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Seasonal occurrence of relapses in inflammatory myopathies: a preliminary study

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Abstract The seasonal occurrence of relapses was analysed retrospectively in a group of 53 patients with treated dermatomyositis (DM) or polymyositis (PM). In DM, the incidence of both myositic and cutaneous relapses was highest in summer whereas in the PM group relapses was more evenly distributed throughout the seasons but lowest in summer. The present findings suggest that environmental factors such as intercurrent infections and light exposure may be involved in reactivating the disease process and causing relapses in DM but less so in PM. Further prospective studies are needed to assess the role of environmental factors in the initiation and reactivation of the inflammatory myopathies.

Key words Inflammatory myopathies · Dermatomyositis · Polymyositis · Relapses · Seasonal occurrence

Introduction

The autoimmune inflammatory myopathies dermatomyositis (DM) and polymyositis (PM) are thought to be triggered in genetically predisposed individuals by exposure to certain environmental agents [19]. However, few studies have investigated the role of environmental factors in the initiation or reactivation of these diseases [2, 16]. Although the majority of patients with DM and PM respond favourably to treatment with corticosteroids or other forms of immunotherapy, in a substantial proportion of cases the underlying immune process may undergo reactivation resulting in a clinical or subclinical relapse of the condition [14, 17].

The aims of the present study were to investigate the possible contribution of environmental factors in the occurrence of disease relapses in patients with inflammatory myopathy and to compare the seasonal patterns of disease reactivation in patients with DM and PM.

Patients and methods

A retrospective analysis of relapses and the month in which they occurred was carried out in a series of 53 consecutive patients with inflammatory myopathy who were treated in a specialised tertiary referral clinic. Patients were referred by clinicians from the metropolitan Perth area as well as country areas. Of the 53 patients, 24 were classified as having definite DM. The PM group comprised 9 patients with isolated PM and 18 patients with overlap syndromes who also had other features of a connective disease such as mixed connective tissue disease, systemic sclerosis or systemic lupus erythematosus, but in whom the myositis was the dominant clinical

problem and features of dermatomyositis were not present. Patients with an associated malignancy were not included. The mean period of followup was 4.3 years (range 1–14.5). The diagnosis of inflammatory myopathy (DM or PM) was definite in all cases and was made on the basis of: clinical features at presentation; elevation of serum creatine kinase (CK) activity; electromyographic findings; and was confirmed by muscle biopsy in all cases. Details of treatment protocols used have been published elsewhere [11, 12].

Patients were examined in the clinic at 1–3 month intervals or at the time of a relapse. At each visit a detailed assessment of muscle function was performed, including MRC grading on a modified 10-level scale [13], measurement of isometric muscle strength in 20 upper and lower limb muscle groups and functional assessments, and the serum CK level was measured. Details of any recent changes in drug therapy were recorded in patients seen at the time of a relapse.

Relapses were defined as: (i) A reduction in muscle strength of sustained or progressive nature with elevation of the baseline serum CK activity (*clinical relapse*). The change in muscle strength was considered to be significant if there was a change of ≥ 1 MRC grade or ≥ 20 % reduction in isometric strength in two or more muscle groups in the upper and lower limbs. Only a minority of relapses were not associated with a CK elevation. These were only classified as relapses if the possibility of steroid myopathy could be confidently excluded on the basis of a low steroid dose (prednisolone < 10 mg/day or < 20 mg on alternate days) and, when performed, EMG findings were confirmatory of active myositis (i. e. spontaneous activity in addition to myopathic motor unit changes); (ii) An elevation of the serum CK activity to 3 times or more above the previous baseline level which was progressive and sustained and which could not be accounted for on the basis of excessive physical activity or other causes (*biochemical relapse*); (iii) The appearance or reactivation of previously quiescent skin changes in patients with DM (*cutaneous relapse*).

