
Autosomal dominant undifferentiated spondyloarthropathy not related to the HLA system

We were interested to read the article by Kidd and colleagues1 on familial aggregation for undifferentiated spondyloarthropathy associated with HLA-B7. The authors described a single family in whom numerous members had a non-specific rheumatoid arthritis or enthesopathy, or both, which fulfilled the European Spondylarthropathy Study Group criteria for spondyloarthropathy2 in the absence of the HLA-B27 tissue type, coexistent psoriasis, or inflammatory bowel disease. They suggested that 'undifferentiated' spondyloarthropathy can be associated with genetic factors other than HLA-B27. We are in total agreement.

A few years ago, we studied a French family of 83 members distributed over five generations divided into four main branches, among whom 18 adult members had destructive arthropathy and enthesopathic changes.3,4 In all patients, the disease began between the ages of 18 and 32 years. It affected predominantly the wrists, fingers, shoulders, and peripheral entheses and progressed as an oligoarthritis, with intermittent inflammatory episodes lasting for one to three months. Axial involvement of the cervical and lumbar spine and the sacroiliac joints was also seen, but was not prominent. The sites of involvement seemed to be influenced by mechanical factors. The right wrist was generally the first joint to be affected. Destructive abnormalities, followed by bony proliferation, and intra- or extra-articular bony ankylosis were the main radiological features of this familial arthropathy (figure).

The transmission of the disease was dominant and autosomal, with 100% penetrance. The clinical and radiological features were strikingly similar in all patients with successive generations and different branches of the genealogical tree, suggesting monogenic transmission. HLA typing of 12 patients and 13 healthy family members was performed. No HLA antigen was linked to the disease. None of the affected subjects had antigens B27, DR4 or DR7. The disease was not transmitted with any particular HLA haplotype.

Tests for rheumatoid factor yielded negative results. There was no history of psoriasis or chronic enteropathy in the members of this family. In none of the 18 patients did the arthropathy fulfill the American Rheumatism Association criteria.3 A diagnosis of ankylosing spondylitis was also eliminated, because the New York criteria were not fulfilled.4 This familial arthropathy could belong to the class of undifferentiated spondyloarthropathies proposed by Bouchier and Calin.5 The spondyloarthropathies have in common a non-specific inflammation of the entheses, involving both the chondrified and the calcified parts. After a destructive phase, which causes bony erosion, repair takes the form of ossification.4,6 An inherited abnormality in the collagen matrix of the entheses may predispose to destructive arthropathy and enthesopathic changes. Linkage analysis with HLA-COL2A1 as the disease causing locus in this family.9 Further studies are needed to identify the genetic locus responsible for the disease.

A GAUCHER
F PERE
P GILLET
F DELLESTABLE
Department of Rheumatology, URA CNRS 1288,
CHU of Nancy Brabois, Rue du Morand,
54511 Vandoeuvre la Nancy, France

Correspondence to: A. Gaucher.

LETTERS TO
THE EDITOR

HLA associations of systemic lupus erythematosus in Chinese from Singapore

A role for genetic factors in systemic lupus erythematosus (SLE) is strongly suggested by the substantial excess recurrence of the disease in monogamous dizygotic twins.1 Genes within the major histocompatibility complex (MHC) contribute to SLE, but it has proved difficult to establish the precise locus(i) involved. Studies of pedigrees from diverse ethnic backgrounds can help to identify these loci for two reasons: first, there are substantial differences in gene frequencies (for example HLA-B27 frequencies) between races; second, different MHC haplotypic combinations of alleles in different races can help to identify the primary relationships with disease, rather than those secondary to linkage disequilibrium. In white populations there has been some association with HLA-DR3 and -DR2, but studies from south east Asia, while revealing a strong association with DR2 in Koreans2 and Chinese from Hong Kong3 and Malaysia,4 did not reveal the association with DR3 observed in white subjects.

We studied HLA-DRB1 and -DQBI alleles in 26 Chinese SLE patients (25 females attending the National University Hospital in Singapore, and in 77 Chinese controls from the same area. All patients met four or more of the American Rheumatism Association criteria for SLE. The mean age was 36 years (range 20-64), and the duration of disease was 7-1 years (range 1-20). Patients with any non-Chinese ethnicity (Indians, Malayans, Europeans) were excluded. Different involvement was present in 57% of the patients, arthritis in 46%, malar rash in 36%, central nervous system involvement in 21%, photosensitivity in 7-1%, and discoid lupus in 3-6%. Anti-nuclear antibodies were present in 96% of patients and 92% had dsDNA antibodies.

