Case report

Growth hormone deficiency in a patient with autoimmune polyendocrinopathy type 2

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ABSTRACT

Autoimmune polyglandular syndrome (APS) type 2 is characterized by the presence of Addison’s disease, in association with autoimmune thyroid disease and/or type 1 diabetes mellitus and is rare in children. A 12.5yr old prepubertal boy presented with symptoms related to Addison’s disease and a large goiter. He was euthyroid with positive thyroid antibodies, low cortisol, aldosterone and very high adrenocorticotropic hormone (ACTH) and renin levels. Growth hormone (GH) secretion and an MRI scan of the pituitary were normal. He was started on hydrocortisone, fludrocortisone and subsequently on L thyroxine. Eighteen months later, decreased growth rate was noted and GH deficiency was detected, apparently secondary to autoimmune hypophysitis. Interestingly, he did not develop any other pituitary hormone deficiencies. He was started on GH therapy and had a good treatment response in the next 3 years. The combination of adrenal and thyroid insufficiencies with autoimmune hypophysitis is a very rare manifestation of APS-type 2. GH deficiency as the only symptom of lymphocytic hypophysitis is extremely rare. In children with autoimmune polyendocrine disorders, careful monitoring of growth is needed. In the case of low growth rate, GH should be evaluated by dynamic tests and, if GH deficiency is detected, treatment with hGH must be initiated.

Key words: Autoimmune hypophysitis, Autoimmune polyendocrinopathy type 2, Growth hormone deficiency

INTRODUCTION

Autoimmune polyglandular syndromes (APS) are rare nosologic entities characterized by the presence of more than one autoimmune endocrine disease.

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Four main types have been described,1,2 APS type 1 is characterized by chronic candidiasis, chronic hypoparathyroidism and autoimmune Addison’s disease; the presence of two of these diseases is necessary for its definition.3 APS type 1 usually presents at a young age, develops completely before the age of 20 yrs and is associated with different mutations of the AIRE (Autoimmune Regulator) gene on chromosome 21.4 APS type 2 is characterized by the presence of autoimmune Addison’s disease (always
present), in association with either autoimmune thyroid disease and/or type 1 diabetes mellitus. It is a rare syndrome which may occur at any age and in both sexes but it is most common in middle-aged females and very rare in childhood. APS type 2 is often inherited in an autosomal dominant pattern with incomplete penetrance and has been associated with various HLA alleles. Autoimmune thyroid diseases associated with other autoimmune diseases (type 1 diabetes, atrophic gastritis, pernicious anemia, vitiligo, alopecia, myasthenia gravis and others), excluding Addison's disease and/or hypoparathyroidism, are the main characteristics of APS type 3.

The various clinical combinations of autoimmune diseases not included in the above categories have been defined as APS-4. Autoimmune hypophysitis, often referred to as lymphocytic hypophysitis, is characterized by infiltration of the pituitary gland by chronic inflammatory cells and can be a rare manifestation of APS type 1 and even more rarely of APS type 2. In a total of 379 patients with autoimmune hypophysitis, 18% of cases were associated with other autoimmune diseases and 1.8% with APS type 2. Autoimmune hypophysitis can cause pituitary enlargement and a variable degree of hypopituitarism. This report describes a 12.5 year old boy who presented with APS type 2 and subsequently developed growth hormone (GH) deficiency.

PATIENT'S DESCRIPTION

A 12.5 year old boy presented with a 4-month history of tiredness and weakness, anorexia and nausea. He had lost 2.5 kg of weight and during the last 12 months had developed a craving for salt. From his family history, his maternal grandmother had suffered from rheumatoid arthritis since the age of 25 years. He was born at term with a birth weight of 2550 gr. There was nothing significant from his past medical history. Father's height was 170.5 cm, mother's height 156.2 cm, and the target height (TH) was 169.9 cm.

On physical examination, his height was 140 cm (-1.26 SDS), his weight 27.5 kg (-1.9 SDS) and he had a large, firm goiter (grade III). He was prepubertal: pubic and axillary hair Tanner stage 1 and testicular volume 3ml.

An ultrasonographic scan of the thyroid revealed enlargement of both lobes (thyroid volume 13 ml, n.v.<10.7) with diffusely reduced echogenicity.

Laboratory investigations showed normal thyroid function indices with triiodothyronine (T3): 2.61 nmol/l (normal range 1.23-3.07), thyroxine (T4): 105.53 nmol/l (72-154) and thyroid stimulating hormone (TSH): 2.2 mIU/l (0.4-5). The thyroid auto-antibodies were strongly positive, suggestive of Hashimoto's thyroiditis: Anti-TPO: 1:25600 IU/ml (n.v: neg), Anti-Tg: 1:2560 IU/ml (n.v: neg). Morning plasma cortisol (08:00) was low: 57.85 nmol/l (NV:318-362), adrenocorticotropin hormone (ACTH) and plasma renin were raised: 1500 pmol/l (NV:1.98-11) and 2200 μU/ml (NV:7-76), respectively. The aldosterone value was low: 0.27 nmol/l (NV:10.8-83.7). These findings were diagnostic of primary adrenal insufficiency. Antidrenal antibodies were positive, whereas islet cell antibodies, anti-GAD, parietal cell antibodies, smooth muscle antibodies and antimitochondrial antibodies were negative. GH secretion following administration of clonidine was normal (peak maximum 12.8 μg/L).

Gonadotropins were at the prepubertal levels: FSH 1.05 IU/L (normal range <3.3), LH 0.48 IU/L (normal range <1) and PRL 710.4 pmol/l (<888). An MRI scan of the pituitary and hypothalamus was normal.

