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Case Report

Hypothalamic Fever and Obesity in Sarcoidosis

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ABSTRACT

Hypothalamic-pituitary involvement in sarcoidosis occurs in less than 5% of patients. Some clinical signs of hypothalamic lesions are non-obvious or can be mistaken in a complex context. Hypothalamus is involved in temperature regulation, food intake, and mood regulation. Few cases have been reported.

INTRODUCTION

Sarcoidosis involves the central nervous system in 5-15% of cases [1] and among them, 17-25% of patients present endocrine dysfunctions related to hypothalomic-pituitary involvement [2]. In recent cohorts (9 and 24 patients), we described the most prevalent deficiencies as diabetes insipidus, hyperprolactinemia and gonadotropin deficiency [3,4]. In these series, the hypothalamic involvement was defined by the presence of diabetes insipidus, which diagnosis was clinical, and evocative radiologic characteristics. On MRI, an infundibulum infiltrative process with enhancement by gadolinium injection can be isolated or associated with increased thickness of the stalk and enlargement of the pituitary gland. However, the hypothalamic area includes many nuclei especially those related to temperature and food intake regulation.

CASE REPORT

62-year-old women presented sarcoidosis for 9 years with pulmonary, ganglionic, dermatological involvement. The histological proof was obtained by bronchial biopsies revealing non-caseating granulomas. Her weight was 72 kgs, and her height was 1.60 m. She received glucocorticoids and hydroxychloroquine during 3 to 5 years only, as she was lost of follow-up. In 2011, her weight was 80 kgs.

In January 2017, after the accidental death of her daughter, she has developed clinophilia, hypersomnia, and polyphagia, all attributed to mourning. In September 2017, she needed to be hospitalized for dyspnea. Pulmonary embolism was confirmed, and the diagnosis of pneumonia was retained, and she was prescribed three antibiotics, without bacteriological documentation. Her weight was 96 kgs. Alterations in psychomotor vigilance and fever appeared. The cerebral MRI was normal except for an old ischemic lesion in the right caudal node. Effexor, introduced in October, was stopped as possibly related to fever, without any effect. No

biological sign of infection, neither bacteriological documentation was found. She stayed for two months in the hospital. She was rehospitalized in April 2018 for chronic fever and persistence of alteration of consciousness. On examination, her weight was 102 kg, her temperature was between 36.9 °C to 38, polypnea 32/Min, pulse 115 bpm, regular and BP 140/81 mmHg. The respiratory auscultation found bilateral crackles. Neurologically, she was drowsy, moving on simple orders and developed clinophilia. A psychiatric evaluation did not confirm depression but oniric visions (visual hallucinations of her dead daughter) and adequate response to multiples loss.

The level of serum angiotensin-converting enzyme (ACE) was normal (69 UI/L). An exhaustive exploration of chronic fever was negative: hepatitis, Lyme, Syphillis, Brucellosis, HSV/VZV, EBV, CMV, HTLV1-2, Whipple PCR, Cryptococcus, Leishmaniosis, toxoplasmosis, paludism, Still disease, and auto-immune exploration. LCR analysis showed normal liquid (one element, proteinorachia at 0.21 g/L, glycorachia 5 mM). Electroencephalography was normal once, and then revealed signs of metabolic encephalopathy.

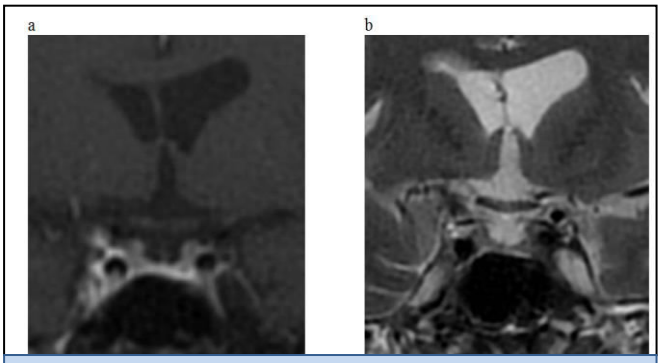

Figure 1: a) T1-weighted section in the coronal plane of the hypothalamic-pituitary area. Compression of one lateral ventricle. Hypothalamic atrophy, more visible on b) T2-weighted image. No enlargement of the pituitary stalk. Normal presentation of chiasma. Flattened pituitary gland.

