

Autoimmune polyglandular syndrome type 2 manifested as Hashimoto's thyroiditis and adrenocortical insufficiency, in Turner syndrome woman, with onset following introduction of treatment with recombinant human growth hormone

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Abstract

Autoimmune polyglandular syndrome is a constellation of signs and symptoms of simultaneous insufficiencies of several endocrine glands. Autoimmune polyglandular syndrome type 2 (APS 2) may be diagnosed when the adrenocortical insufficiency is associated with an autoimmune thyroid disease (Hashimoto's thyroiditis or Graves' disease), and/or insulin-dependent diabetes mellitus. Turner syndrome is the most common chromosomal disorder in females, caused by complete or partial X chromosome monosomy. We present the case of a 20-year-old woman with Turner syndrome, in whom APS 2 (Hashimoto's thyroiditis and adrenocortical insufficiency) has been diagnosed after introduction of recombinant human growth hormone (rhGH) therapy. In Turner syndrome, examination of the patient must regularly be conducted in order to diagnose a possible onset of autoimmune diseases; respective treatment must be applied as soon as the diagnosis is established. In particular, therapy of rhGH, used for short stature treatment, may be a trigger factor of adrenal insufficiency. The cortisol level in blood should be assessed before rhGH administration and carefully monitored during the therapy, especially in case of autoimmune thyroid disease coexistence.

INTRODUCTION

Turner syndrome (TS) is the most common chromosomal disorder in females caused by complete or partial X chromosome monosomy. This genetic disorder affects one (1) per 2000–2500 live-born girls. Clinical features of TS are short stature, pri-

mary ovarian failure, reduced bone mass, congenital cardiovascular defects, endocrine and metabolic disorders, hearing loss and others (Bondy *et al.* 2007). The recombinant human growth hormone (rhGH) is used for the treatment of short stature

Abbreviations:

AACAb	- anti-adrenal cortex antibody
anti-GAD-65Ab	- anti-glutamic-acid decarboxylase 65 antibody
anti-Tg	- anti-thyroglobulin antibody
anti-TPO	-thyroid peroxidase antibody
APS 2	- autoimmune polyglandular syndrome type 2
BMD	- bone mineral density
CT	- computer tomography
FT ₄	- free thyroxine

FT ₃	- free triiodothyronine
GH	- growth hormone
GHD	- growth hormone deficiency
IGF-I	- insulin-like growth factor-I
L-T ₄	- levothyroxine
OGTT	- oral glucose tolerance test
rhGH	- recombinant human growth hormone
TS	- Turner syndrome
TSH	- thyrotropin
21-OH Ab	- 21-hydroxylase antibody

associated with TS (Wasniewska *et al.* 2004). Growth hormone (GH) deficiency or other disturbances of GH/insulin-like growth factor-I (IGF-I) axis are usually detected in TS. It was well documented that the main cause of growth failure in TS is a haploinsufficiency of one copy of the short stature homeobox-containing (*SHOX*) gene located in the pseudoautosomal regions of distal short arm of the X (and Y) chromosome (Reh & Geffner 2010, Richmond & Rogol 2010). The *SHOX* gene encodes a homeodomain transcription factor responsible for a significant proportion of bone linear growth and *SHOX* deficiency (haploinsufficiency) is associated with marked disorganization of chondrocyte differentiation and maturation (Rao *et al.* 1997, Reh & Geffner 2010).

Due to gonadal dysgenesis, estrogen replacement should be started as early as 12 years of age (Spiliotis 2008, Kodama *et al.* 2012). Furthermore, in persons with TS, increasing risk of autoimmune disorders was described (Mortensen *et al.* 2009, Grossi *et al.* 2013).

Here, we present the case of a woman with TS, treated due to gonadal dysgenesis, who was diagnosed with autoimmune polyglandular syndrome type 2 (APS 2), just after growth promoting therapy.

CASE REPORT

A 12.5-years old girl was admitted, for the first time, to the Department of Endocrinology and Metabolic Diseases, Polish Mother’s Memorial Hospital – Research Institute in June 2006. In May 2006 a diagnosis of TS was established after karyotype typing (chromosome analysis showed the presence of 45,X karyotype). She presented the typical features of TS such as short stature, delayed puberty, gonadal dysgenesis and low bone mineral density (BMD); however, the phenotype features of TS were very mild. The patient was born full-term, with normal birth weight and length, with no clinical features suggesting TS. The girl did not suffer from any chronic diseases. A family medical history was irrelevant, especially with respect to autoimmune diseases; the parents were relatively tall (mother – 176 cm, father – 188 cm). A laboratory evaluation showed high thyrotropin (TSH) level, decreased free thyroxine (FT₄) concentration and normal level of free triiodothyronine (FT₃). Unfortunately, at that time thyroid autoantibodies were not assessed. Glucose and insulin levels in oral glucose tolerance test (OGTT), were normal.

