Review paper

Familial localized scleroderma with paediatric onset: a review

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Abstract

Localized scleroderma is an inflammatory disease causing sclerosis of the skin. The aetiology and pathogenesis of localized scleroderma remain unclear. Localized scleroderma is considered a genetically driven disease. It is not well understood if genetic factors or environmental exposure individually can cause its development or if their interaction is needed to trigger the disease. Some authors postulate that familial clustering is evidence of a hereditary disease. Familial localized scleroderma has been rarely reported and is a case worth studying. We present the review of literature on this subject with 3 additional cases of familial localized scleroderma with paediatric onset.

Key words: morphea, localized scleroderma, familial, paediatric onset, juvenile.

Introduction

Localized scleroderma is an inflammatory disease causing sclerosis of the skin. The aetiology and pathogenesis of localized scleroderma remain unclear. Localized scleroderma is considered a genetically driven disease. It is not well understood if genetic factors or environmental exposure individually can cause its development or if their interaction is needed to trigger the disease. Some authors postulate that familial clustering is evidence of a hereditary disease. Familial localized scleroderma has been rarely reported and is a case worth studying. We present the review of literature on this subject with 3 additional cases of familial localized scleroderma with paediatric onset.

Database

We searched databases (PubMed, MedLine, Elsevier) with key words: 'morphea', 'localized scleroderma', 'familial', 'paediatric onset', 'juvenile', and 'hereditary' reviewing all available publications of familial cases of localized scleroderma.

Pathogenesis

Localized scleroderma is an inflammatory sclerosing disease of the dermis and subcutaneous tissue with multiple clinical subtypes. The course of the disease may vary, starting with slight erythematous superficial sclerosis of the skin to more severe cases with a decreased quality of life due to pain, skin thickness, as well as muscle and joint involvement [1, 2]. Outcome of paediatric-onset localized scleroderma is worse than in adult-onset one because of longer duration, more frequent involvement of deeper and extracutaneous tissues and delayed introduction of treatment [1, 3, 4]. Although the aetiology and pathogenesis of morphea remain unknown, autoimmune, environmental, and infectious factors have been proposed [1, 5].

The prevalence of autoantibodies in morphea and the general population is usually the same, but anti-single strand DNA, fibrillin-1, histone and topoisomerase II antibody titre may increase in morphea and antinuclear antibody titre in linear or generalized morphea [1, 4, 6, 7].

Vascular changes and imbalance between collagen destruction and production are components of sclerosis of the skin. Elevated vascular endothelial growth factor is evidence

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of vascular damage. An activation of T-cell derived cytokines (interleukin-4, -6, -8, -10, -13, and -17, TGF-β, PDGF, endothelin-1) and fibroblasts cause abnormal collagen synthesis [2, 4, 8]. There are also well-known suppressors of collagen production for example α and γ interferon, both of which are produced by Th1 lymphocytes. STAT4 factors (responsible for Th1 differentiation) polymorphism are connected to increased susceptibility of localized scleroderma. There were several genome-wide association studies performed to delineate the genetic susceptibility factor [9–11].

Hereditary disease?

Studies involving genome-wide association have been performed in large multinational patient cohorts. In one U.S. study, the relative risk of inheriting localized scleroderma was at a rate of < 2% compared with < 0.1% in the general population [5]. 10–30% of patients reported having a family history of autoimmune disease [7].

The candidate gene for inheritance susceptibility is expected to have single nucleotide change (single nucleotide polymorphisms (SNPs)). The dominant region associated with localized scleroderma is a major histocompatibility complex. HLA class I and class II alleles are linked to the development of localized scleroderma, although in familial cases there is no common HLA haplotype in affected individuals in different families [2, 8]. Within families, patients with morphea share at least one HLA haplotype and other family members with identical HLA haplotypes did not develop disease [1, 12]. The MHC gene is necessary but not sufficient to induce disease, and that environmental triggering factors may be implicated [1, 13, 14]. The role of the genetic factor has been supported by cytogenetic demonstration of chromosome breaks and increased ice frequencies resulting from aberrant DNA reparation process [15].

