POSTSTREPTOCOCCAL REACTIVE ARTHRITIS AND ACUTE RHEUMATIC FEVER:
SIMILARITIES, DIFFERENCES, CLINICAL APPROACH AND THERAPY

ABSTRACT
Poststreptococcal reactive arthritis (PSRA) and Acute rheumatic fever (ARF) are two complications of preceding pharyngeal infections with a group A beta hemolytic streptococcus (GABHS) or Streptococcus pyogenes. Although ARF is much earlier known poststreptococcal complication, PSRA is first described in 1982. There is ongoing debate on whether these two conditions represent distinct clinical entities or are parts at the spectrum of the same disease. In this review, we aim to describe both clinical presentations, and to discuss their similarities and differences, clinical impacts and importance.

Key words: Streptococcal infections, complications, arthritis.

ÖZET

Anahtar kelimeler: Streptokok infeksiyonu, komplikasyonlar, artrit.

Introduction
Poststreptococcal reactive arthritis (PSRA) and Acute rheumatic fever (ARF) are two complications of preceding pharyngeal infections with group A beta hemolytic streptococcus (GABHS) or Streptococcus pyogenes. ARF is a serious disease with major clinical and public health effects with it’s risk of long term damage to heart valves, namely rheumatic heart disease (RHD). Although ARF is much earlier known poststreptococcal complication, poststreptococcal reactive arthritis is first described in 1982 (1). Since 1959, there had been reports of patients who present with polyarthritis after GABHS pharyngeal infections and do not fulfill the classical Jones criteria (2), but this condition was named as poststreptococcal reactive arthritis by Goldsmith and Long (1). There is ongoing debate on whether these two conditions represent distinct clinical entities or are parts at the spectrum of the same disease. In this review, we aim to describe both clinical presentations, and to discuss their similarities and differences, clinical impacts and importance.

Comparison of two clinical presentations

Epidemiology
The incidence of ARF decreased in developed countries, but it is still common in developing countries. The annual incidence of ARF is reported to be 5–51 per 100,000 population for the first attack, the lowest in North America and Western Europe while a higher incidence was documented in Eastern Europe and Middle East (highest), Asia, Avustralasia (3). The incidence rates of PSRA are uncertain. One article reports annual incidence as approximately 2/100000 in Netherlands (4). ARF is a disease of children, and its incidence is highest before adolescence with a single peak around 12 years, and a first episode is rare in adults older than 35 years, although recurrences can occur during adulthood (5). The age distribution of PSRA appears to be bimodal, with a peak at 8–14 years of age and another at 21–37 years of age (6). ARF is
generally known as being more common in female patients, contrarily PSRA is equally seen in both genders (3).

Presentations

Arthritis

Patients with both PSRA and ARF have arthritis that follows a symptomless interval after an episode of GABHS pharyngitis/tonsilitis. In ARF, arthritis usually occurs 10–28 days after the pharyngitis, while in PSRA, arthritis appears after a shorter "incubation" period, approximately 7–10 days after the infection (4, 7). In ARF, although arthritis is the most common clinical feature, it is not obligatory. It usually involves multiple, usually large joints in asymmetrical fashion and can migrate from one location to another, but can also be additive. It’s severe during 1st week and subsides in the next 2 weeks. It’s occurrence increases with age (4, 7). In PSRA, arthritis is obligatory for diagnosis. It has a acute onset is symmetric or asymmetric, usually nonmigratory and additive, which can affect any joint including joints of hands. The characteristic features; it is persistent and/or recurrent, and is poorly responsive to salicylates or NSAIDs contrary to arthritis of ARF (4, 7).

Carditis

Carditis is a major criterion of ARF. It is seen in % 40–60 of patients at the first episode and can develop in a couple weeks (7). It is typically valvulitis with a new murmur suggestive of regurgitation with accompanying myocarditis or pericarditis in varying degrees. Since it is not known how much valvular regurgitation is “normal, the current American Heart Association (AHA) guidelines recommend the use of Doppler echocardiography as a supplement to diagnosis (8). Rheumatic heart disease is potentially fatal complication of ARF and can affect worldwide nearly 20 million people with 500000 deaths annually, especially in developing countries and mainly in adolescence and young adults (3). RHD may be caused by a single attack of ARF, but is often the result of recurrent episodes. Risk of developing RHD is age-related and decreases if the first attack of ARF is at older age (5).

