LETTERS TO THE EDITOR

HLA Antigens in Familial Behçet’s Disease in Ireland

Sir—The occurrence of Behçet’s disease (BD) in several siblings in a single family is rare. We report an Irish family in whom three siblings had BD and shared an identical HLA phenotype. This is the first report of a familial incidence of BD in an Irish family.

The family pedigree is shown in Fig. 1. Both parents and one child were deceased (from non-BD causes); six of the remaining 10 family members were available for evaluation. HLA class I typing was carried out using the standard NIH microlymphocytotoxicity method; local, 9th and 10th HLA Workshop antisera were used [1]. Class II antigens were determined by the Taq1 restriction fragment length polymorphism (RFLP) technique using cDNA probes for pRTV1, pII-β-I and pDCH1; indistinguishable DRB RFLP patterns were inferred from the DQ RFLP type in European Caucasoid populations [2]. Expected frequencies for the HLA alleles were taken from the National Tissue Typing Reference Laboratory (14 596 volunteer blood donors).

II-7: The 46-yr-old sister of the proband complained of polyarthritis of both knees at age 35 yr. This patient also had a history of recurrent orogenital ulceration and EN since age 15. Ocular examination was normal. Serologies were normal. HLA typing was A1, A2, B8, B44, DR2 and DR3.

II-9: The 45-yr-old brother of the proband developed aseptic meningitis at age 22 yr; 4 yr later, he developed recurrent oral ulceration. At age 32, he developed acute EN. Ocular examination was normal. Serologies were normal. HLA typing was A1, A2, B8, B44, DR2 and DR3.

II-10: The proband, a 41-yr-old woman, developed painful mouth ulcers at age 12 yr. At age 16, she developed severe genital ulceration, erythema nodosum (EN) and polyarthralgia. A diagnosis of BD was made. Physical examination revealed orogenital ulceration; the ocular examination was normal. Tests for ANA, RF, extractable nuclear antigen, and anti-double-stranded DNA, anti-cardiolipin antibody and complement levels were normal. The HLA type was A1, A2, B8, B44, DR2 and DR3.

II-11: The 45-yr-old brother of the proband complained of polyarthritis of both knees at age 35 yr. This patient also had a history of recurrent orogenital ulceration and EN since age 15. Ocular examination was normal. Serologies were normal. HLA typing was A1, A2, B8, B44, DR2 and DR3.

In this family, two sisters and a brother had BD and shared an identical HLA phenotype: A1, A2, B8, B44, DR2, DR3. Another male sibling with this phenotype had minor oral ulceration only, without any other clinical manifestations of BD. This suggests that although there may be a strong role for a susceptible HLA phenotype, exogenous environmental factors are also likely to contribute to the aetiology of BD. Three other siblings (two males and one female) had oral ulceration; another sister suffered from recurrent orogenital ulceration. The absence of ocular manifestations in the BD patients is remarkable, although it has been reported that uveitis may relate to the presence of HLA antigens in BD.
of HLA B51, which was notably absent in this family [3]. Studies on the influence of sex and the age of onset on disease severity in BD have shown that young, male patients have more severe disease (including uveitis) than older, female patients [4], a factor that may be relevant in the context of the family reported here.

This family is similar to a Spanish family reported recently in whom three sisters had BD and shared an identical HLA phenotype: A2, B51, Cw6, DR4, Dw53 and Dw7 [5]; all six siblings carried the HLA B51 allele. Interestingly, BD only affected females with this phenotype as both the father and one brother also shared this phenotype, but had no features of BD. The authors postulated that the female predominance may be related to hormonal factors.

