Cladribine 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 polycythemia, photosensitivity 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 haematocrit and proteinuria and renal biopsy revealed WHO Class III lupus nephritis. Treatment with pulsed intravenous cyclophosphamide and methylprednisolone had to be 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.

Table 1: Results of investigations before and after cladribine infusions

<table>
<thead>
<tr>
<th>Case</th>
<th>First infusion</th>
<th>Second infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Patient 1</td>
<td>Proteinuria</td>
<td>12.25 g/24 h</td>
</tr>
<tr>
<td></td>
<td>Serum creatinine</td>
<td>190 µmol/l</td>
</tr>
<tr>
<td></td>
<td>Anti-dsDNA</td>
<td>132 IU/ml</td>
</tr>
<tr>
<td></td>
<td>C3</td>
<td>0.51 g/l</td>
</tr>
<tr>
<td></td>
<td>C4</td>
<td>0.13 g/l</td>
</tr>
<tr>
<td></td>
<td>C3d</td>
<td>22 units/ml</td>
</tr>
<tr>
<td></td>
<td>Urine analysis</td>
<td>red cells, hyaluraneal, cellular 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.

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, and in successful renal transplantation other complications may ensue, particularly avascular necrosis. 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.2 Tacrolimus is a novel macrolide with potent immunosuppressive effects and with a very similar mechanism of action to cyclosporine A—that is, calcineurin phosphatase inhibition.3 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 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.

or increased temperature. She had no signs of autonomic vasomotor disturbances and arterial mobility was normal. Examination of the remaining peripheral and axial joints was normal.

Blood tests showed creatinine levels of 1.3 mg/dl, calcium of 10.1 mg/dl, phosphate of 3.5 mg/dl and urate of 7.2 mg/dl. Other laboratory findings were normal. Patchy osteoporosis in the knees was seen radiographically. Bone scintigraphy showed intense uptake in both the osseous and vascular phases in the knees (fig 1). Calcitonin treatment was begun (three monthly cycles of 10 intramuscular units/day during 20 days) without clinical improvement. Because of the high serum concentrations of tacrolimus (15 µg/ml) and the ineffective calcitonin treatment, tacrolimus was reduced to 2 mg/day. Nine months after transplantation, she was free of symptoms and radiographs and tacrolimus concentration (9.1 µg/ml) were normal. Changes in plasma tacrolimus concentrations subsequent to the resolution of symptoms did not occur and the patient continued asymptomatic.

We describe a complication in a patient treated with tacrolimus after kidney transplantation that is similar to that described by other authors in transplanted patients treated with cyclosporin. Although the radiographic and bone scintigraphy findings suggested RSDS, the symptoms of this patient were not the classic features of this entity. The efficacy of corticosteroids in the treatment of uncompli- cated RSDS has been demonstrated, but it is possible that corticosteroids might have a protective role against a full RSDS development, as she was treated with high doses of prednisone after the renal transplantation. The early onset of symptoms after the administration of the drug and the clinical improvement after the reduction of the immunosuppressant dose, are features that support a possible relation between tacrolimus and the leg bone pain syndrome. The patient had high plasma tacrolimus concentrations at the onset of the clinical symptoms and the improvement appeared only when the drug doses went down. Although recurrence of knee symptoms with an increase in tacrolimus dose would be much stronger proof of this association, it is not ethically justifiable. Furthermore, she was treated with verapamil in addition to other drugs for controlling hypertension. Verapamil might have played a part in a possible increased risk for this clinical complication, because it decreases tacrolimus clearance. However, there are reports that calcium channel block-ers (albeit of the dihydropyridine type) can improve the bone pain syndrome.36 Although leg bone pain syndrome in kidney transplant patients who have received cyclosporin A is very rare, there are case reports described in the literature.36 To our knowledge, this is the first case of a renal transplant patient with pain in the lower limbs, related to tacrolimus treatment. Addi- tional case reports are needed to support this association.

**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 (WG).1 We report on two patients who required splenectomy for symptomatic spleen infarction in the course of WG.

Figure 1 Bone scintigraphy, showing increased uptake in both knees.

