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Acute Rheumatic Fever with Malarial Infection

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Abstract

Fever pattern is helpful to diagnose the associated infection in Acute Rheumatic Fever. The gold standard for diagnosis of GAS (Group A streptococcus) pharyngitis is bacterial culture. However, throat culture takes 24 - 48 hours and requires culture facilities. Therefore, culture tests are difficult to use in primary care practice. To compensate for these shortcomings, a rapid antigen detection test (RADT) was developed to detect GAS within a few minutes without the need of laboratory facilities. The Korean upper respiratory tract infection guideline recommends that the RADT to be performed in patients with modfied Centor score of 3 or above. A rapid slide agglutination test (streptozyme, Carter Wallace test) that looks at antibodies against several (five) streptococcal extracellular antigens and it is thought to improve the detection of streptococcal infection. The coexistence of acute rheumatic fever with malarial infection is uncommon. Relapsing pattern of fever is the short febrile periods occurring between one or several days of normal temperature. Malaria, in particular that caused by infection with plasmodium vivax, produces relapsing fever at 48 hrs interval. The exact mechanism for acute rheumatic fever remains unexplained and 'molecular mimicry' appears to be most likely. Similarly for coexistence of acute rheumatic fever with malarial infection remains unexplained and related to 'altered immune status', particularly with P. vivax infection which may be related to specific duffy blood group antigen.

Key words

Febrile episodes, Acute rheumatic fever, ASO titer, Malarial infection, Carditis, Immune response, Duffy blood group antigen.

1. Introduction

Acute Rheumatic Fever remains a daily challenge to doctors who work in developing countries. Febrile paroxysms synchronous with periodicity develop in partially immune patients who were previously infected with malarial parasites and are cyclic fevers and chills [1] driven by the synchronous rupture of infected red blood cells and the subsequent release of parasites and toxins into the bloodstream [2]. In partially immune patients, these episodes become highly regular and predictable due to acquired defences clearing asynchronous parasites. In nonimmune patients, who were previously not infected with malarial parasites, the febrile paroxysms are asynchronous with no periodicity. Altered immune status occurred in this patient due to previous infection with P. vivax since this patient is partially immune as evidenced by 48 hrs periodicity of fever pattern. Similarly repeated pharyngeal infection with group A β hemolytic streptococci as evidenced by raised ASO titers is necessary to prime the immune response [3] before the first episode of acute rheumatic fever to occur. In tropical countries, there is high prevalence of

mixed infections. So, the possibilities of other infections must be evaluated if fever is not responding to routine therapy in acute rheumatic fever.

2. Case Report

A 12 year old boy was admitted for sudden onset of fever with major joint pains for 10 days duration. The patient was febrile, not anemic, not jaundiced, no generalized lymphadenopathy and no edema legs. Pulse rate was 123/min, Blood pressure was 110/80 mmHg. Cardiovascular examination revealed normal Jugular Venous Pressure, slightly laterally displaced hyperdynamic apical impulse and no precordial bulge or pulsation. Auscultation revealed normal heart sounds with 2/6 apical systolic murmur, a short, soft basal early diastolic murmur and no additional sounds. Respiratory system revealed normal breath sounds with mild basal crackles. Abdominal examination showed just palpable, soft, tender splenomegaly and neurological examination revealed no abnormal findings. ECG revealed sinus tachycardia and X-ray chest showed mild cardiomegaly. Echocardiography revealed thickened mitral valve as shown in **Figure 1** with mild mitral regurgitation, moderate aortic regurgitation as shown in **Figure 2**, suggesting Rheumatic carditis, normal LV function and no vegetation. ESR raised to 80mm/hr, ASO titer was 400 Todd units/ml and mild leukocytosis with slightly increased proportion of polymorphonuclear leukocytes. Other blood, renal and liver parameters were normal. Ultrasound abdomen revealed mild splenomegaly. The patient was diagnosed as Acute Rheumatic Fever with carditis and treated with injection Benzathine Penicillin 12 lakhs intramuscularly and acetyl salicylic acid (aspirin) 300mg three times daily until the ESR became normal and then tapered to reduced doses and continued for 6 weeks. Small doses of diuretics given to clear the crackles. Steroids were not given to the patient. Arthritis responded well to salicylates. The fever was relapsing with a periodicity of 48 hrs interval. Blood culture revealed no organisms. Peripheral smear for malarial parasites showed trophozoites of plasmodium vivax as shown in **Figure 3**. Then the patient was treated with tablets chloroquine for 3 days. Fever subsided and radical treatment with primaquine was given. The patient was discharged in good condition and advised RF prophylaxis and there was no further febrile episodes.

