

# A rare case of coexistence of autoimmune polyglandular syndrome type 3 with growth hormone deficiency and hyperthyroidism in a patient with pseudo-Turner's syndrome

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## Abstract

Autoimmune polyglandular syndrome (APS) is a rare disease that is characterized by autoimmune reactions to multiple endocrine and non-endocrine organs, which can be divided into four main types. The principal manifestations of APS-3 are autoimmune thyroid disease and other autoimmune diseases, such as type 1 diabetes, atrophic gastritis, pernicious anemia, vitiligo, alopecia, and myasthenia gravis, but not Addison's disease or hypoparathyroidism. Here we report a case demonstrating the rare coexistence of growth hormone deficiency and hyperthyroidism with sexual dysgenesis, secondary amenorrhea, cardiomegaly, splenomegaly, hypoproteinemia, pleural effusion, seroperitoneum, pericardial effusion, anasarca, osteoporosis, vitamin D deficiency, iron-deficiency anemia, poor blood coagulation, leucocytopenia, peripheral neuropathy, hyperuricemia, ichthyosis, tinea cruris, and onychomycosis.

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**Keywords**

Autoimmune polyglandular syndrome type 3, growth hormone deficiency, hyperthyroidism, Graves' disease, amenorrhea, osteoporosis

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**Introduction**

The association of autoimmune thyroid diseases, such as thyroiditis and Graves' disease, with gonadal dysgenesis in Turner's syndrome is well established.<sup>1</sup> However, the association of gonadal dysgenesis with growth hormone deficiency (GHD) and amenorrhea, which are caused by Graves' disease, has seldom been discussed. To the best of our knowledge, there have been no reported cases of concurrent GHD and Graves' disease. Here, we report a patient with concurrent GHD and amenorrhea which were caused by a form of hyperthyroidism that might be confused with concurrent Turner's syndrome and Graves' disease. The patient was diagnosed as having autoimmune polyglandular syndrome (APS) type 3. We also discuss the relationships between GHD and Graves' disease, with particular emphasis on sexual dysgenesis phenomena and APS-3.

**Case report**

A 33-year-old rural Chinese woman was admitted to our department due to recurrent anasarca, shortness of breath after mild labor, anorexia, nausea for 6 months and amenorrhea for 3 months. The patient was 130 cm in height, whereas her target height was 151.5 cm (father's height: 161 cm, mother's height: 155 cm). Poor breast development, a "shield-like" chest with widely spaced nipples, the absence of axillary and pubic hair and infantile external genitalia were found on physical

examination. Her intelligence level was normal according to the rural mode of the Wechsler Adult Intelligence Scale, Revised for Chinese (WAIS- RC).

She had a number of other unusual anatomical features, such as a highly arched palate, a slightly high elbow carrying angle, slightly prominent clavicles, and excessive digital dorsiflexion; although she did not have short fourth metacarpals, clinodactylia of the fifth finger, posterior rotation of the ears, ocular hypertelorism, a wide mouth with downturned corners, or a rounded nose; and webbing of the neck was not obvious. Extensive laboratory testing revealed low concentrations of insulin-like growth factor-1 (IGF-1) ( $< 25$  ng/mL; reference range: 117 to 329 ng/mL) and insulin-like growth factor binding protein-3 (IGFBP-3) ( $< 0.5$  ug/mL; reference range: 3.5 to 7.6). Therefore, GH stimulation tests were performed, which showed poor responses to arginine and clonidine (Table 1). This is indicative of GH deficiency.

The patient's mother underwent a normal pregnancy and delivered her at full term, but the patient exhibited highly deficient growth at 6 years of age, despite her parents and sister having developed normally. Her peripheral blood leukocytes were cultured to determine her karyotype using 550 banding and G banding (Adicon Clinical Laboratories, Inc., Hangzhou, China), which 46, XX. Then, magnetic resonance imaging (MRI) of her pituitary gland was performed and her circulating glutamic acid decarboxylase antibody

**Table 1.** GH secretion following the administration of arginine or clonidine.

	Baseline	30 min	60 min	90 min	120 min
Arginine GH stimulation test (ng/ml)	0.58	2.3	3.04*	2.39	3.03
Clonidine GH stimulation test (ng/ml)	1.07	1.72*	1.43	1.38	—

\*The highest GH concentrations that were measured during the arginine or clonidine GH stimulation tests were <7 ng/mL.

GH, growth hormone.

**Table 2.** Comparisons of the serum thyroid hormone and related antibody concentrations on the two occasions the studied patient was examined.

Hormone or antibody	4 years previously	At the present time	Reference range
TT4 (nmol/L)	237*	121.5	58–161
TT3 (nmol/L)	6.4*	1.75	0.9–2.5
FT4 (pmol/L)	>77.2*	26.41*	10.3–24.5
FT3 (pmol/L)	14.3*	8.35*	3.23–7.22
TSH (mU/L)	0.011*	0.015*	0.4–4.0
TPOAb (U/mL)	>1,000*	>6,500*	0–35
TRAb (U/L)	—	>40*	<1.75

\*Value not within the reference range.

