

# Isolated adrenocorticotrophic hormone deficiency due to probable lymphocytic hypophysitis in a woman

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### ABSTRACT

We report a 22-year-old woman who presented with asthenia, weight loss and hypotension in which extensive pituitary and adrenal investigations were diagnostic of isolated adrenocorticotrophic hormone deficiency (IAD) of pituitary origin. Magnetic resonance imaging of the hypothalamus and pituitary showed a normal-sized pituitary, with no mass lesion. The diagnosis of IAD probably secondary to lymphocytic hypophysitis (LYH) was made. IAD is able to be the way of presentation of LYH, although the disease could or could not turn into a panhypopituitarism. Prompt recognition of this potentially fatal condition is important because of the availability of effective treatment. Indeed, regular endocrine and imaging follow up is important for patients with IAD and normal initial pituitary imaging results to detect early new-onset pituitary hormones deficiencies or imaging abnormalities.

**Key words:** Autoimmunity, isolated adrenocorticotrophic hormone deficiency, lymphocytic hypophysitis

## INTRODUCTION

Isolated adrenocorticotrophic hormone deficiency (IAD) is a rare disorder, defined by secondary adrenal insufficiency with low or absent cortisol production, and normal secretion of pituitary hormones other than ACTH.<sup>[1]</sup> It is being recognized with increasing frequency in the last years.<sup>[2]</sup> A genetic origin may come into play in neonatal or childhood.<sup>[1]</sup> In adults, IAD may appear after a traumatic injury or a lymphocytic hypophysitis (LYH), the latter possibly due to autoimmune etiology.<sup>[1]</sup>

During the past decade, LYH has been recognized increasingly as a cause of hypopituitarism, although its

precise incidence remains unclear. It occurs particularly in women during late pregnancy and the post-partum period.<sup>[3]</sup> There is a spectrum of clinical forms. At one extreme, patients may present with symptoms of an expanding pituitary mass and required surgical decompression. At the other, patients may present with varying degrees of hypopituitarism and have normal radiology.<sup>[3]</sup>

In this report, we describe an unusual case of a 22-year-old female, who developed an isolated adrenocorticotrophic hormone (ACTH) deficiency probably secondary to LYH. Then, we discuss potential mechanisms involved in the pathogenesis of this entity.

## CASE REPORT

A 22-year-old unmarried female presented with a 4-year history of general fatigue, weight loss and hypotension. She was born of non-consanguineous parents after a normal full term vaginal delivery. She reported no family or personal history of autoimmune diseases. She had no history of trauma and she did not have a history of receiving glucocorticoids.

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There were no abnormal findings on clinical examination, she was normally pigmented, blood pressure was 95/60 mmHg with no postural fall, and she had normal body hair. Her height was 170 cm and her weight was 53 kg. Thyroid palpation was normal. She had normal pubertal development. Her menarche started at the age of 12 years and she had regular periods. She had no galactorrhea. She had no headaches, visual disturbances, polyuria, or polydipsia.

Blood examinations showed natremia of 138 mEq/L, kaliemia of 4.1 mmol/L, calcemia of 2.38 mmol/L, plasma glucose of 4.3 mmol/L and normal blood cell count.

Clinical findings led us to consider the possibility of adrenocortical insufficiency, and the patient underwent detailed endocrine investigations, the results of which are shown in Table 1.

Cortisol deficiency was shown clearly by both insulin-induced hypoglycemia and depot Synacthen test [intravenous injection (IV), 1µg]. Secondary hypoadrenalism was confirmed by the finding of low basal ACTH level (13.8 pg/mL, reference range: 10.3-48.3), at which the plasma cortisol was 34 ng/mL. Prolactin level was elevated at 39 ng/mL (Normal range: 5-29 ng/mL in females). She had normal growth hormone levels concomitant to hypoglycemia. In contrast, basal concentrations of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, thyroid stimulating hormone (TSH), and free thyroxine (FT4) were normal. These results excluded panhypopituitarism and led us

to diagnose the patient with IAD. Magnetic resonance imaging (MRI) of the hypothalamus and pituitary showed a normal-sized pituitary (pituitary height 6 mm), with no mass lesion. The pituitary stalk has a normal thickness of 2 mm and was not deviated. The hyperintense signal of the posterior pituitary was in the normal location.

The diagnosis of IAD probably secondary to LYH was made. Investigation for autoimmune diseases, including assessment of anti-thyroid peroxidase antibody (anti-TPO), anti-thyroglobulin antibody (anti-TG), anti-ovarian antibodies, anti-adrenal antibodies, anti-glutamic acid decarboxylase (anti-GAD) antibodies, and antinuclear antibodies (ANA) was negative.

