Background: Most patients with acute rheumatic fever report no antecedent pharyngitis.

Objective: To determine the clinical and microbiological characteristics of recurrent group A β-hemolytic streptococcal (GABHS) tonsillopharyngitis.

Design: Prospective randomized trial.

Subjects: Symptoms were recorded and throat cultures were obtained at 4 to 6, 18 to 21, and 32 to 35 days following the start of treatment. A subset of 60 patients with subsequent GABHS episodes occurring were evaluated for a 0.2- or greater log rise in either antistreptolysin O or anti–deoxyribonuclease B titer to confirm a bona fide recurrence.

Results: Sixteen (27%) of 60 patients had recurrent GABHS tonsillopharyngitis of the same serotype that occurred 21 days or longer following the onset of the initial GABHS infection and was associated with a 0.2- or greater log rise in either antistreptolysin O or anti–deoxyribonuclease B titer, indicating bona fide recurrent infection; these recurrences all occurred within 55 days. Fewer patients with recurrent GABHS pharyngitis of the same serotype had headache (P = .02), sore throat (P = .006), fever (P = .008), pharyngeal erythema (P < .001), pharyngeal edema (P < .001), pharyngeal exudate (P = .04), and adenitis (P = .03) compared with the initial episode. Chills, stomachache, scarlatina, tonsillar enlargement, and palatal petechiae were similar for both episodes.

Conclusions: Fewer symptoms occur during recurrent GABHS pharyngitis of the same serotype compared with the initial infection. These patients may be less likely to seek physician attention, yet their infections put them at risk for sequelae.


GROUP A β-hemolytic streptococcal (GABHS) pharyngitis accounts for significant childhood morbidity, but little is known about the morbidity associated with recurrent GABHS pharyngitis. An increase in the cases of acute rheumatic fever (ARF) in children was noted in the late 1980s in the United States.1-10 During this resurgence, many patients with documented ARF had no recurrence of an episode of pharyngitis in the preceding months.5-7,11 During routine follow-up of patients in a comparative antibiotic study protocol, we serendipitously noted that some patients returned with fewer and/or milder symptoms and signs of tonsillopharyngitis, and had GABHS-positive throat cultures. We sought to determine the clinical characteristics and significance of these recurrences.

RESULTS

Sixty (20%) of 295 children had a subsequent GABHS pharyngitis during the study period; 19 patients (6%) had the same streptococcal serotype isolated during the recurrences (Table 1). These recurrences were detected at 21 to 34 days and 35 days or longer following the initial infection in 74% and 26% of cases, respectively (mean, 30 days; range, 21-55 days). Children with same-serotype recurrences had significantly fewer symptoms (headache, sore throat, or fever) and signs (pharyngeal erythema, pharyngeal edema, pharyngeal exudate, or adenitis) compared with the initial infections (Table 2). The frequency of chills, stomachache, scarlatina, tonsillar enlargement, and palatal petechiae were similar on both occasions; however, our statistical power to detect differences was limited by sample size.

Ten patients (3%) had new acquisitions of GABHS infection, which occurred at a mean of 20 days (range, 11-33 days) following the initial infection. These patients did not show statistically significant differences for any sign or symptom
SUBJECTS AND METHODS

STUDY DESIGN

Of the studies undertaken at the Elmwood Pediatric Group in Rochester, NY, one comparative antibiotic trial provided the necessary design to assess same-serotype GABHS recurrences occurring shortly after documented GABHS tonsillopharyngitis. This study prospectively compared the efficacy of cephalixin with penicillin treatment and was conducted between June 1, 1981, and June 1, 1984.12 The protocol was approved by the local institutional review boards and informed consent was obtained. Two hundred ninety-five previously healthy children aged 4 to 17 years were enrolled based on clinical symptoms of acute pharyngitis and a GABHS-positive throat culture. Patients were excluded if they had 2 or more sore throats in the preceding 6 months, if they were treated with antibiotics in the previous 2 weeks, or if they had a sibling concurrently enrolled in the study. The aspects of the original study design relevant to the purpose of this study included a record of all signs and symptoms on case report forms, serotyping of all available GABHS isolates, and confirmation of bona fide initial and recurrent infection by analysis of acute and convalescent serum samples for streptococcal antibodies.

