Workshop I. Features and prognosis of Reiter's syndrome

Clinical aspects of Reiter's syndrome

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Four hundred and ten consecutive patients (400 men, 10 women) with venereal Reiter's syndrome (RS) attending the venereal disease clinics of three London hospitals were observed in the course of 18 years (mean 7.4 years). Although the patients were consecutive and unselected they might not have been wholly representative of the general population. Some selection might be present owing to my known interest in the condition, which resulted in some patients being referred. Also all the patients were seen in hospital, which may have excluded the mildest cases dealt with outside hospital. On the other hand, some systemic complications developing later in our patients may have been seen by others and not associated with the original condition.

Clinical features

The major clinical features and their distribution are shown in Table 1. Some comment is called for. Among the patients with genitourinary infections 16% had gonorrhoea yet were not suffering from gonococcal arthritis. A number had keratoderma blennorrhagica and other lesions associated with Reiter's syndrome, and penicillin, which cleared the gonococcal infection, failed to influence the course of RS. Less than 1% of patients with urethritis developed RS,⁶⁸ and this figure has been nationally confirmed in the UK ever since. At that time we suspected that a genetic factor plus the triggering infection might be involved, and the genetic component has now been amply confirmed by the discovery of the close association of HLA-B27—a genetic marker—in over 95% of the cases of the syndrome. We have now tested 32 cases of venereal RS and found them all to be positive for this antigen.

Conjunctivitis was observed in one-third of the patients. This was probably under-represented since

Table 1 Major clinical features in 410 consecutive cases of Reiter's disease

Lesions	Patients (%)
Genitourinary infection	
NSU	314 (76.5)
Gonorrhoea	66 (16.0)
Others	30 (7.3)
Joint lesions*	395 (96.3)
Plantar fasciitis	80 (19.5)
Eye lesions	
Conjunctivitis	141 (34.4)
Recurrent iritis*	10 (2.4)
Keratitis	5 (1.2)
Balanitis	105 (25.6)
Achilles tendinitis	50 (12.2)
Keratoderma blennorrhagica	55 (13.4)
Stomatitis	45 (10.9)
Thrombophlebitis of deep leg vein	19 (4.6)
Visceral lesions*	
Cardiac lesions (severe)	9 (2.2)
CNS lesions	3 (0.7)
Amyloidosis	1
Obstructive cholangitis	1

*Includes a total of 23 (5.6%) serious lesions; four patients died.

it is usually mild, often asymptomatic, and evanescent and is therefore not always noted by the patient or the referring doctor. Recurrent iritis is not infrequently associated with sacroiliitis. It tended to become serious when it recurred and became the dominant feature of the disease. In such cases the peripheral arthritis often disappeared. Severe loss of vision resulted in four cases.

Plantar fasciitis and achilles tendinitis were present in about 20% of cases and, unlike spinal lesions, tended to become chronic or intermittently active, leading in at least 21 cases to the most pronounced late disabilities. Sacroiliitis, occurring in 20% of cases, was less common than in other published series and caused few or no permanent symptoms. The spine was affected in 2% of cases and both spinal and sacroiliac lesions were associated with

iritis and in general with a more severe presentation. Fully blown ankylosing spondylitis was very unusual, while atypical and often clinically asymptomatic or oligosymptomatic cases were more characteristic. Low backache and early morning stiffness were fairly common but tended to disappear.

Thrombophlebitis of the deep veins of the legs was first reported by us⁷² in 4% of cases of RS. Since then we have seen more cases, occurring invariably early in the attack. There was local tenderness of the calf, pain on forced dorsiflexion of the foot, and some oedema of the affected leg. In recent cases phlebography has confirmed the clinical diagnosis. Heparin was given in some cases, but even without it the condition resolved without sequelae.

SYSTEMIC LESIONS

Systemic lesions were observed in 14 patients (3.4%). The most serious and the commonest were of the cardiovascular system. They ranged from transient ECG changes, especially of the conductive system with prolonged PR interval, to total heart block, aortic incompetence with or without left cardiac failure, pericarditis, and myocarditis. A total of 26 cases (6.3%) were seen (Table 2). All were men aged 25-58 (mean 35.5 years).

There were 15 cases of transient ECG changes, but this may well be an under-estimate since an ECG was done in only two-thirds of the cases. Two patients had transient pericarditis with a pericardial rub and radiological and ECG evidence of pericarditis. They fully recovered and after five and six years respectively have no evidence of constrictive pericarditis. One of the nine severe cases had a complete heart block with cardiac failure. Despite a well-functioning artificial pacemaker the patient died recently. Eight patients had aortic incompetence. Of these, one had a successful aortic valve replacement, one developed progressive heart failure and

died, and the remaining six are stabilised and remarkably well some two to eight years after the diagnosis of aortic incompetence.⁷⁴

The mortality of patients with serious cardiac lesions in this series is at present 22.2%. I would tentatively suggest that patients with aortic incompetence showing signs of progression should be seriously considered for aortic valve replacement as offering probably the best chance for their future.

