# Pitfalls in the Diagnosis of Acute Rheumatic Fever

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**Acute Rheumatic Fever** (ARF) is a sequel of an immunological disorder initiated by Group A beta haemolytic streptococcal (GABHS) infections (such as sore throat). It is believed to be caused by antibody cross-reactivity that can involve the heart, joints, skin, subcutaneous tissue and brain.[1] A first episode of ARF can occur at any age but most often between 5 to 15 yrs and is uncommon before the age of 3 yrs and after 22 yrs (only 20% of first-time attacks occurring in adults). The illness typically develops within 2 to 3 weeks after a streptococcal infection.[2] The current incidence of ARF after GABHS infection is decreased to less than 1%, but the cardiac involvement is reported to occur in 20- 40% of patients with their first attack and 50-70% of patients when all attacks are counted among untreated or undiagnosed cases. In up to a third of cases, the underlying streptococcal infection may not have caused any symptoms.[3]

Rheumatic fever owes its importance due to its involvement of heart that may lead to serious heart disease and death. The prevalence of RF and RHD and the mortality rates varies widely between countries and population. It accounts for about 0.6 cases per thousand of Rheumatic Heart Disease (RHD) and 0.45 per thousand cases of Acute Rheumatic fever (ARF) annually in the NCCRF & HD during 2009.[4] Data from developing countries suggest that mortality due to RF(Rheumatic fever) and RHD (Rheumatic Heart Disease) remains a problem and children and young adults still die from acute RF (about 2-5 % annually).[5]

Ethnigenecity and overcrowding associated with low socioeconomic status are some of the predisposing factors that may be responsible for a higher incidence of ARF in this region.[6] With the advent of penicillin, the incidence of ARF is expected to go down but several other factors including rapid urbanization, increase in population and adverse environmental conditions accounts for its persistence and resurgence in areas where it might have been extinct.[7] Recurrences of the disease are common in developing countries, owing to gaps in the detection and secondary prevention due to lack of health care facilities.[8]

In view of changing pattern of the disease with its variable clinical picture and also other causes ( like viral infection, autoimmune disorders or drugs etc) that are responsible for similar presentation, the diagnostic criteria which were held for many years are being put into questions now. But in absence of any full proof confirmation for the disease entity, the support is still dependant on same clinical and laboratory findings as there is no single, gold standard investigation exist that is pathognomonic of ARF or its recurrences.[9] It has become essential to have a review of the disease profile in terms of the resurgence of RF in certain parts of the world and the reported changing pattern of its clinical characters.[7] A study is contemplated to have an insight into the clinical profile of the disease as observed by the physicians at the NCCRF & HD during the last few years (2008 -2010).

The **Jones Criteria** were first published in 1944 by T Duckett Jones, MD for diagnosing acute rheumatic fever (ARF)[1] has undergone several changes and revisions by the American Heart Association (AHA) and the World Health Organization (WHO) to encompass vexing clinical issues and to improve the specificity. (Table - I & II)[10].

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**Table-I**

*2002-2003 WHO criteria for the diagnosis of rheumatic fever rheumatic heart disease (based on revised Jones criteria)* [10]

| Diagnostic categories | Criteria |
|---|---|
| Primary episode of RF | Two major or one major and two minor manifestations plus evidence of a preceding group A strep infection. |
| Recurrent attack of RF in a patient without established RHD. | Same as above. |
| Recurrent attack of RF in a patient with established RHD | Two minor manifestations plus evidence of group A strep. infection. |
| Rheumatic chorea.<br>insidious onset Rheumatic carditis. | Other major manifestations or evidence of group A strep. infection not required. |
| Chronic valve lesions of RHD( patients presenting for the first time with pure mitral stenosis or mixed mitral valve disease and / or aortic valve disease ) | Do not require any other criteria to diagnose RHD. |
| *** Major manifestations** | - Carditis<br>- polyarthritis<br>- chorea<br>- erythema marginatum<br>- subcutaneous nodules. |
| **** Minor manifestations** | Clinical: fever, polyarthralgia,<br>Acute phase reactants(ESR or leukocyte count).<br>- electrocardiogram: prolonged P-R interval. |
| *** Supporting evidence of a preceding strep infection within the last 45 days. | - elevated or rising antistreptolysin-O, other streptococcal antibody or a<br>- positive throat culture or<br>- rapid antigen test for group A streptococci. |

**Table-II**

*Changes in the Jone's Criteria following reviewns from AHA and WHO*

| Criteria | Year | Manifestations | | | Supportive evidence of recent GABHS infection |
|---|---|---|---|---|---|
| | | Major | Minor | | |
| | | | Clinical | Laboratory | |
| (a) Original 2 major or 1 major & 2 minor | 1944 | Carditis, arthralgia subcutaneous nodules, chorea and pre existing RF/RHD. | Erythema marginatum, fever,epistaxis, anaemia, abdominal pain | Elevated WBC count, ESR and CRP | No need |
| (b) AHA modified 2 major or 1 major & 2 minor | 1956 | Carditis, arthritis, subcutaneous nodules, erythema marginatum and chorea. | Arthralgia, fever, Pre-existing RF/RHD | Prolong P-R interval, elevated WBC count, ESR and CRP | Needed but less importance. |
| (c) AHA revised 2 major or 1 major & 2 minor | 1965 (1984) | Same as before | Same as before | Same as before | Essential. |
| (d) WHO reviewed 2 major or 1 major & 2 minor | 1988 | Same as before | Same as before | Same as before | Essential but in special consideration. |
| (e) AHA update | 1992 | Same as before | Same as before | Same as before | Essential in special consideration |
| (f) WHO Criteria 2 major or 1 major & 2 minor plus Supportive evidence of recent GABHS infection. | 2000- 2003 | | Arthralgia, and fever. | Prolonged PR interval, elevated WBC count, ESR and CRP. | |

