Sleep EEG in growth disorders

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SUMMARY The sleep of 30 children with disorders of growth and development was studied because of the known association between sleep and the secretion of hormones. Thirty three normal children were studied for comparison. The sleep of two consecutive nights was monitored at home using a small portable electroencephalogram and electro-oculogram recorder.

Within the normal group there were no significant differences between sexes nor between the first and second nights of recording. There was a significant decrease in total sleep time with increasing age due to reduction in the amounts of rapid eye movement sleep and stage IV sleep. There was no change in rapid eye movement latency or overall rapid eye movement activity between the three age groups.

Children with genetic short stature and those with poor growth as a result of poor eating habits had an increased percentage of rapid eye movement sleep.

A significant decrease in the percentage of stage IV sleep, increased amount of rapid eye movement sleep (especially active rapid eye movement sleep), and decreased rapid eye movement cycling time was found in five children with severe psychosocial deprivation.

Children with constitutional delay of growth and puberty had an increased rapid eye movement cycling time and thus less rapid eye movement sleep over the whole night.

The study of electroencephalographic (EEG) recordings during sleep has shown a cycle of sleep stages best defined by the criteria of Rechtschaffen and Kales. These consist of stages I and II (light sleep), III and IV (delta wave sleep), and rapid eye movement sleep. Waking from rapid eye movement sleep has been regularly associated with the recall of dreaming. Secretion of growth hormone is regularly associated with the first episode of stage IV sleep. Corticotrophin, prolactin, gonadotrophins, and parathormone are also secreted in pulses during sleep but seem less clearly triggered by a particular sleep stage or event.

The time from going to sleep until the first period of rapid eye movement sleep of duration of at least three minutes (rapid eye movement latency) and a measure of the number of eye movements during a rapid eye movement period (rapid eye movement activity) have been described as important markers of an endogenous depressive trait in adults.

Sleep abnormalities have been prominent in the description of children with severe psychosocial dwarfism, and sleep has been abnormal when studied in four children with failure to thrive. Adults and children with endogenous depression have abnormalities in both their sleep and their endocrine function.

As it seems likely that a sleep abnormality in itself, or as an intermediary mechanism, may be a cause of abnormalities in growth and development we have examined the sleep patterns of normal children and children with genetic short stature, psychosocial dwarfism, and constitutional delay of growth and development to define what sleep abnormalities, if any, are present.

Subjects and methods

The group of normal children consisted of 33 subjects (15 boys and 18 girls) recruited from schools by letter of invitation sent to parents. They were selected by age to span the age range of the subject group evenly. All were of normal stature and had no history of important medical or psychiatric illness.

Children with disorders of growth and development were attending the paediatric endocrinology clinic at The Middlesex Hospital and had regular measurements of growth using standard techniques. Bone age was assessed using the Tanner Whitehouse
TW2 method. Anthropometric data are expressed in terms of standard deviation scores (SDS) using the equation:

$$\text{SDS} = \frac{x - \bar{x}}{S}$$

where $x$ is the measurement, $\bar{x}$ the mean for age and sex, and $S$ the standard deviation.

Parents and children were invited to participate in the study if they met the criteria for one of the groups specified below.

1. **Genetic short stature.** Child's height and midparental height more than 2SD below the mean for age and sex. No past illness in the parent to explain their short stature.

2. **Psychosocial dwarfism type 1.** Moderate long term growth failure (growth velocity consistently less than or equal to 25th centile for age and sex) for at least three years and a history of difficult, fussy eating habits. Normal secretion of growth hormone to provocative stimuli.

3. **Psychosocial dwarfism type 2.** Severe short stature and growth failure, typical behavioural abnormalities, normal or excessive appetite, and growth acceleration on change of environment.

4. **Constitutional delay of growth and development.** Short stature (height standard deviation score <1.5), greater than two year delay in bone age relative to chronological age, and a normal growth velocity.

Families were visited at home and had a semi-structured interview, and the EEG/electro-oculogram recording apparatus was then attached to the child. Sleep was monitored over two nights with a portable tape recorder (Medilog 4–24 Recorder and HDX–82 Preamplifiers, Oxford Medical Systems). This four channel recorder is small (112×86×36 mm) and battery powered and uses one C120 cassette per 24 hours. Two channels were used to record the EEG, one to record eye movement (Meditrace pellet electrode placed at the outer canthi), and one to record a digital time code and event marker. Silver/silver chloride cup EEG electrodes were fixed to the scalp with collodion in the A1C4 and A2C3 positions along with two reference electrodes in the O1O2 positions. Conducting saline jelly was injected between electrode and scalp and the impedance checked to be below 5 kOhm. The filter band width was set at 0.5 and 100 Hz. Electrical activity from the occipitalis muscle was also recorded on the EEG channels, allowing muscle tone to be assessed.