Other non-HLA genes which are likely factors in the pathogenesis of the disease are: the protein tyrosine phosphatase nonreceptor 22 (PTPN22), interleukin (IL)-1β and NLRP1, interferon regulatory factor 5 (IRF5), and a transcription factor in the Toll-like receptor (TLR) [16–18]. Additionally, the downregulation of microRNA let-7a is thought to contribute to the excessive production of collagen in localized scleroderma [14].

Nonhereditary factors play a major role in the pathogenesis of the disease. Trauma is the most common trigger, reported in 7.3–11.8% of patients [11]. Other events, such as B. burgdorferi infection, injury or inflammation of the affected area were revealed to be triggering factors [19–21]. Furthermore, hazards such as vinyl chloride, organic solvents,

Table 1. Reported cases of familial localized scleroderma

Author and year of publication	Descrription
Rees *et al*., 1953 [22]	Localized scleroderma in the father and daughter
Christianson *et al*., 1956 [23]	Familial occurrence of localized scleroderma in three families, one of them with three family members affected
Burge *et al*., 1968 [16]	Two sisters with childhood onset localized scleroderma
Szczepanski *et al*., 1972 [24]	Localized scleroderma in 2 sisters
Wuthrich *et al*., 1975 [2]	Two familial cases of localized scleroderma. Histopathologically confirmed morphea in 3 siblings of first family, and 2 siblings in second
Taj *et al*., 1977 [25]	Identical morphea lesions of the hands of a 13year-old brother and an 11-year- old sister
Kulin *et al*., 1986 [8]	A family (father and child) with childhood onset of hypotrichosis and morphea with apparent autosomal dominant inheritance
Wadud *et al*., 1989 [26]	Clinically and histologically established localised scleroderma in 2 family members
Bunker *et al*., 1990 [15]	39-year-old mother and a 16-year-old daughter with childhood onset morphea lesions
Kaur *et al*.,1993 [14]	Case of familial linear scleroderma in the mother and daughter. First case in Indian literature
Manolios *et al*., 1996 [27]	5 familial cases of scleroderma, 1 of the families affected with morphea
Patrizi *et al*., 2000 [19]	Atrophoderma Passini-Pierini in 3 siblings
De Keyser *et al*., 2000 [17]	Familial scleroderma in 2 monozygotic twin pairs. The first twin pair was diagnosed with the systemic form of scleroderma, the second pair with the localized form
Iranzo *et al*., 2001 [13]	Clinically and histologically established scleroderma en coup de sabre in a 14-year-old girl and her grandfather
Brownell *et al*., 2007 [10]	32-year-old woman and her 35-year-old sister presented with plaques of scleroderma en coup de sabre
Pham *et al*., 2010 [28]	Plaque type morphea affecting a 9-year-old boy and his father
Lis-Święty *et al*., 2014 [11]	20-year-old female monozygotic twins who presented with co-existence of lichen sclerosus and localized scleroderma. Skin lesions typical for localized scleroderma occurred in both patients, at the age of 10

polymerizing epoxy resins, bleomycin and silica have been reported to trigger scleroderma-like disorders [9].

Some authors postulate that we can consider familial clustering as evidence of a hereditary disease. A small number of familial localized scleroderma cases have been reported (Table 1) [22–28]. In 1953 Rees and Bennett documented the first familial case, which involved a father and daughter [19]. Since then, there have been more cases of familial morphea documented (Table 1). And there are more cases presented every year.

The rising number of familial cases reported suggests that the genetic component may predispose individuals to develop morphea.

This is another report to be added to literature: 2 siblings with deep morphea and their second cousin with deep linear scleroderma.

