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Case Report

An Unusual Manifestation of a Hypothalamic Secondary Malignant Damage

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Abstract

Background

Sleep-wake disturbances are common. Description and classification of sleep disorders helped researchers to define precisely roles and interactions between different nervous structures.

Case Presentation

We report here the case of a 72 years old patient, who presented with a small cells lung carcinoma. During his hospitalization, we noticed an excessive sleepiness with unexplained confusion. Plasmatic analysis have shown a hyponatremia with a normal renal function. Cerebral CT scan, MRI, hormonal dosages confirmed a metastatic hypothalamic damage and a central hypothyroidism. The other hypothalamo-hypophysary hormones were at normal levels. This association could be explained by the hypothalamic damage, but wasn't anteriorly described. Put on a supplementation of thyroxin, the patient was still presenting excessive sleepiness.

Conclusions

Interaction between the hormonal hypothalamic function and central sleep control is still unclear.

Key Words: Cerebral Metastase; Hypothalamus; Orexin A; Thyrotropin Releasing Hormone

Background

Various sleep disorders (SD) can occur due to a lesion of a defined structure in the central nervous system, known to be responsible of the awakeness process. Description, classification of SD, exploration of the "sleeping process" helped researchers to define precisely roles and interactions between different nervous structures in control of sleeping process. Many details still remain mis-understood. Sleep-wake disturbances are common. They are estimated to occur in 10 to 20% of all population [1]. In patients with chronic illnesses, they are more frequent. Several publications reported these complaints in patients with illnesses such as HIV, neurologic illnesses [2,3] and cancer [4,5].

Case Presentation

A 72 years old man presented with chronic chest pain and dyspnea at rest. The patient was former smoker. Past medical history included chronic obstructive pulmonary disease (COPD), centrolobular emphysema, right pneumothorax treated with a chest tube during 7 days in 2012. He noted a worsening of his dyspnea, a month before consulting. Interrogation found an intermittent confusion, a continuous day-time sleepiness with a short latency to fall asleep, no paralysis, motor nervous system and sensory nervous function examination were normal. Apneic episodes during sleep, snoring, cataplexy, hallucinatory episodes, sleep paralysis and dream enactment were absent. The patient had polypnea with a percutanous oxygen saturation at 91%, no signs of hemodynamic failure or dehydration, no fever. Pleuropulmonary examination was normal.

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Postero-anterior chest X Ray examination have shown an homogenous well-defined retractile opacity of the upper part of the left lung. Costophrenic sulci were normal. The whole clinical presentation make thoughts about a lung cancer with cerebral metastasis, but there was no explanation for the excessive sleepiness. Bronchoscopy was performed. It showed an obstructive haemorragic bud in the culminal bronchus. Histological analysis confirmed the diagnosis of small cell lung carcinoma. Thoracic CT scan showed a mediastino-pulmonary lobulated mass which invade the left main bronchus, connected with a magma of aggressive mediastinal lymphadenopathies. The tumor was in contact of the descending portion of the intra-thoracic aorta.

Sleep diary was performed for the patient during his hospitalization (fig 1). Besides, biological analyses showed a persistant hyponatremia (natremia = 109 mEq/l), a hypoosmolarity (osmolarity = 238 mEq/l), contrasting with a normal renal function and normal rate of natriuresis. The prescription included sodium supplementation intraveinously in a low flow. The patient received a 40 mn perfusion of 500 ml of sodium chloride solution diluted in 0.9%o twice daily. This supplementation did not fix the electrolyte's concentration. Hormonal dosages were done. Concentration of the thyroid stimulating hormone (TSH) and the free thyroxine (FT4) were collapsed, meaning a central hypothyroidism. Free urinary cortisol concentration and antidiuretic hormone blood concentration were normal.

