Defective neutrophil chemotaxis and raised serum IgE levels in a child with recurrent bacterial infections and eczema

Influence of levamisole

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SUMMARY A 5½-year-old girl, with a life-long history of recurrent staphylococcal infections and eczematous dermatitis had a defect in polymorphonuclear leucocyte chemotaxis and phagocytosis in autologous serum, a high serum IgE level, and a disturbed T cell function. Levamisole improved all the immunological abnormalities and there was a dramatic clinical improvement. Discontinuation of therapy with levamisole resulted in gradual deterioration.

We report a child with eczema, recurrent superficial and deep bacterial infections, and raised IgE levels, a syndrome which has already been described (Clark et al., 1973; Hill and Quie, 1974; Hill et al., 1974; Van Scovy et al., 1975). Treatment with levamisole (Symoens and Rosenthal, 1977) led to clinical and immunological improvement.

Case report

A girl, now 7½ years old, was born after a normal pregnancy and delivery. Soon after birth she started to suffer continually from severe bronchial, antral and middle ear infections, and eczematous dermatitis. Cultures from sputum, ear secretions, and skin lesions invariably showed the presence of Staphylococcus aureus. At the age of 2 she developed bronchopneumonia, resulting in a lung abscess. Regression was obtained after 2 months of antibiotic therapy, but a residual pneumatocele required surgical intervention. At the age of 4 she was again hospitalised for right pyopneumothorax. Cultures of pleural effusion yielded Staph. aureus and chest x-ray showed multiple radiolucencies. Again the symptoms improved with prolonged antibiotic therapy.

In the same year surgical intervention was needed for a cutaneous block of the antrum. At the age of 5 she was admitted to the University Hospital St Raphaël in Louvain. Humoral and cellular immunity tests at that time gave normal values for the immunoglobulins IgA, IgG, and IgM, complement components C3 and C4, the epinephrine- and typhoid-stimulation test, the phytohaemaglutinin (PHA) lymphoblast transformation test, polymorphonuclear leucocyte (PMN) random migration test, nitroblue-tetrazolium test, and the myeloperoxidase test. The abnormalities found were peripheral and bone marrow eosinophilia, high serum IgE levels, and a subnormal lymphoblast response to candidin. At the age of 5½ she was referred to the Clinical Research Unit St Bartholomew, Antwerp, for evaluation of humoral and cellular immunity, where levamisole therapy was started and the effects of treatment were followed.

Material and methods

Chemotaxis assay. 1 ml of a 6% dextran solution was added to 10 ml heparinised blood and allowed to sediment for about 1 hour. The leucocyte-rich plasma was removed and the leucocyte pellet was washed twice in Hanks's balanced salt solution (HBSS). Cell concentration was adjusted to 1 x 10⁶ PMN/ml HBSS. The cells were introduced into the upper compartment of a boyden chamber (Neuro Probe, Bethesda, Maryland) separated by a 5 μm millipore filter (Millipore Corp., Brussels) from the chemotactic substances in the lower compartment. After incubation at 37°C for 3 hours in humidified
Phagocytosis. In vitro phagocytosis of Candida albicans by PMN in autologous and AB serum was assessed as previously described (Verhaegen et al., 1976a).

E-rosette test. The E-rosette formation of T-lymphocytes was determined as previously described (Verhaegen et al., 1977).

Lymphoblast transformation test. A mini-culture technique developed by Eysvoogel et al. (1971) was followed. Mitogens were PHA (PHA-M, Difco Laboratories, Detroit, Michigan), candidin (Hollister-Stier, Atlanta, Georgia), and mumps (Eli Lilly, Indianapolis). The DNCB skin test was done by applying a 2 mg sensitising dose followed 2 weeks later with a 100 μg, 50 μg, and 25 μg challenge.

Complement factors and immunoglobulins. The serum haemolytic complement activity (CH50) was determined by a modified method of Mayer (1961), and the serum complement components C3, C4, and Clq and immunoglobulins IgG, IgM, and IgA by the radial immunodiffusion technique of Mancini et al. (1965) as previously described (Verhaegen et al., 1976b). IgE concentrations were measured by a radioimmunoabsorbent technique using a Phadebas IgE test kit. Normal values ranged between 28 and 700 IU/ml.

Results

Clinical data. After one month of levamisole treatment, 2.5 mg/kg daily for 3 consecutive days each week, the patient was hospitalised for staphylococcal pneumonia which progressed to multiple lung abscesses despite antibiotic therapy. 3 months later the clinical picture remained the same. The treatment schedule was then changed to 2.5 mg/kg levamisole every other day, but the antibiotic therapy remained unchanged. 2 weeks later a dramatic relief of symptoms occurred and the patient was discharged within one month.

