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Angiokeratomas and treatment with enzyme replacement therapy in a patient with Fabry disease

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Abstract

Angiokeratomas are the cutaneous hallmark of Fabry disease. Although it is well established that enzyme replacement therapy (ERT) prevents or slows the progression of disease on target organs in the majority of patients, the long-term effect of ERT on angiokeratomas remains unknown. We present a patient diagnosed with Fabry disease at age 11, with rapid progression of new angiokeratomas in typical regions before beginning treatment with ERT. To date, our patient has been treated with ERT for 10 years. During the treatment period, new angiokeratomas have not arisen nor have existing ones enlarged during puberty, adolescence, and early adulthood. Furthermore, partial regression of the angiokeratomas has occurred in association with regression of left ventricular hypertrophy and anhidrosis. Overall, this case suggests that long-term ERT could stop the progression of angiokeratomas and induce their partial regression but does not produce complete resolution. Importantly, regression of angiokeratomas might be a marker of systemic target-organ efficacy of ERT.

Keywords: Fabry disease, angiokeratomas, enzyme replacement therapy

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Introduction

Fabry disease (FD) is a rare, progressive, X-linked lysosomal storage disease, resulting from deficient or absent activity of the alpha-galactosidase A enzyme. Consequently, progressive accumulation of globotriaosylceramide (Gb3) and related glycosphingolipids (galabiosylceramide) within lysosomes occurs in a variety of tissues, including capillary endothelial cells, renal cells, cardiac cells, and nerve cells. This causes progressive failure of the target organs: the heart, kidneys, and nervous system. The incidence in the general population ranges from 1 in 117,000 to 476,000 persons (1). However, the true prevalence is probably much higher. In newborn screening initiatives, the incidence has been as high as 1 in 1,500 in newborn males (2) or 1 in 3,100 newborns (3).

FD was first described in 1898 by two dermatologists, Johannes Fabry and William Anderson, by observing typical skin lesions: angiokeratoma corporis diffusum (4). Angiokeratomas are the most prominent and pathognomonic signs of FD, presenting as small, dark red, raised papules, which are usually distributed in the so-called bathing trunk distribution of the buttocks, groin, umbilicus, and upper thigh (5). They have the tendency to increase in number and size with age, occurring either singly or in clusters. During puberty they typically increase in size and number, becoming darker with a verrucous surface (6, 7). The development of angiokeratomas is thought to be due to accumulation of undegraded Gb3, especially in the microvascular endothelium, and development of vascular dilatation within the epidermis and dermis (8).

Because skin lesions are not of paramount importance for patients with FD, they have not been the focus of ERT follow-up and interpretation of therapeutic efficacy. However, it should not be neglected that these are important issues from the patient's perspective. In the light of ERT and angiokeratomas, two main issues should be addressed: a) whether the expected progression of angiokeratomas could be blocked or slowed, and b) whether angiokeratomas already present could (partially or completely) regress or even resolve. Of particular interest is puberty, during which the size and number of angiokeratomas intensively progress. We investigate these topics in a young patient that was treated with ERT for 10 years during pre-puberty, puberty, adolescence, and early adulthood.

Case report

A 21-year-old Caucasian male patient was diagnosed with FD in 2006 at the age of 11. His family history was insignificant. The diagnosis of possible FD was first made by a dermatologist, to whom the patient was referred for evaluation of small rosaceous papules on his right thigh, on the lateral portion of the right hip, and on the proximal right shin (Fig. 1). At presentation, the boy also complained of anhidrosis and severe pain in the soles of his feet during febrile episodes. Skin biopsy from the thigh region was performed, and the main histopathological feature was superficial capillary hemangioma of the angiokeratoma type.

Before the introduction of ERT, angiokeratomas were erupting progressively. The lesions were widely distributed on his lower trunk, in the inguinal region, and on the thighs. The occurrence of new angiokeratomas stopped a few months after starting ERT. During the next 2 years (2006–2008) the patient was followed and underwent diagnostic check-ups for FD. He was examined by a cardiologist, nephrologist, and ophthalmologist on an annual basis. Mild hypertrophy of the interventricular septum and mild dilation of the left ventricle with signs of early diastolic dysfunction were revealed by echocardiogram. Thorough ophthalmologic and nephrological examinations were normal. FD was confirmed by deficient activity of α-galactosidase in leukocytes (0.0097 mU/mg; normal range: 0.36–0.84 mU/mg).

