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Caso Clínico

Neurosarcoidosis: A Rare Cause of Hypothalamic-Pituitary Dysfunction

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A B S T R A C T

Although neurosarcoidosis affects 5% - 15% of patients with the disease, hypothalamic-pituitary involvement is unusual. A 44 year-old woman presented at the emergency department with a 3-months history of bilateral vision loss. She also complained of galactorrhoea, oligomenorrhea, polydipsia, polyuria and nocturia. A year before, she started a workup for pulmonary interstitial disease, which was underway. Cranial magnetic resonance imaging showed a midline mass in the anterior and posterior aspects of the sella turcica and dorsum sella, with hypothalamic and optic chiasma swelling (suggestive of granulomatous disease). Baseline laboratory tests revealed anterior hypopituitarism and partial diabetes insipidus. Sarcoidosis diagnosis was confirmed with a pulmonary biopsy. The patient was started on hormonal replacement therapy and immunosuppression with prednisolone and, later on, azathioprine (corticoid-sparing agent). After 3 years of follow-up, she is clinically stable with radiological improvement of the mass but persistent endocrine deficits.

Neurosarcoidose: Uma Causa Rara de Disfunção Hipotálamo-Hipofisária

R E S U M O

Cerca de 5% a 15% dos doentes com sarcoidose têm envolvimento do sistema nervoso central (neurosarcoidose), sendo raro o envolvimento hipotálamo-hipofisário. Os autores apresentam um caso de uma mulher de 44 anos, que recorreu à urgência por diminuição bilateral da visão, com 3 meses de evolução. Ainda a destacar galactorreia, oligomenorreia, polidipsia, poliuria e nocturia. Dos antecedentes pessoais salienta-se doença do interstício pulmonar em estudo, desde há um ano. A ressonância magnética crânio-encefálica mostrou uma massa da linha média interessando o dorso selar, espaço retro-selar e parede selar anterior, edema do hipotálamo e do quiasma óptico (sugestivo de doença granulomatosa). Analiticamente com hipopituitarismo e diabetes insípida central parcial. O diagnóstico de sarcoidose foi confirmado por biópsia pulmonar. Iniciou terapêutica de substituição hormonal e imunossupressão (inicialmente com prednisolona, subsequentemente também azatioprina). A doente encontra-se estável ao fim de 3 anos de seguimento, com melhoria radiológica, mas persistência dos défices endócrinos.

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Introduction

Sarcoidosis is a granulomatous disease.[1] About 5% to 15% of patients have central nervous system (CNS) clinical involvement (neurosarcoidosis - NS).[1-3] Hypothalamic-pituitary (HP) involvement is even less frequent. In a cross-sectional study by Leonhard *et al*,[1] including 52 patients with NS, neuroendocrine dysfunction was present in 6% (3 patients, 2 with pan-hypopituitarism and 1 with diabetes *insipidus*).

HP involvement can be suspected on the basis of clinical, biochemical and radiological findings. These patients might present with symptoms and/or biochemical evidence of anterior hypopituitarism, hyperprolactinemia and diabetes *insipidus*.[4] Visual disturbance due to optic chiasm involvement/compression is also possible.[4] Radiological lesions can be found in the sella, hypothalamus, infundibulum, stalk, adenohypophysis, cavernous sinus and optic chiasm.[5] Stalk thickening or nodules, enlargement of the adenohypophysis and pseudotumours, are all features that can be found in the magnetic resonance imaging (MRI). They are particularly suggestive of this aetiology, especially if associated to other intracranial lesions possibly related to granulomatous disease (detailed description of these is outside the scope of this paper).[5] Signal intensity on T2-weighted images may also be a clue for diagnosis, since granulomatous lesions often are hypo or iso-intense.[5]

The histological hallmark of NS is the presence of non-caseating granulomas.[6]

Several criteria have been proposed to establish NS diagnosis.[6] The most recently published resulted from an expert consensus of physicians from different institutions and admits 3 categories of likelihood for the diagnosis[6]:

- Definite: clinical manifestations and MRI/cerebrospinal fluid (CSF)/electromyogram (EMG)/ nerve conduction study (NCS) findings are typical of granulomatous inflammation of the central nervous system (CNS); other causes have been excluded; there is histologic confirmation of granulomatous disease consistent with sarcoidosis within CNS. Type a: sarcoidosis is evident outside the CNS; Type b: isolated CNS sarcoidosis.
- Probable: clinical manifestations and MRI/CSF/EMG/NCS findings are typical of granulomatous inflammation of the CNS; other causes have been excluded; there is histologic confirmation of granulomatous disease consistent with sarcoidosis elsewhere (systemic).
- Possible: clinical manifestations and MRI/CSF/EMG/NCS findings are typical of granulomatous inflammation of the CNS; other causes have been excluded; no histologic confirmation of granulomatous disease.