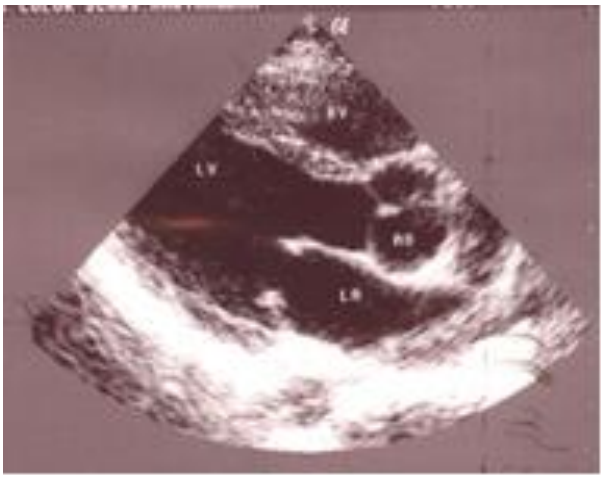

Figure 1 shows Thickened mitral valve tips suggesting Rheumatic involvement

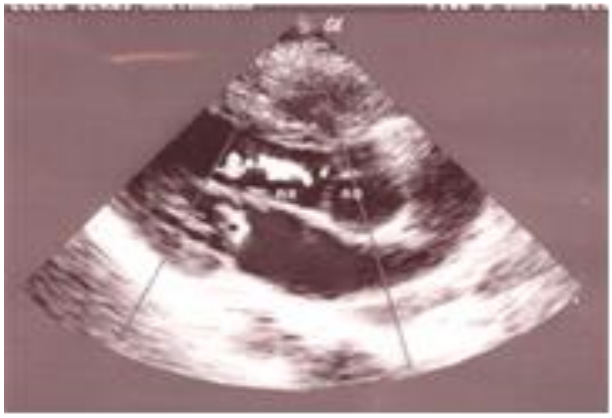

Figure 2 shows mild mitral regurgitation and moderate aortic regurgitation suggesting Rheumatic carditis

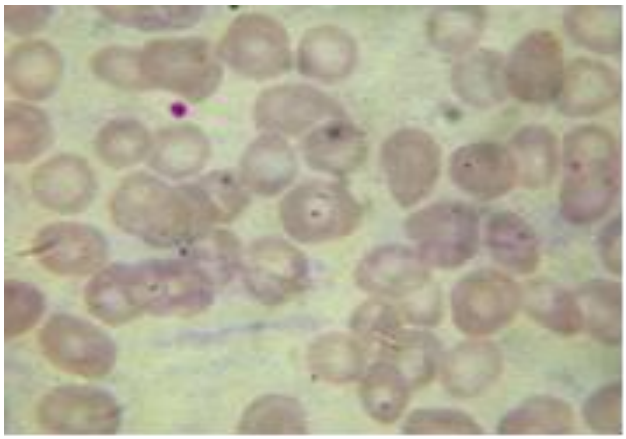

Figure 3 shows Trophozoites of P. vivax

3. Discussion

Malarial fever

Malaria transmission does not occur at temperature below 16˚C or above 33˚C and at altitude greater than 2000 m above sea level [4] since development in the mosquito (sporogony) cannot take place. The ecological assumptions about the thermal physiology of insects, it is found that most malaria models to date assume constant or linear responses of mosquito and parasite life-history traits to temperature, predicting optimal transmission at 31 °C. A large data set on malaria transmission risk in Africa validates both the 25 °C optimum and the decline above 28 °C [5]. The favourable conditions for transmission are high humidity and an ambient temperature between 20°C and 30°C. Although rainfall provides breeding sites for mosquitoes, excessive rainfall may wash away mosquito larvae and pupae. P. falciparum is the

