Arthritis in hyperimmunoglobulinaemia D

Sir: Hyperimmunoglobulinaemia D is a rare disorder characterised by periodic fever with a high serum IgD level. Until now, arthritis has not been recognised as a manifestation of the disease. We report the cases of four Dutch patients with hyperimmunoglobulinaemia D who experienced arthritis during the attacks (table). One patient will be described in more detail.

Patient No 1 (male, 30, Caucasian) had had, since early childhood, recurrent attacks of high fever (>39°C) with lymphadenopathy, a painful erythema with target-like lesions, consisting of a clear red area at the periphery, surrounding a pale pink zone and a central vivid area at the extensor sides of the extremities (histopathologically compatible with erythema multiforme exudativum), and abdominal pain. Attacks usually lasted for five to seven days and remitted spontaneously. During attacks laboratory investigation showed a leukocytosis with a shift to the left, and raised C reactive protein and erythrocyte sedimentation rate. Repeated and extensive immunological and microbiological investigations failed to disclose a disease. In between these periods he was completely healthy.

In 1989 he was admitted with a similar attack and a florid arthritis of his right elbow. As before no infectious agent could be found. Immunological testing showed normal complement concentrations, no organ-specific autoantibodies, no rheumatoid factor, no antinuclear antibodies, antibodies to dsDNA, or extractable nuclear antigens. Serum IgA was slightly increased and the serum IgD was polyclonal and increased: 930 IU/ml (normal <100 IU/ml). A diagnosis of hyperimmunoglobulinaemia D was made. Paracetamol and codeine were given, and his symptoms resolved completely within seven days.

This patient's history is characteristic of the hyperimmunoglobulinaemia D syndrome. The presentation with an arthritis is remarkable, however. In three other patients with a hyper IgD syndrome we have also noted transient arthritis during several of the 'classical' attacks (see table).

In contrast with other periodic fever syndromes, such as familial Mediterranean fever and familial Hibernian fever, arthritis has not, until now, been reported in the hyper-IgD syndrome, though arthralgia has been found.

The presented case histories suggest that arthritis, mostly affecting the large joints, can be part of the syndrome. We noted that the arthritis always disappeared spontaneously, with disappearance of the other symptoms, in five to 10 days. Paracetamol or a non-steroidal anti-inflammatory drug can be prescribed for the treatment of symptoms.

Colchicine seems to influence the frequency of the attacks in some patients, though failure of this treatment has also been reported.

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Use of cyclosporin A in the eosinophilia myalgia syndrome

Sir: The eosinophilia myalgia syndrome (EMS), a newly recognised disorder linked to the ingestion of L-tryptophan containing products, is characterised by peripheral eosinophilia, myalgias, scleroderma-like skin changes, and variable involvement of the pulmonary, cardiac, and neurological systems. Pathologically, the affected tissues display inflammatory infiltrates consisting primarily of lymphocytes and macrophages, endothelial cell swelling and degeneration, variable degrees of eosinophil infiltration, and diffuse tissue fibrosis. The initiating stimulus for this widespread inflammatory reaction is unknown, but two substances, one of which is a dimer of L-tryptophan and the other an aniline compound, are being investigated because they are found in higher concentrations in samples of L-tryptophan associated with EMS than in samples not associated with the syndrome. Corticosteroids have been used to treat EMS, but the disease is often unresponsive or poorly responsive. Therapeutic responses with other immunosuppressive drugs and plasmapheresis have been limited and unpredictable. As cyclosporin A, which can inhibit T cell and eosinophil function, has been used to treat both scleroderma and eosinophilic fasciitis, we began a trial with this drug in EMS.

Eight patients meeting Centers for Disease Control criteria for the diagnosis of EMS, who either had an unsatisfactory response to corticosteroids or were unable to taper corticosteroids, were treated with cyclosporin A, initially at 5 mg/kg/daily. Cyclosporin A concentrations were measured at first weekly and then monthly, and the dose was adjusted to maintain the whole blood trough concentration at 100–200 ng/ml. Hypertension or renal disease resulted in adjustments of dose. The patients' conditions were evaluated regularly by a single observer (DJC) and fasciitis, muscle strength, and neuropathy were determined; myalgias and dyspnoea were subjectively assessed by the patients. Fasciitis was graded on a scale of 0–2 (0=normal skin, 1=mild to severe induration of <25% of body surface, and 2=severe induration of >25% of body surface). Muscle strength was assessed with a standard scale of 0–5, and the extent of neuropathy was noted.

