

Acute rheumatic fever

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Unreliable legend related that Vitus' intercession freed Emperor Diocletian's son of an evil spirit and cured from so called "Saint Vitus Dance". Probably if Vitus was born in our era, he has never been saint, because we know now, chorea is able to resolve without treatment and without a miracle. Saint Vitus (died 303) is the patron of children and invoked against Saint Vitus Dance or Sydenham's Chorea.

A CASE

1838. Ten-year-old girl complained of general rheumatic symptoms; pains in the limbs, with puffiness and swelling of the wrists, and some other joints. Six days later, she developed chorea: her head was constantly tilting from one side of the bed to the other; her lips closed and opened with a smacking sound, and when she tried to put out her tongue it protruded in a forced grimace. A rapid and irregular heart-beat led to suspect that the heart was also affected. Sixteen days later, the girl died. After the autopsy, Bright¹ discovered that both the pericardium and the endocardium were involved. Careful dissection of the brain failed to yield any perceptible abnormalities².

DEFINITION

Rheumatic Fever (RF) is a delayed and inflammatory disease non suppurative sequel of upper respiratory infection with group A *Streptococci*.

HISTORY

Acute migratory arthritis of children appeared in the time of Hippocrates, a physician born in 460 BC on the island of Cos, Greece. The term chorea derived from a Greek word "khoreia" which means "dancing". It was introduced by Paracelsus (1493-1541) to describe hysterical movements of religious fanatics during the Middle Age. The concept of Rheumatic Fever evolved from manifes-

tations known in the 17th Century as "Rheumatism" and it was described first by Guillaume Du Baillou in France (1538) and by Thomas Sydenham in England (1686)³. Sydenham used the designation St. Vitus' dance to describe chorea⁴. In 1761 Morgagni (in Italy) described the valvular lesions. Joseph-Irénée Itard, a Parisian medical student probably was in 1824, the first to study this disease; he sustained a twenty-four-page thesis for graduation from medical school entitled "Considerations sur le Rhumatisme de Coeur"⁵. Richard Bright in 1838, a prominent London physician called attention in his Lecture at the College of Physicians in London, to the association of chorea with diseases of pericardium and he was the first to associate all the anomalies with rheumatic fever². Dr James Kingston Fowler, who was serving as house physician at King's College Hospital in 1874, contracted a rheumatic fever and he was the first to report tonsillitis as a common precursor of rheumatic fever in collaboration with Walter Butler Cheadle⁶. It is in 1904 that Aschoff described the cardiac nodules. In 1928 in New York, F Swift introduced the hypothesis that rheumatic fever results from the development of hypersensitivity to *Streptococci* and is only in 1932 that Edgar W Todd evidenced to support the hypothesis of an immune pathogenesis of rheumatic fever with the discovery of antistreptolysins⁴. In 1944, T Duckett Jones gave the first lecture about RF.

EPIDEMIOLOGY

The frequency of the RF was 100-200 cases per 100,000 in the US population in 1900 and 50 per 100,000 in 1940. Until the early 1980's there was a decline to about 0.5 per 100,000 with a localized outbreaks⁷⁻¹⁴. In Europe, there have been similar declines and it has become a rare disease. Although, in undeveloping countries, RF still endemic and remains the major cause of acquired heart disease in young adults.

Factors relating to the decrease in RF were still unknown¹⁵. Over the past Century, living conditions and crowding were improved in most countries, contributing

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to the declining of the disease. We don't know if virulence of group A *Streptococci* is declining or if human resistance to these bacteria is increasing. Of course, penicillin treatment has contributed to declining mortality and morbidity due to streptococcal infections, including RF, but the reasons for the decline before penicillin were not apparent¹⁶. The incidence and prevalence of this disease steadily have declined as has mortality in the past decade¹⁷⁻¹⁹. Factors that have contributed to the decrease in the incidence of acute rheumatic fever (ARF) may include changes in the host, the environment or the pathogen¹⁷.

RF usually appears between 5 and 18 years old patients and it is rare before the age of 3 years.

PATHOGENESIS

Despite epidemiological and clinical research, the precise pathogenesis of RF remains unknown²⁰. Socio-economic factors have little importance in RF occurrence. Some authors currently favour the theory that ARF is an autoimmune disorder after an immunologic cross-reaction response to the antecedent streptococcal infection²¹.

