IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 22, Issue 6 Ser.8 (June. 2023), PP 13-17
www.iosrjournals.org

Acute Rheumatic Fever And Rheumatic Heart Disease

Mohammad Maaz Ahmad
Asfendiyarov Kazakh National Medical University,Kazakhstan

Abstract
Acute rheumatic fever (ARF) is a nonsuppurative, delayed sequela of a Streptococcus pyogenes *(Strep A) infection through an inflammatory response in untreated or undertreated susceptible individuals(1)Symptoms of ARF typically begin 3 weeks (range: 1 to 5) following the acute Strep A infection(2)*
Although now rare in developed countries, ARF maintains a noteworthy presence in economically disadvantaged populations, driven by factors that include household overcrowding and poor hygiene.(3-4)The major morbidity and mortality result from cardiac involvement known as rheumatic heart disease (RHD).
From a truly global disease in the 19th and 20th centuries, ARF has become a disease of crowding and poverty in the 21st century. Despite this stupendous advancement, the Global Burden of Disease estimates From a truly global disease in the 19th and 20th centuries, ARF has become a disease of crowding and poverty in the 21st century(5) Despite this stupendous advancement, the Global Burden of Disease estimates.
Timely treatment of group A streptococcal infection can prevent ARF, and penicillin prophylaxis can prevent recurrence of ARF. Prevention of recurrent ARF is the most effective way to prevent RHD(6) ARF is diagnosed using the 2015 modified Jones criteria. There is no gold standard laboratory test. Therefore, clinicians need to be aware of the clinical signs and symptoms of ARF to include in their differential diagnosis when seeing such patients(8-9)Secondary prophylaxis with benzathine penicillin G has been shown to decrease the incidence of RHD and is key to RHD control. Clinicians need to understand the implications of secondary prophylaxis for ARF(10). There is also a need to improve ARF diagnosis, to find novel therapies to reduce the incidence of ARF, and to reduce the prevalence of RHD(11).

Keyword:*Acute rheumatic fever(ARF),Rheumatic heart disease(RHD),Jones criteria*

Date of Submission: 05-06-2023 Date of Acceptance: 15-06-2023

I. Introduction:

Acute rheumatic fever (ARF) is a nonsuppurative, delayed sequela of a Streptococcus pyogenes (Strep A) infection through an inflammatory response in untreated or undertreated susceptible individuals. Inflammation of the joints, heart, and brain results in the common clinical manifestations of arthritis, carditis, and chorea. Although now rare in developed countries, ARF maintains a noteworthy presence in economically disadvantaged populations, driven by factors that include household overcrowding and poor hygiene.The major morbidity and mortality result from cardiac involvement known as rheumatic heart disease (RHD).

The bacterium Streptococcus pyogenes (group A streptococcus) can pass easily from person to person in the same way as other upper respiratory tract infections. These infections are most common in childhood.In some cases, repeated strep infections can lead to rheumatic fever, which occurs when the immune system reacts against the tissues of the body, including inflaming and scarring the heart valves.Rheumatic heart disease is caused by damage to the heart valves and heart muscle from the inflammation and scarring caused by rheumatic fever.

Rheumatic heart disease disproportionately affects girls and women, whose risk of developing rheumatic heart disease is two times higher than in men and boys. Rheumatic heart disease is the leading cause of maternal cardiac complications in pregnancy. Pregnant women with rheumatic heart disease are at risk of adverse outcomes, including heart arrythmias and heart failure due to increased blood volume putting more pressure on the heart valves. It is not uncommon for women to be unaware that they have rheumatic heart disease until pregnancy.

