Staphylococcal infections in childhood dermatomyositis—association with the development of calcinosis, raised IgE concentrations and granulocyte chemotactic defect

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Abstract
There is a high incidence of staphylococcal infection in children with dermatomyositis, which is limited to those children who either already have or subsequently develop calcinosis. Of 15 children followed up for 3–10 years after diagnosis, all nine who developed calcinosis had infections with *Staphylococcus aureus* compared with none of six without calcinosis. Of these nine, the occurrence of staphylococcal infections before calcinosis was observed in four, suggested by history in two, and unclear in three children.

Granulocyte chemotaxis to *Staphylococcus aureus* was more severely depressed in those children with calcinosis, whereas those without calcinosis did not differ significantly from controls. The chemotactic defect was due to a serum factor (patients' serum depressed control chemotaxis and control serum corrected the patients' chemotaxis).

The nine children with calcinosis also had significantly higher serum IgE concentrations than non-atopic age matched controls; the six without calcinosis did not differ from controls. The increased IgE concentrations appeared to develop after staphylococcal infection and before calcinosis. Two of five patients with calcinosis had increased antistaphylococcal IgE antibodies; neither of the two patients without calcinosis had such increased antibodies. This suggests preceding immunological differences in patients with dermatomyositis who do and do not subsequently develop calcinosis, either increasing susceptibility to *Staphylococcus aureus* infection or potentially resulting from such infections.

There is a high incidence of *Staphylococcus aureus* infection in patients with childhood dermatomyositis, often mentioned in passing in case reports[1-9] but to our knowledge the subject of no prior systematic investigation. In studying the cause of this predilection, we noted that the staphylococcal infection occurred only in those children who already had, or subsequently developed, calcinosis and that, although infection of calcinosis sites sometimes occurred, the sites of infection and sites of calcinosis were usually different. Clinical and immunological differences to explain this were sought.

Patients and methods

PATIENTS
We studied 15 patients with clinically typical childhood dermatomyositis, with increased levels of muscle enzymes (creatine kinase, lactate dehydrogenase, aldolase, serum aspartate aminotransferase (AST)) at some point in their disease course and with consistent findings on electromyography and muscle biopsy. Seven patients were white and eight black; nine were girls and six boys, consistent with previous reports of childhood dermatomyositis.[10]

At the end of the observation period, the children were divided into two groups: nine in group 1, who had developed calcinosis and six in group 2 who had not developed calcinosis; patients were screened at each visit for calcinosis by careful palpation, with suspicious areas confirmed radiographically. The two groups of patients (with and without calcinosis) were followed up for 3–10 years, although only tests performed on patients with childhood dermatomyositis with active disease (i.e. either before treatment or still requiring treatment) were considered in this study. The two groups did not differ in age at presentation or in race. There was a higher percentage of boys in the group with calcinosis (five of nine in group 1 *v* one of six in group 2), but this was not statistically significant in view of the small sample size. There was no significant difference in the duration of disease from onset to treatment between the two groups or in the apparent severity of disease at the time of presentation. Table 1, however, shows that the disease was more prolonged in group 1 patients, with many requiring treatment for several years after the initial presentation. Table 2 shows that enzyme levels remained raised for prolonged periods of time in group 1 patients but returned to normal within three months for all group 2 patients.

The initially prescribed corticosteroid treatment did not differ between the two groups, but treatment was longer in group 1 patients, with a higher level of non-compliance. Two group 1 patients were also prescribed cytotoxic drugs later in their illness; only one of these was tested during this period. Two patients in group 1 and one in group 2 had a recurrence of the disease after an initial response.

METHODS
IgE concentrations were measured by radio-immunoassay using kits from Pharmacia, (Piscataway, NY, USA) or Behring Diagnostics (La Jolla, CA, USA). Results from the two kits were consistent except for minimal differences at high concentrations.

