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ACUTE RHEUMATIC FEVER IN INDIA- A REVIEW

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ABSTRACT Acute rheumatic fever (ARF) is a autoimmune disease resulting from infection with group A streptococcus and affect multiple systems in human body. Episodes of ARF tend to recur in the same individual unless preventive measures are instituted, and each recurrence increases the chance of long-term damage to the heart valves—that is, rheumatic heart disease (RHD).Now uncommon in the developed world, ARF and RHD remain a major public health problem in developing countries like India. This review will focus upon pathogenesis, clinical presentation, diagnosis, treatment and prevention of rheumatic fever in Indian population.

KEYWORDS :- :Acute rheumatic fever, Arthritis, Cardistis, Rheumatic heart disease.

INTRODUCTION-

Acute rheumatic fever has been known since 1500s.In the1800s ,the relation between ARF and the heart had been depicted as "from tonsillitis to carditis".This condition was described as "ARF licks the joints and bites the heart" by LASEQUE in 1884. The first clinical evidence of rheumatic fever in india came from PUNJAB by WIG in 1935. However , lack of specific criteria had led to diagnostic challenge until the JONES CRITERIA was framed in 1944.

DISEASE BURDEN

The incidence of ARF began to decline in developed countries towardthe end of the 19thcentury, and by the second half of the 20th century,ARF had become rare in most affluent populations. This decline isattributed to more hygienic and less crowded living conditions, betternutrition, improved access to medical care, and, to a lesser extent,the advent ofantibiotics in the 1950s. However, according to theWorld Health Organization (WHO),approximately 500,000 individualsacquire ARF each year, of whom 97% are in developing countries,where the incidence of ARF exceeds 50 per 100,000 children per year. Among the South Easterncountries , India has highest prevalence of around 27%.

Epidemiological data from many developing countries are poor, andthese are very likely to be underestimates. Much higher rates of 80 to500 per 100,000 have been documented in careful studies in the indigenouspopulations of Australia and New Zealand.1 By contrast, theincidence of ARF in industrialized countries is less than 10 per 100,000children.1,2 There have been several outbreaks of ARF in middle-classpopulations in the inter-mountain region of the United States since themid-1980s, associated with mucoid strains of group A streptococcus,particularly of M type 18.3

The peak incidence of ARF occurs in those aged 5 to 15 years, witha decline thereafter such that cases are rare in adults older thanage of 35 years.1 First attacks are rare in the very young; only 5% of firstepisodes arise in children younger than age 5 years, and the disease isalmost unheard of in those younger than age 2 years.4 Recurrence are most frequent inadolescence and young adulthood and are diagnosedinfrequently after age 45 years.ARF is equally common in males and females, but RHD is morecommon in females. Whether this trend is a result of innate susceptibility,increased exposure to group A streptococcus because ofgreaterinvolvement of women in child rearing, or reduced access to preventivemedical care for females is unclear.1 No association with ethnic originhas been found. There is some evidence that between 3% and 6% of anypopulation is susceptible to ARF.5attacks.

PATHOGENESIS- Epidemiologic and immunologic evidence clearly implicates groupA–beta hemolytic streptococcus in the initiation of the disease in asusceptible host. Most patients with ARF have elevated titers ofantistreptococcal antibodies. Outbreaks of ARF usually follow epidemicsofstreptococcal pharyngitis. Adequate treatment of streptococcalpharyngitis reduces the incidence of subsequent ARF, andappropriate antimicrobial prophylaxis prevents recurrences afterinitial attacks.6,7It has generally been considered that certain strains of group A streptococcus are more prone to result in ARF, and this "rheumatogenicity"was thought to be a feature of strains belonging to certain Mserotypes. The long-held opinion that onlystreptococcalpharyngitis, and not streptococcal skin infections such as impetigo,may befollowed by ARF has also been challenged.8

Host factors have been considered to be important ever since familialclustering was reported in the last century. Associations between disease andhuman leukocyte antigen (HLA) class II alleles have been identified.9 There is, as yet, no specificinvestigation that reliably identifies individuals who are at risk of ARFor who will develop chronic rheumatic valvular heart disease.The molecular mimicry theory holds that antibodies or cellularimmune responses directed against group A streptococci cross-reactwith epitopes on host tissue.10 Streptococcal M protein and a carbohydratestreptococcal antigen (N-acetylglucosamine in group A carbohydrate)share epitopes with cardiac myosin and valve tissue. There is nomyosin in cardiac valves, the main site of human cardiac damage, butit is known that laminin invalvular basement membrane is recognizedby T cells against myosin and the M protein. Antibodies to valve tissuecross-react with N-acetylglucosamine in group A carbohydrate.1 In ananimal model, antibodies that caused chorea bound to both the carbohydrateantigen andmammalian lysoganglioside.