Patient 1

A 19-year-old female, diagnosed with deep morphea at the age of 3. Histopathology confirmed the diagnosis. The disease started as deep sclerosing focusing on the right thigh in 1999. It then progressed in 2014, when a new focus appeared on the chest. Currently, physical examination has revealed 2 deep, sclerosing foci involving the deep dermis and subcutaneous fat. Skin lesions involve the right hip, the thigh (15 × 7 cm, 5 cm deep) (Figure 1 B) and chest in the region of the xiphoid process (10 × 8 cm, 2 cm deep) (Figure 1 A). No other complaints have been reported. No irregularities, except for Jo-1 antibody titre elevation, were revealed in the antibody profile. An X-ray, USG of the abdomen and echocardiography did not reveal any abnormalities. Since 2014 the patient has been treated with rheological treatment, i.e. alprostadil administered intravenously at the daily dose of 60 mg for 3 consecutive days given every 6 weeks, 500 lipoprotein lipase releasing units (LSU) of oral sulodexide (daily) and a topical treatment with heparinoid with good result. Due to the progress of morphea, the therapy with methotrexate was initiated in mid-2016 (primarily 20 mg per week, then reduced to 15 mg weekly in 2017) resulting in substantial improvement of the clinical course.

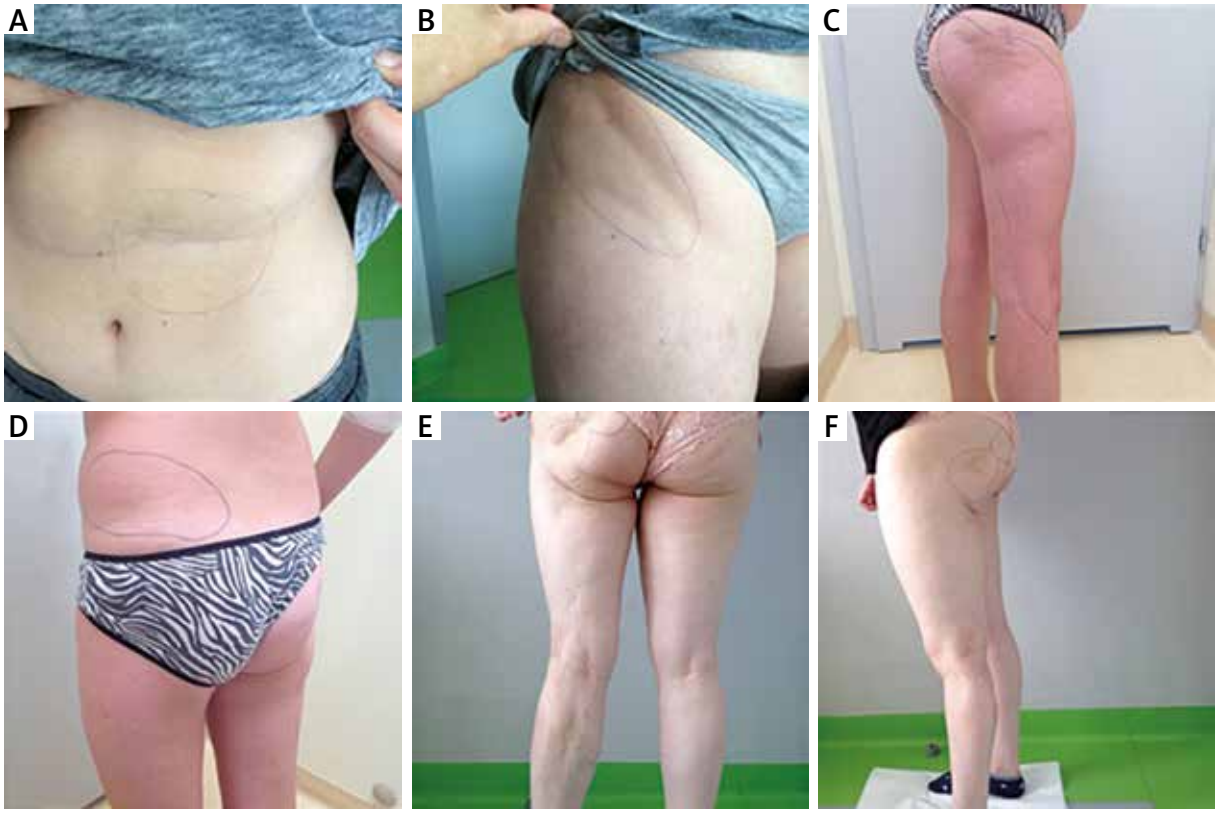

Figure 1. A – Clinical manifestation of the disease in patient 1. Clinical manifestation of the disease in patient 1. Visible deep, sclerosing involvement of the chest in the region of the xiphoid process (10 × 8 cm, 2 cm deep). **B** – Clinical manifestation of the disease in patient 1. Visible deep, sclerosing focus of the right hip, the thigh (15 × 7 cm, 5 cm deep) involving deep dermis and subcutaneous fat. **C** – Clinical manifestation of the disease in patient 2. Skin and subcutaneous sclerosis of the lateral area of the right thigh, the right popliteal fossa, as well as the medial and lateral areas of the right crus. **D** – Clinical manifestation of the disease in patient 2. Visible deep, sclerosing focus of the lumbar area involving deep dermis and subcutaneous fat. **E, F** – Clinical manifestation of the disease in patient 3. Visible sclerosis of the posterior crus with dyspigmentation and subcutaneous atrophy, involving the Achilles ligament, expanding to the left thigh, with atrophy of the muscles, especially deep atrophy of the left gluteal muscle

Patient 2

A 14-year-old female, the sister of patient 1, who developed deep morphea in 2014, probably after a tick bite (Lyme disease was excluded). The disease started as sclerosis of a 5 × 5 cm area of the right posterior thigh. Currently, skin and subcutaneous sclerosis are present in the lumbar area, lateral area of the right thigh, the right popliteal fossa as well as the medial and lateral areas of the right crus (Figures 1 C, D). A biopsy revealed histopathological features of morphea. Antinuclear antibodies in high titre have been present. ENA-8 profile did not reveal a significant elevation of antibody titres. USG of the abdomen revealed no abnormalities. An