Reports for carditis in PSRA are not strong as much as it is in ARF. There are case series and studies with small number of patients, mostly retrospective and not detailed and standardized to compare studies (9, 10). Based on the current research, if there is any risk of development of carditis in PSRA, it is predominantly documented in pediatric patients and developed months later (11–17).

Other symptoms

Sydenham chorea, or St. Vitus’s dance is a major criterion of ARF and not seen in PSRA. There is rapid, uncontrolled movements of the face, trunk, or extremities. There can also be worsening school performance, behavioral changes, and emotional lability (7). Erythema marginatum is a characteristic skin findings in ARF that is a transient rash with central pallor and red, serpiginous borders found on the trunk and extremities. Subcutaneous nodules are paunches, fleshcolored bumps, usually found on the extensor surfaces of the arms and legs (7). They are not seen in PSRA, but erythema nodosum, erythema multiforme and other nonspeifik rashes would be seen (4). Arthralgia is pain, often in multiple joints, without associated redness or swelling. It is a minor criterion of ARF (7). Fever, usually at least 38°C, is common in early ARF (7). Since it is minor criterion, ARF would be diagnosed without fever. Some doctors extend the definition of fever for ARF to include a history of fever with current illness due to possibility of analgesic use (5). Fever also occurs in PSRA, about in 30 to 94 % of pediatric patients (4). Acute-phase reactants, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are expected to be elevated during an episode of ARF or PSRA. These markers can also be followed as signs of resolution of manifestations (4, 7). First-degree heart block is diagnosed by prolongation of the P–R interval on an electrocardiogram, and only seen in ARF. Having first-degree heart block does not predict whether a patient will develop RHD (4).

Diagnosis of Antecedent Streptococcal Infection

In order to diagnose ARF or PSRA, evidence of antecedent GABHS infection is necessary. Documentation of a recent streptococcal infection can be obtained by throat culture and/or rapid antigen detection tests (RADTs). However, both throat culture and RADTs can not differentiate a true GABHS infection from a carrier state (8, 18). Contraversially, both would be negative at the time of disease (8). Serologic tests are another way of confirming a recent GABHS infection. Elevated or increasing antistreptococcal antibody titers can be used in identifying a preceding GABHS infection. The most commonly used and commercially available antibody assays are antistreptolysin O (ASO) and antideoxyribonuclease B (anti-DNase-B). ASO titers begin to rise approximately 1 week and peak 3–6 weeks after the initial GABHS infection. Anti-DNase-B titers begin to rise 1–2 weeks and peak 6–8 weeks after the infection. Elevated titers for both tests may persist for several months or even years after GABHS infection (7). The ASO test is not specific for GABHS and would increase with group C and G infections and with some other bacteria (8). Another problem in the pediatric population is that the normal levels of these antibodies are higher among school age children then among adults. The cutoff level of antistreptococcal antibody titers that can be considered diagnostic for GABHS infection in children is still not clear. Cutoff values of ASO have ranged from 300 to 800 IU/ml and from 200 800 IU/ml for anti-DNase-B (7). Some studies have required that titers to show inreace with time. It was suggested that levels greater than 2 standard deviations of local laboratory norms or a twofold increase in the ASO titer repeated 2–3 weeks after the initial test confirm recent streptococcal infection. Sensivity of serological testing increase when a second antibody test is performed (7, 8, 19).