only human malarial parasite that causes severe microvascular disease (such as cerebral malaria and placental malaria involving the intervillous space, jeopardizing pregnancies [6]) by causing infected red blood cells to stick to blood vessel wall. and can cause recrudescence (the return of symptoms from surviving blood-stage parasites that were never fully cleared). True relapses originate from dormant liver stages called hypnozoites, which are produced by P. vivax and P. oval [7]. A small fraction of intraerythrocytic parasites switch to sexual development, producing morphologically distinct male and female gametocytes that reach the host's dermis and are ingested by a mosquito, rendering the mosquito infectious to humans After ingestion by a female Anopheles mosquito, the male microgametocytes go through exflagellation in the mosquito's midgut, fusing with female macrogametes to form a zygote. The zygote then develops into an ookinete, which migrates through a thin wall and matures into an oocyst, which produces and, upon rupture, releases numerous sporozoites that are dispersed throughout the mosquito's body, including the salivary glands, thereby completing the life cycle. Gametocytes are therefore of vital importance to the transmission cycle of malaria. However, the clinical symptoms predominantly result from the asexual stages of parasite replication in human blood [8]. Clinically, the cardiac involvement is rare in malaria. Histologically, myocardial capillaries are often filled and even distended with an accumulation of parasites, sometimes totally occluding the lumen of the vessels. Thrombosis of capillaries and ischemic myocardial changes may be seen. Definitive diagnosis of malaria generally requires direct observation of malaria parasites in Giemsa-stained thick and thin blood smears. Thick blood smears are more difficult to interpret than thin blood smears but they are much more sensitive as more blood is examined. Thin blood smears, in which parasites are seen within erythrocytes as in **Figure 3,** are used to determine the species of the infecting parasite [9].

Streptococcal pharyngitis

Viral sore throat has more prominent catarrhal, common cold-like symptoms (watery eyes, running nose), gradual onset with uncomfortable throat, and cervical nodes are not enlarged. Tonsils and throat are red with vesicles and ulcers. Streptococcal sore throat may be associated with headache, abdominal pain, nausea, vomiting and no diarrhea. Centor criteria, which are highly effective for estimating the probability of a Group A streptococcal (GAS) infection in adults, but ineffective in children from 2 to 15 years of age [10] and modified centor [11] by Dr. Jack McIsaac, a Canadian physician (Canadian criteria) to include the patient's age as under 15 (3 to 14 years) adds 1 point; Age 15 to 44 years: 0 points, Age 45 years and older: Subtract 1 point for the diagnosis of streptococcal sore throat using the four same features of centor criteria as tonsillar exudates (white patches/pus on the tonsils) or swelling, Tendor or swollen anterior cervical nodes, a history of fever of more than 38°C and lack of cough. It is also known as the McIsaac criteria, a screening tool for the suspicious of group A Streptococcal (GAS) pharyngitis [12]. Score -1 to 1: Very low probability of strep (under 10%), no antibiotics or testing are typically required. Score 2 to 3: Intermediate probability, consider a Rapid Streptozyme Antigen Test (RADT), antibiotics should only be prescribed if the test is positive. Score 4 to 5: high probability of streptococcus infection (up to 50% or more). Empiric treatment or testing can be considered depending on the clinical context.

Following well documented group A streptococcal pharyngitis, vague signs and symptoms and non specific laboratory abnormalities may occur. Discomfort in the extremities, borderline temperature elevation, increased intensity of functional murmurs, tachycardia, elevated ESR and prolonged PR interval can occur in the absence of major manifestations. These patients do not develop RHD (Rheumatic heart

disease) on follow up and so the diagnosis of acute rheumatic fever should not be made in the absence of at least one major manifestations [13]. Rheumatogenic pharyngeal strains are M types 1,3,5,6,14,18,19,27,29 and nephritogenic pharyngeal strains are M types 1,4,6,12,25. Nephritogenic strains associated with pyoderma include M types 49,53,55,56 and 57. Rheumatogenic streptococcal strains fail to elaborate α-lipoproteinase (serum opacify factor-SOF negative) and they are frequently heavily encapsulated which is manifested by the formation of mucoid colonies on blood agar plates. It is probable that not all strains of rheumatogenic serotypes are equally dangerous. Pharyngeal strains having both nephritogenic and rheumatogenic potential are M types 1,6, but nephritogenic pharyngeal strains are SOF (serum opacify factor) positive and rheumatogenic pharyngeal strains are SOF negative [14].

