Uveitis in B27-related disease

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I have always thought that uveitis must be the ocular manifestation of a systemic disease. When the uveitis clinic at the Institute of Ophthalmology in London was started in the 1950s a team of physicians examined all our cases. The results were very disappointing. Apart from a few cases of sarcoidosis and an occasional case of severe ankylosing spondylitis (AS) little of any significance was found. Then some 20 years ago Mr. Ambrose King, venereologist to the London Hospital, suggested that investigating the urogenital tract in patients with uveitis might be profitable. Thus Dr. R. D. Catterall was attached to the clinic.

Findings in 226 patients

Dr. Catterall examined 226 consecutive male patients attending the clinic (Table 1). Nearly 70% of them had chronic prostatitis.^{59, 60} Further analysis showed that the association was strongest in cases of acute anterior uveitis.

Beyond prostatitis and uveitis, joint changes typical of Reiter's syndrome (RS) or AS were present with the following rheumatic features and proportion of cases: prostatitis alone 34%; plantar fasciitis 2%; atypical sacroiliitis 6%; RS 36%; AS 23%.

Prostatitis was much less common in acute posterior uveitis and none of these patients had joint changes. This finding was particularly reassuring, because the cause of the uveitis in this group was considered to be toxoplasmosis. Some patients with other types of uveitis were also found to have urogenital infection and occasionally joint changes, but the results clearly showed that there was a large group of patients with the triad of uveitis, urogenital infection, and joint changes, the uveitis being predominantly an anterior one (Table 2).

Table 1 *Type of uveitis in series of 226 cases examined*

Type of uveitis	Acute (%)	Chronic (%)
Anterior	63	9
Posterior	12	2
Generalised	10	4

Table 2 *Association of uveitis with urogenital infection and joint changes in 226 cases*

	Uveitis alone	Prostatitis	Prostatitis plus joint changes
Anterior uveitis	37	43	72
Posterior uveitis	17	10	3
Generalised uveitis	12	10	7
Non-uveitis cases	15	1	0

Although these findings were substantiated by a similar investigation in Scandinavia²⁰¹ they were greeted with scepticism by many ophthalmologists, particularly in the United States. We were therefore greatly relieved and excited when our proposed association of uveitis, urogenital infection, and joint disease was confirmed from such an unexpected source as the study of histocompatibility antigens.

Association with HLA-B27

It is now clear from the work of Brewerton *et al.*³⁹, Mapstone and Woodrow,^{205, 206} and subsequent workers that about 50% of patients with acute anterior uveitis possess HLA-B27 and that many of them also have some associated rheumatic disease. This type of uveitis is more common in men than in women and women are less likely to have overt rheumatic disease. But the incidence of HLA-B27 is very similar in both men and women with acute anterior uveitis. Combining the figures of Brewerton *et al.*³⁹ with those of Mapstone and Woodrow²⁰⁶ we see that 55% of both men and women were HLA-positive but that the incidence of associated disease was 30% in the women compared with 68% in the men. This is a statistically significant difference ($\chi^2=10.68$; $0.005 > P > 0.001$), and if, as seems likely, the aetiology of the uveitis is the same in all patients with HLA-B27 many women are in some way protected from developing the joint complications.

Our experience from the uveitis clinic confirms this difference between men and women with anterior uveitis. In fact, we have been unable to identify a

clearly defined group of women with the triad of uveitis, urogenital infection, and joint disease comparable to that found in men. Chronic cervicitis was a common finding, but I suspect that until we can identify the causative organism in non-specific urethritis it will be difficult to prove a link between urogenital infection and uveitis in women.

Clinical features

Clinically anterior uveitis in patients with HLA-B27 presents as a sudden attack of redness, pain, and blurred vision. Examination on the slit-lamp microscope shows a massive exudation of protein and cells into the aqueous humour. Fibrin clots may be seen and sometimes the cells settle in the lower part of the anterior chamber to form a hypopyon. The pupil contracts and often becomes adherent to the lens, forming posterior synechiae. If the fundus can be seen there may be some hyperaemia of the optic disc and dilatation of the retinal veins, but focal retinal or choroidal lesions do not occur. This contrasts with the severe uveitis in Behçet's disease, which is always accompanied by signs of a retinal vasculitis and eventual obliteration of the retinal vessels and optic atrophy. The attack responds rapidly to intensive corticosteroid treatment but recurrences are usual, stress being a factor in some cases.

