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THE TREATMENT OF LOCALIZED SCLERODERMA IN CHILDHOOD

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ABSTRACT

Localized scleroderma is a connective tissue disorder of unknown etiology which causes induration and discoloration of the skin as well as induration of subcutaneous tissue and muscles. It is a different disease from systemic scleroderma. It is subdivided into morphea and linear scleroderma. There are still few reports on localized scleroderma in children. There are no studies that demonstrate a proven therapy for localized scleroderma. Even without specific

therapy, many different types of medications are used including corticosteroids, immunosuppressive and several other drugs with different possible mechanisms of actions. The disease's own variable course and lack of standardization of outcome criteria make evaluation of the effectiveness of these treatments challenging.

INTRODUCTION AND CLINICAL CHARACTERISTICS

Localized scleroderma in children is a distinct entity from systemic sclerosis due to the absence of vasospasm, vascular lesions, and involvement of internal organs (1). It is classified into two subtypes: morphea and linear scleroderma. Linear scleroderma includes the typical linear lesions of localized scleroderma as well as "coup de sabre" lesions and facial hemiatrophy (Parry-Romberg Syndrome) (2). Morphea and linear scleroderma are clinically different, but histologically indistinguishable, and the lesions tend to improve in a period of 2 to 3 years (3). The linear form is frequently associated with growth deformities of the involved extremity. Rarely, either subtype may evolve to systemic sclerosis, although linear scleroderma can coexist with the systemic form or with another connective tissue disorder (4).

Morphea is characterized by the presence of one or more hardened and hypopigmented oval plaques on the face, trunk or extremities. In the initial phase, we can identify a reddish or violet inflammatory border. These plaques may be limited in number and size or may become extensive (generalized morphea).

In children, the localized form of scleroderma is more frequent than the systemic form but both of them are rare, constituting less than 3% of rheumatic diseases in childhood.. Approximately 1.5% of all scleroderma cases occur before 10 years of age (5,6). This illness is present in all races and is more frequent in females (3:1). There is no significant familial incidence, and no consistent association with HLA antigens (1,5).

Different etiological factors have been implicated, including: 1.. trauma (6); 2. infectious agents, such as *Borrelia burgdorferi* (7); 3. environmental agents, such as toxic oil (8); 4. treatment with D-penicillamine (9); 5. bone marrow transplant (10); 6. oxygen-free radicals of endogenous and exogenous origin (11).

The main characteristics of linear scleroderma is the presence of one or more linear areas of involvement which affect the skin and can involve the underlying subcutaneous tissue, muscles and even the bones (Figure 1). The extremities, the face or the scalp might be affected. . Joint contractures, functional limitations, digit atrophy, and cosmetic deformities are frequent complications (Figure 2). The denomination “scleroderma en coup de sabre” is used to designate the involvement of the face and/or the scalp and can be followed by profound tissue atrophy (Parry-Romberg Syndrome), most prominent in small children (Figure 3).

LABS AND OUTCOME MEASURES

Labs are of limited benefit in following the clinical course of local scleroderma. Skin biopsy may be required to rule out similar skin lesions such as sclerodema and eosinophilic fasciitis. There is no biochemical marker for diagnosis or serum test that can help in the evaluation of clinical improvement. The complete blood count is generally normal, with the exception of eosinophilia which can occur in 25% of children with active disease. Acute phase reactants are often normal and are not reliable in reflecting disease activity.

The most common laboratory abnormality is the antinuclear antibody (ANA) which is present in 37% to 67% of cases. The filamentous, homogeneous and nucleolar patterns are the most frequent immunofluorescent patterns (1,12). Anticentromere antibodies and low titer anti-double-stranded (denatured) DNA antibodies are occasionally noted (?SITE). Anti-scleroderma antibodies (anti-Scl 70) are negative.

Other techniques are used to follow the response to therapy for local and systemic scleroderma. For localized involvement, photography can help document changes that may occur over time and in response to treatment.