Acute Rheumatic Fever (ARF)

Acute Rheumatic fever (ARF) occurs in people previously infected with Streptococcal sore throat or due to recurrent infection with GAS. Evidence of preceding streptococcal infection is a prerequisite for the diagnosis of Rheumatic fever and raised ASO antibodies are helpful to diagnose recent infection rather than acute infection. In healthy adults, the titers are usually less than 85 Todd units/ml, whereas school age children can have ASO titers up to 170 U. ASO antibodies are present in approximately 85% of patients 2 to 4 weeks after streptococcal pharyngitis. Generally, ASO level of more than 240 U in adults or more than 330 U in children is used for the diagnosis of Acute Rheumatic Fever. A single value of 500 units indicate recent streptococcal infection and a value of 333 units is of borderline significance. If ASO titer is 333units or less, additional antistreptococcal antibody assays such as anti DNase B, antihyaluronidase should be obtained [15]. With pharyngitis associated poststreptococcal acute glomerulonephritis, 90 to 95% of patients have an elevated ASO or anti DNase B titer. With pyoderma associated poststreptococcal acute glomerulonephritis, ASO titer is not consistently elevated since streptolysin O is irreversibly inactivated by lipids (probably cholesterol) present in the skin which in turn unable to induce increased magnitude of the immune response to cause rheumatic fever and this property may be responsible for the lack of association between streptococcal skin infection and Rheumatic fever [16].

Acute Rheumatic Carditis

About 50 to 80% of people with ARF develops carditis (pancarditis), can also present with valvulitis, affecting mitral (50% to 60% and mitral regurgitation is usually the earliest manifestation [17]) and aortic valves (20%) predominantly as shown in **Figure 2** and tricuspid valve (10%). The inflammatory process takes weeks to months to resolve and the average duration of an attack of rheumatic fever, unaltered by anti-inflammatory therapy, is approximately 3 months. Less than 5% of cases persists for longer than 6 months, justifying the designation as ”chronic rheumatic fever”. Stollerman [18],[19] lists the criteria for continuing clinical activity in rheumatic fever as follows: joint symptoms, new organic murmurs, a changing heart size, congestive heart failure in the absence of long standing valvular disease, subcutaneous nodules, a sleeping pulse rate greater than 100 beats/min, erythema marginatum, chorea, a positive test for C- reactive protein and a rectal temperature of 100.4°C or higher for 3 or more consecutive days. The most recent modification of Jones Criteria (updated Jones Criteria) was published in 1992. The Jones Criteria was designed to establish the diagnosis of rheumatic fever during the acute stage of illness and not to measure rheumatic activity, diagnose inactive or chronic RHD, or predict the course or severity

of the disease. Jones Criteria aid in the diagnosis of initial attack of acute rheumatic fever based on combination of clinical and laboratory findings.

In practice, the characteristic murmurs of acute rheumatic fever are almost always present in cases of rheumatic carditis. The diagnosis of carditis require the presence of one of these four manifestations- organic cardiac murmurs not previously present, cardiomegaly, pericarditis, congestive heart failure. For a major criterion of carditis, pathological mitral and/or aortic regurgitation must be present. First degree or even greater degrees of heart block is a toxic phenomenon associated with acute rheumatic fever and rarely complete heart block [20] occurs and may responds to anti-inflammatory therapy (steroids)[21],[22].

