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Growth hormone therapy in a girl with Turner syndrome and diabetes type 1 – case report

Leczenie rekombinowanym hormonem wzrostu dziewczynki z zespołem Turnera i cukrzycą typu 1 – opis przypadku

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Abstract

Introduction. The studies indicate the complex etiology of abnormal glucose metabolism in the Turner syndrome (TS). In the light of these carbohydrate disorders a therapy with recombinant growth hormone (rGH) in TS may be associated with complications, as growth hormone has a diabetogenic potential. **Patient report.** Perinatal history is unknown since the patient was adopted at the age of 4 years. At 11 years old, due to typical phenotype, TS was diagnosed. The karyotype was 45,X[43]/46,X,i(X)(q10)[7]. At the same age, basing on laboratory results, insulin dependent diabetes was diagnosed and the conventional insulin therapy was initiated. During the hospitalization, at the age of 12 years, the patient was 123.5cm (-4.4SD). At the same age rGH treatment was initiated, with the dose 0.045 mg/kg/d. After 3 months of therapy the height velocity rose to 8.2 cm/ year. At the age of 13 years, substitution with 17β-estradiol was started. After 3 years and 4 months the growth hormone treatment was stopped because of poor height velocity. The final height of the patient was 140 cm (-4,OSD). Two years after the end of rGH treatment the height was 141.2 cm. After termination of rGH treatment the need for daily insulin dose decreased from 50–60U/d to 38–44U/d. **Conclusions.** The decision of rGH therapy in TS with diabetes is certainly difficult. While starting the growth hormone treatment the clinician must keep in mind the risk of metabolic complications, but also the awareness that gives the patient a chance to improve the final height. In terms of the proper psycho-emotional development the reduction of growth deficit is very important.

Key words

recombinant growth hormone, Turner syndrome, diabetes mellitus type 1

Streszczenie

Wstęp. Badania wskazują na złożoną etiologię nieprawidłowego metabolizmu węglowodanów w zespole Turnera (ZT). W związku z tymi zaburzeniami leczenie rekombinowanym hormonem wzrostu (rGH) w ZT może być związane z powikłaniami, szczególnie że hormon wzrostu ma działanie diabetogenne. **Opis przypadku.** Wywiad okołoporodowy jest nieznany (pacjent adoptowany w wieku 4 lat). W wieku 11 lat ze względu na typowy fenotyp rozpoznano ZT. Kariotyp: 45,X[43]/46,X,i(X)(q10)[7]. W tym samym wieku rozpoznano cukrzycę insulinozależną na podstawie wyników laboratoryjnych. Rozpoczęto konwencjonalną insulinoterapię. W trakcie hospitalizacji, w wieku 12 lat, wzrost wynosił 123,5 cm (- 4,4 SD), W tym samym wieku rozpoczęto leczenie rGH w dawce 0,045 mg/kg mc/dobę. Po 3 miesiącach tempo wzrastania zwiększyło się do 8,2 cm/rok. W wieku 13 lat zainicjowano terapię preparatem 17β-estradiolu. Po upływie 3 lat i 4 miesięcy leczenie rGH przerwano z powodu niskiego tempa wzrastania. Wzrost dziewczynki wynosił 140 cm (-4SD). Dwa lata po zakończeniu leczenia rGH wzrost wynosił 141,2 cm. Po zakończeniu leczenia rGH zapotrzebowanie dzienne na insulinę zmniejszyło się z 50–60 jm./dobę do 38–44 jm./dobę. **Wnioski.** Decyzja włączenia terapii rGH w ZTz cukrzycą jest z pewnością trudna. W momencie rozpoczęcia leczenia rGH klinicysta musi mieć na uwadze ryzyko powikłań metabolicznych, ale także świadomość, że daje pacjentowi szansę na poprawę wzrostu końcowego. Z punktu widzenia prawidłowego rozwoju psychoemocjonalnego zmniejszenie deficytu wzrostu jest bardzo ważne.

