Clinical significance of antibodies against oxidised low density lipoprotein in early RA

There is increasing evidence to indicate that oxidative stress has a role in the process of tissue damage and perpetuation of inflammation in rheumatoid synovium. In accordance with the enhanced oxidative potential, patients show abnormalities in synovial fluid consistent with oxidative injury, such as end products of lipid peroxidation.

Antibodies against oxidised low density lipoprotein (Ox-LDL) occur in human serum samples, raised levels have been reported to be predictive of myocardial infarction and of the progression of carotid atherosclerosis. It has long been known that the life span of patients with rheumatoid arthritis (RA) is shortened, and it is now well established that deaths due to cardiovascular causes are an important determinant in the increased mortality associated with this disease. In view of the oxidative damage of low density lipoprotein taking place in the rheumatoid synovium, we set out to study the occurrence of antibodies against Ox-LDL in serial specimens from patients with recent onset RA. As we have seen cross-reactivity between Ox-LDL antibodies and cardiopit antibodies previously in systemic lupus erythematosus (SLE) the serum samples were also tested for cardiopit antibodies.

Seventy-eight consecutive patients (63 women, 15 men) with early RA (mean age 43.5 years, range 19–65; mean duration of disease 7.6 months, range 2–12) were included in the study. None of the patients had received any disease modifying antirheumatic drug treatment before entry into the study. Clinical and laboratory assessment of disease activity was carried out every three months during the first year and every four months during the second and third years of the follow up. Radiographs of hands, wrists, and feet were taken at entry into the study and thereafter annually during the follow up. The X rays were evaluated by the method of Larsen et al by the same observer and without knowledge of the clinical data. Blood samples for the determination of antibodies against Ox-LDL and against cardiopit by enzyme linked immunosorbent assay (ELISA) were taken at entry and at 6, 12, 24, and 36 months. All serum samples were stored at −20°C until analysed. The between-run coefficient of variation for an internal positive serum was 7% in the Ox-LDL antibody assay and 5% in the cardiopit antibody assay. The cut off for positive reactions in both assays was set at the mean +2 standard deviations found in serum samples from 30 healthy subjects with the same age distribution as the patients; serum samples from patients and controls were stored in the same way.

Differences between the groups were analysed using the Wilcoxon test for paired data and the Mann-Whitney test for unpaired test. Correlations were calculated using Spearman’s correlation coefficient test.

After starting disease modifying antirheumatic drug treatment a significant improvement was seen in all clinical and laboratory variables reflecting disease activity. Despite the stabilised clinical activity a steady radiological progression was found in hands and feet during the follow up (data not shown). The figure shows the levels of Ox-LDL antibodies during the three year follow up in individual patients. Antibodies to cardiopit behaved in a similar fashion. At the beginning of the study 14% (117/88) of the patients had raised levels of antibodies to Ox-LDL and 19% (15/78) had a raised level of antibodies to cardiopit. At three years these levels were both raised in 4% (3/78) of the patients. None of the patients positive for Ox-LDL or cardiopit antibodies had a history of thrombosis. Progression of atherosclerosis was not looked for.

There was a significant correlation between the initial levels of antibodies against Ox-LDL and cardiopit (r = 0.451; p < 0.001), giving reasons to suppose that in patients with RA these two antibody specificities are in part directed against shared antigenic epitopes. At the start of the study Ox-LDL and cardiopit antibody levels correlated with erythrocyte sedimentation rate and C reactive protein but not with rheumatoid factor, with clinical variables measuring disease activity, or with Larsen’s score (table).

The prognostic significance of Ox-LDL and cardiopit antibody levels was evaluated by dividing the patients according to tertile distribution of the initial antibody levels using indices shown in the table. No significant difference was seen in disease outcome at the end of the study between patients with initially the highest and lowest tertile distribution of antibodies to Ox-LDL and cardiopit (data not shown).

Antibodies to Ox-LDL have been found to occur commonly and in high levels in patients with SLE. In our patients the prevalence of positive reactions in the entry specimens was higher than in controls but not as high as that seen in patients with SLE. Because the Ox-LDL antibody level in entry specimens correlated significantly with erythrocyte sedimentation rate and C reactive protein, the occurrence of these antibodies must somehow be related to inflammation. However, the antibodies did not predict radiological progression. Owing to their low prevalence in follow up specimens, it is unlikely that Ox-LDL antibodies would have any major role, direct or indirect, in the increased mortality of patients with RA from cardiovascular causes.

