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CEREBROSPINAL FLUID LEVELS OF PITUITARY HORMONES AND SLEEP APNEA IN PATIENTS WITH PITUITARY ADENOMAS

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The cerebrospinal fluid (CSF) has anatomical continuity with the brain extracellular space, so its composition is likely to influence various brain functions. In patients with secreting and non-secreting pituitary adenomas (PA), high CSF concentrations of anterior pituitary hormones have been reported. To investigate the possible influence of CSF pituitary hormones on sleep architecture and sleep-disordered breathing in a cohort of patients with pituitary adenoma. We investigated 37 patients with PA followed in a tertiary endocrinology centre, in which surgery was indicated. In each subject a complete polysomnography (PSG) was performed. GH, PRL, FSH and LH were assessed by fluoroimmunoassay in simultaneously collected serum and CSF samples. A group of 78 individuals without any endocrine disease, previously investigated for the CSF hormonal values was the control. We analysed 23 acromegaly cases, 9 non-functioning PA, 5 resistant prolactinoma. In patients, the CSF hormonal values were significantly higher compared to controls. Patients with increased CSF-GH have significantly higher central apnea index (CAI) and total duration of central apnea (TCA). Patients with increased CSF-FSH had more severe obstructive apnea index (OAI), time spent in obstructive apnea (TOA) and rapid-eye-movement (REM) sleep apnea (RAI). In a linear regression model, serum GH independently predicted the CAI and TCA. CSF-FSH is an independent predictor of TOA, OAI. The RAI is independently predicted by serum GH and CSF-FSH. The relatively high CSF concentrations of pituitary hormones, found in many patients with pituitary adenoma are likely to influence the sleep respiratory events.

Key words: sleep apnea, pituitary, adenoma, cerebrospinal fluid, hormones.

INTRODUCTION

The analysis of the cerebrospinal fluid (CSF) is widely used in the diagnosis of numerous conditions affecting the central nervous system because of its direct communication (mediated by the ventricular ependymal cells and pia mater) with the interneuronal extracellular fluid. Anterior pituitary hormones are normally present in the CSF in very small amounts, due to the low permeability of the blood-brain barrier[1,2]. In patients with pituitary adenomas (PA), both secreting and non-secreting, significantly higher CSF values for the anterior pituitary hormones have been reported[3-5]. Only for prolactin, the CSF concentrations appear correlated to the serum level, possibly suggesting a direct transport from blood, while for the other hormones no such correlation was found[6-9].

Both the mechanism of the increased CSF hormonal concentrations in PA patients and their possible biological effects (if any), remain elusive. Possible effects on the sleep-wake cycle have been suggested for numerous neuropeptides present in the CSF. As early as 1909 Ishimori reported that the intraventricular injection of CSF from sleep-deprived animals induces a profound sleep in recipient animals[10]. Similar experiments and results were replicated and published in 1969[11]. Later research described numerous CSF factors influencing sleep – most widely studied being hypocretins/orexins (very low or undetectable CSF lvels in patients with narcolepsia)[12-13].

Sleep-disordered breathing (obstructive, central or mixed-type apnea and hypopnea) is more

prevalent in patients with GH-secreting PA (acromegaly)[14] but disordered sleep patterns have also been described in non-functioning PA (NFPA).

The aim of the study was to assess the possible influence of CSF pituitary hormones on sleep architecture and sleep-disordered breathing in a cohort of patients with pituitary adenoma.

PATIENTS AND METHODS

We investigated by polisomnography (PSG) 37 patients with PA followed in a tertiary centre of endocrinology. 23 were diagnosed with acromegaly (ACM), 9 had NFPA and 5 resistant prolactinomas (PRM). At the time of the study 21 patients had not yet received specific antitumoral therapy, 14 had transsfenoidal surgery and 2 complex treatment (surgery and radiotherapy). Re-do surgery was considered indicated in all cases. Polisomnography was performed in all cases before surgery. At the time of the neurosurgery a small (3 ml) sample of CSF was collected, refrigerated at –20 degrees C and stored until hormonal analysis was performed. All patients gave their informed consent.

