**Cukurova Medical Journal**
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

Cukurova Med J 2019;44(4):1267-1271
DOI: 10.17826/cumj.526857

**ARAŞTIRMA / RESEARCH**

# Sleep problems in children and adolescents with β-thalassemia major

## β-talasemi major hastası çocuk ve ergenlerdeki uyku sorunları

Serkan Güneş[1]

[1]Hatay State Hospital, Department of Child and Adolescent Psychiatry, Hatay, Turkey

*Cukurova Medical Journal 2019;44(4):1267-1271.*

**Abstract**

**Purpose:** The aim of this study was to compare the sleep problems between children and adolescents with β-thalassemia major and healthy controls.

**Materials and Methods:** This study was a case-control survey of children and adolescents with β-thalassemia major. The sample consisted of 76 children and adolescents in the patient group and 68 healthy children and adolescents in the control group, with an age range of 8-16 years. Subjects were recruited from the Department of Child and Adolescent Psychiatry in Hatay State Hospital between January and December 2018. Children and adolescents with β-thalassemia major were consulted from the Department of Pediatric Hematology. The Children's Sleep Habits Questionnaire (CSHQ) was used to evaluate sleep problems between the groups.

**Results:** Mean age of the patient group was 11.66 (SD = 3.22) years, and 47.4% (N = 36) were males. Control group had a mean age of 12.84 (SD = 3.12) years, and 47.1% (N = 32) were males. Total score, night waking and sleep disordered breathing subscores of CSHQ were significantly higher in children with β-thalassemia major than healthy children.

**Conclusion:** As there are more sleep problems in children and adolescents with β-thalassemia major than in healthy children, detailed studies are needed.

**Keywords:** adolescent, child, hemoglobinopathies, sleep, thalassemia

**Öz**

**Amaç:** Bu çalışmada, β-talasemi major hastası çocuk ve ergenler ile sağlıklı kontroller arasındaki uyku sorunlarının karşılaştırılması amaçlanmıştır.

**Gereç ve Yöntem:** Bu çalışma, β-talasemi major hastası çocuk ve ergenlerin vaka kontrol araştırmasıydı. Örneklem, yaşları 8-16 arasında değişen, hasta grubundaki 76 çocuk ve ergen ile kontrol grubundaki 68 sağlıklı çocuk ve ergenden oluşmaktaydı. Ocak ve Aralık 2018 tarihleri arasında Hatay Devlet Hastanesi Çocuk ve Ergen Psikiyatrisi Kliniği'ne başvuran hastalar çalışmaya dahil edildi. β-talasemi major hastası çocuk ve ergenler Çocuk Hematoloji Kliniği'nden konsültasyon istemiyle yönlendirildi. Gruplar arasındaki uyku problemlerini değerlendirmek için Çocuk Uyku Alışkanlıkları Anketi (ÇUAA) kullanıldı.

**Bulgular:** Hasta grubunun yaş ortalaması 11.66 (SD = 3.22) yıldı ve %47.4'ü (N = 36) erkekti. Kontrol grubunda ortalama yaş 12.84 (SD = 3.12) yıldı ve %47.1'i (N = 32) erkekti. ÇUAA toplam skoru, gece uyanma ve uykuda solunum bozukluğu alt skorları, β-talasemi major hastası çocuklarda sağlıklı çocuklardan anlamlı olarak daha yüksekti.

**Sonuç:** β-talasemi major hastası çocuk ve ergenlerde sağlıklı çocuklardan daha fazla uyku sorunları olduğu için ayrıntılı çalışmalara ihtiyaç vardır.

