Site and type of craniopharyngiomas impact differently on 24-hour circadian rhythms and surgical outcome. A neurophysiological evaluation

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A B S T R A C T

This study aimed to quantify 24 h body core temperature (BcT°) and sleep-wake cycle rhythm alterations in craniopharyngioma (CP) patients and to identify markers related to the postsurgical outcomes. Ten consecutive CP patients underwent neuroradiological, endocrinological and ophthalmological evaluations, 24 h BcT° and sleep-wake cycle recordings before and after endoscopic endonasal surgery. The sample included four women and six men. Nocturnal sleep efficiency was pathologically reduced in eight patients before surgery. Seven out of ten patients presented one to three daytime naps. 24 h BcT° rhythm was pathological in six out of ten cases. Post-surgery sleep efficiency normalized in four out of eight patients, whereas nine out of ten patients presented with two to six longer daytime naps. Diurnal naps were mainly present in patients showing pre-operative involvement of the third ventricle floor. 24 h BcT° remained pathological in only one out of six cases, returned to normal in two and improved in three. 24 h BcT° rhythm improved more in papillary CPs than in adamantomatous CPs. Our data confirmed that both CP and surgery frequently disrupt the sleep-wake cycle and BcT° rhythms. Tumour location and histotype may be related to a worse postsurgical outcome. Therefore, in-depth investigation including circadian monitoring is crucial for surgical outcome.

1. Introduction

The hypothalamus plays a key role in the control of body core temperature (BcT°) and sleep-wake circadian rhythms (Saper et al., 2005). Different types of lesion can involve the hypothalamus, including tumours which are the commonest cause of widespread hypothalamic damage. Large pituitary adenomas compressing the hypothalamic region, and craniopharyngiomas (CPs) are the most common subtypes, accounting for 2–5% of CNS tumours (Müller, 2014a; Müller, 2014b). CPs arise from cell rests of the Rathke pouch and show two peaks, one between five and 14 years and the other between 65 and 74 years. CPs are confined to the suprasellar region in 21% of cases, whereas the remainder invade the intrasellar space (Müller, 2014a, b; Karavitaki et al., 2005). CPs in infants are more likely to be histologically adamantomatous (ACP), whereas adult CPs can be either papillary (PCP) or ACP (Cohen, 2015).

Alterations of BcT° and sleep wake cycle rhythms are very common in CP patients with a prevalence ranging from 35 to 80% in different case series (Cohen et al., 2015; Poretti et al., 2014). Although these changes may have a severe impact on quality of life after surgery, they have not been objectively documented in the literature and are seldom addressed in routine clinical management.

Sleep fragmentation, early morning awakening and excessive daytime drowsiness are the most common long-term sequelae of CPs from comprehensive evaluations of objective quality of life (Castro-Dufourny et al., 2015; Snow et al., 2002; Lipton et al., 2009; Pickering et al., 2014). These disturbances have been related to a reduced melatonin secretion along with a phase shift causing low midnight melatonin concentrations. Moreover, optic chiasm compression seemed to cause a dissociation between sleep latency and pre-bedtime distal to proximal skin temperature gradients in 17 patients with a suprasellar tumour (Joustra et al., 2014).

Tumour location and the degree of hypothalamic involvement (assessed by MRI and clinical symptoms at onset) can predict the postsurgical outcome of CP patients in terms of weight gain, endocrinological alterations and diurnal drowsiness (Cohen, 2015; Cohen...
et al., 2015; Poretti et al., 2014). These sequelae (specifically the postsurgical development of diabetes insipidus - DI) have been observed in patients with involvement of the tubero-mammillary complex (Castro-Dufourny et al., 2015).

Surgery-induced hypothalamic injury has been classified into three groups, according to Poulsgaard: 1) minimal injury – if there is a limited adhesion between the tumour and the hypothalamus, 2) moderate injury – if the adhesion is more extensive but some dissections could be performed without structural impairment, 3) severe injury – in cases with strong adhesions not allowing hypothalamic structural sparing (Pickering et al., 2014).

Polysomnography and actigraphic monitoring performed in children after classic CP surgery showed lower sleep efficiency and reduced REM sleep (Palm et al., 1992). In addition, the development of postsurgical narcolepsy was documented in a single case, confirmed by reduced cerebrospinal fluid hypocretin (Hcrt) levels (Tachibana et al., 2005). Otherwise, the endoscopic endonasal approach seems to preserve sleep structure and circadian rhythms (Pascual et al., 2015; Zoli et al., 2016; Baldauf et al., 2015).

The dual aim of our study was to quantify objective BcT° and sleep-wake rhythm alterations in CP patients before and after endoscopic endonasal surgery, and to identify markers allowing a better presurgical identification of cases in which tumoural excision could impact on the regulation of hypothalamic circadian rhythms.

