LETTERS

Cladrabine in the treatment of systemic lupus erythematosus nephritis

Systemic lupus erythematosus (SLE) nephritis often requires treatment with cyclophosphamide, which carries the risk of major side effects including infection, ovarian failure and bladder malignancy. Therapeutic strategies that would specifically target lymphocytes are appealing. Following the first report of the use of the purine nucleoside analogue cladribine (2-chloro-2’-deoxyadenosine), a selective lymphocyte depleting agent, in the treatment of lupus nephritis,1 we report our experience in two patients with severe renal involvement.

CASE 1

A 32 year old woman was diagnosed with SLE at age 28, with polyarthritis, photosensitive rash, subcutaneous nodules, fatigue and lymphopenia. ANA, anti-dsDNA, anti-Sm and anti-RNP antibodies were present. Various immunosuppressants and corticosteroids failed to maintain a sustained remission. Two and a half years after presentation, she developed haematuria and proteinuria and renal biopsy revealed WHO Class III lupus nephritis. Treatment with pulsed intravenous cyclophosphamide and methylprednisolone was subsequently reintroduced and creatinine has again fallen to 118 µmol/l.

Table 1 shows the results of investigations before and after cladribine infusions for both cases.

In the initial study by Davis et al.,3 three of seven patients treated with continuous cladribine infusion for a week responded completely and renal function did not deteriorate in any of the seven patients. Our limited experience suggests that cladribine may be effective in other manifestations of SLE (that is, cutaneous vasculitis), but it does not seem to have a consistent effect in severe nephritis. Good tolerability of the drug was confirmed and although herpes simplex infections occurred in both patients the role of corticosteroids cannot be ignored.

Further studies are required to establish the position of cladribine in the treatment of SLE especially in the presence of other lymphocyte depleting agents such as mycophenolate mofetil, which is reported to be effective in lupus nephritis,5 even in cases refractory to cyclophosphamide.

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Table 1 Results of investigations before and after cladribine infusions

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>12.25 g/24 h</td>
<td>&gt;98 µmol/l</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>112 µmol/l</td>
<td>100 µmol/l</td>
</tr>
<tr>
<td>Anti-dsDNA</td>
<td>6.65 g/24 h</td>
<td>4.2 g/24 h</td>
</tr>
<tr>
<td>C3</td>
<td>0.51 g/l</td>
<td>0.51 g/l</td>
</tr>
<tr>
<td>C4</td>
<td>0.13 g/l</td>
<td>0.51 g/l</td>
</tr>
<tr>
<td>C3d</td>
<td>22 units/ml</td>
<td>23 units/ml</td>
</tr>
<tr>
<td>Urine analysis</td>
<td>red cells, hyalurganular, cellular casts</td>
<td>red cells, few casts</td>
</tr>
</tbody>
</table>

Reference ranges: serum creatinine 50–100 µmol/l, anti-dsDNA: 50–300 IU/ml positive, >300 IU/ml strongly positive, C3: 0.63–1.19 g/l, C4: 0.11–0.43 g/l, C3d: up to 12 units/ml.

Cladribine (continuous IV infusion of 0.05 mg/kg/day) was started. Cutaneous vasculitis resolved within five days and serum creatinine fell from 190 to 118 µmol/l. She also developed a perineal herpes simplex infection but drug was otherwise well tolerated. Pulse intravenous cyclophosphamide and methylprednisolone were subsequently reintroduced and creatinine has again fallen to 118 µmol/l.

Case 2

A 35 year old woman was diagnosed with SLE at age 31, with fever, pancytopenia, and nephrotic syndrome (proteinuria 6.65 g/24h). ANA and anti-dsDNA antibodies were present. Renal biopsy revealed WHO Class III lupus nephritis. In the next four years she required three treatment cycles of intravenous cyclophosphamide (total dose per six month cycle: 9–10 g). Azathioprine, methotrexate, cyclosporin A and prednisolone 5–40 mg/day in the interim had failed to control her disease. Cyclophosphamide, additionally, had resulted in premature ovarian failure. Repeat renal biopsy showed progression to Class IV nephritis with focal necrosis and crescents. Cladribine (continuous IV infusion of 0.05 mg/kg/day for seven days) and prednisolone 40 mg/day proved ineffective as creatinine rose from 149 to 243 µmol/l in two months. She also developed a perineal herpes simplex infection but drug was otherwise well tolerated. Pulse intravenous cyclophosphamide and methylprednisolone had subsequently been reintroduced and creatinine has again fallen to 118 µmol/l.