The patient was started on hydrocortisone 10 mg twice daily (19 mg/m²), fluocortisone 0.1 mg daily and after two months on L thyroxine 100 μg daily.

Eighteen months later growth deceleration was noted. His height velocity was 2 cm/yr (-2.56 SDS) and his height was 143 cm (-3rd centile). GH secretion was re-assessed with 2 different tests (L-Dopa and clonidine), following priming with 50mg of testosterone im given 5 days prior to the testing. The maximum GH response following L-Dopa and clonidine was 4.1μg/L and 2.3μg/L, respectively, indicative of GH deficiency. IGF-1 was low: 13.1nmol/l (-2.8 SD). GnRH test and TRH test were normal. A repeat MRI scan of the pituitary and the hypothalamus was normal.

The patient was started on rhGH therapy at a dose of 0.5IU/kg/wk. He had a good treatment response and grew 27cm in the following 3 years. His puberty started spontaneously at the age of 14.3 years and
proceeded uneventfully. At present, aged 17 years, his height is 170 cm (equal to TH), pubic hair Tanner stage 4, testicular volume 20 ml and serum testosterone 21 nmol/L. The glucagon stimulation test after hGH discontinuation showed a maximum GH response of 6.5 μg/L. A repeat MRI scan of the pituitary and hypothalamus was normal.

DISCUSSION

This patient presents three very interesting and unusual aspects. First, given that APS type 2 occurs most often in middle-aged females, its presentation in a boy during childhood is uncommon. Second, autoimmune hypophysitis presenting as a component of APS type 2, as was the case in our patient, is very rare. Finally, GH deficiency without any other pituitary hormone deficiency is a very rare manifestation of autoimmune hypophysitis.

APS type 2, also known as Schmidt’s syndrome, is a rare condition occurring with a prevalence of 1.4–2.0 per 100,000 inhabitants. It most often presents in middle-aged women (female-male ratio ranges from 2–3.7) and is very rare in childhood. In this communication we report a 12.5 yr old boy with Addison’s disease, autoimmune thyroiditis and subsequent GH deficiency most likely caused by autoimmune hypophysitis. In patients with APS type 2, Addison’s disease is present in 100% of the cases, autoimmune thyroid disease in 69–82%, and type 1 diabetes mellitus in 30–52%. Other autoimmune diseases that are not the major components may be present in APS type 2: hypergonadotropic hypogonadism (4–9% of patients), vitiligo (4.5–11% of patients), alopecia (1–4% of patients), chronic hepatitis (4% of patients), chronic atrophic gastritis with or without pernicious anemia (4.5–11% of patients) and hypophysitis. In this case report, the boy did not develop type 1 diabetes, but he developed GH deficiency which could be attributed to autoimmune hypophysitis, which is a very rare component of the syndrome. Although APS type-2 is often inherited in an autosomal dominant pattern, in our patient there has been no known family history of APS.

At the onset of Addison’s disease, adrenal cortex autoantibodies and/or 21-hydroxylase autoantibodies are detectable in the majority of the patients with APS type 2. Patients with type 1 diabetes mellitus frequently have positive ICA, anti GAD Abs or IA2 Abs. Patients with chronic thyroiditis frequently demonstrate positive thyroid peroxidase and/or thyroglobulin autoantibodies, which was also the case with our patient. Antihypophyseal antibodies could not be determined.

Autoimmune hypophysitis is more common in females than males (3 to 1 predilection), most often during late gestation or in the postpartum period. In approximately 20% of the cases it coexists with other autoimmune diseases, most commonly with thyroid disease, and it is now well established that it is part of the APS. There is a wide variation in the clinical features of autoimmune hypophysitis, including symptoms of sellar compression, such as headaches and visual disturbances. The next most common symptoms result from anterior pituitary insufficiency, mainly ACTH, followed by TSH, gonadotropins and PRL and rarely posterior pituitary insufficiency. The prevalence of GH deficiency among patients with autoimmune hypophysitis, although not always reported, varies between 26–54%. Interestingly, our patient had normal growth and GH secretion at presentation, but several months following diagnosis he developed growth retardation and GH deficiency without developing any other pituitary hormone deficiency or symptoms related to autoimmune hypophysitis. Typical MRI findings of autoimmune hypophysitis include a symmetric enlargement of the pituitary gland, a thickened stalk and an intact sellar floor. However, as in our patient, there are case reports of patients with autoimmune hypophysitis with normal CT or MRI scan. The boy responded satisfactorily to GH treatment and had spontaneous puberty, which proceeded uneventfully.

The combination of autoimmune hypophysitis with adrenal and thyroid insufficiencies is a very rare condition. It was first described by Goudie and Pinkerton in 1962 in a 22 yr old woman who died a few months following delivery, probably because of adrenal insufficiency. Subsequently, the case of a 69yr old woman with the co-existence of panhypopituitarism, adrenal and thyroid insufficiencies and atrophic pituitary on the MRI scan and normal CT scan was described.

In summary, the occurrence of APS type 2 in a
12.5 yr old boy is described. Adrenal insufficiency and autoimmune thyroiditis were the presenting endocrinopathies as well a presumptive autoimmune hypophysis. This combination constitutes rare manifestations of the syndrome, especially at such a young age. Although the boy had normal GH secretion at diagnosis of Addison's disease, he subsequently developed GH deficiency as the only symptom of presumed hypophysitis. He responded satisfactorily to GH treatment. These observations suggest that careful follow-up in children with autoimmune polyglandular syndrome is needed to assess growth and development. When growth failure develops and GH deficiency is proven, treatment with GH should be undertaken to restore normal growth.

REFERENCES