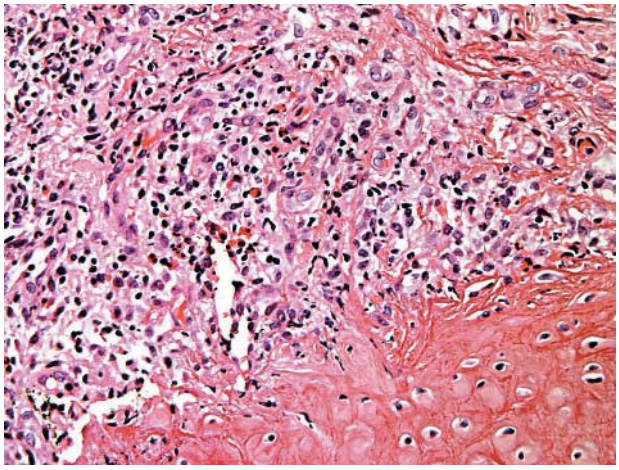

Figure 2 An inflammatory cell infiltrate obscures the chondrodermal interface and partially replaces the auricular cartilage: the findings are associated with RP (haematoxylin-eosin, ×400).

normal pain perception may indicate early destruction of receptors. If such occult damage involves cartilage tissue of large vessels, the consequences may be dramatic. This concealed process should be considered in planning follow up and prophylaxis of a flare.

Authors' affiliations
A P Rozin, B Shine Department of Rheumatology, Rambam Medical Centre and B Rappaport Faculty of Medicine, Israel-Technion Institute of Technology, Haifa, Israel
E Gez, Department of Oncology, Rambam Medical Centre and B Rappaport Faculty of Medicine, Israel-Technion Institute of Technology, Haifa, Israel
R Bergman, Department of Dermatology, Rambam Medical Centre and B Rappaport Faculty of Medicine, Israel-Technion Institute of Technology, Haifa, Israel

Correspondence to: Dr A P Rozin; a_rozin@rambam.health.gov.il

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Cerebral vasculitis as a primary manifestation of systemic lupus erythematosus

A T Rowshani, P Remans, A Rozemuller, P P Tak

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A 46 year old white man was referred to us because of an 8 week history of severe progressive headache and psychosis. Associated symptoms were minor somnolence, poor concentration, and weight loss of 10 kg in 3 months. No photosensitivity, fever, or night sweats were reported. Neurological examination was unremarkable. Also, general examination failed to show any abnormality. Especially, no skin abnormalities were apparent. Medical history disclosed an undocumented period of polyarthritis, and for 1 year he had been receiving acenocoumarol because of diagnosed amaurosis fugax.

Laboratory investigation showed a raised erythrocyte sedimentation rate (30 mm/1st h) with a normal C reactive protein and no signs of anaemia or thrombocytopenia. Leucocyte count was normal with slightly decreased lymphocytes (1.9×10^9/l). An antinuclear antibody (ANA) test was positive with a homogeneous pattern. A positive *Crithidia* test confirmed the presence of anti-dsDNA antibodies. Low avidity antibodies to dsDNA were detected (43 U/ml). IgM and IgG antibodies to cardiolipin could be demonstrated. The test for lupus anticoagulants was positive. Both lues serology and HIV test were negative. There were no signs of renal or liver disease. Lumbar puncture showed 115×10^6 leucocytes/l, containing 95% lymphocytes. The protein content of the cerebrospinal fluid (CSF) was raised (5 g/l) with an increased IgG index (1.06) without oligoclonal bands. Antineuronal and antiribosomal P-peptide antibodies were negative in serum and CSF. Cytological analysis of CSF and also polymerase chain reaction for mycobacterial infections showed no abnormalities. Chest *x* ray and cardiac ultrasound examinations were normal. Brain magnetic resonance imaging (MRI) showed an increased signal intensity on T_2 weighted images in the bilateral white matter and in the basal ganglia, which were progressive on repeat MRI (fig 1). Meningeal involvement could not be seen after contrast administration. Cerebral angiography was normal. Brain biopsy showed vasculitis with mononuclear cells, mainly lymphocytes, infiltrating the whole vessel wall, accompanied by fibrinoid necrosis and deposition of IgG and complement in several vessels (fig 2). The diagnosis was neuropsychiatric systemic lupus erythematosus (NPSLE) due to cerebral vasculitis.

