Evaluation of the results of Turner syndrome patients during the first three years of recombinant human growth hormone therapy

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Key words

Abstract

Introduction. Turner syndrome (TS) is one of the most common chromosomal aberrations. Patients with TS reach a final height that is 20 cm shorter than the average female height in a given population. Recombinant human growth hormone (rhGH) therapy is used, which improves the height gain and allows to achieve a more satisfying final stature. Materials and methods. In this study, we analyzed data of 13 patients of the University Children’s Hospital in Lublin diagnosed with TS. All of the participants were qualified for the growth hormone therapy program and all of them received rhGH for at least 3 years. Results. The patients’ mean height at initiation of therapy was 119.9 ± 19 cm. In all cases, height was <3pc for age and sex. In the first three years of therapy, patients took a mean dose of growth hormone 0.05 ± 0.01 mg/kg/day. After initiating rhGH, the mean height velocity (HV) in the first year of therapy was the greatest and reached 7.77 ± 1.85 cm/year, it was also higher in patients with lower initial height and in those who started therapy earlier. In the second and third year of rGH therapy, the height velocity clearly decreased. Neither the hormone dosage or the age at initiation of therapy significantly affected the three-year treatment effect. After three years of therapy, no side effects, which would be the basis for discontinuation of treatment, were observed. Conclusions. In most patients with TS, rhGH therapy at a dose of 0.05 mg/kg/m.c./dzień

Ocena wyników leczenia pacjentek z zespołem Turnera przez trzy pierwsze lata leczenia ludzkim rekombinowanym hormonem wzrostu

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Słowa kluczowe

Streszczenie

Wstęp. Zespół Turnera (ZT) jest jedną z najczęściej zmlotkowych aberracji chromosomowych. Pacjentki z ZT osiągają wzrost ostateczny średni o 20 cm niższy od przeciętnego wzrostu kobiet w danej populacji. W terapii stosuje się rekombinowany hormon wzrostu (rGH), który poprawia tempo wzrostania i pozwala osiągnąć bardziej satysfakcjonujący wzrost ostateczny. Materiał i metody. W ramach badania przeanalizowano dane 13 pacjentek Uniwersyteckiego Szpitala Dziecięcego w Lublinie z rozpoznaniem ZT, zakwalifikowanych do programu leczenia hormonem wzrostu, które otrzymywały rGH przez co najmniej 3 lata. Wyniki. Wzrost pacjentek w momencie rozpoczęcia terapii wynosił 119,9 ± 19 cm i we wszystkich przypadkach znajdował się <3pc dla wieku i płci. Po włączeniu rGH tempo wzrostu w 1 roku terapii było najwyższe i wynosiło 7,77 ± 1,85 cm/rok, a także było wyższe u pacjentek o niższym wzroście początkowym oraz u tych, które rozpoczęły terapię wcześniej. W drugim i trzecim roku terapii rGH tempo wzrostu wyraźnie spadło. Dawka hormonu przypadająca na kg m.c. ani wiek, w którym rozpoczęto podawanie rGH, nie wpływały znacząco na efekt trzyletniego leczenia. Po tym okresie terapii nie odnotowano skutków ubocznych, które byłyby podstawą do przerwania leczenia. Wnioski. Terapia rGH w dawce 0,05 (± 0,01) mg/kg m.c./dzień
Introduction

Turner Syndrome (TS) is a genetic disorder caused by monosomy of the X chromosome or deletion of its fragment. It is one of the most frequent genetic defects and affects one in two thousand live born girls [1]. Suspicion of TS may appear already in the prenatal period [2] or in the newborn. Turner syndrome is often characterized by dysmorphic and congenital malformations. Patients with TS require multi-specialty medical treatment due to the possible coexistence of defects in the cardiovascular, urinary and bone systems, facial-skeleton disorders, and eye and ear disorders [3].