Families were given the responsibility of changing the cassette every 24 hours so that the tape from each night was recorded separately and the tape subsequently identified by a unique randomly allocated number. Tapes were analysed blind using a page mode display unit (PMD 12, Oxford Medical Systems) that automatically presented the recorded signal as ‘pages’ of data comprising eight or 16 seconds of EEG/electromyogram and electrooculogram. The pages were presented at a 20th or a 60th of real time to allow rapid visual scanning. Each sequential 32 seconds was scored using the criteria of Rechtschaffen and Kales, with further analysis of sleep variables as defined below.

1. **Sleep onset time.** Clock time at onset of the first episode of sleep stage followed by at least five minutes of continuous sleep.

2. **Total sleep time.** From onset of sleep until continuous waking of at least two hours. Brief waking during the night was considered part of the total sleep time.

3. **Wake time.** Time spent awake between onset of sleep and final waking time.

4. **Rapid eye movement sleep period.** Three consecutive minutes of typical EEG associated with definite eye movements.

5. **Rapid eye movement sleep latency.** Time from onset of sleep until the first rapid eye movement sleep period.

6. **Rapid eye movement sleep cycling time.** Time between the beginning of the first rapid eye movement sleep period and beginning of the last rapid eye movement sleep period divided by total number of rapid eye movement sleep periods $-1$.

7. **Active rapid eye movement sleep.** Time spent with rapid eye movement sleep-EEG criteria plus two or more definite eye movements per 16 seconds.

8. **Rapid eye movement sleep activity.**

$$\text{Active rapid eye movement sleep (mins)} \times 100$$

$$\frac{\text{Total rapid eye movement sleep (mins)}}{\text{Total sleep time} - \text{wake time}}$$

9. **Sleep efficiency.**

$$\frac{\text{Total sleep time} - \text{wake time} \times 100}{\text{Total sleep time}}$$

The same sleep recording was analysed roughly every 20 tapes. At the end of the study the 15
analyses of this record were used to derive the coefficient variation for each sleep variable. Each night’s recording required 45 to 90 minutes of analysis on the Oxford Medilog page mode display unit.

A seven day dietary record was kept from which average daily caloric and protein intake were computed. Per cent of recommended calories and protein for age and sex was calculated using Department of Health and Social Security standards. An estimate of intelligence quotient was made by using two subscales of the Weschler Intelligence Scale for Children (vocabulary and block design). These two subscales correlate well with the fullscale score (r=0.8 and 0.75, respectively). A self rated depression questionnaire, the Children’s Depression Indicator, was administered at the initial interview. A score of less than 19 using this indicator is considered normal.

Data analysis was by a standard computerised statistical package (ABSTAT, Anderson Bell). Comparison of nights 1 and 2 was by paired t test. One way analysis of variance was used to compare a variable across all groups and t values computed for differences between each group and the normal group.

The study was approved by the clinical research (ethical) committee of our hospital.

Results

Anthropometric and dietary details are shown in Table 1. The recording apparatus was well tolerated and in some cases was worn to school with no ill effects.

The coefficient of variation for each sleep variable over 15 analyses of the same tape was satisfactory (<12%) except for active rapid eye movement sleep variables where it varied from 22 to 53%.

The only difference between the first and second nights’ recordings was the amount of time spent in stage I (night 1: 2.75 (SD 2.2) minutes; night 2: 1.84 (SD 1.2) minutes, p<0.05). No other differences were found, so mean values of the two nights of sleep were used in subsequent analyses.

Within the normal group there was only one variable (rapid eye movement activity in rapid eye movement sleep cycle 1) where there was a significant difference (p<0.05) between the sexes. Within this group, sex was ignored and three age groups corresponding to their pubertal stages (prepubertal 5–9 years (n=13), peripubertal 10–12.9 years (n=13), and pubertal 13–16 years (n=seven)) were formed.