Table 1 shows the results of investigations before and after cladribine infusions for both cases.

In the initial study by Davis et al.,3 three of seven patients treated with continuous cladribine infusion for a week responded completely and renal function did not deteriorate in any of the seven patients. Our limited experience suggests that cladribine may be effective in other manifestations of SLE (that is, cutaneous vasculitis), but it does not seem to have a consistent effect in severe nephritis. Good tolerability of the drug was confirmed and although herpes simplex infections occurred in both patients the role of corticosteroids cannot be ignored.

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Leg bone pain syndrome in a kidney transplant patient treated with tacrolimus (FK506)

Patients with chronic renal failure often develop musculoskeletal problems such as renal osteodystrophy and amyloid arthropathy,1 and in successful renal transplantation other complications may ensue, particularly avascular necrosis.2 Since the availability of immunosuppressive agents for rejection, there has been a decrease in musculoskeletal problems, however, new complications have been described such as a symmetrical bone pain syndrome and reflex sympathetic dystrophy syndrome (RSDS), some of them related to cyclosporin.3

Tacrolimus is a novel macrolide with potent immunosuppressive effects and with a very similar mechanism of action to cyclosporine A—that is, calcineurin phoshatase inhibition.4 We report on a patient treated with tacrolimus, who developed a leg bone pain syndrome, two months after kidney transplantation.

The patient was a 50 year old woman with severe hypertension, treated with atenolol (100 mg/day), verapamil (240 mg/day) and clonidine (0.150 mg/day). She developed chronic renal failure and was treated with peritoneal dialysis in 1995. In 1997 she underwent a kidney transplant from a cadaver and immunosuppressive treatment with tacrolimus (4 mg/day) and prednisone (15 mg/day) was started. Two months after transplantation she reported progressive bilateral leg bone pain syndrome, two months after kidney transplantation.

The patient was a 50 year old woman with severe hypertension, treated with atenolol (100 mg/day), verapamil (240 mg/day) and clonidine (0.150 mg/day). She developed chronic renal failure and was treated with peritoneal dialysis in 1995. In 1997 she underwent a kidney transplant from a cadaver and immunosuppressive treatment with tacrolimus (4 mg/day) and prednisone (15 mg/day) was started. Two months after transplantation she reported progressive bilateral symmetric pain in the knees. Because of pain and difficulty in walking she was readmitted to our unit. At this time, the patient was receiving tacrolimus (4 mg/day) and prednisone (5 mg/day). Clinical examination revealed pain on movement and tenderness over the bone and joint line, without swelling
Spleen haemorrhagic infarction and hazards of anticoagulation in Wegener’s granulomatosis

In the largest cohort published to date, no splenic involvement is described in Wegener’s granulomatosis.¹ We report on two patients who required splenectomy for symptomatic spleen infarction in the course of WG.

CASE 1

A 42 year old man was admitted with an eight month history of arthritis and lower limb dysaesthesia. Examination showed an acutely ill patient with a 39°C fever, oral ulcers, haemorrhagic gingival hyperplasia, bilateral haemorrhagic nasal discharge with crusts, diffuse necrotic purpura, neuritis, and black discoloration of some fingers and toes. The spleen was not palpable. Silent anterior myocordial infarction was diagnosed because of raised MB-CK levels and ST-segment increase with loss of R waves in leads V1, V2, V3 on electrocardiogram.² Antineutrophil cytoplasmic antibodies (c-ANCA) were disclosed in serum and necrotising vasculitis was shown on skin biopsy specimen.³ No antiphospholipid antibody or coagulopathy or abnormality could be disclosed. Treatment consisted of intravenous administration of prednisolone, cyclophosphamide, sodium heparin, diltiazem, dinitrosoorbide and enalapril. His short-term course was uneventful. At day 14, the patient suddenly developed a severe haemorrhagic shock. Echotomography of the abdomen showed a splenic mass. At laparotomy, the spleen was almost disrupted by voluminous haematoma. Histological analysis of the spleen showed widespread necrotising vasculitis with haemorrhagic infarction. After five years of follow up, the patient is in complete remission with oral corticosteroid treatment.

