

# Scleroderma in Childhood

---

**Carol Wallace, MD**  
*University of Washington*  
*Seattle, WA, USA*

As in adult onset disease, scleroderma in children is classified into the following categories:

1. Localized forms
  - a. morphea, both superficial and deep
  - b. linear scleroderma, including en coup de sabre lesions
  - c. eosinophilic fasciitis
2. Systemic forms
  - a. limited cutaneous scleroderma, including CREST (calcinosis, Raynaud's, esophageal dysmotility, sclerodactyly, and telangiectasias)
  - b. diffuse cutaneous scleroderma (proximal and distal skin affected with internal organ involvement such as esophagus, pulmonary, cardiac, GI and renal)

These categories are best thought of as a framework within which to discuss patients, as many patients with scleroderma may present with one form and evolve into another or become an overlap syndrome. As with most rheumatologic diseases, therapy early is felt to be most effective. Thus, it is critically important to fully evaluate each child that presents for internal organ involvement and during treatment and follow-up to keep alert for clues of additional involvement.

## Incidence

Information about the incidence of these rare diseases is extremely difficult to find. Onset of scleroderma in childhood represents about 2% of cases. A Finnish nationwide prospective study over 4 years, identified 2 children with scleroderma out of a population of a little over one million people.

## Pathogenesis

There is no question that the early lesions are those of microvascular injuries followed by narrowing and obliteration of vessels accompanied by altered metabolism of fibroblasts.

Infectious agents have been sought, especially as a trigger for linear scleroderma. **Borrelia burgdorferi**, the causative agent for Lyme disease, has been intensively investigated as a potential cause, but recent studies using sensitive PCR techniques have not found evidence for its involvement.

Trauma and possible exposure to chemicals have also been suggested as causative factors but are not proven.

Autoantibodies can be found in the majority of cases of childhood scleroderma, but it is not clear if these are a primary or secondary phenomenon. ANA, antihistone, anti-single stranded DNA, and anti-Scl-70 antibodies have been found but their levels do not appear to correlate with disease severity or activity. On the other hand, anti-fibrillerin (U3-RNP), anti-U1RNP antibodies are associated with poor outcome and increased visceral involvement – especially pulmonary hypertension and myositis. Anti-topoisomerase 1 titers have been demonstrated, in one small study, to correlate with new onset or worsening of internal organ involvement.

Vascular endothelial growth factor (VEGF) is felt by many investigators to be important in the pathogenesis of scleroderma, however its exact role is unclear. It has been found to occur in decreased amounts in the serum and tissue of patients with SSc, as well as increased amounts early in disease, along with increased amounts of its soluble receptor. Other investigators have found decreased amounts of VEGF in those SSc patients that develop fingertip ulcers. It remains to be clarified whether VEGF occurs in decreased amounts or is actually over expressed but not effective because of receptor abnormalities.

HLA class II antigens and microchimerism are also thought to play roles in the development of scleroderma. Fetal cells are commonly found in healthy women. It is postulated that the HLA-relationships of mother and child are important in

determining the pathogenic potential of long-term persistent microchimerism. HLA similarity could be detrimental and result in disruption of the communication between mother and fetal immunoregulatory cells. Patients may be distinguished from healthy individuals by quantitative differences in the amount of microchimerism. Aractingi et al recently reported the presence of microchimerism in the labial salivary glands of 5 out of 11 women with SSc but in no women with Sjogren's syndrome.

For children, men and women who have never been pregnant, maternal cells may be involved in microchimerism and development of autoimmune disease. Several investigators have documented persistent maternal microchimerism in the peripheral blood of SSc patients and in the blood and tissues of children with inflammatory myositis (but not in their siblings). Issues such as timing during gestation, quantity and type of maternal cell exposure, and HLA genes could influence whether or not maternal cells that persist in the neonate and adult have pathogenic potential. In the child, the presence of maternal cells during early development could influence the selection of T lymphocytes recognizing self versus non-self, altering the T cell receptor repertoire. This could then potentially lead to altered susceptibility to specific infections or to reactivity of self-antigens in the context of self or maternal HLA molecules.

