Low frequency of recent parvovirus infection in a population-based cohort of patients with early inflammatory polyarthritis

Beverley Harrison, Alan Silman, Elizabeth Barrett, Deborah Symmons

Abstract

Objectives—To determine the contribution of human parvovirus B19 infection in explaining the incidence of early inflammatory polyarthritis (IP) in a population. Setting—The Norfolk Arthritis Register (NOAR) is a community-based programme aiming to ascertain all new cases of IP arising in a population that lead to attendance at primary care. Subjects—147 newly ascertained subjects with IP with a disease duration of less than 16 weeks. Methods—Full clinical appraisal of all subjects who were followed up for three years. B19 IgM assayed with a third generation antibody capture enzyme immunoassay. Results—Only four (2.7%) patients had evidence of recent B19 infection, only one of whom did not satisfy criteria for rheumatoid arthritis (RA). Conclusion—B19 infection does not explain more than a small proportion of either RA or undifferentiated IP cases occurring in the population.

Viral infections have a number of important effects on the immune system, and may trigger rheumatoid arthritis (RA) in a susceptible host. Since its discovery in 1975, it has been noted that human parvovirus B19 frequently causes a self-limiting polyarthritis in adults. It has also been debated whether, in some patients, B19 may act as a trigger for RA. Three hospital-based studies with a combined total of 199 patients with early (< 1 year) RA, found that nine (4.5%) had evidence of recent B19 infection. By contrast, among 190 patients with unspecified inflammatory arthritis, 23 (12%) had recent B19 infection.

The diagnosis of RA is difficult in the early stages, and classification criteria were developed using patients with established disease. Patients in hospital-based studies are subject to referral bias, and are more likely to have seropositive or erosive disease, or both. We therefore tested the hypothesis that evidence of recent B19 infection would be a frequent finding in patients with inflammatory polyarthritis (IP) newly presenting to primary care. We also hypothesised that the frequency would be higher in those with self-limiting disease, and in those who did not develop characteristic features of RA.

Methods

The study population was recruited from patients with IP referred to the Norfolk Arthritis Register (NOAR). This covers all adults registered with a primary care physician in the Norwich Health Authority (population almost 0.5 million). Patients are referred to NOAR if they have IP (swelling of at least two joints that has persisted for a minimum of four weeks) and a disease onset after January 1990. Patients are excluded from the study if they have an alternative specific rheumatological diagnosis that accounts for their symptoms, apart from RA, psoriatic arthritis or post-viral arthritis. For this analysis, subjects were eligible if they were aged 16–65 years, had a disease duration of less than 16 weeks when first seen, and had been followed up for three years.

Between January 1990 and August 1993, 628 patients were referred to NOAR if they were aged between 16–65 years, of whom 214 (34%) had a disease duration of under 16 weeks at presentation. Of these, 147 had serum available at baseline and follow up data at three years. These 147 patients form the study population.

A research nurse performed a structured history and examination at baseline. Blood samples were analysed for rheumatoid factor (RF) using a tube latex dilution test. The presence of IgM antibodies to B19 was determined using a third generation antibody capture B19 IgM enzyme immunoassay (Biotrin International). This was similar to the method used by Naides et al and had no demonstrated cross-reactivity with RF. Radiographs of the hands and feet were taken in those patients who satisfied a sufficient number of the 1987 ARA criteria to be classified as having RA if erosions were present. Disease status of the patients was assigned using two separate approaches. In the first, patients were classified as having RA by applying the 1987 ARA criteria at baseline, in both the traditional “list” format and the classification tree format. Secondly, for patients referred to hospital, the clinical diagnosis made by a consultant rheumatologist was obtained from the hospital case notes.

Results

The median age of the 147 patients was 47 years (range 19–65) and 104 (71%) were female. The median disease duration at presentation was 10 weeks (range 4–16). At baseline, 57 patients (39%) satisfied the 1987 ARA classification criteria for RA in the “list” format, and 86 (59%) in the “tree” format. In total, 36 patients (25%) were seropositive for
RF. Evidence of recent parvovirus infection was detected in only four (2.7%) patients. Furthermore, B19 infection was observed in only one of 61 (1.6%) of those patients who did not satisfy classification criteria for RA. Table 1 shows the clinical characteristics of the patients with recent B19 infection. All were women, and three satisfied classification criteria for RA at baseline, all of whom had persistent symptoms at three years.

**Discussion**

The most important finding from this study was that among the 147 patients newly presenting to primary care, and notified to a population register, with IP of less than 16 weeks duration, only four (2.7%) had evidence of recent B19 infection. This proportion is lower than that previously reported from early synovitis clinics. Given this low frequency, it is impossible to determine whether the association of these cases with recent B19 infection is causal. However, it is important that such patients are not labelled as having “parvovirus arthropathy”, which is considered a mild self limiting disease that does not require treatment with DMARDs.

In people with B19 infection, HLA-DRB1*04 alleles might increase susceptibility to develop arthritis, or in those with arthritis, to have persistent disease. These findings however, are not consistent. In the NOAR study, one of the patients with recent B19 infection was positive for DRB1*04, but none were positive for DRB1*01 alleles.

Finally, a large number of techniques have been used to diagnose B19 infection, and it has been debated whether a possible link between B19 infection and RA could be confirmed if more sensitive methods of detection such as polymerase chain reaction were used. For example, B19 DNA has been detected in the serum or synovial fluid cells of infected patients in some though not all reports. However, even if B19 DNA is detected at the site of joint inflammation, this is not proof of causation, as it may merely represent a passenger in one of the cell populations attracted to the inflamed synovium. For example, a recent study from Finland reported B19 DNA in the synovial membranes of 13 of 27 young adults undergoing investigation of joint trauma. The authors concluded that at present, serology remains the best method for diagnosing B19 arthropathy. However, it has been suggested that improved virological techniques may enable us to determine whether patients with arthritis have persistent B19 infection, or whether B19 has acted as a trigger for the development of RA.

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### Table 1 Clinical characteristics of patients with evidence of recent parvovirus B19 infection

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Satisfied 1987 ARA criteria</th>
<th>Rheumatoid factor</th>
<th>Erosions</th>
<th>Final clinical diagnosis</th>
<th>Outcome at three years</th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
<td>F</td>
<td>No</td>
<td>Negative</td>
<td>—</td>
<td>IP</td>
<td>Swelling of MCP joints at 1 yr resolved after 2 yr</td>
</tr>
<tr>
<td>48</td>
<td>F</td>
<td>Yes†</td>
<td>Negative</td>
<td>Yes</td>
<td>RA</td>
<td>Persistent swelling of hands and feet treated with sulphasalazine</td>
</tr>
<tr>
<td>52</td>
<td>F</td>
<td>Yes*</td>
<td>Negative</td>
<td>No</td>
<td>RA</td>
<td>Treated with prednisolone and sulphasalazine</td>
</tr>
<tr>
<td>66</td>
<td>F</td>
<td>Yes*</td>
<td>Positive</td>
<td>No</td>
<td>not referred to hospital</td>
<td>Swelling of PIP joints only</td>
</tr>
</tbody>
</table>

*Both “list” and “tree” formats; †“tree” format only.


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