Review article

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Paediatric morphoea: a holistic review. Part 1: epidemiology, aetiopathogenesis and clinical classification

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Summary

Morphoea, also known as localized scleroderma, is a debilitating fibrosing disorder of uncertain aetiology, affecting the skin and subcutaneous tissues. Paediatric-onset disease is not uncommon and is associated with frequent relapses. The disease has complex pathogenetic mechanisms and multiple clinical subtypes, and affects children of all ages. Recent research has focused on elucidating the disease pathophysiology and identifying measures of disease activity. We performed a literature search on PubMed, MEDLINE and Google Scholar, using keywords such as 'pediatric morphea', 'juvenile localised scleroderma' and 'juvenile systemic sclerosis'. Relevant studies, including randomized trials, reviews of standard current guidelines and original research articles, were selected, and results were analysed before being summarized. In the first of this two-part review, we provide a bird's-eye view of the current literature concerning the epidemiology, aetiopathogenesis and clinical classification of paediatric morphoea; in Part 2, we review the diagnosis, markers of disease activity, management and natural history.

Introduction

Cutaneous fibrosing disorders comprise multiple disorders, with cutaneous sclerosis and/or fibrosis being a common finding. Although scleroderma or systemic sclerosis (SSc) is a common entity, there is a whole spectrum of scleroderma-like fibrosing disorders,[1,2] which vary according to the degree of dermal sclerosis, presence or absence of extracutaneous involvement, specific laboratory abnormalities, natural history and outcome.

Morphoea, also called localized scleroderma, is an idiopathic chronic fibrosing disorder manifesting as fibrosis and induration of skin and subcutaneous tissues. It is the most common type of scleroderma in childhood.[3] Morphoea can be distinguished from SSc by the absence of sclerodactyly, Raynaud phenomenon, nailfold capillary changes and telangiectasias. Although considered an idiopathic disorder, associations have been reported with connective tissue disorders such as systemic lupus erythematosus, polymyositis, juvenile dermatomyositis, Sjögren syndrome and rheumatoid arthritis as part of an overlap syndrome.[4] Contrary to popular belief that morphoea in the paediatric age group is a benign condition with a good outcome, the evidence indicates that its chronicity and potential extracutaneous complications contribute to significant morbidity in children.[5]

In this article, we review the epidemiology, aetiopathogenesis and clinical types of paediatric morphoea. We performed a literature search to identify studies on paediatric morphoea up to 30 September 2019 on PubMed, MEDLINE and Google Scholar, using keywords such as such as 'pediatric morphea', 'juvenile localised scleroderma' and 'juvenile systemic sclerosis'. Studies with systematic bias or incoherent results were omitted. Data extraction was conducted independently by both authors, and any ambiguity was mutually discussed and reviewed. The data collected were analysed and described.

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Epidemiology

Morphoea is relatively rare, with a reported incidence of 0.4–2.7 per 100 000 population in various epidemiological studies.[6] Children and adults are equally affected, with most children (90%) presenting between 2 and 14 years of age, while adults are commonly affected in the fourth decade. Morphoea has also been reported to occur at birth, known as congenital morphoea.[7] White populations are more commonly affected and there is a female preponderance (female/male ratio between 2 : 1 and 4 : 1). According to some studies, 20–30% of cases of morphoea begin in childhood and almost two-thirds of linear morphoea cases present before 18 years of age.[8]

Aetiopathogenesis

The underlying aetiopathogenesis of morphoea is poorly understood, but current evidence points towards a complex, multifactorial process, with a role for genetic, environmental and autoimmune factors, and with subsequent inflammation, microvascular injury, epidermal activation of signalling pathways and imbalance between production and degradation of collagen, culminating in variable degrees of dermal fibrosis (Fig. 1). The pathogenesis of morphoea is similar to that of SSc, but the inflammation and fibrosis in morphoea is more intense and restricted to skin and subcutaneous tissues, compared with SSc.[9]

Genetic susceptibility has a small but potentially important role in certain forms of morphoea. Up to 2% of cases of morphoea are seen in first- and second-degree relatives. Multiple human leucocyte antigen (HLA) polymorphisms, such as HLA-DRB*04:04 and HLA-B*37, confer increased risk in linear and generalized morphoea.

