SUPPLEMENTARY FILE

Alterations in diurnal rhythmicity in patients treated for nonfunctioning pituitary macroadenoma; a controlled study and literature review


Methods; definition of pituitary insufficiency and adequate hormone replacement therapy
ACTH deficiency was defined as an insufficient increase in cortisol levels (<0.55 μmol/liter) after a CRH stimulation test or insulin tolerance test. TSH deficiency was defined as free T4 levels below the reference range (<10 pmol/L). Hypogonadism was defined as low testosterone levels (<8.0 nmol/liter) in men, and absence of menstrual cycle for more than one year in the presence of low estrogen levels in premenopausal women. GH deficiency was defined as a GH peak response to the insulin tolerance test (ITT) below 3µg/liter (glucose nadir <2.2 mmol/liter) or GHRH/arginine test [with body mass index – adjusted GH cutoffs] in case of contraindications for ITT, according to guidelines (1). Hypopituitarism was supplemented by hydrocortisone, levothyroxine, recombinant human GH (rhGH, unless contraindicated or not preferred), testosterone in men, and estrogen in combination with prostagens in premenopausal women. Dosages were monitored and adjusted as required, and stable substitution was assumed if medication was not adjusted for 6 months, complaints were absent, and basal hormone levels were normal.

Methods; sleep characteristics, sleep-wake rhythmicity, and questionnaires in craniopharyngioma patients
Sleep characteristics were assessed with polysomnography (Titanium Embla; Embla, Broomfield, CO), and recorded and scored by experienced technicians according to the American Academy of Sleep Medicine guidelines for the scoring of sleep, using the Somnologica software (Version 5.1.1, Embla, CO, USA).
Rest/activity cycles were measured for seven days using an wrist-worn actigraph (Actiwatch, CamNtech Ltd., Cambridge, UK), and analyzed using the Actiwatch Activity & Sleep Analysis version 7.31 software (CamNtech Ltd., Cambridge, UK). Near-zero activity periods (NAPs) were defined as periods with less than 10 “activity counts” (i.e. the device recorded ~0.4 g of acceleration) per minute for at least 5 min. The intradaily variability (IV; fragmentation of the rhythm), and interdaily stability (IS; resemblance of rhythm between days), were calculated as previously described (2). Patients kept a sleep diary during actigraphic measurements.
In addition, the following questionnaires were used: Short Form-36 (quality of life), Multiple Fatigue Index (general fatigue), Berlin Questionnaire (sleep disturbances), Pittsburgh Sleep Quality Index (sleep quality), and the Epworth Sleepiness Scale (daytime sleepiness).

**Results; clinical characteristics of craniopharyngioma patients**

All eight craniopharyngioma patients (aged 31-62 yr, 1 female) were treated by transsphenoidal surgery for suprasellar extension. Seven patients presented with VFD that improved after surgery, and 4 patients received adjuvant radiotherapy. At the present evaluation, seven had ACTH deficiency, eight GH deficient, seven TSH deficiency, seven LH/FSH deficiency, and five patients were ADH deficient. All patients received adequate stable hormone replacement for pituitary deficiencies, except for GH deficiency, which was untreated in one for patient’s preference. Comorbidity was present in four craniopharyngioma patients: two had hypertension (angiotensin II receptor antagonist + selective β1 receptor blocker, or ACE inhibitor); one had a history of angina pectoris, transient ischemic attacks, and ocular melanoma; and one self-reported complaints of mild sleep apnea.

**Results; polysomnography and actigraphy in craniopharyngioma patients**

Polysomnographic sleep characteristics were assessed in all eight craniopharyngioma patients. Compared to controls, craniopharyngioma patients showed a decreased percentage of REM sleep ($P=0.001$) (Table 1), and a tendency towards less total sleep time ($P=0.053$), lower sleep efficiency ($P=0.065$), and a higher percentage awake time ($P=0.075$). The results therefore tend to resemble those that were found in NFMA patients (2). No increased prevalence of sleep apnea or periodic limb movement disorder was observed. The actigraphic measurements of seven craniopharyngioma patients (measurement error in one) showed no significant differences with controls. A careful trend however towards increased NAPs (8.1±5.3 vs. 5.2±2.9, $P=0.131$) and intradaily variability (0.38±0.07 vs. 0.34±0.07, $P=0.375$) was observed, but not nearly as profound as in our NFMA cohort (2).

Craniopharyngioma patients reported decreased quality of life in the Short Form-36 (physical problems, $P=0.004$; social function, $P=0.017$; health perception, $P=0.034$) and the Multiple Fatigue Index (general fatigue, $P=0.008$; physical fatigue, $P=0.001$; activity reduction, $P=0.015$; motivational reduction, $P=0.007$), when compared to the controls. Also, subjective sleep quality was impaired in the Berlin Questionnaire (total score, $P=0.004$), the Clinical Symptom Score for sleep disorders ($P=0.001$) and Epworth Sleepiness Scale (total score, $P=0.002$)(2). The results are similar to the previously reported NFMA data (2).
Figure 1. Full study schedule, as reported on in this manuscript and (2).

REFERENCES