From that time until the discontinuation of levamisole, 14 months later, she needed only one course of oral antibiotics during a 10-day period because of bronchopneumonia, which subsided without complications. Otitis never recurred and the superinfection of the skin lesions improved, though a residual eczema persisted.

After discontinuation of levamisole treatment the girl remained in good health for 3 months, thereafter eczema became worse and was complicated with superficial infections. She developed ophthalmitis which was controlled by antibiotics, and after 5 months had to be hospitalised again for bronchopneumonia complicated with pneumatoceles. Levamisole therapy was restarted together with antibiotics and the symptoms subsided after 2 weeks of treatment.

Immunological data. The patient was not receiving antibiotics or suffering from manifest infections when tested. Immunological data before, during, and after discontinuation of levamisole treatment are shown in Tables 1 and 2 and the Fig. Abnormal immunological functions were negative delayed hypersensitivity reactions to mumps and DNCB challenges, high serum IgE, depressed lymphoblast transformation to candidin, low E-rosette forming cells, depressed PMN chemotaxis, and deficient phagocytosis in autologous serum. This serum-dependent impairment of phagocytosis could be confirmed by adding the patient's serum to PMNs of healthy subjects (Fig.).

During levamisole therapy the immunological functions returned to normal or improved (Fig.). After 5 months of no levamisole treatment, the IgE levels, PMN chemotaxis, and PMN phagocytosis in autologous serum reached pretreatment values.

Discussion

Various clinical variants of our patient's disorder have been described (Buckley et al., 1972; Clark et al., 1973; Hill and Quie, 1974; Van Scoy et al., 1975) but
Table 1  Delayed hypersensitivity skin reactions of the patient to different antigens before and during levamisole therapy

<table>
<thead>
<tr>
<th></th>
<th>Pre-values</th>
<th>6 m</th>
<th>14 m</th>
<th>17 m</th>
<th>1/100</th>
<th>1/1000</th>
<th>1/10 000</th>
<th>100γ</th>
<th>50γ</th>
<th>25γ</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PPD (5 U)</strong></td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td></td>
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<tr>
<td><strong>Mumps</strong></td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>I</td>
<td>I</td>
<td>I</td>
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<tr>
<td><strong>Candida</strong></td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>I</td>
<td>I</td>
<td>I</td>
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<tr>
<td><strong>DNCB†</strong></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Pre-values</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>14.5</td>
<td>10</td>
<td>10</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>6 m</strong></td>
<td>0</td>
<td>0</td>
<td>22</td>
<td>12</td>
<td>20</td>
<td>10</td>
<td>10</td>
<td>2</td>
<td>2</td>
<td>+</td>
</tr>
<tr>
<td><strong>14 m</strong></td>
<td>0</td>
<td>0</td>
<td>20</td>
<td>15</td>
<td>23</td>
<td>10</td>
<td>10</td>
<td>2</td>
<td>2</td>
<td>++</td>
</tr>
<tr>
<td><strong>17 m</strong></td>
<td>0</td>
<td>0</td>
<td>20</td>
<td>13</td>
<td>23</td>
<td>10</td>
<td>10</td>
<td>2</td>
<td>2</td>
<td>++</td>
</tr>
</tbody>
</table>

*Diameter in mm. †0 = no reaction; + = erythema; ++ = induration. E = erythema; I = induration.

all have in common severe deep and superficial staphylococcal infections, eczematous dermatitis, high serum IgE, and defective PMN chemotaxis. The patients of Buckley et al. (1972), Clark et al. (1973), and Van Scoy et al. (1975) also suffered from mucocutaneous candidiasis, and represent a mild degree of T cell dysfunction. Apart from the mucocutaneous candidiasis, our patient resembles the patients reported, but she also had a unique serum-dependent phagocytosis defect.

Encouraging results of levamisole treatment have been reported in patients with recurrent infection (De Cree et al., 1974; Vanheule et al., 1976; Verhaeghen et al., 1976a; Van Eygen et al., 1976), and levamisole improved the clinical symptoms of our patient. Furthermore, levamisole normalised or improved her defective phagocyte and T cell functions, which confirms the reported effects of levamisole on phagocyte functions (Verhaeghen et al., 1973; Hoebeke and Franchi, 1973; Schmidt and Douglas, 1976; Anderson et al., 1976) and T cell functions (Biniaminov and Ramot, 1975; Hadden et al., 1975; Lieberman and Hsu, 1976; Whitcomb et al., 1976; Verhaeghen et al., 1977).