The role of autoimmunity is suggested by the association of morphoea with other autoimmune diseases, including connective tissue disorders, vitiligo, type 1 diabetes mellitus and Hashimoto thyroiditis, as well as the presence of autoantibodies, including antinuclear antibody (ANA), antihistone antibody, anti-topoisomerase II and rheumatoid factor. Lichen sclerosus has been found to be a common association in both children and adults with morphoea.[10]

A role of mosaicism and chimerism in morphoea pathogenesis has been proposed in some studies. Some varieties of morphoea (e.g. *en coup de sabre*) follow lines of Blaschko and may be related to genetic mosaicism.[11] Clinical lesions in morphoea often resemble those of chronic graft-versus-host disease, and one study showed the presence of chimeric cells.[12]

Epigenetic mechanisms including altered DNA methylation, histone acetylation and microRNA (miRNA) levels have been reported, with raised levels of profibrotic miRNAs (e.g. miR-21, miR-155) and decreased expression of antifibrotic components (e.g. miR-7) in the skin of patients who develop localized scleroderma.[13]

Potential triggers for the disease process include infectious agents (e.g. *Borrelia* spp.), surgery, radiation, mechanical trauma, koebnerization, vaccinations (e.g. hepatitis B and tetanus) and certain drugs (e.g. bleomycin, vitamin K1, etc.).[13] Sympathectomy and underlying neurocutaneous syndromes have also been proposed. In a predisposed individual, these triggers potentially produce microvascular injury, which produces T-cell activation and inflammation.

Morphoea, similar to SSc, is an inflammatory cascade with raised levels of proinflammatory cytokines. Significantly increased plasma levels of interferon (IFN)-α2, IFN-γ, IFN-induced protein-10, interleukin (IL)-17a, IL-12p70 and monocyte chemoattractant protein-1, have been shown in paediatric morphoea, with activation of both T helper (Th)1 and Th17 types of inflammatory responses.[14] It is proposed that there is a predominantly Th1 type of inflammation in the early/active disease state, whereas in the later, fibrotic stage of morphoea, there is activation of the Th2 type of inflammation.[15] Increased levels of B-cell activating factor have been demonstrated in the sera of patients with morphoea, along with an association with autoantibody production.[16]

Recent research has proposed the role of profibrotic signal pathways originating from epidermal cells, such as the Wingless and int homologue (Wnt), Sonic hedgehog (Shh) and Jagged notch pathways, in response to antigenic stimulation in SSc, and a similar role, though not yet proved, may also be responsible for the upregulation of fibroblast activity and increased dermal fibrosis seen in morphoea.[13] Increased keratinocyte production of fibrillin-1, endothelin-1 and Toll-like receptor-4 activity produce profibrotic action; their upregulation has been demonstrated in SSc, and a similar role is proposed in localized scleroderma as well.[13,17] Melanocyte-stimulating hormone-α via melanocortin-1 receptors has immunomodulatory and antifibrotic actions, but its downregulation has been proposed in pathological fibrosis.[18] Th1/Th17-induced transforming growth factor-β production downregulates matrix metalloproteinases and promotes fibrosis,