One way analysis of variance was performed on each variable across the three age groups and these

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Table 1: Anthropometric and dietary details of the five groups studied

<table>
<thead>
<tr>
<th>Group</th>
<th>No</th>
<th>Age range (years)</th>
<th>Bone age range</th>
<th>Mean (SD)</th>
<th>Standard deviation scores</th>
<th>% Recommended protein for age and sex</th>
<th>% Recommended caloric for age and sex</th>
<th>Triglyceride (mmol/L)</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>33</td>
<td>5.5–15.4</td>
<td>6.1–13.7</td>
<td>156±4</td>
<td>-0.265 (0.278)</td>
<td>70.76 (5.748)</td>
<td>83.55 (5.07)</td>
<td>113.65 (11.871)</td>
<td>51±13.6</td>
</tr>
<tr>
<td>Psychosocial dwarfism</td>
<td>8</td>
<td>5.4–1.8</td>
<td>5.4–1.8</td>
<td>154±4</td>
<td>-0.268 (0.278)</td>
<td>72.75 (5.280)</td>
<td>82.54 (5.250)</td>
<td>112.65 (11.871)</td>
<td>51±13.6</td>
</tr>
<tr>
<td>Psychosocial dwarfism</td>
<td>2</td>
<td>5.5–1.2</td>
<td>5.5–1.2</td>
<td>154±4</td>
<td>-0.268 (0.278)</td>
<td>70.76 (5.748)</td>
<td>83.55 (5.07)</td>
<td>113.65 (11.871)</td>
<td>51±13.6</td>
</tr>
<tr>
<td>Pubertal delay</td>
<td>5</td>
<td>12.5–15.0</td>
<td>13.5–15.0</td>
<td>154±4</td>
<td>-0.268 (0.278)</td>
<td>70.76 (5.748)</td>
<td>83.55 (5.07)</td>
<td>113.65 (11.871)</td>
<td>51±13.6</td>
</tr>
</tbody>
</table>

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Table 2  Sleep variables, mean age, and sex ratio of the three age groups

<table>
<thead>
<tr>
<th>Sleep variables</th>
<th>Group (mean (SD))</th>
<th>F2, n*</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prepuberal</td>
<td>Peripuberal</td>
<td>Puberal</td>
</tr>
<tr>
<td>Total sleep time (h)</td>
<td>9.64 (0.70)</td>
<td>8.89 (0.80)</td>
<td>8.33 (0.80)</td>
</tr>
<tr>
<td>Sleep onset (24 h)</td>
<td>21.3 (76.0)</td>
<td>22.9 (51.0)</td>
<td>22.5 (82.0)</td>
</tr>
<tr>
<td>Stage (min):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>2.58 (1.6)</td>
<td>1.95 (0.9)</td>
<td>2.35 (1.5)</td>
</tr>
<tr>
<td>II</td>
<td>211.2 (39.0)</td>
<td>210.1 (49.0)</td>
<td>218.0 (30.0)</td>
</tr>
<tr>
<td>III</td>
<td>45.7 (11.3)</td>
<td>50.5 (16.3)</td>
<td>34.7 (16.5)</td>
</tr>
<tr>
<td>IV</td>
<td>134.0 (33.4)</td>
<td>130.6 (25.8)</td>
<td>103.36 (26.7)</td>
</tr>
<tr>
<td>Rapid eye movement</td>
<td>178.2 (40.5)</td>
<td>147.5 (23.1)</td>
<td>132.2 (31.5)</td>
</tr>
<tr>
<td>Awake (min)</td>
<td>5.4 (15.6)</td>
<td>5.2 (15.0)</td>
<td>5.2 (15.5)</td>
</tr>
<tr>
<td>No of rapid eye movement periods</td>
<td>5.95 (0.86)</td>
<td>5.03 (0.63)</td>
<td>4.85 (0.80)</td>
</tr>
<tr>
<td>Rapid eye movement latency (min)</td>
<td>126.5 (33.5)</td>
<td>122.5 (47.6)</td>
<td>130.0 (40.4)</td>
</tr>
<tr>
<td>Rapid eye movement cycling time (min)</td>
<td>83.6 (8.1)</td>
<td>91.1 (8.6)</td>
<td>88.3 (5.8)</td>
</tr>
<tr>
<td>Rapid eye activity in cycle (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>39.2 (22.5)</td>
<td>28.6 (14.5)</td>
<td>35.9 (11.9)</td>
</tr>
<tr>
<td>2</td>
<td>47.5 (20.3)</td>
<td>29.3 (16.1)</td>
<td>39.8 (16.6)</td>
</tr>
<tr>
<td>3</td>
<td>42.9 (13.4)</td>
<td>23.7 (14.7)</td>
<td>37.1 (16.5)</td>
</tr>
<tr>
<td>4</td>
<td>43.7 (13.2)</td>
<td>32.5 (14.0)</td>
<td>38.4 (12.9)</td>
</tr>
<tr>
<td>5</td>
<td>40.2 (12.7)</td>
<td>37.0 (21.6)</td>
<td>36.7 (14.2)</td>
</tr>
<tr>
<td>Total active rapid eye movement (min)</td>
<td>80.9 (32.6)</td>
<td>58.2 (22.3)</td>
<td>51.3 (19.5)</td>
</tr>
<tr>
<td>Total rapid eye movement density (%)</td>
<td>45.5 (13.5)</td>
<td>33.0 (13.8)</td>
<td>39.2 (13.5)</td>
</tr>
<tr>
<td>Age</td>
<td>7-98 (1.50)</td>
<td>11.26 (0.79)</td>
<td>14.40 (0.63)</td>
</tr>
<tr>
<td>Sex ratio (M/F)</td>
<td>5.8</td>
<td>9.6</td>
<td>9.4</td>
</tr>
</tbody>
</table>