Group A *Streptococci* vary in their rheumatogenic potential. Strains causing clusters or epidemics usually belong to certain serotypes 1, 3, 5, 6, 18, 19, 24 and are often heavily encapsulated as evidenced by their growth as mucoid colonies on blood agar plates. Approximately 3% of untreated patients could develop ARF²¹.

Rheumatogenic *Streptococci* adhere to pharyngeal cells²². The absorbed products of streptococcal degradation act as antigens and have molecular mimicry with different human tissues. They are identified by the macrophages and presented to the T cell receptors producing cytokines which activates B cells to become immunoglobulin. Antibodies to the *Streptococci* may cross-react with heart, brain and/or joint tissue resulting in carditis, chorea or arthritis. Components of the streptococcal cell wall and of the cell membrane contain epitopes that share antigenic determinants with certain constituents of the human tissues. The hyaluronic acid and the N-Acetyl glucosamine in capsule react with the hyaluronic acid of joint tissue. M-Protein, the group A carbohydrate and the N-Acetyl glucosamine in cell wall react with tropomyosine, myosine and glycoprotein of the heart. Lipoproteins in Protoplasm react with neuronal tissue and affect basal ganglia regions of the caudate and putamen. This *humoral reaction* clears without sequel. Persistent rheumatic heart disease, as Aschoff body, is a result of *cellular reaction* and is the persistence of T cell activity in valve tissue^{23,24}.

Although, several observations show that more than one member is affected in the same family, only small percentage of individuals experienced streptococcal infection, some individuals developing recurrent attacks or

exhibiting specific HLA antigen; all these factors suggest that RF may be modulated by the specific genetic constitution of the host²³.

CLINICAL EXPRESSION

The diagnosis of RF is based on clinical criteria and may be difficult to establish it given the current rarity of the disease and the absence of any pathognomonic laboratory tests.

The migratory polyarthritis with fever was the initial sign of RF in the past in approximately 75% of patients, actually is really less frequently seen. Knees, ankles, elbows and wrists are the most commonly affected joints; arthritis improves without treatment in 1 to 3 days and it has a dramatic response to salicylates²⁵. Recent international studies documented monoarticular arthritis as a presenting sign in ARF²⁶. Although in 2000, the Jones Criteria Working Group²⁷ acknowledged the importance of monoarticular arthritis among people in undeveloped countries, this diagnosis has not been universally accepted as major criteria in developed countries. The Workshop²⁷ did not address the potential need for antibiotic prophylaxis in patients with post streptococcal reactive arthritis who did not fulfill the Jones Criteria.

Carditis, the most serious manifestation of RF occurs within 3 weeks after Group A streptococcal infection. It is a pancarditis: Endocarditis that is almost always present, mitral regurgitation is the most common pathology in RF associated or not to the aortic regurgitation; Myocardial disease with atrioventricular conduction disorders or with congestive heart failure and Pericarditis who is rare (< 5%). Cardiac involvement is seen in about 50% of patients with ARF and with the help of echocardiography in about 70%. The use of Doppler-echocardiography should be used as an adjunctive technique to confirm clinical auscultatory findings; although, it should not be used as a major or minor criterion for establishing the diagnosis of carditis associated with ARF²⁷. Clinical research is needed to determine the prognostic implications of subclinical valvular regurgitation.

Sydenham's Chorea is a delayed manifestation of RF (occurs 1 to 6 months) after a Group A streptococcal infection. Resulting from an autoimmune attack on the CNS, sera from patients with chorea contain antibodies that cross-react with basal ganglia neurons. Pathophysiology of Sydenham Chorea can be divided into four areas: *Neuroanatomy* with basal ganglia regions of the caudate, putamen and subthalamic nucleus dysfunction; *Neurochemistry* with imbalance among the dopaminergic, cholinergic and the inhibitory gamma aminobutyric acid systems; *Immunology* with production of antineuronal antibodies and inflammatory cytokines and *Genetics* as RF frequently appeared in multiple members of a family²⁸. This disorder is characterized by sudden non-voluntary

