

RESULTS

The patient population consisted of 130 patients (101 (77.7%) girls and 29 (22.3%) boys), and the mean age was 15.10±1.74 years. The control group consisted of 110 healthy individuals (85 (77.3%) girls and 25 (22.5%) boys), and the mean age was 15.21±1.94 years. There was no statistically significant difference between the patient and control groups regarding age, gender, and income level. The sociodemographic characteristics of the study groups are given in Table 1.

There was a statistically significant difference between the groups in terms of hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC) values (p=0.001, p=0.001, p=0.014 and p=0.001, respectively). There was no significant difference between the groups in terms of other hemogram parameters (p>0.05). Detailed hemogram values are given in Table 2.

Table 1. Sociodemographic findings of the participants in the study.

		Patients n (%)	Controls n (%)	Statistics (x^2)	p-value
Gender	Female	101 (77.7)	85 (77.3)	0.701	0.794
	Male	29 (22.3)	25 (22.5)		
Income level	Low	34 (26.2)	27 (24.5)	0.041	0.991
	Medium	76 (58.5)	62 (56.4)		
	High	20 (15.3)	21 (19.1)		
Age group	12-15 years	48 (36.9)	35 (31.8)	0.563	0.454
	15-18 years	82 (63.1)	75 (68.2)		

Table 2. Distribution of hemogram values.

	Patients Mean±SD	Controls Mean±SD	t-value	p-value
Hemoglobin (gr/dL)	10.26±1.40	13.86±0.51	25.62	**0.001**
Hematocrit (%)	32.30±3.32	40.49±2.31	24.28	**0.001**
MCV (fL)	71.06±7.20	81.81±5.22	13.02	**0.014**
MCH (pg)	22.42±1.05	24.70±0.98	13.20	0.118
MCHC (g/dL)	31.61±1.39	34.31±0.98	17.07	**0.001**
WBC (mcL)	6.60±1.50	6.92±1.48	1.68	0.356

p<0.05 statistically significant; SD: standard deviation; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; WBC: white blood cell.

Evaluating the subjective sleep score was according to the sub-dimensions of PSQI, the sub-dimensions of subjective sleep quality, sleep latency, sleep time, habitual sleep efficiency, and daytime dysfunction were statistically significantly higher in the patient group (p<0.001, p<0.001, p=0.012, p=0,049 and p<0.001, respectively). No statistically significant difference was found between the two groups in the sub-dimensions of sleep disturbance and the use of sleeping pills (p>0.05). The comparison of the PSQI subscale and total scores between the groups is given in Table 3.

Table 3. Pittsburg sleep quality index score distribution.

Category	Patients (Mean±SD)	Controls (Mean±SD)	t-value	p-value
Subjective sleep quality	1.37±0.91	0.83±0.78	4.88	**0.001**
Sleep latency	1.27±0.98	0.80±0.86	3.96	**0.001**
Sleep time	0.70±0.73	0.45±0.77	2.52	**0.012**
Habitual sleep activity	0.64±0.77	0.44±0.72	1.97	**0.049**
Sleep disorder	1.24±1.00	1.06±0.97	1.45	0.147
Use of sleeping pills	0.04±0.30	0.02±0.19	0.84	0.401
Daytime dysfunction	1.30±0.79	0.74±0.85	5.21	**0.001**
Total sleep disorder score	6.56±3.51	4.36±2.34	5.58	**0.001**

p<0.05: statistically significant.

DISCUSSION AND CONCLUSION

Iron is essential mineral for body metabolism and normal physiological processes.[1] Since it is not produced in the body, it must be taken in sufficient amounts through food. The most important function of iron in the body is the production of hemoglobin. Hemoglobin is found in the red blood cells in our blood and carries out the process of carrying the oxygen necessary for the survival of all tissues.[4] In other words, the more important oxygen is for our life, the more important iron is for the use of oxygen.[2] Iron deficiency anemia may develop due to insufficient iron intake, decreased absorption, increased iron requirement, and increased iron loss due to reasons such as gastrointestinal bleeding, menstrual bleeding or hemolysis.[1] Iron is also required for electron transfer, DNA synthesis, methylation, immunological reactions, and the function of many vitally important enzymes and proteins in the neurologic system.[3,4]

Iron deficiency anemia causes behavioral and developmental disorders by negatively affecting myelination, metabolic activity of neurons, and the balance of serotonin, noradrenaline and dopamine transmitters.[5] Brain functions such as cognition and learning are also adversely affected in children with IDA.[13] Iron has a complex effect on dopaminergic functions. Neuromodulation by dopamine plays a vital role in regulating REM sleep quality, quantity, and time. The mechanisms controlling sleep-wake regulation in human studies were investigated in combination with pharmacogenetics and neurophysiology, and genes encoding dopamine transport (DAT1, SLC6A3) were found to be responsible for these tasks.[14,15] In primate model studies, it has been observed that the circadian rhythm is impaired after a dopaminergic nigro-striatal system lesion.[16] It is now believed more than before that sleep-wake disorders are caused by dopamine loss rather than inadequate lighting conditions.