Polisomnography (PSG). Each subject performed a complete PSG for diagnostic purposes, before the neurosurgical intervention. None of the subjects had stressful life events during the last two weeks, transmeridian flights and did not perform shift work. Administration of any drug affecting sleep or respiratory control was stopped. Full overnight PSG was performed using a computerized system (SleepScan II, Biologic System Corporation). Overnight polygraphical sleep recordings included 4-channel electro-encephalogram (EEG), 2-channel electro-oculogram, electromyogram and electrocardiogram. The adequacy of respiration was monitored by a finger probe oximeter. Oro-nasal airflow was monitored by a 2-channel (oral and nasal) thermocouple. Thoraco-abdominal movements were recorded using respiratory effort bands. Sleep efficiency was defined as percentage sleep during the sleep period time. Sleep was manually staged according to the revised Rechtschaffen- Kales criteria [15] and sleep stages were expressed as percentage of total sleep time. A central apnea episode was defined as an absence of oronasal airflow during sleep for >10 s associated with absent respiratory effort. Obstructive apnea was defined as cessation of oronasal airflow for >10 s in the presence of out-of-phase thoraco-abdominal effort. A hypopnea was defined as a more than 50% fall in oronasal airflow for >10 s with out-of-phase thoracoabdominal movement associated with a 4% fall in SpO_2 or an arousal. A mixed apnea was defined using the above criteria, when a central apnea included or terminated with obstructive components.

Hormonal tests. We assessed the levels of GH, PRL, FSH and LH in simultaneously collected serum and CSF samples using fluoroimmunoassay. We compared the hormonal data obtained in the patients group with a control group of 78 individuals without any endocrine disease, previously investigated for the CSF hormonal values. [1]

Statistical analysis. All data were analyzed using SPSS, version 17.0. To assess the differences between patients and controls as well as between subgroups of patients, the Mann-Whitney U test was used. Spearman correlation test and multiple regression were also used to better define the relationships between the measured parameters.

RESULTS

We included in the analysis 37 cases of pituitary adenoma patients (23 ACM, 9 NFPA, 5 PRM resistant to treatment with dopamine agonists. All patients were adults (median age 46.08 yrs, range 20–69).

The CSF levels of pituitary hormones in the control group were used as a reference for the patients group (See [1]). In patients, the CSF values for all evaluated hormones were significantly higher compared to controls (Table 1).

The nocturnal sleep studies in patients revealed similar parameters in the patients group, irrespective of the type of pituitary adenoma- data not presented graphically. Classic sleep apnea syndrome (SAS) was diagnosed in 8 cases (7 ACM, 1 case with NFPA). 4 were of central type (CSAS), 4 of obstructive type (OSAS). Respiratory events during sleep (global apnea-hypopnea index and total time spent in central or obstructive apnea) were significantly more important in acromegaly patients compared to other types of PA – see Table 2. Based on our analysis of the CSF hormonal values in the control group (results already published, see [1]), we divided our patients into a group with normal CSF value for a certain pituitary hormone (*i.e*. within the range provided by the analysis of the control group)

and a group with high CSF hormonal values (*i.e.* higher than the maximum value recorded in the control group for that hormone).

Compared to patients with normal CSF GH, those with increased CSF GH have significantly higher central apnea index (CAI) and total duration of central apnea as well as longer episodes of central apnea – see Table 3. The serum GH concentrations were similar between the 2 subgroups.

Patients with increased CSF FSH (compared to those with CSF FSH values similar to controls) have a higher obstructive apnea index (OAI) and longer time spent in obstructive apnea – see Table 3. Also, they had more severe REM-related apnea (apnea occurring in the rapid-eye-movement (REM) sleep stage) index RAI. The correlation between CSF FSH and these parameters (OAI, TAO, RAI) was significant and persisted after controlling simultaneously for serum and CSF GH, as well as for serum FSH and BMI (Figure 1).

Table 1

CSF hormonal concentrations in patients (P) and control group (C)

	group	Mean CSF concentration	Range CSF concentration	p	CSF/serum mean ratio	CSF/serum ratio-range	p
GH (ng/ml)	C	0.04	0.00–0.55	**0.000****	0.23	0.00–7.86	**0.004****
	P	1.94	0–51.9		1.12	0–22	
PRL (ng/ml)	C	1.49	0.00–3.99	**0.012***	0.24	0.00–1	**0.038***
	P	21.31	0.01–667.3		0.29	0.03–1.5	
LH (mU/l)	C	0.39	0.00–1.86	0.313	0.07	0.00–0.88	**0.002****
	P	1.30	0–10.73		1.24	0–22.67	
FSH (mU/l)	C	0.57	0.00–2.95	**0.004****	0.08	0.00–1.29	**0.000****
	P	1.99	0–9.57		0.50	0–3.05	
TSH (mU/l)	C	0.01	0.00–0.14	**0.002****	0.07	0.00–0.08	**0.000****
	P	0.10	0–0.67		0.97	0–8	