In women’s somatic cells, one of the two X chromosomes is inactivated in early phases of development. However 15–25% of genes localized on the inactivated chromosome are expressed. Most genes, named pseudoautosomal genes, are focused on a distal fragment of the short arm of the X chromosome. Such phenotypical signs of Turner syndrome as short stature, valgus elbows and knees and shortened IV metacarpal bones are caused by haploinsufficiency of the SHOX gene, expressed in chondrocytes. Haploinsufficiency of the pseudoautosomal region genes is responsible for generalized lymphatic edema and fetal cystic hygromas of the neck. Low hairline, webbed neck, nail deformation and lymphedema of the hands and feet are consequences of the lymphatic disorders [4–6].

Growth deceleration starts in childhood, and the TS patients’ final height is on average 20 cm lower than in the average female in a given population (values given in literature: between 136 and 147 cm) [4,6–9]. Although short stature in TS is not associated with pituitary dysfunction (secretion of somatotropin is normal), the use of recombinant growth hormone (rhGH) improves height velocity and allows patients to achieve a more satisfying final height [5]. The drug is administered daily via subcutaneous injection, and dosages are about twice as high as in the case of substitution therapy in somatotropic or multi-hormonal pituitary failure. It is recommended to start treatment at the age of 6–7 years and to administer 1.0-1.4 unit/kg/week [6,7]. In the case of a severe height shortage (greater than -2.0 standard deviations) early initiation of the drug administration should be considered. Moreover, if the diagnosis is established at later age, the treatment should be started immediately after diagnostic confirmation [4,6,8,9]. Relative contraindications include bone age ≥13.5 years and significant scoliosis [6–9]. The average duration of therapy lasts about 8 years and the goal of therapy is to achieve a final height of ≥151 cm. Estrogen substitution should be implemented to stimulate the development of secondary sexual characteristics after achieving an optimal target height [4,6,9].

Materials and methods

The retrospective study concerned 13 girls with diagnosed Turner syndrome (karyotype 45,X). The patients were diagnosed and treated in the Department of Pediatric Endocrinology and Diabetology at the Medical University of Lublin. Every 3–6 months, measurements of height and weight were taken; rhGH dose corrections were also made. Height standard deviation score (HSDS) was calculated using a height calculator program, version 1.0. Correlation analysis was performed using Statistica 13. Statistically significant differences were assumed at the significance level of p <0.05.

Results

During the first three years of therapy, patients took growth hormone at the average dose of 0.05 (± 0.01) mg/kg/day. Differences in dose per kilogram of body weight did not significantly translate into differences in height gain (p = 0.686).

The analyzed group included patients who started therapy in the years 2009–2014 with an average age of 9.6 (± 3.7) (the youngest was 3.2 years, the oldest 14.2 years). The mean height in patients at the initiation of therapy was 119.9 (±
The height standard deviation score at the start of therapy was -3.33 (± 0.76). The mean HV in the year preceding the initiation of therapy was 5.37 ± 2.27 cm/year. After the implementation of rhGH, HV in the first year of therapy increased to 7.77 ± 1.85 cm/year, and in subsequent years decreased to 5.18 (± 2.18) cm/year and 4.21 (± 1.72) cm/year respectively (Fig. 1).

After three years of therapy, side effects, which could be the basis for discontinuation of treatment, were not observed. Patients reached a mean HSDS -2.36 ± 0.84 (Δ 0.97 ± 0.81). The stature in eight patients was below the third percentile. One reached the third percentile. Two patients were between the third and tenth percentile. One was between the tenth and twenty-fifth percentile, and finally, one reached the twenty-fifth percentile for sex and age (Fig. 2). In the group of patients who exceeded the third percentile, there were two patients who started therapy at a younger age (4 and 5 years of age) and two who had rhGH implemented when they were already teenagers (13 and 15 years of age).

Height gain (HG) in the first year of rGH therapy was greater in patients who started treatment at earlier age (p = 0.012) and in those, whose initial height was lower (p = 0.004). However, there was no similar correlation between initial age and height and annual height gains in the second and third year of therapy. There was no relationship between a mean dose of growth hormone administered and HG in any year of therapy (Table II).

The mean HV in the analyzed three-year period of rhGH therapy depended mainly on height gains in the first two years (p = 0.001), and to a minor extent on the HG in the third year of therapy (p = 0.03) and was greater in patients who at the start of treatment had shorter stature (p = 0.036). The early age of therapy initiation was significant in a lesser degree (p = 0.075). However, the height velocity depended neither on the level of IGF-1 after the first year of treatment (p = 0.455), nor on the dose of rGH (p = 0.865).

