Case Report

Autoimmune polyglandular syndrome Type 3 and growth hormone deficiency


The simultaneous occurrence of prepubertal Graves' disease, type 1 Diabetes Mellitus (DM), and Growth hormone deficiency (GHD) is uncommon. GHD has been reported in Autoimmune Polyglandular Syndrome (APS) Type 1 and Type 2 but not in APS Type 3. We report a 3-yr-old boy who presented simultaneously with type 1 DM and Graves' disease. After he developed urticarial rash to Propylthiouracil and Methimazole with persistent thyrotoxicosis, he received 8 millilicuries of $^{131}$I at 5 yr of age. We diagnosed GHD at age 8 yr 8 months because of growth deceleration (from 95 to 25%) and abnormal growth rate (3 cm/yr) despite euthyroidism, fair glycemic control, and normal weight gain. Both insulin-like growth factor (IGF) 1 (90 ng/mL; normal 113–261 ng/mL) and IGFBP3 (1.3 mcg/mL; normal 2.1–4.2 mcg/mL) levels were low and peak growth hormone level measured by RIA was 5.2 ng/mL after I-Dopa and insulin tolerance test. The rest of his pituitary functions and magnetic resonance imaging of the pituitary gland were normal. Growth hormone treatment (0.3 mg/kg/wk) was administered at 8 yr 9 months until near final adult height (FAH). Near FAH (172 cm) was close to midparental target height of 180 cm. GHD may be a component of all APS even though it is rare. Growth in treated children with Graves' disease should be followed closely as catch down growth below genetic height potential may be a harbinger of underlying GHD.

Autoimmune Polyglandular Syndromes (APS) are characterized by the presence of autoimmune processes against several endocrine and non-endocrine organs. Four main types have been described (1).

APS-1 (Autoimmune-Polyendocrine-Candidiasis-Endodermal-Dystrophy Syndrome (APECED): Chronic candidiasis, chronic hypoparathyroidism, and autoimmune Addison's disease (the presence of two is necessary for the definition).

APS-2 (Schmidt's disease): Autoimmune Addison's disease (always present), in association with either autoimmune thyroid disease and/or type 1 diabetes mellitus (DM).

APS-3: Autoimmune thyroid disease associated with other autoimmune diseases like type 1 DM, atrophic gastritis, pernicious anemia, vitiligo, alopecia, myasthenia gravis but excluding Addison's disease and/or hypoparathyroidism.

APS-4: Combinations not included in the previous groups.

To our knowledge, no case of simultaneous occurrence of prepubertal Graves' disease, type 1 DM and Growth hormone deficiency (GHD) has been reported.
We report a 3-yr-old boy who presented with APS Type 3 and subsequently developed GHD.

Case report

A 3-yr-old boy presented in 1988 with a 4-wk history of profuse diarrhea, weight loss, hyperactivity, polyuria, polydipsia, polyphagia, and insomnia. He was born full term with birth weight at 50th percentile and birth length between 75th and 90th percentile. His father’s height was 183.7 cm and mother’s height was 165.1 cm. His midparental target height (MPH) was 180.9 cm. Paternal grandmother had type 1 DM.

On physical examination height was 106 cm (95th percentile), height age (HA): 3 yr 10 months, height z-score 2.1, and weight 14 kg (50th percentile) with heart rate of 120 beats/min. He had exophthalmos, diffuse thyromegaly measuring 6 × 2 cm, and brisk deep tendon reflexes. There were no vitiligo or café au lait spots.

Laboratory values were T4 15.5 mcg/dL (199.5 nmol/L), normal 4.5–12 mcg/dL; T3 58–154 nmol/L, thyroid-stimulating hormone TSH 0.02 uU/mL, and serum glucose 464 mg/dL (25 mmol/L). Anti-islet cell antibody, antithyroglobulin antibody, and antiparietal cell antibodies were positive but adrenal antibodies were negative. We diagnosed type 1 DM and Graves’ disease and treated him with Propylthiouracil (PTU) 50 mg every 8 h (10 mg/kg/day) and Regular & Lente insulin.