A daily dose of hydrocortisone (25 mg) was administered. After 8 months of follow-up, the patient was well-controlled, and she experienced no signs or symptoms of endocrine dysfunction.

## DISCUSSION

IAD is a rare clinical entity, first described by Steinberg *et al.* in 1954.<sup>[4]</sup> About 200 cases have thus far been described in the literature.<sup>[5]</sup> In our patient, the diagnosis of IAD was based on the fact that baseline values and stimulatory test of the anterior pituitary function revealed an isolated insufficiency of the corticotroph cells.

The main causes of IAD seem to be of pituitary origin and include autoimmune process or LYH, congenital etiologies, and incomplete infarction of the pituitary after delivery.<sup>[1,5,6]</sup> Less frequently, hypothalamic lesion due to birth trauma or head injury is involved in the pathogenesis of this entity.<sup>[7]</sup>

Congenital IAD was thought to be very rare in humans. A few cases had been described with onsets from the perinatal period to the early teen years. Recently, inactivating mutations in the TPIT gene, a T-box factor selectively expressed in developing corticotroph cells, have been found in cases of neonatal IAD.<sup>[6]</sup>

Autoimmune IAD or LYH is suggested if it is associated with other autoimmune endocrinopathies, postpartum onset in women, or serum antipituitary antibodies. Autoimmune disorders include Graves' disease, Crohn's disease, Hashimoto's thyroiditis, myasthenia gravis, type 1 diabetes mellitus, and autoimmune adrenalitis.<sup>[3]</sup>

In our patient, we consider that there is strong evidence for LYH as no other cause of secondary hypoadrenalism could be detected. In fact, iatrogenic, traumatic and vascular causes were rapidly excluded, and the age of onset of the

**Table 1: Results of basal and dynamic endocrine investigations in our patient**

Basal tests					
Parameter (unit)	Value	Normal range*			
Estradiol (pg/mL)	52	30-75			
FSH (IU/L)	6.7	1.8-11.2			
LH (IU/L)	5	2.0-9.0			
FT4 (pmol/L)	19.9	9-22			
TSH (µUI/mL)	0.13	0.3-4.0			
PRL (ng/mL)	39	5-29			
ACTH (pg/mL)	13.8	10.3-48.3			
Dynamic tests					
Determination (min)	0	30	60	90	120
Insulin induced hypoglycemia					
Glycaemia (mg/dL)	78	41	42	67	80
Cortisol** (ng/mL)	154.22	125.43	131.7	143.84	124.46
GH*** (mIU/L)	2	24.5	17.4	16.1	14.5
Cortisol* (ng/mL) after Synacthen test 1µg	34	111	99	-	-

FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, FT4: Free thyroxine, TSH: Thyroid stimulating hormone, PRL: Prolactin, ACTH: Adrenocorticotropic, GH: Growth hormone, \*Values are age and sex adjusted, \*\*Normal value of cortisol after stimulation >200 ng/mL, \*\*\*GH deficiency was excluded by a single level of GH more than 20 mIU/L

disease is not in favour of a congenital hypopituitarism. A tumoral cause of this hypoadrenalism was also excluded by neuroradiological evaluation.

The mechanism involved in the pathogenesis of LYH is unknown, although an autoimmune pathogenesis is suggested by several histopathological, laboratory and clinical findings.<sup>[8]</sup> The frequent association of LYH with other endocrine and non-endocrine autoimmune diseases is a further argument supporting an autoimmune involvement in this disease. The most common association is with Hashimoto's thyroiditis or Graves' diseases. Less frequently, LYH can be associated with central diabetes insipidus, type 1 diabetes mellitus, Addison's disease, hypoparathyroidism, chronic atrophic gastritis, and pernicious anaemia.<sup>[9]</sup>

Antipituitary antibodies have been detected in 30% of patients with LYH but their pathogenetic and diagnostic roles need to be clarified.<sup>[9,10]</sup> In several patients with biopsy-proven autoimmune hypophysitis pituitary autoantibodies were not detected, and the presence of such autoantibodies is not specific of pituitary autoimmunity, as has been described in patients with Cushing's disease, empty sella syndrome and celiac disease.<sup>[3,11]</sup> In our patient, antipituitary antibodies against corticotroph cells antigens were not assessed and screening tests for other autoimmune diseases were negative.

