Sleep and Wakefulness After Treatment for Craniopharyngioma in Childhood; Influence on the Quality and Maturation of Sleep

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Abstract

Craniopharyngiomas are situated in immediate vicinity of sleep regulating structures in the basal forebrain area, and the tumor and its treatment might influence the regulation of sleep and wakefulness. In 10 patients treated for craniopharyngioma nighttime sleep quality and daytime vigilance were examined with polygraphic sleep records and multiple sleep latency tests (MSLT). Two girls and 8 boys, 7.1–22.9 years of age, were studied after a follow-up time of 1.5–16.1 years postoperatively. The results were compared to those of 18 normal children.

The regulation of the ultradian sleep rhythm was normal but the ability to maintain nighttime sleep was severely disturbed. The patients had an increased number of awakenings and spent long time awake during two recorded nights. Two patients had excessive daytime somnolence during this examination, one after severe sleep disturbance, the other without any known cause. The pattern of sleep and vigilance did not change in puberty in the expected fashion.

The disturbances may well have an impact on the psychosocial situation of the patients.

Key words

Craniopharyngioma – Sleep – Wakefulness – School children – Adolescents

Introduction

The craniopharyngioma develops from remnants of the embryonal hypophyseal-pharyngeal duct, located in the vicinity of the hypothalamus, the pituitary stalk and the optic chiasm. It has been known for long time that this area is important for the regulation of sleep and diurnal rhythms (17), and sleep disturbances secondary to tumors close to the hypothalamus and the 3rd ventricle have been repeatedly described (1, 10, 12, 27, 32). The suprachiasmatic nuclei (SNC), situated bilaterally just above the optic chiasm, act as endogenous regulators of the biological rhythm, receiving different signals directly from the optic tract (16, 24). The closely situated mediobasal forebrain area contains neuronal systems that influence sleep, as part of a network including the thalamus, the brainstem and caudal parts of the hypothalamus (30). Experimental lesions in the preoptic area are reported to cause insomnia in cats (26).

Children treated for craniopharyngioma have been found to have perceptual dysfunction and psychological disturbances, and the development of personal independence and social relations has been poor (7, 8, 13, 29). Our experience confirms this impression and also points to the development of a strongly negative self-image (19). The poor psycho-social development may depend on cognitive defects, on visual disturbances, on the endocrine deficiency and on the psychological effect of having an intra-cranial, potentially life-threatening process. However, a disturbance of sleep and wakefulness may also worsen the situation for these patients.

To our knowledge no study of the influence of this kind of tumor and its treatment on sleep and wakefulness has been performed, in spite of its clinical and theoretical interest.

Case reports

Ten patients, 2 girls and 8 boys, treated for craniopharyngioma were examined. Their clinical data are presented in Table 1. The mean age at operation was 8.2 years (range 3.1–14.8). The present study was performed after a follow-up of 1.5–16.1 years. At the time for this study the patients incidentally fell into two age-groups, 7.1 to 12.0 (patients no. 1–5) and 18.4 to 22.9 (patients no. 6–10) years of age. All patients were operated upon by a right-sided subfrontal approach. In Case 2 combined subfrontal and transventricular approach was used. Three patients have had local recurrences, and another recurrence has been detected in Case 1 after this study was completed. Cases 3 and 6 had primary postoperative radiotherapy because of subtotal resection, in Case 4 irradiation was given after a recurrence and in Case 2 stereotactic deposition of 90Yttrium and stereotactic gamma radiation of a cystic local recurrence was performed.

Case 4 post-operatively developed a right-sided fronto-temporal epileptiform EEG-abnormality and seizures
that responded well to carbamazepine. In Case 1, in which a patient had no history of seizures, but later she has developed local recurrence has later been found, a right-sided epileptic focus was incidentally found during this study. This patient was not on any other medication except anti-epileptic and endocrine substitution therapy, no hormone levels were measured in 8 patients, low values were found in all of these. Somatotropine substitution has been given to one younger patient received somatotropine during this study. The other patients were normal. All patients had visual disturbances, mostly affecting the visual fields, but nobody was blind. The poorest vision was found in Cases 5 and 7, both blind on one eye and with a visual field defect and visual acuity 0.1–0.4 on the other. Sexual maturity was rated according to Tanner (31) and in the boys testicular volume was measured according to Prader (22). All patients in the younger group were sexually infantile. The elder patients, all male, had pharmacologically induced puberty with fully mature secondary sexual characteristics but with infantile testicles.

