A child with atopic features, raised serum IgE, and recurrent infection treated with levamisole

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SUMMARY. A 6-year-old girl had a long history of severe eczema, asthma, recurrent otitis media, and staphylococcal infections with disseminated chronic skin abscesses. Immunological studies showed a neutrophil chemotaxis defect, hyperimmunoglobulinaemia E, IgE antibodies against cows' milk proteins, absence of IgM, and absence of staphylococcal haemolysins. Neutrophil phagocytic and bactericidal functions and complement system were normal. In the course of treatment with levamisole (2.5 mg/kg, 3 times a week for one year) a striking clinical improvement occurred: the skin lesions and the staphylococcal abscesses gradually cleared and the girl gained weight. There was also a partial correction of the immune deficiency.

In 1966 Davis et al.1 reported two children aged 9 and 6 years with long histories of chronic staphylococcal abscesses and chronic dermatitis, which they termed Job's syndrome. Several clinically similar disorders with hyperimmunoglobulinaemia E, and abnormal leucocyte mobility have since been described.2-6 Treatment with levamisole has improved the clinical and immunological conditions of a few such patients.7-8

We report a 6-year-old girl who, from age 2 months, has suffered from severe eczema, recurrent staphylococcal infections, and widespread chronic abscesses. Laboratory findings included defect of cellular neutrophil chemotaxis, high plasma IgE level, pronounced eosinophilia, a T-lymphocyte dysfunction, and an IgM deficiency. Treatment with levamisole for one year (2.5 mg/kg three times a week) resulted in clinical improvement, with a partial correction of the immunological defects.

Case report

A 6-year-old girl, the second child of related parents, was admitted to hospital in May 1977. Her mother suffers from allergic rhinitis and bronchial asthma with strikingly positive skin tests and specific IgE to Dermatophagoides pteronysinus and to house dust; no history of recurrent infection was reported by the rest of the family. The patient began to suffer from severe eczema and bronchial asthma when she was 2 months old. At 12 months she developed recurrent upper and lower respiratory infections, staphylococcal sepsis, middle-ear infections, and 'cold' skin abscesses. She was repeatedly admitted to hospitals; cultures obtained from ear discharge and from subcutaneous abscesses grew Staphylococcus aureus on several occasions.

At age 5 she developed chronic herpetic keratitis, and mucosal and cutaneous candidiasis. H1 receptors, antihistamines, steroids, and antifungal treatments had no effect. A milk-free and egg-free diet given over a long period proved unsuccessful.

In May 1977 she was referred to our unit. On admission she appeared very ill: her temperature was up to 39°C, weight and height were on the 3rd centile. The skin was reddened with diffuse lichenification and pruritus; the nails were dystrophic and thickened. Large cold abscesses were present on the back, in the axillae and on the legs, with enlarged lymph nodes in the cervical, axillary, and inguinal regions. There was a corneal ulcer in the left eye, and purulent conjunctivitis in both eyes. Chest x-ray films showed a large infiltration of the left lower lobe.

Repeated blood counts including platelets were normal except for a persistent eosinophilia, of between 30 and 50% (4.2-6.0 x 10^9/l). The blood group was AB. Blood cultures grew a penicillin-resistant S. aureus and intravenous gentamicin 7 mg/kg was given. The staphylococcal sepsis and pneumonia resolved within 2 weeks.

Cellular immunity. Skin tests for delayed hypersensitivity were performed with the following:
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dermatophytin ‘O’ 1:10 (Hollister-Stier), streptokinase-streptodornase 40 units (Lederle), purified protein derivative (PPD) 5 UI (Sclavo). The sites were examined after 24 hours and again at 48 hours, and the reaction was graded as positive if there was an induration of at least 6 mm.

Lymphocytes were isolated by Ficoll-Hypaque gradient centrifugation and adjusted to a final concentration of $10^6$ lymphocytes/ml. The E-rosette-forming lymphocytes were evaluated by the method of Jondal et al., counting 200 cells. In vitro response of lymphocytes to phytohaemagglutinin (PHA) was detected by the method of Park and Good using 0.1 ml lymphocytes at a concentration of $5 \times 10^6$ ml in RPMI 1640. The leucocyte inhibition test was performed by the method of Federlin et al. using as antigens Candida albicans and PHA (normal values <85%).

Humoral immunity. B-lymphocytes were identified by the method of Pernis et al. Serum immunoglobulins and complement fraction were estimated by radial immunodiffusion using a standard technique (Boering Werke). Immunoglobulins E were measured by the Prist method, and specific IgE antibodies to cows’ milk, house dust, D. pteronyssinus, Lolium, and Alternaria tenuis were measured by the Phadebas radioallergosorbent test. Staphylococcal haemolytic titre, and Schick test were performed by standard techniques.