The exact mechanism of the initial insult is unclear. Subsequentdamage appears to be caused by T-cell and macrophage infiltration,which persists for years after the initial event.9 The pathologic lesion ofARF is the Aschoff body, a granulomatous lesion containing T and Bcells, macrophages, large mononuclear cells, multinucleated giant cells,andpolymorphonuclear leukocytes in the myocardium.

CLINICAL PRASENTATION- There is a latent period of ~3 weeks (1–5 weeks) between the precipitating group A

streptococcal infection and the appearance of the clinical features of ARF. The exceptions are chorea and indolent carditis, which may follow prolonged latent periods lasting up to 6 months. Although many patients report a prior sore throat, the preceding group A streptococcal infection is commonly subclinical; in these cases, it can only be confirmed using streptococcal antibody testing. The most common clinical features are polyarthritis (present in 60–75% of cases) and carditis (50–60%). The prevalence of chorea in ARF varies substantially between populations, ranging from <2 to 30%. Erythema marginatum and subcutaneous nodules are now rare, being found in <5% of cases.

JOINT INVOLVMENT-

The most common form of joint involvement in ARF is arthritis, i.e., objective evidence of inflammation, with hot, swollen, red, and/or tender joints, and involvement of more than one joint (i.e., polyarthritis). Polyarthritis is typically migratory, moving from one joint to another over a period of hours. ARF almost always affects the large joints—most commonly the knees, ankles, hips, and elbows—and is asymmetric. The pain is severe and usually disabling until anti-inflammatory medication is commenced.

Less severe joint involvement is also relatively common and has been recognized as a potential major manifestation in high-risk populations in the most recent revision of the Jones criteria. Arthralgia without objective joint inflammation usually affects large joints in the same migratory pattern as polyarthritis. In some populations, aseptic monoarthritis may be a presenting feature of ARF, which may, in turn, result from early commencement of anti-inflammatory medication before the typical migratory pattern is established.

The joint manifestations of ARF are highly responsive to salicylates and other nonsteroidal anti-inflammatory drugs (NSAIDs). Indeed, joint involvement that persists for more than 1 or 2 days after starting salicylates is unlikely to be due to ARF.

CARDIAC INVOLVMENT- Up to 60% of patients with ARF progress to RHD. The endocardium, pericardium, or myocardium may be affected. Valvular damage is the hallmark of rheumatic carditis. The mitral valve is almost always affected, sometimes together with the aortic valve; isolated aortic valve involvement is rare. Damage to the pulmonary or tricuspid valves is usually secondary to increased pulmonary pressures resulting from left-sided valvular disease. Early valvular damage leads to regurgitation. Auscultation may reveal new murmurs or changing murmurs. The commonest valvular lesion is mitral regurgitation causing an apical pansystolic murmur. Aortic regurgitation is less common. Stenotic lesions are uncommon in the early stages of the disease, but a transient apical mid diastolic murmur (Carey-Coombs) may occur in association with the murmur of mitral regurgitation. Over ensuing years, usually as a result of recurrent episodes, leaflet thickening, scarring, calcification, and valvular stenosis may develop.Therefore, the characteristic manifestation of carditis in previously unaffected individuals is mitral regurgitation, sometimes accompanied by aortic regurgitation. Myocardial inflammation may affect electrical

conduction pathways, leading to P-R interval prolongation (first-degree atrioventricular block or rarely higher level block) and softening of the first heart sound. People with RHD are often asymptomatic for many years before their valvular disease progresses to cause cardiac failure.

CHOREA- Sydenham chorea may be associated with other manifestations of ARFbut may also be the sole expression of the disease. It is a neurological disorder characterized by involuntary, purposeless, rapid, and abruptmovements associated with muscular weakness and emotional lability. The choreiform movements affect particularly the head (causing characteristic dartingmovements of the tongue) and the upper limbs . They may be generalized or restricted to one side of the body (hemi-chorea).The abnormal movements disappear during sleep.Mild chorea may best be demonstrated by asking the patient tosqueeze the examiner's hand. This results in repetitive irregularsqueezes labeled as "the milking sign". Emotional lability manifests inpersonality changes, with inappropriate behavior, restlessness, andoutbursts of anger or crying.11.

