

SEVERE HYPONATREMIA REVEALING NEUROSARCOIDOSIS

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Abstract

Sarcoidosis is an inflammatory disease of unknown etiology, characterized by non-caseating epithelioid granulomas. Neurological involvement appears in 5-10% of cases, most frequently leading to involvement of the cranial nerves, the hypothalamus and the pituitary gland (1-3). We hereby present the case of an 82 year old woman with neurosarcoidosis who presented with severe symptomatic hyponatremia.

An 82 year old woman presented to our clinic with fatigue, drowsiness, bradylalia, bradypsychia, all developed in the context of severe hyponatremia. She has been diagnosed with sarcoidosis in 2004 on the basis of histopathological examination. She has been treated with corticosteroids from 2004 until 2007; in 2007 the treatment has been stopped at the patient's initiative.

Clinical examination revealed normal cardiac and pulmonary data; there were no signs of focal neurological involvement. Lab tests showed low levels of ACTH, fT4 and an inadequate normal level of TSH, which raised the suspicion of hypopituitarism. The moderately elevated level of prolactin together with the imaging appearance (enlarged sella turcica on X-ray examination and an expansive process in the sellar and suprasellar regions on computed tomography examination) suggest that hypothalamic-pituitary insufficiency is the more accurate diagnosis. Given the background of untreated pulmonary sarcoidosis, in the absence of another sustainable etiology, we have assigned to sarcoidosis the hypothalamic-pituitary insufficiency. The outcome was good with corticosteroids in moderate dose and thyroid replacement therapy.

Keywords: hyponatremia, pulmonary and mediastinal sarcoidosis, hypothalamic-pituitary insufficiency

BACKGROUND

Sarcoidosis is a multisystemic disease with an estimated prevalence between 8 and 10 cases per 100.000; most frequently it involves the lungs but may involve any organ (2). Clinical manifestations of neurosarcoidosis appear in 5-15% of cases (2-4). Yet, necroptic studies have revealed a prevalence up to 25%; subclinical disease is therefore rather frequent (2). Neurosarcoidosis most frequently involves the cranial nerves, the hypothalamus and the pituitary gland (due to an aseptic basillary meningitis), but sarcoid granulomas may be found in the cerebral parenchyma, the coroid plexuses, the peripheral nervous system and the blood vessels that supply the nervous structures (2). Nevertheless, the signs of hypothalamic-pituitary involvement appear in less than 1% of the cases in which neurosarcoidosis affects sella turcica (2). The most common reported endocrine disorders are diabetes insipidus and hyperprolactinemia (2). The prognosis of neurosarcoidosis is poor with a 10% to 18% mortality (2).

Even if imaging abnormalities diminish or disappear under corticosteroid treatment, the pituitary failure tends to be permanent (2-4). The mechanisms that link hyponatremia to neurosarcoidosis are still unclear; inappropriate anti-diuretic hormone (ADH) secretion and glucocorticoid deficiency were incriminated, but there are also cases of neurosarcoidosis associated with hyponatremia in the absence of hypothalamic-pituitary involvement (1).

CASE REPORT

An 82 year old woman was transferred to our clinic with pronounced fatigue and drowsiness linked to a severe initial hyponatremia (113 mmol/l), partially corrected with the administration of hypertonic saline (NaCl) (when admitted to our clinic serum natremia = 129 mmol/l) but without any improvement of the above mentioned symptoms. The patient was diagnosed in 2004 with pulmonary and mediastinal sarcoidosis and followed treatment with Prednisone from 2004 until 2007 (2 years and seven

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months); the initial dose was 40 mg per day, slowly tapered to 20 mg per day; in 2007 the treatment has been stopped at the patient's initiative.

On clinical examination she had normal pulmonary and cardiac findings, without focal neurological involvement. She presented bradylalia and bradypsychia. Blood tests showed moderate biological inflammatory syndrome, hyponatremia and hypochloremia, normokalemia, normocalcemia, low levels of fT4, ACTH and cortisol, a normally inappropriate TSH and high levels of prolactin (Tables 1, 2, 3).