LYH is characterized by chronic inflammation and destruction of the anterior pituitary. Women are affected more frequently than men with a ratio of about 8:1. The mean age at diagnosis is estimated as being 34.5 years for women and 44.7 years for men, although prepubertal or elderly cases have also been described. The most frequently described allele in the few patients in whom the study has been performed is HLA DR4, but HLA DR5 has also been found.<sup>[8,10,12]</sup>

LYH seems to be strongly correlated with pregnancy, and usually affects women either in the last six months of pregnancy and or in the first six months after delivery. However, as seen in our patient, reports of LYH cases occurring outside pregnancy have been reported.<sup>[8,13]</sup> This finding suggests a higher prevalence of LYH than previously thought. Usually, the affected patients have a family or their own history of autoimmunity.<sup>[8]</sup> In our patient, there was no family history of autoimmune disease.

At the onset of the disease, patients present symptoms and signs of extrasellar pituitary enlargement and only later do features of hypopituitarism become apparent. Thus, headache is the first symptom. This usually precedes or

is coupled with visual field impairment and, more rarely, diplopia due to lateral extension of a pituitary mass to the cavernous sinuses.<sup>[8,14]</sup> Our patient had atypical presentation, as she showed clinical signs of adrenocortical insufficiency without previous onset of headaches or visual disturbances.

Hormonal investigations concluded also to a moderate hyperprolactinemia at 39 ng/mL. The latter affects approximately one third of patients with LYH, causing amenorrhea/galactorrhea in women and sexual dysfunction in men.<sup>[8,15]</sup> Several causes have been suggested to explain this hyperprolactinemia, including diffuse inflammatory process, loss of the inhibitory effect of dopamine, alteration of dopamine receptors, lactotroph hyperplasia and escape of prolactin into the circulation secondary to the massive cell destruction.<sup>[8,15]</sup>

Among the 'isolated' pituitary hormone deficiencies, ACTH deficiency is the earliest and most frequent alteration in patients with LYH. This is present in about 65% of cases. In rare cases, it can induce acute secondary hyposurrealism as the first appearance of the disease, LYH can also cause thyrotropin and/or gonadotropin deficiencies whereas data on the effects on growth hormone/insulin-like growth factor-I (GH/IGF-I) secretions are scarce and inconclusive.<sup>[8,16]</sup> Finally, a hypopituitarism involving almost all hormones usually occurs when the inflammatory process induces pituitary tissue destruction.<sup>[8]</sup> In our patient, hormonal investigations excluded panhypopituitarism and led us to the diagnosis of IAD. Thus, long-term endocrine surveillance of our patient is indicated to detect early new-onset pituitary hormone deficiencies.

Imaging of LYH is particularly important to differentiate it from tumors in the sellar or parasellar region even if this is not always possible. The typical precontrast MRI findings include asymmetric enlargement of the pituitary gland, a thickened but rarely deviated stalk, and a usually intact sellar floor.<sup>[9]</sup> The pattern of signal enhancement after injection of gadolinium may be helpful in differentiating LYH from macroadenoma. Homogeneously intense pituitary enhancement is more suggestive of a LYH rather than a macroadenoma.<sup>[9]</sup> If the autoimmune process also involves the infundibulum and the neurohypophysis, causing an infundibulo-neurohypophysitis, there is a loss of the 'posterior pituitary bright spot', and diabetes insipidus is usually present. In rare cases an empty sella can represent an unusual feature of LYH at MRI.<sup>[8,17,18]</sup> However, as seen in our patient, there have been reports of a few cases of LYH presenting with pituitary dysfunction with normal initial pituitary imaging results.<sup>[19-21]</sup>

Therefore, absence of MRI abnormalities does not rule out the diagnosis of LYH and may indicate an earlier stage of

the disease in which inflammatory changes of the pituitary gland are not identifiable on MRI.

Pituitary dysfunction with no pituitary abnormalities on MRI is often labeled as idiopathic hypopituitarism. Nevertheless, these patients need regular imaging follow-up to detect early new-onset MRI signs such as enlargement of the pituitary gland.

To the best of our knowledge, our patient represents the third case of LYH revealed by IAD.<sup>[22,23]</sup> The first one was a 32-year-old woman, in whom her IAD resulted from postpartum LYH. The second one was a 27-year-old male who presented with severe fasting hypoglycemia in which extensive pituitary and adrenal investigations were diagnostic of isolated ACTH deficiency of pituitary origin. This patient had also an autoimmune subclinical primary hypothyroidism which strongly suggested autoimmune origin of his pituitary disease.

## CONCLUSION

IAD is able to be the way of presentation of an autoimmune hypophysitis, although the disease could or could not turn into a panhypopituitarism. Prompt recognition of this potentially fatal condition is important because of the availability of effective treatment. Indeed, regular endocrine and imaging follow-up is important for patients with IAD and normal initial pituitary imaging results to detect early new-onset pituitary hormones deficiencies or imaging abnormalities.

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