Men are affected more often than women and the first attack usually occurs in the third or fourth decades. There are interesting differences in the racial distribution of this type of uveitis (Figure). I have compared the percentage incidence of this type of uveitis in different racial groups who have

been seen in the uveitis clinic in London with the addition of some figures from a uveitis survey in Japan. The most striking features is the absence of Negroes from West Africa and the very low incidence in Japan. Very probably these findings result from differences in incidence of HLA-B27 in these populations.

Discussion

Unfortunately the HLA-B27 story does not solve all our problems concerning uveitis. About half the patients with acute anterior uveitis do not have HLA-B27, and yet I have been unable to differentiate on the ocular appearances which ones will have B27 antigen. Mapstone and Woodrow²⁰⁶ concluded that patients with HLA-B27 were more likely to have a severe uveitis, particularly with fibrinous exudate in the anterior chamber, than those without HLA-B27. I agree that severe, exudative type of uveitis in a man is very likely to be associated with RS and hence HLA-B27. But if milder cases are further split into B27-negative and B27-positive the most significant difference is that the latter have a higher incidence of a family history of AS and are more likely to have overt joint disease and evidence of genitourinary infection. The similarity of the ocular signs in patients with and without HLA-B27 does not necessarily imply that the aetiology is the same. Quite possibly acute anterior uveitis results from more than one mechanism.

The clinical features of acute anterior uveitis can be mimicked in animal experiments. If a foreign antigen such as bovine serum albumin is injected into the vitreous of a rabbit's eye there is little reaction until some 10 days later. Then there is a sudden hyperaemia and breakdown of the blood aqueous barrier with massive exudation of protein into the anterior chamber. This reaction is thought to result from the combination of circulating antibodies with antigen remaining in the eye, which induces the release of biologically active chemicals which act on the blood vessels. Among these substances are prostaglandins. Our experimental studies have shown that prostaglandin applied to the eye can produce a very similar reaction and that prostaglandins are present in the aqueous of animals with experimental uveitis. We have also shown that prostaglandin is present in the aqueous humour of untreated patients with acute anterior uveitis. It is tempting to conclude that this type of uveitis is induced by antibody-antigen combination in the eye. If this is so we are faced with the problem of identifying the antigen. Numerous investigators have looked for

Figure Proportion of cases of uveitis due to rheumatism in various geographical areas.

organisms in the aqueous humour from cases of uveitis. With few exceptions, nothing has been found. It would greatly help if we knew what to look for. Perhaps the answer will be provided by this meeting.

General discussion

DR. A. CALIN: As clinicians we use the term conjunctivitis and uveitis very loosely and often synonymously. Could you give us some of your views about which patients get conjunctivitis and which get uveitis?

PROF. PERKINS: Yes, these are strictly uveitis patients that we see. Certainly, there may be conjunctivitis with RS. It comes on a bit earlier than the uveitis. An important differentiating point is that when a patient has a red eye and also a *visual change* with *blurring of vision* almost certainly it is not a case of mere conjunctivitis. There may be floating mucous in front of the cornea in conjunctivitis which causes momentary blurring, but if the visual acuity between the two eyes differs I would strongly suspect that it is a case of uveitis.

DR. CALIN: Do you assume that there is different mechanism for conjunctivitis and uveitis?

PROF. PERKINS: I always thought of the conjunctivitis as being a surface reaction or infection, but this may be entirely wrong.

DR. T. L. VISCHER: Did you test for any antinuclear factors in some of the HLA-B27-negative women to find a link with pauciarticular arthritis?

PROF. PERKINS: We are in the process of doing so.

PROF. A. S. RUSSELL: Our figures are obviously very similar to yours. We are using bone scans, and we were able to increase the yield of sacroiliac abnormalities a little across the board. But what is particularly impressive was that it brought the percentage of affected females up to that of males.

PROF. PERKINS: I think that Dr. Brewerton will agree that when he examined the younger women he did not radiograph the sacroiliac joints of all of them.

DR. D. A. BREWERTON: For ethical reasons we stopped radiographing women under 45 at an early stage in our investigations.

PROF. PERKINS: So it is quite likely that many more were involved.