DATA COLLECTION

Patients were evaluated by their regular pediatrician at 4 to 6, 18 to 21, and 32 to 35 days following the start of treatment. Fever was defined by a temperature of 38°C rectally, 37.9°C orally, or 37°C axillary. Symptoms of sore throat, headache, chills, and stomachache and signs of pharyngeal erythema, pharyngeal edema, pharyngeal exudate, scarlatinia, and palatal petechiae were recorded as present or absent. Cervical adenitis and tonsillar size were recorded on a semiquantitative basis using a 0 to 4+ scale with 0 indicating absent; 1+, mild; 2+, moderate; 3+, severe; and 4+, extremely severe adenitis. Absent tonsils, small, average, moderately enlarged, and severely enlarged tonsillar size were assigned a score of 0, 1+, 2+, 3+, or 4+, respectively. For our analysis, tonsillar size was classified as present if greater than 2+, and absent if 2+ or less. A throat culture and blood sample for antibody determination were obtained at each evaluation and sent to the laboratory of the late Hugh Dillon, MD, in Birmingham, Ala, for analysis. Data on signs and symptoms of GABHS were collected from multiple centers on a standardized case report form. The dichotomous rating scale we used to evaluate signs and symptoms reduced the influence of subjective assessments by different observers.

LABORATORY ANALYSIS

All throat cultures obtained were immediately inoculated on 5% sheep blood agar plates, incubated at 37°C for 24 hours, and then examined for β-hemolysis and colony morphology. All available strains of GABHS were typed by the capillary precipitation method for M protein and the agglutination technique for T protein according to standard methods.13,14 Antistreptolysin O (ASO) and anti–deoxyribonuclease B (anti–DNase B) titers were determined simultaneously on acute and on convalescent serum samples, collected at a mean of 19 days later (range, 9-29 days) for the initial and repeated episodes. Antibody titer assays were performed using previously described methods.13,15 A rise in either an ASO titer or an anti–DNase B titer of 0.2 log or greater was considered significant.16-18 Previous studies showed that the peak of the antibody response to these streptococcal antigens occurs 2 to 4 weeks after the acute pharyngitis and is followed by persistence of the peak titer at the same level.19-21 Because an elevated antibody level from serum obtained within this period could represent persistence of an elevated antibody from the previous episode, titers obtained on serum samples during subsequent episodes of pharyngitis were considered significantly increased if their value exceeded the peak titer of the initial serum by 0.2 log or greater.

Drug compliance during the initial episode was confirmed if a throat culture yielded no growth of GABHS during treatment. If adequate compliance was demonstrated and a 10-day antibiotic regimen was completed as determined by a dosing diary and return of empty antibiotic bottles, patients with a throat culture yielding GABHS during a subsequent episode were evaluated for a bona fide GABHS recurrence using additional criteria. A bona fide recurrence included GABHS tonsillopharyngitis of the same serotype that occurred 20 days or longer following the onset of the initial GABHS infection and was associated with a 0.2-log or greater rise in either an ASO titer or an anti–DNase B titer.20,22 Carriers were defined as patients with the same serotype isolated during the initial visit and subsequent follow-up evaluation, but with less than a 0.2-log rise in either an ASO titer or an anti–DNase B titer. Although antibiotics may suppress a rise in antibody titer,20 the 0.2-log or greater rise in either an ASO titer or an anti–DNase B titer was deemed a necessary criterion to distinguish same-serotype recurrences from carriers. Cases in which the isolate from the recurrent GABHS infection differed from the initial infection were considered new acquisitions. Since a shift to a different serotype within a few weeks was highly unlikely to occur in carriers, serotype alone was believed to be sufficient to distinguish new acquisitions of GABHS from carriers.

STATISTICAL ANALYSIS

The McNemar test was used for analysis of significant differences in symptoms and signs of initial and recurrent GABHS infections.