The control children had uncomplicated monarticular or pauciarticular juvenile rheuma-

Table 1 Group 1: patients with childhood dermatomyositis who developed staphylococcal infection and calcinosis

Patient No	Sex*	Race†	Age of presentation (years)	Duration of disease (months) before		Clinical status
				Treatment	Calcinosis	
1	F	W	4	3	48	Recurrent disease; required steroids and cyclophosphamide (Cytoxan); treatment stopped after 70 months; mild functional impairment from calcinosis
2	F	B	9	5	33	Disease still active when lost to follow up after 62 months; receiving prednisone; compliance poor; function limited by extensive calcification and muscle weakness
3	M	B	11	4	24	Disease still active when lost to follow up after 50 months; receiving prednisone; minimal limitation of function
4	F	B	8·5	?	At presentation	Prednisone stopped after 108 months; mild functional impairment from calcinosis
5	F	B	6	24	26	Prednisone stopped after 89 months; compliance poor; extensive calcification and limitation of motion with tendency to erode through skin
6	M	W	10·5	2	26	Died after 37 months with uncontrolled disease despite prednisone and azathioprine (Imuran); scattered early calcification on upper extremities
7	M	W	5·5	5	?	Lost to follow up; seen in consultation only
8	M	W	2·5	12	48	Recurrent disease; last flare 168 months after original diagnosis; still receiving steroids with increased muscle enzymes at 212 months after diagnosis; no limitation of function
9	M	W	5	2	12	Died of pneumonia after 4–5 years of illness; almost completely immobilised by calcinosis at time of death

*F=Female; M=male.
†W=White; B=black.

Table 2 Group 2: patients with childhood dermatomyositis who did not develop calcinosis or staphylococcal infection

Patient No	Sex*	Race†	Age of presentation (years)	Duration of disease to treatment	Clinical status
10	F	B	5·5	6 weeks	Well; treatment stopped after 13 months
11	M	B	12	3 months	Well; treatment stopped after 16 months
12	F	B	15	24 months	Well; treatment stopped after 14 months
13	F	W	6	6 months	Well, except for slight rash around eyes; treatment stopped after 10 months
14	F	W	5	6 weeks	Well; strength normal but decreased from before illness; treatment stopped after 17 months
15	F	W	3·5	6 months	Several recurrences; treatment stopped after 43 months

*F=Female; M=male.
†W=White; B=black.

toid arthritis, or were seen for arthralgias, either with no disease being found, or with minimal orthopaedic reasons for their symptoms. They had no recorded personal or family history of allergy.

IgE antibodies to staphylococcus were measured as described previously[11] and compared with the various patient and control groups. Staphylococcus aureus Wood 46 (a strain deficient in protein A) was grown overnight in glucose tryptone yeast extract broth at 37°C. The bacteria were washed with 0·15 M phosphate buffered saline (pH 7·2) containing 0·1% sodium azide and were stored as a 10% suspension for no longer than one week at 4°C. Aliquots (1 ml) were washed twice with phosphate buffered saline without sodium azide and 0·1 ml of undiluted serum was added to the pellet. Incubation was performed with constant stirring for three hours at room temperature. After two washes with phosphate buffered saline for 15 minutes at 2000 g, the pellet was incubated overnight at room temperature with 0·1 ml of rabbit antihuman IgE labelled with iodine-125 (Pharmacia) specific for the Fc_E of human IgE. After three more washes, the retained radioactivity in the pellet was measured in a Packard autogamma scintillation spectrometer. The results were expressed as a percentage of the IgE labelled with iodine-125 adhering to the pellet. All experiments were performed in duplicate and the standard error of the mean (SEM) of these assays was 2%.

