Growth Hormone Deficiency in Autoimmune Polyglandular Syndrome

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ABSTRACT

We describe a boy with autoimmune adrenal failure and compensated hypothyroidism, associated with isolated growth hormone deficiency (GHD). We suggest an autoimmune mechanism as the underlying etiology for the GHD in this case.

INTRODUCTION

The autoimmune polyglandular syndromes (APS) are characterized by the presence of autoimmune processes against several endocrine and non-endocrine organs /1/. An association between autoimmune endocrinopathy and hypopituitarism is rare. In a few reports in the literature, the pathological changes in the pituitary gland were in the form of lymphocytic hypophysitis. These cases occurred almost exclusively in women during or shortly after pregnancy /2/.

We describe a child with autoimmune process in the adrenal and thyroid glands, a combination that is compatible with APS type 2 /1/. In addition, he showed growth deceleration associated with GHD, with a significant improvement in response to GH therapy. This is the first report of GHD in a child with APS.

PATIENT REPORT

A 14 year-old Caucasian male presented with fatigue and several bouts of nausea and vomiting over a period of several months. In addition, he showed growth deceleration (from a normal growth rate of 5.1 cm/year) with poor weight gain (Figs. 1, 2).

On initial physical examination, his height was 145.5 cm (–2.29 SD) and weight 29.4 kg (79.5% of ideal body weight). Neck examination revealed a slightly enlarged thyroid gland that was grainy in texture. There were no signs of puberty.

Thyroid function tests revealed normal T₄ (8.3 μg/dl) and slightly elevated TSH (7.3 μIU/ml; normal 0.7-5.7). A diagnosis of compensated hypothyroidism with goiter was made, and the patient was placed on Levothyroxine. He still had episodes of nausea and vomiting, and an ACTH stimulation test was done to rule out adrenal failure. Both basal and peak cortisol levels were low (1 and 2.5 μg/dl, respectively) while basal ACTH level was very high at 1400 pg/ml (normal less than 60 pg/ml). Consequently, the patient was started on hydrocortisone replacement therapy.

At the age of 14.2 years, the patient was referred to our endocrine clinic for further evaluation due to growth failure. Results of the endocrine work up are summarized in Table 1.

Two months after initiation of Levothyroxine therapy, T₄ was 8.0 μg/dl and TSH still mildly elevated at 7.0 μIU/ml, but 4 months later TSH was normal at 0.8 μIU/ml. Apparently, this reflects a slow regression in TSH concentration toward normal levels, which can be seen at the beginning of
Fig. 1: Weight to height curve. The initial weight gain happened over a period of seven months, while on Levothyroxine, hydrocortisone and Florinef therapy (see text).

Fig. 2: Growth chart before and during treatment with thyroxine (T), hydrocortisone (H), HCG and growth hormone (GH). The open circles mark the bone age. Parents' heights are marked by F (father) and M (mother).

TABLE 1
Results of endocrine tests

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>Peak</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol (µg/dl)</td>
<td>UD</td>
<td>UD</td>
<td>Basal: 7-20</td>
</tr>
<tr>
<td>ACTH stimulation test</td>
<td></td>
<td></td>
<td>Peak: 15-36</td>
</tr>
<tr>
<td>Insulin tolerance test</td>
<td>UD</td>
<td>UD</td>
<td>Basal: 7-20</td>
</tr>
<tr>
<td>IC cortisol</td>
<td>UD</td>
<td></td>
<td>Peak: &gt;20</td>
</tr>
<tr>
<td>Renin activity (ng/ml/h)</td>
<td>&gt; 46</td>
<td></td>
<td>0.6 - 1.6</td>
</tr>
<tr>
<td>LH/FSH (mIU/ml)</td>
<td>4.6/2.0</td>
<td>22.7/</td>
<td>8.1</td>
</tr>
<tr>
<td>GnRH stimulation test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testosterone (ng/dl)</td>
<td>34</td>
<td>1157</td>
<td>270-1070</td>
</tr>
<tr>
<td>HCG course</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free testosterone (pg/ml)</td>
<td>0.6</td>
<td>40.6</td>
<td>10-40</td>
</tr>
<tr>
<td>HCG course</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Growth hormone (ng/ml)</td>
<td>0.5/2.5</td>
<td>1.5/4.6</td>
<td>Peak: ≥ 10</td>
</tr>
<tr>
<td>(before HCG/after HCG)</td>
<td>0.8/1.9</td>
<td></td>
<td>≥ 3.2</td>
</tr>
<tr>
<td>Insulin-arginine tolerance test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IC growth hormone</td>
<td></td>
<td></td>
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</tbody>
</table>

* UD = Undetectable

* IC = Integrated concentration

* Level obtained after long HCG course (see text)
Levothyroxine therapy in primary hypothyroidism

Following gradual withdrawal of hydrocortisone, the pituitary-adrenal axis was reassessed. Cortisol levels were undetectable in an ACTH stimulation test, insulin induced hypoglycemia and in 24-hour measurement of serum integrated concentration of cortisol, obtained through continuous blood withdrawal. Hyponatremia at a level of 127 meq/l was found, and renin activity level was above the assay's upper limit of detectability. Subsequently, Florinef (fludrocortisone acetate) was started.