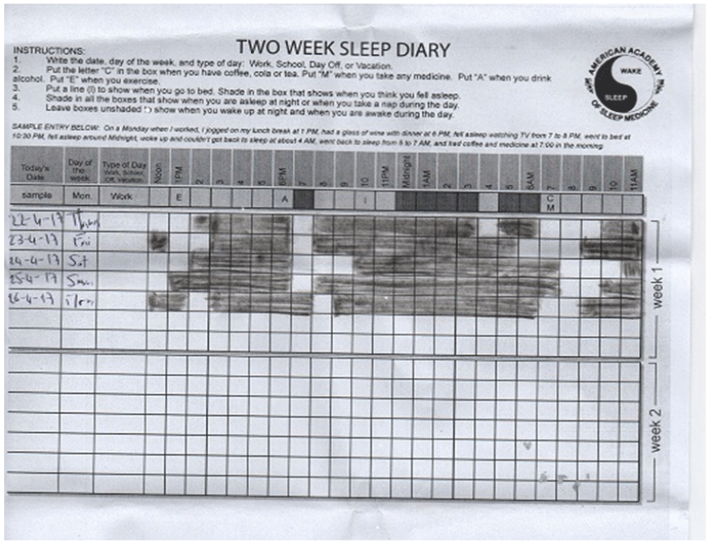

Figure 1: excessive sleepiness shown in a sleep diary

Cerebral CT scan and MRI were done. These exams showed multiple secondary cerebral nodular lesions. Several cerebral lesions had a necrotic center. Lesions were situated in both right and left hemi-cerebellum, frontal lobe, right and left parietal lobe, occipital lobe, right temporal lobe, sellar and supra-sellar zone (fig 2, 3, 4).

At this stage, the hypothalamic damage explained the sleep disorder. Also, the hypothyroidism with TSH concentration decrease was due to the pituitary gland damage. The patient was put on a substitutional hormonal treatment (75 µg/jour of thyroxin orally) and we kept intravenous sodium supplementation for four more days. Electrolytes increased gradually, tended towards normal rates and so did the osmolarity. Reaching normal homeostatic concentration of electrolytes and FT4, awakeness of our patient didn't improve. Dead a few days after, lumbar puncture for Orexin dosage and electroencephalogram could not be done.

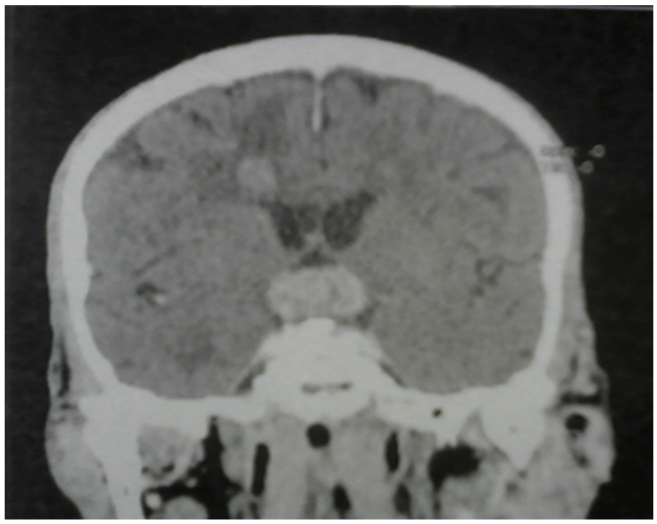

Figure 2: CT scan images showing the hypothalamic metastatic damage (frontal + coronal view)