Several twin and family aggregation studies have suggested a genetic effect, but they have not provided a quantitative estimate of the magnitude of the genetic contribution in acute rheumatic fever. Furthermore, the molecular genetic studies of human leukocyte antigen (HLA) and non-HLA factors have been characterized by small studies with inconsistent and conflicting findings. A quantitative assessment of the genetic effect in twin or adoption studies, which provide a reliable estimate of genetic effect in familial conditions, will provide guidance on the desirability of embarking upon the expensive 'global genome analysis' studies of the condition that have been recommended recently. Higher concordance rates between monozygotic

twins compared with dizygotic twins indicate a greater role for genetic factors in the development of a disease given that monozygotic twins are genetically identical, versus dizygotic twins who, on average, share 50% of their genes, Conversely, concordance of a similar magnitude in both monozygotic and dizygotic twin pairs suggests the involvement of factors not pertaining to genes. It would thus be prudent to invest scarce resources on genetic studies of conditions with good evidence of genetic determination particularly in resource-poor countries where acute rheumatic fever is prevalent.

Recent advances — including the use of echocardiographic diagnosis in those with ARF and in screening for early detection of RHD, progress in developing group A streptococcal vaccines and an increased focus on the lived experience of those with RHD and the need to improve quality of life — give cause for optimism that progress will be made in coming years against this neglected disease that affects populations around the world, but is a particular issue for those living in poverty.

Pathophysiology of Rheumatic heart disease.

The first step is a pharyngeal infection with Streptococcus pyogenes, followed by the presentation of antigens to the immune T and B cells. It is noteworthy that skin infections with the same strain of bacteria do not result in ARF.

Activation of CD4+ cells leads to the production of specific acute and chronic phase antibodies (IgM and IgG, respectively) by B lymphocytes.

These antibodies and activated T cells react with structurally similar proteins or peptides in heart tissue, which is called cross-reaction. As a result, the heart becomes inflamed. Joints develop swelling and pain due to the accumulation of immune complexes, formed by antigen-antibody combinations. Chorea and skin rashes or nodules are other manifestations of this immune activation, in the basal ganglia and the skin respectively.

The molecules which mimic each other may be a spiral protein in M protein and N-acetyl-beta-D-glucosamine antigens found in S. pyogenes, and myosin in the cardiac muscle. In other words, these molecules share some similar antigenic structures with myosin, the human muscle protein. The antibodies formed against these cross-react with tissue in the human heart valve as well.

The overexpression of VCAM-1 molecules causes CD4+ cells to stick to and burrow into the valve endothelium, activating a cellular immune response in the valve. This produces an inflammation of the valve tissue with the growth of new blood vessels.

This leads to further availability of T cells from the increased blood supply brought by these vessels. More and more spots of antigenic attraction may occur on the valve, on other proteins such as vimentin and tropomyosin, so that the T-cell attack extends to more areas. Granulomas (called Aschoff bodies) form underneath the endocardial (innermost) layer of the heart.

Calcification also occurs as part of this inflammation and is linked to the level of a chemical called osteopontin in the blood. Other markers of inflammation such as CRP and oxidation products of proteins are also raised in the blood of patients with RHD.

While this is the accepted mechanism of RHD, newer research is focusing on the endothelium covering the heart valves as the target of immunologic damage in this condition. Hopefully, this will shed light on the paradox of why only throat infection with group A streptococci causes ARF, and not skin infection with the same organism.

Autoimmunity association of Rheumatic heart disease :

RHD follows ARF in 30-45% of cases. ARF involves all three layers of the heart, as a result of cytokines and other inflammatory molecules which are released to act against the streptococci, as well as attack by immune cells upon the cardiac tissues.

A subspecies of T lymphocytes called CD4+ T cells and macrophages are prominent in this attack, and other molecules such as VCAM-1 help these cells attach to the valves. A genetic susceptibility is necessary for RHD to occur.

The basic mechanism of RHD is called T-cell molecular mimicry. This means that antigenson group A streptococci stimulate the activation of CD4+ T cells which then cross-react with similar peptides in the heart tissue.

The antigen-T cell reaction of course leads to destruction of the tissue being attacked, which is in this case the heart valve endocardium. Other soluble molecules such as TNF-α, IL-1 and IL-2 are overproduced in ARF by monocytes in peripheral blood. These cytokines promote acute and long-term inflammatory responses which seem to continue as a chronic process even after the infective agent itself has died out.