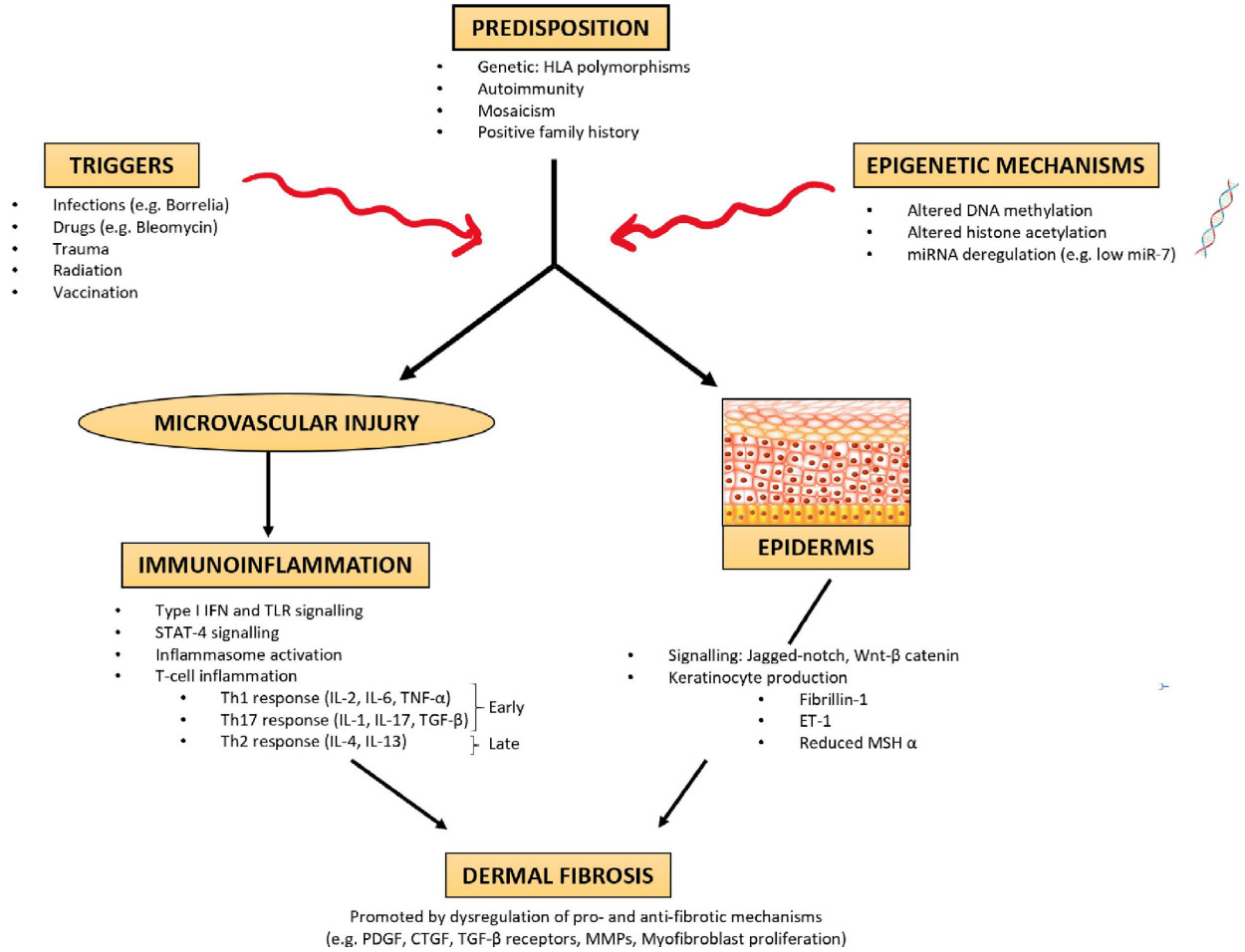

Figure 1 Currently proposed pathogenesis of morphoea. In a predisposed individual, epigenetic mechanisms and trigger factors precipitate microvascular injury, which produces immune-inflammation involving multiple pathways. T helper (Th)1 and Th17 inflammatory responses predominate in early lesions, whereas late, atrophic stages are mediated by a Th2 response. Epidermal signalling by specific pathways as well as keratinocyte production of profibrotic mediators promotes dermal fibrosis. Dysregulation of pro- and antifibrotic mechanisms is an important determinant of degree of dermal fibrosis. CTGF, connective tissue growth factor; ET-1, endothelin-1; HLA, human leucocyte antigen; IFN, interferon; miRNA, microRNA; MMP, matrix metalloproteinase; MSH, melanocyte-stimulating hormone; PDGF, platelet-derived growth factor; STAT-4, signal transducer and activator of transcription-4; TGF, transforming growth factor; TLR, Toll-like receptor; TNF, tumour necrosis factor; wnt, wingless and int homologue.

and IL-4 and IL-13 production by the Th2 pathway inhibits collagenase activity in the late fibrotic stage. Raised levels of platelet-derived growth factor and connective tissue growth factor with proliferation of myofibroblasts (the eventual effector cells) produce dermal fibrosis. However, the fact that the inflammation and fibrosis in morphoea are more restricted to dermal structures and the lack of any documented transition of morphoea into SSc suggests that the pathogenetic processes described above remain to be further elucidated.