## Clinical Features and Treatment

**Localized scleroderma** can occur as a small lesion with mild subcutaneous atrophy, central skin thickening surrounded by prominent skin pigmentation or there can be intense destruction of subcutaneous tissues, fat, muscle and even bone that involve the entire length of a limb resulting in joint contractures, growth disturbances and horrid deformities. Although localized, or linear, scleroderma often does not develop internal organ involvement and thus is not usually fatal, its destruction and deformities can be devastating. En coup de sabre lesions begin over the scalp and forehead and can progress down the face with significant disfigurement. These patients may have intracranial abnormalities such as calcification and atrophy of the skull. For children with localized scleroderma that are referred after long standing disease, full thickness biopsy (skin, fascia and down

into muscle), of the leading edge may be necessary to determine if there is any evidence of active inflammation (which may respond to treatment). When recognized early in its process, there is no way to predict how long linear scleroderma will continue to be active or the full extent of damage that will finally occur. Because of this, most pediatric rheumatologists currently treat aggressively with prednisone and methotrexate. Uziel et al reported 9 children with linear scleroderma or generalized morphea that were treated with MTX (0.3 – 0.6 mg/kg/week, SQ if >15mg) and IV methylprednisolone 30 mg/kg/day for 3 days and then monthly for 3 months. (One child with rapidly progressing disease also received daily prednisone 1 mg/kg). All 9 children responded, usually within 2-3 months, with softening of lesions. At follow up 8 of 9 children had inactive lesions and all nine continued on MTX at 8 to 33 months (median 25 months).

The authors were very honest about the difficulty of trying to measure the size of the lesions month to month, as the borders are often inexact. Does one measure the extent of abnormal pigment, or skin depression; or does only the extent of the thickened skin count as an active lesion? Should the expectation of successful treatment be that all lesions completely resolve, or is softening and stabilization enough? Additionally, as a child grows, a lesion thought to be inactive may increase in size as a consequence of normal growth rather than as a manifestation of active disease. Because disease flare may occur after discontinuation of prednisone or MTX, Uziel and colleagues recommend treatment for at least 1 year of inactive disease before beginning to slowly taper the MTX.

Prior to MTX, D-penicillamine had been the treatment of choice. However with its very slow onset of action and high rate of side effects at therapeutic doses, it is infrequently used. Cyclosporine, with and without MTX and prednisone is advocated by some investigators. Vitamin D ointment and low-dose ultraviolet A1 phototherapy was used to treat 19 children with morphea by Kreuter and colleagues with good success. Topical tacrolimus has been tried in morphea and linear scleroderma with some success.

**Systemic sclerosis** is more rare than localized scleroderma in children. Foeldvari et al have reported favorable outcome in 135 children from a multinational survey. One hundred of the

135 children were girls and their mean age at onset of disease was 8.8 years. The mean disease duration at the last follow-up was 5 years. At this point 82 patients continued to have active disease and required medication, 36 had in active disease on medication and 16 were in remission off of medications. Mortality rate was 6%, with median disease duration of 2 years. The cause of death was heart failure in the majority.

Visceral involvement in children with systemic sclerosis is frequent. Unfortunately, children with internal organ involvement are often asymptomatic, so thorough evaluation is important - with barium swallow to define reflux and abnormal motility; high resolution computerized tomography of the lungs looking for alveolitis, air trapping or micronodules; echocardiogram looking for myocarditis, pericarditis and early pulmonary hypertension; muscle enzymes; and pulmonary function tests with diffusing capacity if the child is able to cooperate. We were surprised in our patients the high rate of involvement of the esophagus, the presence of alveolitis, and abnormal pulmonary function tests (PFT). Garty et al also found a high frequency of pulmonary involvement in their children with systemic sclerosis - 12 of 13 had abnormal PFTs. Additionally they found early involvement of the lungs with indolent progression and patterns of involvement similar to adult patients.

Barbara White and colleagues have reported that one year before the development of pulmonary hypertension, there was no difference in the FVC, FEV1, TLC or RV between those adults with SSc that developed pulmonary hypertension (PH) and those that did not. However, those that did develop PH, had lower diffusing capacity and had an increase of the RV/TLC ratio  $>107$ . Thus, it would make sense to treat aggressively not only those patients with alveolitis on CT, but also those with changes in their PFT.

What constitutes **aggressive treatment** depends on the extent of organ involvement. Widespread skin involvement with or without esophageal abnormalities might well respond to a combination of daily (1-2mg/kg/d) or weekly IV steroids, with SQ MTX (1mg/kg/week, 40mg maximum). The steroids would ideally be tapered to low dose over a 3-month period, with the MTX continuing for several years. The addition of cyclosporine (3-5mg/kg/day) might improve resolution of lesions.