Previous studies on HLA antigens and BD in Europeans have shown varying results. The HLA B51 allele confers a relative risk for BD of 5.8 in Italy, 7.8 in France and 1.7 in the UK [6]. Correlations have also been shown between BD and DR2 and DR7. DR7 has an association with uveal involvement in British patients [7]; Italian BD patients have increased expression of HLA Dw52 [8]. The prevalence of HLA B5 in the normal Irish population is 2%; the strength of its association with BD in Irish patients is unknown. A 1981 study described the immune status and blood fibrinolytic activity in six Irish BD patients in whom HLA B5 was specifically noted to be absent [9]. This concurs with the findings reported here. In the only other study of Celtic Caucasians that described 15 Scottish patients with BD, five (33%) had severe eye involvement and eight (45%) had significant gastrointestinal (GI) involvement; the overall prevalence of HLA B5 was 12% (2/15) [6]. Three patients with posterior uveitis had HLA DR7 and all of the patients with GI symptoms had either DR4 or DR7. The 33% incidence of eye disease in the Scottish BD patients contrasts with the absence of eye involvement reported here.

In summary, we suggest that the familial incidence of BD in Ireland may not be explained solely on the basis of a susceptible genetic haplotype. The actual contribution of the MHC to the genetic predisposition to BD is unknown and it is possible that multiple minor predisposing genes, in addition to the major MHC, are important in the development of BD. The HLA phenotypes and clinical features in this Irish family are different from those previously reported. The absence of HLA B51, as well as the lack of eye involvement, in these BD patients are notable. BD in Ireland is likely to be clinically and immunogenetically heterogeneous, and may be less severe than that seen in patients from Japan and the Middle East.

S. M. Sant, D. KilMartin,* R. A. Acheson* Departments of Rheumatology and *Ophthalmology; Mater Misericordiae Hospital, Eccles Street, Dublin 7, Ireland Accepted 5 June 1998

Correspondence to: S. M. Sant, Division of Rheumatology, University of Michigan Medical Center, 5522 MSRB1, PO Box 0680, Ann Arbor, MI 48109-0030, USA.


Risk Factors for Thrombotic Events in Giant Cell Arteritis and Polymyalgia Rheumatica

Sm—We read with great interest the article by Manna et al. [1] concerning the relationship between the occurrence of antiphospholipid antibodies (aCL) in patients with giant cell arteritis (GCA) and/or polymyalgia rheumatica (PMR) at onset and during follow-up. No correlations between ischaemic events and aCL were found, suggesting that the aCL positivity is not an important factor for the development of vascular complications in GCA/PMR patients.

Recent reports on the presence of aCL and the development of thrombotic events during the course of GCA/PMR are discordant [1, 2]. On the other hand, lipoprotein (a) [Lp(a)] has been suggested to be an important risk factor for the vascular complications in patients with other rheumatic diseases [3, 4]. In the light of these observations, we report our recent experience concerning Lp(a) levels in relation to the positivity of aCL and associated thrombotic complications in patients affected by GCA/PMR.

Twenty-eight consecutive patients (20 women, eight men, mean age 71 ± 8 yr, range 62–83 yr) diagnosed as having PMR were included in the study [5]. Twenty patients showed an associated GCA. The diagnosis of GCA was based on the criteria of Hunder et al. [6]. Lp(a) concentrations were detected by ELISA using commercial kits (Terumo Medical Corp., Elkton, MD, USA). Serum IgG and IgM aCL were assayed by ELISA, as previously described (values were expressed as GPL and MPL units) [7]. The mean values (± s.d.) of 86 healthy subjects (15 GPL and 10 MPL units)
TABLE I
Clinical manifestations, localization of thrombotic events, anticardiolipin antibodies (aCL) and lipoprotein (a) [Lp(a)] levels in aCL-positive or negative patients with GCA/PMR and controls