TABEL 1. Laboratory tests (blood)

Laboratory tests	Determined value	Reference value
Leukocytes	4,34	4-11
Erythrocytes	4,38	4,2-5,6
Hemoglobin	11,7	11,7-15
Platelets	193	150-450
ESR	48	2-30
CRP	19,16	0-5
ALT	23,9	0-32
AST	6,3	0-31
Hb glicozilată	4,93	4,8-5,9
Serum urea	40	<23
Serum osmolality	278	285-295
Creatinine	0,89	0,5-0,9
Triglycerides	109,10	40-150
Glycemia	100	65-115
Total serum proteins	5,74	6,60-8,70
Na	129	135-148
K	4,8	3,6-5,2
Cl	95	98-110
Ionic serum Ca	4,07	3,8-5,6
Total serum Ca	8,29	8,6-10,2

TABEL 2. Laboratory tests (urine)

Laboratory tests	Determined value	Reference values
Urinary urea	362	847-2967
Urinary Na	43	10-250
Urinary Ck	32	10-250
Urinary K	16,44	1-100
Urinary creatinine	47	28-217
Urinary osmolality	453,487	300-900

TABEL 3. Laboratory tests (hormones)

Laboratory tests	Determined value	Reference value
Cortisol	4,31	6,02-18,4
ACTH AM	4,85	7,20-63,30
ACTH PM	6,72	7,20-63,30
fT4	0,914	1,0-1,6
TSH	2.29	0,27-4,20
Prolactin	53,07	5,9-30

Pulmonary radiography showed bilateral hilar adenopathy and bilateral calcified paratracheal adenopathy (Fig. 1).



FIGURE 1. Pulmonary radiography: bilateral hilar adenopathy and bilateral calcified paratracheal adenopathy

Cerebral computed tomography (CT) scanning revealed a solid, well delimited sellar and suprasellar expansive process, with axial diameters of about 2,3/1,3 cm and cranio-caudal diameter of about 1,7 cm. Magnetic resonance imaging (MRI) could not be done because of metallic osteosynthesis material for an old femoral fracture, incompatible with an MRI procedure.

The histopathological report performed in 2004 on a mediastinal adenopathy sustains the diagnosis of sarcoidosis: lots of epithelioid cell granulomas along with giant cells without necrosis, most of the granulomas presenting peri- and intragranuloma sclerosis and sclero-hyalinosis.

The endocrinologic (Table 3) and the imagistic (Fig. 1 and Fig. 2) data are consistent with hypothalamic-pituitary insufficiency manifested with hypocorticism and hypothyroidism and associated with hyperprolactinemia due to an expansive sellar and suprasellar process. Given the background of an untreated neurosarcoidosis (for 11 years), the expansive mass most likely represents a sarcoidotic infiltrate. Prednisone therapy (20 mg per day) and thyroid replacement therapy with Euthyrox (25 mcg) were initiated. The outcome was good, with improvement of the clinical and laboratory data.

DISCUSSIONS

The patient presented with severe symptomatic hyponatremia without previous significant loss of fluids (diarrhea or vomiting) or history of abnormal ingestion of fluids or use of drugs stimulating an-



FIGURE 2. Cerebral CT: sellar and suprasellar expansive process, solid, well delimited, with axial diameters about 2,3/1,3 cm and cranio-caudal diameter about 1,7 cm