It is important to recognize that once GI involvement has been identified, aggressive treatment may halt its progression, but will not result in reversal of damage that has already occurred. Dysmotility and reflux are the result of damaged nerves whose vessels have been obliterated by the sclerodermatous process. It is very important to use H2 blockers, and propulsion agents if indicated (especially at night time), to prevent permanent damage to the esophagus and damage to the lungs from recurrent aspiration.

The two most critical organs in which early aggressive treatment can make a difference are the lung and heart. Cytoxan is usually used and adult scleroderma experts such as Carol Black, Virginia Steen and Barbara White all have their favorite cytoxan regimen. The common elements are short-term use of prednisone, combined with varying lengths of daily cytoxan. In our children with alveolitis, we have been able to resolve the alveolitis and prevent progressive fibrosis and honeycombing in the lung with daily prednisone 2mg/kg/d (tapered to low dose over 3 months) with daily cytoxan 2 mg/kg. Several children have maintained their response when transitioned to monthly cytoxan 500-1,000mg/ m<sup>2</sup>. The length of this aggressive treatment must be individualized for each patient and unfortunately monitored with HRCT. The sensitivity of PFT to change with treatment does not allow their use to guide response to treatment with the same assurance as lung CTs.

The development of pulmonary hypertension is very serious and usually predicts early mortality. Several new medications have been able to remarkably treat this condition in some patients - namely constant infusion of flolan via a catheter into the right heart. Patients who were thought to have fixed and or end stage pulmonary hypertension have had remarkable improvements that have been long lasting suggesting remodeling of the vessels involved. Recent oral medications may be just as effective for some patients and are currently being investigated.

For those patients with severe disease in whom no therapy has seemed to be effective, autologous stem cell transplantation (ASCT) may be considered. Binks et al have described ASCT treatment in 41 patients with severe SSc failing other forms of therapy. In general there was a marked impact on the skin score, and a trend towards stabilization of lung involvement. Unfortunately, there was a 27% mortality rate with

7 of the 11 deaths considered to be related to the procedure. Changes in the protocol have been made, but the anticipated mortality is still about 10%.

## Conclusion

In summary, scleroderma in childhood is rare and often asymptomatic, which may result in late referral of patients. Children can present with a wide range of severity from a few patches to disfiguring total limb or half face involvement. The systemic form of disease in children is usually associated with internal organ involvement, so a thorough evaluation is necessary. Whether localized or systemic, scleroderma in children should be treated aggressively.

## Bibliography

---

- Emery, Helen: Pediatric Scleroderma. *Seminars in Cutaneous Medicine & Surgery* 17:41-7, 1998.
  - Martini, A.: Juvenile systemic scleroderma. *Current Rheumatology Reports* 3:387-90, 2001.
  - Kirby, J et al: Fetal cell microchimerism in multiple tissues from multiple sites in women with systemic sclerosis. *Arthritis Rheum* 44:1848-1854, 2001.
  - Nelson, JL: Maternal-fetal disparity in HLA class II alloantigens and the pregnancy-induced amelioration of rheumatoid arthritis. *N Engl J Med* 329:488-471, 1993.
  - Aractingi S et al: Presence of microchimerism in labial salivary glands in systemic sclerosis but not in Sjogren's Syndrome. *Arthritis Rheum* 46:1039-43, 2002.
  - Uziel, Y et al: Methotrexate and corticosteroid therapy for pediatric localized scleroderma. *J Pediatr* 136:91-5, 2000.
  - Kreuter, A et al: Combined treatment with calcipotriol ointment and low-dose ultraviolet A1 phototherapy in childhood morphea. *Pediatric Dermatology* 18:241-5, 2001.
  - Foeldvari, I et al: Favourable outcome in 135 children with juvenile systemic sclerosis: results of a multi-national survey. *Rheumatology* 39:556-559, 2000.
  - Garty, B et al: Pulmonary Functions in Children with Progressive Systemic Sclerosis. *Pediatrics* 88:1161-1167, 1991.
  - Seely, JM et al: Systemic Sclerosis: Using High-Resolution CT to Detect Lung Disease in Children. *Amer J Radiology* 170:691-697, 1998.
  - Steen, VD et al: Therapy for severe interstitial lung disease in systemic sclerosis. *Arthritis Rheum* 37:1290-96, 1994.
  - Binks, M et al: Phase I/II trial of autologous stem cell transplantation in systemic sclerosis: procedure related mortality and impact on skin disease. *Ann Rheum Dis* 60:577-84, 2001.
-