The table (p. 82) summarises the clinical data. Cyclosporin A was used for a mean of 8½ months, and was eventually discontinued by all patients—in six owing to side effects and in two owing to lack of efficacy. The most common severe side effects included renal insufficiency (responsive to dose modification in two patients but leading to discontinuation at a mean of 14 months in three others) and hypertension (responsive to dose modification in all three patients).

In five patients fasciitis and myalgias improved significantly. Three of these patients, all of whom had stopped taking cyclosporin A because of renal insufficiency, developed objective worsening of these symptoms when treatment was stopped. We attempted to improve in two, remained the same in three, and worsened in two. There were no significant changes in neuropathy or dyspnoea. Despite frequent attempts to taper corticosteroids, there was no consistent change in the daily corticosteroid dose.

The incomplete response to cyclosporin A in this study might be due to many factors. Only seriously affected subjects who had taken corticosteroids for a prolonged period...

Characteristics of the patients

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Age (years)</th>
<th>Age at onset</th>
<th>Race</th>
<th>Sex</th>
<th>Typical attack</th>
<th>Fever &gt;39°C</th>
<th>Rash</th>
<th>Arthritis</th>
<th>Abdominal pain</th>
<th>Lymphadenopathy</th>
<th>Duration of attack (days)</th>
<th>Frequency of attack (years)</th>
<th>Serum IgD (IU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>&lt;4</td>
<td>Caucasian</td>
<td>M</td>
<td></td>
<td>+</td>
<td>Elbow</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>5-7</td>
<td>4-6</td>
<td>930</td>
</tr>
<tr>
<td>2</td>
<td>46</td>
<td>&lt;4</td>
<td>Caucasian</td>
<td>M</td>
<td>+</td>
<td>+</td>
<td>Knee</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>5-10</td>
<td>8-10</td>
<td>1170</td>
</tr>
<tr>
<td>3</td>
<td>32</td>
<td>&lt;4</td>
<td>Caucasian</td>
<td>M</td>
<td>+</td>
<td>+</td>
<td>Knees</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>3-4</td>
<td>8-12</td>
<td>450</td>
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<tr>
<td>4</td>
<td>33</td>
<td>&lt;4</td>
<td>Caucasian</td>
<td>M</td>
<td>+</td>
<td>+</td>
<td>Knees</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>3-5</td>
<td>8-12</td>
<td>680</td>
</tr>
</tbody>
</table>

*Patient described in text.
†Brother of patient 1.
‡All patients had appendectomy; histopathologically no inflammation.
§Before colchicine.
Clinical data

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Age/sex</th>
<th>Duration of EMS before cyclosporin A use (months)</th>
<th>Duration of cyclosporin A use (months)</th>
<th>Significant side effects of cyclosporin A</th>
<th>Reason for discontinuing cyclosporin A</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>44/F</td>
<td>13</td>
<td>3</td>
<td>'Stiffness'</td>
<td>Patient's request</td>
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<tr>
<td>2</td>
<td>61/F</td>
<td>20</td>
<td>3</td>
<td>Abdominal pain, diarrhoeas</td>
<td>Patient's request</td>
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<tr>
<td>3</td>
<td>35/F</td>
<td>7</td>
<td>19</td>
<td>Renal insufficiency, hypertension, taken frusium</td>
<td>Renal insufficiency</td>
</tr>
<tr>
<td>4</td>
<td>41/F</td>
<td>11</td>
<td>8</td>
<td>Renal insufficiency</td>
<td>Renal insufficiency</td>
</tr>
<tr>
<td>5</td>
<td>56/E</td>
<td>15</td>
<td>8</td>
<td>Renal insufficiency</td>
<td>Lack of efficacy</td>
</tr>
<tr>
<td>6</td>
<td>33/M</td>
<td>6</td>
<td>16</td>
<td>Renal insufficiency</td>
<td>Renal insufficiency</td>
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<tr>
<td>7</td>
<td>38/F</td>
<td>18</td>
<td>6</td>
<td>Worsening myalgia</td>
<td>Lack of efficacy</td>
</tr>
<tr>
<td>8</td>
<td>52/F</td>
<td>12</td>
<td>6</td>
<td>Myalgia</td>
<td>Lack of efficacy</td>
</tr>
</tbody>
</table>

*EMS: eosinophilia myalgia syndrome.

were included in this study; this group might have derived a substantial benefit from corticosteroid treatment that cyclosporin A would do little to augment. Alternatively, the manifestations unresponsive to cyclosporin A might have been either irreversible or too slow to reverse to be detected in a small, short-term trial.