These are mostly in accordance with the widely used Zacijek criteria.[7]

Serum angiotensin-converting enzyme (ACE) has limited value in the diagnosis of NS.[8] It might be useful not so much for diagnosis but for follow-up if initially raised.[9]

This disease may have 3 different patterns of clinical evolution: monophasic, relapsing/remitting and progressive.[10]

Treatment usually includes hormone replacement therapy and one or several immunosuppressive drugs.[4] Corticosteroids are the first line treatment and high doses are warranted in acute flares. Many other drugs have been used in addition or in replacement of steroids either if not clinically effective or if they cause significant adverse events.[4]

Case Report

A 44-year-old black woman presented to the emergency room with bilateral vision loss, more pronounced in the left eye. This had started 3 months before and worsened progressively. The patient also referred polydipsia, polyuria, nocturia, oligomenorrhea and intermittent spontaneous galactorrhoea. Physical examination at admission was unremarkable apart from significantly reduced bilateral visual acuity with temporal pallor in the optic papilla and increased bilateral optic papilla excavation.

About 1 year before, she complained of cough, wheezing and fatigue, which led her to perform a chest computed tomography (CT) that raised suspicion for a pulmonary interstitial disease (diagnostic investigation still ongoing). Other relevant past medical history included sinusitis and cerebral malaria at 17 years, with no neurological sequelae. The patient was regularly treated with montelukast 10 mg/day, desloratadine 5 mg/day and inhaled budesonide 160 mcg + formoterol 4.5 mcg twice/day. There was no alcohol, drugs or tobacco abuse.

She was admitted to the hospital and started on dexamethasone for the visual complaints. A head CT was performed, showing a lesion on the tuberculum sellae. Sellar MRI confirmed the presence of a midline mass, in the anterior and posterior aspects of the sella turcica and dorsum sella, extending into the jugum sphenoidale, olfactory fossa (cribriform plate) and foramen cecum, compressing the optic nerves (Fig.1). The mass was hypointense

