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Review Article

Rheumatic Fever, A Review of the Literature

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Abstract

Rheumatic fever (RF) is a multi-organ inflammatory disease that develops on an autoimmune basis as a response to throat infection with group A beta-hemolytic Streptococci in individuals of a particular predisposition. It is revealed, on average, in the 3rd week of the asymptomatic latency period after throat infection, in the form of carditis, arthritis, chorea minor, skin and soft tissue reactions, leaving permanent sequelae only in the area of the heart. The natural course of RF is characterized by relapses, which are a clinical reproduction of the first course of the disease.

The highest incidence of RF involves the population with the highest risk of streptococcal pharyngitis, i.e., children aged 5-15 years, with a peak between the ages of 10 and 12 years, with no gender-related differences. Disease also occurs among younger children as well as adults. Fresh cases of RF in Poland are now encountered only sporadically, and the picture and clinical course of the disease have become considerably milder in the last two decades.

Keywords: Rheumatic Fever; *Streptococcus*; Streptococci

Introduction

Etiopathogenesis

Rheumatic fever is caused only by group A beta-hemolytic Streptococci, and only in the case of throat infection. Streptococcal infections of other locations have no association with the development of this disease. Epidemics of streptococcal infections lead to RF in 3% of the untreated population, while for occasional infections its incidence is much lower and variable. The characteristics of individual streptococcal serotypes that determine their ability to induce RF are not well understood. The autoimmunity that underlies RF develops through a mechanism of molecular mimicry. The similarity between the antigenic epitopes of Streptococci and human tissues makes the humoral and cellular immune response elicited by the *Streptococcus* and originally directed against it, to turn against the host's own tissues, thus initiating the inflammatory process [1,2].

Evidence of streptococcal-triggered autoimmunity in RF includes

- Circulating autoantibodies directed against various structures of the heart and joints, neurons of the basal nuclei of the brain, vascular endothelium, etc., which also have the ability to react with the structural components of the streptococcal cell. They persist in the serum of many patients for several years, and in some cases even for their entire lives. These antibodies mediate the cytolysis of target cells by cytotoxic lymphocytes.
- Circulating immune complexes containing streptococcal antigens likely play a role in the pathogenesis of arthritis.

- Immunoglobulin and complement C3 deposits in the sarcolemma and sub-sarcolemma of myocardial fibers, heart valves and vessel walls.
- Antigens identified in heart muscle (myosin and vimentin) and joint tissues (vimentin) that specifically react with M protein epitopes of certain streptococcal serotypes.
- The specific hypersensitivity of RF patients to streptococcal antigens is probably genetically determined by association with as yet undefined class II antigens of the HLA system [1,2].

Clinical picture and diagnosis of rheumatic fever

The disease is characterized by a variety of initial symptoms and subsequent course, depending on the type and number of organs involved and the severity of the inflammation. Acute onset is typical for arthritis, latent onset for isolated chorea or carditis mainly in young children, while severe course is encountered only in cases of cardiac involvement. The acute phase of RF usually does not last longer than 3 months. If prophylaxis is properly administered, the subsequent recovery period should not be interrupted by a relapse [2,3].

No single clinical sign or laboratory test is pathognomonic for RF.

Evidence of streptococcal infection	Major criteria	Minor criteria
Increased or rising anti-streptococcal antibodies titer: elevated ASO or others. A positive throat culture for group A β-hemolytic Streptococci A recent history of diphtheria	Carditis Arthritis Chorea Erythema marginatum Subcutaneous nodules	**Clinical** Fever Arthralgia
		Laboratory Elevated acute phase reactants (ESR, CRP, leukocytes) Prolonged PR interval

Table 1: Diagnostic criteria for rheumatic fever (according to Jones as modified in 1982).