In accordance with delayed puberty, total and free testosterone levels were undetectable, but a GnRH stimulation test showed a response typical of early puberty. In order to induce puberty and to rule out primary hypogonadism, the patient was placed on biweekly injections of HCG for 6 weeks. Subsequently, he entered puberty (testicular volume > 4 ml) and showed a significant elevation in serum testosterone concentration at the end of the test (Table 1).

Growth hormone level was found to be very low when determined by 24-hour serum integrated concentration and in response to insulin and arginine stimulation tests. Similar results were obtained after induction of puberty by HCG.

A brain MRI scan focusing on the pituitary gland was normal.

Screening for autoantibodies revealed the presence of antithyroglobulin (1182 U/ml; normal < 100), antithyroid microsomal (262 U/ml; normal < 50), and antiafluent antibodies (1:32). Steroid cell antibodies, assayed by indirect immunofluorescence and using both ovarian and testicular tissues, were positive (Pathology Department, University of Florida).

Other autoantibodies, including antinuclear, antiparietal cell, anti-intrinsic factor, anti-insulin and anti-islet cell, were negative. No antibodies against pituitary tissue were found by an indirect immunofluorescence technique, using a section of human hypophysis. The patient has shown a remarkable improvement in weight gain during the first 7 months of follow-up while being on Levothyroxine, hydrocortisone and Florinef (Fig. 1), but he was growing below the 5th percentile, at a rate of 5.8 cm/year. After GH was started and in the following 2 years, the growth rate has increased to 8.5 cm/year (Fig. 2). There was also a progression in puberty from Tanner stage 2 to 4 during this period which also contributed to the growth spurt. This contribution of sex steroids to growth was probably minor, however, since testosterone levels were consistently below 300 ng/dl (i.e. in the prepubertal range) up to the age of 16.8 years, and accordingly, there was a bone age change of only one year over a period of 2 years.

DISCUSSION

Our patient showed a unique combination of APS type 2 /1/ with isolated GHD. Other pituitary hormones were shown to increase in response to stimulation (LH) or end organ failure (TSH and ACTH). In addition, the normal progression of puberty after HCG course indicates intact functioning of the pituitary gonadotrophs. GHD was confirmed by studies performed both before and after induction of puberty, since it can be a transient phenomenon in children with delayed puberty /4/. It is conceivable that both GHD and the delayed puberty (in spite of no family history of delayed puberty) contributed to the growth deceleration of this patient. As expected in GHD, the patient has shown a significant increase of growth rate in response to GH therapy.

A deficiency of pituitary hormones in association with nonpituitary autoimmune endocrine disease has been previously reported in a few adult cases of hypophysitis, which is characterized by lymphoid infiltration of the pituitary gland /2/. In two cases of hypophysitis, GH deficiency was reported as part of panhypopituitarism /5,6/.

Similar to our case, there are several reports of adult patients in whom APS was associated with partial hypopituitarism, namely, deficiency of ACTH /7,8/, gonadotrophins /9/, both growth hormone and ACTH /10/, or with panhypopituitarism /11/. Hypophysitis was postulated but not confirmed histologically in these cases. In a large series of Schmidt's syndrome (currently known as APS type 2), however, hypophysitis was found histologically in several patients /12/.

Lymphocytic hypophysitis is considered an autoimmune disease, based on experimental animal models /13/, detection of antipituitary antibodies /6/.
and the association with other autoimmune diseases. The reported cases of hypophysitis show that immune destruction of one pituitary cell line may occur while all other pituitary cell lines maintain their normal function. Hypophysitis has not been reported in children, and it occurs almost exclusively in women, particularly in relation to pregnancy. The resemblance of our case to previous reports of hypophysitis, however, and the coexistence of GHD with APS, suggest that an autoimmune process confined to the pituitary somatotrophs is the underlying etiology for GHD in this case. Likewise, autoimmune etiology for GHD has been suggested by Bottazzo et al. /14/, who found antisomatotroph antibodies in a girl with Turner's syndrome and partial GH deficiency.

A definite diagnosis of hypophysitis can only be made by biopsy of the pituitary, which was not indicated in our patient. The absence of antipituitary antibodies does not preclude an autoimmune process in the pituitary gland, as these antibodies are non-specific /15/. Furthermore, they were not detected in several patients with biopsy-proven hypophysitis /5,16/.

REFERENCES