<table>
<thead>
<tr>
<th>Patients with GCA/PMR</th>
<th>aCL positive</th>
<th>aCL negative</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients (%)</td>
<td>16/28</td>
<td>12/28</td>
<td>24</td>
</tr>
<tr>
<td>Age (yr ± s.d.)</td>
<td>72 ± 4</td>
<td>70 ± 6</td>
<td>70 ± 8</td>
</tr>
<tr>
<td>No. of patients with thrombotic events (%)</td>
<td>9/16</td>
<td>2/12*</td>
<td>1/24**</td>
</tr>
<tr>
<td>Arterial thrombosis</td>
<td>3</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial thrombosis in lower limbs</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombosis in central retinal artery</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>6</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Deep vein thrombosis in lower limbs</td>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Deep vein thrombosis in upper limbs</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>aCL isotype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgG (GPL units ± s.d.) (n = 12)</td>
<td>52 ± 16</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>IgG-IgM (n = 4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GPL units ± s.d.</td>
<td>46 ± 15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPL units ± s.d.</td>
<td>38 ± 11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lp(a) (mg/dl ± s.d.)</td>
<td>42 ± 12</td>
<td>18 ± 8*</td>
<td>10 ± 6**</td>
</tr>
</tbody>
</table>

Statistical analysis by Wilcoxon’s rank sum test.
*P = 0.01 vs aCL-positive GCA/PMR patients.
**P = 0.001 vs aCL-positive GCA/PMR patients.

were considered as cut-off for both IgG and IgM aCL levels. aCL and Lp(a) levels were determined before and during corticosteroid therapy at 3, 6, 9 and 12 months. Patients were grouped as aCL positive and aCL negative at onset with regard to aCL positivity (see Table I). Twenty-four age- and sex-matched subjects were used as controls (16 women, eight men, mean age 70 ± 7 yr, range 64–80 yr).

The thrombotic events (lasting <1 yr) were carefully assessed by a detailed clinical evaluation. The diagnosis of deep vein thrombosis was confirmed by Doppler ultrasound examination. Cerebral infarction was diagnosed by lesion noted on computed tomography. Retinal arterial thrombosis was diagnosed by funduscopy examination. The total group of patients with GCA/PMR was found to be affected by a significantly higher rate of venous and arterial thromboses compared to controls [n = 11/28 (39%) vs n = 1/24 (4%), respectively; P = 0.01]. As reported in Table I, thrombotic events were significantly higher in aCL-positive than in aCL-negative GCA/PMR patients and controls.

Lp(a) levels were significantly higher in all patients with GCA/PMR compared to the controls (32 ± 18 mg/dl vs 10 ± 6 mg/ml, respectively; P = 0.001), as well as significantly higher in aCL-positive than in aCL-negative GCA/PMR patients and controls (see Table I). Plasma levels of Lp(a) were significantly higher in aCL-positive GCA/PMR patients with thromboses than in aCL-positive patients without thromboses (54 ± 12 mg/dl vs 26 ± 10 mg/dl; P = 0.01).

Interestingly, Lp(a) concentrations in aCL-positive patients with arterial thromboses were significantly increased when compared to those with venous thromboses (72 ± 10 mg/dl vs 42 ± 11 mg/dl, respectively; P = 0.05).

Before corticosteroid therapy, aCL levels were positive in 13/20 GCA/PMR patients and 3/8 PMR patients. Generally, aCL positivity was of the IgG isotype (mean 52 ± 16 GPL units) in 12 patients and of both IgG and IgM isotype (mean 46 ± 15 GPL units and 38 ± 11 MPL units) in four patients. Furthermore, aCL levels appeared higher in GCA/PMR patients with thromboses than in patients without thromboses (68 ± 18 vs 42 ± 19 GPL units; P = 0.03).

After corticosteroid therapy, aCL levels returned to the normal range in 56% of patients with positive aCL at month 3, in 75% at month 6, in 81% at month 9 and in 87% at month 12. No relationship was found between the concentrations of Lp(a) observed at onset and after corticosteroid therapy in all GCA/PMR patients.