Pituitary involvement was diagnosed, with diabetes insipidus controlled by vasopressin and hyperprolactinemia at 1250-1800 mUI/L (102-496), gonadotropin deficiency (FSH 0.6 UI/L, LH < 0.1 UI/L). Other pituitary axes were normal : respectively, cortisol 380 nmol/L, ACTH 16.4 pg/ml (7.2-63.3), T4L 14.9 pmol/L (12-22), T3L 3.39 pmol/L (3.1-6.8), TSH 2.64 mUI/L (0.27-4.20), GH 0.12 mUI/L (0.38-29.6), IGF-1 111 ng/ml (8-596). A hypothalamic-pituitary centered MRI revealed hypothalamic atrophy with a T2 weighted hyperintense signal without gadolinium enhancement (Figure 1 a,b).

As the different etiologies of chronic fever have been excluded, and facing the hypothesis of hypothalamic fever, with hypothalamic atrophy and pituitary deficiencies, the diagnosis of hypothalamic-pituitary involvement was made. The patient has received prednisolone 100 mg per day for three days. The outcome was favorable, the temperature normalized. However, two weeks later, fever returns and fluctuates. Procalcitonin was normal except three days in April, then was negative. Again, the infectious hypothesis was ruled out. The patient was treated with high dose intravenous corticosteroid therapy for a few days. Despite this treatment, fever increased slightly each day, 36.9 to 39, then 38.5 to 40, 37.6 to 39.2, until 40.8 and 42 °c with consciousness alteration, leading to cardiac arrest in May and failure of resuscitations procedures.

DISCUSSION

Our patient died after less than one year of complex clinical picture associating pulmonary embolism, resolutive pneumonia, chronic fever, central neurological signs with clinophilia, consciousness alteration, diabetes insipidus and intake of 22 kgs in 6 years. We suspect that sarcoidosis involved the hypothalamic area leading to destruction and atrophy.

Hypothalamus regulates bodily temperature mainly via the thermosensitive neurons in the preoptic area that induce thermoregulatory responses to defend body temperature from different challenges [5]. 58-year-old women had an enlarged pituitary gland with a thickened stalk associated with diabetes insipidus, gonadotropin, and somatotropic deficiencies. Initially, she presented a low-grade fever that persisted for longer than one month without any sign of infection [6]. In another patient with diffuse sarcoidosis, neurosarcoidosis, and severe encephalopathy, the temperature was highly labile, from 27°C at the presentation (Glasgow Coma Scale score at 3) to a 3 months length's fever. MRI showed leptomeningeal enhancement, cortical ventricle, swelling, and vasogenic edema [6]. In our case, the diagnosis of hypothalamic fever is very hard to establish. Indeed, the patient had episodes of pulmonary infections and suspicion of therapeutic side effects (antidepressant drugs). However, the infectious parameters such

as CRP and procalcitonin were negative in the last months while temperature increased. We need to highlight that dedicated hypothalamic-pituitary MRI was really useful and it is the repetition of this imagery at 7 months interval that led to the diagnosis.

For food intake, it is known that the hypothalamus is involved in central control of appetite and food intake, especially the accurate nucleus [7]. In sarcoidosis, it is difficult to ascertain hypothalamic involvement, especially when glucocorticoids can influence appetite. For our patient, the gain weight in a few months was noteworthy. We cannot exclude the relationship with depressive symptoms; the patient did not declare changes in her diet habits but with really poor insight. In literature, to our knowledge, no case report described hypothalamic obesity in patients with hypothalamic involvement of sarcoidosis. In other fields, patients with tumors in the hypothalamic region are at higher risk of hypothalamic obesity. Obesity could lead to a diagnosis of craniopharyngioma in children and is highly feared after surgery, depending on the extension of the tumor and hypothalamic sequelae of such surgery [8]. Recently, Roth et al. reported a link between the extent of damage following surgery calculated on four hypothalamic areas on MRI (third ventricular floor, mammillary bodies, and anterior, medial posterior hypothalamus) and the risk of gain weight [9].

Finally, our patient presented atypical neuro-psychiatric manifestations; initially identified as reactive depressive symptoms. Psychiatric symptoms can be present in neurosarcoidosis, with delusions, agitation, ataxia and other visual and vestibular-auditory manifestations [10].

The MRI imagery was not described previously. We suspect that it could be the outcome of an infiltrative lesion of the infundibulum or involution of an enlarged pituitary gland [3]. A dedicated MRI would have been helpful earlier. We suggest the diagnosis of severe hypothalamic sarcoidosis as a diagnosis made by elimination and presence of a bundle of arguments. More descriptions are needed and MRI assessment to be able to define diagnostic criteria.

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