He became hypothyroid after 6 months of PTU and Levothyroxine was added to PTU treatment (block and treat method). Insulin regimen was adjusted based on blood glucose targets.

At age 4, he developed PTU-related urticarial rash which persisted with Methimazole therapy. Because of persistent thyrotoxicosis [T4 20 mcg/dL (257 nmol/L), T3 336 ng/dL (5161 pmol/L), and TSH of 0.1 uU/mL], he received Radioactive 131I treatment (8 millicuries) at age 5 1/2 years. Radioiodine (RAI) 123I uptake scan showed abnormally high uptake of 36% at 4 h and 62.2% at 24 h (Normal 24-h uptake is 7–33%) with bilaterally functioning thyroid gland that was diffusely enlarged 3–4 times the normal size.

Between ages 6 and 7, growth rate decelerated to pre-Graves height % of 75% (Fig. 1). However growth continued to slow after 7 yr despite euthyroidism; fair glycemic control (mean HbA1c last 2 yr was 8.7%) and normal weight gain. At age 8.5 yr, height was 128 cm (30th percentile, Height SDS = 0.3), weight 27 kg (50th percentile) and growth velocity was 3 cm/yr. Bone age was 8 yr consistent with his chronological age. Insulin-like growth factor(IGF)-1 was 90 ng/mL (11.7 nmol/L; normal 113–261 ng/mL; 14.7–34 nmol/L) and IGFBP3 was 1.3 mcg/mL (normal 2.1–4.2 mcg/mL).

Both were measured by competitive binding RIA at Esoterix, Calabasas, CA, USA.

Growth hormone provocative test with L-Dopa and insulin-induced hypoglycemia at 8 yr 8 months showed peak GH level of 5.2 ng/mL (normal > 10 ng/mL) at 30 min and peak cortisol of 27 mcg/dL (744 nmol/L). GH was measured by standard double antibody RIA at Esoterix. The rest of his pituitary functions were normal. Predicted adult height of 173 cm was 7 cm below MPH of 180 cm. Magnetic resonance imaging (MRI) of the pituitary gland was normal. The infundibular stalk was midline and showed normal enhancement. Growth hormone replacement was started at 8 yr 9 months at a dose of 0.3 mcg/kg/wk. Growth rate improved from 3–7 cm/yr after 1 yr of growth hormone treatment. Subsequent annual growth rates are shown in Fig. 2.

Pubertal onset occurred at 11 yr 9 months and progression was normal. Bone age progression was consonant with chronologic age. At 14.5 yr, his bone age (BA) was 14 yr. He was Tanner 4 genitalia and pubic hair with 20 cm2 testicular volume. His serum testosterone was 206 ng/dL (7142 pmol/L). His last endocrine visit was at 15.5 yr prior to transferring care to another provider. He was on Levothyroxine 175 mcg/daily and Lente and Regular insulin. He was euthyroid with fair glycemic control of 8.2%. He was fully pubertal with serum testosterone of 327 ng/dL (11 338 pmol/L). Near final adult height was 172 cm (height SDS = 0.01), 8 cm below his MPH of 180 cm.

Discussion

We report the long term follow up of a 3-yr-old boy with APS Type 3 and GHD. He presented with combination of type 1 DM, prepubertal Graves’ disease followed by post-RAI GH deficiency.

The co-existence of type 1 DM and Graves’ disease is one of the variants of APS Type 3. Three genes have been confirmed as major joint susceptibility genes for type 1 DM and Autoimmune Thyroid disease: human leukocyte antigen class II, cytotoxic T-lymphocyte antigen 4, and protein tyrosine phosphatase non-receptor type 22 (2). The simultaneous occurrence of prepubertal type 1 DM and Graves’ disease at diagnosis, however, is uncommon. Riley et al. in a study of 117 out of 771 type 1 DM patients with serologic evidence of chronic thyroiditis found eight patients (7%) with hyperthyroidism and 45 (38%) with hypothyroidism. Hyperthyroidism usually preceded or coincided with the appearance of type 1 DM. The mean age of these eight patients at onset of thyroid disease was 11.2 ± 2.1 yr (3).