TT4, total thyroxine; TT3, total triiodothyronine; FT4, free thyroxine; FT3, free triiodothyronine; TSH, thyroid-stimulating hormone; TPOAb, thyroid peroxidase antibody; TRAb, thyrotrophic receptor antibody.

(GADAb) concentration was measured. The former showed no abnormalities, but her GADAb concentration was significantly higher than normal (198.61 U/mL; reference range: 0 to 30 U/mL).

The patient had been diagnosed with hyperthyroidism 4 years previously, after which methimazole treatment was initiated, but the patient discontinued this after 2 months, and took no medication until her present admission. Physical examination, ultrasonography and <sup>99m</sup>Tc sestamibi (MIBI) scintigraphy all showed moderate enlargement of both thyroid lobes, which were firm and rubbery in consistency. Assay of circulating thyroid hormone and related antibody concentrations (Table 2) showed low thyroid hormone concentrations, consistent with thyrotoxicosis of ~5 years' duration, a high thyrotrophic receptor antibody (TRAb) concentration

(>40 U/L; reference range <1.75 U/L) and a high rate of radioiodine (RAI, <sup>131</sup>I) uptake (71.4% at 2 hours, 80.2% at 4 hours, 83.2% at 6 hours and 83.5% at 24 hours; reference range for 24 hours uptake: 7%–33%).

The conditions of the patient's other organs were also investigated using laboratory tests and imaging. She had low action potential amplitudes in her right ulnar nerve and both peroneal nerves, splenomegaly, and dry skin with a low temperature and high pigmentation. She also had ichthyosis of her lower extremities, tinea cruris of the right groin, onychomycosis of the left thumb, cardiomegaly, splenomegaly, hypoproteinemia, pleural effusion, seroperitoneum, pericardial effusion, vitamin D deficiency and osteoporosis, iron-deficiency anemia, poor blood coagulation, leucocytopenia and peripheral neuropathy.

This study was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (reference no. 2019-1529). We ensured the confidentiality of the patient's identity and obtained the patient's written informed consent for publication.

## Discussion

Concomitant GHD, hyperthyroidism and numerous other clinical defects have never previously been reported in a single patient. Therefore, many rare diseases were considered as potential differential diagnoses for the present case before a definitive diagnosis was made.

POEMS syndrome is a paraneoplastic syndrome that is caused by plasmacytoma. The major diagnostic criteria for this syndrome are polyradiculoneuropathy, clonal plasma cell disorder (PCD), sclerotic bone lesions, high circulating vascular endothelial growth factor concentration, and Castleman disease. The minor characteristics of the syndrome include organomegaly, endocrinopathy, characteristic skin changes, papilledema, extravascular capacity overload, and thrombocytosis. A diagnosis of POEMS requires the presence of three of the major features, including polyradiculoneuropathy and clonal PCD, and at least one minor feature.<sup>2</sup> Though the present patient had low action potential amplitudes in her right ulnar nerve and both peroneal nerves, splenomegaly, endocrine diseases, including GHD and Graves' disease, high skin pigmentation, and other skin diseases, such as ichthyosis, tinea cruris and onychomycosis, she did not have PCD. Therefore, POEMS syndrome was not diagnosed.

The present patient exhibited pseudo-Turner's syndrome, which is characterized by the presence of some features of Turner's syndrome. She had short stature, sexual dysgenesis, amenorrhea (albeit secondary

amenorrhea), poor breast development, infantile vulva, a "shield-like" chest with widely spaced nipples, a highly arched palate, slightly high elbow carrying angle, slightly prominent clavicles and excessive digital dorsiflexion. Furthermore, some patients with Turner's syndrome that had autoimmune thyroid diseases, such as thyroiditis and Graves' disease, have been reported.<sup>3,4</sup> Indeed, we were suspicious of Turner's syndrome because of the presence of these compatible features. However, the present patient did not have short fourth metacarpals or clinodactyilia of the fifth finger, and webbing of the neck was not obvious. Furthermore, she did not have posteriorly rotated ears, ocular hypertelorism, a wide mouth with downturned corners or a rounded nose, and her karyotype was 46, XX. Therefore, Turner's syndrome was ruled out.

