In this Grand Round, two children are described with atypical generalized scleroderma and severe failure to thrive. Neither had Raynaud’s phenomenon nor evidence of gastrointestinal (GI) disease. Treatment with non-steroidal anti-inflammatory drugs, prednisone, d-penicillamine, and interferon was unsuccessful in reversing the sclerodermatous changes and growth arrest. Dietary intake analysis and extensive GI investigation were performed in both. In one case, resting energy expenditure (Ee) was repeatedly measured. His intake did not meet requirements for growth. Supplemental tube feeding (900 kcal in 6 h) was commenced, causing an increase in weight from 11 to 16 kg. The other patient refused supplementary tube feeding and no weight gain has been observed for 5 yr. In conclusion, early-onset generalized scleroderma in the absence of visceral involvement, but with growth failure, may represent an atypical form of systemic sclerosis. The response of the two patients to conventional therapy was disappointing. However, the rapid catch-up growth induced by tube feeding observed in one patient underlines the importance of adequate dietary management.

KEY WORDS: Scleroderma, Failure to thrive.

CASE REPORTS

A 7-yr-old White boy was referred to our hospital with complaints of pain and stiffness in the fingers and feet, and progressive loss of muscle strength since the age of 3 yr. He was on the 10th percentile for length and weight until age 3. From then on there was a growth arrest, despite a good appetite. Dysphagia was absent. His stools were normal. He developed a generalized skin tightness from the distal extremities extending to the trunk and face within 2 yr, causing severe contractures. It was then assumed that he was affected by a form of juvenile chronic arthritis. At the age of 6 yr, he developed a thrombocytopenia under naproxen treatment that persisted after withdrawal of the drug and did not respond to steroid treatment. So far, no major bleeding had occurred. Fractures of the clavicle and tibia occurred after minimal trauma. On examination, the skin showed non-linear sclerodermatous-like changes at the fingers, hands, arms, feet, legs and head (Fig. 1). Both extensor and flexor sides were affected. The trunk was partially affected. Hyper- and hypopigmented areas were seen, as well as telangiectasia. Raynaud’s phenomenon was absent. There was a severe muscle wasting, but no signs of arthritis. There were multiple ulcers on the buttocks, knees and feet. The histology of the affected skin was consistent with systemic sclerosis or morphea. Immunohistochemistry studies of the affected skin did not reveal lymphocytic infiltrates.

Rheumatoid factor (RF), antinuclear antibodies (ANA), anti-double-stranded DNA (aDS-DNA) and Scl-70 were all negative (Table I). Anti-thrombocyte and anti-lymphocyte antibodies were positive (using donor cells and patient’s serum). The antibodies were reactive to 95% of the donor panel lymphocytes, though in vivo they did not cause a lymphopenia. Anti-granulocyte antibodies were absent. A bone marrow aspiration showed a normal presence of megakaryocytes and normal erythroid, myeloid and lymphoid cell lineages. Chimerism studies were performed to detect persisting maternal lymphocytes causing chronic graft vs host disease. The polymerase chain reaction of the highly polymorphic short tandem repeat DNA sequences performed on peripheral blood lymphocytes from the patient and his mother revealed no persisting maternal DNA sequences. The serum creatine phosphokinase (CPK) was normal. A biopsy showed scattered atrophy of predominantly type 2 fibres, without an increase in fibrous tissue. There was no myositis or fasciitis. There was a severe generalized osteoporosis without soft-tissue calcification or loss of distal digital bone mass. Tibial and clavicular fractures occurred after minimal trauma.

Lung function tests were performed with Masterlab (Erich Jaeger Gmbh & Co., Würzburg, Germany). Initially, the flow volume curve showed a low vital capacity (600 ml; 55% of predicted value) and a decreased peak flow (1.8 l/s; 70% of predicted value). Assessment of single-breath carbon monoxide diffusion was not possible due to age and the patient’s inability to hold his breath for more than 5 s. A chest radiograph did not show interstitial changes. The electrocardiogram did not show right axis deviation and the echocardiogram was normal. The serum creatinine was normal and proteinuria was absent. Renal ultrasound was normal.

