Sleep Disruption and Objective Sleepiness in Children With β-Thalassemia and Congenital Dyserythropoietic Anemia

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**Background:** Sleep fragmentation and periodic leg movement syndrome (PLMS) have been reported in adults with iron deficiency anemia. Little is known about sleep function and daytime sleepiness in children with chronic anemia such as β-thalassemia or congenital dyserythropoietic anemia type 1 (CDA-1).

**Objectives:** To investigate if children and adolescents who have β-thalassemia (major or intermedia) or CDA-1 experience sleep fragmentation and objective daytime sleepiness and also to investigate if children and adolescents with β-thalassemia have obstructive sleep apnea.

**Methods:** Ten patients (7 males and 3 females) with β-thalassemia (mean [SD] age, 10.4 [7.3] years), 10 patients (7 males and 3 females) with CDA-1 (mean [SD] age, 13.5 [5.1] years), and 13 healthy volunteer control children (7 males and 6 females) (mean [SD] age, 10 [4] years) underwent nocturnal polysomnographic studies. A multiple sleep latency test was performed for 6 patients who had β-thalassemia and 8 patients who had CDA-1.

**Results:** Both patient groups, that is, those who had β-thalassemia and those who had CDA-1, had multiple arousals during sleep (mean [SD], 27.8 [11.4] events per hour and 23.8 [11.8] events per hour, respectively) compared with the control subjects (12.1 [6.6] events per hour) (P<.002). Thirty-eight percent (10.6 events per hour) of the arousals in patients with β-thalassemia and 25% (6.0 events per hour) of the arousals in patients with CDA-1 were induced by periodic limb movements during sleep. In the control group, most (98%) arousals were spontaneous and unrelated to any definable event. The multiple sleep latency test average was 7.8 minutes for patients with β-thalassemia (n=6) and 10.7 minutes for patients with CDA-1 (n=8). Five patients with β-thalassemia and 4 patients with CDA-1 underwent a second polysomnographic study on the next night to confirm reproducibility. There was no significant change in the total number or index of arousals and no difference in the severity of the periodic limb movements during sleep compared with the results of the first polysomnographic study.

**Conclusion:** Children and adolescents with β-thalassemia or CDA-1 have evidence of impaired sleep function that is partially due to periodic limb movements during sleep and arousals that result in objective diurnal sleepiness.

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Objective sleep assessment as well as objective sleep deficiency anemia improves the quality of life and subjective sleep assessment 

Ten children and adolescents (7 male and 3 female patients; mean [SD] age, 10.4 [7.3] years) diagnosed as having 

Hematologic Unit, Soroka University Medical Center, Beer-Sheva, Israel. Thirteen healthy volunteer children and adolescents (7 male and 6 female subjects; mean [SD] age, 10 [4] years) without a known history of anemia served as control subjects. The controls are not from the Bedouin population. All controls were examined by a pediatrician (A. Tal) and were found to be free of any medical illness. The protocol was approved by the Institutional Ethics Committee and informed consent was obtained from all guardians.

HEMATOLOGICAL EVALUATION

All patients with β-thalassemia or CDA-1 underwent blood testing during their routine monthly visits to the Pediatric Hematologic Unit. Clinical and laboratory evaluations of the patients with β-thalassemia were performed according to guidelines for clinical management of thalassemia. For this study, we used the hematological data that were obtained within 1 month of the sleep study.

POLYSOMNOGRAPHIC EVALUATION

Children and adolescents were encouraged to maintain their usual daily routine and medication regimen. They reported to the sleep laboratory at 8:30 PM and were discharged at 7 AM the next morning. A parent accompanied all children and adolescents for the duration of the sleep study. To compare reproducibility of sleep characteristics, 5 of the 10 patients with β-thalassemia and 4 of the 10 patients with CDA-1 agreed to participate in a second consecutive polysomnographic study conducted the next morning. None of the controls agreed to participate in a second polysomnographic study.

The polysomnographic study was performed as described previously: 2 silver–silver chloride cup electroencephalographic (EEG) electrodes filled with electrolyte were applied to the C3 and C4 locations and reference electrodes were attached behind the ears in the left (A1) and right (A2) mastoid areas. Two electromyographic electrodes were applied over the submental muscles. Two electrooculographic electrodes were applied 1 cm above the outer canthus of one eye and 1 cm below the outer canthus of the other eye. The montage arrangement for polysomnographic reading consisted of C3A2 and C4A1, and 2 electro-oculographic recording electrocardiograms (1 from each eye).

