Hypertrophic scars in a patient with Turner’s syndrome treated with recombinant growth hormone

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Abstract
Turner’s syndrome is a common genetic disorder of girls and women, for which characteristic clinical symptoms encompass short stature, gonadal dysgenesis, systemic defects, multiple dysmorphic features and skin changes, including an increased number of melanocytic nevi, hypertrophic scars and keloids. The affected girls are treated with recombinant human growth hormone to improve the height. We present a case of a 15-year-old girl with Turner’s syndrome, hypertrophic scars and a keloid. At the age of 12 years and 8 months, the girl started recombinant human growth hormone treatment. During the therapy, a surgical excision of 4 out of 42 benign melanocytic nevi was performed. After 2 months the hypertrophic scars as well as a keloid were noted at sites of excision. Parents of girls with Turner’s syndrome undertake various attempts to improve not only the height and maturity of their daughters, but also their appearance by commonly performed surgical corrections of the webbed neck and pigmented nevi. The presented case suggests an increased risk of scars hypertrophy and keloid formations after surgical intervention in Turner’s syndrome patients who are treated with recombinant human growth hormone at the same time. Due to that it should be advised to postpone all planned surgical procedures until the therapy has been completed.

Key words: Turner’s syndrome, scar, hypertrophy, growth hormone.

Introduction
Turner’s syndrome (TS) is a genetic disorder diagnosed on the basis of the analysis of 45, X karyotype or mosaics including cells with that karyotype. The reported incidence of TS varies from 1 in 2000 to 1 in 5000 live female births [1, 2]. The syndrome manifests itself in a number of ways. Girls with TS typically experience short stature and gonadal dysgenesis. Apart from congenital systemic defects (mostly cardiovascular and of the urinary tract), TS patients present with multiple dysmorphic features, including webbed neck, high-arch palate, cubitus valgus, shield chest with widely spaced nipples, short 4th and 5th metacarpals. Skin manifestations, including lower extremity lymphedema in children, low hairline, abnormal fingernails, pigmented nevi (increasing in number with age) [3–6] and a tendency to develop hypertrophic scars and keloids [6–8], constitute other characteristic features of Turner’s syndrome. Recombinant human growth hormone (rhGH) treatment aims at improving the height of affected girls [9].

The presented case raises a question of increased risk of hypertrophic scarring and keloids after surgical intervention in TS patients during rhGH treatment.

Case report
We present a case of a 15-year-old TS patient, 45, X karyotype, treated at the Department of Clinical Auxology since 2010. In 2012, during the routine follow-up the patient was diagnosed with hypertrophic scars and a keloid after the surgical excision of melanocytic nevi. At the age of 12 years and 8 months and at the height of 139 cm, the girl started rhGH treatment, daily injections with an average dose of 0.331 mg/kg b.w./week. Upon first admission
to the clinic, before rhGH treatment, her physical examination revealed short stature, webbed neck, shield chest with wide nipples, cubitus valgus, high-arch palate, bone age 11 years, Tanner 1 genital and pubic hair, Tanner stage 3 thelarche. Endocrine examinations excluded other reasons for growth retardation and her mental development was normal. No other systemic failures were found. Before the treatment commencement, dermatological evaluation revealed 42 pigmented nevi (regular shape, 3–5 mm diameter) on the skin of the face, trunk and extremities. As dermoscopic examination confirmed the lesions to be benign, no surgical excision was recommended. At the age of 14, 10 months after the treatment with rhGH started, 4 of the largest congenital nevi were surgically removed (the parents of the patient claimed the changes had grown in size) without consulting the attending physician. After 2 months all postoperative scars were hypertrophic. The scars in the left preauricular area (Figure 1), on the nucha beneath hairline (Figure 2) and on the left arm (Figure 3) remained hypertrophic but the scar on the back (Figure 4) turned into a keloid. Serum concentrations of insulin-like growth factor (IGF-I) and insulin like-growth factor-binding protein 3 (IGFBP-3) were examined at the beginning of the treatment and after 12 months. The results are presented in Table 1, compared with concentrations found in a group of 26 other TS patients and of 32 patients with GH deficit (GHD), treated with the same medications at an average dose of 0.330–0.334 mg/kg b.w./week and 0.170–0.176 mg/kg b.w./week, respectively. The analysis of IGF-I and IGFBP-3 serum concentrations in the presented case did not reveal significant differences in comparison to parameters of other girls treated for short stature.

Discussion

Hypertrophic scars (HS) and keloids (K) are a result of an excessive fibroblast production, particularly collagen, with absence of increased collagenase activity [10]. Lowenstein et al. described them among other skin stig-

![Figure 1. Hypertrophic scar on the left preauricular area and melanocytic nevi on the left cheek](image1)

![Figure 2. Hypertrophic scar on the nucha beneath the low hairline](image2)
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between the occurrence of the lesions in our patient and the rhGH therapy.

Treatment of TS patients requires 100% higher doses of rhGH than of patients with GHD, while bearing in mind their preserved endogenous secretion of the growth hormone. The question remains whether such large doses of rhGH overlapping with its own secretion will not cause a significant increase in the IGF-I concentration. Maintaining high concentrations of IGF-I in TS patients might have an adverse effect not only on the risk of neoplastic progression, but also on many other aspects connected with the disease. The analysis in Table 1 shows that IGF-I accumulation in girls with TS treated with rhGH is significantly higher than in same sex peers treated for GHD, where IGF-I concentrations merely reach the values close to healthy population reference values, what might be a cause for concern. On the other hand, the concentrations of the IGFBP-3 carrier protein in TS patients are also significantly elevated, up to 2.3 SDS, what seems to have a protective role against mitotic activity of high concentrations of free IGF-I. However, the comparison of the two groups of patients reveals that in the case of GHD, an increased concentration of IGFBP-3 (to the ranges no more than close to the normal values in healthy girls) is accompanied by a smaller (reaching max. 1.5 standard deviation) increase in IGFBP-3. The analysis of the ratio between IGF-I and IGFBP-3 for TS and GHD patients revealed it to be 0.69 and 0.04, respectively. Thus, TS is characterized by a significantly higher concentration of IGF-I and lower concentration of IGFBP-3 than GHD.

Numerous melanocytic nevi occur in TS patients significantly more often than in healthy populations. Nevi are usually benign, from 1 mm to 5 mm in diameter, with no dysplastic features in the clinical and histopathologic profile [3, 17, 18], like in our case. Large atypical lesions are rare in the course of TS [5]. Growth hormone treatment was suspected to contribute to the enlargement of the pigmented nevi but further clinical observations did not confirm that hypothesis [19–21].

Small melanocytic nevi do not increase the risk of melanoma, thus there is no need of immediate surgical intervention in these cases. Excision of pigmented nevi ought to be performed after puberty because neoplastic transformation rarely occurs earlier than that [22]. That rule should apply especially to TS patients treated with GH, whose lesions need to be observed and monitored by means of dermoscopy but not removed. Due to high difficulty and low efficiency of hypertrophic scars and keloids treatment, this management is at the same time prophylactic manner of their development.

Parents of girls with TS undertake various attempts to improve not only the height and maturity of their growth.
daughters, but also their appearance by commonly performed surgical corrections of the webbed neck and pigmented nevi. Due to the risk of stretching of the postsurgical scars caused by the process of growth, they should be advised to postpone these attempts until the rhGH treatment has been completed.

Conflict of interest
All authors declare no conflict of interest.

References