Oesophageal manometry was performed with a microtransducer catheter (Synetics Instruments, Sweden).
Fig. 1.—(a–c) Photographs of patient MR showing extensive scleroderma skin lesions, extending from the toes and fingers to the shoulders, chest and perioral region.

### Table I

<table>
<thead>
<tr>
<th></th>
<th>MR (age 8 yr)</th>
<th>DC (age 4 yr)</th>
<th>DC (age 6 yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR (mm/h)</td>
<td>10</td>
<td>56</td>
<td>30</td>
</tr>
<tr>
<td>Thrombocytes (150–400 × 10⁹/l)</td>
<td>6 × 10⁹/l</td>
<td>1232 × 10⁹/l</td>
<td>400 × 10⁹/l</td>
</tr>
<tr>
<td>Lymphocytes (1–7 × 10⁹/l)</td>
<td>4 × 10⁹/l</td>
<td>0.5 × 10⁹/l</td>
<td>4 × 10⁹/l</td>
</tr>
<tr>
<td>IgG (7–11 g/l)</td>
<td>14.9 g/l</td>
<td>16 g/l</td>
<td></td>
</tr>
<tr>
<td>IgM (0.6–1.3 g/l)</td>
<td>1.2 g/l</td>
<td>1.1 g/l</td>
<td></td>
</tr>
<tr>
<td>IgA (0.5–1.2 g/l)</td>
<td>2.7 g/l</td>
<td>0.82 g/l</td>
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<tr>
<td>IgA anti-gliadin</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>IGF-I (110–900 ng/ml for age 4–7)</td>
<td>139 ng/ml</td>
<td>400 ng/ml</td>
<td></td>
</tr>
<tr>
<td>ANA</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-Scl-70</td>
<td>Negative</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>RF</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-lymphocyte and thrombocyte antibodies</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
</tr>
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</table>

with three electronic orifices spaced at 3 cm intervals from the distal tip [1]. Pressures of upper and lower oesophageal sphincters, pressure-wave amplitude and peristalsis patterns were normal. In the 72 h stool analysis, no fat loss (see also Table II) or increased α₁-antitrypsin excretion were found. Barium radiographs of oesophagus, stomach, small intestines and colon were normal. On presentation in our clinic at age 7 yr, he weighed 11 kg (8 kg below the third percentile of the weight for age chart). Owing to severe contractures, a reliable length could not be obtained. His sitting height was 63 cm, which is 2 cm below the third percentile (sitting height for age chart). His growth chart showed a growth arrest since the age of 3 yr (Fig. 2, left). Nutritional assessment (energy intake, resting energy expenditure and faecal losses of energy) was performed in patient MR at age 7 yr and 6 months. Energy intake was measured during the hospital stay by dietary recordings during 72 h. Resting energy expenditure (EE) was estimated from resting oxygen consumption and carbon dioxide production (measured after overnight fasting with indirect calorimetry;
Fig. 2.—Growth curves of two patients with generalized scleroderma (case 1, left; case 2, right). Both curves show growth on the third percentile until the onset of the disease. From then on a growth arrest of 5 yr (case 1) and 8 yr was documented. Note the rapid catch-up growth in case 1, induced by the start of nocturnal tube feeding (900 kcal/day).

<table>
<thead>
<tr>
<th>TABLE II</th>
<th>Energy balance study in patient MR at age 8 yr</th>
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<tbody>
<tr>
<td></td>
<td>Measured (kcal/day)</td>
</tr>
<tr>
<td>Energy intake</td>
<td>1275</td>
</tr>
<tr>
<td>Energy expenditure</td>
<td>773</td>
</tr>
<tr>
<td>Energy loss in faeces</td>
<td>5</td>
</tr>
</tbody>
</table>

*According to recommendations of the Netherlands Nutritional Board.
†Expected value according to Schofield [3].
‡Assuming that absorption exceeds 98% of intake.

