Shigella induced reactive arthritis

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A long-haul travel syndrome?

Shigella infection is the least common of the gastroenteritis-inducing organisms, which are associated with reactive arthritis (ReA) in developed countries, reflecting the scarcity of the organism in these environments. A recent thorough survey of Shigella infected subjects in Finland describes an annual incidence of Shigella induced ReA of only 1.3 per million. This compares with the incidence figures of 46 per million for ReA due to Chlamydia infection, and 50 per million for other enteric pathogens, noted in a survey of the Oslo population. However, the relevant denominator for Shigella induced ReA is not the population of Finland, but the population visiting distant travel destinations—for example Egypt, India, Thailand, Congo, and Turkey—all countries where the infection was acquired by the Finnish patients. Although these countries, particularly Turkey, are increasingly common holiday destinations for sun-starved Northern Europeans, well under 5% of the population visit such countries in any 1 year, so the incidence of ReA is more like 30–40 per million in the exposed population.

**SHIGELLA SPECIES**

Of the Shigella species encountered in sunny places, the commonest is *S. sonnei*. This might be considered a source of comfort to the intending B27+ traveller, because *S. sonnei* was at one time considered not to induce ReA. The recent paper from Finland dispels this idea; *S. sonnei* was the commonest of the Shigellae isolated from patients who developed ReA, and there appeared to be no significant difference in the incidence of ReA following *S. sonnei* and *S. flexneri* infection. Why this difference from previous reports? Although cases of ReA following *S. sonnei* infection were reported as long ago as 1947, and there were additional reports in 1988 (three cases) and 2002 (a sexually acquired case), two other major reports have been interpreted as exonerating *S. sonnei* in ReA. Simon et al noted two and three cases in two outbreaks of *S. flexneri* infection each involving ~200 patients, but no case among 99 patients infected with *S. sonnei*. More strikingly, Kaslow and colleagues found not a single case of ReA among 1970 patients with *S. sonnei* infection in Puerto Rico. It was argued that additional, undetected pathogens might have had a role in those cases reported as apparently due to *S. sonnei* infection. Thus the conclusion that *S. sonnei* is innocent of inducing ReA seemed reasonable, but additional factors need to be borne in mind.

Firstly, the numbers of cases in the outbreaks described by Simon et al were small, and the *S. sonnei* infected cohort involved children and young adults, a group which seems less susceptible to ReA induced by enteric infection.

"Populations in which the prevalence of enteric pathogens is high may be more resistant to developing ReA"

Secondly, although the number of subjects surveyed in the Kaslow paper is impressive, it is not known what the incidence of ReA would be in a similar number of Puerto Ricans exposed to *S. flexneri*. Populations in which exposure to enteric pathogens is high may be more resistant to developing ReA. Thus, in the International Centre for Diarrhoeal Disease Research in Dhaka where more than 10,000 cases of *S. dysenteriae* infection are seen annually, only one case of ReA has been described—whereas one of the five Finnish patients with *S. dysenteriae* noted by Hannu et al developed ReA. In any case, the incidence of ReA following particular outbreaks of infection varies widely; for example, an outbreak in Fiji in 1897 had a 10% incidence of ReA, whereas no cases occurred in a further outbreak in 1910 (observations of Mason-Bahr, quoted by Good’). Similar observations have been made in outbreaks of infection with *Yersinia* and *Salmonella*.

Thirdly, it is possible that this Finnish survey detected cases which would not have been noted in previous investigations. Sensibly, in order to detect all possible sequelae of *Shigella* infection, Hannu et al used a broad definition of musculoskeletal symptoms—but with demonstrated specificity, because only 1 in 330 controls was positive by the same criteria, as compared with 18 of the 211 subjects infected by *Shigella*.

**WHEN DOES AN INFECTION INDUCE ReA?**

What factors determine whether infection with a particular organism induces ReA? When the idea was in the ascendency that ReA might be due to immune responses which target epitopes common to the infecting organism and an autoantigen in the joint or enthesis (that is, molecular mimicry), apparent differences in the ability of closely related organisms (such as *S. sonnei* and *S. flexneri*) to cause ReA seemed to provide a possible way forward. In principle, one could identify the relatively small number of proteins which differed in the two organisms and screen these for candidate epitopes which would mimic self proteins. Thus, van Bohemen et al noted that certain monoclonal or polyclonal antisera directed against HLA-B27 cross reacted with a 20 kDa protein present in *S. flexneri* but not in *S. sonnei*. Likewise Stiegitz and Lipsky drew attention to a B27 mimicking epitope in the major plasmid of all strains of *S. flexneri*, but absent from *S. sonnei*.

The observation that *S. sonnei* does indeed trigger ReA negates these approaches, and also the attractive hypothesis of molecular mimicry has not been borne out. Not that there are no examples of molecular mimicry—many have been described, involving antibodies and/or T cells—but it is unclear that any of these examples actually produce the disease in which they have been demonstrated. Indeed, molecular mimicry is almost inevitable given the number of epitopes in microorganisms and the likelihood that many of these will have human counterparts. It is now considered more relevant to determine how molecular mimicry is regulated so as to avoid immunopathology, rather than looking for particular examples of mimicry, because these will always be found if the search is wide enough.

"*S. flexneri* is a seriously delinquent *E coli""

Nevertheless, there must be particular properties of ReA triggering bacteria which allow them to induce the syndrome. *Shigella* illustrate this idea rather well; were *Shigella* to be discovered for the first time today, they would be classified as strains of *E coli*, because the organisms are phylogenetically indistinguishable. Specifically, *S. flexneri* shares all but 175 of 3235 open reading frames with two strains of *E coli*. Self evidently, despite their similarity, the
interactions of the two organisms with their human host are wildly different—S. flexneri is a seriously delinquent E. coli. The principal mechanisms which Shigella has acquired to induce disease are the ability to invade human enterocytes, lyse intracellular vacuoles to enter the cytoplasm, and move from cell to cell. E. coli does none of these things, and it is likely that the ability to survive intracellularly is critical to the causation of ReA, because this property is shared with Chlamydia, Yersinia, and Salmonella, though only Shigella has a cytoplasmic residence and moves from cell to cell.

**FACTORS DETERMINING THE INCIDENCE OF ReA**

Given that an organism has the ability to induce ReA, what determines the incidence of ReA in populations which become infected? There are likely to be several factors: some are stochastic, such as the infecting dose and, possibly, comorbidities such as subclinically inflamed joints (for example, weight-bearing joints) to which organisms may traffic more readily within macrophages or neutrophils. Genes will also have a role—more ReA is generally found in sunny climes, and look for it assiduously. Shigella flexneri might occur for aberrant interactions with class I HLA molecules. Opportunities for Shigella flexneri carrying a M2a plasmid and encoding an HLA-B27 mimic epitope. Arthritis Rheum 1993;36:1387–91.

Whether or not further investigation of ReA cases induced by Shigella infection will cast light on the pathogenesis of the arthritis, the practical point highlighted by the study of Hannu et al is clear: suspect Shigella as an infecting organism in patients with inflammatory arthritis recently returned from far off sunny climes, and look for it assiduously.


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Ann Rheum Dis 2005 64: 517-518
doi: 10.1136/ard.2004.030395

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