Higher levels of IGF-1 after the first year was found in patients who were older (p = 0.004) and taller (p = 0.007) at the initiation of treatment. During treatment, IGF-1 levels in patients increased (Table I), but there was no significant correlation between IGF-1 level and height gains in subsequent years (Table II).

Nine of the girls were treated with estradiol since 13-14 years of age. They were placed on hormonal replacement therapy and were later treated with oral contraceptive drugs. The final height range of the girls was 154.3±4.7 cm.

Discussion

Growth deficits are one of the most characteristic features of patients diagnosed with Turner syndrome. Recombinant growth hormone has been used for many years in the treatment of short stature and its positive effect has been demonstrated by numerous researchers [7–9]. Despite a common consensus regarding the legitimacy of using rhGH, the reasons why some patients achieve better treatment results than others still remain unclear.

Table I. Comparison of pre-treatment results and after three years of rhGH treatment

|                      | Pre-treatment          | After 3-year treatment |
|----------------------|------------------------|------------------------|
| Age                  | 9.6±3.7                | 12.8±3.9               |
| Height               | 119.9±19 cm            | 137.2±16.9 cm          |
| HSDS                 | -3.33±0.76             | -2.36±0.84             |
| <3 pc                | 100%                   | 62%                    |
| BMI                  | 18.3±1.9               | 19.9±1.6               |
| IGF-1                | 200.9±121.4 ng/ml      | 358.4±186.9 ng/ml      |

Fig. 1. Growth velocity before the treatment and in the following years

Ryc. 1. Tempo wzrostu pacjentek przed terapią i w kolejnych latach terapii
Fig 2. Patients' growth curves during first 3 years of rhGH therapy

Ryc. 2. Krzywe wzrostania pacjentek podczas 3 pierwszych lat leczenia rhGH
Differences may be attributed to additional factors, such as patients’ age at the time of therapy initiation, dosage of growth hormone, the time of application of hormone replacement therapy, anabolic steroid (e.g., oxandrolone) use in treatment, ethnic genetic differences, or the number of patients in experimental groups.

Our observations show that the dose of hormone per kg of body weight did not significantly affect the three-year treatment effect, which was also reported by other authors [10–12], while some investigators found such dependency [13]. The start of therapy also did not significantly affect the height reached after 3 years. The age gap of the girls at the time of growth hormone implementation was significant and ranged from 3 to 14 years. The results of previous studies in other centers indicate a lack of significant influence of the initiation age and duration of rhGH therapy [12–14], while others imply an important role of these factors [11]. However, Ping-Yi Hsu et al. stress that early initiation of growth hormone therapy allows the induction of maturation at the right time [15].

The most visible acceleration of height velocity was obtained in the first year of treatment (+ 2.4 cm in relation to the HV before the implementation of rhGH), which has been also reported by other researchers [15,16]. In the analyzed group of patients in the second and the third year of therapy, HV decreased significantly, which coincides with the observations available in the literature [17].

Methods to improve the growth of women with Turner syndrome are still being sought. There is a noteworthy study in which a group of patients took growth hormone together with children’s low-dose estrogen [4,6,18–21]. Greater height gain values were observed in these girls than in patients who received rHGH alone. The administration of estrogen alone did not give positive results. The authors explain this dependence with the ability of estrogens to directly increase the response of the skeletal growth plates to IGF-1 or growth hormone. Currently, low dose estrogen therapy is implemented at the age at which the puberty process is supposed to begin, and after the next two years, progesterone is added [18–21]. Promising effects are observed with the use of growth hormone and oxandrolone (an anabolic steroid) at a dose of 0.03 and 0.05 mg / kg / day. However, the virilizing effects of oxandrolone should be taken into account [22].

Nowadays, patients with Turner syndrome can expect comprehensive medical care, growth hormone and hormone replacement therapy as well as psychological support. These regular treatments have a positive impact on the quality of their lives.

Conclusion

The girls with Turner Syndrome demonstrated catch-up of growth velocity in first year of treatment with rhGH. In the following years, growth velocity was comparable to the pretreatment period.
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