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REVIEW

Morphea in Childhood: An Update☆

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Abstract Morphea is an inflammatory, fibrosing skin disorder. When it occurs in childhood, it is also known as *juvenile localized scleroderma*. It is more common in girls and typically appears around the age of 5 to 7 years. According to a recent classification system, morphea is divided into 5 types: circumscribed (plaque), linear, generalized, pansclerotic, and mixed. Approximately 40% of patients present extracutaneous manifestations. Childhood morphea is treated with phototherapy, oral or topical calcitriol, topical tacrolimus 0.1%, methotrexate, topical or systemic corticosteroids, mycophenolate mofetil, bosentán, and topical imiquimod 5%. A variety of measuring tools are used to monitor response to treatment. Few prognostic studies have been conducted, but findings to date suggest that the disease tends to run a chronic or intermittent-recurrent course and frequently causes sequelae.

PALABRAS CLAVE
Morfea;
Infancia;
Esclerodermia juvenil localizada;
Esclerodermia lineal;
Hemiatrofia facial;
Revisión narrativa;
Fototerapia;
Metotrexato

Morfea en la infancia: actualización

Resumen La morfea es una enfermedad de la piel que se manifiesta en forma de inflamación y fibrosis. En niños y jóvenes, también se conoce como esclerodermia juvenil localizada. En edad infantil, afecta con mayor frecuencia al sexo femenino y la edad de comienzo se ha establecido en torno a los 5-7 años. Una clasificación reciente divide la morfea en: circunscrita (en placas), lineal, generalizada, panesclerótica y mixta. Alrededor de un 40% de los pacientes presentan manifestaciones extracutáneas.

Los tratamientos empleados en morfea infantil son: fototerapia, calcitriol oral, calcipotriol tópico, tacrolimus 0,1% tópico, metotrexato, glucocorticoides tópicos y sistémicos, mofetil micofenolato, bosentán e imiquimod 5% tópico. Diversas medidas de resultado pueden ayudar a monitorizar el tratamiento. Los estudios pronósticos son escasos, pero apuntan hacia una enfermedad con tendencia a un curso crónico o intermitente-recurrente y una frecuencia considerable de secuelas.

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Introduction

Morphea is a fibrosing inflammatory skin disorder. When it occurs in children and adolescents, the condition is also known as *juvenile localized scleroderma* to distinguish it from the systemic form of the disease (called *juvenile systemic sclerosis* or *juvenile systemic scleroderma*). When the term *morphea* is used there is no way, equivalent to *juvenile localized scleroderma*, of specifically denoting the disease in childhood or adolescence. In this review, we will use the term *morphea in childhood* to refer to the condition in the pediatric population.

Epidemiology, Etiology, and Pathogenesis

There are very few studies on the incidence and prevalence of morphea. In a study of the incidence of childhood scleroderma in the United Kingdom and Ireland between 2005 and 2007, researchers found an annual incidence rate of 3.4 cases per million children for morphea of all types and 2.5 per million for linear morphea (LM).[1] The authors of a US study on the epidemiology of morphea in Olmstead County (Minnesota) between 1960 and 1993, found an annual age- and sex-adjusted incidence rate per 100,000 population of 2.7 cases for morphea and 0.5 for linear morphea.[2] Patients who were under 18 at diagnosis accounted for 34% of the patients with morphea and 69% of those with LM.

Childhood-onset morphea affects girls more than boys, with a female-to-male ratio of 2-3:1.[3,4] Age of onset has been established at between 5 and 7 years.[5,6] Mean age at diagnosis ranges from 7 to 13 years.[3,4,6] In a series of 750 children with morphea, the mean interval between onset and diagnosis was 1.6 years (median 11 y, range 0-16.7 y).[3] In a series of 52 patients with LM, this interval was 1.8 years (range, 15 d to 8 y).[6] Other studies have identified a delay of 9 to 11 years.[4,5,7]