Three patients had central nervous system changes during attacks of RS. Two had meningoencephalitis with changes in the cerebrospinal fluid (raised protein and cells, normal sugar, normal pressure, and negative tests for syphilis). In one it was noteworthy that he had three similar episodes. Both patients completely recovered, though quite ill during their attacks. The third patient had an isolated seventh nerve palsy early in his second attack, which regressed satisfactorily. Two years later he had an identical episode with seventh nerve palsy on the same side, together with arthritis and urethritis, leaving minimal weakness of his facial muscles. Since then he has had attacks of non-specific urethritis but without other symptoms.⁷³

One patient with complete, severe RS was treated with phenylbutazone. There was little improvement, and he had intermittent activity for the next five years. He then developed a sprue-like syndrome with intestinal haemorrhages. Rectal biopsy confirmed the diagnosis of amyloidosis, and he died. Necropsy was refused. No other known causes of amyloidosis were present.

Hepatitis with cholestasis were seen in a patient who also had severe RS treated with phenylbutazone. He developed progressive jaundice, and a liver biopsy showed cholestasis. Australia antigen was absent. The HLA-B27 test was positive. His illness was brief and he died within 10 days of the jaundice being noticed. Necropsy was refused.

These last two complications associated with venereal RS have been reported but seem to be extremely rare.

Conclusions

There was undoubtedly some selection inherent in this series, with a bias towards more serious cases. Nevertheless 14 patients, of whom four died, had severe systemic complications, and if one adds the other permanently damaging lesions such as recurrent iritis with visual loss and chronically painful deformed feet one must conclude that venereal RS is less harmless than previously thought. The mortality rate might be reduced by judicious early

Table 2 Systemic manifestations of 'venereal' Reiter's 410 cases

Lesion	No.	Died
Cardiovascular system		
Aortic incompetence	8	1
Complete heart block	1	1
Transient pericarditis	2	
Transient incomplete heart block	15	
Central nervous system		
Meningoencephalitis	2	
Eighth nerve palsy	1	
Amyloidosis	1	1
Hepatitis with cholestasis	1	1
Total	31 (7.8%)	4 (0.9%)

aortic valve replacement in patients with progressive aortic incompetence.

Since the aetiology of RS is still uncertain effective treatment and prophylaxis are difficult. It might be reasonable to advise people with the HLA-B27 antigen to avoid non-specific urethritis as constituting a special risk for developing RS. Whether immediate treatment of non-specific urethritis in such people would help to prevent the syndrome developing needs to be carefully investigated. I hope to show in my next paper (see page 24) that, even disregarding systemic visceral lesions, the long-term outlook for patients with venereal RS is not sufficiently favourable for the disease to be regarded too lightly.

General discussion

PROF. A. E. GOOD: I have a question about the thrombophlebitis patients. Did any of them have swelling of the leg above the knee? Was it possible that they actually had a synovial rupture syndrome, as seen with acute synovitis of the knee? Were venograms done to establish the diagnosis of thrombophlebitis?

DR. CSONKA: These patients had all the other clinical signs of this condition, including painful dorsiflexion, local pain and tenderness, and some oedema. Thrombophlebitis was confirmed by venogram in most cases.

PROF. C. M. PEARSON: I would like to inquire about the aortic lesions. Did those patients that came to operation or to necropsy have aortitis of the valve leaflets, or did they have involvement of the aortic ring with dilatation?

DR. CSONKA: They had free aortic incompetence without any doubt. There was marked regurgitation at the aortic valve, and the operation specimen showed that there was thickening of the valves without shortening and dilation of the ring. The histological picture was non-specific.

PROF. PEARSON: Was there more involvement of the aortic ring than of the valves per se?

DR. CSONKA: Yes.

PROF. PEARSON: And did any of the individuals have an aortic aneurism?

DR. CSONKA: No, not one, despite of our keen awareness of syphilitic disease in a venereology clinic.

PROF. PEARSON: I am reminded of the four or five patients that I have seen, and others have described, of relapsing polychondritis in which there has been involvement only of the base of the aorta. Again, the histology was consistent with a luetic aortitis.

PROF. M. ZIFF: Almost all of your first 110 patients had urethritis?

DR. CSONKA: Yes.

PROF. ZIFF: In some cases you label them 'other'. In your next 410 patients, when you insist on the need for urethritis, you bring up the question of urethritis as a criterion.

DR. CSONKA: In some unclassified and some urethritis-negative patients we were probably missing urethritis because we had not realised until fairly recently how very minimal the urethritis may be. In a recent London study some 50% of male partners of women with genital disorders had non-specific urethritis without any symptoms or obvious signs. Thus I would suggest an early morning examination of a urethral smear to avoid missing cases of urethritis.

PROF. ZIFF: With the ordinary clinical history one gets you would not insist?

DR. CSONKA: No, but I would not be certain from the patient's history. Unless you examine him yourself and insist on this rather tedious way of making sure that urethritis is present there would still be uncertainty.