Normal airflow was monitored by a pressure transducer (Pro-Tech Service Inc, Woodinville, Wash), thoracic and abdominal movements were monitored by strain gauge electrodes, and hemoglobin oxygen saturation was monitored by pulse oximetry (model 4700; Ohmeda Inc, Louisville, Colo). Leg movements were measured using a mechanical strain gauge sensor (Scientific Laboratories Products Inc, Tel Aviv, Israel). The mechanical strain gauge sensor has been previously validated in our laboratory.

MULTIPLE SLEEP LATENCY TEST

Six of the patients with β-thalassemia and 8 of the patients with CDA-1 agreed to participate in the Multiple Sleep Latency Test (MSLT) on the morning after the first polysomnographic study. The MSLT was conducted beginning at 8 AM (2 hours after the final morning awakening), 10:30 AM, 1 PM, and 4 PM. The MSLT was performed for 20 minutes according to standard guidelines. Parents were requested to stay in the room with their child to eliminate any external apprehension. The nap sleep latency was determined by the first occurrence of 3 consecutive epochs (90 seconds) of stage 1 sleep or the first epoch of any other stage of sleep.

SCORING

Sleep studies were interpreted according to recently published pediatric criteria. Nocturnal sleep-wake was scored in

### Table 1. Characteristics of 10 Patients With β-Thalassemia and 10 Patients With Congenital Dyserythropoietic Anemia Type 1 (CDA-1)

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Type of β-Thalassemia</th>
<th>Hemoglobin Level, g/dL</th>
<th>Ferritin Level, ng/mL</th>
<th>Spleen</th>
<th>Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Intermedia</td>
<td>8.4</td>
<td>475</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Intermedia</td>
<td>8.1</td>
<td>98</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Intermedia</td>
<td>8.9</td>
<td>53</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>Intermedia</td>
<td>7.2</td>
<td>67</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Major</td>
<td>8.0</td>
<td>361</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>Major</td>
<td>10.9</td>
<td>458</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>Major</td>
<td>7.4</td>
<td>699</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>Major</td>
<td>6.9</td>
<td>896</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>Major</td>
<td>6.0</td>
<td>949</td>
<td>Spx</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>Major</td>
<td>8.0</td>
<td>80</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

**Patients With β-Thalassemia**

| Mean (SD)   | 8.0 (1.3) | 414 (345) |

**Patients With CDA-1**

| Mean (SD)   | 9.8 (1.0) | 356 (342) |

Abbreviations: Spx, splenectomy; -, normal spleen or liver; +, enlarged spleen or liver.

To convert hemoglobin values to grams per deciliter multiple values by 0.8206.

*The normal range for ferritin is 16 to 300 ng/mL.

where anemia is a common feature. Treatment of iron deficiency anemia improves the quality of life and subjective sleep assessment as well as objective sleep assessment, that is, reduction in the number of arousals from sleep and in the sleep fragmentation indices while allowing more restorative sleep.

We investigated if children and adolescents who have β-thalassemia (major or intermedia) or CDA-1 have sleep fragmentation and objective daytime sleepiness. In addition, we investigated if children and adolescents with β-thalassemia have obstructive sleep apnea.

### STUDY POPULATION

Ten children and adolescents (7 male and 3 female patients; mean [SD] age, 10.4 [7.3] years) diagnosed as having β-thalassemia (major or intermedia) and 10 children and adolescents (7 male and 3 female patients; mean [SD] age, 13.5 [5.1] years) without a known history of anemia served as control subjects.
accord with the Rechtschaffen and Kales criteria. Data were collected and streamed to an optical disk using a commercially available sleep monitoring system (model 4100; SensorMedics Inc, Yorba Linda, Calif). Signals were analyzed by computerized software and the results were edited by 2 of us (A. Tarasiuk and B. F.). Sleep latency was defined as time from lights out to the first occurrence of 3 consecutive epochs (90 seconds) of stage 1 sleep, or the first epoch (30 seconds) of any other stage of sleep. Rapid eye movement (REM) sleep latency was defined as the time from sleep onset to the first epoch of REM sleep. Sleep efficiency was calculated as the ratio of total sleep time to time in bed. The time spent in each sleep stage was expressed as the percentage of total sleep time.