Echocardiographic screening

The 2023 World Heart Federation (WHF) [23] guidelines for the echocardiographic diagnosis of rheumatic heart disease present a staging process for RHD diagnosis on the basis of the risk of disease progression in the population category varies between low and moderate to high risk (high-risk populations, as defined by a prevalence of more than 2 cases per 1,000 persons for RHD (all ages) or an incidence of more than 30 cases per 100,000 persons aged 5–14 years annually for ARF). Stage A is the baseline or minimum criteria for individuals ≤ 20 years old who are at clinical risk of RHD with mild mitral regurgitation (MR) or aortic regurgitation (AR) without structural/morphological features of the valve (echocardiographic features from normal variant to mild RHD). The presence of morphological features alone, without valvular regurgitation, does not qualify individuals for stage A disease. Stage B indicates mild RHD with the presence of both pathological regurgitation (MR jet length measures ≥ 1.5 cm (in individuals weighing < 30 kg) or ≥ 2.0 cm (in individuals weighing ≥ 30 kg), AR jet length ≥ 1.0 cm, body of the pan-systolic envelope should be ≥3.0 m/s) and morphological features (the mitral valve: the thickening of the valvular apparatus (defined by the presence of either or both valvular and chordal thickening) and valve mobility (defined by the presence of either or both restricted and excessive leaflet motion). Anterior mitral valve leaflet (AMVL) thickness is age-specific and defined as follows: ≥3.0 mm for individuals aged ≤20 years, ≥4.0 mm for individuals aged 21–40 years and ≥5.0 mm for individuals aged > 40 years and should be measured during diastole at the full excursion, taken at the thickest portion of the leaflet, including focal thickening, beading and nodularity on a frame with maximal separation of chordae from the leaflet tissue. Restricted leaflet motion of either the AMVL or the posterior mitral valve leaflet is usually the result of chordal shortening or fusion, commissural fusion or leaflet thickening. Excessive leaflet tip motion results from elongation of the primary chords and is defined as displacement of the tip or edge of an involved leaflet towards the left atrium, resulting in abnormal coaptation and regurgitation. Pathological regurgitation, but without morphological features, is also classified as stage B. Stage C indicates established valvular disease detected by echocardiography, and are at risk of developing complications and might require medical treatment or surgical intervention. Mitral stenosis (Restricted leaflet motion with reduced valve opening, mean peak gradient ≥ 4.0 mmHg) of any severity is included in this category. Stage D indicates established valvular disease detected by echocardiography (the same as stage C), but with overt clinical complications (such as heart failure, arrhythmia, stroke or the need for cardiac surgery). The stage-based criteria outlined in these guidelines acknowledge the spectrum of early echocardiographic rheumatic changes by incorporating the assessment of the risk of progression and replacing the previously described borderline and definite categories [24].

Valvular regurgitation in ARF is attributable to various mechanisms, including valvulitis, mitral annular dilatation, leaflet prolapse and chordal elongation or rupture, all of which can be detected on echocardiography. [25] The morphological changes associated with RHD often develop at a later stage of disease or might never transpire and thus are not required for the diagnosis of acute carditis in the setting of ARF. Some patients with acute rheumatic fever have echocardiographic evidence of thickened mitral leaflet tips as in Figure 1 with mitral and aortic regurgitations as in Figure 2 are suggesting the rheumatic carditis in this patient was stage B category.

Molecular mimicry

ARF is characterized by an aberrant immune response to GAS infection triggered by molecular mimicry between GAS antigens and self-antigens There are several lines of evidence suggesting that the molecular mimicry always plays a very important role in the development of carditis by stimulating the cross reactive responses of the cellular and humoral immunity. The alpha-helical structures of protein are found in the N-acetyl-beta-D-glucosamine (S. pyogenes carbohydrate antigen). M protein shares the epitopes of cross-reaction antibodies with myosin. Vascular cell adhesion molecule 1(VCAM 1) may be the connection between humoral and cellular immunity at the surface of the valve. VCAM 1 gets upregulated at the surface of the endothelium because of the cross reactive antibodies binding which results in the adherence of CD4+ T cells to the endothelium thereby subsequently infiltrating those cells to the valve [26].

