Ankylosing spondylitis in west Africans—evidence for a non-HLA-B*27 protective effect

Dr Brown and his colleagues are to be congratulated for performing a logistically formidable, but necessary, epidemiological study testing the currently in vogue hypothesis that the B*2703 subtype of HLA-B27 is not related to ankylosing spondylitis (AS). They conclude that the B*2705 subtype, as well as B*2703, possesses a lower risk for developing AS in a group of B27 positive west Africans, the Fula from Gambia, when compared to B27 positive white subjects following the potential protective role of an environmental factor(s). This conclusion is based on an assumed risk of developing AS in B27 positive persons of 11.1% for men and 1.5% for women. In no cases of AS were found among 900 adult Fula men and 215 first degree relatives of 48 B27 positive Fula twin pairs. We would argue that the data warrant the more conservative conclusion implied in their discussion, namely, the risk for AS among B27 positive Fula subjects would need to be at least 2.7% in men and 1% in women to assign significance to the finding of no AS in this population.

The risk of developing AS in HLA-B27 positive subjects clearly varies among different ethnic groups, but it is now generally accepted that among white populations, the prevalence of AS is nearer 1–2% rather than 11.1%.

Tide Norges survey of 14 539 subjects quoted by the authors is in fact based on a highly selected sample of only 375 people responding positively to a questionnaire for low back pain or stiffness who actually turned up for examination and had x rays of sacroiliac joints. You arrive at entirely different conclusion if you apply the AS prevalence figures of 1.4% for B27 subjects from the Buselton population study of 1.3% of Dutch B27 positive subjects. The second study examined 2956 subjects older than 44 years who all had sacroiliac x rays and only three B27 positive subjects had AS according to the New York criteria leading to a prevalence of 0.1%. Recalculating the data of Brown et al according to these more generally accepted prevalence rates leads to the following conclusions. The probability of observing no cases of AS in 900 adult Fula men would be 46.9% (that is, p=0.47). The number of B*2703 persons expected to develop AS would be zero, as in fact observed in this population. Even assuming a risk of 2.7% for AS in B27 positive subjects, the likelihood that no cases of AS would be found in 900 adult Fula men is 23.2% (that is, p=0.232).

Furthermore, we calculate that the prevalence of AS in the population of B27 positive adult Fula men would need to be at least 5.54% before the finding of zero observed cases of AS in 900 adult Fula men would be statistically significantly different. We conclude that the issue of B*2703 and risk for AS remain an open question and in need of further more extensive population prevalence studies.

Authors’ reply

We would like to thank Dr Maksymowych for his interest in our study. We agree with his conclusion that our study shows that B27 is not associated with ankylosing spondylitis (AS) in the Gambia and that the risk of AS in B27 positive men is greater than 2.7% and women is greater than 1% (which we believe to be the case). We feel that most of his criticisms can be satisfactorily answered.

The risk of developing AS in B27 positive subjects is uncertain. The studies mentioned by Dr Maksymowych are among the lowest estimates that have been reported for white populations. Other studies have reported that as many as 20% of B27 positive subjects may develop the disease. The survey by Gran et al is by far the largest reported: 21 329 subjects were invited to participate in a study of cardiovascular disease, of whom 16 621 attended screening sessions. Of these, 14 539 (87%) completed questionnaires including questions about back problems; 2907 reported a history of pain or stiffness in the back—the majority were asymptomatic. From this group a random sample of 806 were invited to attend for clinical screening, of which 449 did; 375 of these had sacroiliac radiographs. Comparisons at each step demonstrated that selection bias was minimal. We believe therefore that not only is this study significantly larger than either of the studies mentioned by Dr Maksymowych, but is also reliable. It is also the only study of sufficient size to determine the risk for AS among men and women with B27 separately, which was a requirement for our analysis.

The risk for AS among B27 positive men is significantly greater than B27 positive women. In our study 1008 participants were male and 107 female. Therefore it was important to use sex-specific risk estimates, which Dr Maksymowych has not used in his calculations. Also, the study examined 215 relatives of 48 B27 positive subjects in addition to the 900 adult Fula men used in Dr Maksymowych’s calculations. Analysing the total study population (n=1115), we showed that the risk associated with B27 in the Gambia (p<0.005), assuming that the risk of AS was ≥1.85% in B27 positive subjects, and that men were 2.7 times more likely to develop disease than women (both of these estimates are conservative). Using a higher male/female ratio would allow us to exclude even lower degrees of association of B27 with AS.

