Commentary

Are Gram negative bacteria involved in HLA-B27 associated uveitis?

The cause of HLA-B27 associated acute anterior uveitis is unknown. Half of the HLA-B27 positive acute anterior uveitis patients, if referred to a rheumatologist, fulfil the criteria for ankylosing spondylitis or reactive arthritis.[1] It has been suggested that in this group of diseases the HLA-B27 molecule functions as a common pathogenetic pathway.[2] Ankylosing spondylitis is also a disease with an unknown aetiology. The situation, however, is different for reactive arthritis. Reactive arthritis develops some weeks after a mucosal infection of the gastrointestinal or urogenital tract with Gram negative bacteria or *Chlamydia trachomatis*. These facts have stimulated research on a pathogenetic role of these bacteria in HLA-B27 associated acute anterior uveitis.

Several interesting results of investigations have recently been reported. Sprenkels *et al* studied sera from patients with HLA-B27 positive acute anterior uveitis with or without ankylosing spondylitis and from controls consisting of HLA-B27 negative acute anterior uveitis patients and HLA-B27 positive and negative healthy persons. They found that serum levels of both subclasses of IgA were increased in HLA-B27 associated acute anterior uveitis and ankylosing spondylitis.[3] This might suggest that mucosal infections are involved in the pathogenesis. Fluctuations of the IgA serum levels, however, showed no correlation with the exacerbations of acute anterior uveitis.[4]

In a collaborative study with bacteriologists in Turku, Finland, it was found that increased IgA antibody titres to extracts of *Klebsiella pneumoniae* were detected in the serum of HLA-B27 negative acute anterior uveitis patients but not in sera of HLA-B27 positive acute anterior uveitis patients.[4] When such sera were tested with an immunofluorescence technique for antibodies to Gram negative bacteria – for example, *Klebsiella* K43, the results were negative.[4]

About 10 years ago, Ebringer's group in London showed that patients with active ankylosing spondylitis had increased IgA antibodies against *Klebsiella pneumoniae*.[5] They recently reproduced this observation by studying the sera from active ankylosing spondylitis patients collected by Sprenkels. However, no increased IgA antibodies to these bacteria were found in the sera from HLA-B27 positive patients having acute anterior uveitis only.

Recently, Sahly *et al* studied whether the antibodies against *Klebsiella* capsular polysaccharides are specific for certain serotypes. About 40% of ankylosing spondylitis patients showed IgG antibodies against the serotypes K26, K36, and K50 in increased titres, while such a reaction was not observed in any of the remaining 74 serotypes studied. Only about 10% of normal controls showed such titres against the three serotypes.[6] They further reported that the incidence of increased titres against these serotypes may be as high as 85% in HLA-B27 positive acute anterior uveitis patients.[7]

These findings stimulate further research for a pathogenetic role of these and other Gram negative bacteria. Traces of Gram negative bacteria and *Chlamydia* have been found in the joints of reactive arthritis patients. Both bacterial antigen and DNA have been demonstrated. On the other hand it is clear that no bacterial infection of the affected joints was present. A similar absence of local infection is probable in the anterior segment of the eye, before or during an acute anterior uveitis exacerbation, when the antigen may be present. The relation between bacterial infections and the HLA-B27 associated diseases is therefore complicated.

Bacteria such as *Salmonella* and *Yersinia* can penetrate and proliferate in lymphocytes. Peptides derived from or generated by, these bacteria can be presented by HLA-B27 molecules to cytotoxic T lymphocytes. Such cytotoxic T lymphocytes, which attack and kill the peptide (antigen) presenting cell, have been found in the affected joints of reactive arthritis patients.[8] It is possible that such a process is responsible for the arthritis.

Whether an analogous activity is present in acute anterior uveitis eyes is, for the moment, a speculation. The problem is even more difficult to explain when one considers that acute anterior uveitis may affect both eyes but mostly one at a time. Nevertheless a possible pathogenetic role of Gram negative bacteria in HLA-B27 associated acute anterior uveitis merits further study.

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