Genetic correlations

HLA genotypes

There is some controversy exists by some authors regarding the definite correlation of HLA (human leukocyte antigen) genotypes and genetic markers with rheumatic fever. HLA antigen may account for individual susceptibility to rheumatic fever. HLA types are genetically determined and are not the same in all individuals of a family cohort, although they are same in monozygotic twins. This may explain why within a family in whom all individuals have been infected with streptococcus, only a few develop rheumatic fever, and why the incidence is three times higher in monozygotic than in dizygotic twins [27]. Studies have shown a statistically significant association between specific HLA class II antigens (HLA DR2 in blacks, HLA DR4 in whites) and rheumatic fever [28]. The risk has been associated with increased prevalence of HLA DR4 in the United States and Saudi Arabia and HLA DR3 and DQw2 in India. There was a significant increase in the frequency of HLA-DR15 and DRB5 alleles in cases group with Mitral valve disease (10%). In contrast, Ozkan et al study revealed HLA-DR5 as a protective factor against RHD [29]. Some other markers such as B cell alloantigen D8/17 have shown a strong association with susceptibility to rheumatic fever. The distribution of class I HLA antigens in rheumatic fever patients is inconclusive.

Duffy Antigen Receptor

HLA BW53 protects against malaria. A polymorphism in TNFα promoter region is responsible for this protection. In the case of infections caused by Plasmodium vivax, the most studied evolutionary change that determines resistance is the genetic polymorphism of parasite receptor known as Duffy Antigen Receptor for Chemokines (DARC) [30], [31], in which form of absent alleles (Duffy-negative

allele with lack of expression of chemokines receptor and Chemokines sink to amplify the immune response) does not allow the receipt and entry of the parasite to the red cell [32]. Concerning the susceptibility to Plasmodium vivax infection, there are two kinds of alleles related to the receptors DARC: Fya and Fyb, which identifies four possible phenotypic presentations: homozygous Fy (ab−) (absence of the receiver or null), homozygous Fy (a+ b+) and heterozygous Fy (a− b+) and Fy (a+ b−). These receptors belong to the family of seven transmembrane molecules, initially recognized as a receptor for the Plasmodium vivax in human red blood cells and the simian Plasmodium Knowlesi and then recognized as a "promiscuous" receptor which is able to bind both CC (β-chemokines, primarily attract monocytes, macrophages, and T lymphocytes to the sites of chronic inflammation) and CXC chemokines (α-chemokines, predominantly recruit neutrophils to sites of acute inflammation) and to have a cleaner role of these molecules [33].

Mannose-binding lectin (MBL)

In RHD patients, there is significantly increased levels of mannose-binding lectin (MBL-an innate mediator) occurs. MBL acts as a primary pathogen-recognition molecule that drives the lectin complement pathway. This cascade exacerbates inflammation and tissue damage, targets the body's own heart valves, causing severe valvular damage. There is a beneficial role for MBL deficiency in these patients [34].

Superantigens

Two streptococcal antigens the pepsin generated fraction of M protein and a streptococcal pyrogenic exotoxin (Spe's) are believed to behave as "Superantigens". These antigens do not bind to antigen binding clefts in T or B cells and can amplify an immune response by clonal expansion of T and B cells, release several cytokines (TNFα, IL I β, IL-6), inducible nitric oxide synthase and adhesion molecules, which could help to localize immune responses to certain tissues. Super antigenic stimulation may help T cells respond to antigens like M proteins suggest a potential mechanism mediating the unrestrained immunologic assault postulated to cause acute rheumatic fever [35].

