Autoimmune Polyglandular Endocrinopathy and Anterior Hypophysitis in a 14 Year-Old Girl Presenting with Delayed Puberty

A. Pinar Cemeroğlu, Ece Bober, Bumin Dündar and Atilla Büyükbüz

Department of Pediatric Endocrinology and Adolescence, Faculty of Medicine, Dokuz Eylul University, Izmir, Turkey

ABSTRACT

We report a 14 year-old peripubertal girl who presented at our clinic with the primary complaint of delayed puberty. She was asymptomatic except for vague complaints of fatigue. Physical examination was significant for mucosal hyperpigmentation and lack of secondary sexual characteristics. Laboratory evaluation revealed a morning cortisol concentration of <0.1 μg/dl (normal range [n.r.]: 4.3-22.4 μg/dl) and a simultaneous ACTH concentration of 2 pg/ml (n.r. 25-62 pg/ml); FSH 66.8 IU/l (n.r. for age: 1-12.8 IU/l); LH 41.1 IU/l (n.r. for age: 1-12 IU/l); E2 38 pg/ml (n.r. for age: 7-60 pg/ml). She had a flat cortisol response to an ACTH stimulation test. MRI of the pituitary gland failed to reveal a lesion. Plasma renin activity, thyroid function tests, parathyroid hormone, prolactin, IGFBP-3 concentrations and serum electrolytes were normal. However, her urinary sodium concentration was high. She was diagnosed with autoimmune polyglandular endocrinopathy including ovarian failure, adrenal failure and autoimmune anterior hypophysitis presenting as isolated ACTH deficiency. We emphasize that autoimmune etiology should be considered in the differential diagnosis of delayed puberty and ovarian failure and that the presence of other endocrinopathies should be searched for even in asymptomatic patients.

KEY WORDS

autoimmune hypophysitis, autoimmune adrenitis, autoimmune ovarian failure, polyendocrinopathy, ACTH deficiency

INTRODUCTION

Autoimmune (lymphocytic) hypophysitis is a rare disorder characterized by lymphocytic infiltration of the anterior and/or posterior hypophysis in adult females during the peripartum or postpartum period. Since its first description by Goudie and Pinkerton in 1962, over 150 patients have been reported. Although most of the patients reported are young women aged 25 to 35 years, male patients and postmenopausal women have also been reported. However, this condition is very rare in children.

Autoimmune hypophysitis is characterized by isolated or combined deficiencies of anterior pituitary hormones and/or diabetes insipidus. Isolated ACTH deficiency suggests autoimmune hypophysitis. While pituitary hormone deficiencies may be the presenting symptom, sometimes signs and symptoms of increased intracranial pressure may predominate if the size of the lesion is large enough. Other autoimmune disorders, most commonly Hashimoto's thyroiditis and adrenitis, are associated with this disorder.

We report here a 14 year-old girl with autoimmune polyglandular endocrinopathy and isolated ACTH deficiency who was referred to the Pediatric Endocrinology and Adolescence Unit for the complaint of delayed puberty. To our knowledge, only a few adolescents without associated pregnancy and only one prepubertal girl have been
reported to have autoimmune hypophysitis during childhood. 

PATIENT REPORT

A 14 year old girl was referred to Dokuz Eylul University Pediatric Endocrinology and Adolescence Unit with the complaint of delayed puberty. She has had no major problems except for a vague complaint of fatigue and intermittent mild abdominal pain for the past 2 years. She had had no breast development or pubic hair growth by the age of 14 years which made her parents seek medical attention. Her parents were first-degree relatives. She was 154 cm in height (10th percentile), 44.6 kg in weight (10-25th percentile) and her blood pressure was 110/80 mm Hg. Physical examination was remarkable for mucosal hyperpigmentation of her lips and gingiva (Fig. 1). However, she had no hyperpigmentation of the nipples or tanning of the skin. Her thyroid gland was not palpable. She had stage I pubic hair and breast development. The rest of her physical examination was unremarkable.