Table 2

Sleep respiratory events in patients – differences according to tumor type
ACM – acromegaly; NFPA – non-functioning pituitary adenoma, PRM – prolactinoma; CAI – central apnea index, OAI – obstructive apnea index, MAI – mixed apnea index, CAD – mean duration of central apnea episodes, OAD – mean duration of obstructive apnea episodes, MAD – mean duration of mixed apnea episodes, AHI – general apnea-hypopnea index, TCA – time spent in central apnea, TOA – time spent in obstructive apnea, TMA – time spent in mixed apnea, RAI – rapid eye movement (REM) sleep-related apnea, NRAI – non-REM sleep apnea index

	Range	Mean±SD	Mean ACM	Mean NFPA	Mean PRM	p ACM-NFA	p ACM-PRM	p NFA-PRM
CAI	0–45.71	4.70±9.47	6.32	1.35	0.89	**0.039***	0.063	1
OAI	0–17.07	3.71±5.1	4.57	2.61	0.26	0.070	**0.013***	1
MAI	0–7.43	0.57±1.50	0.84	0	0	**0.013***	**0.041***	1
CAD	10.30–26.9	17.23±4.33	17.6	15.8	16.03	0.562	0.477	1
OAD	10–51.5	18.61±7.50	20.13	14.32	14.2	0.082	0.059	0.886
MAD	10.6–64.4	28.42±16.67	28.42	–	–	**0.022***	0.089	0.247
AHI	0.2–82.29	13.61±17.60	18.22	5.73	5.11	**0.031***	**0.012***	1
TCA(s)	0-869.23	93.36±198.7	130.37	23.16	17.96	**0.035***	**0.036***	0.943
TOA(s)	0–878.85	83±158.5	109.33	46.88	5.03	**0.013***	**0.013***	1
TMA(s)	0–220.57	15.64±43.08	23.46	–	–	–	–	–
RAI	0–50.76	10.23±12.39	14.38	1.66	3.22	**0.001****	**0.027***	0.435
NRAI	0–82.29	13.45±16.94	17.45	6.45	3.86	**0.035***	**0.022***	0.127

Table 3

Sleep respiratory events in patients with increased CSF hormonal levels as opposed to those with normal (similar to controls) levels. CAI – central apnea index, OAI – obstructive apnea index, MAI – mixed apnea index, CAD – mean duration of central apnea episodes, OAD – mean duration of obstructive apnea episodes, MAD – mean duration of mixed apnea episodes, AHI – general apnea-hypopnea index, TCA – time spent in central apnea, TOA – time spent in obstructive apnea, TMA – time spent in mixed apnea, RAI – rapid eye movement (REM) sleep-related apnea, NRAI – non-REM sleep apnea index

	CSF GH ↑ *vs* normal	CSF PRL ↑ *vs* normal	CSF LH ↑ *vs* normal	CSF FSH ↑ *vs* normal	CSF TSH ↑ *vs* normal
CAI	**0.015***	0.08	0.66	0.59	0.91
OAI	0.69	0.07	0.07	**0.018***	0.29
MAI	0.27	0.15	0.32	0.89	0.46
OAD	0.12	0.25	0.68	0.55	0.08
CAD	**0.025***	0.09	0.45	0.78	0.86
MAD	0.61	0.05	0.27	0.88	0.36
AHI	0.10	0.09	0.94	0.84	0.85
TCA	**0.013***	0.05	0.63	0.55	0.75
TOA	0.68	0.06	0.09	**0.017***	0.32
TMA	0.38	0.11	0.34	0.86	0.49
RAI	**0.014***	0.63	0.55	**0.010***	0.85
NRAI	0.40	0.09	0.69	0.11	0.91

