Epidemic reactive arthritis

Reactive arthritis holds a special fascination for rheumatologists in view of the clear role of infection in causing an aseptic synovitis. Recent years have seen not only interest but considerable advances in knowledge of the pathogenesis of this disease. Many questions remain unanswered, however, and although most patients ultimately recover some do develop more chronic problems and we remain virtually unable to influence the sequence of events.

Sporadic cases constitute the most common experience of this disease and remain a fertile ground for further investigation. The recent report of Inman *et al*[1] serves to remind us, however, that epidemics of causative infection still occasionally occur. These epidemics provide a unique opportunity to observe and study the whole spectrum of reactive arthritis and its relation with a single micro-organism. We are reminded of the overlap between reactive arthritis and Reiter's syndrome and that extra-articular features, including urethritis, may occur from gastro-intestinal infection, as occurred in Reiter's original case.[2] This raises the question as to whether we should continue to use the term 'Reiter's syndrome' or consider the use of reactive arthritis as an all encompassing term, qualifying it as necessary with statements as to the underlying cause,[3] preferably by identification of the organism, and if necessary list the various features that are present. After all we have no difficulty with this approach in relation to many other diseases whether rheumatological or otherwise.

Studies of sporadic cases have shown a high prevalence of HLA-B27 in patients with reactive arthritis.[4] In the series of Inman *et al*, as in other studies of epidemics, an increased prevalence of other B7 CREG antigens was seen.[1 5] It is recognised that there is considerable homology between the DNA sequences of B27 and B7 but at present it is not known if this is relevant to the pathogenesis of reactive arthritis.[6]

A number of epidemics of this type have been reported[5 7–13] and it is appropriate to consider what we have learnt from their study. There is normally a delay between the onset of symptoms of gastroenteritis and those of reactive arthritis. The peak delay is five to 10 days, with the full range lying between one and 30 days.[7–12] Women get reactive arthritis possibly as often as men.[5 9 10] Not all age groups may be equally at risk of reactive arthritis.[5] Arthritis may occur in the absence of symptoms of infection, though there may be serological evidence of recent infection.[5] Equally, positive bacterial cultures may be obtained in individuals who have no symptoms of gastroenteritis.[14] Approximately 1–2% of infected persons develop reactive arthritis, representing approximately 20% of HLA-B27 positive subjects.[15] It is difficult to be precise about the incidence of reactive arthritis as it is almost impossible to define the infected population and as might be expected there is considerable variation between series. In addition, the confidence limits of estimates (1–2%) are large even when the size of some of these epidemics is taken into account.

In contrast with the findings of Inman *et al*[1] it has not been the universal experience that those with more severe infections, as measured by the duration and severity of diarrhoea, are those who necessarily develop reactive arthritis.[5 10] Although it is recognised that salmonella and campylobacter infections cause extra-articular features, it is of interest to note the apparently lower prevalence of these features in many of the epidemics of salmonella and campylobacter than in those due to *Shigella flexneri*.[15] Such differences may relate to methodology, though it is of interest to consider whether different organisms may produce different clinical features.

Only a few epidemics have been subjected to long term follow up. Where they have, long term symptoms and disability do occur in a proportion of individuals,[16 17] though it is difficult to determine how often this occurs.

Study of sporadic cases has also shown that circulating immune complexes may be present in patients with reactive arthritis,[18–20] though this has not been confirmed in all studies.[21] After yersinia infection higher[22] and more persistent concentrations of IgA[23] are present in those patients with reactive arthritis than in those without it. Recent studies of sexually acquired reactive arthritis have shown the presence of chlamydia antigen within the synovial membrane[24 25] and fluid.[26]

Sporadic reactive arthritis will continue to occur and be studied. From time to time epidemics of infection likely to result in reactive arthritis will also occur and their study may have advantages over that of sporadic cases. Unfortunately such epidemics occur without warning. Study of them is often frustrated by the lack of a clear and immediately available plan. This means that unique opportunities may be lost. Indeed, the study of Inman *et al*,[1] though providing further useful information, suffers from many deficiencies: the size of the infected population was never defined, the study design failed to follow up asymptomatic patients who might have developed reactive arthritis, the follow up was essentially by questionnaire, and the only clinical evaluation was conducted about 12 months after the epidemic. Although patients were HLA typed, we do not know the comparative control prevalences and the racial mix of the infected population.