Our study confirmed the previous finding that AS is extremely rare in west Africa—indeed no case has yet been reported from the Gambia. This is despite the prevalence of B27 being as high as 7.8% in some ethnic groups. The fact that 68% of B27 positive subjects in this area carry B*2705 indicates that it is not a difference in B27 subtypes that explains the rarity of the disease. Furthermore, two separate groups have now reported cases of AS in B*2703 subjects.

It remains possible that B*2703 has a lower risk for AS than other disease-prone HLA-B27 subtypes. However AS is not associated with either B*2703 or B*2705 in the Gambia. Future comparisons of the strength of association of B27 subtypes with AS need to consider differences in allele frequencies and genetic differences between the different populations studied.

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LETTERS

Serum uric acid in acute gout

The relation between gout and uric acid is such that in general clinical practice there is a tendency (diminishing) to misdiagnose gout in the presence of hyperuricaemia. Conversely the diagnosis of gout may be rejected when a normal serum uric acid (SUA) value is found. Given that a high proportion of estimations are made at the time of the acute episode a correct diagnosis may depend on a practitioner’s knowledge of the fact that the SUA may be within the ‘normal range’ at this time. Most, if not all rheumatologists, are
Giant cell arteritis of the leg in a patient with hepatitis C virus infection

The potential association of chronic hepatitis C virus (HCV) infection with a variety of dermatological features has been reported. In particular, it has been observed that different types of cutaneous vasculitis may develop during the course of HCV infection, such as mixed cryoglobulinaemia related leucocytoclastic vasculitis and polyarteritis nodosa.

We report a case of giant cell arteritis (GCA) involving the medium sized dermal arteries of the right leg, which appeared after a long history of HCV infection.

A 44 year old man with an eight year history of chronic hepatitis was admitted to the Rheumatology/Clinical Immunology Units of the University of Pisa in July 1995 because of erythematous cutaneous nodules on the legs. Chronic hepatitis had been suspected since 1987 because of raised, fluctuating values of hepatic enzymes. In 1993 the diagnosis was confirmed by liver biopsy. In June 1995 the presence of anti-HCV antibodies was demonstrated by an ELISA test. From the time of the histopathological assessment of chronic hepatitis to that of the appearance of the cutaneous nodules the patient was not receiving any medical treatment.

At the time of his stay in hospital the patient underwent a complete physical examination, which showed no abnormalities except for the cutaneous lesions. These were tender, red, and painful nodules situated on the medial side of the right leg, which appeared to be confluent in some areas.

Routine laboratory investigation showed only a moderate increase of the acute phase reactants (erythrocyte sedimentation rate 20 mm 1st h, C reactive protein 2.9 mg/dl, fibrinogen 600 mg/dl).

Antineutrophil cytoplasmatic antibodies (ANCA), antinuclear antibodies, immune complexes, and cryoglobulins were absent. Hepatitis B virus markers (antibodies to hepatitis B, anti-HBc, and anti-HBe, and HBs and HBe antigens) were not detected in the serum, nor were the antibodies anti-HIV1 and -HIV2.

On the contrary, anti-HCV antibodies were found using a third generation ELISA test (Abbott HCV EIA 3.0, Abbott Diagnostics, Wiesbaden-Dielenheim, Germany). A qualitative ‘dot’ assay (Abbott HCV MABTRIX, Abbott Diagnostics, Wiesbaden-Dielenheim, Germany) showed that these antibodies were directed to the HC34 core antigens. c-100-3 NS4, HC-23 NS4 viral recombinant antigens and HC-29 NS3 recombinant proteins, while there was no serological reactivity against the c-100-3 NS4, HC-23 NS4 viral recombinant antigens.

The presence of viral RNA (indicative of active HCV replication) in the serum was demonstrated by a polymerase chain reaction
The granulomas that may develop are composed of numerous mononuclear cells. Eosinophils are present in very limited amounts (no more than 2% of the infiltrating cells) (magnification ×200, haematoxilin and eosin stain).

**Figure 1.** (A) Medium sized artery with acute and chronic transmural inflammation without signs of extension of the process to the surrounding tissue. The lumen is partially obstructed by a thrombus (magnification ×40, haematoxilin and eosin stain). (B) A typical Langhans-type giant cell can be clearly seen in the upper left corner. Other giant cells are barely discernible along the lower edge. The infiltrate is mainly constituted of granulocytes and mononuclear cells. Eosinophils are present in very limited amounts (no more than 2% of the infiltrating cells) (magnification ×200, haematoxilin and eosin stain).

