Shigellae and Reiter's syndrome

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As an enteric disease capable of inducing arthritis shigellosis must share the stage with yersiniosis and salmonellosis. Shigellosis, however, is unique in that the joint involvement is always 'reactive', presumably immunologically determined, and never by direct infection. In addition the proclivity for rapid spread of shigella among crowded populations has provided clusters of patients with Reiter's syndrome (RS), including women and children, invaluable for the study of this disease.

The monumental study by Paronen of arthritis following epidemic Flexner dysentery in Finland during the second world war introduced many to this subject. Follow-up of some of Paronen's patients by Sairanen and coworkers showed that they were remarkably similar to patients considered elsewhere to be of 'venereal' origin. On a smaller scale, Noer's shipboard experience with epidemic shigellosis and RS (Fig. 1) as well as follow-up data by Calin and Fries clearly showed the latent periods between infection, diarrhoea, and arthritis.

It illustrated the wide spectrum of severity and chronicity of RS and led to the calculation that 20% of B27-positive crew members with diarrhoea developed RS. Postdysentery RS is rare in North America, a land long spared from war and the attendant crowding and breakdown of sanitation within its borders. Nevertheless, the jet-age has promoted admixture of the people and organisms of the world, and should alert us for sporadic cases RS induced by enteric pathogens.

Michigan series

In our current Michigan series of tissue-typed patients with RS, all of whom are men, 24 out of 97 had diarrhoea immediately preceding or during the acute attack (Fig. 2). Some of them had recently returned from the southern United States, the Caribbean, or Mexico. Three gave a history of onset with diarrhoea while on board ship during the

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Fig. 1  Reiter's disease. Shipboard epidemic following shigella infection. Clinical manifestations in 10 patients (From Noer).

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second world war. Another became ill after working aboard a vessel that docked with German prisoners from the Afrika Korps. Tabulation of the diverse features of acute RS shows an incidence of mucocutaneous, ocular, and articular lesions comparable to that of patients without diarrhoea (Fig. 3). All patients with diarrhoea had pelvic spondylitic back pain at some time during the acute illness, compared with back pain in 66 (90%) of 73 patients without diarrhoea. Because diarrhoea had usually cleared before the patients presented with arthritis examinations of the stools were often omitted or limited to microscopic screening for ova and parasites. In only one of our patients, a case recently published137, did we establish shigellosis when the third of four successive stool cultures yielded S. flexneri.

### Table  Postdysentery Reiter's syndrome affecting more than one member of family

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Sex</th>
<th>Age</th>
<th>Diarrhoea</th>
<th>Triad*</th>
<th>Relationship</th>
<th>Age</th>
<th>Diarrhoea</th>
<th>Triad</th>
<th>Interval†</th>
</tr>
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<tbody>
<tr>
<td>Koster and Jansen189</td>
<td>1946</td>
<td>M</td>
<td>15</td>
<td>+</td>
<td>+</td>
<td>Brother</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>14 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Brother</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>15 days</td>
</tr>
<tr>
<td>Glauner127</td>
<td>1947</td>
<td>M</td>
<td>14</td>
<td>+</td>
<td>+</td>
<td>Brother</td>
<td>10</td>
<td>+</td>
<td>+</td>
<td>U</td>
</tr>
<tr>
<td>Schoeneich275</td>
<td>1950</td>
<td>F</td>
<td>13</td>
<td>+</td>
<td>+</td>
<td>Brother</td>
<td>7</td>
<td>0</td>
<td>+</td>
<td>Three days</td>
</tr>
<tr>
<td>Fabregoule103</td>
<td>1951</td>
<td>M</td>
<td>&gt;40</td>
<td>+</td>
<td>+</td>
<td>Wife</td>
<td>&gt;40</td>
<td>+</td>
<td>0</td>
<td>Simultaneous</td>
</tr>
<tr>
<td>Davies, Haverty, and Boatwright76</td>
<td>1969</td>
<td>M</td>
<td>39</td>
<td>+</td>
<td>0</td>
<td>Son</td>
<td>11</td>
<td>+</td>
<td>+</td>
<td>Three days</td>
</tr>
<tr>
<td>Engleman9</td>
<td>1972</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>U</td>
<td>Son</td>
<td>7</td>
<td>+</td>
<td>+</td>
<td>Few days</td>
</tr>
</tbody>
</table>

*Triad = polyarthritis plus at least two of urethritis, mucocutaneous involvement, and ocular involvement (conjunctivitis or acute iritis).
†Interval between onset index case to onset secondary case(s).

U = unspecified.
Shigellosis preceding RS seems to be considerably underdiagnosed. Some cases labelled ‘venereal Reiter’s syndrome’ may in fact be precipitated by bacteria acquired during sexual intercourse with a shigella carrier. Even after mild initial attacks carriage may persist for years. Among 847 individuals nine carriers were found—all of them of S. flexneri. Six of the nine gave a history of dysentry. In contrast to the obvious association between RS and epidemic dysentry, sporadic cases of shigellosis precipitating RS are difficult to prove. Patients do not present with arthritis until a latent period of 7–30 days after the onset of the diarrhoea has elapsed, during which the organism usually disappears from the stool.

Serological methods have had little place in the diagnosis of acute bacillary dysentry because antibodies develop late and irregularly. However, it would seem feasible to devise a battery of agglutination tests utilising antigens from ‘rheumatogenic’ enteric pathogens and to apply this routinely in the workup of a patient with arthritis following diarrhoea—or, indeed, of any acute arthritis of unknown aetiology. If it can be shown that only a narrow range of shigella strains are rheumatogenic the specificity of the serological test could be enhanced. Thus there is need for hard bacteriological data from current patients with well documented postshigella arthritis.