Diagnostic Criteria

Acute rheumatic fever: Jones criteria for the diagnosis of ARF was first published in 1944 (20). Major manifestations described in this paper were carditis, arthralgia, chorea, subcutaneous nodules and recurrences of rheumatic fever. Minor manifestations were fever, abdominal pain, precordial pain, rashes, epistaxis, pulmonary findings and laboratory findings. The diagnosis of ARF was considered reasonable if there was: 1.Any combination of major manifestations, 2. Combination of one major and two minor manifestations, 3. Minor manifestations alone in the presence of rheumatic heart disease and when other causes can be excluded. Over the years, the original Jones criteria for the diagnosis of ARF have been revised and modified several times. According to the 1992 update, the major manifestations were carditis, polyarthrithis, chorea, erythema marginatum and subcutaneous nodules (8). The minor manifestations were arthralgia and fever, elevated acute phase reactants (erythrocyte sedimentation rate, C-reactive protein) and prolonged PR interval. In addition, supporting evidence of antecedent Group A streptococcal infection were included as positive throat culture and/or rapid streptococcal antigen test and/or elevated or rising streptococcal antibody titer. The presence of two major manifestations or of one major and two minor manifestations indicates a high probability of ARF, if there is evidence of a preceding group A streptococcal infection. In 2000, another working group chaired by Patricia Ferrieri was set up by the AHA (21). They decided that there was no need to revise the criteria for the diagnosis of first episode of ARF. They also concluded that although echocardiography was useful in the
The distinction between rheumatogenic and non-rheumatogenic strains of group A streptococcus, and between those with tropism for the skin or the throat, is blurred in places with high rates of superficial infection with group A streptococcus for the ability to cause the disease. In such settings, multiple genetically different strains of group A streptococcus circulate at the same time, often within small populations (5).

Treatment
Best for the management of poststreptococcal complications is to prevent, to diagnose, and to treat infections. But, in many cases, streptococcal infections are not recognized before complications. Generally, it is advised that all patient with ARF or PSRA should have antibiotics, usually penicillin as in primary therapy of streptococcal pharyngeal infection, even if the throat culture is negative. Antiinflammatory treatment is also recommended. Salicylates were main therapy for ARF in the past, but studies comparing aspirin with naproxen showed that it is as effective as aspirin with fewer side effects (29). Some groups do recommend the use of corticosteroids for carditis in patients who are in severe heart failure (5). Antiinflammatory medications are given until the inflammatory markers normalize, usually at 4–6 weeks. There have been studies showing decreased severity and duration of chorea with prednisone therapy (5,7).

Antibiotic prophylaxis in ARF
Those patients who develop ARF are at high risk of developing subsequent attacks when infected with GABHS, and so this population is best treated with secondary antibiotic prophylaxis after their initial attack. Patients who have recurrences of ARF are at risk of developing carditis, if they have not already, or of worsening existing valve damage.

Intramuscular benzathine penicillin G (BPG) (1.2 million unit IM or 600000 units<27 kg, every 4 weeks) is used generally for secondary prophylaxis. BPG dosed every 3 weeks would provide better prevention of recurrent ARF in endemic areas. If patients are compliant with oral regimens, these can be equally effective (phenoxyemethylpenicillin/penicillin V, 250 mg orally, twice daily or if there is allergy to penicillin, erythromycin 250 mg orally, twice daily). The AHA guidelines state that individuals who have had ARF without carditis should be treated until the age of 21 years or 5 years after their last attack, whichever is longer (18). Those with RHD should be treated until 40 years of age or 10 years after tehir last attack, whichever is longer (18). Each patient’s clinical situation should be assessed individually to determine whether they have continued high-risk exposure to GABHS, which could warrant lifelong prophylaxis.

Antibiotic prophylaxis in PSRA
The 2009 AHA Scientific Statement recommends that patients with PSRA should be observed carefully for several months for clinical evidence of carditis (18). It suggests that secondary prophylaxis be given for up to 1 year after the onset of symptoms and discontinued if there is no evidence of carditis. If valvular disease is detected, the patient should be classified as having had ARF and should continue to receive secondary prophylaxis. The level of evidence for this recommendation is C, “only consensus opinion of experts, case studies, or standard of care,” and IIb, usefulness/efficacy, less well established by evidence/opinion (18).

In conclusion, ARF and PSRA must be considered in differential diagnosis of acute onset arthritis especially in areas where streptococcal infections are prevalent. To document recent streptococcal infection would be challenging, and to combine different laboratory methods would be necessary. Although current knowledge do not show increased rates for carditis in PSRA, it would be seen in months after the incident, especially in pediatric cases. It would be reasonable and recommended to follow patients longitudinally for months, and to give prophylaxis as in ARF but only 1 year, especially for pediatric patients. Further studies are...
required to investigate associations between PSRA and ARF, to determine the risk of carditis in PSRA, especially in adults, and whether antimicrobial prophylaxis is needed after PSRA in adult patients.

**KAYNAKLAR**