arrhythmic and clonic purposeless movements. Sometimes, children present hypotonia, gait disturbance, incoordination, loss of fine motor control, facial grimacing, gross fasciculations of the tongue, and speech abnormalities with dysarthria, explosive speech and emotional labilities. Chorea is a clinic diagnostic due to the lower frequency of others positive results of the laboratory and may present without any other major or minor features of RF. She was frequently seen in the 1950's and her incidence declined substantially to 10-30%. Neuro-imaging as increased signal in the caudate and putamen nucleus have been reported in patients with Sydenham's chorea. Chorea resolves in 2 to 3 months, the treatment of Sydenham's Chorea is purely symptomatic and different drugs are used in her treatment although a few studies strongly support their efficacy. Susan Swedo²⁹ was the first to describe the paediatric auto-immune neuropsychiatric disorders associated with *Streptococcus* (PANDAS) as different diagnosis from Sydenham's chorea.

Transient erythema marginatum occurs to less than 2% of patients; it consists of erythematous serpiginous, macular lesions with pale central clearing on the trunk and extremities. Subcutaneous nodules occur in less than 1% of cases and they resolve within one month without long-term sequelae. They are firm, non-tender, varying in size from a few millimetres to 1-2 cm of diameter, over bony prominences and in tendon sheaths³⁰.

CRITERIA

Criteria are used at the acute stage of the disease. The first criteria were established by Jones³¹ in 1940 and there were some updates, the last one in 1992^{25,32-34}. In 2000, the American Heart Association agreed that there were insufficient data to support a revision of the Jones Criteria and reaffirmed the guidelines iterated in the 1992 statement²⁷.

The diagnosis of RF is highly suggested when two major criteria or one major and two minor criteria are fulfilled in a patient with previous streptococcal infection diagnosed by positive culture of throat and/or elevated or rising streptococcal antibody titer.

Major criteria are polyarthritis, carditis, chorea, erythema marginatum and subcutaneous nodules. Minor criteria are fever, arthralgia, elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) and prolonged PR interval on the electrocardiogram.

RF is now a rare disease in most of Europe and North America, making its diagnosis more difficult to establish.

DIAGNOSIS

Positive throat culture of Group A Streptococcal infection is infrequently found and the absence of a positive culture does not exclude the diagnosis of RF^{35,36}. Anti-streptolysin O antibody (ASO) and anti-DNase B are of limited diagnostic value because 20% of cases presented

without raised antibody levels³⁰. The ESR or CRP should be measured and usually they are increased. Chorea could be present as isolated manifestation, frequently when a patient presents, acute phase reactant levels may have normalized.

OUTCOME

Deaths are related to heart failure and it is really rare in industrialized countries. Prophylaxis prevents recurrences. Relapses are more frequent in the first 3 years after a first episode of RF. Patients with residual valve disease must be followed by echocardiography every 6 months for the first 2 years after first episode of RF.

TREATMENT

The therapeutic management of the ARF need to treat the inflammatory process, to eradicate the *Streptococcus* and to continue for long term prophylaxis.

An anti-inflammatory treatment are required if severe carditis is present: prednisolone 2 mg/kg/day and less than 80 mg/day, given in 1 dose/day for 3-4 weeks decreasing over 6-8 weeks and followed by aspirin who is started 1 week before termination of steroids. The dose of aspirin is 80-100 mg/kg/day, 4 doses/day during 4-8 weeks; decreasing over the following 4 weeks. In mild to moderate carditis, corticosteroids are not essential and we can treat with aspirin directly.

Patients need to receive penicillin for ten days to eradicate *Streptococcus*.

The prophylaxis consisted to receive intramuscular penicillin benzathine given every 28 days, if bodyweight is less than 27 kg the dose is 600,000 international units (IU), if bodyweight is more than 27 kg, the dose is 1.200,000 IU. In the cases where intramuscular penicillin is not safe, we can give 250 mg twice per os of Penicillin V and in the case of allergy to penicillin we can use erythromycin 250 mg twice per os.

All children who have suffered cardiac sequelae must be thoroughly instructed on risk prevention of bacterial endocarditis (AMH)³⁷.

In conclusion:

1. Although the acute rheumatic fever has become a rare disease in industrialized countries, it remains prevalent.
2. In 2000, the American Heart Association agreed that there were insufficient data to support a revision of the Jones Criteria and reaffirmed the guidelines iterated in the 1992 statement.
3. In pediatrics, Criteria are a guide but should not replace clinical judgment.

Acknowledge

The author would like to thank Mrs Ana Maria C. Blanchard for her English expertise.

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