*From one way ANOVA between the three age groups.

A between group comparison of percentage of sleep time spent in each sleep stage is illustrated in Figure 1. Children with psychosocial dwarfism type 2 had significantly less stage IV sleep (p<0.05) and spent more time awake. Children with genetic short stature and psychosocial dwarfism types 1 and 2 had a significant increase (p<0.01) in the percentage of time spent in rapid eye movement sleep.

Fig. 1  Between groups comparison of percentage of total sleep time (mean (SE)) spent in each sleep stage and awake (*p<0.05, **p<0.01 compared with the normal group).

are documented in Table 2. When sleep stage was expressed as a percentage of total sleep time there was no significant sleep stage differences from ages 5 to 16 years.

Within the group of children with disorders of growth and development there were two cases where the record of the second night was of such poor recording quality as to render sleep analysis invalid. The data from the first night alone were used in these cases. The mean value for the two nights was used for all the others in the analysis.

Fig. 2  Between groups comparison of rapid eye movement sleep activity during the first five cycles of rapid eye movement sleep.
Table 3  Rapid eye movement sleep measures in the five groups. Values are mean (SE)

<table>
<thead>
<tr>
<th>Group</th>
<th>No of rapid eye movement periods</th>
<th>Rapid eye movement latency (min)</th>
<th>Total rapid eye movement (min)</th>
<th>Total active rapid eye movement (min)</th>
<th>Overall rapid eye movement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>5-4 (0-2)</td>
<td>124-5 (7-1)</td>
<td>157-2 (6-8)</td>
<td>59-9 (5-6)</td>
<td>38-29 (2-77)</td>
</tr>
<tr>
<td>Genetic short stature</td>
<td>5-8 (0-2)</td>
<td>104-8 (11-6)</td>
<td>188-5 (10-6)*</td>
<td>91-4 (6-9)**</td>
<td>47-44 (2-56)</td>
</tr>
<tr>
<td>Psychosocial dwarfism type 1</td>
<td>5-7 (0-4)</td>
<td>115-8 (14-3)</td>
<td>186-4 (12-7)</td>
<td>68-1 (6-6)</td>
<td>37-70 (3-73)</td>
</tr>
<tr>
<td>Psychosocial dwarfism type 2</td>
<td>6-7 (0-4)*</td>
<td>103-5 (18-2)</td>
<td>192-4 (13-4)</td>
<td>116-7 (18-7)**</td>
<td>60-76 (7-53)**</td>
</tr>
<tr>
<td>Constitutional delay</td>
<td>4-9 (0-1)*</td>
<td>133-0 (12-5)</td>
<td>139-3 (5-9)</td>
<td>59-9 (7-6)</td>
<td>42-70 (4-64)</td>
</tr>
</tbody>
</table>

*p<0.05 compared with normal group.
**p<0.01 compared with normal group.
***p<0.001 compared with normal group.

Rapid eye movement sleep latency and total active rapid eye movement and overall rapid eye movement sleep activity figures are shown in Table 3. There were no significant differences (at the 5% level) in the rapid eye movement sleep latencies. Rapid eye movement sleep activity assessed over the whole night and individually within each sleep cycle (Fig. 2) was significantly increased in children with psychosocial dwarfism type 2.