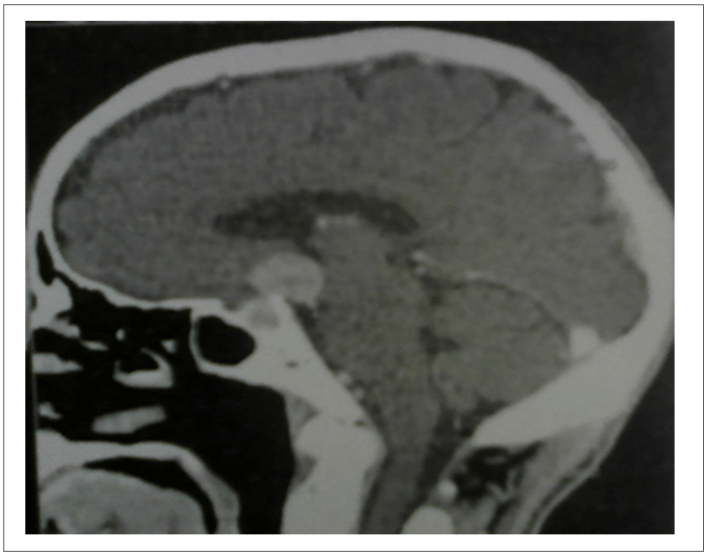

Figure 3: CT scan images showing the hypothalamic metastatic damage (frontal + coronal view)

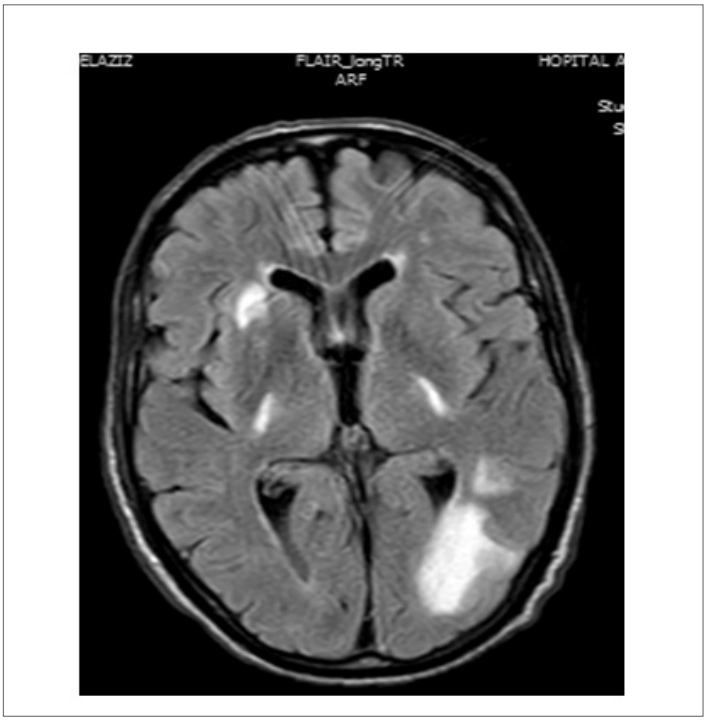

Figure 4: Cerebral MRI showed multiple secondary cerebral nodular lesions, including those in the hypothalamus

Discussion and Conclusions

Central hypothyroidism is defined as hypothyroidism due to insufficient stimulation by TSH of an otherwise normal thyroid gland. It results from hypothalamic and/or pituitary dysfunction. It is rarely isolated, and occurs more commonly in conjunction with other pituitary hormone deficiencies, neurological symptoms and signs resulting from the hypothalamic/pituitary lesion whatever was the causal etiology. In the euthyroid state, thyroxin releasing hormone (TRH) transcription is induced both in the paraventricular nucleus of the hypothalamus (PVH) and in the anterior/lateral hypothalamus. However, in the hypothyroid state, transcription is activated in the PVH only, which can be switched off by instituting exogenous thyroid hormone. TSH is synthesized and secreted by the thyrotrophs of the anterior pituitary gland. The β subunit of TSH determines the biologic specificity [6] since it's the part linked to the membranous receptors in the thyreocytes.

For our patient, an exogenous TRH test should have been done to test the response of the anterior pituitary gland in order to differentiate between a pituitary or hypothalamic shortage. But considering the isolated deterioration of the thyreotrope axis, a hypothalamic lesion is more likely to be considered.

