May primary empty sella turcica be a cause of isolated ACTH deficiency? A case report and the review of related literature

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Abstract

Isolated ACTH deficiency is an uncommon cause of secondary adrenocortical insufficiency and accompaniment with primary empty sella has been reported in several cases. We present a case of isolated ACTH deficiency associated with empty sella. A sixty-two year old woman was admitted to our endocrine clinic with complaints of weakness, fatigue, weight loss, nausea, vomiting, and lack of appetite for about one month. Physical examination indicated orthostatic hypotension and epigastric tenderness. Laboratory investigations revealed hypoglycemia, hyponatremia and anemia, in addition low plasma cortisole and ACTH levels. Serum cortisole responses to short and prolonged ACTH stimulation were tested and partial and accurate responses were obtained, respectively. Plasma ACTH and serum cortisole levels failed to respond after intravenous injection of human corticotropin releasing hormone. Other hypophysial hormone levels were within the normal reference ranges. Although cranial and abdominal computerized tomography images were evaluated as normal, cranial magnetic resonance imaging of the pituitary gland revealed 'primary empty sella turcica'. Replacement therapy with methylprednisolon resulted in the improvement of hypoglycemia, hyponatremia and clinical symptoms. Based on these results, the patient was diagnosed as isolated ACTH deficiency and was scheduled for follow up by our outpatient clinic. Our report is consistent with other reports pointing out that primary empty sella may be responsible for pathogenesis of isolated ACTH deficiency.

INTRODUCTION

Isolated adrenocorticotropin (ACTH) deficiency (IAD) is a rare cause of secondary adrenocortical insufficiency. The diagnosis is made by the demonstration of low cortisol production with low plasma ACTH, absence of adrenal responses to pituitary or hypothalamus stimulation; with intact adrenal response to exogenous ACTH, and normal secretion of other pituitary hormones [1]. Although the pathogenesis of isolated ACTH deficiency is uncertain, an autoimmune mechanism may be responsible, as suggested by the frequent detection of anti-pituitary antibodies and associated with other

CASE REPORT

autoimmune diseases such as autoimmune thyroiditis [2] and type 1 diabetes mellitus [3] and autoimmune hypophysitis [4]. There have been several reports of IAD together with empty sella [5–13]. Since our patient had both disorders simultaneously, empty sella is considered as a cause of IAD.

CASE

A sixty two year old woman was admitted to the internal medicine outpatient clinic of Duzce Medical School, with one month history of weakness, fatigue, weight loss (7 kg), nausea, vomiting and lack of appetite. Physical examination was normal except orthostatic hypotension (110/80 mmHg supine, 80/55 mmHg standing) and epigastric tenderness. Laboratory investigation revealed anemia (Hb: 11.1 g/dl), hypoglycemia (fasting plasma glucose (FPG): 20 mg/dl) and hyponatremia (Na: 122 mmol/l). The patient was treated with 20% dextrose, 3% NaCl. During the treatment serum glucose and sodium levels increased to maximum 94 and 129 mg/dl, respectively (Table 1). When the treatment was ceased, plasma glucose and sodium levels decreased with a renewal of the symptoms.

Owing to the fact that the patient had hypoglycemia, hyponatremia and orthostatic hypotension, with a suggestion that the diagnosis was likely to be adrenal failure plasma basal cortisole, dehydroepiandrosterone, LH, FSH, ACTH levels were measured. Plasma basal cortisole (2.4 ug/dl, reference range (rr): 5.0–25); dehydroepiandesterone (12.5 ug/dl, rr: 35–430); and ACTH (5.6 pg/ml, rr: 10–40) levels were found under the reference range. The serum LH and FSH levels were within respective reference ranges (Table 2). Short ACTH stimulation test was carried out. Although serum cortisole level was partially responsive to short ACTH stimulation test, it was acutely responsive to prolonged ACTH stimulation test. Plasma ACTH and serum cortisole levels failed to respond after intravenous injection of human corticotropin releasing hormone (hCRH) (Table 3). In order to eliminate an autoimmune process like polyglandular autoimmune syndrome, which includes IAD, hypophysitis and hypothyroidism, we checked out the thyroid-related antibodies and antipituitary auto-antibodies and both were found negative (Table 2). So we decided that our patient did not have an autoimmune disease related with hypophysis.

Cranial CT scan failed to reveal any anatomic abnormality of sella or suprasellar area related with an IAD. Following this, cranial MRI (Figure 1) with contrast in T1 weighted sagittal sections revealed that suprasellar system had widened and the adenohypophysis was thinner. These findings were consistent with empty sella. Because of absence the seconder reasons of empty sella, the patient was diagnosed as primer empty sella.