Słowa kluczowe

rekombinowany hormon wzrostu, zespół Turnera, cukrzyca typu 1

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Introduction

Turner syndrome (TS) is the most common genetic disease on the sex chromosomes in females.The syndrome results from the total or partial loss of genetic material in the X chromosome. There is a wide spectrum of clinical pictures of TS. The most common features are short stature and gonadal dysgenesis. Metabolic disorders are also observed in patients with TS. Epidemiological data suggest that women with TS present an increased risk of developing metabolic syndrome, which consists of hypertension, dyslipidemia and type 2 diabetes [1]. Until now, there has been no correlation between the type of karyotype and the presence of glucose intolerance. Studies indicate the complex etiology of abnormal glucose metabolism. In the light of these carbohydrate disorders, a therapy with recombinant growth hormone (rGH) in TS may be associated with complications, since growth hormone has a diabetogenic potential. TS is also connected with the increased risk of developing autoimmunologic diseases, such as autoimmune thyroiditis, vitiligo, celiac disease, Crohn's disease, and ulcerative colitis.

Aim of this study is to present the results of long-term treatment with rGH in a 15.5-year-old girl with Turner syndrome and diabetes type 1.

Patient Report

Perinatal history is unknown as the patient was adopted at age 4. At age 11, due to phenotype and deceleration in growth chart (height SDS was -4.36) the girl was referred to a genetic consultation. Karyotype 45,X[43]/46,X, i(X)(q10)[7], estimated by using giemsa-trypsin (GTG) banding, confirmed the diagnosis of Turner Syndrome. The patient presented the following symptoms typical for TS: short stature, broad chest with nipples wide apart, cubitus valgus and webbed neck. In addition, Madelung deformity was observed and a positive Archibald's sign (fourth metacarpal bone shortening) (Fig. 1).

Because of the elevated TSH level (4.9 IU/ml), but no goiter, L-thyroxine treatment was started.

At age 11, glycosuria without any accompanying symptoms typical for diabetes was revealed. High fasting glucose levels (127–157 mg%) were observed. Because there were no clinical symptoms of diabetes the oral-glucose-tolerance test was performed. At 120 min the level of glucose was 296 mg%. C-peptide concentration at the lower range and positive GAD (glutamic acid decarboxylase) antibodies confirmed the autoimmunologic process (Table I). Conventional insulin therapy based on a mixture of short and long-acting insulin (Mixtard 30) and short acting insulin (Actrapid) was initiated. Daily insulin requirement was 0.5 U/kg.

The patient was also diagnosed with hyperopia, astigmatism in both eyes, and nystagmus. Additional studies have shown left ureter stenosis.

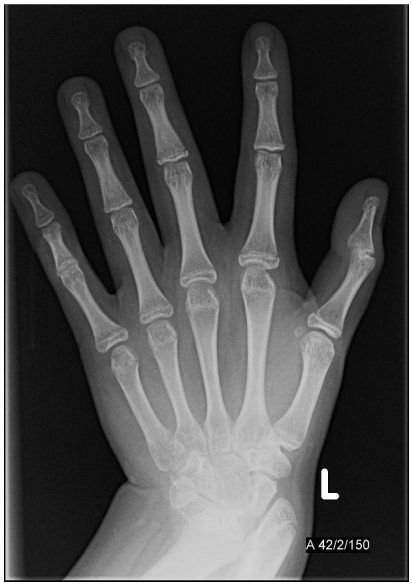

Figure 1. X-ray of left hand of the girl. Noticeable Madelung deformity
Rycina 1. *Zdjęcie rtg lewej dłoni. Proszę zwrócić uwagę na deformacje Madelunga*

During the first hospitalisation in the Department of Pediatric Endocrinology, at the age of 12 years, physical examination showed: height of 123.5 cm (by Lyon and Preece 25–50 c, compared to a healthy population -4.4 SD), the growth rate of 2.8 cm/year, BMI 20 kg/m^2 (75c), and no signs of puberty. Laboratory tests showed: hypercholesterolemia, elevated thyroid peroxidase antibodies (ATPO), and hypergonadotropic hypogonadism (Table I) thus confirming chronic autoimmune thyroiditis and primary ovarian failure. Further studies revealed normal ECG and ECHO, the ultrasound of the thyroid gland – heterogenous structure with hypoechogenic places. Bone age was assessed according to Greulich and Pyle scale of 11 years, and hearing loss was found in the left ear in audiometric testing and adenoid hypertrophy. Adenotomy was carried out at the age of 12 years.