A group of 18 healthy volunteers with mean age 10.7 (range 8.8–12.6) years, examined with the same technique and separately published (20) served as controls. All the children were sexually infantile, Tanner stage 1–2. One boy had a testicular volume of 8 ml as only sign of beginning puberty. There was no history of disease in any of the controls. Thorough physical and neurological examination of each child gave normal results.

### Methods

The recording technique has been reported elsewhere (20). In brief, sleep was recorded with 9-channel portable tape cassette recorders (Medilog 9000, Oxford Medical Systems, Abingdon, England) during 2 consecutive nights in the neuro-pediatric ward. Sleep staging was performed screen by screen directly from the Oxford Display Unit, according to the criteria of Rechtschaffen and Kales (23), by the same examiner (LP) as in the controls. The sleep variables evaluated are presented in Table 2. The cyclic alternations between sleep stages and the amount of rapid eye movements sleep (REM), slow wave sleep (SWS) and wakefulness occurring in each sleep cycle were analyzed.

### Table 1: Clinical data including findings at diagnosis and type of hormonal substitution.

<table>
<thead>
<tr>
<th>Pat. nr</th>
<th>sex</th>
<th>Age at invest.</th>
<th>ICP high</th>
<th>growth retard.</th>
<th>visual symptoms</th>
<th>Tumor site</th>
<th>resection</th>
<th>radiation</th>
<th>At investigation</th>
<th>Sexual maturity</th>
<th>Hormonal substitution</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>3.1</td>
<td>7.1</td>
<td>Yes</td>
<td>None</td>
<td>Papilloedema</td>
<td>Suprasellar, chiasma-3rd ventr.</td>
<td>Total</td>
<td>None</td>
<td>Infantile</td>
<td>L + D</td>
<td>Recurrence after the study</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>6.6</td>
<td>10.1</td>
<td>Yes</td>
<td>0.5–1 yrs</td>
<td>Papilloedema</td>
<td>Suprasellar- 3rd ventr.</td>
<td>Total</td>
<td>40 Gy</td>
<td>Infantile</td>
<td>L + D + C</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>9.0</td>
<td>10.5</td>
<td>No</td>
<td>2 yrs</td>
<td>Papilloedema</td>
<td>Infra + suprasellar, chiasma-3rd ventr</td>
<td>Subtot.</td>
<td>50 Gy</td>
<td>Infantile</td>
<td>L + D + C</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>8.7</td>
<td>11.9</td>
<td>Yes</td>
<td>None</td>
<td>Bilat. hemianopopy, papilloedema</td>
<td>Infra + suprasellar, chiasma-left of 3rd ventricle</td>
<td>Total</td>
<td>52 Gy</td>
<td>Infantile</td>
<td>L + D + C</td>
<td>Local recurrence: subtotal resection + radiation</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>3.3</td>
<td>12</td>
<td>No</td>
<td>None</td>
<td>Reduced vision, central</td>
<td>Suprasellar, lifts chiasma and optic nerves</td>
<td>Total</td>
<td>None</td>
<td>Infantile</td>
<td>L + D + C + S</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>11.6</td>
<td>18.4</td>
<td>Yes</td>
<td>3–4 yrs</td>
<td>Leftsided hemianopopy</td>
<td>Suprasellar, fills 3rd ventricle</td>
<td>Subtot.</td>
<td>50 Gy</td>
<td>Induced puberty</td>
<td>L + D + C + T</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>8.8</td>
<td>19.1</td>
<td>Yes</td>
<td>None</td>
<td>Reduced vision, limited visual fields</td>
<td>Infra + suprasellar, chiasma – carotid arteries</td>
<td>Total</td>
<td>None</td>
<td>Induced puberty</td>
<td>L + D + T</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>14.8</td>
<td>20.0</td>
<td>No</td>
<td>2 yrs</td>
<td>Rightsided hemianopopy, optical atrophy</td>
<td>Infra + suprasellar, right lateral extension</td>
<td>Total</td>
<td>None</td>
<td>Induced puberty</td>
<td>L + D + C + T</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>4.9</td>
<td>21.0</td>
<td>Yes</td>
<td>2–3 yrs</td>
<td>None</td>
<td>Infra + suprasellar, chiasma + optic nerves</td>
<td>Subtot.</td>
<td>None</td>
<td>Induced puberty</td>
<td>L + D + C + T</td>
<td>Recurrence after 10 months totally resected</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>11.5</td>
<td>22.9</td>
<td>No</td>
<td>None</td>
<td>Reduced vision, central</td>
<td>Infra + suprasellar, chiasma - 3rd</td>
<td>Total</td>
<td>None</td>
<td>Induced puberty</td>
<td>L + D + C + T</td>
<td></td>
</tr>
</tbody>
</table>