**Anahtar kelimeler**: ergen, çocuk, hemoglobinopati, uyku, talasemi

## INTRODUCTION

β-thalassemia is a hereditary disease caused by several mutations which affect the hemoglobin synthesis and divided into two types as major and intermediate[1]. β-thalassemia is one of the most common forms of chronic hemolytic anemia. It is reported that almost 60.000 thalassemic children are born around the world every year[2,3]. β-thalassemia can show a variety of clinical symptoms in children and adolescents. Children with β-thalassemia usually have hepatosplenomegaly, developmental delay, and bone deformities. The resulting ineffective erythropoiesis may cause osteoporosis and severe enlargement of marrow space in many types of bones. Children with severe anemia may present complications in multiple

Yazışma Adresi/Address for Correspondence: Dr. Serkan Gunes, Hatay State Hospital, Department of Child and Adolescent Psychiatry, Hatay, Turkey. E-mail: dr_sgunes@hotmail.com
Geliş tarihi/Received: 13.02.2019 Kabul tarihi/Accepted: 01.04.2019 Çevrimiçi yayın/Published online: 15.09.2019

organ systems and require blood transfusions[1,4,5]. With the presence of better blood transfusion methods, iron chelation therapy, appropriate handling of complications, it is now possible for a thalassemic child to have a normal life period[6].

The causes of anemia such as iron deficiency or sickle cell disease have been suggested to be associated with many findings indicating disrupted sleep. Among the common sleep related symptoms in patients with anemia are insomnia, disrupted sleep, respiratory problems, and poor daily cognitive functions[7–11]. Repeated periodic limb movements during sleep and restless legs syndrome have been defined as being common symptoms in patients with iron deficiency anemia[1,12]. Treatment of iron deficiency anemia may improve subjective and objective sleep evaluation, that is, a decrease in the number of sleep arousals and in the sleep disruption indices while letting more restful sleep[13].

To the best of our knowledge, there is limited literature about sleep habits and behaviors of children and adolescents who have β-thalassemia major which causes chronic hemolytic anemia. In this context, this study aims to compare the sleep problems between children with β-thalassemia major and healthy controls.

## MATERIAL AND METHODS

This study was a case-control survey of children and adolescents with β-thalassemia major who were recruited from the Department of Child and Adolescent Psychiatry in Hatay State Hospital between January and December 2018. Children and adolescents with β-thalassemia major were consulted from the Department of Pediatric Hematology.

The nature and purpose of the study were explained to all children and parents and written informed consent was obtained. This study was conducted in accordance with the Declaration of Helsinki and the study protocol was approved by the Ethics Committee of Adana City Hospital in Adana in Turkey. The approval number was 2017/105.

The inclusion criteria for the patient group were as follows: 1) An age range of 8-16 years. 2) Not having a chronic physical illness other than β-thalassemia major. 3) A diagnosis of β-thalassemia major for 2-4 years. 4) Normal intelligence based on either a Wechsler Intelligence Scale for Children-Revised (WISC-R) full-scale IQ score above 80 or the average/above academic functioning documented with the last year's final school grades.

For the control group, the following inclusion criteria were used: 1) An age range of 8-16 years. 2) Not having a chronic physical or mental illness. 3) Normal intelligence based on either a WISC-R full-scale IQ score above 80 or the average/above academic functioning documented with the last year's final school grades. The control group consisted of healthy children and adolescents without any physical and mental illness who were referred to the child and adolescent psychiatry clinic.

Initially, 86 children with β-thalassemia major diagnosis were recruited. However, ten children were excluded for the following reasons: Two parents of children did not want to participate in the study and seven children had another chronic medical illness. In total, 76 children and adolescents with β-thalassemia major and 68 healthy controls completed the study requirements and included to the study.

### Instruments

### The Children's Sleep Habits Questionnaire

The Children's Sleep Habits Questionnaire (CSHQ) is a retrospective, 45-item parent questionnaire that has been used in previous studies to examine sleep habits and problems in children[14]. The CSHQ includes items: bedtime resistance (1st, 3rd, 4th, 5th, 6th, 8th items); sleep onset delay (2nd item); sleep duration (9th, 10th, 11th items); sleep anxiety (5th, 7th, 8th, 21st items); night waking (16th, 24th, 25th items); sleep-disordered breathing (18th, 19th, 20th items); parasomnias (12th, 13th, 14th, 15th, 17th, 22nd, 23rd items); and morning waking/daytime sleepiness (26th, 27th, 28th, 29th, 30th, 31st, 32nd, 33rd items). Items are rated on a three-point scale: "usually" if the sleep behavior occurred five to seven times/week; "sometimes" for two to four times/week; and "rarely" for zero to one time/week[15]. The 1st, 2nd, 3rd, 10th, 11th and 26th items in the scale are reverse coded.