The physiopathological mechanism which underlies the phagocyte and T cell dysfunctions of these rare disease entities and the interaction of levamisole are still in doubt. Hill and Quie (1974) showed that PMN chemotaxis could be inhibited in vitro by histamine, which is known to increase the intracellular concentration of cyclic AMP, suggesting that the IgE-mediated histamine release in their patients could represent an etiology for the defective chemotaxis (Hill and Quie, 1974). Of further relevance is the fact that substances which increase intracellular cAMP levels depress both phagocytic and T cell functions (Bourne et al., 1974). Levamisole has been reported to interact with the cyclic nucleotide metabolism; the drug decreased cAMP levels and increased cGMP levels in mouse lymphocytes (Hadden et al., 1975), maintained higher cGMP levels in human chemotactic PMN (Anderson et al., 1976), and restored histamine inhibited E-rosette forming cells in patients with allergies (De Cock et al., 1976).
Table 2  Immunological data of the patient before, during, and after discontinuation of levamisole therapy

<table>
<thead>
<tr>
<th>Immunoglobulins</th>
<th>Complement</th>
<th>Lymphoblast transformation</th>
<th>E-rosettes</th>
<th>Phagocytosis</th>
<th>Chemotaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA (g/l)</td>
<td>IgG (g/l)</td>
<td>IgM (g/l)</td>
<td>IgE (IU/ml)</td>
<td>C3 (g/l)</td>
<td>C4 (g/l)</td>
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<tr>
<td>Normal (mean ± SE)</td>
<td>2-236 ±0-13</td>
<td>11-55 ±0-25</td>
<td>1-61 ±0-093</td>
<td>110-9 ±6-85</td>
<td>0-80 ±0-023</td>
</tr>
<tr>
<td>Pre-values</td>
<td>1-44</td>
<td>10-8</td>
<td>1-15</td>
<td>3600</td>
<td>116</td>
</tr>
<tr>
<td>Start of levamisole therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 m</td>
<td>2-10</td>
<td>12-5</td>
<td>1-62</td>
<td>2400</td>
<td>107</td>
</tr>
<tr>
<td>14 m</td>
<td>2-35</td>
<td>12-2</td>
<td>1-7</td>
<td>2400</td>
<td>119</td>
</tr>
<tr>
<td>17 m</td>
<td>1-82</td>
<td>9-4</td>
<td>1-85</td>
<td>1200</td>
<td>88</td>
</tr>
<tr>
<td>18 m: Discontinuation of levamisole therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 m</td>
<td>2-0</td>
<td>13-8</td>
<td>1-96</td>
<td>2500</td>
<td>125</td>
</tr>
<tr>
<td>2 m</td>
<td>1-98</td>
<td>11-7</td>
<td>1-8</td>
<td>ND</td>
<td>104</td>
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<tr>
<td>3 m</td>
<td>1-95</td>
<td>15-3</td>
<td>2-8</td>
<td>ND</td>
<td>151</td>
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<tr>
<td>4 m</td>
<td>2-62</td>
<td>15-3</td>
<td>2-08</td>
<td>2450</td>
<td>128</td>
</tr>
<tr>
<td>5 m</td>
<td>3-0</td>
<td>22-0</td>
<td>1-38</td>
<td>3500</td>
<td>114</td>
</tr>
</tbody>
</table>

*See immunological assessments. †MnN/PMN = mean number of C. albicans per neutrophil. RMI = relative mitotic index; ND = not done.
De Cree, Emmery, Timmermans, Eeckels, De Cock, and Verhaeegen

1977). This may suggest that the phagocyte and T cell dysfunctions of this disease entity may be due to a pathological number of receptors for histamine or substances which increase intracellular cAMP on phagocytes and T cells. The beneficial effects of levamisole on the clinical symptoms and the abnormal immunological functions in our patient fit this hypothesis.

The differences in symptomatology between our patient and those of Hill and Quie (1974), Buckley et al. (1972), Clark et al. (1973), and Van Scoy et al. (1975) may be due to a different distribution of these receptors for histamine or similar substances on T cells and phagocytes. The number of receptors on phagocytes is probably the same but those on T cells may differ. All patients have high serum IgE, suggesting that suppressor T cells for IgE-production are involved (Okumura and Tada, 1971; Tada et al., 1971). In our case and those of Hill and Quie (1974) some other T cells may be involved but in the patients of Buckley et al. (1972), Clark et al. (1973), and Van Scoy et al. (1975) T cells were probably greatly involved, accounting for the mucocutaneous candidiasis.

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References


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