Secondary antibiotic prophylaxis (SAP)

RHD results from cumulative valvular damage that is largely preventable by secondary antibiotic prophylaxis (SAP) [36] to reduce the global burden of RHD. The echocardiographic features of RHD might regress, remain unchanged or progress over time. The GOAL study [37] showed that treating early-stage RHD with SAP reduced disease progression at 2 years of follow-up. However, the study also highlighted the heterogeneous nature of early disease, with 50% of borderline and 30% of mild cases regressing spontaneously (without the need for SAP). In high-risk populations, some individuals with mild valvular changes do indeed have RHD (and are at risk of disease progression), whereas the mild changes in other individuals might be classified as being normal. Of note, individuals might oscillate between these two classifications. All children with stage A disease must have to monitor the disease progression and SAP to be continued until a follow-up echocardiogram has been obtained and also recommended for all individuals aged ≤20 years with stage B disease, who have a moderate-to-high risk of disease progression and stage C or stage D disease [38]. This patient belongs to Stage B with carditis (Rheumatic Heart Disease): Prophylaxis must continue for at least 10 years after the most recent episode, or until the patient

is 21 to 40 years old (whichever is longer). First-Line: Intramuscular (IM) Benzathine Penicillin G (Dose: 1.2 million units for patients ≥ 30 kg; 600,000 units for patients < 30 kg) every 3 to 4 weeks. (Every 3 weeks is often preferred in highly endemic or high-risk regions). Alternative (if allergic or for severe heart failure): Oral Penicillin V or Erythromycin (Penicillin V: 250 mg taken orally twice daily is advised). Cephalosporins are recommended in cases of documented penicillin allergy with a history of anaphylaxis [39] The most common cephalosporins administered are cephalexin, cefuroxime, cefpodoxime, or cefdinir. Clindamycin is another alternative; some have touted it as the best at eradicating the GAS carrier state. However, clindamycin has significantly more gastrointestinal adverse effects [40].

If clinical evidence of acute carditis exists, initiate anti-inflammatory therapy alongside SAP. Corticosteroids are indicated for acute rheumatic carditis as adjunctive therapy and Prednisone 1-2 mg/kg/day for 1-2 weeks is advisable for myocarditis associated with acute rheumatic fever [41].

Epidemiological surveys

In tropical countries, mixed infections of streptococci both in the throat and skin due to various strains are more common and there is high prevalence of rheumatic fever in patients with skin lesions even though streptococcal pyoderma does not cause Rheumatic Fever definitely [42]. Group C or G streptococcus are more commonly isolated from the throat than Group A streptococcus in Rheumatic Fever patients in specific high-incidence populations—such as Aboriginal communities in Australia [43] and they can occur virulence factors by horizontal transmission from Group A streptococci. Epidemiological surveys are necessary to find out whether any higher incidence of acute rheumatic fever in endemic areas of malaria and any association with specific blood group antigen especially with duffy factor. More recent progress in the area of point-of-care tests for GAS pharyngitis include Nucleic Acid Amplification Tests (NAATs), which have much better sensitivity and specificity than RADTs [44]

Therapeutics

In 1965, American chemist Robert Burns Woodward was awarded the Nobel Prize in Chemistry for the first total synthesis of quinine, one of the earliest and most effective antimalarial drugs. Mefloquine is not recommended for patients with cardiac conduction defects or who are taking β blockers. Arrhythmogenic effects of chloroquine are not seen at normal doses, but do occur with rapid intravenous infusion or massive overdoses. In areas co-endemic for P vivax and Plasmodium falciparum, there is an increased risk of P. vivax parasitaemia with sexual stages [45] and it is a rationale for opportunistically eradicating P. vivax hypnozoites from the liver, an approach termed universal radical cure. Most endemic countries currently recommend a low-dose regimen of primaquine (total dose 3·5 mg/kg) for the radical cure of P vivax malaria, administered over 14 days [46],[47]. This prolonged treatment limits the daily dose of primaquine to 0·25 mg/kg per day to improve tolerability and reduce the risk of drug-induced haemolysis [48]. In 2022, WHO endorsed a 7-day regimen (0·5 mg/kg per day, total dose 3·5 mg/kg primaquine), which has been widely used for more than a decade in South America [49]. A single-dose tafenoquine combined with chloroquine for the radical cure of P vivax infection has also become available [50], but poor efficacy against latency has been observed [51]. This effectively prohibits the use of tafenoquine where P vivax is resistant to chloroquine and no longer usable, as occurs in Indonesia and the Western Pacific [52]. Primaquine requiring activation by CYP2D6 to kill latent hypnozoites [53], whereas tafenoquine does not appear to be CYP2D6-dependent. Whether tafenoquine or primaquine is applied, the

treatment is potentially dangerous without screening for glucose-6-phosphate dehydrogenase (G6PD) deficiency, a highly prevalent (on average, 8%) genetic abnormality among people residing in malaria-endemic zones [54].