Clinical types and classification

A common way to classify morphoea in children is based upon the clinical findings. One system is the Mayo clinical classification, which describes five types of localized scleroderma (morphoea): linear, plaque, generalized, bullous and deep.[8] The second, relatively newer classification (the Padua classification), is similar, but mentions a distinct, relatively common category of 'mixed' morphoea, seen in about 15% of paediatric cases.[19] Both systems are summarized in Table 1.

Table 1 Classification systems for clinical categorization of morphoea.[19]

Mayo classification	Padua preliminary[a] classification
Linear morphoea	Circumscribed
Linear morphoea of the extremities	Superficial lesions/plaques
En coup de sabre	Deep lesions/deep morphoea
Progressive hemifacial atrophy	Linear scleroderma
Plaque morphoea	Generalized
Morphoea en plaque	Pansclerotic
Guttate morphoea	Mixed
Atrophoderma of Pasini and Pierini	
Generalized morphoea	
Bullous morphoea	
Deep morphoea	
Subcutaneous morphoea	
Morphoea funda	
Eosinophilic morphoea	
Disabling pansclerotic morphoea of children	

[a]This is a newer classification, still preliminary.

Linear morphoea

Often considered as the most common variety of paediatric morphoea,[20] linear is characterized by linear induration developing along the lines of Blaschko, and involves the dermis.[21] It may be complicated by atrophy and deformity of the underlying structures. It has three subtypes, as follows:

Linear morphoea of the extremities. Linear, band-like lesions appear on the skin of the extremities. Often heals with residual pigmentation, or may cause contractures, growth retardation, atrophy and limb shortening.

Morphoea en coup de sabre. This is found on the frontoparietal region of the scalp, and may be associated with scarring alopecia, seizures, ocular involvement and frequent headaches.

Progressive facial hemiatrophy (*Parry–Romberg syndrome).* This produces significant facial asymmetry due to hemiatrophy of the face (Fig. 2a). Skin changes are less prominent than other forms of linear morphoea, but atrophy of underlying structures is severe. It can coexist with morphoea *en coup de sabre*.

Plaque/circumscribed morphoea

Plaque/circumscribed morphoea appears as discrete, oval plaques on the skin, which begin as lesions with an erythematous border, but gradually develop sclerosis and appear as white, indurated lesions (Fig. 2b). It can have superficial or deep variants according to the Padua preliminary classification; the superficial variants occur on the trunk and show less induration, whereas the deep variants can involve deep subcutaneous tissues.

Superficial morphoea (atrophoderma idiopathica of Pierini and Pasini) is a rare type of plaque morphoea with symmetrical, nonindurated, hyperpigmented patches on the trunk or limbs.

Generalized morphoea

A rare type, characterized by ≥ 4 large (> 30 mm) indurated plaques, involving ≥ 2 distinct anatomical sites. Lesions are limited to the dermis, are often symmetrical and tend to spare the hands and face. This variety shows a strong association with autoantibodies, especially ANA.[20]

Bullous morphoea

Bullous morphoea is a rare variant with tense, subepidermal bullae developing within the sclerotic plaques.

Deep morphoea

Deep morphoea shows a diffuse and often symmetrical presentation, with the subcutaneous variety showing sclerosis of deeper structures such as the subcutaneous tissue and muscles, and tense, taut overlying skin, often on the extremities. Variants include morphoea profunda (dense inflammation in subcutaneous tissues) and eosinophilic fasciitis (EF). EF, also known as Shulman syndrome, presents with symmetrical, painful swelling of the skin, with induration and contractures occurring during later stages. It shows physical signs such as the 'negative vein sign' (depression of cutaneous veins compared with the surrounding tissue) and the 'groove sign' (linear depression along the course of superficial veins, caused by relative perivascular sparing). It has been reported to be associated with eosinophilia, raised levels of acute phase reactants and increased risk of haematological malignancies.[22]