**CASE 1**

A 42 year old man was admitted with an eight month history of arthritis and lower limb dyspnoea. 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, neutritis, and black discoloration of some fingers and toes. The spleen was not palpable. Silent anterior myo-cardial infarction was diagnosed because of raised MB-CK levels and ST-segment in- crease with loss of R waves in leads V1, V2, V3 on electrocardiogram.3 Antineutrophil cyto-plasmic antibodies (c-ANCA) were disclosed in serum and necrotising vasculitis was shown on skin biopsy specimen.4 No antiphospholi-pid antibody or coagulation protein abnormality could be disclosed. Treatment con-sisted of intravenous administration of prednisolone, cyclophosphamide, sodium heparinate, diltiazem, dinitrosorbide 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 haem-orrhagic infarction. After five years of follow up, the patient is in complete remission with oral cortimomuzole 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 pulmo- nary nodules. Intranasal endoscopic biopsies demonstrated necrotising vasculitis with epite-thelioid and giant cells. Treatment included oral prednisone and intravenous cyclophos- phamide pulses. After a few days, serum creatinine concentration abruptly increased to 198 µmol/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 the patient eventually achieved remission. In October 1996, abdomen computed tomogra-phy showed an intraspinal lesion that was consistent either with a splenic infarction and haem-atomata (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 treatment and oral anticoagulation with acenocoumarol were given. Because of persistent left hyponocondrium tenderness, splenectomy was performed in Sep-tember 1997. Histological examination showed spleen infarction with organised haemato-mata and sequelae of vasculitis (fig 2).

**COMMENT**

Because they are vessels without collateral flow, occlusion of distal parenchymal splenic vessels may be caused by atheromatous obstruc- tion or infarction.7 Because of persistent left hyponocondrium tenderness, splenectomy was performed in September 1997. Histological examination showed spleen infarction with organised haemato-mata and sequelae of vasculitis (fig 2).

**References**

showed massive or multiple areas of splenic necrosis, associated to a variable extent with central arteritis, splenic trabeculitis, follicular arteriolitis, disseminated parenchymatous granuloma and capsulitis (fig 2). Patients with splenic infarction in WG usually remain asymptomatic. Prominent splenomegaly is rare. With computed tomography, focal splenic infarction appears as well defined, peripheral wedge shaped areas of low attenuation. In WG, the diffuse vasculitis process often results in massive hypodense lesions involving the spleen parenchyma (fig 1). A peripheral rim of enhancement may be seen, as for spleen abscess, haematoma and lymphoma. Splenectomy has been performed successfully in some patients. Splenic lesions may also appear to heal on repeated computed tomography under medical treatment only, consisting of prednisone and cyclophosphamide.

Few recent reports of splenic involvement in WG provide histological analysis from live patients. Inaugural spontaneous rupture of a normal sized spleen with only subcapsular neutrophil infiltrate has been described in a patient who subsequently developed full-blown WG. In another case, a spontaneous splenic haemorrhage was ascribed to vasculitis in a patient who had severe WG that required haemodialysis.

In our two patients, microscopical study of the spleen also showed haemorrhagic infarction caused by specific WG related vasculitis.
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 chromosomes 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 lymphoblastic 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. Low 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 and anti-cardiolipin antibodies—positive for la amiodarone and anticardiolipin antibodies. The kidney in collagen-vascular diseases is frequent and, as in classic SLE, renal involvement is rare. Pleuropericardial effusion associated with amiodarone ranges from 40% to 93% and, in consequence, the immune response might progress despite discontinuation of the treatment.

Antinuclear antibodies in relapsing polychondritis

The prevalence of antinuclear antibodies (ANA) in relapsing polychondritis (RP) has been recently reported by Zeuner et al. 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, mesenteric 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 cells or liver sections as substrate, or both. Most patients had repeated ANA determinations, including initial testing before onset of corticosteroid treatment, and the higher titres were considered for analysis. Figure 1 shows the histogram of ANA positivity according to ANA titre.
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, aplastic crisis in persons with inherited sickle cell disease, and cyclic thrombocytopenia, it has been described in recent reports. Parvovirus B19 has been associated with a range of rheumatic diseases, such as relapsing polychondritis and acute polyarthritis.

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 infectious aetiology 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-glycoprotein (F-glycoprotein) of parvovirus B19 may have a role in PMR pathogenesis.