The patient was treated with 5 mg metilprednisolon in the morning and 2.5 mg in the evening. After this treatment, plasma glucose and serum sodium levels returned to normal and the symptoms disappeared. The patient was discharged and scheduled for follow up in the outpatient clinic.

DISCUSSION

IAD, which was reported first time in 1954 [14], is known a rare cause of secondary adrenocortical deficiency [1]. It has been reported that pituitary anomalies were associated with approximately 80% of IAD cases. This association was more than hypothalamic anomalies [12]. Case studies related with coexistence of ACTH deficiency and empty sella have been reported [5–13,15]. Among these reports, a number of cases indicate that coexistence of IAD and empty sella was frequently associated with thyroid disease including primary hypothyroidism [9–10] or chronic thyroiditis [13]. These reports were focused on an autoimmune process- polyglandular autoimmune syndrome, which includes IAD, hypophysitis and hypothyroidism [5,9,10,13]. Since both the thyroid-related antibodies and anti-pituitary autoantibodies were negative, our patient was considered as has not hypothyroidism or any other autoimmune disease related with pituitary gland.

Table 1. Laboratory findings at admission of patient.

Haematology		Blood chemistry				Urine analysis	
WBC (mm^3)	6.39	Glucose (mg/dl)	20	T. proteine (mg/dl)	7.3	Glucose	(–)
RBC (mm^3)	3.90	CRP (mg/l)	7.2	Albumine (mg/dl)	3.97	Protein	(–)
Htc (%)	32.8	Na (mEq/L)	122	BUN (mg/dl)	17	O.B	(–)
Hb (g/dl)	11.1	K (mEq/L)	4.3	Creatinine (mg/dl)	1.01	Na (mM)	153
Plt (mm3)	385	Cl (mEq/L)	87	AST (IU/L)	37	K (mM)	9.1
		Ca (mg/dl)	8.4	ALT(IU/L)	8		
		P (mg/dl)	5.1	LDH(IU/L)	387		
				ALP(IU/L)	281		

O.B. – occult blood; CRP – C-reactive protein; TP – total protein; BUN – blood urea nitrogen; ALP – alkaline phosphatase.

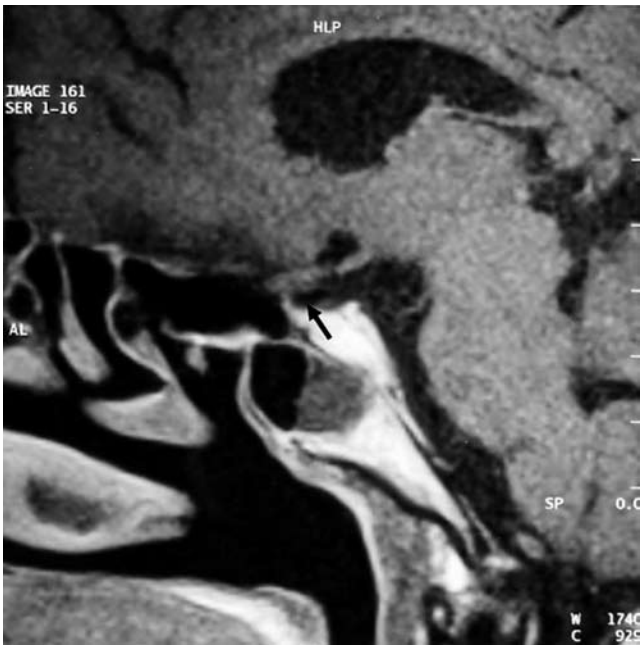

Figure 1. T1 weighted midsagittal MRI image of a 62-year-old woman with isolated ACTH deficiency shows empty sella (arrow).

Table 2. Basal hormone levels of patient

Hormone	Value	Reference Range
ACTH (pg/ml	5.6	10–40
TSH (IU/l)	1.28	0.27–8.8
LH (IU/l)	35.4	7.7–59
FSH (IU/l)	57.8	26–135
GH (ng/ml)	7.8	>6.0
PRL (ng/ml)	12.05	3.4–29.9
Cortisol (µg/dl)	2.4	5–25
DHEA-S (µg/dl)	12.5	35–430
Aldosterone (µg/dl)	8.2	3–24
Urinary free cortisole (µg/day)	7.2	11.2–80.3
FT3 (pmol/ml)	2.3	2.8–10.4
FT4 (pmol/ml)	12.5	11.6–22
TPOAb	negative	
TgAb	negative	
Antipituitary antibody	negative	

TSH – thyroid stimulating hormone; LH – luteotropic hormone; FSH – follicular stimulating hormone; GH – growth hormone; PRL – prolactin; PRA – plasma renine activity; FT3 – free triiodothyronine; FT4 – freee thyroxine; TPOAb – anti-thyroperoxydase antibody; TgAb – anti-thyroglobulin antibody

Table 3. Results of endocrinological functional tests of patient.