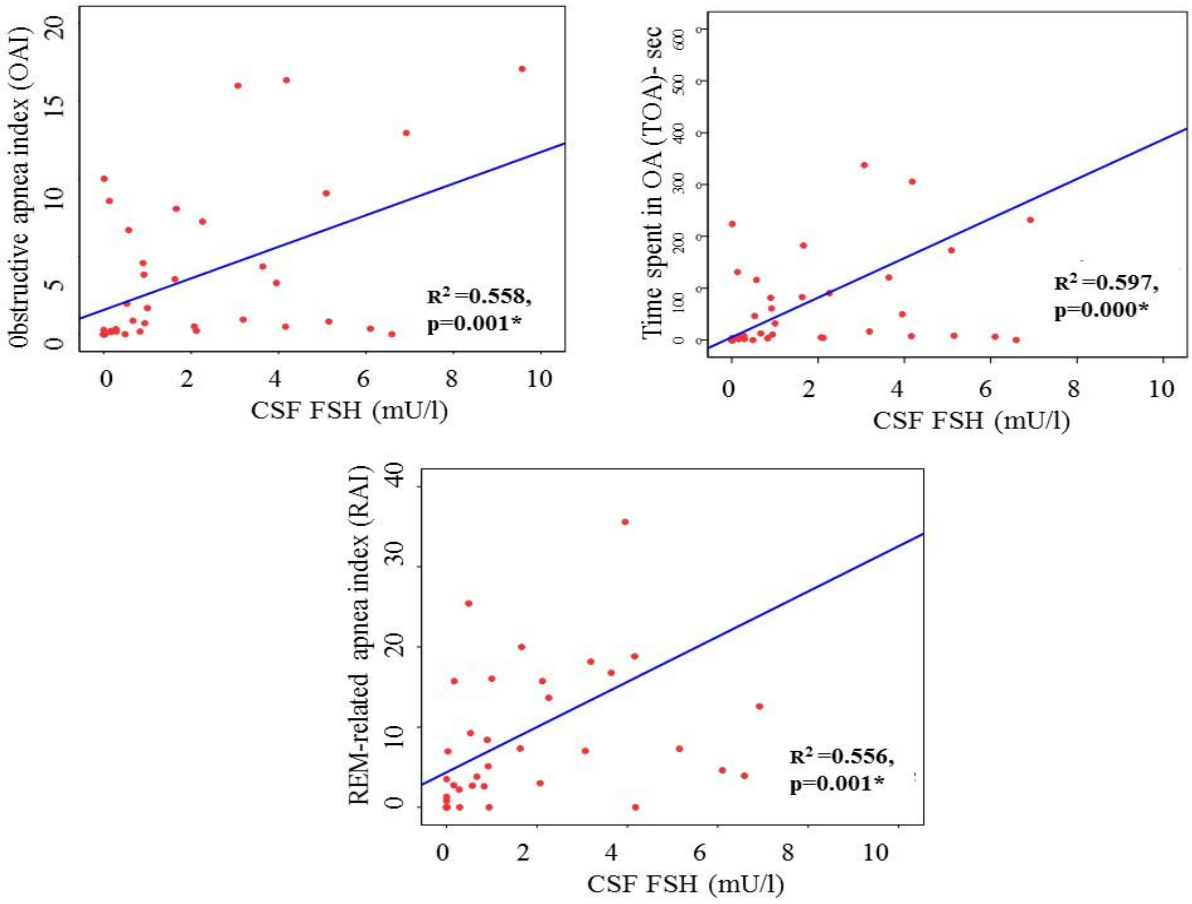

Fig. 1. Correlations between CSF FSH and obstructive apnea-related parameters (OAI, TOA, RAI).

Table 4

Multiple regression analysis results

		sFSH	cFSH	sGH	cGH	sex	age
TAO	R^2	0.416					
	β	–0.042	**0.591**	0.091	0.045	0.065	0.056
	p	0.789	**0.001****	0.576	0.764	0.692	0.752
OAI	R^2	0.298					
	β	0.001	**0.487**	0.012	–0.048	0.010	0.126
	p	0.993	**0.011***	0.946	0.772	0.957	0.470
IAR	R^2	0.654					
	β	0.031	**0.414**	**0.378**	0.223	–0.093	0.021
	p	0.17	**0.004****	**0.006***	0.067	0.463	0.865
OAD	R^2	0.315					
	β	0.040	**0.499**	0.112	0.200	0.012	0.074
	p	0.845	**0.025***	0.598	0.322	0.957	0.712
IAC	R^2	0.370					
	β	0.046	0.069	**0.491**	0.009	0.226	–0.126
	p	0.781	0.685	**0.007***	0.953	0.191	0.446
TAC	R^2	0.239					
	β	0.073	0.179	**0.423**	0.027	0.267	–0.127
	p	0.654	0.297	**0.017***	0.865	0.124	0.440