Laboratory tests revealed a blood glucose of 80 mg/dl, BUN 12 mg/dl, creatinine 0.7 mg/dl, Na+ 139 mEq/l, K+ 4.0 mEq/l, Cl− 110 mEq/l, Ca2+ 9.5 mg/dl, P 5.5 mg/dl, alkaline phosphatase 358 IU/l, AST 19 IU/l, ALT 15 IU/l. Endocrine tests revealed FSH 66.8 IU/l (normal range for age [n.r.] 1-12.8 IU/l), LH 41.1 IU/l (n.r. 1-12 IU/l), E2 38 pg/ml (n.r. 7-60 pg/ml), total T3 1.8 ng/ml (n.r. 60-1.81 ng/ml), total T4 10.6 µg/dl (n.r. 4.5-10.9 µg/dl), and TSH 3.42 IU/l (n.r. 0.35-5.5 IU/l). Antithyroglobulin and antimicrosomal antibodies were negative. Initial differential diagnosis included gonadal dysgenesis and autoimmune ovarian failure. Karyotype analysis revealed 46XX. Morning cortisol was 0.1 µg/dl (n.r. 4.3-22.4 µg/dl) and evening cortisol <0.1 µg/dl (n.r. 3.1-16.6 µg/dl). These results indicated that in addition to ovarian failure she had autoimmune primary adrenal failure which would explain her mucosal hyperpigmentation (Table 1). However, a repeat morning cortisol was 0.1 µg/dl (n.r. 4.3-22.4 µg/dl) with a simultaneous ACTH level of 2 pg/ml (n.r. 25-62 pg/ml). ACTH stimulation test (short acting synacthen® 0.25 mg i.v.) resulted in a flat cortisol response with a baseline of <1 µg/dl and a peak of 1 µg/dl at 60 min. This unexpected finding of a very low ACTH level in the face of unmeasurable morning cortisol indicates ACTH deficiency. Other pituitary hormone evaluations, including TSH and gonadotropins, did not suggest panhypopituitarism. Prolactin level was 15 ng/ml (n.r. 1.8-20.3 ng/ml). IGF-I was 232 ng/dl (within -1 SD for chronological age), and IGFBP3 3500 ng/ml (within -1 SD for chronological age), both of which do not suggest GH deficiency. MRI of the pituitary gland was normal. Evaluation for mineralocorticoid deficiency revealed plasma renin activity of 1 ng/ml/h (n.r. 0.5-5 ng/ml/h) and aldosterone of 2.1 ng/ml (n.r. 0.8-2.8 ng/ml). On ultrasound, she had a normal prepubertal uterus, and ovaries and adrenal glands were normal. Anti-ovarian and anti-adrenal antibodies (immunofluorescence technique, Enzyme-laboratory, Switzerland) were both negative.

She was started on oral replacement therapy of 10 mg/m2/day hydrocortisone equivalent dose of prednisolone and 0.625 mg/day of estradiol (premarin®). After glucocorticoid replacement, her parents noticed an increase in the mucosal hyperpigmentation. Repeat blood tests after 3 months of glucocorticoid replacement revealed a morning plasma cortisol of 3.48 µg/dl with a simultaneous ACTH level of 190 pg/ml. Therefore the glucocorticoid replacement dose was increased to 14 mg/m2/day. Although she was clinically well, her ACTH level continued to increase, up to >1250 pg/ml with a simultaneous cortisol concentration of 0.14 µg/dl at 6th month of treatment. During follow-up, she continued to have normal serum sodium concentrations, ranging between 136 and 143 mEq/l (n.r. 136-146 mEq/l) and serum potassium ranging between 3.6-4.6 mEq/l (n.r. 3.5-5.5 mEq/l). Although her renin and aldosterone concentrations and serum electrolytes were within normal ranges, she had spot urinary sodium of 144 mEq/l (n.r. 20-40 mEq/l) on a low sodium diet and 186 mEq/l on an ad libitum sodium diet. Therefore she was also started on mineralocorticoid replacement (fludrocortisone acetate, 0.05 mg/day). Currently she is also on 17 mg/m2/day of hydrocortisone in three divided doses.
Fig. 1: Mucosal hyperpigmentation, most notable on the mucosa of the lower lip and gingiva.

**TABLE I**

Findings of the patient with polyendocrinopathies

<table>
<thead>
<tr>
<th>Endocrinopathy</th>
<th>Related clinical findings</th>
<th>Laboratory evidence (normal range)</th>
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<tbody>
<tr>
<td><strong>Ovarian failure</strong></td>
<td>Absence of pubertal development</td>
<td>FSH: 66.8 IU/l (1-12 IU/l) LH: 41.1 IU/l (1-12 IU/l) E2: 38 pg/ml (7-60 pg/ml)</td>
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<tr>
<td><strong>Primary adrenal failure</strong></td>
<td>Mucosal hyperpigmentation</td>
<td>Basal morning and evening cortisol levels &lt;0.1 μg/dl (am: 4.3-22.4 μg/dl, pm: 3.1-16.6 μg/dl)</td>
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<td>(Fig. 1)</td>
<td>Fatigue</td>
<td>ACTH stimulation test: flat response</td>
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<td></td>
<td></td>
<td>Gradual increase in ACTH concentration following glucocorticoid replacement</td>
</tr>
<tr>
<td><strong>Anterior hypophysitis</strong></td>
<td>Fatigue</td>
<td>ACTH: 2 pg/ml (25-62 pg/ml) with simultaneous am cortisol of &lt;0.1 μg/dl (4.3-22.4 μg/dl)</td>
</tr>
<tr>
<td>(isolated ACTH deficiency)</td>
<td></td>
<td>Improvement with glucocorticoid treatment in replacement dose</td>
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<td></td>
<td></td>
<td>Pituitary MRI: normal</td>
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DISCUSSION