ICP = intracranial pressure, L = l-thyroxine, D = desmopressine, C = cortisoneacetate, T = testosterone, S = somatotropine, growth retard = the time with recorded growth retardation before diagnosis.

Clinical data including findings at diagnosis and type of hormonal substitution. ICP = intracranial pressure, L = l-thyroxine, D = desmopressine, C = cortisoneacetate, T = testosterone, S = somatotropine, growth retard = the time with recorded growth retardation before diagnosis.

A standardized neurologic examination was performed in all patients by the same examiner (LP) and recorded on video-tape. The tapes were evaluated jointly by two pediatric neurologists (LP and VN). Cases 1, 3 and 4 had clearly distinguishable abnormalities of coordination and gross movement pattern. Cases 2 and 5 had minor neurological abnormalities. The other patients were normal. All patients had visual disturbances, mostly affecting the visual fields, but nobody was blind. The poorest vision was found in Cases 5 and 7, both blind on one eye and with a visual field defect and visual acuity 0.1–0.4 on the other. Sexual maturity was rated according to Tanner (31) and...
In order to control for the amount of sleep disturbing events occurring in the ward used for recordings, records obtained with the same recording equipment in the same ward during 7 nights from three other children were checked respectively. Long-time EEGs were recorded in these children because of epilepsy; one of them had no antiepileptic treatment, the other two had their treatment reduced before recording. They had no clinical or electrographic seizures during the recording period previous to or during the nights checked. The sleep of these children was quite undisturbed.

Daytime multiple sleep latency test (MSLT, 5) was performed in the laboratory the day after the second night recording. The patients were given 30 minutes to go to sleep on 4 occasions and the sleep onset latency was recorded. Patients falling asleep were awakened after 10 mins. The records were controlled for REM sleep and epileptiform activity.

In Table 3, the sleep data are presented separately for the patients older and younger than 13 years, and separately also for the first and second night. There was no significant difference between the sleep results of the first and second night and there was no difference between the sleep results of the two groups.

As seen in Figure 1, the craniopharyngioma patients had shorter total sleep periods and shorter actual sleep time than the controls. The patients had less REM sleep in absolute as well as in relative amount during the first night than the controls. Time spent in SWS was somewhat shorter than in the controls, but this difference did not reach statistical significance. Figure 2 shows that the patients woke up more often than the controls, and spent more time awake which means that the sleep efficiency was lower. Only 2 of the 10 patients, the Cases 5 and 8, spent less than 30 mins awake during both nights.

The first sleep cycles were longer in the patients than in the controls (Fig. 3). In logical consequence the patients also completed fewer sleep cycles. Four cycles were completed...
in 88% of the craniopharyngioma nights (97% of the controls); 5 cycles in 53% (75%) and 6 cycles in only 12% (40%). However, the distribution of the different sleep stages over the night was the same as in the controls, i.e. there was a long period of deep SWS in the beginning of the night and the amount of REM sleep increased towards the end of the night. The first REM period was short or skipped as described by Roffwarg et al (25) as often as in the controls, and also abortive REM sleep (20) occurred to the same extent.