Methods

We tested serum samples from 110 PMR patients (patients with a positive NS1 IgG antibody, age 24–97 years (mean 65.5) and 34 healthy controls (age 19–94 years (mean 74.2 years)), representing a normal distribution of ages.

Results

We found a significant difference between PMR patients (NS1 IgG positive) and healthy controls in terms of disease duration, with a median disease duration at the time point of blood sampling of 0.6 years in PMR patients and 3 years in healthy controls.

We investigated the association between polymyalgia rheumatica and acute parvovirus B19 infection. We found no significant association between NS1 IgG positivity and polymyalgia rheumatica in our patient group.

Discussion

The results of our study suggest that parvovirus B19 infection does not play a role in the pathogenesis of polymyalgia rheumatica. Further studies are needed to clarify the role of parvovirus B19 infection in the development of other rheumatic diseases.
Neutrophil chemotaxis in Behçet’s syndrome

It has been suggested that the marked cellular inflammatory response, which characterises Behçet’s syndrome (BS), may be attributable to increased neutrophil locomotion.1,2 However, others disagree.3,4 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. Behçet patients with severe disease were those with active major vessel involvement and/or eye involvement.

We measured chemotaxis with the “under the agarose method”.5,6 The measurements were masked with the assessors not knowing the diagnoses. An inverted microscope fitted with an ocular micrometre disc to measure the migration of neutrophils from middle wells to outer (chemotaxis) and inner wells (chemokinosis) was used. Zymosan activated sera (patients or controls) were used as a source of CSa. 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 be preferred to be used to differentiate chemokinosis from chemotactic migration.

There is marked heterogeneity in disease expression in men and women in BS and we realised that some of the confusion in the literature about neutrophil activity might be related to this. Thus we analysed our data separately for either sex. Although there was a tendency for patients with severe disease to have higher CSa, Results were expressed as micrometre square (1 mm²=8 squares). Additional the plates were evaluated macroscopically for the observation of the migration between neutrophil wells. In our experiments we observed maximal chemotaxis (3 mm) frequently, however, we did not find any significant differences in chemotactic indices between diseases and healthy subjects.

An interesting aspect of our study was the migration between neutrophil wells that was observed in many of the Petri dishes. This was observed even though we had not used cellular materials as chemotactic agents. Presumably the gravity of the cellular materials overcame the chemical gradient of zymosan activated sera in some Petri dishes. Because of the observed migration between neutrophil wells, we suggest that there should be only one “triple well rank” in a Petri dish. On the other hand our method of preincubation of the whole blood for 45 minutes at 37°C before harvesting the PMNs (intended for better viability) might have been responsible for this phenomenon by increasing the chemotactic activity in all groups studied. Further studies are needed to clarify these issues.

BINNUR TÜZÜN
Department of Dermatology, Trakya University Medical Faculty, Edirne, Turkey

YALCIN TÜZÜN
CEM MAT
Department of Dermatology, Istanbul University Cerrahpaşa Medical Faculty, Istanbul, Turkey

SEBAHATTIN YURDAKUL
VEDAT HAMURYUDAN
HASAN YAZICI
Department of Rheumatology, Istanbul University Cerrahpaşa Medical Faculty, Istanbul, Turkey

YILMAZ OZAYZGAN
Department of Ophthalmology, Istanbul University Cerrahpaşa Medical Faculty, Istanbul, Turkey

Correspondence to: Dr B Tüzün, Büyükçekili Sokak Bele Apt 24/3, Nisantasi, Istanbul 80200, Turkey

Supported by TUBITAK (Turkish Scientific and Technical Research Council) (TAG 754).

Table 1 Chemotactic indices in men*  
<table>
<thead>
<tr>
<th>Groups</th>
<th>Number</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behçet’s</td>
<td>54</td>
<td>6.4 (8.0)</td>
</tr>
<tr>
<td>Severe Behçet’s</td>
<td>9</td>
<td>11.3 (12.1)</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>18</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<0.05, **p<0.01.

Table 2 Chemotactic indices in women*  
<table>
<thead>
<tr>
<th>Groups</th>
<th>Number</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behçet’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>
</tbody>
</table>

*not a regular feature of ocular BS (personal communication).