Our data seem to be in agreement with those of Manna et al. [1] confirming the high prevalence of aCL positivity in GCA/PMR patients, whereas we also found a significant correlation between aCL levels and vascular complications. In addition, this study suggests that a large number of GCA/PMR patients with elevated levels of aCL and Lp(a) at onset show an increased risk of developing thrombotic events. Furthermore, the association of increased levels of aCL and Lp(a) might be considered an independent
prognostic marker for the development of the vascular complications in a subgroup of GCA/PMR patients.

B. SERIOLO, M. CUTOLE, A. GARNERO, S. ACCARDO
Division of Rheumatology, Department of Internal Medicine, Viale Benedetto XV, 6, 16132 Genova, Italy
Accepted 19 May 1998


Reply: Thrombotic Events in Giant Cell Arteritis

Sir—We are surprised about the unexpected high prevalence of deep vein thrombosis (21%) in the reported giant cell arteritis (GCA) series, since GCA is a vasculitis affecting only arterial vessels. In our clinical experience, and also in literature reports, venous thrombosis is a rare event in GCA [1] and so we think that there has been a bias in patient referral and/or selection.

In their study, the authors found a correlation between anticardiolipin antibody (aCL) levels and thrombotic events, but they considered arterial and venous thrombosis together, without a distinction between GCA and polymyalgia rheumatica; therefore, the evaluation of these results is difficult, since the population with only arterial thrombosis is very small (three patients). As we stated, venous thrombosis is a rare event in GCA and in most cases is not due to the vasculitic process, but more likely to a complication of steroid treatment [2].

The results of several studies have reported that aCL are associated with an increased risk of arterial or venous thrombosis [3, 4]; for this reason, in our study we wanted to point out that thrombotic events in GCA do not seem to be due to aCL activity, but possibly to the vascular inflammation and endothelial alterations by themselves. In this view, we found it very interesting that the authors found higher lipoprotein (a) [Lp(a)] levels in those patients with either aCL or arterial thrombosis, in opposition to those with venous thrombosis. Hypofibrinolysis due to increased Lp(a) levels could promote thrombotic events in the arterial wall damaged by the inflammatory process.

We think that it would be interesting to correlate the incidence of ischaemic events due to arterial thrombosis with Lp(a) levels in a larger population of patients with GCA, and to evaluate the hypothesis that Lp(a) could represent a risk factor for arterial ischaemic events independently from aCL.

R. MANNA, M. LATTERI, G. CRISTIANO, L. TODARO, G. GASBARRINI
Department of Internal Medicine, Catholic University of the Sacred Heart, Rome, Italy
Accepted 19 June 1998

Correspondence to: R. Manna, Istituto di Medicina Interna e Geriatria, Policlinico A. Gemelli, L.go F. Vito, 8, 00168 Roma, Italy.


Re: Use of Cyclic Etidronate and the Prevention of Non-vertebral Fractures

Sir—Although the van Staa et al. [1] paper presents interesting observational data on the use of etidronate in post-menopausal osteoporosis, the limitations of this study need to be clearly elucidated. Randomized control trial data are the standard for medical efficacy and side-effects. In the absence of this quality of data, medical regulatory agencies and physicians are reluctant to recommend changes to the care of their patients.

The trial structure is unusual, even for observational data. The criteria for the diagnosis of osteoporosis requiring therapy and for osteoporosis not requiring therapy are not known. Perhaps it would have been clearer to present only the etidronate group, as, in these patients, we do know that a physician has decided that they have osteoporosis and merit therapy.

Between treatment and non-treatment groups, it is not clear whether there has been a significant reduction in the rate of vertebral fractures. However, within the etidronate group, incident vertebral fractures are decreased after a variable period of follow-up. Details on the reasons for discontinuing therapy are not given and we are not sure whether patients remaining on therapy longer might be those who have had more success with therapy. Other measures known to impact upon fracture risk in this group, such as activity, fall prevention, calcium intake and vitamin D nutrition, are not elaborated on.

