The diagnostic value of streptococcal serology in early arthritis: a prospective cohort study

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Abstract

Objective. To evaluate the diagnostic value of streptococcal serology in adult early arthritis patients in discriminating between post-streptococcal reactive arthritis (PSRA) and arthritis with other causes.

Methods. The antistreptolysin-O (ASO) and anti-DNase B tests were performed at baseline in 366 consecutive, newly referred early arthritis patients. After 1 yr of follow-up the patients were classified according to international classification criteria and were evaluated for the presence of persistent arthritis. The outcome measures were the predictive value of streptococcal serology for the diagnosis of PSRA and the ability of this serology to discriminate at the first visit between the self-limiting and persistent forms of arthritis.

Results. With a positive serological result, the probability of having PSRA increased from 2 to 9%, whereas the probabilities of having rheumatoid arthritis or undifferentiated arthritis continued to be high (23 and 29% respectively). The serological tests did not discriminate between the self-limiting and persistent forms of arthritis. The major Jones criteria apart from arthritis were not observed.

Conclusion. Streptococcal serology has no diagnostic value in adult early arthritis patients in whom major Jones criteria other than arthritis are not present.

Key words: Post-streptococcal reactive arthritis, Streptococcal serology, Antistreptolysin-O, Anti-DNase B, Early arthritis, Diagnosis.

In the last two decades numerous published reports have described a resurgence of acute rheumatic fever in the USA and Europe, afflicting adults as well as children [1–3]. During this period, several investigators have described paediatric patients with reactive arthritis that occurred after streptococcal infection and did not fulfil the Jones criteria [4–6]. It was suggested that this might be a disease entity separate from acute rheumatic fever, and the term 'post-streptococcal reactive arthritis' (PSRA) was suggested [6]. Since it was initially described in 1982, PSRA has been reported with increasing frequency in children [4–13] as well as in adults [8, 14–19]. In these reports the diagnosis of PSRA was based in part on the finding of positive streptococcal serology. However, the value of streptococcal serology as a diagnostic tool in adult patients with recent-onset arthritis is unknown.

A major problem to be dealt with in studying this issue is the lack of an independent gold standard for the diagnosis of PSRA. This is because the diagnosis of PSRA is dependent on the information provided by the diagnostic variable studied—the results of the serology—which leads to overestimation of the diagnostic properties of the serology. Expressing the gold standard in terms of clinical outcome is a way of avoiding this circularity and generating more relevant and valid diagnostic information for use in practice [20, 21]. On the assumption that PSRA in adults is always a self-limiting form of arthritis, it is important to know whether streptococcal serological tests enable the clinician to discriminate at disease onset between the self-limiting and persistent forms of arthritis.

The objectives of the present study were to determine the predictive value of streptococcal serology for the different rheumatological diagnoses, including PSRA, and to assess the value of streptococcal serology in discriminating between the self-limiting and persistent forms of arthritis.
Patients and methods

Patients
In 1993 a special Early Arthritis Clinic (EAC) was started at the Department of Rheumatology of the Leiden University Medical Center, the only centre for rheumatology in a health-care region of more than 300,000 inhabitants. Patients enrolled in this programme should have had arthritis of at least one joint diagnosed by a rheumatologist in the department and the symptoms should have lasted less than 2 yr. The present study included the 377 consecutive patients who had visited the EAC between 1993 and July 1997 and had a symptom duration shorter than 6 months. As the duration of symptoms of reactive arthritis patients at the first visit is usually short, the ability of serology to discriminate between the self-limiting and persistent forms of arthritis was also calculated in the subgroup of patients with a symptom duration shorter than 6 weeks.

Methods
A standard diagnostic work-up was performed at the first visit, consisting of patient history and physical, laboratory and radiological examinations. The anti-streptolysin-O (ASO) (Bio-Mérieux, Hertogenbosch, The Netherlands) and anti-DNase B (Behring, Marburg, Germany) tests were performed according to the manufacturer’s guidelines in all patients, using serum samples obtained at the first visit. Patients were considered to have had an antecedent streptococcal infection if the ASO and/or anti-DNase B titre was higher than 200 U. This upper limit of the expected or normal level, as determined for the tests in our laboratory, was defined as the highest titre that was exceeded by only 20% of the normal population. In the first 116 patients the ASO and anti-DNase B tests were performed on paired, acute and convalescent sera, the latter obtained 2 weeks after the first visit, to detect increases in titres. An increase in titre was considered to be significant when it was at least twofold and the increased titre exceeded 200 U [1]. Throat cultures and electrocardiograms were performed on clinical indication. All patients were followed for at least 1 yr except for patients with transient arthritis caused by crystal-induced conditions, who were not followed routinely. Definite diagnoses were made after 1 yr of follow-up according to international classification criteria or information in rheumatology textbooks. The diagnosis of PSRA was based on the presence of clinical characteristics compatible with the diagnosis of reactive arthritis, as judged by the rheumatologist, in combination with serological evidence of an antecedent streptococcal infection. When a diagnosis could not be made, the condition was classified as undifferentiated arthritis (UA).