SKIN MENIFESTATIONS- The classic rash of ARF is erythema marginatum , which begins as pink macules that clear centrally, leaving a serpiginous, spreading edge. The rash is evanescent, appearing and disappearing before the examiner's eyes. It occurs usually on the trunk, sometimes on the limbs, but almost never on the face.

SUBCUTANEOUS NODULES– Subcutaneous nodules occur as painless, small (0.5–2 cm), mobile lumps beneath the skinoverlying bony prominences, particularly ofthe hands, feet, elbows, occiput, andoccasionally the vertebrae. They are a delayed manifestation, appearing 2–3 weeks after the onset of disease, last for just a few days up to 3 weeks, and are commonly associated with carditis.

DIAGNOSIS AND INVESTIGATION-

There is no definitive laboratory test for ARF, and diagnosis is basedon a combination of clinical manifestations and laboratory evidenceof previous streptococcal infection. This uncertainty led Dr. T. Duckett Jones in 1944 to develop a set of criteria (subsequently known as the Jones criteria) to aid in the diagnosis. The most recent revision(2015) of the Jones criteriarequire the clinician to determine if the patient is from a setting or population known to experience low rates of ARF. For this group, there is a set of "low-risk" criteria; for all others, there is a set of more sensitive criteria.Evidence of preceding streptococcal infection may be demonstrated byincreased orrising antistreptolysin-Otiter, or other streptococcal antibodies,or a positive throat swab culture, or rapid antigen test for groupA –beta hemolytic streptococci. Prolongation of the PR interval serves as a useful minorcriterion and a clinically helpful clue, which may be particularly relevantin recurrences where previous electrocardiograms are available.Clinical evaluation is central to the diagnosis of ARF, and echocardiographyis not widely available in populations in which the diseaseis common. Used correctly byexperienced clinicians,echocardiography is an excellent tool that mayprevent overdiagnosis of ARF by excluding physiologic flow murmursand undetected congenital heart disease.

Jones Criteria (2015)

A. FOR ALL PATIENT POPULATIONS WITH EVIDENCE OF PRECEDING GROUP A STREPTOCOCCAL INFECTION	
Diagnosis: initial ARF	Youth welfare programmes
Diagnosis: recurrent ARF	2 major or 1 major and 2 minor or 3 minor
B. MAJOR CRITERIA	
low risk populations	moderate and high risk populations
carditis	carditis
clinical and/or subclinical arthritis	clinical and/or subclinical arthritis
polyarthritis only	mono arthritis or polyarthris
	poly arthralgia
chorea	chorea
erythema marginatum	erythema marginatum

sc nodules	sc nodules
C. MAJOR CRITERIA	
Low-risk populationsa	Moderate- and high-risk populations
polyarthralgia	monoarthralgia
fever (> 38.5)	fever (> 38.5)
ESR ≥60 mm in the first hour and/ or CRP ≥3.0 mg/dLd	ESR ≥30 mm/h and/or CRP ≥3.0 mg/dLd
Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion	Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion

aLow-risk populations are those with ARF incidence ≤2 per 100,000 school-age children or all-age rheumatic heart disease prevalence of ≤1 per 1000 population per year. bSubclinical carditis indicates echocardiographic valvulitis. (See source document.) cPolyarthralgia should only be considered as a major manifestation in moderate- to high-risk populations after exclusion of other causes. As in past versions of the criteria, erythema marginatum and SC nodules are rarely "standalone" major criteria. Additionally, joint manifestations can only be considered in either the major or minor categories but not both in the same patient. (See source document for more information.) dCRP value must be greater than upper limit of normal for laboratory. Also, because ESR may evolve during the course of ARF, peak ESR values should be used.

TREATMENT-

MANAGEMENT OF THE ACUTE EPISODE- The aims of treatment of ARF are to suppress the inflammatoryresponse so as to minimize cardiac damage, to provide symptomaticrelief, and to eradicate pharyngeal streptococcal infection.11 Patients areusually hospitalized, and the long-standing recommendation of bedrestor chair rest is appropriate if heart failure is present. Ambulation isusually started once fever has subsided and joint pain and heart failureare controlled.Although evidence of activeinfection is unusual during the acutephase, it is recommended that patients receive a single dose of benzathinepenicillin or a 10-day course of penicillin-V (or erythromycin if allergic to penicillin) to curtail exposure to streptococcal antigens. After completionof the course, secondary prophylaxis should be commenced.Anti-inflammatory agents, including salicylates andcorticosteroidsin appropriate dose, provide dramatic improvement in symptoms suchas arthritis and fever soon after starting treatment. Doses of aspirin of 80 to 100 mg/kg/d in children and 4 to 8 g/d in adults may be neededinitially. The usual dose of prednisone or prednisolone is 1 to 2 mg/kg/d.There is no good evidence that steroids are superior to aspirin in termsof altering the natural history of the disease.12 Anti-inflammatory agents are usually used in high dosefor approximately 2 weeks and thendecreased by approximately 20%each week, depending on clinical response and laboratory measurementof inflammatory markers. When tapering steroids, it is recommended tooverlap with aspirin to prevent the rebound of disease.Patients with severe heart failure require usual antifailuretreatment.Whencarditis complicated by marked valvular regurgitationcauses severe hemodynamic compromise, valve surgery is life-saving. Valve replacement rather than repair is the preferred option underthese circumstances.