Granulocyte chemotaxis was measured in Boyden Blindwell (Millipore) chambers[12] with a 3 μm filter on top and a 0·45 μm Millipore filter

below. The granulocyte rich buffy coat, adjusted to give a concentration of 5×10^6 granulocytes per millilitre, was placed in the upper chamber. The degree of mononuclear cell contamination was not controlled. The chemotactic factor was produced by adding a suspension of *S aureus* (to correspond to No 5 turbidity; Bacto McFarland barium sulphate standard set, Difco, Detroit, MI, USA) to 0·2 ml serum in 1·5 ml Hanks's balanced salt solution, previously incubated at 37°C for five minutes. The diluted serum was then incubated at 37°C for five minutes and finally incubated at 56°C for 30 minutes.

The controls were healthy laboratory or medical staff. All tests were run in duplicate and the patient and control cells were run with patient and control derived chemotactic factor. *S aureus* chemotaxis was defined as the total number of cells in 10 fields under oil on the bottom layer of the top (3 μm) filter and 10 fields under oil on the top layer of the bottom (0·45 μm) filter, in response to *S aureus* chemotactic factor, minus the number of cells in response to incubated serum alone. The results of *S aureus* chemotaxis for patients were compared with the results of the adult controls, and with results obtained for 28 control children, aged five months to 16 years, referred for a variety of reasons. None of those children had immunological disorders, problems with staphylococcal infection, skin ulcers, muscle disorders, nor soft tissue calcification. All were healthy when the tests were performed.

As the IgE concentrations and chemotactic assay results were distributed logarithmically in the control population, numerical data from these tests were converted to their logarithms for analysis.

Results

All nine patients who developed calcinosis had infections with *S aureus* (table 3) and staphylococcal infection developed only in those patients who already had or subsequently developed calcinosis. The staphylococcal infections sometimes occurred in calcinosis sites, as in patient 5, but more often other sites without calcinosis were affected: a septic knee in patient 7, a major axillary abscess in patient 3, and multiple abscesses in patients 2, 4, and 9. In four of these nine patients the onset of staphylococcal infections was found to precede the clinical onset of calcinosis (by six weeks, 12 months, 16 months, and 16 months, respec-
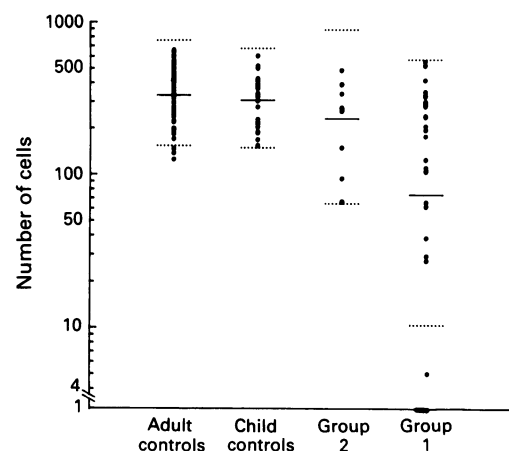

Figure 1 Staphylococcus aureus chemotaxis. Adult controls, 67 determinations on 29 control adults; child controls, 29 determinations on 28 control children; group 2, 10 determinations on four patients without calcinosis; group 1, 29 determinations on seven patients with calcinosis. Mean (2 SD) (229·5 for group 2; 72·7 for group 1) are shown. The group means using mean values for each patient were 249·7 and 49·55, respectively, for groups 2 and 1. Six of seven patients in group 1 had at least one determination more than two standard deviations below the mean of either the adult or child controls. This was also true in two of the four patients in group 2. Chemotaxis was not determined in two patients in each of the groups.

tively), and the calcinosis developed in sites distant from the infection sites. Patient 1, followed up during her course at a neighbouring institution, reportedly had staphylococcal infection at about the same time and patient 8, seen later in his course after relocating to this area, two and a half years before the calcinosis developed. In three of the nine patients it could not be determined which problem began first. None of the six children who did not develop calcinosis had staphylococcal infections, determined either by history or while under observation ($p < 0.005$). The boys were more likely than the girls to have staphylococcal infection (and to develop calcinosis; five of the six boys v four of the nine girls), though this was not statistically significant.