Outcome measures
The occurrence of the different rheumatological diagnoses, including PSRA, was determined for the patients with positive and negative streptococcal serology, thereby indicating the predictive values of the serology for these diagnoses [22]. The value of serology as a diagnostic test for PSRA will thus be overestimated, because the classification of the disease as PSRA is possible only if the serology is positive. To avoid this bias, the diagnostic characteristics of the ASO and anti-DNase B tests were also determined when they were used to discriminate between self-limiting and persistent arthritis [21]. It was assumed that PSRA in adults is always a self-limiting articular disease and that a test which is used to identify PSRA should at least be able to differentiate between the self-limiting and persistent forms of arthritis in order to have prognostic significance. Persistent arthritis was defined as the presence of arthritis of at least one joint and/or treatment with disease-modifying anti-rheumatic drugs or steroids within the previous 3 months at the 1-yr follow-up. When natural remission (defined as no arthritis on examination in a patient who had not taken disease-modifying anti-rheumatic drugs or steroids in the preceding 3 months) was present at the 1-yr follow-up, the arthritis was classified as self-limiting [23]. The sensitivities and specificities of the ASO and anti-DNase B tests used to discriminate between self-limiting and persistent arthritis were calculated at different cut-off titres and are presented graphically using receiver operating characteristic (ROC) curves [24]. These curves plot the relationship between sensitivity on the y-axis and 1-specificity on the x-axis at different cut-off titres. The sensitivity, specificity and predictive value of the combination of the ASO and anti-DNase B tests were calculated at the clinically used cut-off titre of 200 U. The combination of the two tests was regarded as positive if the ASO and/or anti-DNase B titre was higher than 200 U and was regarded as negative if both tests had a titre equal to or lower than 200 U. To calculate the positive and negative predictive values of the combined tests, the observed prevalence (pretest probability) of self-limiting arthritis of 58% was used.

Statistics
The Statistical Package for the Social Sciences (SPSS) version 9.0 was used to analyse the data. A non-parametric distribution was assumed in the construction of the ROC curves.

Results
Of the total number of 377 patients included in the study, six patients who died before the 1-yr follow-up and five patients who were lost to follow-up were excluded from the analysis. The disease classification at the 1-yr follow-up is shown in Table 1. The median age (range) in the total group of patients and in the PSRA subgroup was 50 yr (17–90) and 36 yr (27–80) respectively. Of the PSRA patients, 54% were female and all were Caucasian. The median duration (range) of symptoms at the first visit was 45 days (1–181) in the total group of patients and 12 days (5–35) in the PSRA subgroup.
Characteristics of PSRA patients

The clinical and laboratory characteristics of the eight patients diagnosed as having PSRA are shown in Table 2. None of these patients showed any of the major Jones criteria: carditis, chorea, erythema marginatum and nodules [25] at the first visit or during follow-up. The arthritis was migratory in one patient (Patient 4). All patients were treated with non-steroidal anti-rheumatic drugs; the two patients with a positive throat culture were treated with fenitcillin for 10 days. None of the patients received penicillin prophylaxis. In all patients the arthritis subsided within 4 months after symptom onset.

Ability to predict different rheumatological diagnoses

Positive streptococcal serology was found in 91 of 366 (25%) patients. The pretest and posttest probabilities of the different rheumatological diagnoses are shown in Table 3. The pretest probability of a particular diagnosis is equal to the prevalence of that diagnosis in the population studied. The post-test probability of a particular diagnosis for a positive or negative test result is the proportion of patients with a positive or negative test result that have that diagnosis. The table shows that the probabilities of having PSRA, rheumatoid arthritis (RA) or UA were hardly influenced by the results of the streptococcal serology. In the case of a positive serological result, the probability of having PSRA increased only from 2 to 9%, whereas the probabilities of having RA or UA continued to be high (23 and 29% respectively). For a negative serological result the probability of having PSRA is 0% by definition.

