LETTERS TO THE EDITOR

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 livid 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 leucocytosis 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 diagnosis. 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.¹⁻³ The presentation with an arthritis is remarkable, however.

In three other patients with a hyper IgD syndrome at our department we 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.^{1,4}

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^{1,3} in some patients, though failure of this treatment has also been reported.²

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1 Meer J W M van der, Vossen J M, Radl J, et al. Hyperimmunoglobulinemia D and periodic fever: a new syndrome. *Lancet* 1984; i: 1087-90.
2 Reeves W G, Mitchell J R A. Hyperimmunoglobulinemia D and periodic fever. *Lancet* 1984; i: 1463-4.
3 Ostuni P A, Lazzarin P, Ongaro G, et al. Hyper IgD syndrome: a new case treated with colchicine. *Clin Rheumatol* 1988; 7: 398-401.
4 Meer J W M van der. Keer op keer koorts. *Ned Tijdschr Geneesk* 1987; 131: 1178-80.

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 early peripheral eosinophilia, myalgias,¹ scleroderma-like skin changes, and variable involvement of the pulmonary,² cardiac,³ and neurological⁴ 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.^{5,6}

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 8.1 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 serious 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. Weakness improved 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

Patient No	Age (years)	Age at onset (years)	Race	Sex	Typical attack					Duration of attack (days)	Frequency of attack (years)§	Serum IgD (IU/ml)
					Fever >39°C	Rash	Arthritis	Abdominal pain‡	Lymphadenopathy			
1*	30	<4	Caucasian	M	+	+	Elbow	+	+	5-7	4-6	930
2	46	<4	Caucasian	M	+	+	Knee	+	+	5-10	8-10	450
3	32	<4	Caucasian	M	+	-	Knees + Ankles	+	+	3-4	8-12	1170
4†	33	<4	Caucasian	M	+	-	Knees + Ankles	+	+	3-5	8-12	680

*Patient described in text.
†Brother of patient 3.
‡All patients had appendectomy; histopathologically no inflammation.
§Before colchicine.