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Yersinia-induced uveitis in Ireland

D F P LARKIN,[1] M T CAFFERKEY,[2] AND P EUSTACE[1]

From the [1] Eye Department, Mater Misericordiae Hospital, Dublin 7, and [2] Department of Clinical Microbiology, St James's Hospital, Dublin 8

SUMMARY A prospective study was undertaken on 54 patients with an apparently idiopathic first attack of acute anterior uveitis. Blood samples were assayed for antibodies to *Yersinia enterocolitica* and *Yersinia pseudotuberculosis*, and tested for HLA type. Thirteen patients were found to have serological evidence of recent yersinia infection, eight with *Y. enterocolitica* and five with *Y. pseudotuberculosis*. The clinical course of uveitis did not differ from that typically found in HLA-B27 positive patients. Five patients were observed to develop non-ocular inflammation at a variable interval. The means by which eye inflammation follows yersinia infection is discussed in the light of recent theories on pathogenesis of HLA-B27 associated diseases.

Acute anterior uveitis (AAU) is defined as iridocyclitis lasting less than three months[1] and constitutes a significant proportion of all cases of uveitis. The incidence has recently been calculated at 8·2 new cases per 100 000 population.[2] The differential diagnosis of the precipitating cause has continued to change with new or more clearly defined clinical entities and improved laboratory diagnosis; however one recent retrospective analysis has shown that 43% of cases of AAU remain idiopathic.[3] Reported data on the prevalence of HLA-B27 in AAU vary, with an average of 50%, and the role of environmental and genetic factors in the pathogenesis of HLA-B27 associated disorders is not clear. It has long been suspected that AAU and related systemic inflammations result from a triggering agent acting across a mucosal surface such as the intestine. *Klebsiella* species have attracted particular interest, and variable recovery rates from faeces of AAU patients have suggested, but not confirmed, an association.[4,5] Two retrospective studies in Finland have reported AAU associated with yersinia infection.[6,7]

Yersiniae are Gram-negative rods. The genus comprises the species *Y. pestis*, *Y. enterocolitica*, and *Y. pseudotuberculosis*, and the latter two are divided into several serotypes. Yersiniae have the capacity to grow in refrigerator temperatures, and contaminated food is thought to be the most common route of infection.[8] *Y. enterocolitica* and *Y. pseudotuberculosis* are intestinal pathogens causing acute enteritis but may initiate immunological complications such as erythema nodosum and arthritis. *Y. enterocolitica* and *Y. pseudotuberculosis* are endemic in Finland, where antibodies against them are found in 3 to 8% of the general population.[9] Yersiniae are not considered common pathogens in Britain or Ireland. However, a recent large survey in Dublin revealed that 31% of patients with acute appendicitis had serological evidence of yersinia infection.[10] Accordingly it was decided to undertake a prospective study of patients with AAU for evidence of yersinia infection.

Correspondence to Mr D F P Larkin, MRCPI, FRCSGlas, University Department of Ophthalmology, Bristol Eye Hospital, Lower Maudlin Street, Bristol BS1 2LX.

Patients and methods

PATIENTS

Patients who presented between June 1985 and February 1987 with their first attack of AAU were eligible for inclusion in the study if no underlying cause was clinically evident. These patients had only eye symptoms. Patients were ineligible (1) if they had a prior diagnosis of a disease related to AAU, such as sarcoidosis or ankylosing spondylitis, or (2) if they had non-ocular symptoms, such as joint pain. Patients with chronic or primarily posterior uveitis were excluded. Fifty-four consecutive patients (35 male and 19 female) were recruited. The mean ages were 32·6 years for male patients and 30·2 for female patients.

Blood samples from the study group were compared with those from 120 healthy, asymptomatic controls. This control population was composed of

medical students, blood donors, and antenatal clinic patients.