Ability to discriminate between self-limiting and persistent arthritis

Joint scores at the 1-yr follow-up were available for 313 patients. The 37 patients with transient arthritis caused by gout or pseudogout, who were not routinely followed for 1 yr, were considered as having self-limiting arthritis and were included in the analysis. Of the total number of 350 patients analysed, 202 (58%) had self-limiting disease. Figure 1 shows the ROC curves of the ASO and anti-DNase B tests when used to discriminate between self-limiting and persistent arthritis. These curves plot the relationship between sensitivity on the y-axis and 1 – specificity on the x-axis at different cut-off titres of the tests. The higher the cut-off titre that is chosen, the lower the sensitivity and the higher the specificity, and vice versa. The area under the ROC curve (ROC AUC) provides a measure of the overall discriminative ability of a test. The greater the distance of the curve from the diagonal, the higher the overall discriminative ability of a test. As a general rule, ROC AUC = 5 indicates no discrimination (no better than flipping a coin), ROC AUC ≥ 7 acceptable discrimination, ROC AUC ≥ 8 excellent discrimination and ROC AUC ≥ 9 outstanding discrimination (very unusual). The discriminative ability of both tests was poor, as indicated by the position of the curves near the 45° line and the ROC areas under the curve of 0.52 [95% confidence interval (CI) 0.47–0.58] and 0.54 (95% CI 0.48–0.60) for the ASO and anti-DNase B tests respectively. The subgroup of patients with a symptom duration shorter than 6 weeks consisted of 167 patients, of whom 128 had self-limiting arthritis and 39 persistent

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### Table 1. Diagnosis after 1 yr of follow-up of the 366 patients analysed

<table>
<thead>
<tr>
<th>Diagnosis after 1 yr of follow-up</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undifferentiated arthritis</td>
<td>105 (29%)</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>99 (27%)</td>
</tr>
<tr>
<td>Crystal-induced arthritis</td>
<td>37 (10%)</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>22 (6%)</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>19 (5%)</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>14 (4%)</td>
</tr>
<tr>
<td>Post-streptococcal reactive arthritis</td>
<td>8 (2%)</td>
</tr>
<tr>
<td>Other inflammatory arthropathies</td>
<td>62 (17%)</td>
</tr>
</tbody>
</table>

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### Table 2. Clinical and laboratory characteristics of eight patients diagnosed as having PSRA

<table>
<thead>
<tr>
<th>Patient</th>
<th>Throat complaints</th>
<th>Rash</th>
<th>Latency perioda (days)</th>
<th>Arthritis</th>
<th>ESR (mm/h)</th>
<th>Antibiotic treatment by GP</th>
<th>Throat culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>Right wrist</td>
<td>112</td>
<td>–</td>
<td>ND</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>EN</td>
<td>+</td>
<td>Left elbow</td>
<td>128</td>
<td>+</td>
<td>ND</td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>Right ankle</td>
<td>78</td>
<td>+</td>
<td>Negative</td>
</tr>
<tr>
<td>4</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>Knees</td>
<td>69</td>
<td>+</td>
<td>Negative</td>
</tr>
<tr>
<td>5</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>Left st.clav.</td>
<td>26</td>
<td>–</td>
<td>Negative</td>
</tr>
<tr>
<td>6</td>
<td>+</td>
<td>MR</td>
<td>–</td>
<td>Left wrist</td>
<td>47</td>
<td>–</td>
<td>GAS</td>
</tr>
<tr>
<td>7</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>Right wrist</td>
<td>18</td>
<td>–</td>
<td>Negative</td>
</tr>
<tr>
<td>8</td>
<td>+</td>
<td>EN</td>
<td>+</td>
<td>Right ankle</td>
<td>60</td>
<td>–</td>
<td>GCS</td>
</tr>
</tbody>
</table>

aPeriod between pharyngitis and onset of articular symptoms; ESR, erythrocyte sedimentation rate; GP, general practitioner.