CASE 2

A 23 year old young man was admitted in August 1996 because of repeated otitis media, sinusitis, epistaxis, headache, arthralgia with fever and weight loss. Despite a short course of oral corticosteroids and antibiotics, his general condition worsened. Antiproteinase 3 c-ANCA were disclosed in serum. Chest computed tomography showed pulmonal nodule. Intranasal endoscopic biopsies demonstrated necrotising vasculitis with epithelioid and giant cells. Treatment included oral prednisone and intravenous cyclophosphamide pulses. After a few days, serum creatinine concentrations abruptly increased to 198 mmol/l and urine analysis showed microscopic haematuria and proteinuria. High dose methylprednisolone pulses were then given, intravenous cyclophosphamide was changed to a 100 mg oral daily regimen and acetylsalicylic acid the patient eventually achieved remission. In October 1996, abdomen computed tomography showed an intrapleural lesion that was consistent either with a splenic infarction or haematoma (fig 1). The latter course was marked by a WG flare in January 1997, which was complicated with massive thrombosis of the left iliofemoral vein and the inferior vena cava. No thrombophilic disorder could be found. Intravenous heparin and dextran infusion with acenocoumarol were given. Because of persistent left hypocoordinen terness, splenectomy was performed in September 1997. Histological examination showed spleen infarction with organised haematoma and sequelae of vasculitis (fig 2).

COMMENT

Because they are vessels without collateral flow, occlusion of distal parenchymal splenic arteries leads invariably to infarction. Of note, two of the three patients described by Wegener in 1936 had splenomegaly.⁴ The frequency of spleen infarction ranges from 50% to 100% of WG cases at necropsy.⁵ Histological data in frequen-
Amiodarone induced lupus

Lupus related to amiodarone has not previously been described. We report on a patient who developed drug induced lupus (DIL) in association with amiodarone treatment. To our knowledge, this is the first report of amiodarone induced lupus (CD ROM: Medline, USA National Library: 1966–98).

A 31 year old white woman was admitted because of two weeks of pleuritic chest pain, dyspnea on exertion, and non-productive cough. She had malaise, intermittent fever, arthralgia, and weight loss for more than six months. There was no history of Raynaud’s phenomenon, oral ulcers or photosensitivity. She had a six year history of arterial hypertension and atrial fibrillation treated with amiodarone, digital and amiodarone (200 mg twice daily) for this indication.

Physical examination disclosed malar rash, an aortic systolic murmur (grade II/V), and hypovention in both pulmonary bases. Laboratory studies showed an erythrocyte sedimentation rate of 90 mm 1st h. Peripheral blood examination revealed a mild normochromic and normocytic anaemia (10 g/dl), normal white blood cells count (4000/µl), and normal platelets count (180 000/µl). Coagulation tests were normal. All serum chemistries, including thyroid function tests, creatinine phosphokinase, immunoglobulins, complement levels, and urine analysis were within normal limits. Coombs’s tests were negative. Anti-Ro/Lu factor and anti-C1q factor were not detected. Rheumatoid factor was 1:320. Circulating immune complexes (IgG-C1q) were positive. Antinuclear antibodies (ANAs) were positive at 1:640; anti-Ro, anti-La, anti-dsDNA, anti-Sm, anti-histone antibodies, antiphospholipid antibodies, cryoglobulins, C reactive protein, VDRL and Mantoux test were negative. Blood and urine cultures were negative. Electrocardiogram was within normal limits, and the two dimensional echocardiogram showed mild aortic stenosis. Chest radiography revealed bilateral pleural effusions, without fibrosis or cardiomegaly. Pleural fluid was exudative, with lymphocytic predominance, without cytological findings for malignancy. Cultures of pleural fluid for bacteria, including for Mycobacterium tuberculosis, were negative. Bone scan with technetium-99m showed increase uptake in hands, elbows, and knees. The histopathological examination of biopsy specimens of the skin, including indirect immunofluorescence stain, muscle and temporal artery and skin showed no evidence of systemic lupus erythematosus (SLE) association with amiodarone treatment. To our knowledge, this is the first report of amiodarone induced lupus (CD ROM: Medline, USA National Library: 1966–98).

