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Rheumatic heart disease in children: from clinical assessment to therapeutical management

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Abstract. – Rheumatic heart disease is still a relevant problem in children, adolescents and young adults. Molecular mimicry between streptococcal and human proteins has been proposed as the triggering factor leading to autoimmunity and tissue damage in rheumatic heart disease. Despite the widespread application of Jones' criteria, carditis is either underdiagnosed or overdiagnosed. Endocarditis leading to mitral and/or aortic regurgitation influences morbidity and mortality of rheumatic heart disease, whilst myocarditis and pericarditis are less significant in determining adverse outcomes in the long-term. Strategy available for disease control remains mainly secondary prophylaxis with the long-acting penicillin G-benzathine.

Key Words:

Rheumatic heart disease, Pediatrics.

Introduction

Rheumatic heart disease is the only clinical manifestation of rheumatic fever (RF) which results in residual or permanent damage occurring in 14 to 99% patients: such a wide difference in prevalence is due to a twofold explanation: on one hand the difficult recognition of RF first episode, often associated with only mild manifestations, and on the other hand the recent availability of echocardiographic investigations for RF diagnosis, which can result extremely effective in recognizing subclinical carditis too[1]. Initial episodes of acute RF are commonly encountered in children aged 5-15 years and are rarely observed before the age of 5 years. The more consistent clinical signs of rheumatic carditis include the presence of a pathologic murmur, particularly the one referred to aortic or mitral insufficiency. The presence of valve disease or carditis can be easily recognized through echocardiographic examinations, but the combination of clinical tools and echocardiography consents the most accurate assessment of heart involvement[2]. It is well known however that minimal physiological mitral regurgitation can be identified in normal people and might overdiagnose the possibility of carditis. Only in 30% patients serial electrocardiogram studies are helpful in the diagnosis of acute RF with non-specific findings including prolonged PR interval, atrio-ventricular block, diffuse ST-T changes with widening of the QRS-T angle and inversion of T waves. Carditis as an initial sign might be mild or even remain unrecognized.

Pathogenesis

Interactions involving *streptococci* and the host play an essential pathogenetic role for RF occurrence. Of the *β-hemolytic streptococci* that can produce infection in humans, only those belonging to group A can lead to RF, almost exclusively after tonsillitis or pharingitis[3]. One of the first mechanism proposed to explain injury in RF was a direct invasion of the affected tissue by the *Streptococcus*. Evidence of a latency period of about 3 weeks between the acute streptococcal infection and the clinical appearance of tissue injury suggests that tissue damage is mediated by an immunological reaction with an autoimmune component. Kaplan and his coworkers have proposed the concept of "antigenic mimicry": antibodies produced by the streptococcal infection against the bacterial antigens cross-react with the host tissues

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leading to tissue injury[4]. The description of the immunologic cross-reactivity between the M protein and myocardial sarcolemma lends support to this concept. After the immune reaction there is a subsequent inflammatory process involving myocardium and valvular endocardium. With progression and persistence of inflammation valve fibrosis and calcification might occur. It is extimated that only 0.3% of individuals with an untreated streptococcal pharyngitis will present an episode of RF. Moreover RF incidence following pharyngitis in patients who have had a previous episode of RF is approximately 50%. This observation, together with clinical studies indicating a familiar clustering of the disease, suggests that genetic factors might play a role in the susceptibility to RF. It has been reported the presence of specific B-cell alloantigen in the 99% of patients with RF and in only 14% of controls. Genetic susceptibility to RF is also supported by the association with HLA-DR2 and DR4 antigens[5,6].

Clinical Manifestations

Myocarditis

Diagnosis of rheumatic myocarditis can be sustained upon the basis of soft first sound, third sound gallop (or protodiastolic gallop), cardiomegaly, Carey-Coombs' murmur or congestive heart failure. These clinical signs are non-specific because also due to hemodynamic overload on the left ventricle from acute/subacute mitral and/or aortic regurgitation. Echocardiographic evaluation provides information related to degree of myocardial contractility, ejection fraction, measurement of ventricular size and presence of valvular regurgitations[7]. Myocardial biopsies performed during acute RF have failed to improve clinical diagnosis of RF because histological changes may be minimal in the early stages and are not necessarily correlated with severity of peculiar clinical pictures[8]. Histologic findings associated with rheumatic myocarditis can be divided in 2 stages: (1) *stage I*, in which exudative and proliferative reactions with CD4-lymphocyte infiltration and few granulocytes are predominant in the subendocardial, subepicardial and perivascular connective tissue, and (2) *stage II*, in which the Aschoff nodules can be observed in the perivascular areas (Figure 1). Aschoff nodule consists of large vimentin-positive cells of mesenchymal origin with polymorphous nucleus and basophilic cytoplasm standing around a fibrinoid centre, and can be considered the pathognomonic marker of rheumatic myocarditis. Laboratory markers of myocardial damage result normal in patients with acute RF, while in patients with acute RF and congestive heart failure unresponding to medical therapies valve replacement might be life-saving: these observations let us suggest that acute rheumatic myocardial damage plays a less significant role in morbidity or mortality rates associated with RF[9,10].