The most important issue in sleep quality is the dynamic balance between neurotransmitter systems.[14] The alternation of NREM and REM sleep ensures the balance of brainstem aminergic and cholinergic neuronal discharges.[13] In studies on sleep segments and their organization, a longer REM period in the first part of the sleep, a shorter REM in the third part, and a shorter NREM 2 transition to REM were observed. This result showed that IDA caused long-term changes in the temporal organization of sleep patterns.[17]

Iron deficiency continues to be a common problem that may have detrimental and potentially irreversible effects on long-term neurodevelopment and behavior in growing children.[18] The effect of iron deficiency on sleep has been well documented, especially in the pathogenesis of restless legs syndrome (RLS). The diagnostic criteria of RLS rely on the patient description of an often-unpleasant urge to move the legs that lead to significant disturbance not explained by another medical or behavioral condition.[19] Parents are concerned that their child's poor sleep quality is leading to daytime dysfunction such as increased sleepiness, behavioral outbursts, or hyperactivity. Many of these children are diagnosed with behavioral insomnia in childhood, and behavior modification therapy is recommended with variable degrees of success. Although behavioral therapy has been the mainstay for these patients, we consider other possible contributing factors, like poor sleep, that could stem from an easily diagnosed and treatable cause such as iron deficiency.[20]

Many studies highlight the importance of evaluating for underlying iron deficiency even without anemia in patients with restless sleep and associated poor daytime behavior.[20,21] Kotagal reported a boy had an iron deficiency that was treated with ferrous sulphate tablets and gabapentin at bedtime was added to provide symptomatic relief from the sensory discomfort of restless legs syndrome. Concurrent with a rise in the serum ferritin level, the sleep quality improved over the next 2 to 3 months.[22] A study about iron deficiency and its role in sleep disruption in patients with Angelman Syndrome shows that there is an increased prevalence of sleep-wake disruption in children with Angelman syndrome. In part, this is related to iron deficiency, with or without the associated polysomnographic marker of increased periodic limb movement in sleep. The treatment of Angelman syndrome–related sleep fragmentation with oral or intravenous iron may be helpful in improving subjective sleep quality.[23] Evidence-based and consensus clinical practice guidelines for the iron treatment of restless legs syndrome/Willis-Ekbom disease in adults and children Ferric carboxymaltose (1000 mg) is effective for treating moderate to severe RLS in those with serum ferritin <300 mg/l and could be used as first-line treatment for RLS in adults. Oral iron (65 mg elemental iron) is possibly effective for treating RLS in those with serum ferritin <75 mg/l. There is insufficient evidence to make conclusions on the efficacy of oral iron or IV iron in children.[19]

Studies conducted with hemogram values in adult patients have shown that sleep quality decreases with low hemoglobin values.[24,25] In a prospective and cross-sectional study conducted with adult IDA patients and controls in Turkey, in terms of haemoglobin, hematocrit and MCV values, there was a statistically significant difference between the groups (t=16.95, p=0.001; t=6.77, p=0.001; t=15.78, p=0.001, respectively). The other hemogram parameters did not show any differences between the groups. In PSQI, 70 (67.3%) patients and 32 (40.5%) controls reported a bad sleep quality. The number of patients who reported a bad sleep quality was statistically significantly higher than the controls (x^2=13.072; p<0.001). The total sleep quality score was 6.71±3.02 in patients and 4.11±1.64 in controls. In terms of total PSQI score, there was a statistically significant difference between the groups (t= 6.94, p<0.001).[24] In our study we found statistically significant differences between the groups in terms of hemoglobin, hematocrit, MCV, and MCHC values. The sub-dimensions of subjective sleep quality, sleep latency, sleep time, habitual sleep efficiency, and daytime dysfunction were statistically significantly higher in the patient group. Our results were similar, and no difference was found between children and adults. In a recent study PSQI, scores decreased significantly following iron supplementation, whereas the scores of almost subscales improved significantly at week 12. No participant had hemoglobin levels <12 g/dL. Serum ferritin concentration increased significantly, whereas hemoglobin and MCV remained unchanged. At baseline, 74% of the participants did not attend school regularly; this number improved to varying degrees by week 12. Since our study was retrospective, ferritin levels were not studied in most participants, so we could only compare them with hemogram parameters.[26]

The association of attention deficit hyperactivity disorder (ADHD), depression, low intelligence capacity and poor concentration in pediatric patients with iron deficiency anemia has been shown in studies.[13,27] Yehuda et al. conducted a study with the effects of essential fatty acids in iron-deficient and sleep-disturbed ADHD children patients generally suffer from sleep disturbance and malnutrition that can account for tiredness during the day, poor concentration, poor eating and depressed mood, along with anemia and an n-3 polyunsaturated acid deficiency. The change in ADHD behavior in children (9–12) was studied, following 10 weeks of treatment with a polyunsaturated acid mixture on six variables: cooperation, mood, concentration, homework preparation, fatigue, and sleep quality. Iron status was also examined. Polyunsaturated acid administration was associated with significant improvement in quality of life, ability to concentrate, sleep quality and hemoglobin levels.[28] In this study it is not clear if iron deficiency is one of the core symptoms of this group or it is a consequence of poor food intake habits.

In conclusion, this study showed that subjective sleep quality in pediatric patients with IDA was worse than in healthy controls. The effects of anemia treatment on sleep quality could not be evaluated due to the study's cross-sectional nature. Multicenter advanced studies are needed for long-term follow-up and treatment of IDA patients, which is also a significant public health problem. Sleep quality is measured with polysomnographic objective evaluations. There are some limitations in the study. First, polysomnography is not performed, and objective sleep quality cannot be evaluated. Second, regional and cross-sectional studies may not reflect the overall results.

Ethics Committee Approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was guaranteed by the Non-Interventional Clinical Research Ethics Committee of the University of Health Sciences, Samsun Training and Research Hospital (Date: 26.2.2022, decision no: 2022/3/1).

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