LETTERS TO THE EDITOR

Antibodies Against Retinal S-antigen in Patients with Juvenile Chronic Arthritis-Associated Uveitis

SIR—Uveitis associated with juvenile chronic arthritis (JCA) is the only type of uveitis that is consistently associated with a high prevalence of autoantibodies. The specificity of the antinuclear antibodies that are present include nucleosomal proteins [1], low-molecular-weight antigens [2] and histone autoantibodies [3]. Østensen found that antibodies to histone H3 were particularly associated with the presence of uveitis; in an earlier study, we confirmed that the prevalence of autoantibodies to five histone proteins is raised in JCA and that H3 histone antibodies were the most common [4].

Uveitis is thought to have an autoimmune pathogenesis: strong evidence for this lies in the models of autoimmune uveitis that can be produced in experimental animals using a variety of retinal autoantigens. The most widely studied experimental uveitogen has been retinal S-antigen, a photoreceptor protein, and it has excited particular interest that there are sequence homologies between retinal S-antigen and histone H3. Histone peptides sharing sequences with the uveitogenic peptides of S-antigen can induce an identical experimental autoimmune uveoretinitis. It has been proposed that homologies between retinal antigens and widely conserved nucleoproteins may allow an immune response directed against microbial antigens to trigger autoimmune uveitis through the mechanism of molecular mimicry [5].

Antibodies to bovine retinal S-antigen have been reported in patients with JCA-associated uveitis [6–8] and anti-photoreceptor antibodies have been found by immunofluorescence [9]. This is unexpected, as the uveitis of JCA does not typically involve the retina where S-antigen is found. Recent ELISA studies in adult uveitis patients, using human S-antigen, have failed to demonstrate raised levels of antibodies in patients compared to controls [10, 11], even when the retina is inflamed.

In a previous study, we were unable to detect any association between antibodies to histone H3 and the presence of uveitis, but antibodies to N- and C-terminal peptides were associated with the presence of uveitis. We therefore sought to confirm whether raised levels of human S-antigen antibodies occur in children with JCA-associated uveitis, and whether they correlate with the presence of antibodies to histone H3 or peptides derived from it.

Standard ELISA assays were performed using retinal S-antigen prepared from human and bovine eyes. Antigen-free wells were used for controls, and normal sera from children and adults, as well as adults with uveitis were used as control populations. Raised levels were defined as sera with levels >2 s.d. from the mean of the normal adult controls.

The prevalence of raised S-antigen antibody titres was as follows: adult controls, 2/24; paediatric controls, 0/7; adult uveitis, 1/12; JCA-associated uveitis, 1/69. There were no significant differences in prevalence between any of the groups; there were also no significant differences in antibody level between any of the groups (Mann–Whitney > 0.1).

Antibody levels to human S-antigen correlated with antibodies to histone H2B and the antinuclear antibody titre (P < 0.05 Spearman), but did not correlate with antibodies to histone H1, H2A, H3 or H4, or the histone H3 peptides 1–25 and 130–135.

Antibody titres against bovine S-antigen were similar in 46 patients and 28 controls, and again there was no difference in the prevalence of high-titre sera or the titres of antibody. The only association of antibodies to bovine S-antigen was with the total level of serum IgG.

Contrary to previous reports, we could find no evidence for abnormal levels of antibodies to human or bovine retinal S-antigen in children with JCA-associated uveitis. Antibody levels did not correlate with antibodies to histone H3, and neither immunogen is likely to participate in the pathogenesis of the uveitis found in JCA. The association of antibodies to bovine S-antigen with total immunoglobulin suggests that scrupulous internal controls are required when studying these autoantibodies in subgroups of patients with increased autoantibodies and hyperglobulinaemia.

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Familial Presence of Primary Cryofibrinogenaemia, A Report of Three Cases

Sir—Cryofibrinogenaemia (CryoF) is defined by the presence of cold-precipitable fibrinogen in plasma. Primary CryoF usually manifests itself by a Raynaud’s phenomenon, acrocyanosis or skin necrosis [1-4]. It also occurs in association with a variety of disorders and is then described as secondary. The histology of affected skin shows a leucocytoclastic vasculitis and an intravascular proteinaceous clot consisting of fibrinogen, sometimes with IgG [3, 4]. We report here three cases of primary CryoF in children. The known causes of secondary CryoF were excluded. In all children there was a familial occurrence of Raynaud’s phenomenon and/or acrocyanosis (Table 1).

Patient 1, an 11-yr-old boy, was admitted to our clinic with a 5 yr history of relapsing fever, generalized muscle weakness and arthralgia in hands and feet. Prior to admission, there had been a prolonged exposure to cold. His mother and two brothers are healthy. His father suffered from a myocardial infarction several years earlier. The mother’s sister is affected by a Raynaud’s phenomenon and a ruptured carotid artery. Her clotting tests were normal. The grandfather also suffered from a Raynaud’s phenomenon in association with a vascular disease; no clotting tests were available. Physical examination of the boy showed hypertension, iridocyclitis, painful cyanotic swelling of the fingers and feet, and numerous purpura on the legs and arms. Biopsy of a skin lesion showed a leucocytoclastic vasculitis, subcutaneous thrombosis and endothelial immune complex depositions. In some vessels a proteinaceous clot was seen (Fig. 1). He was treated with prednisone 30 mg daily for 4 weeks. He showed a marked remission and the prednisone treatment was slowly withdrawn. One year later he was well, but the CryoF was still present.

The second patient, a 10-yr-old girl, was referred for evaluation of a Raynaud’s phenomenon that had existed since infancy. One year ago, she developed purpura in reaction to minor trauma. Two older sisters had the same symptoms, but here the symptoms resolved spontaneously around age 5 yr. Her mother was healthy, but the father died suddenly at age 32 yr. Autopsy showed a fatty degeneration of the liver and cardiomyopathy. Physical examination of the girl showed purpura on the legs. A Raynaud’s phenomenon could be induced. No biopsies were taken. The purpura disappeared spontaneously, but the CryoF was still present 2 yr later.

Patient 3 is a 5-yr-old boy with a severe acrocyanosis of the hands and feet. Symptoms occur mainly in the morning after exposure to cold. There is also delayed wound healing. His mother and grandmother are affected with acrocyanosis and Raynaud’s phenomenon. The father is healthy. Physical examination of the boy showed a Raynaud’s phenomenon and superficial skin lesions on the feet.

The ESR was elevated in patient 1, but normal in patients 2 and 3. Whole blood cell counts, serum immunoglobulins and haemolytic complement were normal. In addition, ANA, RF, C1q binding and cryoglobulin tests were all negative. The plasma fibrinogen was elevated in patient 1 (7.8 g/l), but normal in patients 2 and 3, and all screened family members. Clotting tests were normal in all patients and their relatives. For the determination of CryoF, 5 ml blood were kept at 37°C in either heparin- or citrate-containing tubes. The plasma was stored at +4, 17 and 37°C for 5 days. The presence of a cryoprecipitate was then assessed by visual inspection. If present, the cryoprecipitate was separated from the