METHODS

Patient assessment. Diagnosis of AAU was in all cases made by slit-lamp biomicroscope examination and details recorded. Patients were questioned about non-ocular symptoms. In each case a venous blood sample was taken at presentation for HLA typing and assay for antibodies to yersinia. In 21 patients a second blood sample was taken after seven or more days (group 1), leaving 33 patients in whom only acute phase samples were taken (group 2). More wide ranging investigations were later performed on selected patients as indicated: in particular, sacroiliac or other joint *x*-rays were performed if joint symptoms or signs developed.

Serology. All blood samples were assayed for antibodies to *Y. enterocolitica* serotypes 0:3 and 0:9, and *Y. pseudotuberculosis* I to V, the principal pathogenic serotypes in Europe. Titres were measured by tube saline agglutination tests on serum. This test detects IgM and agglutinating IgG antibodies, both of which are present in the acute and early convalescent phases of yersinia infection.[11] Control cultures, antisera, and a protocol for serological testing were kindly supplied by the Yersinia Reference Laboratory, Leicester. Single high titres or a four-fold rise in titre were considered evidence of yersinia infection.

Results

The clinical features of patients in group 1 (with sequential samples) and group 2 (with acute phase samples only) are shown in Table 1. Thirty of the total of 54 patients, including all 13 patients with yersiniosis, were HLA-B27 positive.

Group 1. Seven of the 21 patients who underwent sequential sampling had serological evidence of yersinia infection. *Y. enterocolitica* 0:3 was the most common serotype. Patients with higher titres tended to develop more non-ocular abnormalities, particularly arthritis. It is consistent with previous reports that yersinia antibody titres are higher in patients with joint involvement.[12]

Group 2. Yersiniosis was diagnosed in six of the patients who had acute phase sampling only. More varied serotypes were identified in this group. Titres were lower than in group 1, but rising titres would be expected if sequential blood samples had been taken. Ocular inflammation was the only evidence of disease in these patients, and this may have been a reason for poorer compliance with follow-up.

In patients who had yersiniosis the clinical features of AAU were similar regardless of species or titres. Unilateral severe AAU was the rule, with visual acuity markedly reduced as with all HLA-B27 patients. No patients had mutton fat keratic precipitates or secondary ocular hypertension. There was marked protein extravasation in the aqueous in 10, posterior synechiae in nine, and anterior vitritis in seven of the 13 cases. In addition to topical therapy, subconjunctival corticosteroid and a mydriatic were required in 11 cases and oral corticosteroid in four. Uveitis resolved in all cases after treatment. Visual acuity improved to normal in all except patient number 7. Recurrence of AAU was seen in six cases, sometimes alternating to the fellow eye. In patient 7 secondary cataract developed which required extraction.

Five yersiniosis patients proceeded to develop non-ocular symptoms (arthralgia with or without diarrhoea or dysuria), in all cases within weeks of presentation (see Table 1). Joint symptoms developed in all five and sacroiliac joint *x*-rays were performed on these. Sacroiliitis was radiologically confirmed in three; knee and ankle effusions occur-

Table 1 *Anti-yersinia antibodies and clinical features in 13 patients with AAU after yersinia infection. Patients 8–13 had only acute phase blood samples taken*

Patient	*Age*	*Sex*	*Yersinia serotype*	*Maximum titre*	*Diarrhoea*	*Arthritis*	*Urethritis*
1	23	M	*pseudotuberculosis* III	160	–	–	–
2	28	F	*enterocolitica* 0:3	320	–	+	+
3	34	M	*enterocolitica* 0:3	320	–	+	–
4	29	M	*pseudotuberculosis* IV	320	–	+	+
5	22	M	*enterocolitica* 0:3	640	+	+	–
6	37	M	*enterocolitica* 0:3	>1280	+	+	+
7	45	M	*enterocolitica* 0:3	160	–	–	–
8	29	F	*enterocolitica* 0:3	80	–	–	–
9	30	F	*pseudotuberculosis* II	160	–	–	–
10	23	M	*pseudotuberculosis* IV	160	–	–	–
11	24	F	*pseudotuberculosis* III	160	–	–	–
12	43	M	*enterocolitica* 0:9	80	–	–	–
13	20	F	*enterocolitica* 0:3	80	–	–	–

red in the other two patients. Urethritis occurred in three patients, in whom chlamydia was excluded as the cause.