Seven group 1 patients and four group 2 patients had granulocyte chemotaxis measured on one or more occasions before and after the development of staphylococcal infection and calcinosis. Figure 1 shows the results of determinations in 29 adult controls, 28 child controls, four group 2 patients without calcinosis, and seven group 1 patients with calcinosis. The mean of 72·7 for group 1 patients is significantly lower ($p < 0.001$ Student's *t* test) than the mean of 229·5 for group 2 patients or the means for the adult (329·7) or child (304·7) controls. The group means using mean values for each patient were 49·55 and 249·7, respectively, for groups 1 and 2. No control child had results outside the two standard deviation confidence limits of the adults but six of the seven group 1 patients and two of the four group 2 patients had at least one determination more than two standard deviations below the mean of either the control adults or the control children (the seventh group 1 patient was only tested a long time before and after calcinosis was detected).

Figure 2 shows sequential studies of granulocyte chemotaxis at various times in two patients
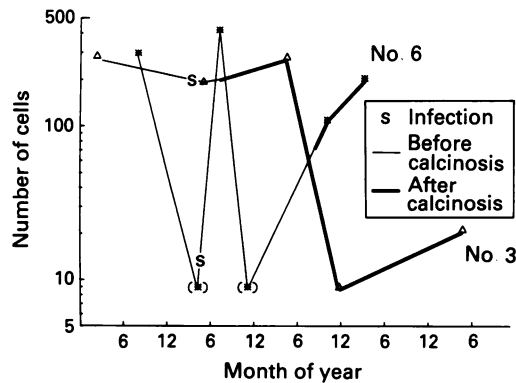
Table 3 Staphylococcus aureus infection history in group 1 patients with calcinosis

Patient No	Infection
1	Infected skin ulcers, axilla, groins, chin
2	Abscesses on hands, elbows, base of right thumb
3	Abscesses of axilla
4	Abscesses, multiple sites
5	Infected calcinosis sites
6	Infected toe
7	Septic joint
8	Infected skin ulcers on abdomen
9	Multiple abscesses

Figure 2 *Granulocyte chemotaxis in two patients observed from the onset of disease for three to four years. There was no temporal relation between the abnormal chemotaxis, staphylococcal infections, or the onset of calcinosis. Patient No 6 had abnormal chemotaxis before and after staphylococcal infection and considerably before the onset of calcinosis. Patient No 3 had a severe staphylococcal infection followed within a few months by the onset of calcinosis but did not show abnormal chemotaxis until much later.*

observed for about three and four years and shows its variability. There was no apparent consistent temporal relation between abnormal chemotaxis, staphylococcal infections, or the onset of calcinosis, but the defect was sómetimes seen well before the onset of calcinosis. The observed chemotactic defect was intermittent and was due to a serum factor rather than an inherent cell defect. Chemotactic ability could be restored in the patients' cells by incubation with chemotactic factor derived from normal

cells from adults and chemotaxis in controls was decreased in response to chemotactic factor derived from the serum of the patients with dermatomyositis of either group (p=0·005 in group 1; p=0·02 in group 2; Wilcoxon matched pairs signed ranks test). The reduction in chemotaxis was more marked with chemotactic factor derived from group 1 patients, resulting in levels more than two standard deviations below the adult control mean in 11 of the 29 determinations. In contrast, cells from adults were unaffected by chemotactic factor derived from serum obtained from normal children. The nature of this serum factor has not yet been identified but the decreased granulocyte chemotaxis did not correlate with levels of muscle enzymes in the serum, or with IgE concentrations. All patients had normal concentrations of C3, C4, and total haemolytic complement. Many of the patients were receiving prednisone, which is known to decrease chemotaxis,[13][14] though primarily by affecting the cells, but correlation with the prednisone dose at the time of testing or over the previous three and six months was very weak (r=0·49 and r=0·48, respectively), and some patients receiving no treatment had very abnormal chemotaxis. The one patient tested while receiving azathioprine had normal and abnormal results.

