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Case Report

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Fatigue and hyponatremia in a 75-year-old woman: unusual presentation of hypophysitis

J. Klein, W. Kern, H. L. Fehm

Department of Internal Medicine I, Medical University of Lübeck, Germany

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Summary: A 75-year-old woman presented with general fatigue progressing to somnolence. Laboratory tests showed marked hyponatremia, TSH in the normal range, but low levels of free T3 and free T4. Evaluation of pituitary hormones and magnetic resonance imaging of the pituitary unmasked findings characteristic for hypophysitis with secondary adrenal insufficiency and secondary hypothyroidism. Hormonal substitution with hydrocortisone and levothyroxine resulted in rapid improvement of all symptoms and signs. Without additional treatment shrinkage of the pituitary gland could be documented. Our report extends the known clinical and pathological spectrum of hypophysitis and illustrates the need to include this uncommon entity in the differential diagnosis of hyponatremia even in elderly patients.

Introduction

Hypophysitis is a rare inflammatory disorder, first described by Goudie in 1962, which may lead to destruction of the anterior pituitary and usually affects young women in late pregnancy or postpartum (Beressi et al., 1999; Goudie and Pinkerton, 1962). Histological examination classically reveals infiltration of the pituitary tissue by lymphocytes and macrophages (Beressi et al., 1999), a finding that has led to the coining of the term 'lymphocytic hypophysitis'. Typical features of the clinical presentation include headaches, hypopituitarism with predominant symptoms and signs of adrenal insufficiency, and visual field loss (Beressi et al., 1999; Cosman et al., 1989; Jenkins et al., 1995; Powrie et al., 1995). Here, we describe the unusual case of a 75-year-old woman with general fatigue and hyponatremia as only prominent features that turned out to be caused by secondary adrenal insufficiency and hypothyroidism due to hypophysitis.

Case report

A 75-year-old woman presented with complaints of increasing fatigue and general loss of energy that had progressively been developing over the last five days. Furthermore, she had noticed a puffy face and felt nauseous. She did not report weight loss, night sweats, or fevers, and the remaining functional enquiry was unremarkable. She did not smoke and was on no regular medication. Except for the treatment of tuberculosis forty years ago, the past history was uneventful.

On examination, the patient appeared somnolent, but fully oriented. She was 1.63 m tall and weighed 56 kg. She was afebrile, her blood pressure was 180/90 mmHg, the heart rate was 80 beats/min and regular. Her face was pale and appeared slightly puffy, skin turgor was normal, there were no signs of oedema and no pathological findings on examination of the lungs, heart and abdomen. All peripheral pulses were palpable. Neurological examination revealed no abnormality of the cranial nerves, particularly no visual field deficits. Apart from symmetrical distal hypaesthesia in both feet and diminished ankle reflexes, there were no signs of motor or sensory dysfunction.

The results of routine hematological, blood chemical and enzyme tests were normal with the exception of a marked hyponatremia and elevated values for C-reactive protein, fibrinogen and CK (Table 1). TSH was in the normal range, but free T3 and T4 were decreased. Furthermore, anti-TPO antibody levels were raised (Table 1).

The electrocardiogram, a chest radiograph and an abdominal ultrasound showed no significant abnormalities. Magnetic resonance imaging of the brain revealed a slightly enlarged pituitary that partially extended above the sella. Gadolinium enhancement showed homogeneous uptake in the entire pituitary with a prominent rim along the sellar diaphragm (Fig. 1).

Table 1 Pathological blood chemical values at presentation

Na^+	119 mmol/l	(133–146 mmol/l)	TSH	1.94 mE/l	(0.27–4.15 mE/l)
CK	596 U/l	(10–70 U/l)	free T3	2.0 pmol/l	(2.8–7.1 pmol/l)
CRP	16 mg/l	(0–5 mg/l)	free T4	7.3 pmol/l	(12–22 pmol/l)
Fibrinogen	6.21 g/l	(1.5–4.5 g/l)	anti-TPO	1550 kE/l	(0–60 kE/l)

(range of normal values in parenthesis)