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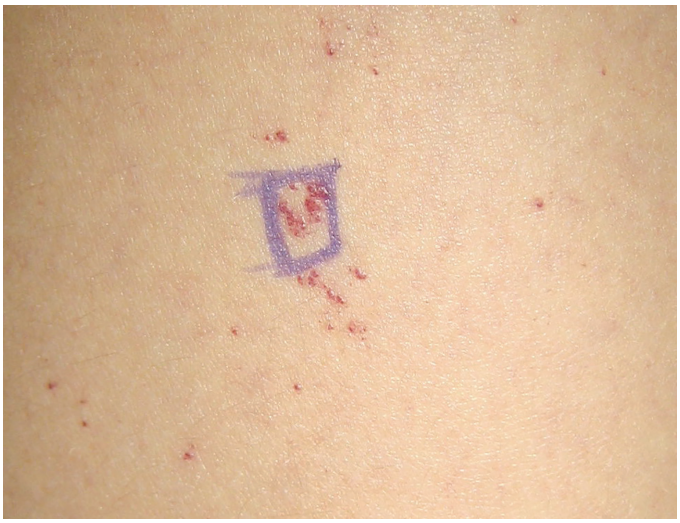

Figure 1 | Angiokeratoma on the patient's thigh before he started enzyme replacement therapy.

Genotyping revealed a nonsense mutation (TGA; p.R227X) with a stop codon and truncated inactive protein as a consequence. Enzyme activity of less than 1% was consistent with the classical type of FD, which is suitable for treatment with ERT. Treatment started in 2008, initially with agalsidase-alpha, and was then switched to agalsidase-beta after 7 years based on the decision of an endocrinologist. Both treatments were well tolerated. Autoantibodies against ERT were absent.

After 10 years of treatment with ERT, the following improvements were observed: a) regression of left ventricular hypertrophy and improvement of diastolic dysfunction, b) improvement of anhidrosis to slight hypohidrosis, c) no (expected) progression of angiokeratomas during puberty and adolescence; no new angiokeratomas appeared, and many flattened and became more violaceous (Fig. 2), and d) no involvement of other target organs (kidney or eyes). Based on these facts, the efficacy of ERT in our patient was substantial.

Discussion

FD begins early in childhood. Usually FD becomes clinically evident in boys a few years before age 10 (median age 6 years) and in girls a few years later (median age 9 years) (9). Deposition of accumulated Gb3 in endothelial and other cells leads to gradual and progressive damage to vital organs (heart, kidney, central nervous system, arteries, and eyes) with final organ failure. Early symptoms and signs of FD include pain in the hands and feet (acroparesthesia), fever, hypohidrosis or anhidrosis, diarrhea, cornea verticillata, and angiokeratomas. The establishment of diagnosis of FD is often delayed into adulthood in the absence of a positive family history (10).

Angiokeratomas are more common in men than in women with FD, presented in 66% of male and in 36% of female patients (11). They become evident between 5 and 10 years of age and are therefore clinically significant for early recognition of FD (12). Other possible, but not pathognomonic and much less frequent, dermatologic manifestations are telangiectasias and lymphedema of the limbs (5).

Angiokeratoma is a capillary vascular malformation that is not only associated with Fabry disease. The term *angiokeratoma* is deceiving because there is usually no hyperkeratosis present (13). It develops due to dilatation of the capillaries in the papillary dermis. There are five clinical types of angiokeratomas, which differ by location and morphology, but are histologically similar: a) angiokeratoma corporis diffusum (bathing trunk pattern; in FD), b) angiokeratoma Mibelli (on the dorsa of the hands and feet; associated with chilblains), c) angiokeratoma Fordyce (on the scrotum; associated with increased venous pressure, such as varicocele), d) angiokeratoma circumscriptum (unilaterally on a lower extremity), and e) solitary and multiple angiokeratomas (anywhere on the body, but most commonly on the lower extremities) (14). Diffuse angiokeratomas can also be found in other lysosomal storage diseases: fucosidosis, sialidosis, GM1 gangliosidosis, galactosialidosis, beta-mannosidosis, Schindler disease type II, and aspartylglucosaminuria (15).