Helpful in the diagnosis of RF are the criteria developed by T.D. Jones in 1944 and now used according to a 1982 modification. The so-called major symptoms are characteristic of RF, while the minor symptoms are only of secondary importance in its diagnosis (Table 1). The diagnosis of RF requires 2 major symptoms or 1 major symptom and 2 minor symptoms. Evidence of a history of streptococcal throat infections is also mandatory [4].

Without the Jones criteria, RF can only be diagnosed in cases of isolated chorea and carditis of latent onset after excluding other causes of these conditions. In other situations, failing to demonstrate a streptococcal etiology raises questions about the accuracy of diagnosing RF. It should be noted that, given the high sensitivity and low specificity of the Jones criteria, even strict adherence to them does not always protect against diagnostic error [2,4].

Diagnostic criteria for rheumatic fever (according to Jones as modified in 1982)

Major criteria

- Carditis
- Arthritis
- Chorea
- Erythema marginatum
- Subcutaneous nodules

Minor criteria

- Clinical
  - Fever
  - Arthralgia
- Laboratory
  - Elevated acute phase reactants (ESR, CRP, leukocytes)

- Prolonged PR interval

- Evidence of streptococcal infection

- Increased or rising anti-streptococcal antibodies titer: elevated ASO or others

- A positive throat culture for group A β-hemolytic Streptococci

- A recent history of diphtheria

Presence of 2 major symptoms, or 1 major and 2 minor symptoms, is highly suggestive of rheumatic fever if a prior group A streptococcal infection has been confirmed [4].

Carditis

Carditis occurs in about 50% of patients with first-episode RF. It usually manifests in the first 3 weeks of the illness, in various combinations with the other major RF symptoms, or in isolation. In young children, isolated carditis is the only presentation of RF. The presentation of onset and clinical course varies from patient to patient. Carditis occurring in the first episode of RF means progressive heart damage with each relapse, as the reproducibility of the first episode in subsequent flare-ups is the rule in RF.

There is an inverse relationship between the severity of the carditis and the joint response.

The most characteristic symptom is a pathological heart murmur, which in fact always accompanies carditis in RF. If it is permanently absent, the rheumatic etiology of carditis becomes questionable. Other symptoms of carditis, such as heart enlargement, circulatory failure, and pericarditis, are much less common. In the first episode of RF, only murmurs of valve regurgitation on the left side of the heart are present, including most commonly a holosystolic murmur of mitral valve regurgitation. The diastolic murmur of aortic regurgitation usually accompanies the murmur of mitral regurgitation. Valve failure that can only be detected by Doppler in the absence of an audible murmur is of questionable value in the diagnosis of carditis and has not yet achieved the status of a diagnostic criterion.

The degree of cardiac silhouette enlargement is usually proportional to the severity of the carditis. A precise differentiation of the causes of cardiomegaly is possible by means of echographic examination. Circulatory failure in the first episode is always indicative of severe myocarditis and usually occurs in patients with an already enlarged cardiac silhouette. Pericarditis is the least common acute cardiac reaction and indicates severe inflammation of the entire heart (rheumatic pancarditis). It does not occur in isolation, and in absence of symptoms of endomyocarditis, a non-rheumatic etiology should be considered. The symptoms are not specific to RF. Pericarditis occurs quite suddenly and resolves quickly with anti-inflammatory treatment, leaving no noticeable sequelae. Changes in the ECG are not specific to rheumatic carditis.

The sequelae of carditis in GR are usually acquired heart defects, often requiring cardiac surgery. Postinflammatory cardiomyopathy also develops in severe cases [1,5,6].