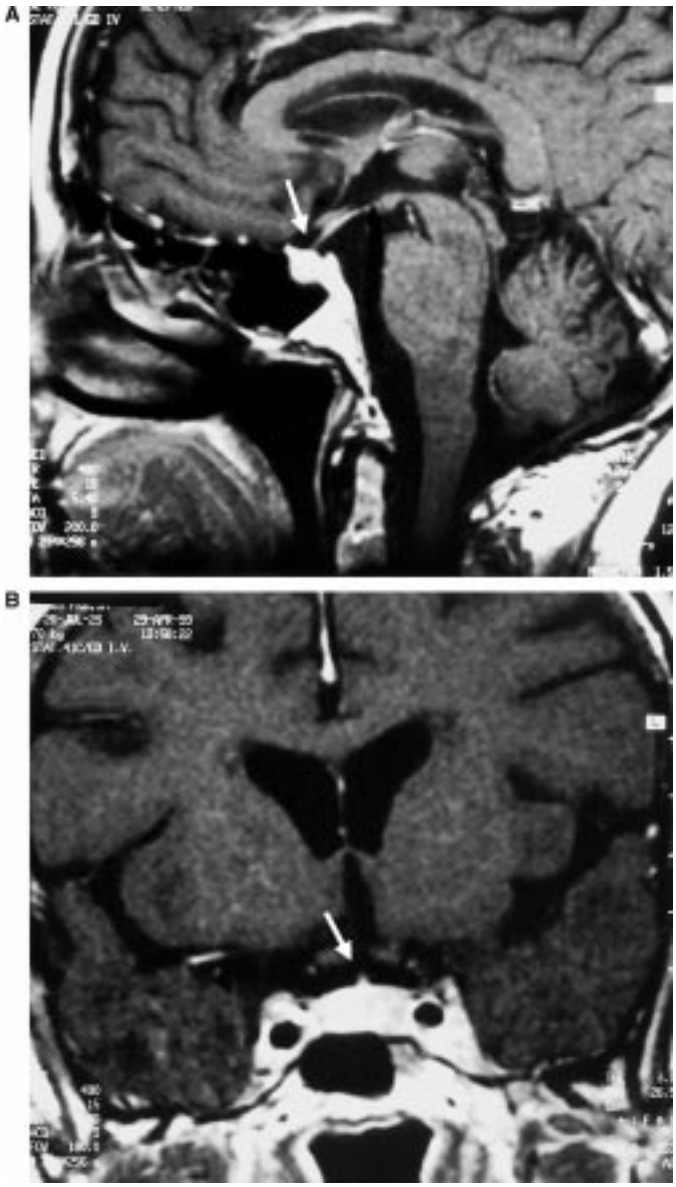

Fig. 1 Contrast-enhanced computed tomography of the pituitary gland in sagittal (**A**) and coronal (**B**) planes at first presentation. In both views there is enlargement of the pituitary gland which extends beyond the sellar diaphragm (arrow in **A**). The entire pituitary takes up the contrast medium with accentuation of a small rim along the diaphragm ("dural tail", arrow in **B**)

Pituitary hormone tests and clinical course

Results of pituitary stimulation tests are shown in Table 2. They revealed an inadequate response of ACTH and cortisol (from very low baseline levels) to Corticotropin-Releasing Hormone stimulation. Similarly, Thyrotropin-Releasing Hormone stimulation did not elicit an adequate response of TSH. Finally, secondary hypogonadism was detected as evidenced by low FSH and LH baseline levels and the absence of a significant rise of these hormones after Gonadotropin-Releasing Hormone stimulation.

Treatment with 200 mg hydrocortisone per day and subsequently 50 μg levothyroxine resulted in rapid improvement of all symptoms. Sodium values returned to normal within the following four days with free water restriction only. Furthermore, the levels of plasma free T3 and T4 as well as basal cortisol also normalized. Magnetic resonance imaging of the pituitary three months later showed a rather small but otherwise normal appearing pituitary with only minimal enhancement of the sellar diaphragm (see Fig. 2). Seventeen months after the initial presentation the patient is well. She is currently taking 100 μg levothyroxine and 30 mg hydrocortisone per day.