TREATMENT

As for the systemic form, there is not any pharmacological therapy proven as definitely effective for the treatment of localized scleroderma. Studies are few in

number and mostly uncontrolled. Despite this situation, or because of this situation, many therapeutic modalities are currently utilized for localized scleroderma, including corticosteroids, methotrexate, D-penicillamine, Vitamins D and E, phototherapy, and plasmapheresis. Possible new therapies include anti-TNF- α monoclonal antibodies and other biologics, as well as the use of thalidomide.

In linear scleroderma and in generalized morphea, physical therapy and occupational therapy play a critical therapeutic role. Their objectives are maintaining functional ability, muscular strength and the joint range of motion. It is essential to prevent flexion contractures. Massage of the involved skin can be taught to the parents. It improves cutaneous elasticity and thereby the joint movement (5).

Corticosteroids:

Oral corticosteroids or the intravenous administration of high dose corticosteroids (pulse therapy) are indicated for localized scleroderma in two clinical situations. The first would be when linear scleroderma and morphea are in the initial edematous phase. The second would be for rapidly progressive linear scleroderma, characterized by a relatively fulminant development of cutaneous lesions with progressive tissue atrophy, muscular loss and contractures as well as growth delay of the involved limb (1). Corticosteroids appear to quickly control the inflammatory component of the illness, allowing early use of adequate physiotherapy and splinting.. Some authors advocate the maintenance of low oral doses of corticosteroids for many years, as linear scleroderma may often have a long period of low grade, subacute activity (5).

D-Penicillamine:

This drug has been used since the 1980's in the treatment of localized and systemic scleroderma as well as for rheumatoid arthritis and JRA. Falanga & Medsger observed improvement in the cutaneous lesions of their patients at 3 to 6 months after the onset of treatment (13). There has been no controlled double-blind study corroborating its efficacy. The recommended dosage is 5mg/kg/day.

The dose can be gradually increased according to the tolerance and the clinical response of the patient, until the maximum of 10 mg/kg/day (14). The side effects are a major concern and the drug appears to be utilized less now than in the 1980's due to those side effects.

Chan et al ⁽¹⁵⁾ described the case of a twelve-year-old boy with linear scleroderma who developed over a 3 month period progressive cutaneous induration with erythema in the left lower limb. The child was treated initially with oral prednisolone with some success and continued to do well for the long-term on D-penicillamine and an emollient applied topically.

Methotrexate

Methotrexate (MTX) has been used since the mid-1980's for rheumatoid arthritis and JRA. MTX has multiple other indications as a second line agent in pediatric rheumatology diseases such as dermatomyositis, SLE, vasculitis and sarcoidosis. The mechanism of action is based on its similarity with folic acid. It inhibits the folate-dependent enzymes involved in the synthesis of ribonucleic and deoxyribonucleic acids. The exact mechanism of action in localized scleroderma has not been well elucidated yet (16).

Uziel et al utilized MTX (0.3 to 0.6 mg/kg/week) in the treatment of 10 patients with local scleroderma. The ten patients, 6 girls and 4 boys, had a mean age of 6.8 years, and had an average duration of disease of 4 years before the onset of treatment. In addition to the weekly MTX, nine of the 10 patients received intravenous methylprednisolone pulse therapy (30 mg/kg/day). They received 3 consecutive days of the pulse initially, followed by one pulse per month for 3 months. One patient discontinued the MTX after a month. The other nine patients obtained a good response in 3 months. The authors concluded, despite the absence of a control group, that the combination of MTX and pulse methylprednisolone is well tolerated and appears to be effective in the treatment of localized scleroderma (17). Krafchik, using slightly different doses of MTX and intravenous pulse methylprednisolone, also noted positive results when treating

children with localized scleroderma during the acute stage or when rapid progression of symptoms was present (12).