Arthritis

Arthritis is the most common but least specific major symptom of RF. It occurs in three quarters of the cases of the first episode of RF, either alone or in association with other symptoms, which makes the diagnosis much easier. Arthritis in RF does not occur in children under the age of 6, and its incidence increases with the patient's age. The characteristic feature of GR is acute inflammation of multiple joints (> 5) with high fever, asymmetrical involvement of large peripheral joints (knees, ankles, elbows and wrists), migratory (disappears in one joint and reappears in another) and transient (leaves no permanent changes) nature of inflammation, extremely severe pain in the affected joints with the presence of all objective signs of inflammation, and rapid response to treatment with salicylic compounds (24-48hours with anti-inflammatory drug concentration in serum). Involvement of a single joint does not last more than a few days, and spontaneous complete remission of arthritis in untreated patients usually occurs within 3 weeks. Local signs of inflammation are also characteristic: redness of the skin is usually mild and confined to a small area directly over the joint, while swelling is soft and diffuses into the tissues adjacent to the joint. The affected joint is remarkably warmer. The immobilization of the joint is a response to the pain, the severity of which is the greatest and out of proportion to the other symptoms. There may also be a transient, mild, sterile exudate in the joint. Any deviation from the described presentation of arthritis, especially with regard

to the duration of the inflammation, the type of joints involved, the distribution of the reaction, and the lack of response to salicylate treatment, should raise doubts about the diagnosis of RF. It can be particularly difficult to distinguish the classic form of RF from reactive post-streptococcal arthritis [7,8,9].

Chorea minor

Chorea minor (synonyms: Sydenham's chorea, St. Vitus dance) occurs mainly in children, always over the age of 6, and exceptionally in young women. Nowadays, it occurs only occasionally. It can present in combination with other RF symptoms, manifest itself after they have subsided, or occur in an isolated form as so-called pure chorea. In multisymptomatic episodes, it is accompanied by carditis. Pure chorea is characterized by a very long latency period. Acute phase reactants are usually normal and ASO titer is low. The diagnosis is established on the basis of the clinical picture, i.e., characteristic involuntary movements of unusual speed, completely chaotic and irreproducible. They can affect the whole body, but always spare the eye muscles. In addition, impaired coordination of purposeful movements, weakened muscle tone and strength, and emotional instability are noted. Recovery is complete, despite a tendency to relapse. The risk of acquired heart valve disease in the form of stenosis of the mitral valve orifice is also associated with pure chorea in RF. This form can be diagnosed only after ruling out other diseases, such as generalized lupus erythematosus, antiphospholipid syndrome, and others [2,4,9,10].

Erythema marginatum and subcutaneous nodules

Erythema marginatum and subcutaneous nodules only occur only in patients with carditis and never as independent forms of RF. Both erythema and nodules are now very rare major symptoms of RF. The erythema can appear at any time during the RF episode. It is resistant to anti-inflammatory treatment and tends to recur after other signs of disease activity have subsided. Macular pink lesions, sometimes resembling measles, that enlarge from the center, leaving unaltered skin in the central area, surrounded by a distinct pink border. Diffuse or confluent lesions in the form of closed rings and/or girland-like figures involve the trunk and proximal parts of the limbs, sparing the face. The erythema exhibits outstanding variability in shape and distribution in the same patient.

It is also encountered in systemic connective tissue diseases, drug reactions and sepsis.

Subcutaneous nodules, located deep in the subcutaneous tissue, arise from the joint capsules and tendon sheaths. Their characteristic locations are the dorsal sides of the area of the large peripheral joints, the spinous processes of the vertebrae, and the occipital and temporal regions of the skull along the hairline. The skin over them is movable and unaltered. They appear in flares and subside within 1 week to a dozen or so months. They are a late manifestation of acute RF.

Isolated nodules in healthy children are called pseudoreumatoid nodules and do not require treatment.

Marginal erythema and subcutaneous nodules do not cause any discomfort [9,10].

Minor criteria

These symptoms do only play auxiliary role in the diagnosis of a first episode of RF. Their diagnostic value increases significantly when identifying a subsequent episode of RF in patients with chronic rheumatic heart disease (= acquired heart defect), which may be manifested only by the presence of minor symptoms and evidence of a history of group A streptococcal infection [4,9,10].