Oxycon Champion, Jaeger) according to Weir’s equation [2] and compared with predictions for age, gender and body weight as described by Schofield [3]. Energy loss in the faeces was estimated from faecal fat loss in 72 h stool collections, assuming that 1 g of fat corresponds to 9 kcal. The results are shown in Table II. Energy intake was only 64% of the recommended daily allowance for Dutch children of his age. The Ee rate was in close agreement with the predicted value [3]. Faecal energy loss was negligible (0.55 g in 24 h). Thus, we concluded that a diminished energy intake could be related to the patient’s growth failure. Increasing energy intake through dietary means proved to be unsuccessful. Six months later, measurement of the energy balance was repeated and showed a similar deficit in energy intake as depicted in Table II. Ee and faecal energy loss were again close to expected values. Given the growth arrest in the period between these measurements, it was inferred that the difference between the energy intake and Ee plus faecal loss (i.e. 497 kcal/day) was used to cover the boy’s physical activity, and was not available for growth. Therefore, supplemental nocturnal tube feeding (Nutrison Paediatric, 900 kcal in 6 h through a nasogastric tube) was instituted at age 8 yr. Simultaneously, the patient was encouraged to sustain his oral food intake during the day. On this regimen, a weight gain of 5 kg was achieved in a 6 month period, still 4 kg below the third percentile (Fig. 2, left). The boy’s mid upper arm circumference increased from 12 to 14.5 cm (still 1 cm below the third percentile) after 6 months of supplemental feeding. During the catch-up growth, he felt less dyspneic and was able to raise his voice. Lung function tests were then normal (vital capacity 1.2 l; peak flow 2.4 l/s).

The second patient is a boy who presented elsewhere elsewhere at the age of 3 yr with fever, rash and arthritis. Six weeks earlier, he received a BCG inoculation. He was an unexpected twin and was the smaller of the two babies. A putative diagnosis of systemic-onset juvenile chronic arthritis was made and he was treated with corticosteroids. He was then lost to follow-up until the age of 6 yr, when he was referred to one of us (PW) for a generalized scleroderma over the arms, legs, trunk and face (Fig. 3). He was on d-penicillamine for 6 months with no clinical improvement. Raynaud’s phenomenon was absent. Severe contractures of the knees, ankles, elbows, wrists and fingers were present. There was a generalized osteoporosis with terminal absorption of the phalanges and calcinosis. In addition, there was a history of multiple fractures with minimal trauma and poor wound healing. He had a growth arrest since the age of 4 yr (Fig. 2, right). At the present time, there was no spiking fever, rash or cardiorespiratory complaints.

The results of the laboratory investigations are given
in Table I. The histology of the skin biopsy was consistent with systemic sclerosis or morphea. Lymphocytic infiltrates were absent. In the muscle biopsy, a scattered atrophy of type 2 fibres was seen. Investigation of heart and renal function was normal. Lung function tests showed a reduced vital capacity probably due to chest wall restriction. A CT scan of the lungs was normal.

A low amount of fat (0.7 g in 24 h; normal values 1.0–5.0 g/24 h) was present in the stools. Barium radiographs of oesophagus, stomach, small intestines and colon were normal, as was endoscopy of the upper gastrointestinal tract. Duodenal and rectal biopsies did not show scleroderma-like changes or amyloidosis. Indirect calorimetry could not be performed as this was not available at that time. A high-protein and high-calorie diet was advised. Unfortunately, the patient refused a nasogastric tube. No catch-up growth could be achieved. A trial of 1 yr of nasal calcitonin has not improved the osteoporosis or growth arrest. Treatment with α interferon for 1 yr led to hair loss and deterioration in bone density, but coincided with the beginning of a regression of skin thickening over the face and trunk. Owing to severe osteoporosis, and
intolerance of the daily injections, z interferon was stopped. The skin texture over the above areas continued to improve for another 6–9 months.