**MSLT**

Analyzable records were obtained from all patients. Data from the younger and elder patients were treated separately. The results are presented in Figure 4. In the patients under 13 years of age the sleep latencies were significantly shorter at 14:00 hr in the afternoon. The results of the investigations at 10:00, 12:00 and 16:00 hr did not differ from those of the controls. Two of the younger patients (Cases 2 and 5) had sleep latencies < 10 mins on two occasions and also daily mean sleep latencies < 20 mins, values not found among the controls. Case 2 had an extremely disturbed sleep during the preceding nights, with a sleep efficiency of 82 and 69% respectively. Case 5 on the contrary had slept soundly with a sleep efficiency of 99 and 96% respectively.

The elder patients had shorter daily mean sleep latencies than the younger controls. The sleep latencies at 10:00, 14:00 and 16:00 hr were shorter than corresponding tests in the controls (Fig. 4).

**Discussion**

The basic pattern of sleep regulation remained normal in our patients – except for longer initial sleep cycles –
in spite of the fact that sleep regulating structures are situated in the vicinity of the craniopharyngioma.

Still the patients had poorer sleep quality at night than the healthy controls. They woke up often and most patients spent more than half an hour awake during the night. Such a sleep disturbance is severe enough to influence the general well-being. According to the present classification of sleep disorders (Association of Sleep Disorders' Centers 1979) these patients as a group could be considered to suffer from a Disorder of Maintaining Sleep. This sleep disturbance could have direct cerebral causes. It is noteworthy that experimental lesions in the preoptic area of the cat cause severe insomnia with diminished deep slow wave sleep and REM sleep (26). Also, psychological factors secondary to the disease and its sequelae may be of importance. No one of our patients was blind, and the visual defects present can hardly have had enough impact on the circadian rhythm to cause nighttime wakenings (11, 18, 21).

It is remarkable that there was so little difference between the sleep data in the younger and the elder group of patients. A change of the sleep pattern is to be expected during the years around puberty. Among other things, the total sleep time and the amount of REM sleep normally decrease (9, 15, 33). The question arises whether the tumor and its treatment could have caused the absence of this expected normal development, for instance as a secondary effect of the hypopituitarism, not amended by the endocrine substitution. The role of growth hormone after completed growth is not known; the hormone influences the metabolism and the body composition as well as the immune system (14). Åström and Jochumsen (3) found altered sleep patterns in young adults with isolated growth hormone deficiency.

**MSLT**

The MSLT results in the younger and elder patients have to be considered separately, as an increase in day-
time sleepiness is to be expected in puberty (4). Two patients out of the five younger ones, were sleep-prone enough to be suspected of hypersonomolence (20). In one of these, sleepiness was a result of poor night-time sleep, in the other it seemed to be a primary condition. Otherwise the younger patients did not differ remarkable from the controls.

As expected after puberty, the patients of the elder group were more sleep-prone during daytime than the prepubertal controls. The values didn't reach in any patient of this group the level of pathology (< 5 mins) defined for adults (6). On the contrary, as seen in Figure 5, they had longer sleep latencies, i.e., were less sleep-prone than the young adults studied by Seidel (28), a somewhat astonishing result. Could the hypopituitarism possibly influence also the development of daytime wakefulness? The group, however, was too small for definitive conclusions.

In this study it was not possible to delineate any difference between the results regarding sleep and wakefulness in the patients who had the larger tumors or complicated disease with recurrences, and the other patients. The operative trauma to the right frontal lobe cannot be disregarded, as two of our ten patients had partial epilepsy originating from this area.

In summary, in these 10 patients treated for craniopharyngioma, the regulation of the ultradian sleep rhythm was normal. The ability to maintain nighttime sleep was so much disturbed, that the well-being of the patients ought to be influenced. Two patients had daytime insomnia, one after severe sleep disturbance, the other without any known cause. The pattern of sleep and vigilance did not change in puberty in the expected fashion, which could be an effect of the secondary hypopituitarism not amended by the endocrine substitution.

Acknowledgment

This study was supported by the Swedish Medical Research Council (grant no. B90-14X-00084-26), by Roche-Produkter AB and by the Folke Bernadotte Foundation.

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