PROF. T. BITTER: This may be the reason why, in Lausanne, we get quite a different sex ratio (M:F=2:1) than in the Anglo-Saxon reports.

PROF. PERKINS: I would emphasise that the rheumatic signs and symptoms of the female patients with uveitis that we see in an eye clinic are very slight. They have to be actively asked for any symptoms.

PROF. RUSSELL: Indeed, so many of the patients with grossly abnormal radiological sacroiliac changes vigorously deny any symptoms whatsoever. They have no restriction of back movement and yet radiologically they are clearly abnormal.

PROF. PERKINS: Moreover, as Dr. Amor shows, the iritis tends to come on years after the initial attack.

PROF. V. WRIGHT: I am glad you have brought us back to the prostatitis story. I am not sure, however, what it means. You used the phrase 'urogenital infection'. I think that to equate prostatitis with urogenital infection goes a little bit further than the data really warrant.

DR. G. R. V. HUGHES: I must confess to a personal prejudice. I trained at a hospital where everybody with spondylitis was sent over to the venereology department where a resident weighing 14 stone gave vigorous prostatic massage. Cell counts were a bit high in many patients.

PROF. C. M. PEARSON: Professor Perkins, since your cultures of anterior uveal fluid have been negative so far, might it be worthwhile to do some more sophisticated studies—for instance, to make a search for cell wall products such as peptidoglycans or proteoglycans utilising a gas liquid chromatography system? Many bacterial cell wall products are non-metabolisable in humans, as I will discuss later, over long periods.

PROF. PERKINS: It is a small amount of fluid so there is not very much to play with.

PROF. PEARSON: There would probably be enough to use the methods I have mentioned. There was a report at the ARA meeting in New York in early June 1978 that peptidoglycan products of bacterial cell wall were present in almost 70% of synovial fluid and synovial fluid cell pellets in rheumatoid arthritis.²⁰

DR. BREWERTON: First, may I answer Dr. Vischer's question? Patients without B27 do not have antinuclear factor. May I now add a small observation. We saw 16 patients with RS in whom the uveitis was asynchronous, being unrelated in time to the activity of the urethritis. All of these patients had B27. We saw four patients without rheumatic disease whose uveitis often followed recurrences of urethritis. None of them had B27. This suggests two separate mechanisms. To rheumatologists it is reminiscent of the situation in chronic inflammatory bowel disease where the spondylitis is asynchronous and related to B27, whereas enteropathic peripheral arthritis goes in time with the bowel disease and does not have B27.

DR. CALIN: Is the eye disease usually unilateral and

are future attacks in the same eye or the contralateral eye?

PROF. PERKINS: It is usually one eye to start with. It may remain in that eye but more often it flits from eye to eye.

PROF. M. ZIFF: Do you know the incidence of uveitis in RS?

PROF. PERKINS: No, I am not sure what constitutes Reiter's!

DR. G. W. CSOKA: If I may just go back to prostatitis. Like Dr. Hughes, I am very sceptic about the diagnosis in general. We have not got a vigorous 14-stone resident to massage the prostate but I did it myself in patients with RS and in unselected patients who happened to be, unfortunately for them, inpatients in the medical ward with miscellaneous conditions. We found, by the criteria laid down by Dr. Oates at the London Group, that 30% of those in the medical ward had prostatitis! We went back to them and found that none had any urogenital disease whatever. They had cardiac lesions, neurological lesions, and you-name-it but not urogenital disease. I have no doubt that chronic prostatitis does exist

but the criteria at the moment are very, very vague indeed.

PROF. PERKINS: I would agree entirely with Dr. Csonka. About 30% of other types of uveitis had a prostatitis but they did not have the accompanying joint diseases. If you compare the acute anterior uveitis cases with the posterior and generalised groups there is a significant difference even in the prostatitis let alone the joint changes. So, using the same technique and the same examiner in different types of uveitis there were significant differences.

PROF. A. E. GOOD: Is keratitis associated with RS?

PROF. PERKINS: I have not seen it. I think it can be, but I have not seen it.

DR. HUGHES: I was interested to hear that you found free prostaglandin in the fluid. There have been recent interesting studies from Ralph Williams's group, who have shown in sarcoid patients who have anergy by Mantoux testing a subpopulation of glass-adherent suppressor T cells which secrete prostaglandin E. I wonder whether this might come up in the discussion later on yersinia-associated erythema nodosum?