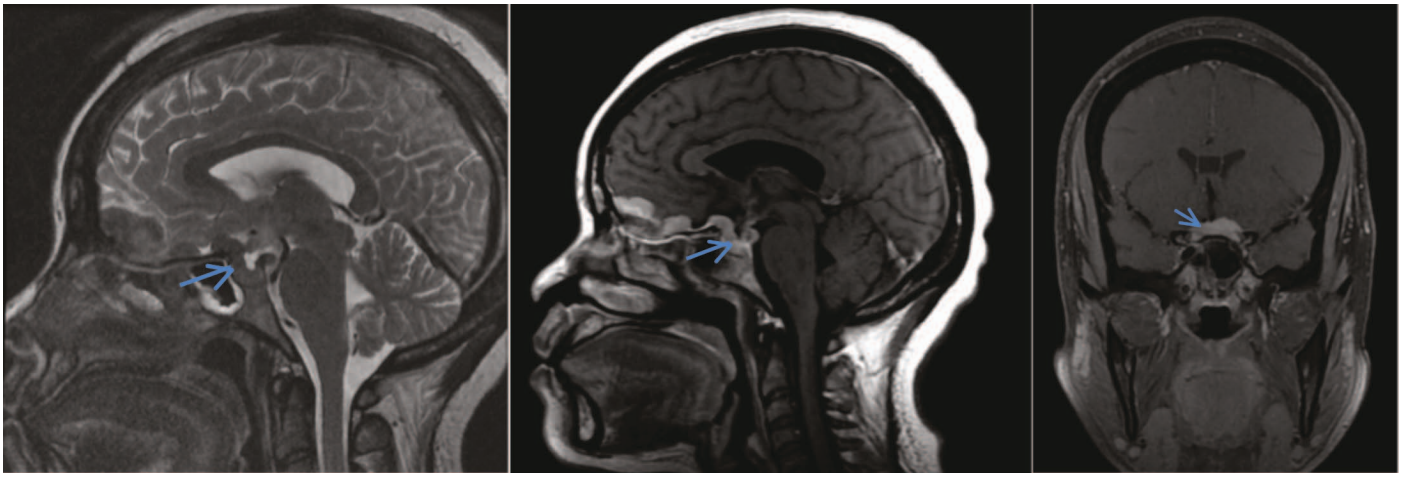

Figure 1. Cranial MRI showing a mass around the hypothalamic-pituitary area (arrow) in a sagittal T2-weighted sequence (left), a sagittal T1-FLAIR sequence after gadolinium administration (middle) and a coronal T1-weighted sequence (fat sat) after gadolinium administration (right).

in T2-weighted sequences (Fig.1). It had significant enhancement after gadolinium injection. Concomitantly, there was hypothalamic and optic chiasm swelling (Fig.1). Extensive sinusitis was also noted. Neuroradiologist admitted granulomatous disease as the most likely explanation for these findings.

Visual field test revealed peripheral arciform scotomas on the right eye (superior and inferiorly) and markedly reduced left side vision with only a small superior temporal area spared.

Baseline laboratory investigation showed anterior hypopituitarism (gonadotroph, thyrotroph and somatotroph lines), hyperprolactinemia and partial diabetes insipidus. ACE levels and erythrocyte sedimentation rate were raised (Table 1).

Table 1. Baseline laboratory tests.

Laboratory test	Result	Reference range
Sodium	145 mmol/L	135-145
Plasma osmolality	303 mOsmol/L	275-295
Urine osmolality	482 mOsmol/L	300-900
TSH	1.56 mUI/L	0.27-4.20
Free T4	0.41 ng/dL	0.93-1.70
Free T3	1.05 pg/mL	2.0-4.4
Prolactin	122 ng/mL	1.6-27.0
FSH	<0.1 UI/L	3.5-12.5
LH	<0.1 UI/L	2.4-12.6
Oestradiol	<10 pg/mL	12.5-166
IGF-1	72 ng/mL	101-267
Calcium	9.8 mg/dL	8.1-10.2
ACE	80 UI/L	8-52
ESR	101 mm (1st h)	<21

ACE – angiotensin-converting enzyme; ESR – erythrocyte sedimentation rate.

Adrenal axis was not tested because the patient was already on dexamethasone for a few days to treat the visual symptoms. Mantoux test was negative. Sarcoidosis diagnosis was confirmed with a pulmonary biopsy, which revealed non-caseating granulomas.

Upon discharge, the patient was started on levothyroxine (50 mcg/day) and cabergoline (SOS according to galactorrhoea symptoms). Dexamethasone was switched to prednisolone (1 mg/kg/day – 60 mg/day). Oestroprogestative contraceptive pill and desmopressin 0.06 mg twice/day were added subsequently. In our country, the national health system did not pay for growth-hormone replacement therapy in adults at the time, which is the reason why this treatment was not started.

As clinical and biochemical improvement was observed, prednisolone was tapered to 20 mg/day in 4 months and reduced to 10 mg/day at 6 months. MRI performed at this time showed a smaller midline mass associated with a significant decrease in the swelling of the optic chiasm and hypothalamus. Azathioprine was then added to treatment (starting dose 75 mg/day, up-titrated to 150 mg/day).

After 3 years of follow-up, the patient is clinically stable from the neuroendocrine point of view, with appropriate replacement treatment. Visual symptoms have improved with immunosuppression (azathioprine 150 mg/day and prednisolone 10 mg/day) that is still ongoing. CNS mass is stable, optic chiasm and hypothalamic swelling resolved and there are no signs of direct hypothalamic-pituitary damage. Although radiological improvement has occurred, hypopituitarism and diabetes *insipidus* have persisted. Only prolactin levels have normalized, with no current need for cabergoline.

So far, no other organs have been found to be involved by the disease, besides the CNS and the lungs.

Discussion

NS with neuroendocrine involvement is rare, which is why evidence to guide clinical approach and management of these patients comes from case reports and small case series. Anthony *et al* [8] performed the most extensive review of case series including 4 or more patients described in English literature since 1995 to 2015 with a total of 46 patients (including 4 of their own). These patients were mostly male (n= 30; 65.2%), with a mean age of 37 years (ranging from 18 to 69). Hypothalamic-pituitary dysfunction was the initial presentation in 54.3% (n=25). The most frequent pituitary deficit was hypogonadism (40/45 patients), followed by hypothyroidism (31/46), GH deficiency (20/40) and ACTH deficiency (22/45). Central diabetes *insipidus* was also common (19/46). Hyperprolactinemia was found in 23/45 patients.

