Rheumatic Fever and Postgroup-A Streptococcal Arthritis

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Group A beta hemolytic streptococci (GAS) cause both acute infection and several postinfectious syndromes. This review focuses on acute rheumatic fever (ARF) and poststreptococcal reactive arthritis (PSRA).

RHEUMATIC FEVER

General Considerations

The global prevalence of ARF has been estimated to be approximately 15.6 million cases, with 282,000 new cases per year. Presently, the annual incidence of ARF among children aged 5 to 14 years is highest in sub-Saharan Africa. Historically, ARF is most frequent among 5 to 15 year-olds, and is extremely rare in children less than 3 years of age. The latent period between GAS infection and symptoms of ARF (excluding chorea) is approximately 3 weeks.

Pathogenesis

The pathogenesis of ARF is not clearly understood, but appears to involve immune responses to GAS antigens that then cross react with human tissue through molecular mimicry. Only a small percentage of individuals with untreated GAS pharyngitis go on to develop ARF. ARF is not considered as sequelae of cutaneous GAS infections. The incidence of ARF has declined markedly in the United States over the past 4 decades. GAS strains considered to be rheumatogenic have also declined in prevalence during this time.

Host genetic factors appear to influence the susceptibility to ARF. Observational studies in the 19th century recognized familial tendencies to develop ARF; in the 1940s, studies showed familial clustering of ARF, with greatest risk occurring in children if both parents had rheumatic heart disease. The human leukocyte antigen (HLA) types DRB1*0701, DR6, and DQB1*0201 are associated with the development of rheumatic fever. However, ARF usually does not develop in both monozygotic twins, indicating that there are probably important environmental factors involved in pathogenesis.

Diagnosis

The diagnostic criteria for ARF (first episode) are based on T. Duckett Jones’ proposed criteria which are based on clinical observation of hundreds of patients with ARF. These have been updated several times, most recently in 1992. Diagnosis requires 2 major criteria or 1 major and 2 minor criteria, plus supporting evidence of current or recent GAS infection (given in the next section). A key exception is chorea, which can be the sole finding, and is sufficient to confirm the diagnosis of ARF.

Major Clinical Criteria

Arthritis occurs in 75% of patients with ARF; it is typically migratory, exquisitely tender to minimal contact, and responds dramatically to salicylates. Left untreated, affected joints become inflamed and resolve spontaneously, with a migrating pattern of polyarthritis that persists for 1 to 4 weeks. The arthritis mainly affects larger joints, but can also affect the smaller joints of the hands and feet; the axial skeleton is rarely involved.

Carditis occurs in 50% to 60% of ARF cases and accounts for significant morbidity and even mortality. Endocarditis, the hallmark, is manifest by mitral and/or aortic valvulitis; the tricuspid and pulmonary valves are rarely affected. The revised Jones criteria require auscultation of a new valvular murmur to meet the criterion of “carditis”; echocardiographic findings of valvular regurgitation without a murmur are not sufficient. Pericarditis is the least common finding in rheumatic carditis. Myocarditis and/or pericarditis in the absence of valvular involvement are unlikely to be due to ARF; in this circumstance, etiologies other than ARF should be explored.

Sydenham chorea is the manifestation of central nervous system involvement in ARF and occurs in 10% to 15% of patients. It is usually a later manifestation of ARF, occurring several months after the inciting streptococcal infection. The characteristic features of chorea are purposeless involuntary movements, incoordination, difficulty with handwriting, facial grimacing, and emotional lability. Hemichorea was seen in 29% of patients in 1 series.

Erythema marginatum occurs in <2% of patients. It is an erythematous, serpiginous macular rash with pale central clearing. The rash characteristically spares the face and tends to be exacerbated by warmth. Subcutaneous nodules occur in <1% of cases of ARF, most often in those with severe carditis. The nodules are firm, nontender, and less than 2 cm in diameter; they tend to be over bony prominences or tendons.

Minor criteria are fever, arthralgia (if no arthritis), prolonged PR interval on electrocardiogram, and elevated erythrocyte sedimentation rate or C-reactive protein.