At the same age, recombinant growth hormone (rGH) treatment was initiated with theTS standard dose of GH 0.045 mg/kg/d. The tendency toward hyperglycaemia and acetonuria was observed. After 5 weeks of growth hormone treatment the rGH dose was reduced to 0.033 mg/kg b.w./d. The insulin dose was increased at the same time. Glucose levels normalized. After 3 months from the start of treatment the height velocity rose to 8.2 cm/year. Insulin therapy was based on a mix of long-acting insulin with rapid-acting insulin analogue (NovoMix 30) and insulin analogue (NovoRapid), and the dose was 27 U/d corresponding to approximately 0.8 U/kg/d.

Table I. Levels of hormones and other biochemical parameters in blood samples (abnormal values are given in bold). Marked LH, FSH and estradiol levels were marked during 17β-estradiol treatment
Tabela I. *Stężenia parametrów biochemicznych w surowicy krwi (pogrubioną czcionką zaznaczono nieprawidłowe wyniki). Stężenia LH, FSH i estradiolu były oznaczane w trakcie podawania 17β-estradiolu*

Laboratory tests Testy laboratoryjne	12 yrs / *lat*	13 yrs / *lat*	14 yrs / *lat*	15 yrs / 15 *lat*	Reference range / *Zakres normy*
TSHftilU/ml)	2.9	3.54	2.38	3.9	0.470-4.640
fT4(ng/dl)	1.23	1.22		1.35	0.71-1.85
LH (mlU/ml)	**18**	12		1.9*	2.0-12.0
FSH (mlU/ml)	**66.2**	**66.4**		**8.2***	1.0-8.0
Estradiol (pg/ml)	21	0.0		65*	39-189(follicular phase/ *faza folikularna*)
IGF-1 (ng/ml)	697	943	676	738	Depending on age /*W zależności od wieku*
HbA1c(%)	5.44	**7.03**	**8.4**	**6.7**	<6.1
anti-GAD (U/ml) *anty-GAD*		**1.7**		**4.1**	<1
IAA.1%)				4.3	<5.5
IA-2(U/ml)		0.0		<0.1	<1
C-peptide /*C-peptyd*	0.6	0.64			0.59-1.56
Cholesterol (pg/ml)	**240**	165		**246**	110-230
Triglycerides (mg/dl) / *Trójglicerydy*	88.3	**114**		**174**	30.6-105
AspAt(U/l)	39	31		36	1-40
AlAt(U/l)	31	35		31	1-45
Creatinine (mg/dl) / *Kreatynina*	0.69	0.55	0.52	0.63	0.6-1.3
ATPO [U/ml]	**2835**	**2216**		**>3000**	<60
ATG[U/ml]	19	39		<20.0	<60
IgAGAF		neg			neg
IgAtTG				neg	

The selected auxological parameters during rGH therapy are shown in Table II. The best height velocity was observed in the first year of treatment. The mean HbA1c concentration during the rGH was 6.76%, the lowest – 5.26%, and the highest – 8.9% (Table III). Hyperglycaemia and acetonuria never occurred again. From an early age the girl had a tendency to be overweight. Although with rGH treatment there was a rise in BMI from an initial 19.35t kg/m^2 (75centile) to 30.1 kg/m^2 (over 97centile) at the highest, but at the end of rGH administration the BMI was 26.3 kg/m^2 (95–97centile).

At the age of 13 years and 1 month, substitution with 17β-estradiol was started (0.125 mg/day), the dose was gradually increased until it reached a dose of 1 mg/d. At the age of 15 years and 5 months dydrogesterone was added (5 mg for 14 days) to the treatment.

At the age of 13 years and 9 months the treatment of diabetes was switched to a personal pump, using rapid-acting insulin analogue (NovoRapid).