Statistical comparisons of relapses between the 4 seasons were made using χ^2-tests. Because of the small number of patients with pure PM these were combined with the overlap cases with PM for the purposes of the statistical analysis.

Results

A total of 42 relapses occurred in the DM group (16 patients) and 38 relapses in the PM group (15 patients) during the period of follow-up. In the DM group 25/42 relapses were clinical (myositic) relapses (16 with an associated cutaneous relapse), 8 were biochemical relapses only, and 9 were cutaneous relapses only (Table 1). In the PM group 19/38 relapses were clinical relapses and 19/38 were biochemical (Table 2). Most relapses occurred in patients who were on stable maintenance therapy (51 %) or off treatment (15 %), while the remainder occurred during periods when corticosteroid or immunosuppressive therapy was being changed (Tables 1 and 2).

In the DM group (Table 1), the incidence of clinical relapses was significantly higher during summer than autumn (χ^2=4.367, p=0.036) and winter (χ^2=9.921, p=0.002) but not spring (χ^2=3.125, p=0.07). Cutaneous relapses were also significantly more frequent in summer (χ^2=7.768, p=0.006) than in winter in the DM group, but not significantly different from those in spring or autumn. In the PM group (Table 2), the incidence of clinical relapses was more evenly distributed with no significant differences between the 4 seasons but, in contrast to the DM group, was lowest in summer. There were no significant differences in seasonal relapse frequency between the isolated PM and PM-overlap subgroups of patients (data not shown). Biochemical relapses were more common in the PM group, accounting for 50 % of relapses, than in the DM group (19 %), and did not show significant seasonal variation in either group.

To eliminate the possible confounding effect of treatment changes, the data for clinical relapses were re-

Table 1 Seasonal breakdown of relapses in the dermatomyositis group of patients

	Summer	Autumn	Winter	Spring
Muscle relapses				
Clinical	12/25[2] (48 %)	5/25 (20 %)	2/25 (8 %)	6/25 (24 %)
Biochemical	1 (12.5 %)	3 (37.5 %)	2 (25 %)	2 (25 %)
Cutaneous relapses[1]	10/25[2] (40 %)	6/25 (24 %)	2/25 (8 %)	7/25 (28 %)
Clinical relapses during treatment change	6	3	1	5
Clinical relapses during stable therapy or no treatment	6	2	1	1

[1] Includes both cutaneous relapses occurring alone or with a relapse of myositis
[2] Statistically significant (see text)

Table 2 Seasonal breakdown of relapses in the polymyositis group of patients

	Summer	Autumn	Winter	Spring
Clinical relapses	3 (16 %)	4 (21 %)	5 (26 %)	7 (37 %)
Biochemical relapses	7 (37 %)	5 (26 %)	3 (16 %)	4 (21 %)
Clinical relapses during treatment change	1	1	1	2
Clinical relapses during stable therapy or no treatment	2	3	4	5

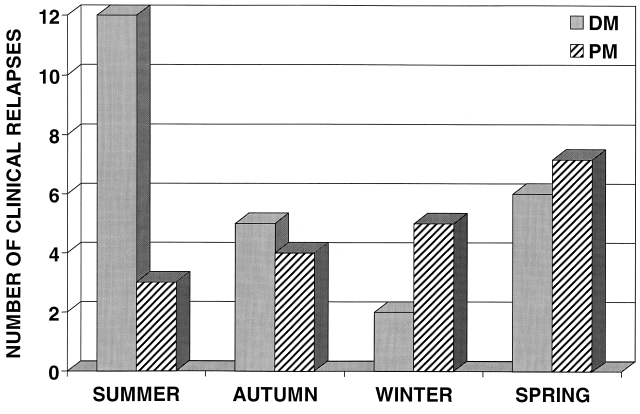

Fig. 1 Comparative seasonal distribution of clinical myositic relapses in the dermatomyositis and polymyositis groups.

analysed in patients who had been on steady maintenance therapy for at least 3 months or off treatment for at least 1 year. The number of clinical relapses in the DM group was again higher in summer (60% of relapses) than in the other 3 seasons, but the differences were not statistically significant because of the smaller numbers.