Most of these patients had also systemic sarcoidosis (n=37; 80.4%), the majority in more than one organ/system (n=25; 54.3%). By far, the most frequently involved organ was the lung (n=35), followed by perinasal sinus (n=16). Accordingly, the diagnosis was confirmed mainly with biopsy from extra-neuronal organs (n=31; 67.4%), as in the patient described. Pituitary biopsy was performed in 4 patients and hypothalamic biopsy in one. Two other patients had a definite diagnosis with a brain biopsy and the remaining 8 had a possible diagnosis. This way, in most cases, the diagnosis was, in fact, probable and not definite. Performing CNS biopsies requires surgery, increasing morbidity and costs, so combining clinical, biochemical and radiological findings with pathology confirmation elsewhere might be more feasible for current patient management. A positive response to immunosuppression can also add information to the clinical picture, strengthening a probable or possible diagnosis.

Apart from endocrine imbalance, these patients very frequently have visual deficits, as our own. They might be related to optic neuropathy, optic atrophy, compression or direct involvement of the optic chiasm.[8] Improvement, stabilization or worsening have all been described.[8]

Treatment includes hormonal replacement therapy and immunosuppression. In the above review,[8] high dose of steroids was used in 93.5% of the patients (n=43) with subsequent down-titration. In 20% of the subjects (n=23), addition of other immunosuppressive drugs, including (in decreasing order) methotrexate, mycophenolate mofetil, cyclosporine, azathioprine, infliximab and hydroxychloroquine, was necessary. However, only a small subset of patients had some endocrine improvement (10.9%; n=5). Importantly, radiological improvement of hypothalamic-pituitary lesions did not correlate with resolution of hormonal deficits.[8]

A few other case reports were described after this review was published.[3,9,10] The main characteristics of these patients are summarized in Table 2.

The first 3 patients had diagnostic confirmation in places outside the CNS, the fourth patient had surgery because the mass was thought to be a pituitary adenoma, with histology confirming sarcoidosis. Unfortunately, little data on follow-up of these patients is available.

In conclusion, NS with hypothalamic-pituitary involvement is rare and requires close, prolonged follow-up of the patients because endocrine deficits may persist chronically, even when adequate immunosuppressive treatment of the disease is instituted, and apparent radiological improvement occurs.

Table 2. Case reports of neurosarcoidosis.

Authors	Age Gender	Clinical presentation	Endocrine deficits	Imaging (HP)	Treatment (for sarcoidosis)	Outcome
Non *et al* [11]	45 y Female #	Anterior hypopituitarism, DI and neurological symptoms	DI Adrenal insufficiency (most likely from acute high dose steroid withdrawal) "Central hypothyroidism" interpreted as euthyroid sick syndrome	No hypothalamic or pituitary lesions	Hydrocortisone, then switched back to prednisone	Discontinued desmopressin in a few weeks (hyponatremia) Lost to follow-up afterwards
Sanghi *et al* [10]	40 y Female *	Neurological symptoms	DI Central hypothyroidism	No lesion described in hypothalamus/ pituitary	Methylprednisolone	Neurological improvement. No other data
Alsahwi *et al* [9]	36 y Female	Anterior hypopituitarism and neurological symptoms	Pan-hypopituitarism (all axis) hyperprolactinemia (DI not mentioned)	Sellar mass with supra-sellar extension; optic chiasm deviation	Prednisone	Radiological improvement of the mass (6 months) Persistent adrenal insufficiency, hypothyroidism and hypogonadism
Prayson *et al* [3]	38 y Female	Hyperprolactinemia and neurological symptoms	Hyperprolactinemia (Normal remaining pituitary function tests)	Sellar mass with optic chiasm compression	Prednisone Methotrexate	No data

HP – hypothalamic-pituitary; DI – diabetes insipidus.

Sarcoidosis diagnosis was previous, already with CNS involvement (but no neuroendocrine dysfunction), treated with prednisone and azathioprine (not compliant for a month before acute symptoms began).

* Sarcoidosis diagnosis 6 years before, already with CNS involvement, treated with prednisolone, methotrexate and infliximab (low compliance).

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