At the age of 14 years and 9 months the patient was hospitalized because of frequent nausea and vomiting, described as similar to regurgitation. A gastroscopy revealed severe inflammation of the stomach with *Helicobacter pylori* infection and inflammation of the oesophagus. Combined treatment with proton-pump inhibitor, amoxicillin and metronidazole was started. At the same time hypertension (129/79 to 141/88 mmHg) was noticed and she was scheduled for further cardiologic evaluation. Subsequent measurements of blood pressure were within normal limits. At the age of 17 years and 10 months, on the basis of 24-hour Holter assessment of blood pressure, hypertension was found, and ramipril treatment started at a dose of 2.5 mg/d.

Table II. Selected parameters during rGH therapy
Tabela II. *Wybrane parametry podczas terapii rGH*

	Age (years) *Wiek (lata)*	Height (cm) *Wzrost (cm)*	Weight (kg) *Masa ciała*	Bone age (Greulich&Pyle) (years) / *Wiek kostny (lata)*	htSDS	Height velocity (cm/year) *Tempo wzrastania (cm/rok)*	Predicted adult height (PAH) based on Bayley Pinneau method(cm)/ *Wzrost prognozowany* (cm)	rGHDose (mg/kg/24h) *Dawka rGH* (mg/kg/24h)
The beginning of rGH therapy/ *Początek terapii rGH*	121/12	124.6	30	12	-4.56	2.8	135.4	0.05
After 6 months of rGH therapy / *Po 6 miesiącach terapii rGH*	127/12	129.2	32.5	12	-4.3	9.2	140.1	0.04
After 12 months of rGH therapy / *Po 12 miesiącach terapiirGH*	13 1/12	132.0	34.4	12	-4.1	7.4	141.6	0.04
After 2 years of rGH therapy / *Po 2 latach terapii rGH*	14 1/12	136.7	43	13	-4.2	4.7	142	0.045
After 3 years of rGH therapy / *Po 3 latach terapii rGH*	15 1/12	139.6	47.5	14	-4.1	2.9	142	0.045
After 3years and 4 months of rGH therapy / *Po 3 latach i 4 miesiącach terapii rGH*	155/12	140	51.5	14	-4.0	1.2	142.5	Stop of treatment *Koniec leczenia*

Table III. Glycosylated hemoglobin before, during, and after rGH therapy (abnormal values are given in bold)
Tabela III. *Hemoglobina glikowana przed, w czasie oraz po leczeniu rGH (nieprawidłowe wyniki podane są pogrubioną czcionką)*

Time /Czas	HbA1c (%);
Before rGH therapy / *Przed terapią rGH*	5.44
1 months of rGH therapy / *2 miesiące terapii rGH*	**6.23**
4 months of rGH therapy / *4 miesiące terapii rGH*	**6.58**
6 months of rGH therapy / 6 *miesięcy terapii rGH*	5.26
1 year of rGH therapy / *Rok terapii rGH*	4.81
1 year and 6 months of rGH therapy / *1,5 roku terapiirGH*	**8.4**
2 years of rGH therapy / *2 lata terapii rGH*	**7.2**
2 years and 6 months of rGH therapy / 2,5 *roku terapii rGH*	**7.3**
3 years of rGH therapy / 3 *lata terapii rGH*	**6.7**
Termination of rGH therapy / *Zakończenie terapii rGH*	**8.9**
Mean value during rGH therapy / *Średnia wartość podczas terapii rGH*	**6.76**
1 year after rGH therapy / *Rok po zakończeniu terapii rGH*	5.9
Mean value after rGH therapy / *Średnia wartość po zakończeniu terapii rGH*	**6.4**

After 3 years and 4 months growth hormone treatment was stopped because of poor height velocity. The final height of the patient was 140 cm, the bone age was still delayed compared to the chronological age. At the end of rGH treatment the pubertal staging was as follows: thelarche 4, axillarche 4, pubarche 4. Two years after the end of rGH treatment the height was 141.2 cm. The growth curve of the patient is shown in the Figure 2.

After termination of rGH treatment the need for a daily insulin dose decreased from 50–60 U/d to 38–44 U/d.