	Basal	30 min	60 min	120 min
CRH TEST				
ACTH (pg/ml)	4.1	3.9	3.9	3.8
Cortisol (µg/dl)	2.4	2.3	2.4	2.4
SHORT ACTH TEST				
Cortisol (µg/dl)	3.2	9.1	12.4	14.7
PROLONGED ACTH TEST	**0 h**	**24 h**	**48 h**	**72 h**
Cortisol (µg/dl)	5.4	31.6	44.5	38.3
Urinary free cortisol (µg /day)	8.6	47.6	84.2	156.8

Pituitary hormone dysfunctions and pituitary abnormalities could accompany in patients with IAD. For example, impairment of growth hormone secretion was noted in 20–30% of patients with IAD [16,17]. Furthermore Hatazoe et al. reported a case of IAD associated with GH deficiency and empty sella [7].

There are two forms of empty sella; ie, primary empty sella and secondary empty sella. Primary empty sella is idiopatic. But, several etiopathogenetic hypotheses have been proposed, including a congenital incomplete formation of the sellar diaphragm and supra sellar factors such as stable or intermittent increase in intracranial pressure as well as volumetric changes in the pituitary [18–20]. On the other hand, secondary empty sella may be caused either by pituitary adenomas undergoing spontaneous necrosis (ischemia or hemorrhage) [21] or by infective, autoimmune, and traumatic causes or by radiotherapy, drugs, and surgery [22]. After all investigations to check out aforementioned causes, if there was no reason to lead empty sella the case could considerable as primary empty sella. Also several studies had suggested that empty sella might have a role in pathogenesis of isolated ACTH deficiency [8,12,23,24].

It has been stated that findings of cranial radiography and tomography for patients with IAD are generally normal [25]. In our patient, this was corroborated by the normal cranial computerized tomography (CT) findings. However, cranial magnetic resonance imaging (MRI) revealed the presence of empty sella. Therefore, this situation shows the superiority of cranial MRI than CT for causal diagnosis related with sella turcica.

The diagnosis of IAD can not be made by clinically, since patients exhibit a range of non-specific signs and symptoms which common to those with hypocortisolism. Nevertheless, a patient who has hypoglycemia, hyponatremia and orthostatic hypotension without accompanied darkening of the skin, an initial diagnosis is generally secondary adrenal deficiency [1]. Among the causes of secondary adrenal deficiency, the most common reason is suppression of the adrenal-pituitary axis which depends on iatrogenic glucocorticoid using. Other causes include acquired and rarely congenital hypopituitarism and seldom ACTH unresponsiveness. However, IAD is a seldom cause of secondary adrenal deficiency.

Several case reports have indicated that hypoglycemia and severe hyponatremia might be accompanied with IAD [11,26]. Hypoglycemia is the most common finding in secondary adrenal insufficiency possibly due to concomitant growth hormone insufficiency and in isolated ACTH deficiency [27]. Since our patient had moderate

hyponatremia and severe hypoglycemia and both clinical conditions were improved by corticosteroid replacement thus she was considered as has not GH deficiency.

There are several causes of IAD. In adults, IAD may appear after a traumatic injury or a lymphocytic hypophysitis, the latter possibly due to autoimmune etiology. [28]. IAD has been reported in patients with autoimmune diseases, such as Hashimoto's thyroiditis, type 1 diabetes mellitus, and lymphocytic hypophysitis, the disease is presumed to be partly ascribable to an autoimmune mechanism [2–4]. However, it remains undetermined whether such autoimmunity play an important role in the etiology of this disease [29]. Moreover, it has been identified that some kind of defects in the corticotropin-releasing hormone gene, AAAS gene, TBX19 gene and alfa MSH, could be cause of IAD [30,31,32].

In several cases, it has been indicated that empty sella might be cause of IAD like as our case. [8,12,23,24].

Our patients' clinical, laboratory and radiological findings indicated empty sella associated with IAD. This is consistent with other reports which suggested that primary empty sella may cause IAD. Based on our case study, we recommend that patients with suggested secondary adrenal deficiency should be investigated for IAD related with primary empty sella.

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