Disabling pansclerotic morphoea of childhood

This is a severe, rapidly progressive form that affects children < 14 years of age, causing extensive contractures of the skin, subcutaneous tissue, underlying

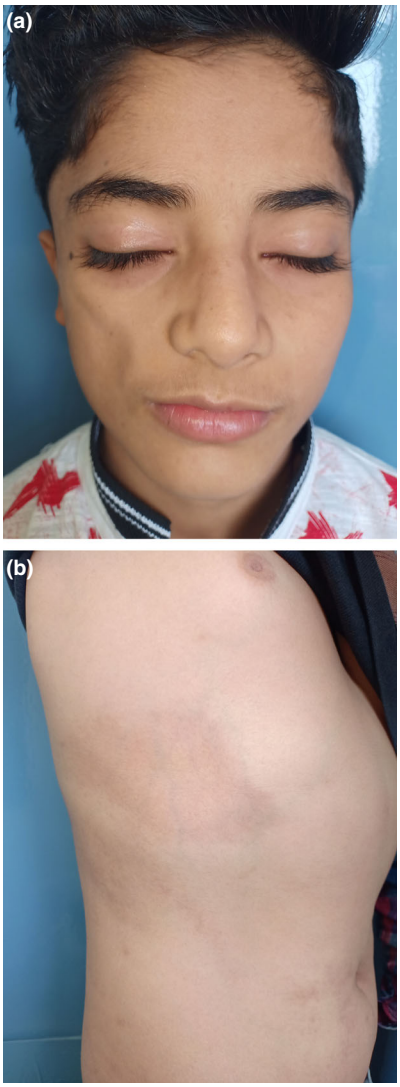

Figure 2 (a) A child with Parry–Romberg syndrome, showing hemiatrophy of the right side of the face; (b) superficial plaque variant of morphoea on trunk with induration.

muscle and bone. It is associated with contractures, serious deformities and poorly healing ulceration. High-dose immunosuppression is indicated, but the disease generally carries significant long-term morbidity.[23]

Mixed type

The mixed type is common in children. It often presents as coexistence of linear morphoea with other forms such as plaque or generalized morphoea.

Congenital morphoea

Some rare forms of morphoea are present at birth but are often detected much later because they are not easily suspected and are confused with lesions such as naevus simplex and port-wine stain. In a recent study, linear morphoea (including its subtypes) was found to be the most common variety (76%) of congenital morphoea, with a median age of diagnosis of 2.9 years.[24]

Extracutaneous manifestations have been reported in paediatric morphoea, and include muscular involvement, arthritis, neurological involvement (e.g. headache, seizures) and ocular manifestations (e.g. uveitis). In a large study involving 750 children with localized scleroderma, extracutaneous features were reported in 168, with 25% of extracutaneous features occurring unrelated to the site of cutaneous morphoea.[25] In a retrospective review of 136 patients with paediatric morphoea, 1.5% went on to develop the type of serious, life-threatening complications seen in SSc, including pulmonary, cardiac and gastrointestinal complications, without any other obvious feature of SSc.[4]

Conclusions

Paediatric morphoea is the most common type of scleroderma in childhood. The disease most commonly affects children aged 2–14 years and shows a female preponderance. The aetiopathogenesis is complex, involving multiple inflammatory pathways, genetic and autoimmune predisposition, and environmental triggers. The linear form is the most common variety in children, developing along the lines of Blaschko. Extracutaneous manifestations occur in up to 25% cases, and often involve the musculoskeletal, neurological and ocular systems.

Learning points

- Paediatric morphoea is a chronic fibrosing disorder with frequent relapses, extracutaneous manifestations and serious adverse effects on quality of life.
- Most cases in paediatric morphoea occur between 2 and 14 years of age and show a female preponderance
- Morphoea has a complex aetiopathogenesis akin to systemic sclerosis; genetic, environmental and autoimmune triggers produce a proinflammatory state eventually culminating in fibrosis

• The linear form is the most common variety in children, developing along the lines of Blaschko.
• Extracutaneous manifestations occur in up to 25% cases, and often involve the musculoskeletal, neurological and ocular systems.

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