Discussion

In this report, we describe a 75-year-old woman in whom fatigue and hyponatremia were the leading clinical and laboratory features at the first presentation. The clinical course, evaluation of pituitary hormones, and imaging studies led to the diagnosis of hypophysitis causing secondary hypothyroidism and adrenal insufficiency. Not only the initial imaging characteristics – demonstrating suprasellar extension of the pituitary and dural contrast enhancement described as pathognomonic "dural tail" (Ahmadi et al., 1995; Honegger et al., 1997) – but also the radiographic changes three months later – characterized by an almost complete *restitutio ad integrum* – corroborated the diagnosis. Furthermore, for hypophysitis, a preference for destruction of ACTH and TSH secreting cells has been reported (Beressi et al., 1999; Jensen et al., 1986; Mayfield et al., 1980; McDermott et al., 1988; Richtsmeier et al., 1980), a finding that is in exact concordance with our case. Yet, a number of features of the case presented here merit special emphasis.

First, the age of onset of hypophysitis is very unusual. Normally, the onset of this rare entity is seen most commonly in young women in late pregnancy or in the postpartum period with a mean age at

Table 2 Results of pituitary function tests at presentation

time (minutes)	Cortisol µg/dl (5–25)	ACTH ng/l (0–60)	LH mIU/ml (13.1–85.5)	FSH mIU/ml (21.5–131)	Prolactin ng/ml (3.01–18.6)	TSH mE/l (0.27–4.15)
−60	1.2	4.3	0.5	5.8	5.8	1.7
−15	2.7	3.3	0	5.6	5.9	1.6
0	2.9	5.1	0	6.1	6.2	1.7
+15	6.9	19.3	1.9	6.3	9.5	4.3
+30	9.3	24.4	2.7	6.7	10	6.3
+45	11.7	20.5	2.7	7.1	9.2	8.2
+60	11.7	18.9	3.1	7.1	8.4	8.8
+90	10.7	13.9	2.9	8.3	8.1	8.5

Plasma hormone levels were measured before (−60, −15), at the time (0), and after (+15, +30, +45, +60, +90) the application of an intravenous bolus injection of 60 µg CRH, 1.5 mg LHRH, and 12 mg TRH; range of normal values in parenthesis