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Age of onset in successive generations of patients with a spondyloarthropathy

Juvenile spondyloarthropathy (JSPA) is as yet not a fully defined disorder,1 but can be considered as a juvenile form of the adult spondyloarthropathy (SPA). Preliminary criteria for the latter have been proposed,2 the tip of the iceberg being ankylosing spondylitis. These criteria are also applicable for JSPA.3 The clinical presentation of JSPA may differ from adult onset SPA,4 but eventually a considerable percentage of patients with JSPA will develop a clinical picture indistinguishable from adult SPA.5 Ankylosing spondylitis has a strong association with the presence of the HLA-B27 antigen.6 The risk for a first degree HLA-B27 positive relative of a patient with ankylosing spondylitis developing that disease is about 20%.7 The clinical presentation of SPA in parents of children with early onset pauciarticular juvenile chronic arthritis than in the general population was reported previously.7 Possibly, the prevalence of SPA among parents with a child with SPA might also be higher than in the general population. We report that there is a tendency towards an earlier onset of SPA in the next generation.

Seven index patients were seen in the paediatric rheumatology clinic and presented with JSPA according to the European Spondyloarthropathy Study Group (ESSG) criteria,2 around the age of 10 (table). The age of onset in the children varied from 5 to 10 years (mean 8.3) and in the parents from 21 to 42 years (mean 31.1). The year of onset is the year the first complaints relating to the SPA were noticed. The clinical picture of the juvenile patients consisted of an asymmetric, IgM rheumatoid factor negative oligoarthritis with a predilection for joints in the lower extremities combined with features of enthesitis. Symptoms of inflammation of the lower lumbar spine were rare at presentation. All the children carried the HLA-B27 antigen. One of the parents of these seven index patients developed SPA (retrospectively diagnosed) according to the ESSG criteria in their third or fourth decade.

There may be several explanations for our observation. It could be a coincidental finding or biased by our daily practice: a parent might pay more attention to joint or back complaints when his/her child is diagnosed as having JSPA. It might also be explained by a simultaneous infection in the presence of the HLA-B27 antigen in the family members of two generations. A marked discrepancy between the calendar years of onset for the children and parents suggests an age of onset over subsequent generations. This phenomenon has been described in several monogenic neudegenerative disorders and possibly exists in familial rheumatoid arthritis.8 Recent observations have suggested that factors other than genetic factors may be associated with SPA.9 A variation in age of onset (8-51 years) was noted in one mult case family with a tendency towards an earlier age of onset in successive generations.10

Extended studies of HLA and non-HLA genes are required to answer the question whether the phenomenon of genetic anticipation occurs in SPA.

As unstable trinucleotide repeats have been described in neurodegenerative diseases correlating with the clinical phenomenon of genetic anticipation it may be worth looking for unstable genetic elements in familial SPA.

The authors are greatly indebted to Dr C. M. Deighton for his critical reading of the manuscript.

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Quinine induced lupus-like syndrome and cardiolipin antibodies

A large number of drugs are known to cause a clinical syndrome resembling systemic lupus erythematosus.1 The antirrhymic agent quinidine has been occasionally reported to cause such a syndrome.2,3 Additionally, the presence of cardiolipin antibodies has been described in patients receiving phenothiazine,4 procainamide,5 and ethosuximide treatment.6 Ankylosing spondylitis also has been associated with HLA-B27.7,8

Quinine is an antimalarial drug analogue to quinidine that can also produce several autoimmune abnormalities,1,2 but a lupus-like syndrome and production of cardiolipin antibodies induced by this drug have not been previously described. We report a case of well documented quinine induced lupus-like syndrome in which cardiolipin antibodies were also found.

A 30 year old white woman was admitted to our hospital in May 1994 because of fever, chills, and diaphoresis of three days duration. Six weeks before admission the patient had been on vacation in Cameroon, but she did not take any prophylaxis for malaria. Physical examination was unremarkable at time of admission except for fever up to 40°C. Laboratory examinations disclosed a packed cell volume of 0.37, haemoglobin 11 g/l, white blood cell count 3.8-10³/μl (76% neutrophils, 20% lymphocytes, 4% monocytes), and platelet count of 10.5 x 10³/μl. Thick smear showed Plasmodium falci num parasites of 10% to 10% of red blood cells. Direct examination of stool and culture tests were negative for other parasites. Blood cultures were also negative. Antinuclear, antitissue, and phospholipid antibodies were not detected.

The patient was diagnosed as having malaria and treated with quinine sulphate 600 mg three times daily.

Forty eight hours into treatment the patient was afebrile and a thick smear became negative for malaria. A biopsy of treatment the patient complained of dyspnoea and constant retrosternal chest pain.
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Ann Rheum Dis 1996 55: 558-559
doi: 10.1136/ard.55.8.558