Endocarditis

Endocarditis is the most typical outline of rheumatic heart disease, characterized by leaflet inflammation of mitral and/or aortic valves; pulmonary and tricuspid valves are more rarely involved. Histologic findings in rheumatic endocarditis can be divided in *stage I*, with edema and cellular infiltration of valvular tissue or chordae tendineae, and *stage II*, with persistent inflammation leading to fibrosis or calcification with eventual valvular stenosis. Mitral insufficiency occurs in 92 to 95% cases, of which about 20 to 25% have also aortic insufficiency; isolated aortic insufficiency occurs in about 5 to 8% patients. The presence of mitral insufficiency is characterized by a high-frequency apical holosystolic murmur with maximal intensity at the apex and radiation to the left axilla. When mitral insufficiency arises acutely it is possible to appreciate the Carey-Coombs

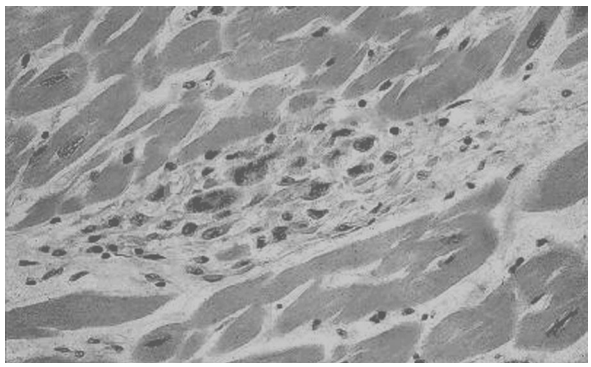

Figure 1. Aschoff nodule in the myocardial tissue.

murmur, a low-frequency diastolic flow murmur from relative stenosis. Aortic insufficiency is characterized by a diastolic murmur, best heard over the left third intercostal space. Severe mitral or aortic regurgitation may lead to left heart failure with soft first sound, third sound gallop and cardiomegaly. In the diagnostic approach of RF echocardiographic evaluation is extremely sensitive in recognizing the severity of endocarditis, specifically the degree of mitral and/or aortic regurgitation, in association with Jones' criteria (which are listed in Table I)[11].

It is possibile to diagnose with high probability rheumatic fever when 2 major criteria or when 1 major criterium and 2 minor criteria are fulfilled, after having demonstrated a previous infection by group *A β-hemolytic Streptococcus* with culture of a throat swab.

Pericarditis

Pericardium involvement is the less common clinical manifestation of rheumatic heart disease and is present in 15% patients. Pericarditis is justified by visceral and parietal pericardium surface inflammation which can give rise to precordial pain or friction rub.

Treatment

Treatment of acute RF remains controversial: which patients can be treated with aspirin and which patients require steroids or other therapeutical tools to reduce cardiac morbidity have not been definitely established. It is now recommended that salicylates have to be used in patients with mild or moderate carditis, whilst steroids have to be reserved for patients with severe carditis. Aspirin is administered at the dosage of 80 to 100 mg/kg/day for 4 to 8 weeks, controlling its serum level which must remain below 25 mg/dl. Steroid therapy (with oral prednisone) is administered at the dosage of 2 mg/kg/day for 2-3 weeks, followed by gradual withdrawal over the following 2-3 weeks. One week prior to withdrawal, salicylates can be used in combination with steroids in order to avoid clinical rebound. In patients with severe carditis or heart failure the use of digoxin, diuretics and vasodilators is recommended[12].

Prophylaxis

Primary prophylaxis leads to the eradication of streptococci from tonsillar or pharyngeal sites: antibiotics with demonstrated efficacy against *group A beta-hemolytic Streptococcus* include penicillin and congeners (e.g., ampicillin, amoxicillin, semisynthetic penicillines), a number of cephalosporins, macrolides and clindamycin. Dosage and duration of therapy should be sufficient to eradicate streptococci from tonsils or pharynx. There is a tendency to RF recurrence in the absence of secondary prophylaxis, so that patients who have had asymptomatic carditis in a first episode could become symptomatic after the second or third episode. Secondary prophylaxis (defined in Table II) is aimed at the prevention of RF recurrence in patients with a first episode of RF. Administration of monthly intramuscular injections of long-acting penicillin G-benzathine is recommended by the American Heart Association, but prophylaxis duration is still debated: this can be established upon the presence or absence of cardiac involvement[13]. Actual management

Table I. Jones' criteria (1944) for the diagnosis of rheumatic fever.

Major criteria	Minor criteria
Migrating polyarthritis	Fever
Carditis	Arthralgias
Chorea minor (Sydenham's chorea or St. Vitus' dance)	Positive acute phase reactants
Erythema marginatum	Prolonged PR interval
Subcutaneous nodules	Previous rheumatic fever

Table II. Secondary prophylaxis for rheumatic fever.

Drug	Dosage
Penicillin G-benzathine with intra-muscular injection	1.200.000 Units every 21 days (600.000 children aged less than 6 years)
Erythromycin per os (in case of *allergy to penicillines*)	250 mg for 2 administrations in a day

Table III. Duration of secondary prophylaxis for rheumatic fever.

Category of patients	Duration of secondary prophylaxis
Rheumatic fever without carditis	For a minimum period of 5 years or until 21 years
Rheumatic fever with mild carditis, but without valvolar damage	For a minimum period of 10 years (or until advanced adulthood)
Rheumatic fever with carditis and valvolar damage	For a minimum period of 10 years or until 40 years or lifelong

strategies which are currently used in the definition of secondary prophylaxis duration are listed in Table III.

In conclusion, patients with acquired valvular dysfunction as a consequence of RF are considered moderate-risk category subjects for whom bacterial endocarditis prophylaxis is recommended. Therefore, dental procedures (extractions, periodontal scaling and root planing, endodontic surgery beyond the apex, prophylactic cleaning of implants with possibility of bleeding), surgical operations involving tonsils or adenoids, bronchoscopy, biliary tract surgery, cystoscopy, etc. require constantly a prophylactic regimen with amoxicillin (50 mg/kg per os 60 minutes before the specific procedure in children or 2 grams per os 60 minutes before procedure in adults).

(Special Statement by the Committee on Treatment of Acute Streptococcal Pharyngitis and Prevention of Rheumatic Fever, American Heart Association, 1995).

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