As a result of the known association of recurrent staphylococcal infection and chemotactic defects in the hyper IgE syndrome, we also studied the IgE concentrations in the two groups of patients.

Figure 3 shows that despite considerable overlap, the mean IgE concentrations were significantly higher (p<0·01, Student's *t* test) in group 1 (with calcinosis) than in age matched non-allergic children or in the group 2 patients (without calcinosis).

The IgE concentrations in group 1 children varied widely over the course of their illness, tending to become higher as the disease progressed, though some were raised at presentation. Figure 4 shows the longitudinal study of two patients in group 1. Both initially had low IgE concentrations, but developed much higher levels after staphylococcal infections and before the onset of calcinosis. Although we were unable to see any difference between the groups with childhood dermatomyositis in either personal or family history of allergy, there were patients in the two groups with histories of allergic symptoms, and some seasonal fluctuation in IgE concentrations was seen in these two patients as well as others in group 1, with peaks in July to September or October. No seasonal fluctuation was seen in either group 2 or the non-allergic controls.

We next tested for antistaphylococcal specific IgE in five group 1 patients and two group 2 patients. Patients 2 and 3, with calcinosis, had antistaphylococcal IgE binding as high as 16·9 and 15·6%. Patients 6 and 5 had levels as high as 8·2, whereas the two patients without calcinosis, 15 and 12, had levels of 5·8 and 1·8%, respectively. Values for control serum samples in this test are generally below 5%; atopic subjects often have binding in the range 5–10%. Levels
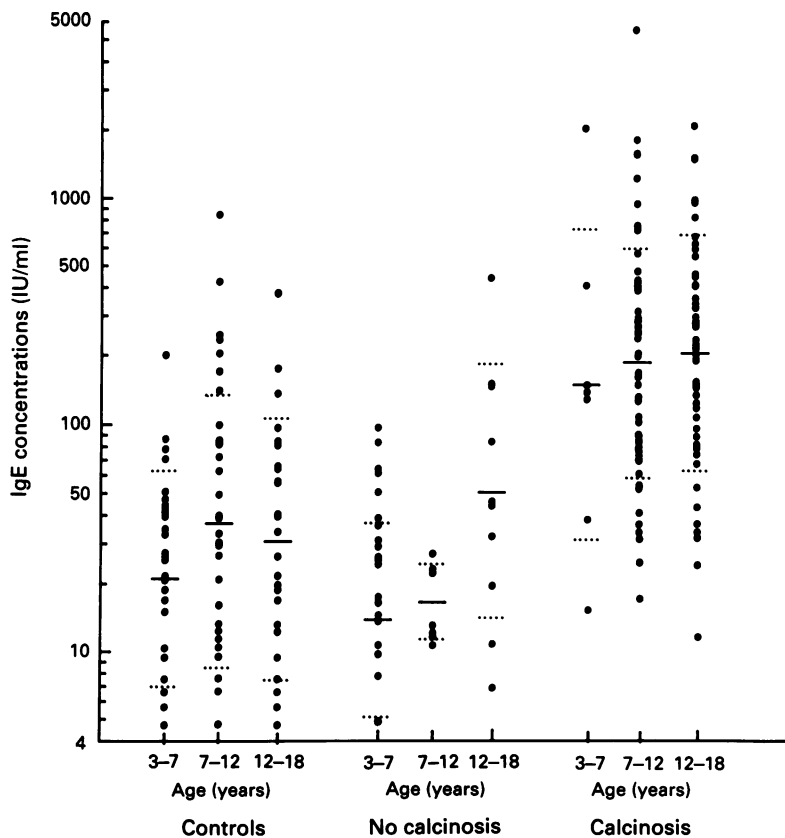