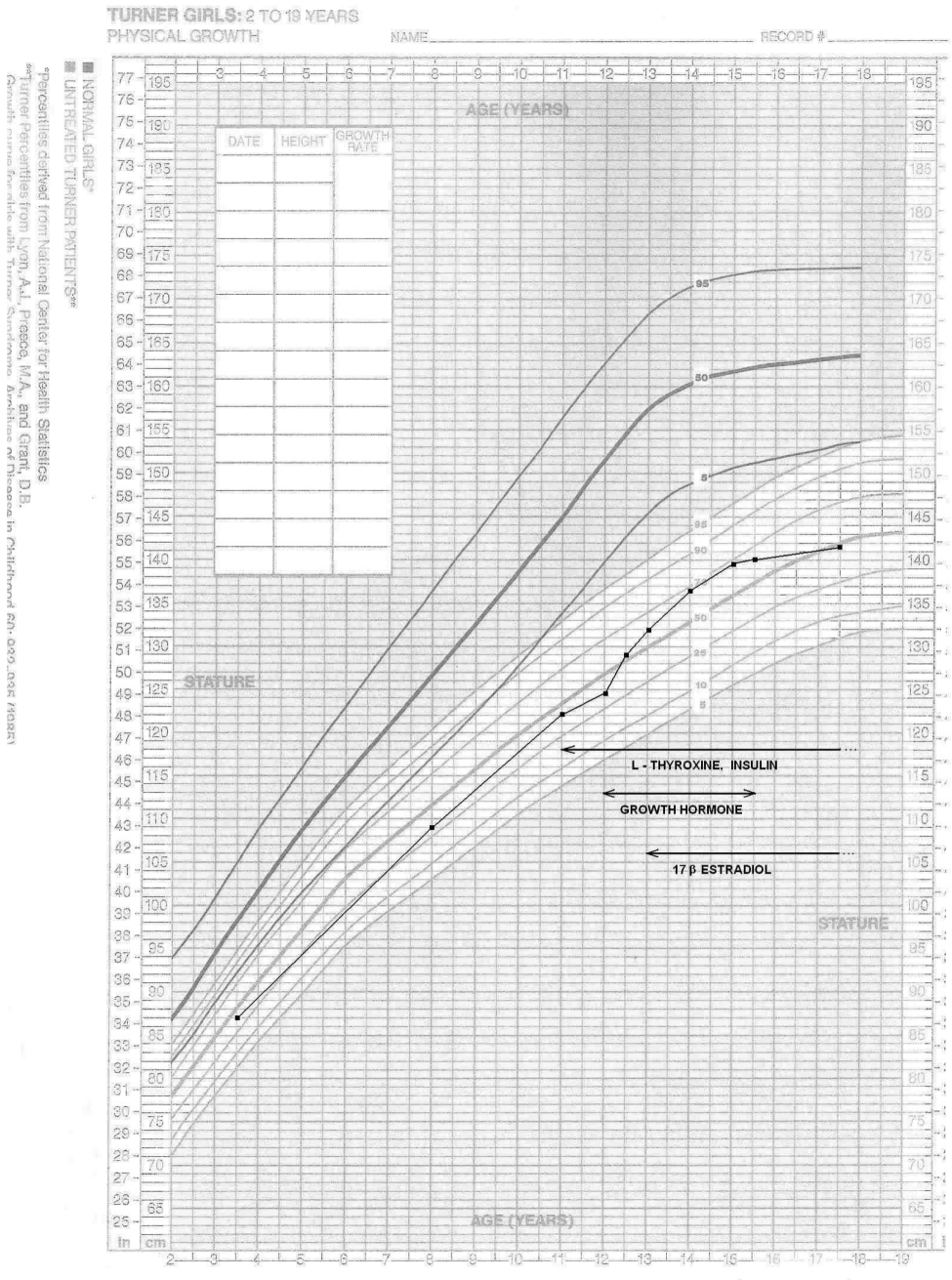

Figure 2. The patient's growth chart. Growth curve for girls with Turner syndrome. Lyon AJ, Preece MA, Grant DB. *Growth curve for girls with Turner syndrome*. Arch Dis Child. 1985;60:932-935

Rycina 2. *Karta wzrastania pacjentki. Siatka centylowa dla dziewczynek z zespołem Turnera. Lyon AJ, Preece MA, Grant DB. Growth curve for girls with Turner syndrome. Arch Dis Child. 1985;60:932–935*

Discussion

Growth hormone affects the secretion and action of insulin. Growth hormone, as an insulin antagonist, increases the peripheral and hepatic insulin resistance and reduces glucose uptake by the muscles. Its diabetogenic effect, i.e. increasing insulin resistance, may have an important influence during rGH treatment, especially in diseases with normal pituitary function and proper growth hormone levels.