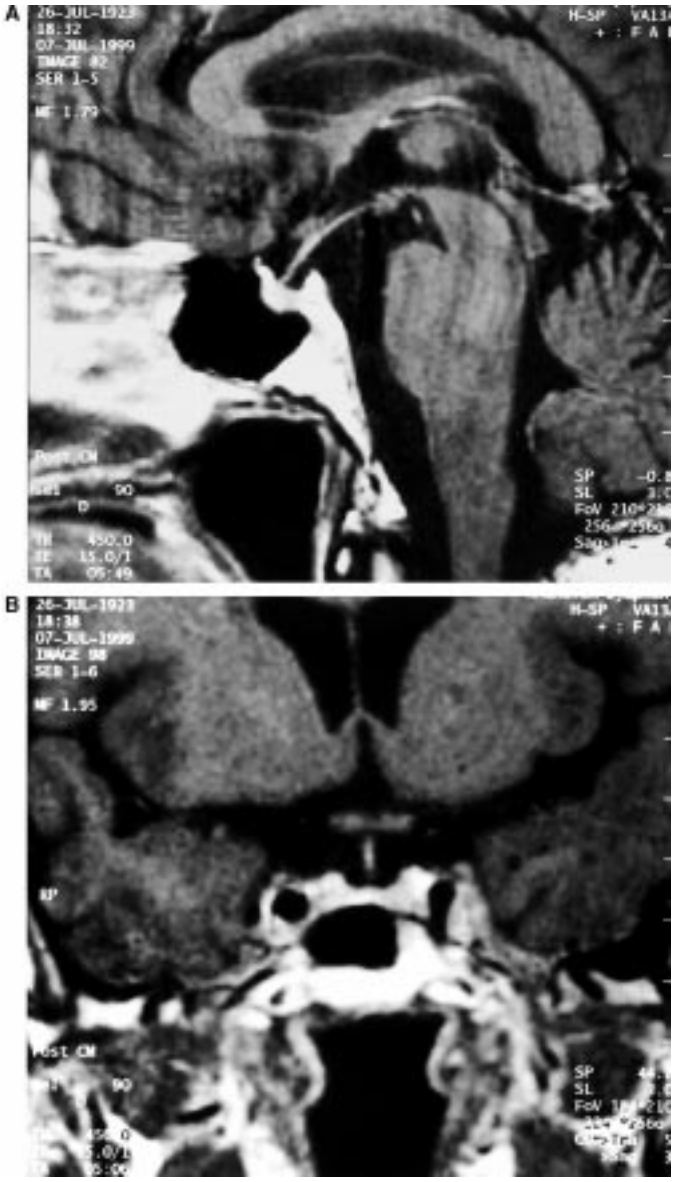

Fig. 2 Contrast-enhanced computed tomography of the pituitary gland in sagittal (**A**) and coronal (**B**) planes at follow up three months after the first presentation. The pituitary gland has significantly decreased in size and now appears rather small. There is no dural contrast enhancement along the diaphragm sellae any more

presentation of 31 years (Beressi et al., 1999; Powrie et al., 1995). To our knowledge, this is the first report of a woman 75 years of age presenting with hypophysitis. Interestingly, we also found elevated TPO-antibodies in the patient presented. This is in keeping with previous reports (Barbaro and Loni, 2000; Beressi et al., 1999; Goudie and Pinkerton, 1962; Nagai et al., 1997; Pestell et al., 1990; Sobrinho-Simoes et al., 1985) and lends support to the hypothesis of an autoimmune origin of hypophysitis.

Second, in contrast to the typical clinical presentation with headaches – that often appear inappropriately severe for the degree of pituitary enlargement (Beressi et al., 1999; Honegger et al., 1997; Ikeda and Okudaira, 1987; Meichner et al., 1987) – our patient only reported fatigue as her main complaint. This symptom as well as the laboratory finding of hyponatremia can be explained by a combination of secondary adrenal insufficiency and secondary hypothyroidism. In this context, elevation of CK indicates the presence of hypothyroidism-induced myopathy. The case of our patient illustrates that in elderly individuals, hypophysitis may present differently. Especially in patients in this age group, many non-specific complaints are frequently encountered. As highlighted by the findings in this case, serum TSH alone may not be sufficient in the laboratory work up of some patients since central hypothyroidism can easily be missed.

Finally, treatment with physiological doses of hydrocortisone and levothyroxine substitution resulted in marked and sustained improvement of the patient with normalization of pituitary size. Currently, no uniform treatment recommendations for hypophysitis exist. Options employed to date comprise operative removal of the infiltrated pituitary tissue (Beressi et al., 1999; Honegger et al., 1997; Jenkins et al., 1995) and supraphysiological cortisol treatment (Beressi et al., 1994; Gagneja et al., 1999; Powrie et al., 1995; Virally-Monod et al., 1996). A "wait and see" strategy with replacement of potentially existing hormonal deficiencies has also been used (Gagneja et al., 1999; Powrie et al., 1995;

Thodou et al., 1995). In our case, this approach has been successful. It is the least invasive and may therefore be the most appropriate in elderly patients, even more so as spontaneous radiological resolution has been documented (Beressi et al., 1999; Gagneja et al., 1999). In this context, it should be emphasised that the diagnosis of hypophysitis in our patient was established solely on clinical grounds, as we considered a histological examination inappropriately invasive.

In summary, our report highlights the need to widen the clinical spectrum of hypophysitis hitherto known. From this, we conclude that this uncommon entity typically seen in young women must not be missed in the differential diagnosis of hyponatremia even in the elderly.

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Dr. Johannes Klein
Department of Internal Medicine I
Ratzeburger Allee 160
D-23538 Lubeck
Germany
Tel.: +49-451-5002867
Fax: +49-451-5004193
E-mail: johannes.klein@medinf.mu-luebeck.de