COMMENT

During the recent resurgence of ARF in the United States, a low frequency of antecedent pharyngitis was noted in most cases.3,7,8 The number of children reporting pharyngitis prior to the onset of ARF ranged from 23% to 58%. While 33% to 52% of the patients gave no history of an
Table 1. Same-Serotype, Bona Fide Recurrent Streptococcal Infections Tonsillopharyngitis*

<table>
<thead>
<tr>
<th>Symptom or Sign</th>
<th>Initial Episode</th>
<th>Recurrent Episode</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial Episodes</td>
<td>No. (%)</td>
</tr>
<tr>
<td></td>
<td>(n = 19)</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>8 (42)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Sore throat</td>
<td>11 (58)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Headache</td>
<td>9 (47)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Chills</td>
<td>5 (26)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Stomatococcal</td>
<td>5 (26)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Pharyngeal erythema</td>
<td>11 (58)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pharyngeal edema</td>
<td>11 (58)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pharyngeal exudate</td>
<td>10 (53)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Adenitis</td>
<td>6 (32)</td>
<td>3 (0)</td>
</tr>
<tr>
<td>Enlarged tonsils</td>
<td>4 (21)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Scarletina</td>
<td>3 (16)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Palatine petechiae</td>
<td>5 (26)</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

* Calculated using the McNemar test. Boldfaced numbers indicate statistically significant values.

antecedent illness, the remainder of the patients reported having mild flu-like symptoms 1 to 3 weeks before the onset of ARF. The occurrence of ARF in patients with no definite clinical signs of pharyngitis emphasizes the challenge faced in our continuing efforts at the primary prevention of ARF. These observations prompted the present study to expand our understanding of the clinical presentation of streptococcal disease that may precede ARF.23

We used the information from a study completed in the 1980s because its design included multiple throat cultures, serotyping of all strains, follow-up, and multiple blood samplings for antibody testing.13 Recurrent GABHS tonsillopharyngitis occurring 21 days or longer following the onset of the initial GABHS episode was confirmed by a throat culture showing the same M and T strain of GABHS during an initial and repeated episode, and a 0.2-log or greater rise in either an ASO titer or an anti-DNase B titer after each episode. A significant increase (≥0.2 log) in streptococcal antibody after each episode differentiated a streptococcal infection from persistent throat carriage. Although our definition of same-serotype recur-
current infection is sound, we cannot exclude the possibility that concurrent viral infection caused signs and/or symptoms of infection in either or both GABHS episodes. Nineteen (6%) of 295 patients who were part of a prospective study had recurrent GABHS pharyngitis with the same serotype during the study. Fewer symptoms were associated with these infections. No difference in the frequency of signs or symptoms was observed with newly acquired GABHS infections. The presence of fewer symptoms during same-serotype recurrent streptococcal tonsillopharyngitis continues to be observed in the 1990s (M.E.P., unpublished data, 1990-1997).

The same-serotype recurrent GABHS infections we studied occurred at a mean of 30 days after the initial episode (Table 1), tended to be seen with fewer signs and symptoms and could have been easily missed. These patients did not seek medical attention during any interim period prior to the prescheduled follow-up visit. The duration of symptoms with recurrent infections could not be assessed owing to the study design.

In our study, of the 17 children with same-serotype recurrent GABHS infection for whom age-adjusted ASO and anti–DNase B normal values were available,8 of the 9 children had either elevated preexisting ASO or anti–DNase B titers and 1 child had elevated preexisting titers of both ASO and anti–DNase B. For these 9 children, the possibility cannot be excluded that the initial episode for enrollment in our study was itself a recurrent infection. Regardless of whether the first infection at enrollment in the study represented an initial episode or a recurrent infection, fewer signs and symptoms were observed during the subsequent GABHS infection due to the same serotype.

CONCLUSIONS

Patients with same-serotype bona fide recurrent GABHS pharyngitis may be at risk of developing the complications of this streptococcal infection. Since fewer signs and symptoms occur in these patients, they may not be diagnosed and treated for a bona fide GABHS pharyngitis. The lack of typical symptoms in same-serotype recurrent GABHS tonsillopharyngitis suggests the need to re-evaluate our current practice regarding the follow-up management of these infections. At a minimum, physicians should be aware that this phenomenon can occur and advise patients that a recurrence of a throat infection with fewer symptoms within 6 weeks of the initial episode should not be ignored. If a subsequent throat infection with fewer symptoms does occur, we recommend a careful follow-up medical history and physical examination. If observations justify it, a throat culture should be obtained.

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This article is the view of the authors and is not intended to represent the opinion of the Food and Drug Administration.

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REFERENCES