The average rapid eye movement sleep cycling time of the normal group was 87-06+1-58 minutes. Children with severe psychosocial dwarfism type 2 had a shorter rapid eye movement sleep cycling time (77-64+3-79 minutes, p<0.01), and children with constitutional delay of growth and development had a significant increase (92-84+3-00 minutes, p<0.05) in rapid eye movement sleep cycling time.

Discussion

Our method of recording sleep at home was non-invasive, well tolerated, and easily performed. The analysis of a record of sleep from a single night is very accurate for sleep stage data but only moderately accurate for those variables that involve assessing the amount of eye movement during each period of rapid eye movement sleep. Thus much care must be taken in future in interpreting the importance of eye movement variables using this methodology, especially if used for the diagnosis of endogenous depression.19 20 Indeed, there is a need for a more clear definition of eye movement type and frequency during rapid eye movement sleep.

The descriptions of normal sleep in childhood are based on studies in sleep laboratories of about 186 children from 6 to 16 years.21–25 Our results confirm that there is little difference between sexes in any sleep variable. The changes in sleep with increasing age are all expected. Total sleep time decreased, and this consisted mainly of decreases in the amount of rapid eye movement sleep and stage IV sleep. Rapid eye movement sleep latency, which is considered a psychological sign of the endogenous depressive trait,26 did not vary in children aged 5 to 17. The frequency of rapid eye movement sleep periods showed an increasing trend that was not significant.

All reports of EEG monitored sleep in childhood have involved the recording of sleep in the laboratory. Early reports showed a significant 'first night' effect.27 More recently, as sleep laboratories have become more 'homelike', first night effects have become less,28–30 though they are still appreciable. This report documents a lack of first night effect with home recordings.

Comparison of our results with a recent report from Pittsburgh21 shows that our children, at comparable ages, slept roughly one hour longer and spent much less time in stage I sleep (42-7 minutes ∨ 2-6 minutes) and more time in stage IV and rapid eye movement sleep. Taken that there are methodological differences, rapid eye movement latencies were remarkably similar. The comparison suggests that there is a major difference between home and laboratory recordings with, as expected, the third night laboratory recordings being more like our home recordings than the first laboratory night. It seems sensible to focus on home recordings of sleep in most circumstances and to include the data on sleep from the first night at home in any analysis.

Children with severe psychosocial dwarfism (type 2) have abnormalities of rapid eye movement sleep that are especially striking. The amount of active rapid eye movement sleep (sleep with more than two distinctive eye movements per 16 seconds) and the proportion this makes of rapid eye movement sleep within each sleep cycle as well as over the whole night was increased. This pattern is similar to the sleep of adults with endogenous depression and is one feature that clearly distinguished the children with severe psychosocial dwarfism type 2 from the other groups studied.

Children with constitutional delay of growth and development showed an abnormal slowing of rapid eye movement sleep cycling. As other studies have
suggested a link between rapid eye movement sleep cycling and frequency of secretion of gonadotrophin. This is consistent with the current understanding of the mechanism of control of onset of puberty, which requires the pulsatile release of gonadotrophins from the pituitary determined by pulsatile secretion of gonadotrophin releasing hormone from the hypothalamus.

Children with genetic short stature had more rapid eye movement sleep and had a trend towards less stage IV sleep. These findings are probably secondary to their psychosocial environment.

The function of rapid eye movement sleep may be to remove undesirable modes of interaction in networks of cells in the cerebral cortex by a reverse learning mechanism. Thus acute and chronic stress might be expected to increase the amount of rapid eye movement sleep and in the three groups with increased rapid eye movement sleep chronic stress was indeed present.

The frequency of eye movements during rapid eye movement sleep seems to be a separate variable from the total amount of rapid eye movement sleep during the night. It may be that this measure will identify a predisposition to react to deprivation with decreased secretion of growth hormone and growth failure in childhood and endogenous depression in adult life.

The most robust sleep variable associated with endogenous depression has been a shortened rapid eye movement sleep latency. Within our groups there was no significant difference between rapid eye movement sleep latencies, although the severe psychosocial depression group did have the lowest values.

In conclusion, the analysis of sleep recordings of normal children and those with different growth disorders has shown significant abnormalities of sleep, especially in children with severe psychosocial dwarfism.

The cooperation of the children and parents and the financial support of The Middlesex Hospital Special Trustees is gratefully acknowledged. Oxford Medical Systems kindly lent a Page Mode Display unit for the analysis of the sleep records.

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