Arousals and awakenings were scored according to the American Sleep Disorders Association’s Sleep Disorders Atlas Task Force recommendation, modified for children. Arousals were defined by the presence of any of the following: (1) exceeding a 1.5-second period of a frequency EEG activity with augmentation of submental electromyographic signal; (2) presence of an EEG K-complex or desynchronization of EEG if clearly associated with leg movement or apnea; and (3) sleep stage shift if clearly associated with leg movement or apnea.

Awakenings were defined as the presence of more than 15 seconds waking EEG following sleep onset with augmentation of the submental electromyographic signal. The arousal index and awakening index were calculated as the number of arousals or awakenings per hour of sleep. In addition, all arousals and awakenings were defined as one of the following: (1) associated with leg movement (jerks); an awakening or arousal was designated as associated with leg movement if a jerk signal preceded the EEG or submental electromyographic signal; (2) associated with obstructive apnea or obstructive hypopnea (see next paragraph); and (3) spontaneous leg movement (jerks). We did not score movements separately because in children most arousals and awakenings are associated with nonspecific movements.

Determining the number of shifts from deeper to lighter sleep stages between the control group, there were no significant differences in latency to sleep or in the cumulative percentage of any of the sleep stages. None of the patients with β-thalassemia or CDA-1 had sleep onset REM.

Sleep Fragmentation

The most striking sleep abnormality noted in both patient groups was severe sleep fragmentation. The patients with β-thalassemia had 27.8 (11.4) arousals and awakenings per hour of sleep (or events per hour); the patients with CDA-1 had 23.8 (11.8) events per hour compared with 12.1 (6.6) events per hour in the control group (P < .002). Furthermore, in 8 (80%) of the 10 patients with β-thalassemia and in 5 (50%) of the 10 patients with CDA-1, the arousals and awakenings index exceeded 20 events per hour. Only 2 (15%) of the 13 controls had an arousals and awakenings index exceeding 20 events per hour.

Patients with β-thalassemia had a PLMS index of 13.9 (12.1) events per hour (range, 9.3-36.1 events per hour) and 37.6% (5.1%) of the arousals were induced by PLMS. Comparatively, patients with CDA-1 had a PLMS index of 7.3 (11.1) events per hour (range, 0-51.1 events per hour) and 25.3% (27.8%) of the arousals were induced by PLMS. In the control group, 98% of the arousals and awakenings were spontaneous and were unrelated to any specific polysomnographic definable event. The percentage of arousals or awakenings associated with obstructive apneas or obstructive hypopneas was in the range of 0.8% to 1.0% for all groups.

Frequency analyses of consecutive sleep in stage 2, slow wave sleep, and REM were similar in the 3 groups. There were no significant differences in the number of shifts from deeper to lighter sleep stages between the controls (15.6 [5.0] events per study) and the patients with β-thalassemia or CDA-1 (16.2 [4.4] and 14.4 [5.3] events per study, respectively).

Respiratory Activity

There were no significant differences in respiratory disturbance index between the groups (Table 2). Wake SaO2,
mean SaO2 during sleep, and nadir SaO2 were in the normal range for all groups (Table 2). Thus, we did not find polysomnographic evidence to support a diagnosis of obstructive sleep apnea.

**SECOND POLYSOMNOGRAPHIC STUDY**

Reproducibility of the findings was confirmed in 9 patients. Five patients in the β-thalassemia group and 4 in the CDA-1 group consented to a second polysomnogram. This polysomnographic study was done on the next night (Table 3). Total sleep time did not significantly improve in the second polysomnographic study and sleep efficiency improved by 10% (P<.01). The improvement of sleep efficiency was caused by the combination of prolonged total sleep time and shorter sleep latency. There was neither change in the total number or index of awakenings and arousals nor a change in the PLMS index compared with the results of the first polysomnographic study.

**SECOND MSLT RESULTS**

Six patients with β-thalassemia and 8 patients with CDA-1 underwent an MSLT (Figure). The mean sleep latency on an MSLT was 7.8 (3.5) minutes for patients with β-thalassemia and 10.7 (7.5) minutes for patients with CDA-1. The evaluation of sleep latencies throughout the day is shown in the Figure. Both patient groups demonstrated an increase in sleep propensity throughout the day. We did not observe sleep-onset REM periods during MSLT in any patients.

**COMMENT**

This study provides objective evidence of sleep fragmentation in children and adolescents with 2 types of chronic anemia. The main polysomnographic manifestations were an increased arousal index and PLMS. These sleep abnormalities led to daytime hypersomnolence that was manifested by shortened MSLT.