Laboratory test results are summarized in Table 1. The constellation of gonadotropins was typical for hypergonadotropic hypogonadism and ovaries were not found in the examination of minor pelvis by ultrasonography. The patient started a therapy with levothyroxine (L-T₄) in dose 25 µg a day which was gradually increased to 75 µg a day, calcium and vitamin D. Furthermore, after qualification to the Therapeutic Program, she received rhGH therapy (Genotropin) and during treatment her growth rate increased significantly (from 4.6 cm/year before treatment, to 8.7 cm/year in 1st year of rhGH administration) and IGF-I concentration increased from 66 ng/mL to 353 ng/mL (normal range: 183–850 ng/mL).

After 5 months the patient was admitted to hospital due to hypoglycaemia (glucose concentration decreased to 30 mg/dL), with disturbances of consciousness and accompanying convulsions. The neurological evaluation and electroencephalography were conducted and epilepsy was excluded. The patient reported fatigue, especially while casual respiratory infections. These symptoms occurred in the patient for the first time shortly after rhGH therapy onset. On the basis of clinical examination, decreased cortisol levels in blood in diurnal profile and the results of Synacthen test (see in Table 2) the diagnosis of primary adrenal insufficiency was established. Adrenal glands were not visualized in abdominal sonography. The patient was discharged from the hospital, being on hydrocortisone replacement in dose of 15 mg/daily. No carbohydrate metabolism disturbances have been observed since that time. Anti-adrenal cortex autoantibodies (AACAb), anti-glutamic-acid-decarboxylase immunoglobulin G (anti-GAD-65Ab) and anti-transglutaminase immunoglobulin A were below the level of detection or they were in normal range. Thyroid peroxidase antibodies (anti-TPO) were above the upper limit of reference range and Hashimoto’s thyroiditis was diagnosed. Anti-thyroglobulin antibodies (anti-Tg) concentration were also elevated.

The patient was implemented estrogen substitution at the age of 13.5 years and – subsequently – when she was 15.5 years old, she received the sequential estrogenic-gestagenic therapy. The therapy with rhGH was continued up to the age of 15 years and then – it was withdrawn, when the patient’s height was 157.9 cm, according to the rules of the Therapeutic Program of the Ministry of Health of Poland. During further

Tab. 1. Laboratory test results.