The CSHQ is completed retrospectively by the parents. The parents are asked to assess the child's sleep habits over the previous week. It generally takes 5 to 15 minutes to fill in the questionnaire. A total of 41 points is suggested as a cut-off point. The points above this score are considered to be clinically significant. Fiş et al. conducted the Turkish translation of the scale and the Cronbach's alpha coefficient was determined as .78[16].

### Statistical analysis

The collected data were analyzed by using SPSS version 21.0. Demographic variables were presented using descriptive statistics. Categorical variables were compared by using the Chi-square test. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to verify normality in all continuous variables. Normally distributed parametric variables were compared between groups by using Independent Samples T test. The *p*-value <0.05 was accepted to be statistically significant.

## RESULTS

The sample consisted of 76 children and adolescents in the patient group and 68 healthy children and adolescents in the control group, with an age range of 8-16 years (M = 12.21, SD = 3.16). Mean age of the patient group was 11.66 (SD = 3.22) years, and 47.4% (N = 36) were males. Control group had a mean age of 12.84 (SD = 3.12) years, and 47.1% (N = 32) were males. There were no statistically differences in age and gender between the groups (p > 0.05) (Table 1)

Table 2 shows the comparison of CSHQ scores between the patient and control groups. Total score (p = 0.016), night waking (p = 0.043), and sleep disordered breathing (p = 0.047) subscores were significantly higher in the patient group when compared to the control group. Bedtime resistance (p = 0.078), sleep onset delay (p = 0.611), sleep anxiety (p = 0.114), daytime sleepiness (p = 0.864), and parasomnias (p = 0.245) subscores were higher in the patient group, but these findings were not statistically significant.

**Table 1. Demographic variables of the sample.**

| | | Patients, N=76 | Controls, N=68 | Cohen's *d* | *p** |
|---|---|---|---|---|---|
| Age (mean, SD) | (Years) | 11.66 (3.22) | 12.84 (3.12) | 0.372 | 0.149 |
| | | | | RR (95% Cl) | *p*** |
| Gender (N, %) | Male<br>Female | 36 (47.4)<br>40 (52.6) | 32 (47.1)<br>34 (52.9) | 0.98 (0.69-1.37) | 0.894 |

*Independent Sample T test was used. **Chi-square test was used.

**Table 2. The comparison of CSHQ scores between the patient and control groups.**

| | Patients, N=76 Mean (SD) | Controls, N=68 Mean (SD) | Cohen's *d* | *p** |
|---|---|---|---|---|
| Total Score | 54.08 (8.34) | 49.34 (8.22) | 0.572 | 0.016 |
| Bedtime Resistance | 10.21 (2.25) | 9.98 (2.19) | 0.103 | 0.078 |
| Sleep Onset Delay | 6.45 (1.42) | 6.36 (1.41) | 0.063 | 0.611 |
| Sleep Anxiety | 5.80 (2.12) | 5.60 (1.84) | 0.100 | 0.114 |
| Night Waking | 4.89 (1.23) | 3.73 (1.17) | 0.966 | 0.043 |
| Daytime Sleepiness | 13.39 (3.44) | 13.16 (3.07) | 0.070 | 0.864 |
| Parasomnias | 9.04 (2.46) | 8.33 (2.51) | 0.285 | 0.245 |
| Sleep Disordered Breathing | 4.25 (1.15) | 3.26 (1.16) | 0.857 | 0.047 |

*Independent Sample T test was used.

## DISCUSSION

The aim of the present study was to determine the sleep problems in a group of children with β-thalassemia major to fill a gap in the current literature. In this context, this study compared sleep habits and behaviors between children and adolescents with β-thalassemia major and typically developing healthy controls based on parent reports.

In the available literature, there are many reports about sleep problems among children and adolescents with hemoglobinopathies. Most of these reports are associated with sickle cell disease which is an inherited hemoglobinopathy characterized by chronic hemolysis and increased extramedullary hematopoiesis like β-thalassemia. However, the number of studies investigating the relationship between thalassemia and sleep problems is limited[11,17].