Environmental health officers have contingency plans for the public health management of these epidemics. Recent major tragedies have also shown the importance of prior planning which can be put into immediate operation. The authorities responsible for such forward planning communicate freely with each other within and across national boundaries to improve the management of similar events in the future. Perhaps it would be worth considering how a future similar epidemic could be appropriately studied in order to increase our basic knowledge of the mechanisms surrounding the development of reactive arthritis.

The ideal circumstances for such a study would be those experienced by Noer in the outbreak of shigellosis, which occurred on board a United States naval vessel after it had left port.[8] There was a well defined population, which was studied in a very careful and detailed way despite the many practical problems. Such circumstances, however, are unlikely to occur in the future. At the other end of the spectrum are the circumstances under which Inman *et al*[1] attempted to study the phenomenon of reactive arthritis. A large number of people, together in one place, were exposed to the micro-organism but dispersed to many other centres before the development of the disease. Other outbreaks have, however, occurred in single communities where there was a reasonable approximation to the situation studied by Noer; however, the size of the infected population still remains a problem in these studies.[5 10–12] Therefore the first aspect of any study must be to try to define the infected population as closely as possible. This means taking stool specimens for culture from all those reasonably expected to

be infected and their immediate close contacts. It would be necessary to determine how many samples should be taken in view of the known sampling errors that may occur. Basic documentation of the severity and duration of infection together with the age and sex of the infected population would be essential information. At this stage, however, it would not be known which members of the infected population would develop reactive arthritis and bearing in mind the results of the previous studies we know that this will be a small proportion. A suitably sized sample, therefore, of the potentially infected population should be chosen for measurement of their immune complexes, determination of specific and non-specific immunoglobulin responses, and follow up of bacteriological cultures for persistence of infection. Serum samples might also be of value in developing better diagnostic serology than currently available for the investigation and diagnosis of presumed gastroenterological infection in other circumstances.[27 28]

At an appropriate time after the onset of the outbreaks and possibly on repeated occasions it would be necessary to survey the whole population or a major sample of it in order to detect cases of reactive arthritis. It may be necessary to compare this population with a similar non-infected population either in the same locality or a similar locality as rheumatic disorders are not uncommon, and it would be necessary to know that the cases studied were indeed those of reactive arthritis and not some coincidental event. This becomes particularly important when diagnosing milder cases, which are known to occur after these epidemics. Those subjects developing reactive arthritis would need to be studied in a similar way to the infected population as a whole for comparative purposes. Careful follow up of an appropriate number of infected though non-arthritic persons over a suitable period of time would also be needed to determine similarities and differences in immune response. In addition, it would be useful to look at peripheral blood and synovial fluid lymphocyte responses in mixed lymphocyte culture to preparations of the organism causing the epidemic as well as other organisms not involved but able to cause reactive arthritis.[29] HLA typing of the cases of reactive arthritis and of a suitable sample of the infected population would be appropriate.

In addition to looking for cases of classical reactive arthritis it would also be interesting to look for examples of other post-infective phenomena, such as erythema nodosum and Guillain-Barré syndrome, which have been reported after some of these infections.[30–32] Finally, a plan for long term follow up should be devised.

No doubt it would be possible to add to and modify this list of suggestions. For instance, the development of DNA probes may allow us to look more precisely for evidence of bacterial antigen in various tissues and body fluids, such as synovial membrane and synovial fluid, and for us to determine whether these are present in isolation or in complexes.

It is most unlikely that an outbreak of gastroenteritis will occur in a locality where all the necessary expertise is readily available. Perhaps it is timely to consider discussions between those with interest and particular expertise in order to draw up a contingency plan which could be readily incorporated within those of environmental health officers so that any subsequent outbreaks are studied by methods likely to produce the highest possible yields of valuable information, allowing us to advance our knowledge of the pathogenesis of this disease.

It always remains possible that by doing so we may ultimately be able to influence the course of the disease in a more fundamental way than we are at present and perhaps, more speculatively, learn something of how to direct our study of the more chronic seronegative spondyloarthropathies, which appear to have many similarities and a similar genetic predisposition.

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