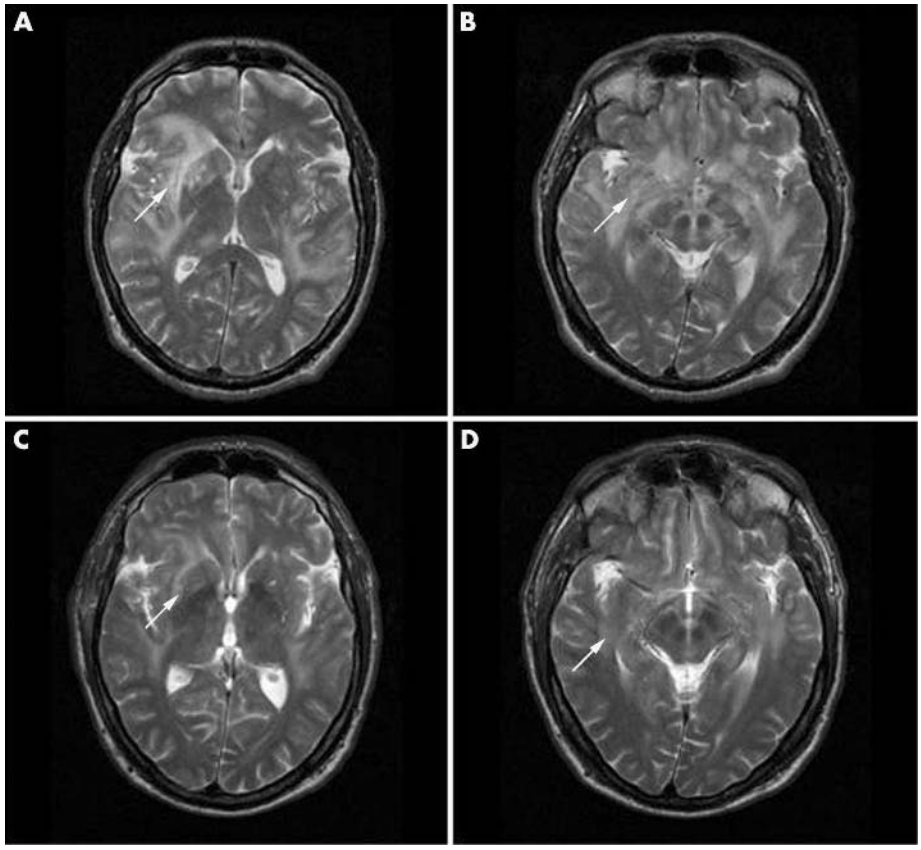

Figure 1 (A, B) Axial T_2 weighted fast spin echo MR images of the brain show increased signal intensity in the bilateral white matter and basal ganglia (arrows). (C, D) Follow up MRI shows a dramatic improvement of the white matter and basal ganglia abnormalities only 8 weeks after starting treatment.

Treatment consisting of intravenous methylprednisolone (3 days, 1 g/day), cyclophosphamide monthly (750 mg/m^2), and haloperidol resulted in an impressive and sustained clinical and radiological improvement after 6–8 weeks (fig 1). As evaluated by a psychiatrist and a neurologist, he no longer had psychosis, and his severe headache was relieved. He received another two methylprednisolone pulses at weeks 3 and 7 after starting treatment while continuing to receive prednisone 20 mg/day by mouth. Cyclophosphamide pulses will be repeated monthly for 6 months and then every 3 months until he completes 2 years of treatment.

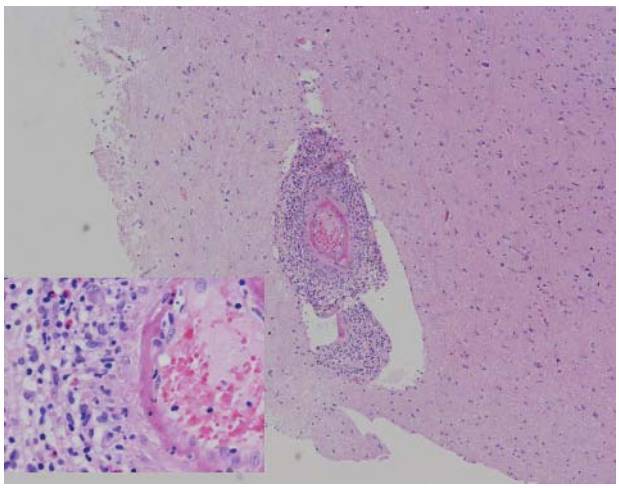

Figure 2 A cerebral biopsy specimen was taken from the right parietal hemisphere, leptomeninx, and cortex (original magnification ×200 and ×40). Severe histopathological signs of cerebral vasculitis in the cortex and leptomeninx can be seen, consisting of a diffuse mononuclear cell infiltrate through the whole vessel wall with fibrinoid necrosis in the presence of a normal cerebral angiogram of the same hemisphere.