Discussion

Polymyositis and dermatomyositis are immune-mediated inflammatory myopathies which may occur in isolation or as part of a systemic connective tissue disease, or in association with other autoimmune diseases, retroviral infection or malignancy [14]. In PM there is invasion of muscle fibres by CD8+ T cells which induce cytotoxic injury and muscle fibre necrosis, whereas in DM a complement-dependent humoral attack on as yet unidentified endothelial cell antigens results in depletion of the endomysial capillary bed and ischaemic muscle damage [4, 10]. The factors responsible for initiating the autoimmune process remain uncertain, but genetic factors such as the MHC (B8, DR3) and polymorphisms in genes encoding certain cytokines and their receptors are thought to predispose to loss of tolerance [7, 19].

While earlier studies failed to show any consistent seasonal patterns of disease onset in the inflammatory myopathies [1], more recent studies have demonstrated some seasonal trends. In a study of PM-DM patients admitted to hospital in Greece a more frequent onset of symptoms during spring was found [9]. A similar trend was also found in the subgroup of patients with inflammatory myopathy and anti-Jo 1 antibody in a study in the United States [8]. In a large study of juvenile DM from the United States more children were found to have onset of symptoms during the summer months (June to September) [16]. The present findings in a group of patients with adult DM indicate that reactivation of both the myositis and the cutaneous manifestations of the disease is also more likely to occur during summer and spring. On the other hand, in PM no significant seasonal trends were found suggesting that different factors may be involved in reactivating the disease process in the two conditions.

The possibility that intercurrent infections may be involved in the initiation or reactivation of the inflammatory myopathies has received little attention, although a possible link with Coxsackie B infection has been suggested in some studies [2]. As the present study was retrospective, we do not have data on intercurrent infections in our patients. However, it is known from laboratory surveillance data that the peak incidence for a number of viral (eg Echo 9, adenovirus 3, rhinovirus) and mycoplasma infections in Australia is during the spring and summer months [3].

It is becoming clear that the T cell receptor is relatively flexible in its recognition of peptide-MHC complexes and that many microbially-derived peptides have the potential to activate self-reactive T cells [18]. Further, the inflammatory cytokines generated during both adaptive and innate responses to infective agents create a cytokine milieu conducive to reactivation of autoreactive T cell clones [20]. Seasonal differences in the infective agents could result in activation of immune cells of differing specificities and the secretion of different sets of cytokines, so altering the antigenic specificity and the nature of the ensuing autoimmune response.

Another factor which could be relevant in DM is the greater exposure time to ambient light (i. e. the photoperiod) during summer and spring. It has been proposed that the duration of the photoperiod may be responsible for mediating hormonally-regulated seasonal changes in immune function [15]. The effect of increased exposure to ultraviolet light on local immune responses in the skin is complex. Ultraviolet light induces an influx of CD4+ T cells into the skin [6] and may alter local autoantigen exposure and promote the local release of pro-inflammatory mediators, such as IL–1 and TNFα. All could contribute to exacerbations of diseases such as DM [21]. Alternatively, exposure to ultraviolet light can have immunosuppressive effects [5]. The net effect of increased ultraviolet exposure on an individual is presumably determined by the strength and duration of exposure, the genetic make-up of the host and the presence of underlying disease. Perturbation of local or systemic immunoregulatory processes as a consequence of exposure to ultraviolet light could therefore play a part in disease reactivation in both muscle and skin in the inflammatory myopathies.

Further prospective studies of relapses in DM and PM, and their seasonal occurrence and temporal relationship to viral or mycoplasma infections and light exposure, are needed to throw further light on the mechanisms of disease reactivation in these conditions. Such studies may also have implications for the management of patients with inflammatory myopathies and for the prevention of relapses.

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