Diagnostic Tests

About one-third of individuals with RF will have no history of a clinically apparent GAS infection, and therefore, it is necessary to pursue laboratory confirmation of a current or past GAS infection. This supporting evidence can be (a) throat culture or rapid antigen test from a throat swab positive for GAS, or (b) documentation of an elevated or rising serum antistreptococcal antibody titer. It is important to recognize that normal antistreptococcal antibodies in the general population vary by patient’s age, geographic location, and season, with highest values observed in 10 to 12 year-olds, and at the end of the streptococcal season.

The antistreptolysin O (ASO) titer is the most commonly used streptococcal antibody test to establish a recent GAS infection. An ASO titer of 240 Todd units or higher in adults or 320 Todd units or higher in children is considered modestly elevated. Because ASO titers can be normal in approximately 20% of ARF patients, other tests are useful to establish a recent GAS infection; these include antideoxyribonuclease B, antistreptokinase, and antihyaluronidase. A single low set of titers does not exclude the diagnosis of ARF. If all titers are normal initially, it is highly advisable to repeat these tests for a few weeks to see whether the titers have risen.

Treatment

Treatment of ARF requires anti-inflammatory treatment, prevention of future streptococcal infections, and symptomatic care. After diagnosis, a dose of intramuscular benzathine penicillin, 10 days of oral penicillin, or erythromycin (for penicillin-allergic patients) is recommended for ARF pa-
TABLE 1. Recommendations of Duration of Antimicrobial Prophylaxis in Patients With Acute Rheumatic Fever

<table>
<thead>
<tr>
<th>Patients with carditis and persistent valvular disease (echocardiographic or clinical)</th>
<th>At least 10 yr since last episode or until age 40; sometimes lifelong prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with carditis but no residual heart disease (no valvular disease)</td>
<td>10 yr or until age 21*</td>
</tr>
<tr>
<td>Patients without carditis</td>
<td>5 yr or until age 21 yr*</td>
</tr>
</tbody>
</table>

*Whichever is longer.

TABLE 2. Proposed Criteria of Poststreptococcal Reactive Arthritis

<table>
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<th>Characteristics of arthritis</th>
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<tbody>
<tr>
<td>1. Acute in onset, symmetric or asymmetric, usually nonmigratory</td>
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<tr>
<td>2. Persistent or recurrent symptoms</td>
</tr>
<tr>
<td>3. Lack of a dramatic response to nonsteroidal anti-inflammatory drugs</td>
</tr>
</tbody>
</table>

Evidence of an antecedent group A streptococcal infection

Does not fill the modified Jones criteria for acute rheumatic fever

Poststreptococcal Reactive Arthritis

General Considerations

The diagnostic criteria for PSRA are not clearly defined, but the criteria proposed by Ayoub et al. are detailed in Table 2. Those patients who do not fulfill the diagnostic criteria for ARF but who develop arthritis after a streptococcal infection are deemed to have PSRA. The incidence peaks at ages 8 to 14 years and 21 to 37 years.\(11,13\)

Clinical Findings

The arthritis of PSRA is generally nonmigratory and predominantly affects the large joints of the lower limbs. It may be mono- or polyarticular, and symmetrical or asymmetric. The axial skeleton is affected in about 20% of patients. The interval between the streptococcal infection and the onset of arthritis (usually 3–14 days after infection) is generally shorter than that of ARF. The symptoms of PSRA resolve slowly over a few weeks to several months. Observed laboratory differences between ARF and PSRA include relatively lower inflammatory markers in PSRA.\(^{14}\) The most concerning possible sequelae of PSRA are that of late-onset carditis, which occurred in 4 of 13 (31%) patients with PSRA in the original case series. These patients did not meet criteria for and did not have a clinical history of ARF; they developed evidence of cardiac disease 1 to 18 years after their original illness. Late development of carditis in patients with apparent PSRA now seems much less frequent than initially suggested.

Treatment

Characteristically, PSRA patients have a slow response to nonsteroidal anti-inflammatory drugs therapy in contrast to ARF patients,\(^ {14,13} \) but they can be used. Some experts recommend a baseline echocardiogram, antibiotic prophylaxis for up to 1 year, and a follow-up echocardiogram after this time due to concern of occult carditis.\(^ {15} \)

REFERENCES