ti-diuretic hormone (ADH) release or stimulating ADH action and without diuretic therapy that could explain the sodium loss. There were no arguments for cirrhosis, renal or heart failure. In the presence of a normal level of urinary sodium (Na) we could also rule out a salt wasting nephropathy. Normal levels of glycemia, lipids and serum proteins were not consistent with pseudohyponatremia. Slightly low serum osmolality, normal urinary osmolality and persistent hyponatremia despite fluid restriction ruled out the inappropriate anti-diuretic hormone release syndrome. So, we were dealing with a severe symptomatic hyponatremia without a common cause at the initial evaluation. Furthermore, the symptoms (especially fatigue) persisted in spite of partial correction of hyponatremia. During correction, care has been taken to prevent an osmotic demyelination syndrome. In this situation we decided to order endocrinologic laboratory tests. Thus, we noticed low levels of fT4, cortisol, ACTH, high levels of prolactin and a pseudonormal level of TSH. A diagnosis of pituitary insufficiency was made. Given the abnormal laboratory test results characteristic for hypopituitarism, we performed an X-ray examination of the sella turcica that revealed an enlarged sella. This abnormality was confirmed by a CT scan, showing an expansive sellar and suprasellar process; in this situation a more accurate diagnosis is hypothalamic-pituitary insufficiency. The suprasellar mass and the moderately elevated level of prolactin are solid arguments for the hypothalamic failure (hypothalamic dopamine production deficiency, dopamine being

an inhibitor for the prolactin production) (15).

Differential diagnosis of the hypothalamic-pituitary infiltrating processes is extensive and involves: pituitary adenoma (6), infections like tuberculosis or syphilis, autoimmune hypophysitis (12), histiocytosis X, lymphomas, germinomas, hyper-IgG4 disease (5). In the presence of an inappropriately treated sarcoidosis and in the absence of another valid etiology, we assigned the hypothalamic-pituitary insufficiency to neurosarcoidosis.

Clinical data related to neurosarcoidosis from the medical literature are relatively poor, probably due to the extremely low prevalence of the neurologic involvement.

Neurosarcoidosis has a predilection for young ages (2) and frequently coexists with other cerebral or medular lesions (7). A simultaneous involvement of the cranial nerves is possible, often a multiple one (10) (most frequently – optic neuropathy). The most frequently described endocrinologic manifestations include: diabetes insipidus, hypogonadism, hyperprolactinemia, hypothyroidism (14). In an extremely low number of cases neurosarcoidosis can appear isolated, without a systemic involvement (11).

A useful investigation in this setting is PET-CT with 18F-FDG (13). It has a complex role in diagnosis, stadialization, guiding the biopsy and in monitoring disease evolution.

The essence of the therapeutic choices is, of course, corticotherapy. Often an association with immunosuppressants is prescribed, such as Methotrexate, Mycophenolate Mofetil, Cyclosporine A, Aza-

thioprine. Hydroxychloroquine may also be indicated (8). Anti TNF-alfa agents, especially Infliximab, have a special role in cases of refractory neurosarcoidosis (8,9). In spite of the favorable effect, this therapy corrects only 3 % of the endocrinological abnormalities (8); the rest need replacement hormonal therapy. Mortality rate in neurosarcoidosis remains relatively high: 8,7 % (8).

Our case has several peculiarities as compared to data in medical literature. First, hypothalamic-pituitary involvement appeared late in the disease course, after many years of evolution and at an advanced age. Generally, pituitary involvement in sarcoidosis appears early, sometimes even at the onset. Another peculiarity consists in the onset with hyponatremia of unknown etiology, whereas the most frequent manifestations of neurosarcoidosis are diabetes insipidus and hyperprolactinemia (2). Another peculiarity is the lack of any treatment for pulmonary sarcoidosis for 11 years. Pulmonary lesions were still present on admission in our clinic and come to contradict the general „benignity” regarding pulmonary and mediastinal sarcoidosis evolution (frequently

the lesions disappear after less than 5 years from the onset). Regarding therapy, the advanced age and the altered general state of the patient limited the therapy to corticosteroids in moderate dose, without associating immunosuppressive agents, as it is frequently indicated in the medical literature.

CONCLUSIONS

Sarcoidosis must be taken into account in the differential diagnosis of a hyponatremia of unknown etiology.

Sarcoidosis can be, although seldom, the cause of an expansive hypothalamic-pituitary process.

The corticotherapy is the essence of the treatment. In spite of its efficiency, many patients need chronic hormonal replacement therapy.

The treatment of pulmonary sarcoidosis is controversial; many authors contest the utility of treatment, because of spontaneous remissions. Development of such severe complications, even after so many years of evolution, supports the idea of treating pulmonary sarcoidosis.

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