ASA (Aspirin (Acetylsalicylic Acid) (60 to 100 mg/kg/day in divided doses until symptom resolution) is the most commonly used NSAID in the treatment of ARF with a dramatic response and resolution of fever and arthritis in 1 to 3 days. However, there is no documented evidence showing superior efficacy of any drug (steroids or NSAIDs) in reducing the risk of rheumatic valve disease (RVD) in patients with ARF [55]. The successful use of NSAIDs other than ASA has been reported in the treatment of other childhood rheumatic disease. However, such studies are lacking for the treatment of ARF. There are a few reports showing good results with naproxen (NXN-5 to 10 mg/kg every 12 hours) [56] and tolmetin [57] and the outcomes have not been tested in a randomised and controlled manner. A recent study suggests that ibuprofen may be equally effective [58]. 'Rebound' occurs while tapering or within weeks after stopping initial therapy. 'Relapse' is a worsening of symptoms while still actively on treatment and 'Recurrence' is a new episode of ARF caused by a new Group A Streptococcal infection, usually appearing > 8 weeks after treatment has ceased. "Rebound" manifested by reappearance of mild symptoms or of acute phase reactants, may occur in some patients after discontinuation of anti-inflammatory therapy [59] usually within 2 weeks. Many centers use salicylates in full doses at the same time and continue this beyond the course of steroid therapy in the hope of avoiding a rebound until the active inflammation subsides. Acetyl Salicylic Acid (Aspirin) do not decrease the incidence of residual RHD and corticosteroids produce prompt control of the subcutaneous nodules, erythema marginatum, fever and arthritis in Acute Rheumatic Fever. Recently it is found that Immunoglobulins are of no value in the management of acute rheumatic fever [60].

IE prophylaxis is necessary in rheumatic fever patients with residual heart disease. Antibiotic regimens used to prevent recurrence of acute rheumatic fever are inadequate for prevention of bacterial endocarditis. Because α hemolytic streptococci in the oropharynx may have developed resistance to oral penicillin being used for secondary prevention of rheumatic fever, the agent selected to prevent endocarditis should not be a penicillin. The standard general prophylaxis is Amoxicillin, clindamycin, clarithromycin, cefadroxil are also used in IE prophylaxis of RHD patients. Amoxicillin is the globally preferred, administered as 2 g for adults and 50 mg/kg for children, administered orally 30 to 60 minutes before the procedure [61].

4. Conclusion

Acute rheumatic fever (ARF) is an autoimmune response to untreated Group A streptococcal throat infections, whereas malaria is a parasitic infection. These two distinct conditions are often medically intertwined due to overlapping symptoms—such as high fevers and joint pain—which frequently leads to delayed or complicated diagnoses, which can make it difficult to differentiate them in tropical regions of India. Studies have shown diagnostic overlaps where patients (especially children) test positive for malaria but also meet the criteria for ARF. Failing to treat ARF can lead to permanent Rheumatic Heart Disease. Clinicians rely on rapid diagnostic tests for malaria, throat cultures, antistreptolysin O (ASO) titers and echocardiography to distinguish and treat both diseases appropriately. ARF Treatment requires immediate antibiotic therapy to eradicate the streptococcus bacteria, anti-inflammatory medications (like aspirin) to

control joint and heart inflammation, and long-term antibiotic prophylaxis to prevent recurrences. Malaria Treatment via standard antimalarial medications (e.g., Artemisinin-based Combination Therapy or chloroquine), depending on the specific parasite strain (P. falciparum or P. vivax) and local resistance patterns. India bears a significant burden of both diseases. Because a missed ARF diagnosis can cause irreversible heart valve damage and treating ARF aggressively alongside malaria is crucial for preventing RHD. Local healthcare infrastructure continues to focus on improving both public awareness and early echocardiographic screening.

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