**DISCUSSION**

**Differential diagnosis**

This report describes two cases with rapidly progressive scleroderma at a very early age and characterized by generalized skin changes, severe contractures and a cessation of growth despite the absence of visceral involvement. Childhood scleroderma can be divided into two groups of different clinical syndromes: localized scleroderma (localized SSc) and systemic sclerosis (diffuse SSc) [4–7]. SSc is rare in childhood [7–10]. The initial signs are usually Raynaud’s phenomenon and skin tightening on the hands. In a later phase, severe contractures develop. Systemic involvement, a key symptom of SSc, includes the gastrointestinal tract, heart, lungs and kidney. A symmetrical but transient polyarthritis mimicking juvenile chronic arthritis has been described in SSc and arthritis seemed to be the presenting symptom in both children [7, 11].

SSc must further be differentiated from other forms of systemic scleroderma, such as the CREST syndrome, the disabling pansclerotic morphea of childhood in which the linear lesions can affect large skin areas [12], chemically induced scleroderma, and immunological disorders such as the overlap syndromes (mixed connective tissue diseases) and chronic graft vs host disease. Growth hormone or insulin-like growth factor I (IGF-I) deficiency were excluded. The observed skin changes, the thrombocytopenia and the exclusion of other diseases mimicking scleroderma leave little doubt as to the diagnosis of SSc [10]. According to the classification of Barnett and Giordano, our patients belong to type 3 SSc, characterized by a diffuse scleroderma, including the trunk [13–15].

**Failure to thrive**

Failure to thrive has been described, but only in patients with extensive visceral involvement [7, 16–18]. To the best of our knowledge, this is the first report of failure to thrive in SSc in the absence of gastrointestinal symptoms. The severe failure to thrive can either be explained as a consequence of a severe chronic disease or as a key symptom of an atypical form of SSc. The occurrence of the growth arrest early in the course of the disease in both patients, and the absence of visceral involvement, Raynaud’s phenomenon and ANA, favour, in our opinion, the concept of an atypical form of SSc. Interestingly, repeated observations with indirect calorimetry in our patient MR showed that the resting energy expenditure was not elevated. The importance of maintenance of adequate caloric intake in patients with this form of the disease is illustrated by the rapid catch-up growth in patient MR. This was only achieved after tube feeding was instituted, however. This therapy was well tolerated. So far the skin has not improved. This report further shows the relevance of quantitative nutritional assessment in patients with protracted failure to thrive.

Measurement of resting energy expenditure and faecal fat loss may provide additional information. In patient MR, these tests were within normal limits, suggesting that his appetite control could have been affected.

**Thrombocytopenia**

The presence of anti-thrombocyte antibodies causing thrombocytopenia has been described in generalized morphea and SSc [17, 19–21]. It has been related to the use of diclofenac and p-penicillamine, and may be due to naproxen in patient 1 [22, 25]. Anti-granulocyte antibodies associated with renal failure and anti-lymphocyte antibodies have also been described [24]. In our patient MR, the binding of the anti-lymphocyte antibodies to the donor lymphocytes could be prevented by chemical inactivation of the HLA molecule. Such a pattern is usually seen in patients receiving multiple blood transfusions, or renal allograft patients, and may reflect widespread vascular intima destruction.

**Prognosis**

The prognosis of SSc is largely dependent on the progression of visceral disease. Cardiopulmonary involvement and renal failure especially carry the worst prognosis [8, 14, 18, 23, 24]. The 5 and 10 yr survival rates in type 3 SSc adult patients are 50 and 25%, respectively [14]. The follow-up in our patients is 6 and 8 yr. The absence of renal and pulmonary pathology may indicate a more favourable prognosis. However, the severe growth arrest and osteoporosis are serious clinical problems. These cases clearly illustrate the clinical diversity of connective tissue disease in children. Although the cause of the failure to thrive in this disorder is not clearly understood, the observed catch-up growth clearly underlines the importance of adequate caloric intake.

**REFERENCES**