(C) 5' UTR, Roche Diagnostic Systems, Branchburg, NJ, USA. The viral genotype was 2a (Inno-LiPA HCV, Nuclear Laser Medicine, Milan, Italy). Liver biopsy showed a mild, chronic hepatitis that was classified as grade 2, stage 2 according to a recently proposed scoring system. A skin biopsy specimen taken from a nodular lesion on the right leg showed inflammation and thrombosis of a medium sized dermal artery with presence of a number of Langhans type multinucleate giant cells (Fig 1). An immunohistochemical procedure, using an anti-CD68/P1 monoclonal antibody (DAKO, Glostrup, Denmark) showed a specific staining of the multinucleate giant cells, this confirming that those cells were monocytic/macrophagic elements in origin. On the way, this feature could be considered suggestive of a giant cells arteritis. An angiomatous of the coeliac axis and the superior mesenteric artery did not show any aneurysmal dilatations in the small and medium sized arteries suggestive of polyarteritis nodosa. A clinical examination was completed that excluded any other infectious, immunomediated or neoplasic disorders, which could potentially be linked to the presence of granulomatous lesions of the medium sized arteries. Corticosteroid therapy (6-methylprednisolone 16 mg per day) was started and was progressively tapered to a low dose maintenance regimen of 4 mg. The cutaneous lesions completely disappeared within four weeks after beginning this treatment.

In the patient described here GCA developed in limited areas in the skin of the right leg during the course of a chronic HCV infection. The persistence of HCV infection was demonstrated by the presence of anti-HCV antibodies, and of viral RNA in the liver histopathology. This case adds yet another to the list of the different vasculitides that may be associated with HCV infection, and in addition provides support for the interesting, but as yet unproved hypothesis that granulomatous vasculitides of the medium sized vessels, including giant cell arteritis, may be an antigen driven process, possibly triggered by an infectious agent.  

**Long term follow up of von Willebrand factor and plasminogen activator inhibitor-1 in patients with polymyalgia rheumatica**

In polymyalgia rheumatica (PMR) subclinical vasculitis is suggested in the pathogenesis of the disease. von Willebrand factor (vWF), produced by endothelium and megakaryocytes, is an important haemostatic factor. In healthy people with ABO blood group O, vWF values are lower than in people with a blood group other than O. Increased plasma concentrations of vWF indicate endothelial damage and are found in diseases that involve blood vessels including vasculitis. In PMR and patients with high vWF concentrations persist after acute phase proteins are normalised, but a gradual decline over time is also reported. Plasminogen activator inhibitor-1 (PAI-1) is an inhibitor of tissue plasminogen activator and is released from endothelial cells. Decreased fibrinolysis because of increased plasma concentrations of PAI-1 was found in patients with vasculitis, cryoglobulinemia, and chronic liver disease. Effective therapy with interferon-α. Dig Dis Sci 1995;40:1221–4.

of corticosteroid treatment on these values were also evaluated.

Thirty seven patients (25 women, 12 men), mean (SD) age 70 (8) years, with PMR (criteria of Bird et al.

Table 1 Laboratory data in 31 patients with PMR at diagnosis and at follow up after a median time of 5.8 years. Data are presented as medians and (interquartile range) and core analysed using Wilcoxon signed rank test

<table>
<thead>
<tr>
<th>Variables</th>
<th>At diagnosis</th>
<th>At follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR (mm 1st h)</td>
<td>72 (49–84)</td>
<td>18** (13–29)</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>34 (13–76)</td>
<td>10** (5–18)</td>
</tr>
<tr>
<td>Platelets (×10⁹/l)</td>
<td>5.6 (4.8–6.2)</td>
<td>5.2** (3.8–5.7)</td>
</tr>
<tr>
<td>vWF (%)</td>
<td>175 (137–223)</td>
<td>199* (162–246)</td>
</tr>
<tr>
<td>PAI-1 activity (RU/l)</td>
<td>10.8 (6.7–16.3)</td>
<td>11.6* (9.3–14.3)</td>
</tr>
</tbody>
</table>

* p < 0.05,  ** p < 0.0001. vWF = von Willebrand factor, PAI-1 = plasminogen activator inhibitor.

Figure 1 Plasma concentrations of vWF in 25 patients with PMR at diagnosis and at follow up subgrouped according to ABO blood group O (open and -non- (filled) data). Data were presented with 16th, 25th, 50th, 75th, and 85th percentiles. Wilcoxon signed rank test was used for paired data and Mann-Whitney U test for unpaired data.

In patients with non-O blood groups there was a correlation (Spearman rank test) between vWF and ESR, CRP, fibrinogen, and age at disease onset (r=0.01, p2.0, r=0.05, p=0.01, p=0.01 respectively), but not in patients with blood group O. PAI-1 correlated with CRP (r=0.39, p<0.05) in all patients at diagnosis. There were no differences in ESR, CRP, fibrinogen or platelet count between patients with and without blood group O.