In a study conducted by Tarasiuk et al., the authors concluded that children and adolescents with β-thalassemia or congenital dyserythropoietic anemia type-1 showed impaired sleep function which is partially related to periodic limb movements and arousals resulted in daytime sleepiness[1]. Another study designed by Sritippayawan et al. showed higher

prevalence rates of obstructive sleep apnea in children with severe β-thalassemia[17]. In the present study, our findings were consistent with the literature. Parents of children with β-thalassemia major reported more sleep disturbances than those of healthy children. Furthermore, night waking and sleep disordered breathing were reported to be more common in children with β-thalassemia major. Reporting of these two types of sleep problems together may be an important point. It may be speculated that sleep disordered breathing may cause children to wake up more often during the sleep period.

The mechanism of sleep disturbances in children with β-thalassemia has not been well determined. Kapelushnik et al. reported a child with thalassemia intermedia and obstructive sleep apnea. They suggested extramedullary hematopoiesis in the nasopharyngeal area of the child to be the possible cause of obstructive sleep apnea[18]. In the study of Sritippayawan et al., all patients with obstructive sleep apnea had adenoid hypertrophy and 80% had associated tonsil enlargement. In this study, all adenotonsillar lymphoid tissues presented reactive lymphoid hyperplasia without any evidence of extramedullary erythropoiesis. The authors suggested that lymphoid hyperplasia might be related to repeated adenotonsillar infections, as in sickle cell disease[17].

The results of the present study should be evaluated within the context of its limitations. A major limitation is the reliance on parent reports. Parental problems may influence their perception of child condition. For example, depressive parents may view their children's sleep quality more negatively. Polysomnography and actigraphy are objective measures and can be used to exactly determine sleep problems in children and adolescents. The lack of familial and environmental variables like marital problems, socioeconomic status, and sleeping environment is another limitation. These factors may have impacts on children's sleep efficacy.

In conclusion, the current study suggests that sleep problems may be more prevalent in children and adolescents with β-thalassemia major. Therefore, it is very important to evaluate sleep disturbances in children with β-thalassemia major during routine clinical appointments. Previous studies have been reported that disrupted sleep may be related to decreased cognitive and academic performance and increased psychiatric disorders such as behavioral problems, depressive and anxiety symptoms[19–21]. Sleep disorders may limit children's overall daily functioning, development, and their ability to cope with the symptoms of β-thalassemia major. The evaluation of sleep problems like insomnia, night waking, sleepwalking, sleep apnea, or daytime sleepiness during regular clinical examinations is particularly significant in this disease group. In addition, the regulation of sleep problems can improve children's compliance with treatment. Cooperating with parents to make the sleeping environment more suitable (e.g., providing a quieter environment) can improve sleep efficiency and quality. On the other hand, educating parents and children about efficient sleep and the significance of bedtime routines are suggestions that can be made during routine clinical appointments to increase the child's sleep efficacy.

**Yazar Katkıları:** Çalışma konsepti/Tasarımı: SG; Veri toplama: SG; Veri analizi ve yorumlama: SG; Yazı taslağı: SG; İçeriğin eleştirel incelenmesi: SG; Son onay ve sorumluluk: SG; Teknik ve malzeme desteği: -; Süpervizyon: SG; Fon sağlama (mevcut ise): yok.
**Bilgilendirilmiş Onam:** Katılımcılardan yazılı onam alınmıştır.
**Hakem Değerlendirmesi:** Dış bağımsız.
**Çıkar Çatışması:** Yazarlar çıkar çatışması beyan etmemişlerdir.
**Finansal Destek:** Yazarlar finansal destek beyan etmemişlerdir.

**Author Contributions:** Concept/Design : SG; Data acquisition: SG; Data analysis and interpretation: SG; Drafting manuscript: SG; Critical revision of manuscript: SG; Final approval and accountability: SG; Technical or material support: -; Supervision: SG; Securing funding (if available): n/a.
**Informed Consent:** Written consent was obtained from the participants.
**Peer-review:** Externally peer-reviewed.
**Conflict of Interest:** Authors declared no conflict of interest.
**Financial Disclosure:** Authors declared no financial support

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