Sarcoidosis was later diagnosed in two patients who were yersinia-negative. Brucellosis was diagnosed in one patient whose acute-phase specimen contained antibodies to *Y. enterocolitica* 0:9 in titre 1:320. This cross reaction is well described.[13] Subsequent sampling gave negative results for yersinia and brucella agglutinating titres of 1:1280.

Two members of the control population had titres to *Y. pseudotuberculosis* IV of 1:160. The remaining 118 were negative to all yersinia serotypes tested.

Discussion

This study has shown that a considerable proportion (24%) of patients who presented with an apparently idiopathic first attack of AAU had serological evidence of yersinia infection. Joint disease was the most common non-ocular consequence of infection, later becoming evident in five of the 13 patients with yersiniosis. Higher titres of antibody to yersinia were noted in this group.

Two retrospective studies from Finland reported a total of 45 cases of AAU; 42 of these followed *Y. enterocolitica* infection and three followed *Y. pseudotuberculosis*.[6,7] In contrast, AAU was associated with antibodies to *Y. pseudotuberculosis* in five of the 13 yersiniosis patients in this study. This reflects the relatively high reported incidence in Dublin of infection with this pathogen.[10]

Reiter's syndrome follows genital infection, and the classical triad of urethritis, arthritis, and ocular inflammation is frequently incomplete. Similar arthritis developing in association with gastrointestinal infection is termed 'reactive arthritis'. More than 23 named organisms have been convincingly implicated in reactive arthritis, including *Y. enterocolitica* and *Y. pseudotuberculosis*.[14,15] Association with HLA-B27 has been confirmed in several studies.

Timing of uveitis and arthritis after abdominal disease suggests that some kind of host reaction is involved in pathogenesis. Association with HLA-B27 implies genetic factors. Bacterial factors influencing the outcome of infection are serotype and carriage of plasmids (extrachromosomal genetic material) which encode virulence. While these host and bacterial factors can be identified which influence outcome of infection by organisms such as yersinia, a hypothetical model must be discussed to explain the pathogenesis of inflammation. According to the molecular mimicry hypothesis, there is cross reactivity between antigenic determinants on bacteria and the HLA-B27 antigens. A consequence of shared determinants between host and foreign antigens is the production against foreign antigens of antibodies which attack target cells (for example, anterior uvea) bearing self antigens and thereby initiating an inflammatory reaction. Cross reacting antigenic determinants are shared by all enteric organisms isolated from B27-positive patients.[16,17] However, cross reactivity cannot explain why the uveal tract (or sacroiliac joints) are preferentially affected, since B27 is not organ specific. The uveal tract is anatomically an isolated area, relatively inaccessible to microbial infection but accessible to diffusible antibodies from the circulation. If target tissue in the uveal tract has molecular structures similar to those on microbes cross reacting with HLA-B27, then perhaps uveitis could be induced.

In a follow-up period of more than one year in most cases we have found inflammation to be confined to the eye in eight of 13 yersiniosis cases. This emphasises that a complete reactive arthritis syndrome is unusual in AAU following yersinia infection, a fact apparent in another series.[7] Acute anterior uveitis following yersinia infection may manifest independently of joint, gastrointestinal, or urethral symptoms. However, these allied abnormalities may be subclinical rather than absent. Intestinal inflammation has been histopathologically confirmed in 67% of reactive arthritis patients, 73% of whom had no symptoms.[18] Similarly, eye inflammation may be subclinical in patients who have clinically evident inflammation elsewhere due to yersinia or similar infection. In other cases the opposite may be true, with eye inflammation dominating the clinical picture.

In recruitment of AAU patients for this study we selected patients who would probably not otherwise be investigated or in whom investigation would not yield a definitive diagnosis. The significant number of these patients with yersinia infection has prompted this report. While it may indicate unusually high prevalence of yersiniosis in Ireland, it is likely that the condition is underdiagnosed by ophthalmologists outside Scandinavia.

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