Cladribine in the treatment of systemic lupus erythematosus nephritis

Systemic lupus erythematous (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, 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 polyarthropathy, 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 II lupus nephritis. Treatment with pulsed intravenous cyclophosphamide and methylprednisolone was subsequently re-introduced 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., 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 monoclonal mofetil, which is reported to be effective in lupus nephritis, even in cases refractory to cyclophosphamide.

VLASSIS KONTOGIANNIS
PETER C LANYON
RICHARD J POWELL
CLINICAL IMMUNOLOGY UNIT
QUEEN'S MEDICAL CENTRE
NOTTINGHAM NG7 2UH
Correspondence to Dr V Kontogiannis.

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.1,2 Tacrolimus is a novel macrolide with potent immunosuppressive effects and with a very similar mechanism of action to cyclosporin 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.
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). 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 myo-cardial infarction was diagnosed because of raised MB-CK levels and ST-segment increase with loss of R waves in V6, V7, V3 on electrocardiogram. Antineutrophil cytoplasmic antibodies (c-ANCA) were disclosed in serum and necrotising vasculitis was shown on skin biopsy specimen. No antiphospholi-pid antibody or coagulation protein abnormality could be disclosed. Treatment consisted of intravenous administration of prednisolone, cyclophosphamide, sodium heparinate, diltiazem, dinsorsobide 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 corticosteroids 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. Intransanal endoscopic biopsies demonstrated necrotising vasculitis with epitheliod and giant cells. Treatment included oral prednisone and intravenous cyclophosphamide pulses. After a few days, serum creatine concentrations 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/day and the patient eventually achieved remission. In October 1996, abdomen computed tomogra-phy showed an intrasplenic lesion that was consistent either with a splenic infarct or haematoma (fig 1). The later cause 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 thrombophlebitic disorder could be found. Intransanal endoscopic biopsy revealed necrotising vasculitis with acencomocaral were given. Because of persistent left hypocondrium tenderness, splenectomy was performed in Sep-tember 1997. Histological examination showed spleen infarction with organised haematomata and sequelae of vasculitis (fig 2).

COMMENT
Because they are vessels without collateral flow, occlusion of distal parenchymal splenic arteries leads inevitably to splenic infarction. Of note, two of the three patients described by Wegener in 1936 had spleen infarction. The frequency of spleen involvement ranges from 50% to 100% of WG cases at necropsy. Histological data frequently reveal a severe arterial and venous thrombosis associated with intramyelinic c-ANCA, different from the pattern of Wegener's granulomatosis. Although granulomatous arteritis is rare without a necrotising component, we think that a diagnosis of Wegener's granulomatosis should be considered in all patients with concomitant splenic infarction and necrosis.
showed massive or multiple areas of splenic necrosis, associated to a variable extent with central arteritis, splenic trabeculitis, follicular arteriolitis, disseminated parenchymatous granulomatata 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. Inhalation infectious 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. A severe splenic haemorrhage occurred in patient 1, which was clearly related to both necrotising vasculitis and hypocouagulable state. Anticoagulation was indicated for inaugural myocardial infarction in case 1 and deep venous thrombosis in case 2, in both cases during active WG flare. Splenectomy was required in both our cases.

Our data suggest that antithrombotic treatment entails a specific risk of bleeding complications in patients with WG vasculitis. When anticoagulation is necessary in WG patients, computed tomography of the abdomen should be systematically performed and, if splenic infarction is disclosed, splenectomy should be considered.

THOMAS PAPO
DU NYT HEUONG
JEAN-CARLES PIETTE
Internal Medicine, Hôpital Pitié-Salpêtrière, Paris, France

MARK ANDRE
OLIVIER AUMAÎRE
Internal Medicine, Hôpital Gébats, Clermont-Ferrand, France

FRÉDÉRIC CHARLOTTE
Histopathology, Hôpital Pitié-Salpêtrière, Paris, France

JEAN-LOUIS KEMENY
Histopathology, Hôpital Gébats, Clermont-Ferrand, France

Correspondence to: Dr T Papo, Internal Medicine Unit, Hôpital Pitié-Salpêtrière, 83 Boulevard de l’Hôpital 75651 Paris cedex 13, France.


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 65 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 the past two years.

Physical examination disclosed malar rash, an aortic systolic murmur (grade II/VI), and hypothoemia 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), with lymphopenia (20 per cent), and normal platelet 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 test was negative.

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 cardiomegally. Pleural fluid was exudative, with lymphocytic predominance, without cytological features 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 did not show abnormal features.