The amiodarone was stopped and the patient progressively improved. No corticosteroids were given. On the third week she developed a transient relapse, with fever, malaise and with evidence of unilateral pleural effusion. One year after no clinical, immunologic and radiological findings were abnormal.
patients with DIL are usually older; the prevalence of men and women is similar and the presenting symptoms are usually mild, with the patient usually complaining of malaise, fever and arthralgia, with or without arthritis, while skin, central nervous system or renal involvement is rare. Pleuropulmonary disease is frequent and, as in classic SLE, anaemia and leucopenia may be present. Serum complement components are usually normal, ANAs are positive but anti-dsDNA and anti-Sm are negative, while anti-histones antibodies can be detected in most of patients. The pathogenic mechanisms proposed for DIL include: cross reactivity between drug and the nucleic acid; hapten complex formation between drug and nucleic acid, or structural damage to the chromosomal DNA; action of drug as an adjuvant or immunostimulant, which, in concert with appropriate immune response genes, triggers polyclonal B/T cell activation; and interference with the complement pathway. The incidence of side effects associated with amiodarone ranges from 40% to 93% and, in most of cases, these side effects are consequence of its potential to be directly toxic to several organ systems. However, there is also some evidence of immunologically mediated phenomena related to amiodarone. A positive skin and basophil degranulation tests with amiodarone, secretion of leucocyte inhibitory factor, positive lymphoblast transformation and circulation of a specific antibody of the IgG class have been described. Moreover, several studies suggest that various biological and immunological markers of "systemic" disease activity are present in patients taking this drug. Circulating immune complexes, ANAs, and non-specific increase in ESR and white blood cell count, sometimes with eosinophilia, are common findings.

The ANA titre is not uncommon in an elderly patient. However, spontaneous SLE in elderly people is not usual and DIL must always be considered in the differential diagnosis. This case, presenting with malaise, fever, arthralgia, circulating immune complexes, and autoantibodies strongly suggests an immunological underlying condition. Moreover, this patient meets four SLE criteria: malar rash, serositis, haematological disorder (lymphopenia), and positive ANA test. Imputability criteria of amiodarone disorder (lymphopenia), and positive ANAs criteria: malar rash, serositis, haematological plexes, and autoantibodies strongly suggests fever, arthralgia, circulating immune complexes, ANAs, and non-specific increase in ESR and white blood cell count, sometimes with eosinophilia, are common findings.

The prevalence of antinuclear antibodies (ANA) in relapsing polychondritis (RP) has been recently reported by Zeuner et al to be as high as 66%, usually in a low titre with a speckled pattern. We report here on our experience of ANA testing in patients with RP. The charts of 180 patients followed up in our institution fulfilling the criteria for RP proposed by Michet et al have been recently retrospectively reviewed, with special focus on dermatological manifestations and their relation with myelodysplasia. This aim led us to exclude 36 patients because the association of RP with potentially confounding diseases, such as systemic lupus erythematosus (SLE) present in nine, mixed connective tissue disease (MCTD) in five, rheumatoid arthritis in three, Takayasu arteritis in three, mesentric panniculitis in three, spondyloarthritis in two, Crohn's disease in two, psoriasis in two, or Lichen planus in two. Among the 144 patients remaining, 111 have been tested for ANA by using either Hep-2 assay or Crithidia fluorescence) were found positive in our cases with "pure" RP—that is, RP not associated with another connective tissue disorder except for a possible Sjogren's syndrome—agrees with the negative results of tests for IgG antinucleosome antibodies recently reported by our group in this condition. We conclude that: (a) the prevalence of ANA observed in RP is low and, (b) as suggested by other authors the finding of a significant titre of ANA in a patient with RP strongly suggests the presence of an associated disorder, such as SLE, MCTD, Sjogren's syndrome or acquired myelodysplasia.

Figure 1 Prevalence of ANA in "pure" RP according to ANA titre.

**Antinuclear antibodies in relapsing polychondritis**

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There is no association between polymyalgia rheumatica and acute parvovirus B19 infection

Parvovirus B19 has been associated with a growing number of diseases. Besides the frequent manifestations such as erythema infectiosum, aseptic meningitis in persons with underlying haemolytic anaemia, hydrops fetalis in pregnant women, and acute or chronic arthritis a range of rather rare diseases have been described in recent reports. Among them are case reports on persistent parvovirus B19 infection in immune incompetent people, encephalitis, myocarditis, systemic lupus erythematosus (reviewed by Anderson and Younossi), and rheumatoid arthritis. Furthermore, parvovirus B19 has been suspected to play a part in the aetiology of polymyalgia rheumatica (PMR). Because of the acute onset of PMR and its systemic symptoms an infection with parvovirus B19 may be a relevant factor. Additionally, autoimmune processes have been demonstrated in both, PMR and parvovirus B19 infection. As the receptor for parvovirus B19, the F-blood group antigen (glycophorin), is also present on endothelial cells, an interrelation between parvovirus B19 and giant cell arteritis or PMR may be possible.