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**Table 2. Sleep Characteristics**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control Subjects (n = 13)</th>
<th>Patients With β-Thalassemia (n = 10)</th>
<th>Patients With CDA-1 (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep pattern</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sleep time, min</td>
<td>370.0 (30.5)</td>
<td>362.8 (26.5)</td>
<td>314.9 (66.8)†</td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>89.6 (4.1)</td>
<td>84.0 (7.2)</td>
<td>79.6 (66.8)‡</td>
</tr>
<tr>
<td>Latency to sleep, min</td>
<td>32.5 (21.5)</td>
<td>32.4 (24.5)</td>
<td>43.0 (32.7)</td>
</tr>
<tr>
<td>Stage 1 sleep, %</td>
<td>1.8 (1.9)</td>
<td>3.3 (2.0)</td>
<td>2.8 (3.0)</td>
</tr>
<tr>
<td>Stage 2 sleep, %</td>
<td>58.0 (8.0)</td>
<td>61.8 (13.7)</td>
<td>56.1 (9.0)</td>
</tr>
<tr>
<td>SWS, %</td>
<td>21.2 (10.1)</td>
<td>18.6 (8.5)</td>
<td>26.3 (9.8)</td>
</tr>
<tr>
<td>REM, %</td>
<td>18.1 (6.9)</td>
<td>15.4 (7.0)</td>
<td>10.8 (7.4)</td>
</tr>
<tr>
<td>WASO, min</td>
<td>22.2 (16.0)</td>
<td>33.4 (23.7)</td>
<td>50.6 (50.2)</td>
</tr>
<tr>
<td>PLMS, events/h</td>
<td></td>
<td>13.9 (12.1)</td>
<td>7.3 (11.1)</td>
</tr>
<tr>
<td>MSLT, min§</td>
<td>7.8 (3.5) (n = 6)</td>
<td>10.7 (7.5) (n = 8)</td>
<td></td>
</tr>
<tr>
<td>Respiratory pattern</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RDI, events/h</td>
<td>1.1 (0.8)</td>
<td>0.5 (0.5)</td>
<td>1.3 (1.3)</td>
</tr>
<tr>
<td>REM RDI, events/h</td>
<td>2.9 (3.5)</td>
<td>2.0 (1.8)</td>
<td>3.5 (5.6)</td>
</tr>
<tr>
<td>T90, %</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Wake SaO2, %</td>
<td>97.9 (1.2)</td>
<td>97.5 (2.8)</td>
<td>98.0 (0.8)</td>
</tr>
<tr>
<td>Nadir SaO2, %</td>
<td>94.6 (1.5)</td>
<td>92.1 (4.5)</td>
<td>92.2 (4.5)</td>
</tr>
</tbody>
</table>

**Table 3. Reproducibility of the Polysomnographic Findings in Patients With Thalassemia and CDA-1**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients With β-Thalassemia (n = 5)</th>
<th>Patients With CDA-1 (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST, min</td>
<td>346 (14.1)</td>
<td>395.0 (51.8)</td>
</tr>
<tr>
<td>SEF, %</td>
<td>79.4 (5.9)</td>
<td>94.6 (2.7)†</td>
</tr>
<tr>
<td>Stage Sleep 2, %</td>
<td>51.6 (3.9)</td>
<td>49.9 (10.4)†</td>
</tr>
<tr>
<td>SWS, %</td>
<td>19.4 (7.8)</td>
<td>25.3 (5.7)</td>
</tr>
<tr>
<td>REM, %</td>
<td>20.6 (6.0)</td>
<td>22.2 (8.2)</td>
</tr>
<tr>
<td>Ar and Aw, index, events/h</td>
<td>28.2 (12.4)</td>
<td>24.1 (9.4)</td>
</tr>
</tbody>
</table>

**Abbreviations:** CDA-1, congenital dyserythropoietic anemia type 1; DI, desaturation index; MSLT, multiple sleep latency test; PLMS, periodic limb movements syndrome; RDI, respiratory disturbance; REM, rapid eye movement; SaO2, arterial oxygen saturation; SWS, slow wave sleep; T90, the percentage of time with an oxygen saturation below 90%; WASO, wake after sleep onset.

*Data are given as mean (SD).
†P<.01, 1-way analysis of variance compared with control subjects.
‡P<.05.
§Values given for 6 patients with β-thalassemia and 8 patients with CDA-1.
throughout the day. There was no evidence for obstructive sleep apnea in our study group. To our knowledge, the association between sleep function and \(\beta\)-thalassemia, or CDA-1, or both has not been reported in the literature. There is no evidence to support a genetic link between these 2 disorders and the sleep disruption we observed.