The non-therapy group were not given therapy for reasons known only to the treating physician. Perhaps they were too frail, had problems ambulating, were less insistent, chose to neglect their health, etc. Any of these factors might increase their risk of future fracture and bias the comparison. If there were adjustments
made for confounding variables (p. 88), it is essential to know what these were and what adjustment was made. As far as we can discern, the groups were not comparable at baseline with respect to vertebral fractures, back pain, steroid use, and prior use of HRT. There was no standardized method of determination of the diagnosis of osteoporosis or of collection of vertebral fracture data.

Although observational data can be useful in planning definitive studies, we agree with the authors that the limitations in their dataset underscore the need for a randomized control trial to determine the non-vertebral fracture efficacy of cyclic etidronate in the therapy of osteoporosis.

D. Kendler, A. A. Khan

Department of Medicine, University of British Columbia, Vancouver, BC and *Department of Medicine, McMaster University, Hamilton, Ontario, Canada

Accepted 19 May 1998


Reply

We thank Drs Kendler and Khan for their interest in our study. We agree with them about the importance of randomized trials, but would like to emphasize the examples of the value of observational epidemiological studies. The field of osteoporosis provides one of the best examples of the limitations in their dataset underscore the need for a randomized control trial to determine the non-vertebral fracture efficacy of cyclic etidronate in the therapy of osteoporosis.


S. Kendler, A. A. Khan

Department of Medicine, McMaster University, Hamilton, Ontario, Canada

Accepted 19 May 1998


Reply

We thank Drs Kendler and Khan for their interest in our study. We agree with them about the importance of randomized trials, but would like to emphasize the examples of the value of observational epidemiological studies. The field of osteoporosis provides one of the best examples of the value of observational epidemiological research. The evidence for a protective effect of hormone replacement therapy against fractures and myocardial infarctions has been obtained, in large part, from such studies. The results of any observational study, including this study, should be interpreted in the context of all available information. It is for this reason that observational studies, in some situations, have resulted in changes in labelling, drug reimbursement policies and physician practice.

T. P. Van Staa, L. Abenhaim, * C. Cooper

Procter & Gamble Pharmaceuticals, Staines, UK, *McGill University/Jewish General Hospital, Canada and †MRC Environmental Unit, Southampton, UK

Serum Dehydroepiandrosterone Sulphate Levels in Patients with Early Rheumatoid Arthritis: Positive Association with C-reactive Protein, but not with HLA-DR Genotype

Serum dehydroepiandrosterone sulphate (DHEAS) is a weakly androgenic steroid hormone synthesized as dehydroepiandrosterone (DHEA) by the adrenal glands. DHEAS circulates in higher and more stable levels than DHEA. Low serum levels of DHEAS have been found in female and (less impressively) in male patients with chronic (mean disease duration > 9 yr) rheumatoid arthritis (RA) [1–3]. DHEAS levels correlated positively with disease activity parameters [3]. A prospective community survey showed that women

Accepted 19 May 1998


Reply

We thank Drs Kendler and Khan for their interest in our study. We agree with them about the importance of randomized trials, but would like to emphasize the examples of the value of observational epidemiological studies. The field of osteoporosis provides one of the best examples of the value of observational epidemiological research. The evidence for a protective effect of hormone replacement therapy against fractures and myocardial infarctions has been obtained, in large part, from such studies. The results of any observational study, including this study, should be interpreted in the context of all available information. It is for this reason that observational studies, in some situations, have resulted in changes in labelling, drug reimbursement policies and physician practice.