Parvovirus B19 can only replicate in erythroid precursor cells in human bone marrow, but it is known that infection of cells non-permissive for viral replication leads to an excess production of the viral non-structural protein NS1, which may play a part in the pathogenesis of PMR. However, the overall muscle score was lower in NS1 positive than in NS1 negative patients (0.5 (0.2) SEM score points; p=0.021). With respect to other PMR related symptoms, no significant differences were found. In patients with a positive NS1 IgG antibody, interleukin 6 (4.6 (0.9) SEM v 11.3 (2.2) SEM; p=0.037) and soluble ELAM (48.2 (4.8) SEM v 71.4 (5.2) SEM; p=0.024) were significantly! lower as compared with patients without NS1 IgG. Furthermore, disease related immune mediators such as interleukin 6 or soluble ELAM were lower in patients with as compared with patients without NS1 IgG. As a positive NS1 IgG indicates an active infection, an acute parvovirus B19 infection does not seem to be a pathogenetic factor in our patients with PMR.

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7 In an interrelation between parvovirus B19 and NS1 specific antibodies in healthy controls and patients with PMR. Non-parametric Kruskal-Wallis one way analysis was used to compare means of different subgroups. The significance level was p<0.05.

Figure 1. Seroprevalence of IgG antibodies against VP1/VP2 (black bars) and NS1 (open bars) in control subjects and patients with polymyalgia rheumatica (PMR). The number of healthy control subjects was at least 20. p=0.057 v seroprevalence of IgG in NS1 and NS1 IgG versus the age matched control group: 10%; fig 1). With respect to the NS1 IgG prevalence, patients with PMR were older (median age 66 years, range: 0—7.3, mean (SEM): 1.4 (0.2) years), 35 patients had no corticosteroids and 75 patients had a disease duration of 7.3 years (median disease duration at the time point of blood sampling (median disease duration at the time point of blood sampling: 7.3 years). Overall IgG seroprevalence of IgG against VP1 and VP2 was 78% (fig 1). Overall IgG seroprevalence of IgG against VP1 and VP2 was 88% in patients with PMR (not significantly different versus the age matched control group). With respect to the NS1 IgG antibody, overall seroprevalence in the control group was 22% (fig 1) and in patients with PMR 20% (p=0.057 versus the age matched control group). Furthermore, we investigated the association between the presence of NS1 IgG antibodies and PMR related symptoms or laboratory parameters (patients with NS1 as compared with patients without NS1 IgG antibodies were not different in age, sex, and medication). The symptoms were assessed using standard record forms from the medical history (at the time serum was collected). We asked the patients for muscular pain in the left/right shoulder, left/right upper arms, left/right neck, left/right gluteal muscle, and left/right thigh. If one muscle group was painful, the corresponding item was scored with one point (the sum of the item points was the overall muscle score). In PMR patients with NS1 IgG as compared with patients without NS1 IgG, arthralgia was more frequent (with versus without: 73% (40%); p=0.024). However, the overall muscle score was lower in NS1 positive than in NS1 negative patients (0.5 (0.2) SEM v 1.6 (0.3) SEM score points; p=0.021). With respect to other PMR related symptoms, no significant differences were found. In patients with a positive NS1 IgG antibody, interleukin 6 (4.6 (0.9) SEM v 11.3 (2.2) SEM; p=0.037) and soluble ELAM (48.2 (4.8) SEM v 71.4 (5.2) SEM; p=0.024) were significantly lower as compared with patients without NS1 IgG. Furthermore, disease related immune mediators such as interleukin 6 or soluble ELAM were lower in patients with as compared with patients without NS1 IgG. As a positive NS1 IgG indicates an active infection, an acute parvovirus B19 infection does not seem to be a pathogenetic factor in our patients with PMR.
Neutrophil chemotaxis in Behcet’s syndrome

It has been suggested that the marked cellular inflammatory response, which characterises Behcet’s syndrome (BS), may be attributable to increased neutrophil locomotion. However, others disagree. We have re-evaluated chemotaxis of polymorphonuclear leucocytes (PMNs) in BS among a greater number of patients in a controlled setting.