From these results we conclude that even in an inflammatory disease such as PMR, the ABO blood group and age influence the magnitude of the vWF concentrations and may explain the contradictions pertaining to vWF values reported in inflammatory diseases. In agreement with our earlier study PAI-1 values, and not vWF, were increased in PMR patients after several years of prednisolone treatment. Persistently high concentrations of vWF about six years after PMR diagnosis, suggest a continuous vascular dysfunction despite clinical and laboratory determined remission.

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Septic arthritis by Mycoplasma hominis: a case report and review of the medical literature

Septic arthritis caused by Mycoplasma hominis is rarely diagnosed. We present a case of M hominis septic arthritis in a renal transplant recipient.

A 36 years old white man receiving haemo- dialysis was admitted to hospital for renal transplantation. Two weeks later, while taking cyclosporin A, azathioprine, prednisolone, valacyclovir, aztreonam, and mycophenolate mofetil, he developed infection of the right knee. Serological examinations for cytomegalovirus (Ig G and M), hepatitis B and C, HIV, and Epstein-Barr virus were negative. A Mantoux test was positive. On physical examination he was not febrile and had arthralgia of the right knee. Laboratory findings included a whole blood cell count of 9570/mm³, packed cell volume 22%, platelet count 224 000/mm³, creatinine 5 mg/dl, and urea 9 mg/dl. A chest radiograph was normal. A right knee arthrocentesis showed soft tissue swelling without erosions or bone lesions. Arthrocentesis yielded 60 cc of cloudy yellow synovial fluid containing white blood cell count of 50 000/mm³ (80% polymorphonuclear neutrophils), glucose 114 mg/dl, and lactate dehydrogenase 341 IU/l; no crystals were seen. A direct Gram stain of the aspirate showed no microorganisms. There was no bacterial, fungal, and mycobacterial growth on cultures. Arthritis recurred and two further arthrocenteses were performed. The last aspiration revealed 120 cc of cloudy yellow synovial fluid containing white blood cell count of 68 000/mm³ (82% polymorphonuclear neutrophils), glucose 30 mg/dl, and lactate dehydrogenase 728 IU/l. Deep venous thrombosis in the right leg was diagnosed and antiocoagulant treatment was started. Twenty four hours later he developed a spontaneous haemarthrosis in the knee. Because there was no improvement of the haemarthrosis and the suspicion of septic arthritis by M tuberculosis was high, open synovial biopsy and synoven- tomy was performed. Histological examination showed synovial hyperplasia and infiltrations with polymorphonuclear cells. No granulomatous reaction nor amyloid were seen. Direct Gram and Ziehl-Nielsen stains...
reactive arthritis that is sexually acquired 

tion after 12 months of follow-up. The patient had a gradual response 
doxycline 100 mg orally twice daily was 
given. The patient had no evidence of recurrent infec-
tions, and there was no evidence of recurrent infection after 12 months of follow-up. Mycoplasma sp have been associated with 
reactive arthritis that is sexually acquired and with septic arthritis. They do not grow satisfactorily on bacteriological media routinely used for joint aspirates, and anaerobic or special mycoplasmal media must be used. On the other hand, many mycoplasmas and bacterial L-forms are ubiquitous and not generally recognised as important pathogens. They may be present in commercial bovine serum and in tap water and are frequent contaminants of tissue culture. Our patient presented with acute monarticular arthritis with clinical features that did not differentiate it from other bacterial joint infections. Synovial fluid leucocyte counts were high with a low glucose concentration. Only 17 cases of M hominis septic arthritis have been reported in the medical literature. There are no unifying predisposing factors of these cases, although a review of the medical literature shows that eight of these patients were immunocompromised (47%) (table 1), and only one case after renal transplantation. With only one exception, all the reported cases presented with monarticular or oligarticular arthritis involving large joints. Our case occurred in a renal transplant recipient and although, antibody deficiency is particularly prone to chronic mycoplasmal infections, serum immunoglobulin concentrations were normal. We only performed one measurement and we do not exclude transient hypogammaglobulinaemia. Optimal treatment for M hominis joints infections is unknown. Doxycycline apparently only suppresses and does not eradicate the infection. However, our patient had a good clinical response without recurrent arthritis. If bacterial antigens in the joint are critical in the persistence of arthritis, it is possible that the removal of the synovium contributed to the resolution of the arthritis. We illustrate the importance of considering infection with unusual organisms in immunocompromised hosts. Correct diagnosis will be made only if mycoplasma infection is considered, and appropriate investigations performed.