Medications to control the abnormal movements do not alter the duration or outcome of chorea. In patients with severe chorea, carbamazepine or sodium valproate is preferred to haloperidol. A response may not be seen for 1–2 weeks, and medication should be continued for 1–2 weeks after symptoms subside. There is recent evidence that corticosteroids are effective and lead to more rapid symptom reduction in chorea. They should be considered in severe or refractory cases. Prednisone or prednisolone may be commenced at 0.5 mg/kg daily, with weaning as early as possible, preferably after 1 week if symptoms are reduced, although slower weaning or temporary dose escalation may be required if symptoms worsen. Small studies have suggested that IVIg may lead to more rapid resolution of chorea but have shown no benefit on the short- or long-term outcome of carditis in ARF without chorea.

PREVENTION-

PRIMARY PREVENTION- The mainstay of primary prevention for ARF remains primary prophylaxis (i.e., the timely and complete treatment of group A streptococcal sore throat with antibiotics). If commenced within 9 days of sore throat onset, a course of penicillin will prevent almost all cases of ARF that would oth¬erwise have developed. In settings where ARF and RHD are common but microbiologic diagnosis of group A streptococcal pharyngitis is not available, such as in resource-poor countries such as India , primary care guidelines often recommend that all patients with sore throat be treated with penicillin or, alternatively, that a clinical algorithm be used to identify patients with a higher likelihood of group A streptococcal pharyngitis. Although imperfect, such approaches recognize the importance of ARF prevention at the expense of overtreating many cases of sore throat that are not caused by group A streptococcus.

SECONDARY PREVENTION -The mainstay of controlling ARF and RHD is secondary prevention. Because patients with ARF are at dramatically higher risk than the gen¬eral population of developing a further episode of ARF after a group A streptococcal infection, they should receive long-term penicillin prophylaxis to prevent recurrences. The best antibiotic for secondary prophylaxis is benzathine penicillin G (1.2 million units, or 600,000 units if ≤27 kg) delivered every 4 weeks. It can be given every 3 weeks, or even every 2 weeks, to persons considered to be at particularly high risk. In India we routinely administer benzathine penicillin every 3 weeks .Oral penicillin V (250 mg) can be given twice daily instead but is less effective than benzathine penicillin G. Penicillin-allergic patients can receive erythromycin (250 mg) twice daily.

The duration of secondary prophylaxis is determined by the duration since the last episode of ARF,age, and the severity of RHD.

DURATION OF SECONDARY PROPHYLAXIS

American Heart Association Recommendations for DURATION OF SECONDARY PROPHYLAXIS	
CATEGORY OF PATIENT	DURATION OF PROPHYLAXIS
Rheumatic fever without carditis	For 5 years after the last attack or 21 years of age (whichever is longer)
Rheumatic fever with carditis but no residual valvular disease	For 10 years after the last attack, or 21 years of age (whichever is longer
Rheumatic fever with persistent valvular disease, evident clinically or on echocardiography	For 10 years after the last attack, or 40 years of age (whichever is longer); sometimes lifelong prophylaxis

CONCLUSION- Rheumatic fever is said to be a disease that "licks the joints and bitesthe heart."11 This underlines the fact that cardiac involvement is themost serious manifestation of ARF. The failure to put patients with ARFon antibiotic prophylaxis to prevent future attacks leads to

repeatedepisodes of ARF, scarring of the heart valves, chronic valvular heartdisease, heart failure, and death, usually before middle age.Patients who are diagnosed with streptococcal sore throat infection ,should be treated with penicillin to prevent above maintained drastic complications.Once the acute episode has resolved, the priority in management is to ensure long-term clinical follow-up and adherence to a regimen of secondary prophylaxis. Patients should be entered onto the local ARF registry (if present) and contact made with primary care practitioners to ensure a plan for follow-up and administration of secondary pro¬phylaxis before the patient is discharged.

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