Fifty four male BS patients, nine male patients with ankylosing spondylitis, eight with psoriasis and 37 male healthy controls were studied with 28 female patients with BS and 16 healthy female controls. Behcet patients with severe disease were those with active major vessel and/or eye involvement.

We measured chemotaxis with the “under the agarose method”. The measurements were masked with the assessors not knowing the diagnoses. An inverted microscope fitted with an ocular micrometer disc to measure the migration of neutrophils from middle wells to outer (chemotaxis) and inner wells (chemokinesis) was used. Zymosan activated sera (patients or controls) were used as a source of C5a. Results were expressed as micrometre square (1 mm² = 8 squares). Additionally the plates were evaluated macroscopically for the observation of the migration between neutrophil wells.

Tables 1 and 2 show the results. There were no significant differences between the chemotactic indices of the various groups of patients and controls studied of either sex. Maximal chemotaxis rates in the groups varied from 67% to 100%.

The Boyden millipore filter system has extensively been used for chemotaxis experiments. The agarose method is simple and cheap. This method can preferentially be used to differentiate chemokinetic from chemotactic migration.

There is marked heterogeneity in disease expression in men and women in BS and we reckon that some of the confusion in the literature about neutrophil activity might be related to this. Thus we analysed our data separately for each sex. Although there was a tendency for male patients with severe disease to have higher chemotactic indices this was not statistically significant (p=0.62). We did not study any diseased controls for female patients with BS.

Abdulla and Lehner observed decreased chemotaxis in BS. Fordham et al., on the other hand reported increased chemotaxis, but normal random migration. While Wilkinson, similar to our experience, observed normal chemotaxis in BS, more recently Carletto et al. reported augmented chemotaxis especially in the active phases of the disease. In the Carletto study clinically active Behcet patients demonstrated increased chemotaxis to sera by Sen’s modified in vivo assay. Others had found hyperchemotaxis to be responsible for this phenomenon by increasing the chemotactic activity in all groups studied. Further studies are needed to clarify these issues.

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Table 2 Chemotactic indices in women*

<table>
<thead>
<tr>
<th>Groups</th>
<th>Number</th>
<th>Mean (SD)</th>
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<tbody>
<tr>
<td>Behcet’s</td>
<td>28</td>
<td>7.2 (8.2)</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>16</td>
<td>10.1 (10.2)</td>
</tr>
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</table>

*p<0.05

Neuropsychiatric systemic lupus erythematosus

The considerable difficulties in making sense of the literature on patients with lupus involving the central nervous system are re-emphasised in the paper by Rood et al. The authors, who to be fair take a sensibly cautious approach to their results, nevertheless seek to persuade us that the IL10 locus is associated with neuropsychiatric lupus on the basis of a historical case notes review of 42 patients with neuropsychiatric disease, compared with 50 who lack such involvement.

Their conclusion needs to be treated with caution. Does it make sense to lump together 42 highly diverse patients and make the kind of claim they have made? The authors suggest that CNS lupus is attributable to either antiphospholipid antibody related thrombotic events, or “immune mediated” disease. This division is artificial. There is a considerable literature on CNS lupus that proposes that a wide variety of immunopathogenic mechanisms may be responsible in individual cases. These mechanisms include thrombotic effects, which may be linked to antiphospholipid antibodies, a true vasculitis, a cross reaction between antibodies that recognise the lymphocyte surface targets and neurologcal antigens, and autoantibodies to a wide variety of neurological targets. A considerably larger number of patients will have to be studied before any claims of links to an IL10 promoter haplotype can be truly convincing.

We agree with the authors that patients with SLE have a higher innate production of IL10 than controls. However, as there is no significant difference in the frequency of the IL10 promoter single nucleotide polymorphism (SNP) in SLE patients when comparing with SLE controls for female patients with BS

Table 1 Chemotactic indices in men*

<table>
<thead>
<tr>
<th>Groups</th>
<th>Number</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behcet’s</td>
<td>54</td>
<td>6.4 (8.0)</td>
</tr>
<tr>
<td>Severe Behcet’s</td>
<td>9</td>
<td>11.3 (12.1)</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>9</td>
<td>5.9 (7.1)</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>8</td>
<td>10.8 (11.0)</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>37</td>
<td>10.0 (10.3)</td>
</tr>
</tbody>
</table>

*Kruskal-Wallis one way analysis of variance, corrected for ties: &p<0.1381, DF=4, p>0.05.
compared with controls in their study, we suspect that the difference in IL10 production is not attributable to functional differences between patients with SLE and controls in terms of the IL10 SNP alleles frequencies. Differences have been described with respect to microsatellites and one awaits confirmation from other populations or family studies. To our knowledge, a difference in IL10 production between patients with neuropsychiatric disease SLE and non-neuropsychiatric disease SLE has not been described. The described associations would be biologically meaningless if IL10 production is similar between these two groups.