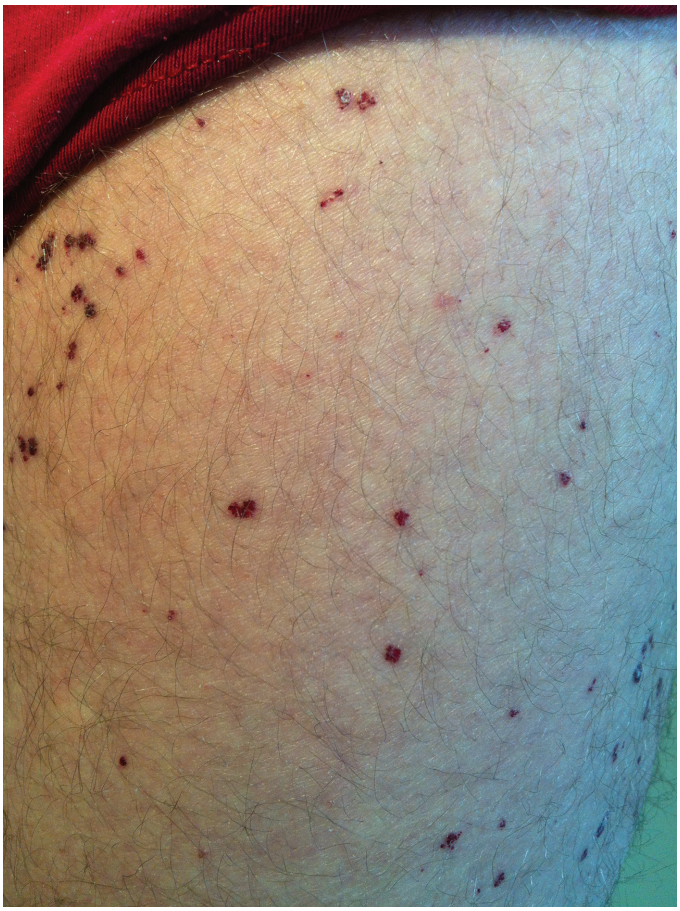

Figure 2 | Angiokeratoma on the patient's thigh after 10 years of enzyme replacement therapy.

In 2001, ERT using recombinant human α-galactosidase was introduced for treatment of patients with FD (1). Being a relatively new treatment, only sparse data concerning long-term efficacy are available. The focus of treatment with ERT is the prevention of target organ damage (heart, kidneys, arteries, eyes, and central nervous system).

It has been shown that ERT reduces the load of Gb3 microdeposits in the kidneys, heart, nerves, and skin, and consequently it reduces target organ damage in various populations (males, females, and pediatric patients) (16–18). On the other hand, studies exploring the effects of ERT on dermatological manifestations are limited and contradictory. By using repeated skin biopsies in 58 patients with FD, Thurberg et al. showed that long-term treatment with ERT slows the progression of angiokeratomas due to clearance of Gb3 in endothelial cells (19). Furujo et al. described the efficacy of ERT in partial resolution of angiokeratomas in Japanese twins with FD. The authors found that the angiokeratomas par-

tially disappeared and reduced in size gradually over 48 months of ERT (20). Similarly, Fauchais et al. showed a reduction in both the size and number of scrotum angiokeratomas in a case report of a 31-year-old male with FD after 1 year of ERT (21). On the other hand, Bongiorno et al. reported no effect on angiokeratomas after 1 year of ERT in two patients (22). Ries et al. conducted a meta-analysis including two pediatric population studies and observed a progression of angiokeratomas in some patients during ERT and no proofs of regression of angiokeratomas (23). Overall, the results presented in the literature are conflicting. Therefore, this issue deserves particular attention in order to explain whether ERT is an effective treatment for angiokeratomas, if so to what extent, and whether it is effective only in the early stages of disease or also at more advanced stages.

There are some other issues still unsolved regarding ERT and angiokeratomas in FD. Thus, it seems intriguing to investigate whether a beneficial response of ERT on angiokeratomas can predict beneficial effects on target organs and thereby represents a surrogate marker of overall (current and future) clinical efficacy of ERT, and whether the presence of angiokeratomas correlates with the extent of end-organ abnormality. The clinical effect of ERT on angiokeratomas could be a marker of overall efficacy of ERT, or a marker of severity and prognosis of the disease. It is known that male patients more frequently have worse clinical presentations and outcomes in comparison to female patients, and that angiokeratomas are more frequent in males (11). It seems possible that angiokeratomas are associated with the clinical extent and severity of FD. There are no data yet to confirm this association. Nevertheless, in a meta-analysis of pediatric cohorts, angiokeratomas were associated with a higher risk of end-organ involvement, but only in male children and adolescents (23). However, analyzing the data from a large multicentric FD outcome survey, which included 751 patients, it was shown that cutaneous lesions (predominantly angiokeratomas) correlate with a systemic manifestation of FD (renal failure, cardiac disease, pain, and premature cardiovascular disease) as assessed by a severity scoring system used for assessing the severity of the condition. Importantly, there are no data about associations between the efficacy of ERT on angiokeratomas and target organ damage. Because there could be a correlation between angiokeratoma presence and the severity of systemic involvement, it is likely that a reverse correlation might also exist; that is, improvement in angiokeratomas with ERT could correlate with reversal of systemic manifestations induced by ERT. Even in this large registry, the effect of ERT on angiokeratomas was not addressed by data (11). Undoubtedly, such information, if proven, would be clinically very relevant and useful.

In our case described here, after 10 years of treatment with ERT, no (expected) progression of angiokeratomas during puberty and adolescence was found, although complete resolution of angiokeratomas was not observed. This was associated with no further involvement of target organs and the regression of cardiac involvement and anhidrosis. Collectively, these results suggest that the beneficial clinical efficacy of ERT on angiokeratoma can be a marker of its efficacy on target organs.

Finally, one should not neglect the fact that in many patients angiokeratomas could represent a psychological issue due to their localization, appearance, and progression during puberty and adolescence. Due to several reasons explained above, a dermatologist should be part of the multidisciplinary team for long-term care of patients with FD.

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