DISCUSSION

CSF analysis is a relatively easy method to assess the CNS environment. The composition of the CSF is likely to influence various brain functions, including sleep. The proteic composition of the CSF is represented by 80% blood-derived proteins and 20% proteins synthesized in the CNS (neurons, glial and leptomeningeal cells).[16] Once released into the CSF, such proteins are able to influence distant brain areas[17] and exert specific effects on the central nervous system functioning (including behaviour and sleep). It has been reported that in some PA patients, increased CSF concentrations of certain pituitary hormones are present [5,8,18,19]. In our study the same results were found: patients had significantly increased CSF levels and CSF/serum ratio of pituitary hormones. The mechanism is still elusive: some studies suggest choroid plexus filtration or retrograde transport from the pituitary into the CSF [20] or even simple diffusion [21] as the dominant mechanisms.

Patients with acromegaly are frequently diagnosed with SAS, especially of the obstructive type but also central or mixed forms.[22] PRM patients have similar SAS prevalence to that in obese patients. [23] In NFPA normal sleep architecture is impaired [24] but there is no evidence of increased sleep-disordered breathing. Indeed in our patients, the group with ACM had significantly worse sleep respiratory disturbance parameters compared to both NFPA and PRM (obstructive, central and mixed episodes).

Therefore, we aimed to study the possible effects on nocturnal sleep of these chronically increased hormonal concentrations in the CSF. We chose to focus especially on the nocturnal sleep respiratory events and in particular central sleep apnea (a syndrome with largely unknown pathogenesis).

In the control group the CSF sample was collected by lumbar pucture. The CSF communicates with the cerebral extracellular fluid (ECF) [25] but the extent of the communication is regionally determined by the intercellular junctions between the ependymal cells. [26] The concentrations of various substances in the CSF vary over time and also depend on the region. It is, therefore, possible that the peripituitary concentrations of the hormones analysed is significantly elevated compared to the medularry ones. However, in order to decrease the possibility of bias in the comparison to the control group, we decided to collect CSF at the same level in the patients group (rather than intraventricular CSF at the time of the surgery).

Compared to patients with normal CSF GH, those with increased CSF GH have significantly higher central apnea index (CAI) and total duration of central apnea as well as longer episodes of central apnea, despite similar serum GH concentrations. We considered a possible bias exerted by the serum GH concentration and body mass index (BMI) since in acromegaly[14] and

obesity[27] the incidence of sleep apnea syndrome (SAS) is increased. Indeed, after correcting for these parameters the magnitude of the corellation diminished but remained significant.

Possible explanation for these results can be sought in the distribution of the cerebral receptors for the pituitary hormones. Specific GH receptors are found in many SNC areas (choroid plexuses, hippocampus, hypothalamus, pituitary, putamen)[28,29] – a particular area is the periventricular hypothalamic nucleus, an area rich in somatostatin (SS)-producing neurons. Stimulation of SS-neurones in the periventricular nucleus by GH (through local GH injection) induces SS release.[30] Somatostatin injection induces apnea [31-33] and suppresses the central respiratory drive in animals.[32,34] We hypothesise the implication of central SS release (with secondary inhibition of central respiratory drive) as a mediator between raised CSF GH and increased central apnea duration.

We also observed a significant correlation between the CSF FSH concentration and the obstructive apnea index (OAI) and total time spent in obstructive apnea (TAO). For gonadotropins, the distribution of cerebral receptors has been well described for LH (in many areas of the brain, mostly in the hippocampus [35]), mediating exploratory or stereotypic behavior [36] but for FSH, specific brain receptors have been described in some animal species[37] but not in others[38]. However, clinical data suggest that the SAS incidence increases in postmenopausal women (odds ratio 3.5).[39] In postmenopause, the CSF gonadotropin concentration increases (threefold for FSH, twofold for LH) and the CSF/serum ratio decreases compared to premenopausal women. [40] Whether this CSF increase has any contribution to the increased SAS observed in postmenopausal women is not known.

The serum GH concentration was significantly correlated with the REM-related apnea index. This is a new observation, of interest for future research. It is well known that REM-associated apnea is associated with an increased relative risk for diabetes mellitus [41] and suboptimal glycemic control[42]; the possible role of serum GH concentration in this relationship deserves further investigation.

CONCLUSIONS

The CSF content and particularly the relatively high CSF concentrations of pituitary hormones, found in many patients with pituitary adenoma are likely to influence the sleep respiratory events. Further study of the mechanisms involved are needed to better characterize sleep-disordered breathing commonly occurring in certain subgroups of patients with pituitary adenoma.

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