The amiodarone was then 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, analytical or radiological findings were present, and three years later she still remained free of symptoms, and the ESR, complete blood count, and radiological data were normal. The titre of ANA decreased but remained weakly positive at 1:40. 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 cardiomegally. Pleural fluid was exudative, with lymphocytic predominance, without cytological features for malignancy.

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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. Pleuropneumonial 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 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, haematoological disorder (lymphopenia), and positive ANA test. Imputability criteria of amiodarone induced lupus are present on a semilogarithmic basis with classic features of DIL and on a chronological basis with disappearance of most of the symptoms after amiodarone withdrawal. The relapse could be explained because of the long elimination half time of the drug 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. 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, mesenteric panniculitis in three, spondyloarthropathy 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.

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, Sjögren's syndrome or acquired myelodysplasia.

Jean-Charles Piette
Roula El-Rassi
Zahir Amoua

Internal Medicine Unit, Hôpital Pitié-Salpêtrière, 83 Boulevard de l'Hôpital, 75651 Paris Cedex 13 France
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 infectiousum and transient erythematous rash 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 Young), dermatomyositis and polymyalgia rheumatica. 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 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-type blood group antigen (globoside), 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 in infected individuals. J Gen Virol 1988;69:1001–11.

Further, 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 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-type blood group antigen (globoside), 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 in infected individuals. J Gen Virol 1988;69:1001–11.

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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. However, others disagree. We have re-evaluated chemotaxis of polymorphonuclear leukocytes (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 pulmonary sarcoidosis, 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 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 micrometre 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 mm = 8 squares). Additionally the plates were evaluated macroscopically for 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 used to differentiate chemokinesis from chemotactic migration.

There is marked heterogeneity in disease expression in men and women in BS and we re-evaluated 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 male patients with BS 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, but not a regular feature of ocular BS (personal communication).

In vivo assays do not differentiate chemotaxis from chemokinesis. In the Carletto study clinically active Behçet patients demonstrated increased chemotaxis to sera by Senn's modified in vivo assay. Others had found hyperchemotaxis to 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 TUZUN
Department of Dermatology, Trakya University Medical Faculty, Edirne, Turkey

YALCIN TUZUN
CEM MAT
Department of Dermatology, Istanbul University Cerrahpasa Medical Faculty, Istanbul, Turkey

SEBAGHTIN YURDAKUL
VEDAT HAMURYUDAN
HASAN YAZICI
Department of Rheumatology, Istanbul University Cerrahpasa Medical Faculty, Istanbul, Turkey

YILMAZ OZYAZGAN
Department of Ophthalmology, Istanbul University Cerrahpasa Medical Faculty, Istanbul, Turkey

Correspondence to: Dr B Tuzun, Buyukciftlik Sokak 24/3, Nisantasi, Istanbul 80200, Turkey

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compared with controls in their study, we suspect that the difference in IL10 production is not attributable to functional difference 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 a 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 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 neuropsychiatric disease patients and therefore they are described with a low 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.

3. 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 both the non-neuropsychiatric and neuropsychiatric SLE patients. 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 mentioned above, there was an excess of patients with neuropsychiatric disease SLE.

The second explanation for the skewing found in IL10 promoter polymorphisms might be that the ATA SNP is associated with neuropsychiatric disease SLE in the ATA patients is not confirmed via an increased IL10 production at all, but that it is merely a marker for the real neuropsychiatric disease SLE susceptibility allele. It is not clear whether or not IL10 promoter SNPs are associated with low or high IL10 production, because of the ambiguous reports in the literature. In our laboratory, the -1082 A allele has been found to be associated with high IL10 production. In this light we have speculated that the susceptibility link of high IL10 production and the pathogenesis of neuropsychiatric disease SLE. Isernberg et al have referred to another group stating that -1082 A is associated with a lower vivo IL10 production 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. 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 may 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, that increased serum ferritin may be of use in both diagnosis and monitoring of AOSD. 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 observed 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

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 thrombocytopenic disease is too rigid, better polyclonal cytokine upregulation and imbalance 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 poorly 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 mismatched 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 thrombocytopenic events do not fit in the pathogenetic model of B cell mediated CNS lupus. However as stated clearly in the article, even after exclusion of these ambiguous patients 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 performing 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 present in the ATA promoter polymorphisms of patients with systemic lupus erythematosus. Arthritis Rheum 1998;41: 1090-5.


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.

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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.

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

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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 Hug(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?

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

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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!”

DONNCHA O’GRADAIGH
DAVID SCOTT
Department of Rheumatology, Norfolk and Norwich Hospital, Brunswick Road, Norwich NRI 3SR
Antinuclear antibodies in relapsing polychondritis

JEAN-CHARLES PIETTE, ROULA EL-RASSI and ZAHIR AMOURA

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