The lesion, called the Aschoff nodule, is the characteristic feature of an RHD lesion, and consists of a clump of granuloma cells. It passes through different stages and contains a variety of immune cells. Their

growth and progression is linked to the production of these cytokines, first by the monocytes in the acute phase and thereafter by T cells as the lesion becomes chronic.

Diagnosis and clinical features of acute rheumatic fever:

ARF is a systemic inflammatory autoimmune reaction that appears 2–4 weeks after GAS pharyngitis with major manifestations including carditis (50–78%) arthritis (35–88%), erythema marginatum (<6%) , and subcutaneous nodules (<1–13%) . Additionally, 2–19% of patients present with Sydenhams' chorea, a neurological condition characterized by involuntary movements and behavioral changes .Minor manifestations include PR prolongation, less severe joint manifestations, fever, and elevated inflammatory markers.

The carditis of ARF is a pancarditis, with valvulitis being the most common presentation . It ranges widely in severity from mild sub-clinical involvement (16.8%) to severe carditis with congestive heart failure and/or death (20%) .Most cases involved the mitral valve. Isolated aortic valve disease occurs in only 2% of patients and right-sided valvulitis is seen only in combination with left .

The arthritis of ARF is most classically a painful large joint migratory polyarthritis. The arthritis improves dramatically with anti-inflammatory therapy and a history of self-medication prior to presentation can mask recognition. Evidence from Australia India, and the Pacifichas highlighted the importance of monoarthritis and polyarthralgia in the presentation of ARF, and the most recent diagnostic criteria now take these presentations into account .

Sydenham's chorea occurs 1–8 months after GAS infection .Choreiform movements are non-rhythmic, involuntary, often asymmetrical, and disappear with sleep. Concurrent muscular weakness and emotional disturbances (crying, restlessness, obsessive-compulsive symptoms, rare psychosis) can occur .Alternate diagnoses should be excluded. Evidence of recent GAS infection and/or carditis provides supporting evidence of ARF, but is not needed to make the diagnosis .

Revised Jones criteria:
In order to establish a diagnosis of rheumatic fever, there must be:
Evidence of recent group A Streptococcus infection

- Positive throat swab
- Positive rapid streptococcal antigen test
- Raised streptococcal antibody titre (ASO or DNAse B titres)
- Recent episode of scarlet fever

plus either:

- two major criteria
- or one major criterion and two minor criteria.

MAJOR CRITERIA:
Polyarthritis (80% of patients)
Multiple joints are affected, predominantly the larger ones, which become red, hot and swollen. Individually, each joint is usually affected for less than a week.
The arthritis is described as a "flitting" arthritis because it migrates to other joints within the next 1-2 months.
Carditis (50% of patients)
The heart consists of three layers (endocardium, myocardium and pericardium). In rheumatic fever, every layer of the heart can be affected, resulting in a pancarditis.
Damage to the endocardium leads to endocarditis, which can cause valvular dysfunction. Patients may present with clinically significant murmurs.
Myocardial inflammation (myocarditis) may result in heart failure and conduction defects, which are both potentially fatal complications.
Pericarditis may present clinically with a fairly benign pericardial rub or may lead to more serious complications such as pericardial effusions or cardiac tamponade.
The most common valve affected in rheumatic fever is the mitral valve.
In an attack of rheumatic fever, valve incompetence (i.e. regurgitation) is more likely to develop than valve stenosis. Valve stenosis tends to develop as a feature of chronic disease many years later.[5]
Sydenham's chorea (10% of patients)
Sydenham's chorea is a rare, and late-presenting sign of rheumatic fever, appearing around 2-6 months after the initial streptococcal infection.
It consists of involuntary, semi-purposeful movements of the body which may be unilateral or bilateral. Occasionally the chorea is preceded by emotional lability or behaviour which is out of character for the patient.
Sydenham's chorea is also sometimes referred to as St Vitus' dance.
Erythema marginatum (<5% of patients)
Erythema marginatum is a rash found in rheumatic fever which may present early on in the disease process. However, it is a rare sign and therefore should not be relied on as a means of diagnosis.
Erythema marginatum is a pink macular rash predominantly affecting the trunk and limbs while sparing the face. It expands outwards, leaving a pale centre and is described as a "geographical rash" because its borderlines resemble