Figure 3 *Serum IgE concentrations in patients with childhood dermatomyositis. Individual determinations and mean (SD) values are shown. Despite considerable overlap, patients with calcinosis and staphylococcal infection had significantly higher concentrations than either controls or patients without calcinosis and staphylococcal infection. IU=2·4 ng/ml IgE.*
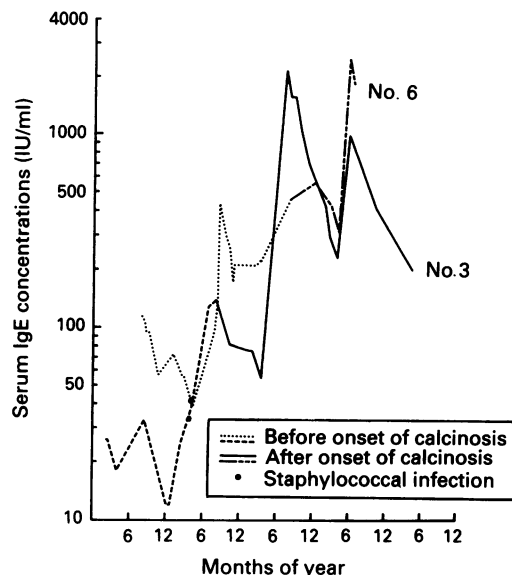
Figure 4   IgE concentrations in two patients who developed calcinosis (Nos 3 and 6), showing the time of staphylococcal infection and the time of onset of calcinosis. IgE concentrations increased after the staphylococcal infection, but there appeared to be some superimposed seasonal variation.

higher than 10% have most commonly been seen in patients with the hyper IgE syndrome or in patients with severe atopic dermatitis and staphylococcal infection.[11][15][16]

Discussion

Increased staphylococcal infections in childhood dermatomyositis previously reported by our group as associated with calcinosis[17][18] have received little consideration and the cause has not been studied previously.

The occurrence of these staphylococcal infections before the onset of calcinosis and in sites distant from sites of calcinosis suggests that the 'foreign body effect' of calcific masses or their occasional disruption of skin integrity cannot be the only factors involved.

In this report we have shown granulocyte chemotaxis to staphylococcus in these patients to be intermittently defective due to a serum factor. These patients also tended to have raised IgE concentrations and high levels of IgE antibodies to staphylococcus, often even before the onset of calcinosis. There have been no previous studies of granulocyte chemotaxis in patients with dermatomyositis of any age group. Granulocyte chemotaxis has, however, been shown to be defective in several of the collagen vascular disorders[19–22] and has generally been related to serum factors.[19][21–29] This has sometimes been felt to be related to an increased susceptibility to infections[19][24–26] but has not been linked with a specific susceptibility to S aureus.

There is, however, a known association between susceptibility to staphylococcal infection, defective granulocyte chemotaxis, and raised IgE.[30–33] Raised IgE concentrations were noted in our patients and have been previously reported in children with dermatomyositis who were incomplete responders to

treatment (Olson N Y, Lindsley C B. Paper presented at the American Rheumatism Association Central Meeting; 1988 November; Chicago, IL). In our patients, high IgE concentrations were often found long before the clinically detectable onset of calcinosis and often appeared to increase after staphylococcal infection. As in the hyper IgE syndrome, these patients also had specific increases of IgE antibodies to staphylococcus. If mechanisms similar to the hyper IgE syndrome are leading to the increased staphylococcal infection in the patients with childhood dermatomyositis, similar methods of treatment (H₂ blockers have been reported to be helpful in the hyper IgE syndrome[34–36]) might be helpful in reducing the rate of such infections in severely affected patients with childhood dermatomyositis. The nature of the association between these immunological abnormalities, the staphylococcal infections, and the development of calcinosis is unknown, but preceding immunological differences in patients with childhood dermatomyositis who do and do not subsequently develop calcinosis are suggested.

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