DR. F. C. ARNETT: Were there any differences in your females, specifically with respect to age at onset and menopausal status?

DR. CSONKA: Yes, very much so. First, the disease was milder; secondly, the patients were older except for one—a very unusual case of a man who came to me with Reiter's syndrome. He was bisexual but married. He had had RS about five or six times before. I called in his wife just as a routine measure. She did say that, by coincidence, a very good lady friend of theirs was also in the same hospital with the 'same disease.' So I rushed to see that patient. She was a girl aged about 19 or 20 and she had RS with keratoderma and all the other salient features. She turned out to be the mistress of my male patient. Since then I have seen two more similar cases where sexual transmission to a woman partner was at least a possibility, more highly suggestive in view of the great rarity of RS in women.

PROF. E. S. PERKINS: When you talk about patients having another attack of RS does this imply that they had had a fresh attack of non-specific urethritis or is it a recurrence?

DR. CSONKA: Recurring attacks differ in some respects from the first attack. In a patient who had the full syndrome at onset the second and subsequent episodes often repeat the very features of the first attack but are milder and less complete. Indeed, incomplete recurrent attacks were common. In over 40% of our patients there was no evidence of

non-specific urethritis during recurrent attacks, whereas we found them consistently at onset.

PROF. A. S. RUSSELL: The question about reactivation versus recurrent infection seems to be unsolved. Clinically, one has the impression that in some patients, perhaps those with a more vigorous life style, reinfection is a problem and one might have to counsel them about this. How prophylactic do you think contraception is?

DR. CSONKA: I wish I knew the answer. We counsel more selection of sexual partners and the practice of protected intercourse, but we have no way of knowing whether the patient has taken our advice. Some patients swear blindly that they have done so, but reliability is not of a high order in these patients. For example, 2% of our patients with gonorrhea say that they have never had intercourse in their lives.

DR. G. R. V. HUGHES: I wonder if I could challenge the concept that the overriding aetiology of this syndrome is venereal. We now know that in reactive arthritis after dysentery urethritis is a prominent feature. While I agree that sexual promiscuity is a feature in many cases, I wonder whether some patients with 'reactive' urethritis are wrongly accused. I would make the probably contentious point that an over-zealous sexual history may, in some circumstances, do more harm than good.

DR. CSONKA: Patients come to us at the venereal disease clinic by their own free will in the first instance. They come because they have got urethritis, gonorrhea, or other symptoms they attribute to sexual exposure.

DR. HUGHES: I was worried lest it was our bias as rheumatologists towards a high incidence of arthritis in RS and it is gratifying to see a figure of 96% arthritis from Dr. Csonka's large venereal disease clinic. May I ask whether you make arthritis a major criterion? Does your rheumatology department see all your cases?

DR. CSONKA: Rheumatologists are very good in this respect and send us most of their cases of RS.

PROF. R. F. WILLKENS: Some years ago you suggested that patients who developed the complete triad early were the ones who later got sacroiliitis. Are they also those who get systemic manifestations late?

DR. CSONKA: Yes. Those who have systemic lesions usually have a much more severe disease. Incidentally we did tests in 32 patients for B27 and the last six or seven with systemic disease were all B27-positive.

They were also very severely affected. The sedimentation rate is probably the best single test indicating disease activity, especially in those patients with arthritis.

PROF. T. BITTER: I am impressed by the rarity of vasculitis and cardiac manifestations in B27-associated diseases, and even in your series of patients with RS. Could the carditis be a superinfectious complication—for example, by Coxsackie virus²⁸¹—rather than a systemic manifestation of RS?

DR. CSONKA: I don't know. We have not studied that point.

DR. J. C. WOODROW: Is this the right moment to clarify a fundamental concept—that is, what we mean with the word 'disease'? We envisage triggering factors and describe the resulting clinical picture. When Reiter's disease relapses urethritis might be missing, making the clinical picture definitely different, and yet we talk about recurrence although the actual trigger is unknown. But if subsequently in these mostly B27-positive former RS patients an environmental factor triggers a clinical bout of ankylosing spondylitis wouldn't it be obviously wrong to consider that as a late complication of RS? That later bout might have nothing to do with the fact that these B27-positive patients had had RS before.

DR. CSONKA: Some patients start with the incomplete syndrome—for example, balanitis going on for years. These patients often develop the full syndrome later on.

DR. WOODROW: I think the important thing in the absence of non-specific urethritis is to keep an open mind about the other triggering infections.

DR. CSONKA: On the other hand, non-specific urethritis is so often overlooked. It may be the commonest infection in young men apart from the common cold.

DR. J. T. SCOTT: I was very interested in your comments about treatment and that you don't think Reiter's disease can be prevented however early the urethritis is treated. In an analogy with the prevention of recurrences of rheumatic fever with prophylactic penicillin, have you, or anyone else, tried prophylactic chemotherapy to try to diminish the incidence of relapses?

DR. CSONKA: No, and I will tell you why not. Intervals between attacks may amount to 20 to 30 years. Would you care to give prophylactic tetracycline to any patient for this period? I would not.