Studies of thyrotoxicosis in children and adolescents are associated with accelerated growth without detrimental effect on final height (4–6). Although children had advanced BA and HA in relation to chronologic age, the BA/HA ratios was close to one. In
a study of growth of treated prepubertal children with thyrotoxicosis who were euthyroid, height standard deviation scores remained positive, showing slight reduction (about 0.3 change in Ht Z-score) after 3 yr of treatment (4). Our patient’s height z-score declined from +1.98 to −0.27.

Thyroid dysfunction may affect the Growth hormone-IGF1-IGFBP3 system. Growth hormone secretion and alteration of the IGF1 and IGFBP3 system has been studied in children and adults with thyrotoxicosis with conflicting results (7–10). Growth hormone response to insulin-induced hypoglycemia in thyrotoxic adults was normal in one study (7) and low in another study (8). Our patient was euthyroid at the time of GH testing and had subnormal GH secretion with low IGF1 and IGFBP3 levels.
Despite the patient’s GH deficiency, there was no BA delay because of effect of thyroid hormone excess on the growth plate. Whereas hypothyroidism slows longitudinal bone growth and endochondral ossification, hyperthyroidism accelerates both processes (11). T4 and T3 are needed for chondrocyte hypertrophy and for vascular invasion of the growth plate and metaphyseal bone formation (12).

To our knowledge, there has been no reported case of isolated GHD with APS Type 3. However, GHD has been reported in cases of APS Type 1 and 2 (13–16). Partial GH deficiency was associated with empty sella in one case (13) and autoimmune hypophysitis was proposed as the etiology of the other cases (14–16). However in Papathanasiou’s report, despite GH deficiency, IGF1 and IGFBP3 levels were not reported. This 14-yr-old boy with Addison’s disease also received a generous Hydrocortisone dose (19 mg/m²/day) that may have affected growth hormone secretion resulting in decrease growth velocity (16). MRI of the pituitary gland was normal in two cases (15, 16) and was not done in one case (14).

Typical MRI findings of autoimmune hypophysitis include symmetric enlargement of pituitary gland, thickened stalk and intact sellar floor. Pituitary biopsy showing infiltration of pituitary gland with chronic
inflammatory cells provides definitive diagnosis. We did not test for anti-pituitary antibodies. Antibodies against pituitary antigens have been measured mainly by indirect immunofluorescence. Pituitary antibodies have both low sensitivity (26–36%) and poor specificity for diagnosing autoimmune hypophysis (17).

Autoimmune hypophysitis results in anterior pituitary insufficiency, mainly adrenocorticotropic hormone, followed by TSH, gonadotropins, growth hormone, prolactin, and rarely posterior pituitary insufficiency (17). In approximately 20% of cases of autoimmune hypophysitis, other autoimmune diseases co-exist with commonly thyroid disease. Possible mechanism for GHD may involve selective loss of somatotrophs from targeted autoimmune destruction (13, 15) or gammaglobulins that have inhibitory effect on anterior pituitary hormone secretion (18).

One limitation of our case report is the lack of screening tissue transglutaminase IgA Ab or anti-endomysial antibody at the time of growth failure. Five percent of patients with type 1 DM may develop Celiac disease and may present with growth failure without gastrointestinal symptoms. However, continued weight gain, lack of gastrointestinal symptoms and improvement of growth rate 7 yr after growth hormone treatment argues against celiac disease.

In conclusion we presented the long term follow up of a child presenting with APS Type 3 and GH deficiency. GHD may be a component of all APS even though it is rare. Growth in treated children with Graves' disease should be followed closely as catch down growth below genetic potential may be a harbinger of underlying GHD.

References