those drawn on a map
Subcutaneous nodules
Hard, mobile, pea-sized nodules, typically found on the extensor surfaces (e.g. back of the elbows) or the spine. They are often painless and normally disappear within one month.
Subcutaneous nodules are a rare finding in rheumatic fever and are usually only seen when severe carditis is present.[13]
MINOR CRITERIA
Polyarthralgia
Pain present in multiple joints. This is not included in the criteria if polyarthritis is already present.
Prolonged PR interval on ECG
This is only used as a criterion if there are no signs of pancarditis.
History of rheumatic fever
A previous history of rheumatic fever is a risk factor for subsequent flare-ups.
Fever
Typically, temperatures of more than 39 degrees centigrade.
Raised inflammatory markers
This includes markers such as CRP, ESR and leukocyte (white cell) count.

II. TREATMENT:

1. The key to ARF/RHD management is secondary prevention with continuous antibiotic prophylaxis to prevent recurrent infection with Group A streptococcus. Benzathine penicillin G dosed every 3-4 weeks is superior to oral penicillin.
2. Data on appropriate duration of treatment are based mostly on expert opinion and vary among different countries. Considerations include ARF presentation (age, time since last ARF, ± rheumatic carditis), and presence and severity of chronic RHD. Typical treatment durations are 5-10 years, or until age 21 (whichever is longer). For severe chronic RHD, treatment can be life-long, even after surgical intervention.
3. For patients under age 35 years without a documented history of ARF, treatment durations are a minimum of 5 years or until age 40 (whichever is longer). Life-long prophylaxis is recommended following valve surgery.
4. While typical guidelines for severe valvular heart disease stress surgical and catheter-based interventions, the majority of cases occur in regions of the world where these options may not be available. Typical agents such as diuretics, afterload reducers, and beta-blockers are recommended for symptomatic relief of heart failure.
5. For atrial fibrillation or flutter, anticoagulation with oral vitamin K antagonists or direct oral anticoagulants is still recommended. However, the INVICTUS-VKA study is currently evaluating noninferiority of rivaroxaban to warfarin.
6. For isolated mitral stenosis in symptomatic patients with favorable valve anatomy, balloon mitral valvuloplasty is generally preferred given the lower cost and rapid recovery time. While complications (such as tamponade or valve leaflet rupture) are rare (2-5%), on-site surgical back-up is typically still required. Long-term benefit after balloon mitral valvuloplasty is seen in about 75% of patients.
7. While surgical mitral valve repair by experienced surgeons is feasible in >75% of cases, the most important consideration in RHD-endemic regions is limiting the risk of a redo operation. This makes valve replacement the more common practice, especially for double-valve surgery (with a subsequent need for lifetime anticoagulation).
8. Access to surgeons remains the most important problem in RHD endemic areas, with three cardiothoracic surgeons per 1 million inhabitants in North Africa and one cardiothoracic surgeon per 3.3 million people in Sub-Saharan Africa. International declarations to improve access to surgery in endemic areas through global alliances and structured training of more cardiac surgeons will be essential.

III. Conclusion:

Moving forward, the focus should be to continue to decrease the incidence, prevalence, backlog, and surgical waiting lists of RHD patients. This will require local government and public health cooperation and support with the local clinical medical and surgical sectors. Building increasing capacity and quality of cardiac surgery in LMICs requires devoted and sustained leadership, public (government), and private (corporate) participation, and a well-trained and confident experienced cardiac team that is supported and trusted by the patients they serve.

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