T. P. Van Staa, L. Abenhaim, * C. Cooper

Procter & Gamble Pharmaceuticals, Staines, UK, *McGill University/Jewish General Hospital, Canada and †MRC Environmental Unit, Southampton, UK

Serum Dehydroepiandrosterone Sulphate Levels in Patients with Early Rheumatoid Arthritis: Positive Association with C-reactive Protein, but not with HLA-DR Genotype

Serum dehydroepiandrosterone sulphate (DHEAS) is a weakly androgenic steroid hormone synthesized as dehydroepiandrosterone (DHEA) by the adrenal glands. DHEAS circulates in higher and more stable levels than DHEA. Low serum levels of DHEAS have been found in female and (less impressively) in male patients with chronic (mean disease duration > 9 yr) rheumatoid arthritis (RA) [1–3]. DHEAS levels correlated positively with disease activity parameters [3]. A prospective community survey showed that women

Accepted 19 May 1998


Reply

We thank Drs Kendler and Khan for their interest in our study. We agree with them about the importance of randomized trials, but would like to emphasize the examples of the value of observational epidemiological studies. The field of osteoporosis provides one of the best examples of the value of observational epidemiological research. The evidence for a protective effect of hormone replacement therapy against fractures and myocardial infarctions has been obtained, in large part, from such studies. The results of any observational study, including this study, should be interpreted in the context of all available information. It is for this reason that observational studies, in some situations, have resulted in changes in labelling, drug reimbursement policies and physician practice.

T. P. Van Staa, L. Abenhaim, * C. Cooper

Procter & Gamble Pharmaceuticals, Staines, UK, *McGill University/Jewish General Hospital, Canada and †MRC Environmental Unit, Southampton, UK

Serum Dehydroepiandrosterone Sulphate Levels in Patients with Early Rheumatoid Arthritis: Positive Association with C-reactive Protein, but not with HLA-DR Genotype

Serum dehydroepiandrosterone sulphate (DHEAS) is a weakly androgenic steroid hormone synthesized as dehydroepiandrosterone (DHEA) by the adrenal glands. DHEAS circulates in higher and more stable levels than DHEA. Low serum levels of DHEAS have been found in female and (less impressively) in male patients with chronic (mean disease duration > 9 yr) rheumatoid arthritis (RA) [1–3]. DHEAS levels correlated positively with disease activity parameters [3]. A prospective community survey showed that women
had reduced serum levels of DHEA years before the onset of RA [4]. These data suggest that serum DHEAS may have value as a prognostic factor. Possible interactions between the HLA system, androgens and the immune system may be relevant in the aetiology or perpetuation of RA. Expression of the HLA genotype DR4 is a risk factor for developing RA [5, 6], and is associated with slightly lower serum levels of testosterone, the main androgenic steroid, in women with and without RA [7], but not so in male RA patients [5]. Since DHEAS levels are partly genetically determined [8], it could be hypothesized that DHEAS levels are also associated with DR4 expression. Here we report associations between serum DHEAS levels and disease activity parameters in patients with early RA, participating in the COBRA trial [9]. Furthermore, associations of the HLA-DR genotype and DHEAS levels were investigated.