EN, erythema nodosum; GAS, group A β-haemolytic streptococcus; GCS, group C β-haemolytic streptococcus; MR, macular rash; MTPs, metatarsophalangeal joints; ND, not done; PIPs, proximal interphalangeal joints; st. clav., sternoclavicular joint.
Table 3. Pretest probabilities (prevalence in EAC population) and post-test probabilities given positive and negative serological results of the different rheumatological diagnoses

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>RA</th>
<th>UA</th>
<th>PSRA</th>
<th>Crystal/OA&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Sarcoidosis</th>
<th>Other&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretest probability (n = 366)</td>
<td>27%</td>
<td>29%</td>
<td>2%</td>
<td>15%</td>
<td>6%</td>
<td>21%</td>
</tr>
<tr>
<td>Post-test probability if positive test (n = 91)</td>
<td>23%</td>
<td>29%</td>
<td>9%</td>
<td>11%</td>
<td>10%</td>
<td>18%</td>
</tr>
<tr>
<td>Post-test probability if negative test (n = 275)</td>
<td>29%</td>
<td>28%</td>
<td>0%</td>
<td>17%</td>
<td>5%</td>
<td>21%</td>
</tr>
</tbody>
</table>

<sup>a</sup>Crystal-induced arthritis or osteoarthritis; <sup>b</sup>other forms of arthritis.

**Increases in titres**

Significant increases in titres for ASO and/or anti-DNase B were found in six (5%) of the 116 patients who were tested twice. In none of the six PSRA patients tested twice was a significant increase in titre found. When a significant increase in titre was used as the criterion for positivity, the sensitivity decreased to 7% and the specificity increased to 97% without improvement in the overall diagnostic value of the serology in discriminating between self-limiting and persistent disease.

**Discussion**

The present study shows that the ASO and the anti-DNase B tests were unable to differentiate between the self-limiting and persistent forms of arthritis in patients with recent-onset arthritis. As the major Jones criteria, apart from arthritis, were not found in any of the patients studied [25], the tests had no value in predicting these non-purulent complications of group A streptococcal infections either. The positive predictive value of streptococcal serology for PSRA was low (9%), which was caused by the low prevalence of the clinical diagnosis of PSRA in the population studied (2%) in combination with the moderate specificity of the tests for PSRA (77%). The predictive values for PSRA will have been overestimated because the gold standard on which they were based is dependent on the results of the serology.

The term PSRA was introduced in 1985 for post-streptococcal reactive arthritis not fulfilling the Jones criteria [4–6, 26]. In the studies describing adult PSRA patients, the selection of patients was based on the combination of a suggestive clinical presentation, as judged by the physician, and positive streptococcal serology [8, 14–19]. Cases of PSRA in adult patients complicated by persistent arthritis or carditis have not been described so far.

Because throat cultures performed at the onset of the non-purulent complications of a group A streptococcal pharyngitis are positive in only 29–37% of tests [27], serological tests are generally used to provide evidence for an antecedent group A streptococcal infection. Diagnostic studies on the value of streptococcal serology in newly referred arthritis patients have not been performed so far. It is known that, when both the ASO and the anti-DNase B tests are performed, elevated
antibody titres in at least one of the tests are found in 92% of patients with acute rheumatic fever and in 30% of normal controls [28]. The antibody response to streptococcal antigens peaks 2–3 weeks after the acute infection, remains at a plateau for 3–6 months and thereafter declines gradually [29]. A proportion of the patients, however, develop a prolonged raised titre [30]. A rise in antibody titre between an acute-phase and a convalescent-phase serum sample can be used to identify an acute infection, but generally does not contribute to the diagnosis of an antecedent infection at the time the non-purulent complications appear. This is because the moment the antibody response peaks is about the same as that of the occurrence of non-purulent complications, namely 2–3 weeks after the infection [28, 29]. Moreover, the presence of a lag time between the onset of the arthritis and presentation at the out-patient clinic further reduces the probability of finding rising antibody titres. This is in accordance with the results of this study, which show that the detection of significant increases in titres does not lead to improvement in the diagnostic value of the serology. In a recent study on PSRA, a relatively long delay, of about 6 weeks, was found between throat complaints and the maximum antibody response. This long delay may be attributable to the selection in the study of only patients with significant increases in ASO and anti-DNase B titres [19].

The present study shows that streptococcal serology has no diagnostic value in adult patients with recent-onset arthritis. Performing diagnostic tests in a clinical situation is only valuable if the results of the tests have prognostic or therapeutic consequences. In this study the streptococcal serological tests were unable to discriminate between the self-limiting and persistent forms of arthritis. Apart from arthritis, the major Jones criteria were not observed. Therefore the results of the serology did not have prognostic or therapeutic consequences. On the basis of the results of this study, the use of streptococcal serology in the diagnostic work-up of adult early arthritis patients in whom other major Jones criteria than arthritis are not present is not recommended.

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References