DISCUSSION

This patient had cerebral vasculitis as a primary manifestation of NPSLE based on psychosis, an earlier episode of polyarthritis, histopathological findings, positive ANAs, anti-dsDNA antibodies, and antiphospholipid antibodies (aPLs). Active SLE as reflected by systemic organ involvement was notably absent, which made a differential diagnosis with other cerebrovascular events appropriate. This patient is a middle age man who was receiving acenocoumarol because of amaurosis fugax and had low titres of ANAs and anti-dsDNA, all of which is compatible with a low risk profile to develop (NP)SLE. Therefore, we performed a brain biopsy, which clearly demonstrated vasculitis. Cerebral vasculitis in SLE is rare and its incidence in postmortem studies does not reach 10%.[1–3] Various pathological mechanisms like ischaemic and haemorrhagic events, white matter abnormalities due to aPLs, accelerated atherosclerosis, small vessel vasculopathy, and thromboembolic processes can all play a part. Based on previous studies, it might be argued that aPLs had a role in direct neuronal damage and in the pathogenesis of endothelitis in this patient, although this has not been proved.[4 5] Cross reactivity between a subset of anti-DNA antibodies with *N*-methyl-D-aspartate type receptors in SLE supports the notion of shared antigenic target hypothesis as a possible underlying mechanism.[6]

No ''gold standard'' diagnostic test is available at present. Various attempts to link the pathogenesis with sensitive and specific tests have failed so far. Serum or CSF markers to detect NPSLE are lacking. MRI findings correlate with clinical manifestations only with a moderate sensitivity. Angiography may be normal if predominantly small vessels are affected. A recent European survey showed a high degree of perceived attention for cerebral angiography as a diagnostic tool for cerebral vasculitis.[7] This patient clearly demonstrates that a normal angiograph cannot rule out fulminate cerebral vasculitis. Despite the low risk of complication, a brain biopsy is usually not needed unless primary cerebral vasculitis is suspected. However, a combination of clinical, serological, and imaging data usually has sufficient diagnostic value and can be used to make the diagnosis in order to institute adequate immunosuppressive treatment.[8–10] This case report demonstrates that cerebral vasculitis as demonstrated by brain biopsy is a primary and early manifestation of NPSLE.

Authors' affiliations
A T Rowshani, P Remans, P P Tak, Division of Clinical Immunology and Rheumatology, Department of Internal Medicine, Academic Medical Centre, University of Amsterdam, The Netherlands
A Rozemuller, Department of Pathology, Academic Medical Centre, University of Amsterdam, The Netherlands

Correspondence to: Dr A T Rowshani, Academic Medical Centre, University of Amsterdam, Division of Clinical Immunology and Rheumatology, Department of Internal Medicine, PO Box 22700, 1100 DE Amsterdam, The Netherlands; T.Rowshani@amc.uva.nl

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C reactive protein: protecting from lupus in familial Mediterranean fever

S Ozen, A Bakkaloglu

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C reactive protein (CRP), a member of the pentraxin family, is a widely measured acute phase reactant. CRP concentrations have been shown to be increased in familial Mediterranean fever (FMF), which is the most common autoinflammatory disorder around the world.[1–3] Interestingly, CRP is not only increased during the attacks of FMF but in between the attacks as well.[3] Serum amyloid A protein levels are also increased in these patients.[4]

We have observed in our paediatric registry of over 1000 patients with FMF that many rheumatic diseases such as vasculitis and juvenile arthritis accompany FMF; we suggested that this might be due to the increased inflammatory milieu in these patients.[1] However, none of the patients had systemic lupus erythematosus (SLE). Conversely, none of our patients with SLE had associated FMF.

Again in a multicentre study including about 3000 Turkish patients, certain inflammatory diseases were markedly increased, whereas SLE was not.[5]

We suggest that this is because of the high levels of CRP in these patients.[1] These molecules are known to play an important part in the removal of apoptotic material by binding to the exposed small nuclear ribonucleoprotein (snRNP) particles. CRP mediates the removal of apoptotic cells.[6] Defective disposal of the potential autoantigens presented in the apoptotic blebs is a contributory factor in the pathogenesis of SLE. CRP has also been shown to bind to snRNPs.[7] Recently, Russell *et al* have shown that a polymorphism in the CRP gene associated with lower CRP levels was associated with antinuclear antibody formation and they suggested that reduced basal CRP expression predisposes to the development of SLE.[8] The rarity of SLE in patients with FMF may yet be further indirect clinical evidence of the role of CRP in protection against autoimmune diseases.

On the other hand, Adebajo and Davis drew attention to the decreased prevalence of SLE in West Africa[9]; they suggested that increased tropical infections might be a protective factor in this case.[9]

FMF is a very common disease in people of the eastern Mediterranean. Protection against SLE was probably not the selective advantage of the mutated gene; however, the augmented acute phase response seems to offer these patients at least one advantage.

Authors' affiliations
S Ozen, A Bakkaloglu, Department of Paediatric Nephrology and Rheumatology, Hacettepe University Faculty of Medicine, 06100 Ankara, Turkey

Correspondence to: Professor S Ozen; sezaozen@hacettepe.edu.tr

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