The authors suggest that the -1082A allele is associated with higher innate IL10 production, however, they appear to ignore the only published study to date that showed that the A allele was associated with lower IL10 production. In addition we have confirmed that the A allele is associated with lower IL10 production in transient transfection studies and the ATA/ATA genotype is associated with lower IL10 production in whole blood culture. The increase in the A allele is mainly accounted for by an increase in the ATA haplotype in their neuropathiatric disease patients and therefore they are described with a lower IL10 producing haplotype, not a high IL10 producing haplotype. One interpretation of this would be that patients with neuropsychiatric disease symptoms are unable to adequately control inflammation from a variety of different pathological mechanisms because of low IL10 production.

**Authors’ reply**

We thank Drs Isenberg, Crawley and Woo for their interest in our paper. They argued that the dichotomy of the pathogenesis of CNS lupus in “immune mediated” and thromboembolic disease is too rigid, but both mechanisms of immunopathogenetic mechanisms can be deemed responsible for CNS lupus. As the hallmark of SLE is the production of autoantibodies, it seems to be justified to assume that the pathogenesis of CNS lupus is B cell mediated. Based upon this assumption we clustered the individual neuropsychiatric disease SLE patients and tested the hypothesis that a genetic marker in the promoter of the IL10 gene is associated with the phenotype of CNS-SLE.

In general, a positive result in a genetic association study is only possible after a correct definition of the phenotype. After all, if the phenotype is not well defined, the magnitude and statistical significance of the association will be less or lost because of the random distribution of the genetic marker in the misclassified patients. If misclassification occurred in the sense that CNS lupus patients were attributed to the non-neuropsychiatric disease SLE population, the fact that we still found a positive result strengthens our conclusions instead of weakening it.

It might be argued that thromboembolic events do not fit in the pathogenetic model of B cell mediated CNS lupus. But, as stated clearly in the article, even after exclusion of these ambiguous reports, the distribution of the frequencies in the neuropsychiatric disease SLE and non-neuropsychiatric disease SLE patients remains the same.

Of course we agree with the notion that our findings must be repeated in another group of patients. Interestingly, the increased prevalence of ATA in neuropsychiatric disease SLE patients has already been reported by Mok in a group of Chinese SLE patients. Currently we are investigating the distribution of the IL10 promoter haplotypes of neuropsychiatric disease SLE patients in an ethically different population.

In our article we have elaborated on two possible explanations of our findings. Firstly, the increased frequency of the ATA haplotype might be associated with an increased production of IL10. We made this assumption in the light of previous studies stating that SLE as a whole is characterised by an increased innate IL10 production. It is wrong to extrapolate these conclusions to our population. Because of the retrospective character of our study, we were not able to measure IL10 production in all these ambiguous patients, and therefore, we cannot say whether or not IL10 production in our SLE patients as a whole was similar to or different from the control population. It might well be that differences in IL10 production would only emerge after stratifying into neuropsychiatric disease SLE and non-neuropsychiatric disease SLE patients. Furthermore, it might be that in the populations mentioning the ATA ATA genotype, there was an excess of patients with neuropsychiatric disease SLE.

The second explanation for the skewing mentioned before, there was an excess frequency of ATA in neuropsychiatric disease SLE patients. Isenberg et al have referred to another group stating that -1082 A is associated with a lower risk for disease activity and they interpret our results with this finding in mind. In conclusion, we do not know the relevance of the IL10 promoter in the in vivo regulation of IL10 production and therefore both explanations are equally speculative.

**A man with intermittent fever and arthralgia**

Knight and Symmons report a very interesting case of a man with Whipple’s disease and provide us with a timely update on this rare condition.