A total of 155 patients (64 men and 91 women) with early RA, satisfying the American College of Rheumatology (ACR) 1988 criteria for RA, with a mean age of 49 (s.d. 12) yr and a median disease duration of 4 months (range 0–24), were included in a randomized trial [9]. Combination therapy, consisting of sulphasalazine (2 g/day), methotrexate (7.5 mg/week) and prednisolone (initially 60 mg/day, tapered in six weekly steps to 7.5 mg/day) (n = 76), was compared to sulphasalazine alone (n = 79). Baseline serum was available for 116 patients (75%; 47 men and 69 women; mean age 50 ± 12 yr): 60 receiving combination therapy and 56 sulphasalazine alone. The following disease activity parameters were assessed at baseline and after 56 weeks of treatment: erythrocyte sedimentation rate (ESR, Westergren method), C-reactive protein level (CRP), tender and swollen joint counts (68 joints), overall assessment by the independent assessor and the patient [on a visual analogue scale (VAS)], VAS patient’s pain assessment, grip strength (by vigorimeter), Health Assessment Questionnaire (HAQ, validated Dutch version) and disease activity score (DAS). Bone densitometry was assessed using a dual-energy X-ray absorptiometer at baseline in 95 patients. For the present study, the main outcome measures were the ACR 1995 20% response criteria and the European League Against Rheumatism (EULAR) response criteria based on the DAS. HLA-DR genotypes were available in 105 of 116 patients (Tissue Typing Laboratory, Maastricht University Hospital), being positive for DR1 in 27 patients, for DR2 in 21, for DR3 in 27 and for DR4 in 60. Serum samples at baseline were tested for DHEAS levels using a radioimmunoassay (Diagnostic Products Corporation, Los Angeles, CA, USA). The CRP level was logarithmically transformed before analysis to approximate normalization of its distribution. To compare differences in DHEAS levels between men and women, a Student’s t-test was used. Partial correlation coefficients were used to analyse associations between DHEAS levels and age, adjusting for sex, and between DHEAS levels and disease activity parameters, adjusting for sex and age. Multivariate analysis of variance was used to analyse associations between DHEAS levels and HLA-DR genotype and clinical response status (response and no response for ACR criteria; good, moderate and no response for EULAR criteria) after 56 weeks of treatment, after adjustment for sex, age and treatment status. Two-sided P < 0.05 was considered statistically significant.

Serum DHEAS levels, measured at baseline in RA patients, were in the normal range (range 0.5–14 μmol/l), and higher in male compared to female RA patients (5.5 ± 3.1 vs 3.7 ± 2.1 μmol/l; P < 0.001). DHEAS levels in RA patients did not differ significantly from those in 60 healthy controls and 30 outpatients with soft-tissue rheumatism, after adjustment for age and sex (P = 0.47, data not shown). The DHEAS level correlated negatively with age (r = −0.20, P = 0.03), and did not correlate significantly with body mass index (weight/height²), bone mineral density or disease duration. DHEAS levels were positively associated with CRP levels (r = 0.30, P = 0.001; Fig. 1), but not with any other parameter of disease activity at baseline. DHEAS levels did not differ significantly between subjects positive or negative for expression of HLA-DR1 (P = 0.94), HLA-DR2 (P = 0.13), HLA-DR3 (P = 0.17) and HLA-DR4 (P = 0.72; Fig. 1). After 56 weeks of treatment, patients who responded according to the ACR or EULAR criteria did not differ in baseline DHEAS levels from non-responders. Baseline DHEAS was not associated with any of the disease activity parameters after 56 weeks of treatment.

Our only positive finding is that DHEAS levels are associated with CRP levels at baseline. CRP levels are increased in RA as a consequence of the inflammatory process, which also leads to increased circulating cytokines, which can stimulate the hypothalamic–pituitary–adrenal (HPA) axis. Adrenocorticotropic hormone (ACTH), produced by the pituitary, will stimulate the adrenal cortex not only to produce cortisol, but also DHEAS [10]. In this respect, it is noteworthy that compared to controls the patients did not show decreased DHEAS levels, possibly reflecting a somewhat stimulated HPA axis. In these patients with early
RA, DHEAS levels may, therefore, be increased as part of an enhanced stress response. Under chronic RA conditions, however, adaptations of the HPA axis could take place, leading to increased ACTH and decreased cortisol levels [11]. This may also explain the low DHEAS levels that were found in chronic RA patients [1–3]. Hypoandrogenism in chronic RA may be the result of the chronic illness [12] or, alternatively, a consequence of long-term treatment with prednisone, instead of being of aetiological importance.

Our findings demonstrated no association between the DHEAS level and HLA-DR genotypes. The lack of association with HLA-DR4 could be due to the heterogeneity of DR4 subtypes, since no less than 28 different sequence variants have already been described [6]. We also did not find serum DHEAS to be of predictive value for the clinical outcome at 1 yr. Therefore, serum DHEAS in subjects already diagnosed with RA did not have prognostic value. We conclude that DHEAS levels are positively correlated with CRP levels in early arthritis, which may be the result of adrenal hypersecretion as part of a general stress response.