Autoimmune gonadal failure may present early during childhood as total or partial failure of pubertal development in young girls - less commonly in boys. Autoimmune ovarian failure in association with adrenal failure is most commonly seen in type I and less frequently in type II autoimmune polyglandular syndrome. Even though it is a rare association, anterior hypophysitis has been described in a child with type I autoimmune polyglandular endocrinopathy with ectodermal dysplasia. Therefore this patient will be monitored closely for development of other endocrinopathies.

It is interesting that the patient presented here had normal electrolytes, renin and aldosterone concentrations and very vague clinical findings, despite very low plasma cortisol and increased urinary sodium concentrations. Autoimmune adrenalitis usually has an insidious onset and the symptoms may be vague, until a frank Addisonian crisis develops. Furthermore, mostly the failure of all layers of the adrenal cortex is not simultaneous, and one may occur months or years before the other. Therefore the clinical picture of this patient at presentation is not unusual. Although she seemed to have compensated mineralocorticoid deficiency, given her increased urinary sodium excretion, she was also started on mineralocorticoid replacement during follow up.

In autoimmune adrenalitis, only 75% of the patients have positive adrenal antibodies at the onset of the disease. Therefore absence of anti-adrenal antibodies does not rule out an autoimmune etiology in a patient, especially in the presence of other endocrine end organ failures. Although we were unable to demonstrate adrenal autoantibodies, autoimmune polyglandular endocrinopathy is the most likely diagnosis for the patient presented here since she had both ovarian and adrenal failure.

Autoimmune hypophysitis is commonly associated with autoimmune adrenalitis and Hashimoto's thyroiditis. However, when adrenalitis and ACTH deficiency coincide, diagnosis could be quite challenging. Autoimmune hypophysitis is most commonly diagnosed clinically, and some cases are proven histologically, either by autopsy or in biopsy specimens. MRI or CT findings are commonly encountered, but sometimes the lesion cannot be demonstrated by imaging studies. Even in patients with pituitary mass lesions, the size of the mass lesion may wax and wane. Therefore follow up with MRI of the pituitary gland will be necessary in suspected cases, even if the initial MRI of the pituitary gland is normal. The patient reported here had very low ACTH in the face of an unmeasurable cortisol concentration, no response to ACTH stimulation test, and mucosal hyperpigmentation, all of which indicate that, in addition to isolated ACTH deficiency, she had primary adrenal failure before the hypophysitis developed. Although we were unable to demonstrate a pituitary lesion by MRI, follow-up imaging studies are required, especially when anterior hypophysitis is overt clinically.

Autoimmune hypophysitis is thought to be due to a cellular defect causing development of multiple organ-specific antibodies. Pituitary antibodies have been detected in 28-70% of the patients with biopsy-proven lymphocytic hypophysitis and in 28% of their relatives. Prognosis of autoimmune hypophysitis is usually favorable if hormone deficiencies are appropriately replaced. Since it is an autoimmune process, corticosteroids have been tried, but the results are controversial. However, most patients with anterior hypophysitis showed a temporary improvement in clinical and/or radiological findings in response to steroids or immunosuppressive treatment. It has also been reported that pituitary lesion mass may regress spontaneously even without any intervention. Therefore, conservative measures are the usual approach in autoimmune lymphocytic hypophysitis. Surgery is indicated only if there is a need for decompression in patients with increased intracranial pressure. In the patient presented here, glucocorticoid treatment in replacement dose caused a progressive increase in ACTH concentration. Therefore, isolated ACTH deficiency in this patient seemed to respond to steroids by a remarkable increase in ACTH concentrations. However, this response may be temporary, and continued follow-up is required for this patient for recurrence of autoimmune hypophysitis and subsequent development of other pituitary hormone deficiencies.

In conclusion, we report a rare association of anterior hypophysitis, adrenalitis and ovarian...
failure in a peripubertal girl who presented with delayed puberty. We emphasize that autoimmune polyendocrinopathy should be considered in the differential diagnosis of ovarian failure in peripubertal girls, and the presence of other endocrinopathies should be looked for even in the absence of obvious signs and symptoms of endocrine organ failure.

REFERENCES