The occurrence of a sleep disorder in this case could also be explained indirectly by hyponatremia itself. In fact hypo-osmolarity would lead to a cerebral eodema and an intracranial tension. These conditions are known as sleep disturbance providers at all age [7,8]. But after getting normal analyses of the electrolytes serum level, the persistence of sleepiness rule out this hypothesis.

So the sleep disorder seems to be a direct result of the hypothalamic damage. This cerebral center is a key effector in the sleep process. The interaction between the Hypothalamus and the suprachiasmatic nucleus maintain the circadian sleep-wake rhythm [9]. Recent studies have described the role the lateral hypothalamic area (LH), as a regulating structure that control feeding behavior, energy balance and wakefulness. Biologically active neuropeptides selectively isolated from The LH include Orexin A and Orexin B, also named hypocretin-1 and hypocretin-2. These peptides where described as appetite inducers after injection in the dorsomedial hypothalamus. They can modulate the activity of both the locus coeruleus and the basal forebrain neurons involved in the complex mechanism of arousal, sleep-to-wake transition and circadian rhythm maintaining.

It has been suggested that hypocretin-1 is implicated in the regulation of hypothalamo-hypophysary endocrine axes, such as prolactin secretion, luteinizing hormone, somatotropic, adrenal and thyroid axes also [9].

According to Date [10], PVH is one among multiple brain areas to which orexigen neurons project. In Mitsuma's study, intracerebroventricular injection of the Orexin A in rats leaded to a decrease in TRH release, TSH and FT4 plasmatic secretion [11]. Another study noted a suppression of plasmatic TSH after intracerebroventricular injection of Orexin A, but without decline in FT4 concentration [12]. The same study showed that chronic Orexin injections in the PVH did not al-

ter plasmatic hormonal concentrations or the thermoregulation [12], which is a conflicting result, putting doubts about the direct ability of Orexin to control the pituitary release of TSH through the hypothalamic TRH. Another study compared the transcription of the pre-pro-Orexin gene in severe hypothyroid, hyperthyroid and euthyroid rats [13]. The study found a similar mRNA level in each subgroup despite of dysthyroidism.

Describing the endocrine troubles in narcoleptic patients would be helpful to understand the role and the interactions binding the hypothalamic nuclei. Type-1 narcolepsy is a sleep disorder characterized by a persistent irresistible sleepiness, predominance of rapid-eye-movement (REM) stage of sleep and shortage of Hypocretin-1 secretion. This disease reflects a damage of the LH. However, these patients present usually cataplexy, tonus troubles, troubles in food behavior, but no hypothalamo-hypophysary endocrine disorders [14].

According to our knowledge, there was no similar case of a metastatic hypothalamic damage, manifested by a sleep disorder associated to a selective impairment of the thyrotrope endocrine axis, preserving the other hypothalamo-hypophysary hormones. In this case, cerebral imaging described precisely the hypothalamic damage, contrary to publicated cases of endocrine troubles occurring after radiation therapy or neurosurgery.

The existence of an Orexin A mediated neuronal circuit, modulating the paraventricular secretion of TRH is proven in murine models, but the importance of this control system in vivo is still controversial. All these findings may lead to the hypothesis of the existence of a common hypothalamic stimulus, inducing the TRH and the Orexin A release, or a brake factor for the Orexin A secretion, switched-on after the paraventricular nucleus damage.

This observation argues in favor of the existence of complex neuronal and/or paracrine interactions between hypothalamic nuclei. A better description may lead to pertinent preventive measures or give the potential for intervention.