E. J. Giltay, A. C. Verhoeven,† D. van Schaardenburg,* C. Popp-Snijders, M. Boers,† L. J. G. Gooren, B. A. C. Dijkmans*

Institute of Endocrinology, Reproduction and Metabolism and *Departments of Rheumatology and †Clinical Epidemiology, Hospital Vrije Universiteit, Amsterdam and ‡Department of Internal Medicine, Maastricht University Hospital, Maastricht, The Netherlands

Accepted 18 June 1998

Correspondence to: E. J. Giltay, Department of Endocrinology, Division of Andrology, Hospital Vrije Universiteit, PO Box 7057, 1007 MB, Amsterdam, The Netherlands.

IgM according to the manufacturer’s instructions; captured serum immunoglobulin specific for CMV was detected using purified CMV antigen labelled with horseradish peroxidase, and o-phenylenediamine as substrate.

Twelve out of 15 (80%) of the FS patients with LGL expansions, 30 out of 37 (81%) of the FS patients without LGL expansions, 16 out of the 20 (80%) RA patients, 17 out of the 20 (85%) OA patients and 29 out of the 35 (83%) healthy controls were positive for IgG anti-CMV antibodies (indicative of past infection). χ² analysis revealed no significant difference (P > 0.99) in the proportions of CMV IgG positivity between groups; hence, there was not a higher prevalence among the FS patients nor between the FS patients with or without LGL expansions. We also investigated whether there was evidence for recent acute CMV infection or possible reactivation of latent virus by the presence of IgM anti-CMV antibodies. One FS patient with an LGL expansion, and two FS patients without LGL expansions, were positive for both IgG and IgM anti-CMV antibodies; the latter two being positive for RF. None of the RA or OA patients were positive for IgM anti-CMV antibodies, although one healthy control was positive for IgM antibodies. Furthermore, one FS patient with an LGL expansion who had both IgG and IgM anti-CMV antibodies had previously been shown to be positive for antibodies to HTLV-II ([12] FS/LGL3) and was also negative for RF. This finding was of interest because of evidence suggesting that CMV reactivation is able to transactivate retroviruses [11].

The above data do not suggest a general role for CMV infection or reactivation in the aetiology of FS over and above that in RA and OA. Previous studies in RA, using either PCR or antibody-based techniques to examine either the peripheral blood or synovial fluid for evidence of infection with CMV, have demonstrated variable results with no clear-cut role for CMV in RA [12–14]. Other human herpesviruses, such as human herpesvirus 6, 7 or 8, could be alternative candidate viruses in FS, but these have not yet been studied in this context. Furthermore, it is possible that other herpesviruses might transactivate human endogenous retroviruses [3] which through molecular mimicry, or by encoding a superantigen, may explain the paradox of detecting serum antibodies to retroviral products, but not PCR amplicons of exogenous retroviruses, in rheumatic patients [9].

P. N. NELSON, G. PINTO-BASTO,* A. SHIPP,* J. C. BOOTH (DECEASED),* J. S. LANCHBURY, G. S. PANAYI,† AND S. J. BOWMAN‡

Division of Biomedical Sciences, University of Wolverhampton, Wolverhampton WV1 1DJ, *PILLS Tooting, St George’s Hospital, Blackshaw Road, Tooting, London SW17 0QT, †Molecular Immunogenetics and Rheumatology Units, United Medical and Dental School, Guy’s Hospital, London SE1 9RT and ‡Department of Rheumatology, The Medical School, University of Birmingham, Edgbaston, Birmingham B15 2TT

Accepted 1 July 1998

Correspondence to: P. N. Nelson, Division of Biomedical Sciences, University of Wolverhampton, Wolverhampton WV1 1DJ.