Vitamin D

The efficacy of vitamin D and its analogs in the treatment of scleroderma was initially described by Humbert et al in 11 patients with systemic sclerosis and 7 with morphea, who showed improvement of the cutaneous disease with the use of oral calcitriol (11). Its favorable results were corroborated by subsequent reports that suggested the efficacy of oral calcitriol for localized scleroderma (19,20)

Cunningham et al (21) evaluated the effectiveness of calcipotriene ointment 0.005% (a synthetic analog of vitamin D) in an open study of 3 months duration. The ointment was applied twice a day to the scleroderma plaques. The authors treated 12 patients between 12 and 38 years of age with active and biopsy-proved linear scleroderma or morphea. At the end of the study, the authors observed significant improvement of cutaneous induration in all patients and a lack of side effects and of abnormalities in mineral metabolism. They concluded that this drug is effective in the treatment of localized scleroderma.

Vitamin E

Vitamin E has been used in the treatment of localized scleroderma at a dosage of 400 mg/day. The mechanism of action appears to be stabilization of the liposome membranes preventing the release of hydrolytic enzymes. It also acts as antioxidant, contributing to the inactivity of free radicals.

Eubanks et al reported two children with linear scleroderma who showed progression of the disease during the treatment with vitamin E (22). ??

Phototherapy

Skin irradiation with 340 to 400 nm of ultraviolet rays A1 (UVA1) can reduce collagen deposition activity of human fibroblasts in scleroderma lesions. This finding has led to some studies using the phototherapy modality in localized scleroderma (23,24,25)

Kerscher et al evaluated phototherapy therapy in 20 patients with severe linear scleroderma. The patients, 11 women and 9 men, were between 10 and 73 years of age. Each patient was irradiated with 20 J/cm² UVA1 for 2 weeks. Their results suggested that low doses of UVA can be highly effective for sclerotic plaques, even in those patients with advanced disease and whose lesions rapidly progressed despite the conventional treatment (25).

The experience with children is limited. There are only two reported cases in the literature, an 8-year-old girl and a 16-year-old boy with pansclerotic morphea. This is a variant of localized scleroderma characterized by a rapid progression of cutaneous fibrosis with extension to joints and fascia. Severe joint contractures and cutaneous ulcers are common. The children received UVA1 irradiation for 6 months and 2 months, respectively. At the end of treatment, the patients showed healing of ulcers, improvement of joint mobility and important reduction of cutaneous sclerosis (26,27)

Kreuter et al (29) reported a study with 19 children with morphea treated with low doses of UVA1 at 20 J/cm², four times a week for 10 weeks combined with topical calcipotriol (0.005%) applied twice a day (28). The children had a mean age of 8.5 years, with a range of 3 to 13 years. At the completion of the treatment, significant improvement of the cutaneous lesions was noted. These results indicated that the combined therapy appears to be effective in the treatment of morphea. A controlled study is needed.

Plasmapheresis

Wash et al reported 3 patients with localized scleroderma treated with plasmapheresis combined with prednisone for 5 months. One patient was a 5-year-old girl with severe generalized morphea and high titers of ANA. The efficacy of this therapeutic modality was assessed by evaluating the improvement of the cutaneous lesions and any joint limitations. In all three cases, significant improvement occurred after 2 months of treatment. The authors concluded that plasmapheresis can be recommended for the treatment of severe cases of localized scleroderma associated with high ANA titers.

New therapies

There are several therapies that may hold promise. Anti-tumor necrosis factor treatments (etanercept, infliximab) have been used in adult scleroderma and may be beneficial for severe cases of localized scleroderma (31). Thalidomide has been shown to improve SLE skin rash in multiple studies and may be useful for severe localized scleroderma (32).

CONCLUSION

The diagnosis of localized scleroderma is based on the history, physical examination, and often skin biopsy. There is no specific laboratory test available. The cause of localized scleroderma remains unknown. Many treatments are currently in use, none evidence-based. The difficulty in evaluating the efficacy of the different types of treatment is partly due to the low-grade, episodic course of localized scleroderma and to the lack of standardization of outcome measures. Corticosteroids, methotrexate, Vitamin D, and phototherapy may be beneficial. New therapies, such as biologics and thalidomide, need to be evaluated for use in severe cases of localized scleroderma.

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