Shigellae and arthritis

Shigellae are currently classified in four species: dysenteriae, flexneri, boydii, and sonnei. S. dysenteriae is often associated with severe diarrhoea, and includes the only strain with a neurotoxin and a potent enterotoxin, type I—the original Shiga bacillus. S. boydii is rarely isolated. Currently most common indigenous human pathogens in North America in order of prevalence are S. sonnei and S. flexneri, types 2a, 3a, 6, 4a, and 2b. S. Sonnei is associated with very mild diarrhoea. Volunteers infected with S. flexneri type 2a, the organism of most interest the rheumatologist, show three types of illness: one quarter have fever with minimal enteric symptoms; another quarter have merely watery diarrhoea; and the remaining half have fever one to two days after inoculation, diarrhoea and cramps two days later, and dysentery after another 2–3 days.

Mason-Bahr stated that arthritis was usually associated with S. dysenteriae infections, sometimes S. flexneri, and never with S. sonnei. Reports of serological tests in patients with postdysentery RS have shown antibody titres predominating for S. flexneri. Workers culturing Shigella from patients have uniformly reported S. flexneri characterised as type 2 or 2a in recent cases.

Striking difference in the incidence of arthritis have been discussed by Mason-Bahr. The incidence in an epidemic of shigellosis in the Fiji Islands in 1897 was 10%. There was no arthritis associated with an epidemic in the same place in 1910. The incidence in an epidemic in Mesopotamia in 1920 was 1%–2%, and in a German epidemic in 1900 4%. The experience in the Fiji Islands perhaps illustrates the effect of a rheumatogenic or a non-rheumatogenic strain of bacteria in successive epidemics. The different incidences of arthritis encountered in different lands may also reflect population differences in the prevalence of the B27 antigen.

RS in children is associated with diarrhoea in 70% of cases, a large proportion probably being shigella bacterial dysentry. The enteritis may be mild or even subclinical, as in the case of a 9-year-old boy without diarrhoea who had high agglutination titres for S. flexneri during the height of an acute RS. Careful questioning in childhood cases with diarrhoea may reveal siblings or parents with diarrhoea and various manifestations of RS.

A syndrome, we call it ‘the Mexican connection’, has been delineated in which North American tourists return from Mexico with family outbreaks of diarrhoea and ultimately one or more family cases of RS. S. flexneri type 2 has been cultured from two of these families. Such family outbreaks of bacterial dysentry are not only a potential source of genetic data but help elucidate the spectrum of RS in children and women (Table), and may actually improve the odds for recovering the instigating bacterium. The family unit sometimes maintains the organism for weeks as various members and contacts develop clinical disease at intervals.

Conclusion

In a series of 97 North American patients with RS examined retrospectively shigellosis was established in only one case. Since 24 patients had diarrhoea with acute attacks of RS the incidence of shigellosis was probably underrated.

Although S. flexneri is the species currently predominantly if not exclusively associated with postdysentery RS, there are insufficient published reports identifying shigellae from patients with RS. I suggest that routine bacterial stool cultures should be done as early as possible when patients present with possibly reactive arthritis. Stools should be...
cultured repeatedly in patients with diarrhoea, with a history of exposure in epidemics, or in a family that has outbreaks of diarrhoea. When stools are not readily available for culture rectal swabs should be obtained.

In order to determine the range of species, types, and strains of shigellae involved any recovered pathogen should be sent to a laboratory capable of comprehensive bacterial classification. Diagnostic agglutination tests utilising antigens from appropriate ‘rheumatogenic’ enteric pathogens should be re-evaluated among patients presenting with acute arthritis.

General discussion

PROF. M. ZIFF: Why is it said that RS in Asia is usually dysentery-related and in the Western World sexually related? Is it because there is not so much shigellosis in the West as there is east of the Urals or north of the Baltic, or is it a population difference, a genetic difference?

PROF. GOOD: I think some of it might indeed be a population difference, as with the higher B27 prevalence in Finland. Some of the difference might just be epidemic dysentery and lack of therapeutic facilities. Finally, we are probably missing many sporadic cases and perhaps writing them off as venereal.

DR. A. CALIN: I will try to answer the specific point that Professor Good raised about specific arthritogenic strains with specific cell wall components. In conjunction with the Centres for Disease Control we recently followed an epidemic due to Shigella sonnei in a small Puerto Rican community. The community included some 4200 inhabitants, of whom about one half developed dysentery. Evaluation included a questionnaire and, when relevant, clinical assessment for diseased and healthy subjects. We expected HLA-B27 to be present in some 3%-4% of Puerto Ricans, 20% of whom may be expected to develop a reactive arthropathy. In fact, we found no cases of RS. Thus the particular strain of S. sonnei causing that epidemic seems to have been non-arthritogenic. It remains possible that patients with neither venereally acquired nor postdysenteric disease may have clinically silent bowel infection.

PROF. D. FORD: Do the people who have postdysenteric RS have any organisms in their urethral exudate, such as mycoplasma or chlamydia?

PROF. GOOD: My single patient with proved shigellosis had a florid urethritis in the second week after the onset of diarrhoea. It looked just like the so-called non-specific urethritis I associate with RS in general. The cultures were negative for bacterial pathogens.

PROF. FORD: Did you get chlamydia or mycoplasma out of them?

PROF. GOOD: No.