Inflammatory response. Preparation of a suspension of granulocytes was as reported previously. The nitroblue tetrazolium (NBT) dye test was performed by the plate method of Balducci et al. The bactericidal test was that of Quie et al. using S. aureus 502 A as the test strain; results were expressed as the percentage of bacteria still alive after 120 minutes of incubation with neutrophils. Opsonisation, phagocytosis, and candidicidal activity were estimated microscopically by a method previously described. The myeloperoxidase was assessed by Kaplow’s colouration. Leucocyte adherence was tested by the method of MacGregor et al. and chemotaxis as previously reported.

All the immunological tests were performed several times—before, during, and after treatment with levamisole.

Results

Specific immunity. Serum immunoglobulins IgA and IgG were respectively 187 and 2380 mg/100 ml; serum IgM and staphylococcal haemolsyns were consistently absent in repeated tests. Schick test, after three injections of diphtheria toxoid, was negative. Total and specific IgE against cows’ milk were greatly raised: 16 000 U/ml and 49 PRU/ml respectively. Ig-bearing lymphocytes were: IgG 7, IgA 2, and IgM 7%.

Delayed hypersensitivity responses to candida, SK–SD, and PPD were absent. Circulating T-lymphocytes were persistently low (12%, 204/mm$^3$) and the in vitro lymphocyte response to PHA was depressed (stimulatory index, 6); the inhibition of leucocyte migration with candida antigen (1:10, 1:100, 1:1000) was respectively 25, 22, and 26% of normal, according to our laboratory standards. All the immunological tests were repeated several times on different days.

Inflammatory responses. Total haemolytic complement, C3, C4, C3PA, serum opsonic activity, phagocytic, and bactericidal activity of the patient’s neutrophils against S. aureus, myeloperoxidase content, and NBT test were all normal.

In vitro studies of chemotaxis showed a severe defect in the migration of the patient’s granulocytes. In several tests performed before treatment, the cellular chemotactic response was only 5% that of the age control group, while the humoral generation of chemotactic factors was normal (80%).

Clinical and immunological findings after treatment. The high levels of specific IgE antibodies to cows’ milk prompted us to continue a milk-free diet for 3 months. During this period the immunological tests and the clinical conditions remained unchanged.

After this observation period, levamisole was started at a dose of 2.5 mg/kg orally 3 times a week for one year. No side effects were observed during this time. The cows’ milk-free diet was continued. After 2 months there was a pronounced clinical improvement; the dermatitis gradually cleared up, and the recurrent infections and skin abscesses became less and less frequent and eventually disappeared. A partial correction of the immunological defect could also be observed (Table).

T-lymphocyte count increased; the blastogenic response to PHA became normal; and delayed skin test to candida became positive; the motile response of neutrophils became normal. Total and specific IgE decreased, while serum IgM and staphylococcal haemolysin remained undetectable.

After one year of treatment with levamisole, this medication was stopped while maintaining the egg-free and milk-free diet. Now, after two years without levamisole, the clinical and immunological improvements continue, the girl’s clinical condition is good and she attends school regularly.
### Table Immunological data before, during, and after levamisole treatment

<table>
<thead>
<tr>
<th></th>
<th>Normal values (mean±SD)</th>
<th>Before</th>
<th>During*</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellular chemotaxis</td>
<td>100±18</td>
<td>5</td>
<td>85</td>
<td>90</td>
</tr>
<tr>
<td>Random motility</td>
<td>100±15</td>
<td>5</td>
<td>85</td>
<td>110</td>
</tr>
<tr>
<td>Total IgE (U/ml)</td>
<td>18±3</td>
<td>16000</td>
<td>8000</td>
<td>1570</td>
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<tr>
<td>Specific IgE cows' milk (PRU/ml)</td>
<td>—</td>
<td>49</td>
<td>—</td>
<td>10</td>
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<tr>
<td>IgM (mg/100 ml)</td>
<td>65±25</td>
<td>Undetectable</td>
<td>Undetectable</td>
<td>Undetectable</td>
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<tr>
<td>Staphylococcal haemolytic titre (U/ml)</td>
<td>—</td>
<td>Undetectable</td>
<td>Undetectable</td>
<td>Undetectable</td>
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<tr>
<td>T-lymphocytes (%)</td>
<td>61±5</td>
<td>12</td>
<td>43</td>
<td>50</td>
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<tr>
<td>T-lymphocytes (×10³/l)</td>
<td>&gt;1-5</td>
<td>0·204</td>
<td>0·86</td>
<td>1·2</td>
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<tr>
<td>In vitro lymphocyte response to PHA SI</td>
<td>&gt;10</td>
<td>6</td>
<td>14</td>
<td>30</td>
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### Discussion

The clinical findings in this patient were similar to those of the children with cellular chemotaxis defect associated with hyperimmunoglobulinaemia E reported by a number of authors.
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References


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