Dates of subsequent stays in the Department	June, 2006	November, 2006	September, 2009	November, 2012	July, 2013	July, 2014
Age (years)	12 ⁵ / ₁₂	12 ¹⁰ / ₁₂	15 ⁸ / ₁₂	18 ¹⁰ / ₁₂	19 ⁶ / ₁₂	20 ⁶ / ₁₂
Height (cm)	143.0	144.5	159.5	160.0	160.0	160.0
TSH (μIU/mL) N: 0.27-4.2	13.13 (the beginning of therapy L-T ₄ 25 μg)	1.97 (L-T ₄ 75 μg)	1.77 (L-T ₄ 75 μg)	3.47 (L-T ₄ 75 μg)	3.07 (L-T ₄ 75 μg)	1.88 (L-T ₄ 75 μg)
Free T ₃ (pg/mL) N: 2.6-4.4	3.63	4.53	3.47	2.95	3.35	3.03
Free T ₄ (ng/dL) N: 1-1.8	0.76	1.09	1.56	1.3	1.46	1.68
Anti-TPO (IU/mL) N: < 34	-	97.03	10.63	28.78	63.04	6.22
Anti-Tg (IU/mL) N: < 115	-	39.94	158.8	160.2	75.04	49.3
Anti-TSHr (IU/L) N: 0-1.75	-	-	-	< 0.3	< 0.3	< 0.3
Cortisol at 8 ⁰⁰ (μg/dL) N: 6.2-19.4	-	<0.018	< 0.018	21.48 (2 hours after 10 mg hydrocortisone)	9.24 (2 hours after 10 mg hydrocortisone)	22.39 (2 hours after 10 mg hydrocortisone)
Cortisol at 17 ⁰⁰ (μg/dL) N: 2.3-11.8	-	<0.018	< 0.018	15.75 (2 hours after 5 mg hydrocortisone)	7.12 (2 hours after 5 mg hydrocortisone)	16.36 (2 hours after 5 mg hydrocortisone)
Cortisol at 24 ⁰⁰ (μg/dL) N: <6	-	<0.018	< 0.018	1.56	2.6	-
IGF-1 (ng/mL) N: 183-850	66.3	353	142	230	191.7	246
IGFBP3 (μg/mL) N: 3.1-9.5	3.93	5.59	4.76	-	5.31	-
LH (IU/L) N: 2.4-12.67	20.7	-	< 0.1 (estradiol)	5.75 (estradiol/ norethisterone)	5.09 (estradiol/ dydrogesterone 2 ¹⁰ / ₁₀)	10.35 (estradiol/ dydrogesterone 2 ¹⁰ / ₁₀)
FSH (IU/L) N: 3.5-12.5	150.6	-	< 0.248 (estradiol)	8.22 (estradiol/ norethisterone)	14.9 (estradiol/ dydrogesterone 2 ¹⁰ / ₁₀)	12.36 (estradiol/ dydrogesterone 2 ¹⁰ / ₁₀)
Estradiol (pg/mL) N: 12.5-166	7.14	-	30.73 (estradiol)	159 (estradiol/ norethisterone)	109.8 (estradiol/ dydrogesterone 2 ¹⁰ / ₁₀)	55.4 (estradiol/ dydrogesterone 2 ¹⁰ / ₁₀)
Testosterone (ng/mL) N: 0.06-0.8	<0.02	-	< 0.02 N: 0.06-0.8	-	< 0.03 N: 0.07-0.78	-
DHEAS (μg/dL)	-	-	< 0.1 N: 65.1-368	0.37 N: 65.1-368	< 0.1 N: 148-407	-
Androstendione (ng/mL)	-	-	< 0.3 N: 0.3-3.5	-	< 0.3 N: 0.3-3.3	-
HbA _{1c} N: < 6%	5.0	4.8	-	4.85	4.5	-
Sodium (mmol/L) N: 137-145	136	138	141	136	137	141
Potassium (mmol/L) N: 3.5-5.1	4.6	4.3	4.3	3.90	4.1	4.44
Calcium (mmol/L) N: 2.1-2.55	2.37	-	2.29	2.14	2.26	2.31
Phosphates (mmol/L) N: 0.81-1.45	1.86	-	1.61	1.35	1.47	1.39
Glucose (mg/dL) N: 60-99	76	72	-	76	73	-

Tab. 2. Results of 250 µg short Synacthen test.

	0 min	30 min	60 min
Cortisol (µg/dL)	<0.018	0.58	0.57

follow-up, after rhGH treatment and estrogen replacement she attained the final height of 160 cm. At present, the patient is treated with hydrocortisone 15 mg per day, L-T₄ in dose 75 µg a day, combined replacement therapy with estradiol and norethisterone, as well as calcium and vitamin D preparations. In computer tomography (CT) examination, which was performed in 2015, the adrenal glands were shown to be atrophic, without focal lesions. AACAb and anti-GAD-65Ab antibodies concentrations were in reference ranges.

DISCUSSION

Turner syndrome is one of the most common causes of short stature in females. Poor growth velocity occurs in 100% women with this genetic disorder and congenital gonadal dysgenesis affects approximately 85% patients with TS (Reh & Geffner 2010).

The therapy with rhGH is a standard procedure in girls with TS. The average adult height of untreated women with TS is 20 cm lower than their target height (calculated on the basis of the height of the parents) (Wasniewska *et al.* 2004, Richmond & Rogol 2010). The effectiveness of rhGH therapy in TS is well documented. The data from the randomized studies indicate height gains from 5 to 8 cm in the patients treated to final or near-final height (Richmond & Rogol 2010). The recommended GH doses for TS patients are approximately twice higher than the doses for children with growth hormone deficiency (GHD) (Reh & Geffner 2010). In Poland, in TS patients rhGH is used at a dose of 0.33–0.47 mg/kg per week, divided into six (6) to seven (7) daily doses and administration is recommended until either epiphyses are closed or the patient's height exceeds 158 cm. Individual response to rhGH is variable. In the study of Clayton *et al.* (2013), 10 genes (for example *LHX4*, *PTPN1*) in TS were significantly associated with growth response. It has been reported that rhGH – applied in doses higher than those currently recommended for TS – may improve final height; however, the possible long-term consequences of sustained supraphysiological concentrations IGF-I should be taken into account (Bondy *et al.* 2007).