2. Material and methods

2.1. Characteristics of the population

We enrolled 12 consecutive patients with neuroradiological evidence of hypothalamic tumour at suprasellar MRI, who underwent endoscopic endonasal surgery at our Institution from 2014 to 2016. Exclusion criteria consisted in former surgery or radiotherapy and age <18 years old. Two patients were excluded because histological analysis classified the tumours as a null cell adenoma and a pylc cytoma.

2.2. Clinical and neurophysiological evaluations

Patients underwent MRI and a complete neurological, endocrinological (including prolactin, cortisol, TSH, ACTH, FT4, GH, LH, FSH and serum electrolytes) and ophthalmological work-up before surgery and at one, three and 12 months after surgery.

Patients were considered to have normal weight if BMI ranged between 18.5 and 22.9, overweight if BMI ranged between 23 and 29.9 and obese if BMI was >30.

24 h urine samples were analysed for osmolarity, sodium, potassium and urinary catecholamine metabolites.

The hypothalamic involvement was classified in anterior and/or posterior considering the extension of the tumour in relationship to the mamilary bodies (Pascual et al., 2015).

Before and after surgery, all patients underwent a 24 h sleep-wake cycle recording, including electroencephalogram (F3-A1, C3-A2, O1-A1, Cz-A1), right and left electro-oculogram (EOG), electrocardiogram (ECG) and electromyogram (EMG) of mylohyoideus and left and right tibialis muscles. In addition, all patients underwent nocturnal cardiorespiratory monitoring before surgery to detect snoring or obstructive sleep apnoeas.

BcT° rhythm was synchronously evaluated by continuous monitoring of rectal temperature every 2 min for 24 h by means of a Mini-logger tm portable device (Mojon et al., 2015).

24 h circadian rhythms were monitored after biochemical demonstration of the efficacy of hormone replacement therapy, to avoid any confounding results due to hypopituitarism. Sleep stages were scored for 30s epochs according to the American Academy of Sleep Medicine criteria (Iber et al., 2007). Sleep efficiency (SE - rate between the total sleep time and the total sleep period) was calculated and defined as pathological if it was below 85%. The number and duration of diurnal naps were also calculated considering their distribution throughout the daytime period and the phase of sleep onset.

A BcT° rhythm within a 24 h period (p < 0.05) was determined in association with the following parameters with their 95% confidence limits: 1) Midline Estimating Statistic of Rhythm (mesor): rhythm adjusted 24 h average; 2) amplitude: the difference between the maximum value measured at the acrophase and the mesor in the cosine curve; 3) acrophase: lag between reference time (12 pm) and time of the highest cosine function used to approximate the rhythm. BcT° rhythm was defined as pathologic (Path) if one of the three parameters (mesor, amplitude or acrophase) was clearly impaired with respect to control values obtained in our laboratory in ten normal controls (NC) matched for age and sex.

2.3. Statistics

Data were analysed using a pure descriptive statistical method.

2.4. Compliance to ethical standards

The study was approved by the local ethical committee (CD:14124, PI: Mazzatenta D).

3. Results

The sample comprised four women and six men (mean age at symptom onset 48 years). CP was purely endoventricular in six cases and primarily suprasellar with third ventricle involvement (or tuberoinfundibular) in four. The tumour involved the anterior hypothalamus in all cases, also extending to the posterior hypothalamus in five patients. Complete tumour excision was achieved in eight cases. At histological analysis five patients presented an ACP and five a PCP. Subpial infiltration of the hypothalamus was observed in five cases.

3.1. Presurgical evaluation

3.1.1. Clinical features

Headache was the commonest initial symptom (7 patients out of 10). Visual disturbances were observed in eight patients (Table 1). Mean pre-operative BMI was 23.5 (SD: 3.3). Only one patient complained of hyperphagia. Weight gain was reported by four patients with a mean value of + 2.5 points. Patients with third ventricle floor invasion showed a higher mean BMI before surgery (24.8 ± 2.2 vs 22.7 ± 3). Anterior pituitary function was partially compromised in five out of ten cases since one patient had hypothyroidism and four had hypogonadism. The most common endocrinological symptoms were oligo-amenorrhoea in women, erectile dysfunction and decreased libido in men. No cases of pre-operative DI were observed (Table 1).

3.1.2. Sleep-wake cycle

24 h SE was markedly reduced in eight out of ten patients (mean 69.6%; SD: 22; normal value - NV > 85%). Light (stage 1–2) and deep (stage 3) NREM sleep stages were normally represented (mean 57.8 ± 12.8% and 27.6 ± 9.4% respectively; NV 47–60% and 15–25%). REM sleep was reduced (14.6 ± 6.9%; NV 20–25%). REM latency was normal in five patients, increased in four and markedly reduced in one (7 min; NV 60–120 min). Seven patients showed one to three diurnal NREM naps lasting a mean of 35 ± 14 min, more frequently in the afternoon (Table 2). No differences were observed between intraventricular and tubero-infundibular CPs in terms of daytime naps. Only two patients showed a pathological number of periodic limb movements of sleep per hour of sleep (PLMS index > 10). Two patients had ≥ five sleep-related obstructive apnoeas per hour.
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