List of Abbreviations

SD: sleep disorders

COPD: chronic obstructive pulmonary disease

TSH: thyroid stimulating hormone

FT4: free thyroxin 4

CT: computed tomography

MRI: magnetic resonance imaging

TRH: thyroxin releasing hormone

PVH: paraventricular nucleus of the hypothalamus

mRNA: messenger ribo-nucleotid acid

REM: rapid-eye-movement

LH: lateral hypothalamic area

Declaration

- Consent for publication
- Availability of data and material : Not applicable
- Competing Interests : All authors declare having no conflict of interest in relation to the main topic of the manuscript
- Authors' Contributions : Management of the patient was a collective work ensured by the medical team of the department. Discussion with radiologists and redaction of the manuscript was principally done by NB.

References

1. Messina A, De fusco C, Monda V, Esposito M, Moscatelli F et al. (2016) Role of orexin system on the Hypothalamus-Pituitary-Thyroid Axis. Front Neural Circuits 10: 66 DOI: 10.3389/fncir.2016.00066

2. Čarnická Z, Kollár B, Šiarnik P, Krížová L, Klobučníková K, et al. (2015) Sleep Disorders in Patients with Multiple Sclerosis. J Clin Sleep Med 11(5): 553-557.

3. Fogelberg DJ, Hoffman JM, Dikmen S, Temkin NR, Bell KR (2012) Association of sleep and co-occurring psychological conditions at 1 year after traumatic brain injury. Arch Phys Med Rehabil 93(8): 1313-1318.

4. Armstrong TS, Shade MY, Breton G, Gilbert MR, Mahajan A, et al. (2017) Sleep-wake disturbance in patients with brain tumors. Neuro-Oncol 19(3): 232-235. DOI: 10.1093/neuonc/now119

5. Johnson JA, Rash JA, Campbell TS, Savard J, Gehrman PR, et al. (2016) A systematic review and meta-analysis of randomized controlled trials of cognitive behavior therapy for insomnia (CBT-I) in cancer survivors. Sleep Med Rev 27: 20-28.

6. Scranton RA, Baskin DS (2015) Impaired Pituitary Axes Following Traumatic Brain Injury. J Clin Med 4(7): 1463-1479.

7. Merdad RA, Akil H, Wali SO (2017) Sleepiness in Adolescents. Sleep Med Clin 12(3): 415-428.

8. Lewis SR, Pritchard MW, Schofield-Robinson OJ, Alderson P, Smith AF (2018) Melatonin for the promotion of sleep in adults in the intensive care unit. Cochrane Anaesthesia.

9. Messina A, De Fusco C, Monda V, Esposito M, Moscatelli F, et al. (2002) Role of the Orexin System rats does not alter thyroid axis or uncoupling protein-1 in brown adipose tissue. Regul Pept 104(1): 61-68.

10. Date Y, Ueta Y, Yamashita H, Yamaguchi H, Matsukura S, et al. (1999) Orexins, orexigenic hypothalamic peptides, interact with autonomic, neuroendocrine and neuroregulatory systems. Proc Natl Acad Sci U S A 96(2):748-753.

11. Mitsuma T, Hirooka Y, Mori Y, Kayama M, Adachi K, et al. (1999) Effects of Orexin A on Thyrotropin-Releasing Hormone and Thyrotropin Secretion in Rats. Horm Metab Res 31(11): 606-609.

12. Russell SH, Small CJ, Sunter D, Morgan I, Dakin CL, et al. (2014) Chronic intra-paraventricular nuclear administration of orexin A in male Ford ES, Wheaton AG, Cunningham TJ, giles WH, chapman DP, croft JB et al. Trends in outpatient visits for insomnia, sleep apnea, and prescriptions for sleep medications among US adults: National Ambulatory Medical Care Survey 37: 1283-9123.

13. López M, Tena-Sempere M, Diéguez C (2010) Cross-talk between orexins (hypocretins) and the neuroendocrine axes (hypothalamic-pituitary axes). Front Neuroendocrinol 31(2): 113-127.

14. Chieffi S, Carotenuto M, Monda V, Valenzano A, Villano I, et al. (2017) Orexin System: The Key for a Healthy Life. Front Physiol 8: 357. DOI:10.3389/fphys.2017.00357