- Fever of 38-39°C with an uncharacteristic course lasts no longer than 3 weeks and resolves spontaneously without treatment.
- Migrating arthralgia of varying severity occurs throughout the day. It cannot serve as a minor symptom in cases of RF with arthritis.
- Laboratory indicators of the acute phase - increased erythrocyte sedimentation rate, usually reaching a three-digit value after 1 hour, neutrophilia and the presence of acute phase protein (CRP) in serum are only non-specific measures of the severity of inflammation. They are useful in assessing disease dynamics and treatment progress. Their normal values contradict the diagnosis of RF (with the exception of pure chorea).
- A-V I° block, usually transient, occurs in approximately 40% of episodes regardless of their clinical presentation. In cases of carditis, it cannot be used as a minor symptom in the diagnosis of RF [11].

Evidence of past streptococcal infection

Only a history of diphtheria, isolation of group A β-hemolytic *Streptococcus* from the throat, or an elevated serum titer of anti-streptococcal antibodies may serve as evidence of prior infection.

The first two are of relatively limited use - diphtheria because of the current low incidence, while isolation of *Streptococcus* from the throat requires the fulfillment of technical conditions that are not always feasible and differentiation between actual infection and the more common situation of children being asymptomatic carriers [12,13].

Dynamics of ASO changes after infection with group A beta-hemolytic *Streptococcus*, according to G. Gutowska (Clinic of Rheumatology of the Developmental Age, Institute of Rheumatology, Warsaw, Poland), are following: by the first four weeks, the ASO titre in Todd units increases to the level of about 600 (or more), then from the fourth to the sixteenth week it remains at a constant level, and from the sixteenth week to about 40 weeks it decreases steadily to the limit of normal.

Of the antibodies to various streptococcal extracellular antigens, the determination of antibodies to streptolysin O (ASO) has the broadest practical application. Elevated ASO titers are present in approximately 80% of RF patients, and only the detection of antibodies to at least 2 additional streptococcal antigens, such as hyaluronidase or deoxyribonuclease B, allows confirmation of a history of infection in 100% of patients. The cutoff value for ASO titer in children is 333 units, in adults 250 units. ASO titers peak 4 weeks after infection and remain at this level for 2-4 months. More accurate information than a single assay is provided by an increase in the titer by a minimum of two dilutions in blood samples taken at intervals of 2 weeks and 4 weeks. This procedure is particularly useful when the baseline ASO titer is low or in the borderline range.

A high ASO titer in the absence of clinical symptoms does not mandate a diagnosis of RF and only serves to indicate a history of streptococcal infection. It may also be the result of non-specific biochemical factors such as lipid metabolism disorders or an infection with group C or G Streptococci. The differential diagnosis in patients with high ASO titers should include the possibility of incidental streptococcal infection in the course of other diseases that may present similarly to RF, such as systemic lupus erythematosus, juvenile arthritis with acute systemic onset, and others, as well as other acute inflammatory conditions resulting directly from streptococcal throat infection, such as reactive post-streptococcal arthritis, cutaneous form of nodular arteritis, in some cases also the classical form of this disease, or Takayasu's arteritis and others. Only in isolated chorea and hidden-onset carditis is a prior streptococcal infection not required to diagnose RF. In other situations, while the absence of this evidence does not absolutely negate the diagnosis of GR, it casts doubt on its accuracy and always mandates extensive diagnostic caution [12,13].

Treatment and prevention of rheumatic fever

Pharmacotherapy in rheumatic fever includes

- Causative treatment to eliminate group A β-hemolytic Streptococci from the throat with a bactericidal antibiotic.
- Symptomatic treatment, i.e., anti-inflammatory and possibly other supportive treatment, as needed.