**SLEEP FRAGMENTATION**

Our finding of an arousal and awakening index in the controls was comparable to healthy individuals in the same age group. Healthy individuals in the age range of 15 to 30 years have an arousal index of 11 to 15 events per hour.\(^9\) Both groups of patients with anemia demonstrated frequent arousals and awakenings from sleep. We found an awakening and arousal index of 27.8 events per hour in our patients who had \(\beta\)-thalassemia and 23.8 events per hour in our patients who had CDA-1. Fifty percent to 80% of our patients had an arousal index above 20 events per hour. In adults, experimentally induced arousals at a rate of 20 events per hour led to impairment of daytime alertness.\(^23,24\) Considering these findings, we would expect to find excessive daytime sleepiness in our patients.

In adults, iron deficiency anemia can induce PLMS, which is associated with considerable sleep fragmentation. However, the severity of the observed PLMS in our patients was considerably lower than previously reported in adults\(^6,9\) and, therefore, may only partially explain the sleep disruption. Recently,\(^25\) it was suggested that both iron deficiency and overload can cause motor impairment and cognitive deficits and that they may play a role in the pathophysiology of the restless leg syndrome. Iron overload is a feature of \(\beta\)-thalassemia and CDA-1. Finally, we found no evidence of obstructive sleep apnea. Thus, the sleep disturbances seen in this study are unrelated to obstructive respiratory events.

**EXCESSIVE DAYTIME SLEEPINESS**

Unlike adults in whom poor sleep may lead to excessive daytime sleepiness\(^20\) and impairment of daily activities and mood,\(^23,24,27\) daytime sleepiness\(^20\) in children is difficult to evaluate. The clinical signs of mild sleepiness (yawns, irritability, impaired concentration, momentary inattention, or lapses in performing a vigilance task) are similar to those of learning disabilities or behavior disorders in children and can often lead to misdiagnosis. In a previous study in children with juvenile rheumatoid arthritis,\(^11\) the severe sleep fragmentation was associated with an afternoon nap, reflecting significant daytime somnolence.\(^29\) Multiple sleep latency tests are probably the most reliable approach for evaluating daytime sleepiness.\(^12,14\) A limitation of our study is that MSLT data were not collected from our controls. We compared our data with available information for MSLT results in children. Palm et al\(^13\) studied 18 healthy children between the ages of 8 and 12 years using polysomnography and MSLT. They reported an average sleep latency on MSLT of about 24 minutes. Thus, it becomes apparent that an MSLT result of less than 10 minutes is exceedingly rare in healthy children and clearly differentiates sleepy from nonsleepy children. Gozal et al\(^31\) reported excessive daytime sleepiness as defined by an average sleep latency on MSLT of less than 10 minutes occurs in a small proportion of children with severe obstructive sleep apnea. Indeed, in children with juvenile rheumatoid arthritis, we reported an average sleep latency on MSLT of 10.3 minutes.\(^11\) Our families of the children and adolescents with anemia that we studied, all of whom are Bedouins, did not report habitual afternoon naps. The Bedouin population, as whole, does not report habitual afternoon naps. In the current study we noted excessive daytime sleepiness and an average sleep latency on MSLT of 7.8 minutes in patients with \(\beta\)-thalassemia. The short time in bed is a relative limitation of the study since it may effect the MSLT result. However, since we noted considerable excessive daytime sleepiness in these patients, we assume that it may have little effect on MSLT results.

**DATA REPRODUCIBILITY**

In the current study, 9 of 20 children and adolescents performed 2 consecutive sleep studies, and data were comparable. The distribution of sleep stages was normal in both our patient and control groups. Reproducibility of our findings was established in a second polysomnographic test the next morning, in which sleep efficiency and latency to sleep improved, yet there was no change.
What This Study Adds

To our knowledge, this study is among the first to characterize the sleep pattern and daytime sleepiness in children and adolescents who have β-thalassemia and CDA-1. In adults, iron deficiency anemia has been associated with impairment of sleep. Children and adolescents who have chronic anemia have objective evidence of severe sleep abnormality. The results of this study indicated that there was a 2-fold increase in the number of arousals and awakenings for those who have anemia compared with healthy volunteer controls. This sleep disruption may result in excessive daytime sleepiness.

We found objective evidence of sleep dysfunction with excessive PLMS and arousals based on overnight polysomnographic test results, with a suggestion of excessive daytime sleepiness.

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