APSs are relatively rare entities that are characterized by multiple endocrine and non-endocrine autoimmune diseases. To date, four types of APS have been described.<sup>5</sup> APS-1 (Autoimmune Polyendocrine Candidiasis Ectodermal Dystrophy Syndrome (APECED)) represents a combination of chronic candidiasis, hypoparathyroidism and Addison's disease. The age of onset of APS-1 is low, it usually fully manifests before the age of 20, and it is related to a mutation in the AIRE (Autoimmune Regulator) gene on chromosome 21.<sup>6</sup> APS-2 (Schmidt's disease) comprises Addison's disease, along with autoimmune thyroid disease and/or type 1 diabetes mellitus. It can develop at any age and in both sexes, but it is most frequently diagnosed in middle-aged women, and rarely in childhood.<sup>7</sup> The principal manifestations of APS-3 are autoimmune thyroid disease and other autoimmune diseases, such as type 1 diabetes, atrophic gastritis, pernicious anemia, vitiligo, alopecia, and myasthenia gravis, but not Addison's disease or hypoparathyroidism.<sup>7</sup> Other

combinations of autoimmune adenopathy that do not fit the criteria for the above three types are classified as APS-4. To our knowledge, no case of concomitant Graves' disease and GHD has been reported, and we suspect that this is a manifestation of APS-3.

Autoimmune hypophysitis, also known as lymphocytic hypophysitis, is characterized by substantial inflammatory cell infiltration in the pituitary, and is a rare manifestation of APS.<sup>7</sup> It has been reported that patients with APS types 1 and 2 may manifest GHD. Thus, although it is rare, GHD may be a component of APS. Quintos has previously reported a boy who was diagnosed with type 1 diabetes and Graves' disease at the age of 3 years and subsequently diagnosed with GHD at the age of 8 years and 8 months because of growth deceleration.<sup>8</sup> In a previous study of 379 patients with autoimmune hypophysitis, 18% had other autoimmune diseases, the most common being thyroid disease.<sup>9</sup> In the present patient, although the clinical manifestation of type 1 diabetes was borderline, she was GADAb-positive and developed GHD. This GHD may have been caused by autoimmune hypophysitis and is a rare component of APS. Autoimmune hypophysitis is three times more common in women than men and often develops in late pregnancy or postpartum.<sup>9</sup>

The typical MRI features of autoimmune hypophysitis are a symmetrically enlarged pituitary and a thickened pituitary stalk, without any changes in the sellar floor,<sup>10</sup> but patients without abnormalities on pituitary CT and MRI have previously been reported, as in the present case.<sup>11</sup> In addition, Papatnasiou previously reported a patient with APS-2 who developed growth arrest due to autoimmune hypophysitis 18 months after the initial diagnosis, and in whom there were no defects in other pituitary hormones.<sup>12</sup> GHD as the

only finding associated with lymphocytic hypophysitis is extremely rare. Therefore, it is necessary to monitor the growth of children with autoimmune polyendocrine diseases. In cases of growth retardation, GH should be evaluated using a stimulation test, and if identified at an early stage, GH replacement could be initiated straightaway.

Graves' disease is an autoimmune disease in which hyperthyroidism is caused by thyroid-stimulating antibodies that bind to and activate thyroid-stimulating hormone receptors.<sup>13</sup> Although the present patient had no typical clinical symptoms of hyperthyroidism and no ocular signs, she had a high serum concentration of thyroid hormones. Furthermore, she had had moderate diffuse goiter with a firm, rubbery consistency for nearly 5 years, and was positive for thyroid antibodies, and TRAB antibody in particular. Therefore, having also demonstrated a high thyroidal rate of <sup>131</sup>I-uptake, we considered that she might have Graves' disease and a similar autoimmune reaction to Hashimoto's thyroiditis.

Thyroid dysfunction can also affect the GH-IGF1-IGFBP3 axis. There have been differing reports regarding the GH secretion and defects in the IGF1-IGFBP3 system in cases of thyrotoxicosis in children and adults.<sup>14,15</sup> The GH response to insulin-induced hypoglycemia was normal in one study and low in another study,<sup>15</sup> but the GH response to the administration of arginine or clonidine has not been reported in thyrotoxic adults.

The sexual dysgenesis, poor breast development and infantile genitalia of the present patient might have been caused by GHD, rather than Turner's syndrome, because she had undergone menarche and had previously experienced normal menstrual cycles. The findings of secondary amenorrhea, cardiomegaly, splenomegaly, hypoproteinemia, pleural effusion, seroperitoneum, pericardial effusion and anasarca

could be explained by her hyperthyroidism. Furthermore, her vitamin D deficiency and osteoporosis, iron-deficiency anemia, poor blood coagulation, leucocytopenia and peripheral neuropathy could have been the results of malnutrition caused by the hyperthyroidism. Finally, her ichthyosis, tinea cruris and onychomycosis might have been the results of autoimmune disorders associated with APS.

In conclusion, an association between GHD and Graves' disease has only occasionally been encountered previously and there have been few epidemiological reports published. We have reported the present case to stimulate further contributions regarding the relationship between these diseases. We hope that the information we have provided regarding the present patient will help other researchers clarify the pathogenesis of type 3 APS in the future.

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### Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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