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Anti-prostate Antibodies in Arthritis

A. GRIMBLE,* M.D., M.R.C.P.; M. H. LESSOF,† M.D., M.R.C.P.

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Little evidence has been offered to explain the association between the lower genito-urinary inflammation of Reiter's syndrome and the polyarthritis and conjunctivitis which follow. The presence of an infective agent has seemed likely but remains unproved. The syndrome follows a urethritis, though this may go unrecognized at the time. Subacute prostatitis is thought to be an important feature, as it may also be in ankylosing spondylitis (Mason *et al.*, 1958). It is possible, therefore, that the joint manifestations of this disease may depend on a hypersensitive reaction, and that an underlying prostatitis may play a part. In a number of cases a circulating antibody to a prostatic antigen has been demonstrated (Grimble, 1964).

This paper is concerned with a review of 400 cases in which tests were made for antibody to a prostatic antigen. The test used was the haemagglutination test previously described (Grimble, 1964). The majority of male patients in this series had been diagnosed as having Reiter's syndrome, ankylosing spondylitis, rheumatoid arthritis, prostatitis, conjunctivitis, or uveitis. A miscellaneous group of 116 subjects had other disorders, usually affecting the joints, genito-urinary tract, or eyes. The object of this study was to assess the clinical usefulness of the test and to consider whether the results had a significant bearing on the aetiology of these diseases.

Patients Studied and Methods

For a presumptive clinical diagnosis of Reiter's syndrome (Brodie, 1818) in the acute stage two criteria were required—arthritis together with urethritis. The presence of conjunctivitis made the diagnosis a firm one. Joint pains and prostatitis in the presence of clinical or radiological evidence of plantar fasciitis or periostitis, or in the presence of a history or clinical evidence of conjunctivitis, uveitis, or keratodermia blennorrhagica, were likewise thought to be sufficient evidence for a presumptive diagnosis of Reiter's syndrome. In a number of cases lacking these full criteria a diagnosis of possible Reiter's syndrome was made.

The diagnosis in other groups of cases rested on the generally accepted clinical features, aided by *x*-ray evidence of sacro-iliac involvement in the case of ankylosing spondylitis, and by a positive latex or Rose-Waaler test in 35 of the males and 42 of the females with rheumatoid arthritis. The miscellaneous group included undiagnosed polyarthritis (48 cases), degenerative arthritis (22 cases), psoriatic arthropathy (7 cases), and 39 other cases presenting with limb pain, genito-urinary symptoms, or eye disease.

For the haemagglutination test a 4% suspension of tanned sheep red cells was used. These cells were sensitized by exposure for 30 minutes to a mixture of proteins derived from human prostate by phenolic extraction. The prostatic material was obtained at necropsy from young subjects who had no obvious prostatic disease. Two to 2.5 mg. of the freeze-dried antigen was suspended in 5 ml. of isotonic saline for the sensitizing procedure, the concentration being selected to give uniform results with known positive sera from patients and serum from immunized rabbits. Each patient's serum was tested at serial dilutions of between 1 in 20 and 1 in 320; in the light of previous experience agglutination at 1 in 20 was regarded as a positive result. Despite the known sensitivity of haemagglutination procedures, titres above 1:160 were not very common. Titres greater than 1:1,000 have, however, been noted.

A minor modification of the test has involved a more prolonged absorption of test serum with an equal volume of packed sheep red cells for 20 minutes. This was found to diminish the tendency of certain sera to cause non-specific agglutination, affecting not only sensitized but also unsensitized sheep red cells. Each serum found to be positive in the routine test was then rechecked to ensure the specificity of the agglutination. This was done by adding 0.25 mg. of prostatic antigen to 0.1 ml. of serum, and after this specific absorption with antigen various dilutions of the serum were retested. A specific positive reaction was one in which haemagglutination occurred in the original test but did not occur after absorption of the serum with prostatic antigen. As only one concentration of antigen was used this technique may have failed to absorb out true antibody in certain cases. Since completing this study we have had evidence of this in two cases of ankylosing spondylitis and one of Reiter's syndrome which now give positive results of proved specificity but had previously been reported as giving non-specific agglutination.

Results

Reiter's syndrome was diagnosed in 28 cases, 23 of which gave positive reactions and 15 had specific positive tests for antibody to prostatic antigen (see Table I). Four out of 20 possible cases of Reiter's syndrome were also specifically positive, and so also were 18 out of 46 cases of ankylosing spondylitis. This was evidently not an exclusive test for Reiter's syndrome and ankylosing spondylitis, since it was found

* Physician in charge of Department of Venereology, Guy's Hospital, London.
† Senior Clinical Tutor, Guy's Hospital, London.

to be positive in 5 out of 28 cases of prostatitis in which there were no joint symptoms. On the other hand, where arthritis occurred together with a specific positive reaction the case was nearly always one of Reiter's syndrome or ankylosing spondylitis, or had suggestive features of one or other of these diseases (see below).