A family history of rheumatic and autoimmune diseases is reported in between 12.1%[3] and 24.3%[8] of cases. This proportion falls to between 6%[3] and 8.8%[8] in first-degree relatives. The diseases most frequently associated with morphea are rheumatoid arthritis, scleroderma, systemic lupus erythematosus and thyroiditis.[3,8] The skin diseases most often associated with morphea are psoriasis (16.3%),vitiligo (2.3%), and lichen sclerosus et atrophicus (0.8%).[3]

Environmental factors, that is events occurring close to disease onset, have been reported in between 13.2%[8] and 13.3%[3] of patients. The most common were mechanical events (8.9%), including traumas and insect bites.[3]

The etiology and pathogenesis of morphea are poorly understood. The condition appears to be caused by interactions between inflammatory, fibrotic, and vascular processes. One hypothesis that would explain how fibrosis is triggered in morphea is the transformation of $CD34^+$ fibrocytes into $CD34^-$ myofibroblasts and an increase in $XIIIa1^+$ dermal dendrocytes.[9] Some authors have reported the almost complete disappearance of $CD34^+$ dermal dendritic cells and an increase in factor $XIIIa1^+$ dermal dendrocytes in fibrosed lesions in patients with active morphea.[10]

Clinical Presentation, Classification, and Extracutaneous Manifestations

Traditionally, morphea has been classified into 5 subtypes: plaque or circumscribed, linear, generalized, bullous, and deep (including subcutaneous morphea).[11] The Pediatric Rheumatology European Society (PReS) has proposed a more exclusive and precise classification (Table 1).[12,13] They propose replacing the term *plaque morphea* (PLM) with the term *circumscribed morphea*. This form can be further divided into superficial and deep subtypes (Table 1). In the present review, we have used the term *plaque morphea* because it is the one used in the studies we cite, most of which were carried out before the PReS classification was proposed.

The classification proposed by PReS also includes the term *mixed morphea* (MM), a variant that appears to be more common than previously believed. This decision indicates a shift towards viewing morphea as a term encompassing a spectrum of clinical variants characterized by inflammation and fibrosis occurring at different depths (Figures 1 and 2). Another factor supporting this view is the overlap between morphea en coup de sabre (ECDS) and Parry-Romberg syndrome (PRS) or progressive hemifacial atrophy, a condition that occurs in between 24% and 48% of patients.[4,14,15] The PReS classification does not, however, recognize certain other subtypes, such as the bullous, deep, and subcutaneous forms of morphea.[11] Traditionally, deep morphea (DM) is characterized by thickening of the skin, subcutaneous tissue, and fascia. It is a rare form, appearing in around 4% of patients with morphea.[8] Subcutaneous morphea is defined by incipient involvement of subcutaneous tissue. Bullous morphea is characterized by the appearance of edema and tense dermal or subepidermal bullae secondary to lymphatic obstruction caused by fibrosis, which can also lead to edema in the limbs.[16] The PReS classification proposes the inclusion of these forms as new morphea subtypes (depending on the clinical presentation)[12] and the exclusion of eosinophilic fasciitis,[11] lichen sclerosus et atrophicus, and atrophoderma of Pasini and Pierini as forms of morphea at the extreme end of the spectrum.[17]

Extracutaneous manifestations are observed in up to 40% of patients with morphea (Table 2).[8]

Laboratory Parameters

No correlation has been observed between abnormal laboratory test results and the activity, course, or prognosis of the disease in patients with morphea.[3,8] Elevation of acute phase reactants is more common in the deeper forms of morphea, in LM, and during the inflammatory phase of the disease. An elevated white blood cell count is found in 37.5% of patients and an increased erythrocyte sedimentation rate in 25%.[3] Peripheral blood eosinophilia is seen in up to 62.6% of patients with DM, falling to between 12% and 18.5% in patients with other clinical forms of the disease.[3,8] Creatinine phosphokinase can be elevated in the deeper forms and this anomaly is associated with muscle pain and weakness.[3] Some patients present abnormalities in immune electrophoresis of serum proteins associated with elevation of diverse immunoglobulins.[3] Antinuclear antibodies have