HLA-DRBI alleles were assigned by polymerase chain reaction (PCR) amplification of genomic DNA probe with sequence specific oligonucleotides.1 HLA-DQBI alleles were typed by PCR using sequence specific primer pairs.6 The statistical significance of differences between the groups was assessed using the x2 test. The table shows the DR and DQ frequencies. There were non-significant increases in DR3, DR8, and DR9, but not in DR2. Furthermore, DQ2 and DQ6001 were increased in the patients, but this was almost certainly due to linkage with DR3 and DR9, respectively. None of the DR or DQ antigens was associated with particular clinical manifestations of SLE.

Our data are interesting with respect to other published results from Asian populations. HLA-DR9, for instance, was found to be increased in Chinese SLE patients from Hong Kong5 and Korea, in whom there was
HLA-DR and DQ antigen frequencies observed in SLE patients and controls from Singapore

<table>
<thead>
<tr>
<th>Antigen</th>
<th>SLE (n = 26)</th>
<th>Controls (n = 77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DR1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>DR2</td>
<td>7</td>
<td>26-9</td>
</tr>
<tr>
<td>DR3</td>
<td>8</td>
<td>26-9</td>
</tr>
<tr>
<td>DR4</td>
<td>2</td>
<td>26-9</td>
</tr>
<tr>
<td>DR5</td>
<td>0</td>
<td>17-21</td>
</tr>
<tr>
<td>DR6</td>
<td>0</td>
<td>21-22</td>
</tr>
<tr>
<td>DR7</td>
<td>0</td>
<td>9-1</td>
</tr>
<tr>
<td>DR8</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>DR9</td>
<td>23-6</td>
<td>13</td>
</tr>
<tr>
<td>DQ1</td>
<td>1</td>
<td>9-1</td>
</tr>
<tr>
<td>DQ2</td>
<td>7</td>
<td>6-13</td>
</tr>
<tr>
<td>DQ3</td>
<td>3</td>
<td>5-15</td>
</tr>
<tr>
<td>DQ4</td>
<td>2</td>
<td>15-9</td>
</tr>
<tr>
<td>DQ5</td>
<td>2</td>
<td>7-7</td>
</tr>
<tr>
<td>DQ6</td>
<td>1</td>
<td>5-15</td>
</tr>
<tr>
<td>DQ7</td>
<td>0</td>
<td>11-7</td>
</tr>
<tr>
<td>DQ8</td>
<td>0</td>
<td>10-7</td>
</tr>
<tr>
<td>DQ9</td>
<td>1</td>
<td>12-9</td>
</tr>
</tbody>
</table>

\[ *p \leq 0.05; \text{odds ratio} 2-0; 95\% \text{confidence interval} 0=51 \div 0=83; p \leq 0.09. \]

...a non-significant increase in DR8. However, our most striking finding was the absence of a DR2 association with SLE, as this has been found in the studies from Hong Kong and Korea1,3 and in a further study from Kuala Lumpur, Malaysia.3

One possible explanation for these differences could be genetic admixture in the Singapore Chinese population, as there has been extensive intermarriage with Malays, Indians, and Europeans since the seventeenth century. In contrast, Hong Kong Chinese rarely marry non-Chinese. This could explain the presence in the Singapore SLE patients of the typical white population SLE susceptibility haplotype carrying DR3 and DQ2. Another explanation could be ethnic heterogeneity among the southern Chinese. In Singapore, for approximately 75% of the Chinese migrated from Fujian Province, whereas 90% or more of the Hong Kong Chinese came from Guangdong Province. Unfortunately, the HLA distributions in these populations are not well characterised, but there may be significant differences which could have implications for the relative frequencies of MHC haplotypes (particularly DR2) predisposing to SLE in these populations.

MARTIN RUDWALEIT
KATHRYN GIBSON
PAUL WORDSWORTH
Nuffield Department of Clinical Medicine, John Radcliffe Hospital, Oxford, United Kingdom
KEVIN PILE
Queen Elizabeth Hospital, Woodville, Adelaide 5011, Australia
VERNON OH
National University Hospital, Singapore 119230

Correspondence to: Dr P Wordsworth, Nuffield Department of Clinical Medicine, John Radcliffe Hospital, Oxford OX3 9DU, United Kingdom

M Rudwaleit is supported by the Deutsches Akademisches Austauschdienst (DAAD). The authors are grateful for the financial support of the Arthritis and Rheumatism Council.