	ACUTE PHASE	PROPHYLAXIS
Penicillin		
Benzathine benzylpenicillin i.m. (Bicillin L-A) [podałam nazwę handlową pod jaką występuje międzynarodowo - przyp. tłum.]	1 x 600,000 units (< 30 kg bw) 1 x 1,200,000 units (> 30 kg bw)	1 x every 3-4 weeks
Phenoxymethylpenicilin p.o. (Ospen)	250 mg 2-4 times a day – for 10 days	250 mg twice a day – continuously
Sulfadiazine p.o.	Do not use	500 mg once a day (< 30 kg bw) 1000 mg once a day (> 30 kg bw)
Eryhromycin p.o.	250 mg 4 times a day 40 mg/kg bw/d – for 10 days	2 x 250 mg/d

Table 2: Causative treatment of RF (According to WHO).

1 mg = 1600 international units.

For eradication of Streptococci, both in the acute phase of RF and for prevention of recurrence of the disease, the drug of choice is penicillin, administered intramuscularly or per OS (Table 2). Its therapeutic level should be maintained for 10 days during the acute phase and continuously for prophylactic purposes. This is achieved by a single dose of benzathine benzylpenicillin of 600,000-1,200,000 units, administered by intramuscular injection every 21 days in the acute phase and as a prophylaxis, or phenoxymethylpenicillin (V-Cillin, Ospen) at a dose of 250 mg* 3-4 times a day for 10 days in the acute phase and twice a day as a prophylaxis.

An alternative drug is erythromycin, administered p.o. for 10 days in the acute phase of RF at a dose of 40 mg/kg, not exceeding 1 g/day, and in prophylaxis at a dose of 250 mg twice daily. Sulfonamides are not used in the acute phase of the disease. For RF prophylaxis, in case of penicillin allergy, sulfadiazine is recommended once daily in a dose of 0.5 g for patients weighing up to 30 kg and 1 g for those weighing more than 30 kg. The highest risk of RF relapse occurs when the disease develops at the youngest age, in patients with a history of carditis, and during the first five years after the last episode of the disease. These facts will help to determine the length of time that RF prophylaxis should be used. Prophylactic treatment in people who have had carditis should be long-term, preferably lifelong. In patients without a history of carditis, prophylaxis may be discontinued at the earliest 5 years after the last episode of RF, provided the patient has reached full maturity, i.e., is over 21 years of age [2,9,10].

Anti-inflammatory treatment with corticosteroids and salicylates is used for an average of 3 months. The choice of drug, the dosage, the route of administration and the duration of use are determined on an individual basis for each patient. According to generally accepted principles, corticosteroids are reserved for patients with carditis, administered at a starting dose of not less than 1 mg/kg daily dose equivalent to prednisolone. After resolution of the acute symptoms, the dose is reduced once a week until discontinuation, which is usually at the end of week 6. After reducing the initial corticosteroid dose by 1/3, additional treatment with salicylates (aspirin, etc.) at a dose of 60 mg/kg bw/d is implemented. After 6-8 weeks, the aspirin dose is gradually reduced until withdrawal. In arthritis, it is sufficient to use salicylates only, at an initial dose of 75-80 mg/kg bw/d. There is no consensus on the need for anti-inflammatory treatment in pure chorea. Various medications ranging from phenobarbital to haloperidol to pimozide and valproic acid have been used to control hyperkinesis with varying success in individual patients. Prophylaxis should be the same as for other forms of rheumatic fever [1,2,5,10].

Primary prophylaxis

Primary prophylaxis is the prevention of the first episode of rheumatic fever, which includes the proper treatment of pharyngitis, i.e., the use of antibiotics with bactericidal effect on Streptococci (penicillins, erythromycin, cephalosporins) for a period of 10 days [14,15].

Summary

Only carditis is of prognostic significance, as there are no other sites of inflammation that leave permanent sequelae. The course of the acute phase does not determine the prognosis of an individual patient. Even in severe carditis, complete recovery or hemodynamically insignificant valve dysfunction may be achieved. Factors that worsen the prognosis are the young age of the child at the onset of the disease and the frequency of relapses.

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