echocardiography revealed a mild retrograde wave, requiring an annual cardiological check-up. Since 2014, the girl has been treated in the exactly same manner as her sister (patient 1), i.e. a combination of intravenous alprostadil, oral sulodexide and a topical heparinoid achieving good clinical outcome. In mid-2014 progress of the disease was observed, then 10 mg of methotrexate weekly has been initiated with good result. The dose of methotrexate was increased in late 2017 up to 15 mg per week due to lack of satisfactory response and disease progression. Further remission of skin lesions was observed.

Patient 3

A 31-year-old female, and second cousin to Patient 1 and 2, was diagnosed with deep linear scleroderma in 1995 (at the age of 7). Skin lesions, which first appeared as a slight dyspigmentation at the posterior crus, developed as sclerosis of the posterior crus with dyspigmentation and subcutaneous atrophy, involving the Achilles ligament, expanding to the left thigh, with atrophy of the muscles; especially deep atrophy of the left gluteal muscle (Figures 1 E, F). Histopathology revealed thick crowded collagen bundles. Antinuclear antibodies, ENA-8 profile antibodies and anti-dsDNA antibodies were absent. Early and late R loops, meandering loops, capillary disorganizations and avascular fields were revealed in capillaroscopy. The USG performed within the skin lesions revealed dermal atrophy and an increase of echogenicity. The patient was treated with procaine penicillin in 1995, penicillamine and piascledine in 1996, penicillamine and chloroquine in 1997, and hydroxychloroquine in 1998 with no satisfying results. PUVA therapy was initiated in 2000 and continued until 2003 resulting in substantial improvement of the skin lesions. Calcineurin inhibitor monotherapy (0.1% tacrolimus ointment) was applied until 2008. In 2008, due to the disease progression, PUVA therapy was reintroduced and continued until 2009 and then in 2011. Since 2011 no further exacerbation of the morphea course has been reported.

Conclusions

Based on epidemiological, genetic, familial, and twin studies we might assume that scleroderma is not a heritable disease but may arise in genetically susceptible individuals when exposed to environmental triggers. Yet the growing number of familial cases might lead to the conclusion that localized scleroderma has multifactorial, polygenic inheritance.

As the cause of localized scleroderma as well as the contributing genetic and environmental factors were neither completely understood, nor properly studied it would be beneficial to determine if there are more frequent cases of familial morphea and if heredity should be taken into consideration for this disease. This review should be understood as an introduction and could lead to further studies involving more patients. Finding more cases of familial localized scleroderma and performing genetic examinations would contribute to the full understanding of this problem.

Conflict of interest

The authors declare no conflict of interest.

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