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

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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 stigmata in patients with TS but questioned their common occurrence [6]. Nevertheless, keloids after surgical correction of the webbed neck have been reported [7, 8, 11]. The difference between hypertrophic scars and keloids lies in the fact that the former are thickened but confined to the margins of the injury site, while the latter migrate over the initial wound site. Nevertheless, differentiation may still be challenging [10]. Hypertrophic scars develop due to excessive collagen type III production, which is localized alongside nodules containing myofibroblasts and large collagen fibers and its reduced use. Keloid tissue is composed of unorganized collagen type I and III. None of the lesions contain elastic fibers, hair follicles, sebaceous and sweat glands [12]. Huang *et al.* are of the opinion that hypertrophic scars and keloids are stages of the same skin disease connected with fibroblast growth, what was confirmed by histopathological examinations of lesions [13]. Hypertrophic scars and keloids occur in all age groups, although sporadically in children and the elderly. They may be found in various localizations but are relatively rare on the eyelids, central part of the face or genital organs [10]. Recombinant human, as well as the endogenous, growth hormone causes IGF-I accumulation. Insulin-like growth factor affects the tissues directly and causes intensification of cell division. Receptors for GH and IGF-I have been found in cells of numerous tumors, for example of the brain, breast, colon, and others. The issue whether high concentrations of IGF-I in fact trigger the development of *de novo* neoplastic lesions or only stimulate the growth of existing tumors is currently being investigated [14]. Hypertrophic scars and keloids are considered benign tumors whose pathomechanism remains not fully elucidated. The role of genetic factors, apoptosis, endogenous factors (nitric oxide), growth factors, cytokine and exogenous factors (oxygen deficiency and diet) is emphasized [10, 12, 13]. Insulin-like growth factor is also mentioned among many other growth factors that influence the development of both scar abnormalities [15, 16], what might support the connection

Figure 1. Hypertrophic scar on the left preauricular area and melanocytic nevi on the left cheek

Figure 2. Hypertrophic scar on the nucha beneath the low hairline

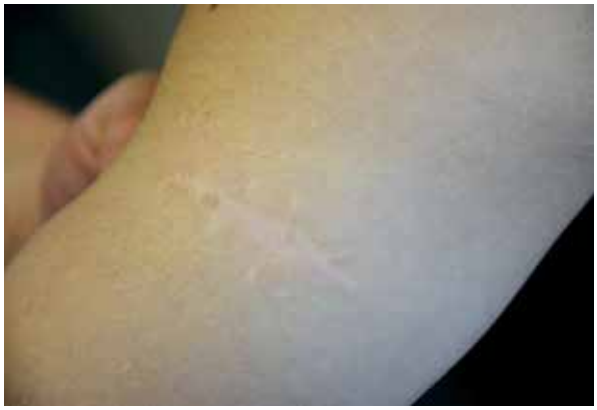

Figure 3. Hypertrophic scar on the left arm

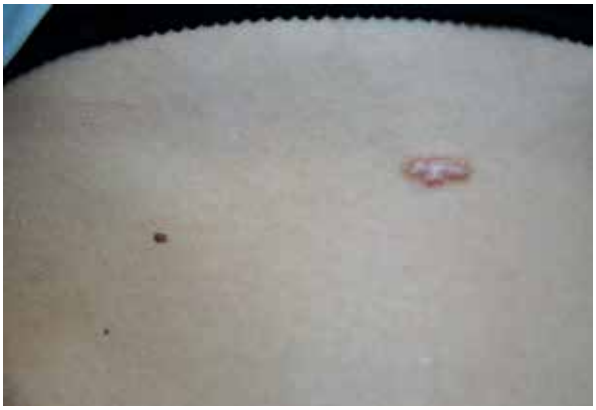

Figure 4. Keloid on the back and two melanocytic nevi

Table 1. Comparison of mean IGF-I and IGFBP-3 concentrations and the rate of growth between the presented TS case and relevant groups

Studied patients	Mean IGF-I concentrations SDS (value range)	Mean IGFBP-3 concentration SDS (value range)	Mean growth rate [cm/year]
TS patient with hypertrophic scars	+1.43 (–0.6 to +3.2)	+2.3 (+1.8 to +2.4)	4.86 (3.2 to 7.0)
26 TS patients	+1.62 (–1.5 to +5.5)	+2.34 (+1.5 to +2.8)	5.70 (3.4 to 9.4)
32 GHD patients	+0.059 (–2.6 to +5.4)	+1.47 (+1.0 to +2.0)	7.62 (3.6 to 10.4)

SDS – standard deviation score

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 IGF-I (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

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.

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