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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 recurrent seronegative arthropathy 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 in 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 fulfil the American Rheumatism Association criteria.⁵ A diagnosis of ankylosing spondylitis was also eliminated, because the New York criteria were not fulfilled.⁶ This familial arthropathy could belong to the class of undifferentiated spondyloarthropathies proposed by Burns and Calin.⁷ 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.^{8,9} An inherited abnormality in the collagen matrix of the entheses may predispose to destructive arthropathy and enthesopathic changes. Linkage analysis excluded COL2A1 as the disease causing locus in this family.¹⁰ Further studies are needed to identify the genetic locus responsible for the disease.

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Radiograph of the right wrist of a 29 year old female patient (disease duration six years), showing destruction of the radiocarpal joint.

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 monozygotic compared with 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. Studying populations from diverse ethnic backgrounds can help to identify these loci for two reasons: first, there are substantial differences in gene frequencies (for example HLA) between different 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. Previous studies in white populations have shown associations with HLA-DR3 and -DR2;^{2,3} however, studies from south east Asia, while revealing a strong association with DR2 in Koreans⁴ and Chinese from Hong Kong⁵ and Malaysia,⁶ did not reveal the association with DR3 observed in white subjects.

We studied HLA-DRB1 and -DQB1 alleles in 26 Chinese SLE patients (25 female) attending the National University Hospital in Singapore, and in 77 Chinese controls from the same area. All patients met four or more American Rheumatism Association criteria for SLE. The mean age was 36 years (range 20-64), and mean disease duration 7.1 years (range 1-20). Patients with any known non-Chinese ethnicity (Indians, Malaysians, Europeans) were excluded. Renal 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-DRB1 alleles were assigned by polymerase chain reaction (PCR) amplification of genomic DNA probed with sequence specific oligonucleotides.⁷ HLA-DQB1 alleles were typed by PCR using sequence specific primer pairs.⁸ The statistical significance of differences between the groups was analysed using the χ^2 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 DQ*0601 were increased in the patients, but this was almost certainly due to linkage with DR3 and DR8, 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

Antigen	SLE (n = 26)		Controls (n = 77)	
	n	%	n	%
DR1	0		0	
DR2	7	26.9	21	27.3
DR3	7	26.9 *	12	15.6
DR4	7	26.9	17	22.1
DR7	0		7	9.1
DR8	7	26.9	13	16.9
DR9	9	34.6	19	24.7
DR10	1	3.8	4	5.2
DR11	2	7.7	12	15.6
DR12	5	19.2	20	26.0
DR13	1	3.8	3	3.9
DR14	1	3.8	9	11.7
DQ2	6	23.6	13	16.9
DQ4	4	15.3	9	11.7
DQ5	7	26.9	18	23.4
DQ6	15	57.7	33	42.8
DQ*0601	10	38.4	23	29.9
DQ*0602	3	10.7	7	9.1
DQ*0603-8	2	7.6	3	3.9
DQ7	7	26.9	31	40.3
DQ8	5	19.2	8	10.4
DQ9	8	30.7	25	32.5

* $\chi^2 = 0.99$; odds ratio 2.0; 95% confidence interval 0.51 to 7.83; $p = 0.09$.

also a non-significant increase in DR8.⁴ However, our most striking finding was the absence of a DR2 association with SLE, as this had been found in the studies from Hong Kong and Korea^{4,5} and in a further study from Kuala Lumpur, Malaysia.⁶

One possible explanation for these differences could be genetic admixture in the Singapore Chinese population, as there has been some 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 example, 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.

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

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Treatment of refractory reflex sympathetic dystrophy with pamidronate

Reflex sympathetic dystrophy (RSD) is a condition affecting part or 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.¹ On radiographs, it is characterised by local osteoporosis, which corresponds to osteoclast hyperactivity. Calcitonin, an anti-osteoclastic drug, has been shown to help some patients.² Pamidronate, a second generation bisphosphonate, is a potent anti-osteoclastic agent,³ 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.⁴ The involved sites were the foot (n = 5), the hand (n = 2), the upper limb (n = 2), the knee (n = 1), the lower 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 osteopenia 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 consisted of a visual analogue scale for pain (VAS), and a physician global assessment (no improvement, moderate, significant or excellent improvement) based on objective signs on clinical evaluation (hyperhidrosis, vasomotor 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 classical minor adverse effects: two patients had a transient fever, two patients had brief, asymptomatic hypocalcaemia (2.05 mmol/l) and one patient had hypocalcaemia (2 mmol/l) associated with perioral paraesthesia 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.

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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 abnormalities, or cardiac arrhythmias.¹ Cardiac symptoms do not usually appear until late in the disease, but exceptionally may precede the recog-