The disease has been described how six months after initial presentation the diagnosis of adult onset Still’s disease (AOSD) was made and despite regular review at several centres, this diagnosis was upheld for a further five years. Multiple investigations were performed adding little to the original diagnosis. It is not mentioned whether a serum ferritin was taken. This may have been useful given the initial diagnosis of AOSD as it might have provided some clues in the differential diagnosis. The ferritin levels rarely exceed 25,000 µg/l, whereas in AOSD values up to 25,000 µg/l have been recorded. However exclusive to AOSD, as various malignancies, hepatic necrosis and haemachromatosis can all cause it. However, values up to 25,000 µg/l have been recorded in AOSD and reportedly, values rarely exceed 3–5000 µg/l in the above conditions. The pathogenesis is not clearly understood, but it has been hypothesised that in AOSD, cytokine upregulation of ferritin mRNA
translation may occur. This compares with the iron regulated pathway of ferritin synthesis in haemachromatosis and iron overload syndromes.

A comparative study of diagnostic criteria in AOSD by Mason et al suggest the Yamaguchi criteria are superior to the others tested, including Cush et al quoted by Knight and Symmons. However, none of the criteria to aid diagnosis make use of serum ferritin measurement despite the claims for its use in the literature and acceptance in clinical practice. Although undoubtedly useful if very high, it is not clear what the relevance of a normal value in AOSD is, in a case satisfying clinical diagnostic criteria (although we have never seen such a case). In rare diseases such as AOSD, it is difficult to assess and evaluate diagnostic criteria and calculate sensitivity and specificity of possible disease markers. If serum were stored on this patient it would be interesting to know the serum ferritin measurement and how, if at all, it would have affected this patient’s management.

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Authors’ reply

We thank Drs Quinn and Gough for their interest in our paper. Our patient did have his serum ferritin measured in 1992. It was 197 µg/l (normal range 15–200). This was therefore a situation in which the patient satisfied clinical diagnostic criteria for adult onset Still’s disease (AOSD) but had a normal ferritin concentration. As the authors point out, had the ferritin concentration been high, this would have helped to confirm the diagnosis but given that it was in the normal range, it could not actually be used to refute the diagnosis. It was always felt that this patient’s disease was not typical of AOSD and the various physicians who looked after the patient were always willing to consider alternatives. However, it is difficult, even with the benefit of hindsight, to conclude that Whipple’s disease could have been diagnosed earlier. Although the normal serum ferritin was not in keeping with the diagnosis of AOSD it did not point towards any other diagnosis in particular.

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Ear, ear, what’s going on in Norfolk?

Having recently started work in the rheumatology department of the Norfolk and Norwich Hospital I read with great interest the article on Hugh(h)e’s(’) ears: an unusual presentation. Amazingly we have recently seen an almost identical, but less catastrophic case.

A 27 year old white man presented with a 24 hour history of ears so swollen and painful, that he could not lie in bed with them touching the pillow. One year previously he was diagnosed with primary antiphospholipid syndrome (APLS) after recurrent deep vein thromboses and a raised IgG anticardiolipin antibody at 92 iu/ml. He was subsequently given warfarin.

On admission this time, his INR, while taking warfarin 7 mg per day, was subtherapeutic at 1.6. Biopsy from his left ear lobe showed numerous fibrin thrombi with no associated vasculitis, consistent with thrombosis secondary to APLS.

His warfarin dose was increased to obtain an INR between 3 and 4. Within a few days he had recovered and was discharged home well.

Perhaps Hughes’ ears should be renamed Norfolk ears?

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Authors’ reply

We note with interest the report from Dr Gaffney. While the coincidence is indeed curious, these cases do suggest possible mechanisms for activation of thrombosis. The external ear is characterised particularly by a lower average temperature than core body temperature, and by its susceptibility to trauma and pressure effects. In our case, cryoglobulins were not identified, and no comment in this regard is made by the authors. There is no specific reference to any aural trauma; though presumably, as in our case, it is difficult to assess what pressure was exerted on the external ear during sleep. It is plausible that such pressure causes a degree of blood stasis, which together with inadequate anticoagulation, resulted in thrombosis. Such speculation may be interesting, but it is this latter point that deserves emphasis—patients with antiphospholipid syndrome who have had thrombi will do so again, potentially with serious consequences, if the INR is not scrupulously maintained above 3.0, a message that must be spread widely: “Friends, Norfolk countrymen, lend me your ears!”

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Leg bone pain syndrome in a kidney transplant patient treated with tacrolimus (FK506)

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