Our data show limited usefulness of cyclosporin when used relatively early in this disease. Given what is now known about EMS, one would expect that the efficacy of any regimen aimed at reduction of inflammation would diminish further as the syndrome progressed, and that any advances in treatment are unlikely to be found among the immunomodulatory drugs.

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Postural variation in von Willebrand factor antigen

Sir: von Willebrand factor antigen (vWF:Ag) is the antigenic component of von Willebrand factor and is synthesised by endothelial cells and megakaryocytes. Raised concentrations of vWF:Ag have been reported in a variety of connective tissue diseases, including vasculitis, systemic lupus erythematosus, and systemic sclerosis. Although it is an acute phase reactant, raised levels in some of these diseases may reflect damage to the endothelial cell. As most inpatients lie quietly on a bed, and most outpatients are subject to movement during their clinic visits we sought to determine whether differences in vWF:Ag between these groups might be due to posture and activity.

We tested the effect of different postures on circulating levels of vWF:Ag in healthy hospital and laboratory staff. In the first study blood was taken into an EDTA tube from a group of five men and five women (mean age 29 (SD 5) years) immediately after normal kinetic laboratory activity. After resting quietly in the sitting position for 15 minutes, blood was taken from the opposite arm. Plasma was obtained after centrifugation at 3000 rpm for 10 minutes and vWF:Ag estimated by enzyme linked immunosorbent assay (ELISA). Mean (SD) concentrations of vWF:Ag were immediately after activity were 1160 IU/L (150), but after the rest period they had fallen to 1040 (220) (p<0.05), Wilcoxon rank sum test applied.

In a separate study six men and five women (aged 22–38) were rested lying down, face up, for 25 minutes, after which blood was taken. They then sat upright in a chair for a further 25 minutes and blood was taken a second time. After 25 minutes lying down plasma vWF:Ag concentrations were 950 (270) IU/L, but after 25 minutes sitting up levels increased to 1070 (200) IU/L (p<0.05).

This small study identified changes in vWF:Ag concentrations depending upon variations in posture and activity. As vWF:Ag has been shown to rise after exercise this finding is not surprising. It points, however, to a possible artefact in vWF:Ag determination in patients. This may become important in the case of patients with, for example, rheumatoid arthritis, who are often admitted to hospital for bed rest. Reductions in vWF:Ag in these patients may reflect their posture and not necessarily reduced activation/injury of the endothelium. To avoid the possible problem in outpatient clinics we suggest that patients rest sitting for a minimum of 15 minutes before venepuncture.

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Hypertrophic osteoarthropathy and AIDS

Sir: Rheumatic manifestations of human immunodeficiency virus (HIV) are diverse. One of the conditions associated with HIV infection is hypothyroidism, the patient becomes dehydrated and eosinophilic pneumonia.

A 29-year-old man, an intravenous drug and alcohol abuser, known to be HIV positive, was admitted owing to development of severe pain and oedema in his arms and legs two months previously. He also complained of a persistent cough, with foul smelling sputum, occasionally haemoptoic, fever, and pleuritic chest pain. He had lost 10 kg of weight.

On admission, the patient appeared cachectic, was unable to walk, and had a temperature of 38.5°C. His mouth showed oropharyngeal candidiasis. Inspiratory rates were heard in the superior field of the right hemithorax. As sounds were normal at auscultation, the patient complained of a persistent cough, with foul-smelling sputum, occasionally haemoptoic, fever, and pleuritic chest pain. He had lost 10 kg of weight.

It was thought possible that the patient had developed a cardiac rhythm, but a recent electrocardiogram showed few pathological changes.

Blood studies showed haemoglobin 90 g/l, leucocytes 7·3 × 109/l (lymphocytes 1·965 × 109/l, neutrophils 5·55 × 109/l, monocytes 0·55 × 109/l, platelets 367 × 109/l, haemoglobin 7·1 g/dl). Serum alkaline phosphatase was 425 U/l (normal <279).

The patient was discharged from hospital with the diagnosis of AIDS (acquired immune deficiency syndrome) and a variety of other conditions, including arthritis, and oedema. Further investigations were carried out to determine the cause of these symptoms.

On examination, the patient was found to be cachectic, with a temperature of 38.5°C. His mouth showed oropharyngeal candidiasis. Inspiratory rates were heard in the superior field of the right hemithorax. As sounds were normal at auscultation, the patient complained of a persistent cough, with foul-smelling sputum, occasionally haemoptoic, fever, and pleuritic chest pain. He had lost 10 kg of weight.

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