In vivo assays do not differentiate chemotaxis from chemokinosis. In the Carletto study clinically active Behçet patients demonstrated increased chemotaxis to sera by Senn’s modified in vivo assay. Others had found hyperchemotaxis might have been responsible fractions again by using an in vivo assay. Although it is difficult to compare the results of in vitro and in vivo assays, we thought these reported increases might have resulted from increased chemokinosis. In our experiments we observed maximal chemotaxis (3 mm) frequently, however, we did not find any significant differences in chemotactic indices between diseases and healthy subjects.

An interesting aspect of our study was the migration between neutrophil wells that was observed in many of the Petri dishes. This was observed even though we had not used cellular materials as chemotactic agents. Presumably the gravity of the cellular materials overcame the chemical gradient of zymosan activated sera in some Petri dishes. Because of the observed migration between neutrophil wells, we suggest that there should be only one “triple well rank” in a Petri dish. On the other hand our method of preincubation of the whole blood for 45 minutes at 37°C before harvesting the PMNs (intended for better viability) might have been responsible for this phenomenon by increasing the chemotactic activity in all groups studied. Further studies are needed to clarify these issues.

BINNUR TÜZÜN
Department of Dermatology, Trakya University Medical Faculty, Edirne, Turkey

YALCIN TÜZÜN
CEM MAT
Department of Dermatology, Istanbul University Cerrahpaşa Medical Faculty, Istanbul, Turkey

SEBAHATTIN YURDAKUL
VEDAT HAMURYUDAN
HASAN YAZICI
Department of Rheumatology, Istanbul University Cerrahpaşa Medical Faculty, Istanbul, Turkey

YILMAZ OZAYZGAN
Department of Ophthalmology, Istanbul University Cerrahpaşa Medical Faculty, Istanbul, Turkey

Correspondence to: Dr B Tüzün, Büyükçekili Sokak Bele Apt 24/3, Nisantasi, Istanbul 80200, Turkey

Supported by TUBITAK (Turkish Scientific and Technical Research Council) (TAG 754).


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.1 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 neurologically antigens, and autoimmune mechanisms, and 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 compared with controls

Downloaded from http://ard.bmj.com/ on June 26, 2017 - Published by group.bmj.com
Authors’ reply

We thank Drs Isenberg, Crawley and Woo for their interest in our paper.1 They argued that the dichotomy of the pathogenesis of CNS lupus in “immune mediated” and thromboembolic disease is too rigid, and both pathogenetic 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 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 pathogenic model of B cell mediated CNS lupus. But, as stated clearly in the article, even after exclusion of these ambiguous events 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.2 Currently we are investigating the distribution of the IL10 promoter haplotypes of neuropsychiatric disease SLE patients in an ethnically 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 ATA is a whole cluster of genes and therefore both explanations are equally speculative.

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.

References


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.2 They describe 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 resulted in questioning this diagnosis, permitting an earlier diagnosis of Whipple’s disease. It is widely reported in the literature, as far back as 1975,1 that increased serum ferritin may be of use in both diagnosis2 and monitoring of AOSD.1 Hyperferritinaemia is not 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 described 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
translational research. This comparison with the iron regulated pathway of ferritin synthesis is both intriguing and potentially revealing.

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.

MARK QUINN
ANDREW GOUGH
Department of Rheumatology, Old Home, Leeds General Infirmary, Great George Street, Leeds, West Yorkshire, LS1 3EX

Correspondence to: Dr M A Quinn.

4 Ota T, Higashi S, Suzuki H, Eto S. Increased ferritin levels and response to treatment in patients with 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.

DEBORAH SYMONNS
S M KNIGHT
Rheumatology, Macclesfield District General Hospital, Victoria Road, Macclesfield, Cheshire SK10 3BL

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. Biosis 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?

EMMA CLARK
KARL GAFFNEY
PETER MERRY
Department of Rheumatology, Norfolk and Norwich Hospital, Brunswick Road, Norwich NRI 3SR


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!”

DONNCHA O’GRADAIGH
DAVID SCOTT
Department of Rheumatology, Norfolk and Norwich Hospital, Brunswick Road, Norwich NRI 3SR
Amiodarone induced lupus

RUI SUSANO, LUIS CAMINAL, DAVID RAMOS and BERNARDINO DIAZ

Ann Rheum Dis 1999 58: 655-656
doi: 10.1136/ard.58.10.655