TABLE I.—*Results of Haemagglutination Test for Prostatic Antibody*

Diagnosis	Total No. of Cases	Positive Results on Preliminary Testing	Specific Positives
Reiter's syndrome	28	23	15 (54%)
Possible Reiter's syndrome	20	10	4 (20%)
Ankylosing spondylitis	46	30	18 (39%)
Prostatitis	28	10	5 (18%)
Rheumatoid arthritis (male)	73	14	3 (4%)
Rheumatoid arthritis and miscellaneous cases (female)	95	27	2 (2%)
Miscellaneous diseases (male)	110	23	6 (5%)

TABLE II.—*Evidence Suggesting that Reiter's Syndrome is:*

An Infection	*An Immunological Disorder*
Sudden onset, with fever and urinary symptoms	Slow progress, with continuing polyarthritis
Improvement may follow treatment with tetracyclines, prostatic massage, and short-wave therapy	Improvement may follow treatment with cortisone or A.C.T.H.
Raised α_2-globulin	Raised γ-globulin
Various infective agents reported	Prostatic antibody commonly present

In three cases it was possible to test the serum of patients with Reiter's syndrome on four or five separate occasions through the acute and convalescent phases of their illness. In all three it was found that an initially positive test became negative in the later stages. In a further case, where serum was first tested at the start of the disorder, joint manifestations preceded the appearance of prostatic antibody, the antibody being detected in the second week of the disease.

There were three specific positive results in rheumatoid arthritis in the male. One was a patient aged 71 presenting with pain in the feet and with a mainly large-joint arthritis, *x*-ray evidence of bilateral calcaneal spurs, and a positive latex test. The second case was one of polyarthritis thought to be due to rheumatoid arthritis but with a negative latex test. The third case was one with an apparent rheumatoid arthritis and positive latex test.

In the miscellaneous group of cases specific positive results occurred in six cases. In the light of previous experience these results were regarded as being of diagnostic value, suggesting the presence of prostatitis. The first case was that of a patient with polyarthritis who also had a prostatitis and epididymitis. The second was a case of severe haematuria and renal calculus. Two cases had had multiple lower genito-urinary infections, but were not followed clinically. The fifth was a case of amyotrophy with no genito-urinary assessment recorded, and the sixth one of bilateral plantar fasciitis.

Amongst the large group of cases tested and found to give a negative or a non-specific reaction there were seven cases of psoriatic arthropathy, two cases of ulcerative colitis with polyarthritis, and a number of patients with other diseases, including spondylosis, postural backache, and osteoarthritis.

Discussion

In just over half of the cases of Reiter's syndrome and in over a third of the cases of ankylosing spondylitis the results suggest that the serum contained a true antibody to prostatic antigen. Negative results in the later stages of the disease and the low titres generally found may mean that the phenomenon we are observing is a secondary change. The fact that some positive results are found in uncomplicated prostatitis suggests that the formation of antibody may follow the release of prostatic antigen which occurs with inflammation. This fits well with the view that prostatitis is a common component of Reiter's syndrome, of ankylosing spondylitis, and that it may occur to a less extent in the male population at large. The positive findings in four women (see Table I) require an explanation. They may reflect an imperfect technique, the presence of a cross-reacting antibody, or a third possibility—the presence of a true antibody to a substance of prostatic origin, comparable to the antibodies to sperm that may be induced in the female (Katsh, 1959). In the cases of two of the women these positive results were confirmed on retesting, but in the other two the results were not reproducible in a further series of tests, which revealed only non-specific agglutination.

Waksman (1959) has drawn attention to the association of several infections with "auto-allergic" reactions, especially if the infection is due to a virus. There is therefore no conflict between the finding of antibody to prostate and the theory that there is an infective basis to this disease (see Table II). The possibility that a mycoplasma is responsible has not been ruled out and is supported by the recent work of Bartholomew and Hines (1964) but not by the evidence of Ford and Rasmussen (1964). It is also of interest that in primary atypical pneumonia (a mycoplasmal disease) the transient appearance of antibodies reacting with lung tissue was described by Thomas *et al.* (1943). This antibody to lung tissue usually appeared during the second week and persisted for two to three weeks, presumably as a consequence of lung inflammation. As appears to be the case with prostatic antibody in Reiter's syndrome, the auto-antibody found in atypical pneumonia can no longer be demonstrated in the late stages of the disease.

The serum in eight out of 24 cases of classical Reiter's syndrome and five out of 43 cases of ankylosing spondylitis gave a positive latex test for "rheumatoid" factor. These results showed no correlation with either a positive or a negative result in the prostate antibody test. The lack of specificity of the latex test, already noted in other diseases (Glynn, 1963), was thus underlined. The latex test taken by itself does not appear to be reliable enough to establish the nature of undiagnosed cases of polyarthritis.

Summary

A specific antibody to a prostatic antigen was detected in the serum of 15 out of 28 cases of Reiter's syndrome, in 18 out of 46 cases of ankylosing spondylitis, and in five out of 25 cases of uncomplicated prostatitis. Positive results were also obtained in three out of 73 males and two out of 95 females with rheumatoid arthritis. Apart from the occasional false-positive results the common feature in these positive cases may be an immunological reaction to an underlying prostatitis.

Whatever the infective basis of Reiter's syndrome or ankylosing spondylitis, the results suggest that these diseases have an auto-allergic aspect which merits further study and which may also be of diagnostic value.

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