Type 2 diabetes is 2–4 times more frequent in women with TS and occurs earlier as compared to the healthy population. Impaired carbohydrate tolerance is observed in 10–34% of women with TS [2,3]. Turner Syndrome demonstrates reduced sensitivity of cells to insulin leading to hyperinsulinemia and glucose intolerance [4]. Type 2 diabetes mellitus is 2–4 times more frequent and occurs at younger age in girls with TS than in the general population [1,3]. Impaired glucose tolerance occurs even in lean patients with normal BMI. It was also found that BMI has no impact on these disturbances. Higher values of glucose and insulin levels during oral glucose-tolerance test (OGTT) compared with the control group has been observed [5]. While the basal glucose and insulin concentrations in OGTT were comparable with the healthy population, the intravenous glucose-tolerance test shows reduced initial insulin secretion in TS [5]. This points to the impaired function of the pancreatic beta cells islet. The statistical calculations performed suggest the coexistence of insulin resistance in TS.

Also in other studies, reduced insulin secretion during oral and intravenous glucose tolerance was observed [6]. This suggests that impaired function of the pancreas is the primary metabolic defect in TS. In young women, this defect is compensated by a relatively higher insulin sensitivity. With age, there is a decrease in insulin secretion and sensitivity to its action, which results in impaired glucose tolerance. This type of disorder is not synonymous with type 1 diabetes mellitus that results from an autoimmune process.

In some studies the increased percentage of islet cell antibodies is not observed inTS [7]. Danish authors report that insulin-dependent diabetes occurs ten times more frequently and insulin-independent four times more frequently in TS than in the healthy population [1]. However these investigators recognized insulin-dependent diabetes mellitus based on the need of administration of exogenous insulin, and not due to positive islet cell antibodies.

On the other side, Mortensen et al. in their study revealed that 4% (4 patients in a cohort of 106 patients) of examined TS patients had positive anti-GAD-65 antibodies, none had insulin dependent diabetes mellitus, but two were classified as having insulin-independent diabetes mellitus [8].

The data in the literature indicate that insulin resistance increases inTS during rGH therapy [9,10]. However, after completion of the treatment with growth hormone insulin and glucose levels return to normal ranges for the age [10,11].

In the literature there are only a few reports of patients with TS and coexisting type 1 diabetes, especially treated with rGH [12–14]. However, it seems that growth hormone therapy in patients with insulin-dependent diabetes and TS may be beneficial and safe [12].

It must be emphasised that the karyotype with isochromosome gives a higher predisposition to autoimmunologic diseases. The patient had two – diabetes type 1 and autoimmune thyroiditis.

In the presented case the rGH treatment was possible and effective. It seems that the decision to start rGH treatment was the correct one, with attention paid to whether the starting dose was adequate. It should be noted that the patient was diagnosed late, bone age was advanced and the time to succeed with rGH therapy was shortened, therefore to reach the growth potential a higher rGH dose was recommended. On the other side, we should be aware that high glucose levels counteract endogenous GH secretion and GH action.The height gain during 3 years of treatment was 15.4 cm and htSDS decreased from -4.56 to -4.0.

It is very likely that the final height could have been better. The possible negative factors which determined the adult height were the late diagnosis of TS and coexisting health problems. The increase of BMI during rGH therapy was caused mainly by high caloric intake. The parents had some educational problems with the girl and she had an increased appetite. The girl suffered two serious chronic diseases requiring subcutaneous injections. In the teenage period she had some problems to accept the diseases and a different style of life.

The case shows that during growth expansion the insulin demand was very high, but after termination of the rGH therapy it decreased significantly.

Conclusion

The decision to apply rGH therapy in TS with diabetes is certainly a difficult one. While starting growth hormone treatment, the clinician must keep in mind the risks of metabolic complications, but also be aware that the treatment gives the patient a chance to improve their final height. In terms of the proper psycho-emotional development, the reduction of growth deficit is very important.

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