Table 1 Summary data from reported cases of immunocompromised patients with M hominis septic arthritis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age/sex</th>
<th>Site of infection</th>
<th>Predisposing factor(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>32/M</td>
<td>Knee and shoulder</td>
<td>Immunosuppressive drugs</td>
</tr>
<tr>
<td>1</td>
<td>25/F</td>
<td>Hip and knees</td>
<td>Immunosuppressive drugs</td>
</tr>
<tr>
<td>1</td>
<td>54/F</td>
<td>Hip and wrist</td>
<td>Immunosuppressive drugs</td>
</tr>
<tr>
<td>1</td>
<td>60/F</td>
<td>Knee and wrist</td>
<td>Immunosuppressive drugs</td>
</tr>
<tr>
<td>1</td>
<td>39/F</td>
<td>Shoulders, knees, thoracic and lumbar spine, toes, blood</td>
<td>Immunosuppressive drugs</td>
</tr>
<tr>
<td>1</td>
<td>63/M</td>
<td>Knee</td>
<td>Immunosuppressive drugs</td>
</tr>
<tr>
<td>1</td>
<td>NS</td>
<td>Knee</td>
<td>Hypogammaglobulinaemia</td>
</tr>
<tr>
<td>6</td>
<td>42/F</td>
<td>Knee</td>
<td>Hypogammaglobulinaemia</td>
</tr>
<tr>
<td>This paper</td>
<td>36/M</td>
<td>Knee</td>
<td>Immunosuppressive drugs</td>
</tr>
</tbody>
</table>

NS = not stated.

were negative. Normal aerobic and anaerobic cultures were also negative. Urethra, phar-
ynx, and rectal cultures were negative. Serological tests for Salmonella, Brucella, Lyme, Q fever, Rubella, cytomegalovirus, and Epstein-Barr virus were negative. C reactive protein, rheumatoid factor, antinuclear anti-
body, complement, and immunoglobulin val-
ues were normal. After 48 hours incubation, the microbiology laboratory reported a 
growth in blood culture bottles (Bactec Plus, BACTEC 9240, BBL) from the second and 
third synovial fluid culture. The isolate grew as minute colonies on anaerobic agar me-
dium and was Gram stain negative. On A7 agar (bioMérieux), it showed a typical ‘fried egg’ appearance and hydrolysed arginine and was identified as M hominis. Treatment with 
doxycycline 100 mg orally twice daily was 
given. The patient had a gradual response and there was no evidence of recurrent infec-
tion after 12 months of follow-up. Mycoplasma sp have been associated with 
reactive arthritis that is sexually acquired and with septic arthritis. They do not grow satisfactorily on bacteriological media routinely used for joint aspirates, and anaerobic or special mycoplasmal media must be used. On the other hand, many mycoplasmas and bacterial L-forms are ubiquitous and not generally recognised as important pathogens. They may be present in commercial bovine serum and in tap water and are frequent contaminants of tissue culture. Our patient presented with acute monarticular arthritis with clinical features that did not differentiate it from other bacterial joint infections. Synovial fluid leucocyte counts were high with a low glucose concentration. Only 17 cases of M hominis septic arthritis have been reported in the medical literature. There are no unifying predisposing factors of these cases, although a review of the medical literature shows that eight of these patients were immunocompromised (47%) (table 1), and only one case after renal transplantation. With only one exception, all the reported cases presented with monarticular or oligarticular arthritis involving large joints. Our case occurred in a renal transplant recipient and although, antibody deficiency is particularly prone to chronic mycoplasmal infections, serum immunoglobulin concentrations were normal. We only performed one measurement and we do not exclude transient hypogammaglobulinaemia. Optimal treatment for M hominis joints infections is unknown. Doxycycline apparently only suppresses and does not eradicate the infection. However, our patient had a good clinical response without recurrent arthritis. If bacterial antigens in the joint are critical in the persistence of arthritis, it is possible that the removal of the synovium contributed to the resolution of the arthritis. We illustrate the importance of considering infection with unusual organisms in immunocompromised hosts. Correct diagnosis will be made only if mycoplasma infection is considered, and appropriate investigations performed.

1 Luttrell LM, Kanji SS, Corey R, Lins RE, Spin-
6 Steuer A, Franz A, Furr PM, Taylor-Robinson D, Webster ADB, Hughes GRY. Common variable immunodeficiency presenting as a Myco-

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Septic arthritis by Mycoplasma hominis: a case report and review of the medical literature

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