The optimal age of the onset of rhGH therapy is still a matter of debate. According to current guidelines, treatment with rhGH should be considered as soon as a growth failure is demonstrated (Bondy *et al.* 2007). However, some studies have shown that the rhGH therapy initiation at younger age may lead to the higher rate of bone age progression, with an unfavorable effect on final height (Van Teunenbroek *et al.* 1996). In turn, Gawlik *et al.* (2005) demonstrated that neither chrono-

logical age nor bone age delay of TS patients at rhGH therapy onset had an influence on the height improvement during treatment.

Our patient was treated with rhGH in dose 0.35 mg/kg/weekly, injected ones daily, that is – the standard dose (although small) for the girls with TS, and the therapy was withdrawn when she attained the height of 157.9 cm. Despite the fact that the estrogen therapy was introduced relatively late – due to the late age of TS diagnosis and because the intention not to initiate estrogen therapy together with rhGH therapy to increase growth promotion – the patient reached quite normal final height. It seems that the favorable effect of tall parental height could be a very important factor in this case.

An increased frequency of autoimmune diseases has been observed in TS patients (Goldacre & Seminog 2014). In girls with TS, TSH level should be screened at least once a year for early detection of subclinical hypothyroidism (Wikiera *et al.* 2006). Thyroid auto-immunological processes and disturbances of thyroid function in TS may proceed without any clinical symptoms and signs; nevertheless, their prevalence increases with age. A long-term follow-up study in 86 TS girls has shown the increased prevalence of thyroid abnormalities, related to the age (the prevalence increased from 25.5 to 50%) (Gawlik *et al.* 2011). Some data indicated that there was a statistically significant association between karyotype and the prevalence of autoantibodies (Elsheikh *et al.* 2001, Wikiera *et al.* 2006, Mortensen *et al.* 2009, Grossi *et al.* 2013). The increased frequency of autoimmune diseases may result from the change in expression of the X-linked *FOXP3* gene. This gene fulfills a role in the development of regulatory T cells, and complete loss of *FOXP3* expression has been shown to result in severe autoimmunity (Su *et al.* 2009). Moreover, a decrease in the ratio of CD4 to CD8 lymphocytes may be a cause of autoimmune disorders in TS patients (Su *et al.* 2009).

In our patient hypothyroidism was diagnosed prior to rhGH therapy administration and the diagnosis of Hashimoto's thyroiditis was confirmed by the increased concentrations of antithyroid autoantibodies, while the diagnosis of adrenal insufficiency was established after a few months of rhGH therapy. This constellation of at least 2 endocrine disorders leads to the diagnosis of APS 2. It should be diagnosed when adrenocortical insufficiency is associated with autoimmune thyroid disease, and/or insulin-dependent diabetes mellitus (Kahaly 2009). It is obvious that thyroid hormones increase the metabolic clearance of cortisol and replacement therapy of L-T₄ could be a trigger factor of adrenal insufficiency (Gordon & Southern 1977).

The autoimmune nature of adrenocortical insufficiency should be confirmed by the presence of AACAbs or 21-hydroxylase antibodies (21-OHAb) or – in their absence – by imaging examinations (Betterle *et al.* 2013). Unfortunately, in our patient these autoan-

tibodies were not assessed on the onset of the disease and later on, they were absent. It has been documented that more than 90% patients with adrenocortical insufficiency have positive titres of these antibodies; however, autoantibody positivity decreases with time after the disease onset (Betterle *et al.* 1997). Our patient had typical atrophic adrenal glands, visualized in CT scanning. This observation seems to be a useful tool to distinguish cause of adrenal insufficiency (Sun *et al.* 1992).

It is to be recalled that GH therapy may additionally decrease the amount of cortisol in a mechanism different from autoimmunological one. Growth hormone increases IGF-I that – in turn – inhibits the expression of 11 β -hydroxysteroid dehydrogenase type 1; this leads to a decrease in conversion of cortisone to cortisol (Gelding *et al.* 1998, Bell *et al.* 2010). Growth hormone therapy enhances also the activity of CYP3A4, a cytochrome P450 enzyme involved in glucocorticoid catabolism (Liddle *et al.* 1998). In our patient, the adrenal failure was diagnosed after a few months of rhGH treatment; simultaneously, an almost 5-fold increase of IGF-I level was observed. That phenomenon could possibly contribute to the development of adrenal insufficiency.

It is important to detect thyroid abnormalities in TS patients as soon as possible and to initiate L-T₄ substitutive therapy in due time. In TS women, Addison's disease is a rare condition but after all, can sometimes be diagnosed. Therapy of rhGH, as well as L-T₄ substitution may be trigger factors of the adrenal insufficiency. Therefore, cortisol level in blood should be assessed before the treatment and – next – monitored during the therapy. Moreover, adrenal failure should be included in the differential diagnosis of hypoglycaemia.

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