Treatment of refractory reflex sympathetic dystrophy with pamidronate

Reflex sympathetic dystrophy (RSD) is a condition affecting part of the whole of a limb, and is characterised by pain, vasomotor disturbance and trophic changes. RSD can persist for months or years and be severely disabling. Marked vasomotor disturbance, which is characterised by local osteoporosis, which corresponds to osteoclast hyperactivity. Calcitonin, an anti-osteoclastic drug, has been shown to help some patients. Pamidronate, a second generation bisphosphonate, is a potent anti-osteoclastic agent, which is the rationale for using it in the treatment of RSD.

In an open prospective study, we evaluated the efficacy of pamidronate in the treatment of refractory RSD. Eleven patients (three men and eight women; mean age 51-3 (SD 12-8) years) suffering from RSD of at least six months duration (mean of 14-6 (10-3) months) refractory to calcitonin and physical therapy, were included. All patients fulfilled Doury’s criteria for the diagnosis of RSD.1 The involved sites were the foot (n = 5), the hand (n = 2), the upper limb (n = 2), the knee (n = 1), the lesser limb (n = 1). In eight cases, the RSD was related to local injury. Six patients had had to stop work because of RSD.

Radiographs of the affected sites showed osteoporosis in all cases. The patients were given 30 mg of intravenous pamidronate in 500 ml of saline over four hours, daily, for three consecutive days. The patients received no standard treatment for their RSD from one month before the administration of pamidronate until three months after it. Patients were assessed by the same observer at baseline and after one and three months. Evaluation included the visual analog scale for pain (VAS), and a physician global assessment (no improvement, moderate, significant or excellent improvement) based on objective signs on clinical evaluation (hypertrophic changes, joint stiffness). Blood cell count and serum calcaemia (corrected with serum albuminaemia) were measured before, during, and one and three days after the administration of pamidronate.

The mean VAS decreased from 58-8/100 (20-2) before therapy, to 41-1/100 (26-8) at one month (p < 0-05; Wilcoxon paired test) and 33-8/100 (29) at three months (p < 0-01). In the physician global assessment, the results were: no improvement (n = 4), moderate improvement (n = 1), significant improvement (n = 3), and excellent improvement (n = 3) at one and three months. Three of the six patients who had had to stop work had returned to work after three months. We were unable to find predictive factors for efficacy (age, gender, affected site, degree of osteopenia). Pamidronate was well tolerated, apart from clinical minor adverse effects: two patients had a transient fever, two patients had mild, asymptomatic hyponcaemia (2-0 mmol/l) and one patient had hypocalcaemia (2 mmol/l) associated with pericardial paraeasthesia which resolved rapidly with oral calcium treatment (1 g/day).

It is not possible to say whether the observed improvements were attributable to the treatment, the natural history of the disease, or psychological factors, as pamidronate was not compared with placebo in a double blind trial. However, more than 50% of the patients suffering from chronic disease, previously refractory to treatment, showed significant or excellent improvement while taking pamidronate, suggesting that it was effective.

In conclusion, this study suggests that pamidronate is a safe and effective drug for the treatment of some refractory cases of RSD. Further double blind trials are required to confirm these results.

JEAN FRANCIS MAILLEFERT CHRISTINE CHATARD SUSANNAH OWEN THIERRY PERRE CHRISTIAN TAVIERNIER Department of Rheumatology, Hospital General, Dijon, France

JACQUES TEIB Department of Rheumatology, Centre Hospitalier Lyon-Sud, Pierre Bénite, France

Correspondence to: Dr J F Maillefert, Service de Rhumatologie, Hospital General, 3 rue du Pib Raines, 21000 Dijon, France.


Pericardial tamponade preceding cutaneous involvement in systemic sclerosis

Cardiac involvement in systemic sclerosis may be primary, or secondary to involvement of other organ systems. Primary cardiac involvement in systemic sclerosis may be manifested as pericardial disease, myocardial disease, conduction system disturbances, and cardiac arrhythmias.1 Cardiac symptoms do not usually appear until late in the disease, but exceptionally may precede the recog-