The importance of a preceding streptococcal infection has been emphasized in subsequent revisions. The 1992 update addresses the diagnosis of the first attack of ARF and previous RF, which were not included in the revised criteria. In the recent revision of 2003, a set of clinical guidelines along with a history of RF or pre-existing RHD was considered to be a major criterion, since RF tends to recur and the incidence of recurrence with subsequent untreated infection is substantially greater ie 50%, especially during the first 3-5 yrs after the initial episode.[2]

Major manifestations are least likely to lead to an improper diagnosis but minor ones are not sufficient for a definitive diagnosis of RF as they lack diagnostic specificity.[11] It is difficult to establish the definitive diagnosis of ARF as some of the characteristic manifestations have become less common. It is important to note that some patients who fulfill the Jones criteria are not RF patients and, conversely some patients who do not fulfill the criteria, are RF patients. [8] At times rheumatic fever is over diagnosed and also the immediate administration of anti rheumatic drugs masks the typical manifestations and may confuse the clinical profile, leading to wrong diagnosis of ARF.[12]

The migratory **poly arthritis** of the big joints (knee, ankle, elbows and wrist) is the most common symptom and is frequently the earliest manifestation of ARF, occurring in about 40-70 % often accompanied by fever.[4] Sometimes, a distinction between arthritis and arthralgia remains difficult because of a long interval from

the onset of illness to visiting the physician or because of uncertain information on salicylates / steroids medication. Thus, the possibility of polyarthritis cannot be excluded with certainity. Occasionally, some cases may present as mono arthritis or additive arthritis when clinical progression of the illness becomes more important to establish a final diagnosis.[13]

**Post streptococcal reactive arthritis** (PSRA) is a separate clinical entity and is often difficult to distinguish from ARF. The classical clinical features are that of an additive rather than migratory arthritis, poorly responsive to NSAIDS (eg salicylates) and lasting for more than 8-12 weeks virtually rule out ARF. Children with PSRA do not fulfill modified Jones Criteria but may have elevated acute phase reactants (ESR, CRP) and positive anti DNase B.[14]

**Carditis** is the single most important prognostic factor in RF. It may occur alone or in combination with pericardial rub, murmurs, heart failure. Murmurs are common but may not be heard at initial examination and can persist indefinitely. The murmurs of acute RF results from valve regurgitation and those of chronic RF cases are from valve stenosis.[15] Acute RHD often produces pancarditis which is serious and the second most common complication (50%) and is characterized by endocarditis, myocarditis and pericarditis. Endocarditis is manifested as mitral and aortic valve insufficiency. Severe scarring of the valves develops during a period of months to years after an episode of ARF and recurrent episodes may cause progressive damage to the valves.[5] The mitral valve is affected most commonly and severely (65-70%) in patients presented with valvulitis at the initial phase of the illness. [4]

Currently, clinical examination remains the basis of a diagnosis of RF and RHD but, it is now advisable to use Doppler echocardiography as a supplementary diagnostic tool to confirm sub clinical valvular lesion and to identify the congestive cardiac failure in difficult situations of established RHD.[10] But, Doppler criterion to distinguish physiological from pathological mitral regurgitation is not universally accepted and remained specifically excluded in the revised Jones Criteria because of insufficient supporting data.[16]

**Subcutaneous nodules** are not common, only 2-8% of children with ARF have nodules. [4] They rarely occur alone and in most cases appear several weeks after the onset of cardiac findings, They are usually painless and transitory and may be missed if not looked for actively. Sometimes nodules and erythema marginatum tends to occur together.[5]

**Erythema marginatum** is a rare finding in our population which usually occurs early in the course of a rheumatic attack and persist or recur for years, often continuing when other manifestations of the disease have subsided .It is not influenced by anti-inflammatory therapy.[8] It is a serpinginous, flat or slightly raised, non scarring and painless rash which is difficult to assess in dark skinned individuals and may be confused with rashes occurring in conditions such as sepsis, drug reactions or juvenille idiopathic arthritis (JIA).[16]

**Sydenham's chorea** occurs in about 1-2 % of female children.[4] The onset is typically insidious and is frequently found when other manifestations have subsided. Polyarthritis and chorea never occur together and indeed the onset of chorea calls attention to subclinical carditis.[17] Chorea consists of rapid and irregular jerking movements of hand, face and feet. The presence of chorea warrants a careful exclusion of other diseases like SLE, Wilson's disease and drugs ( eg phenytoin, oral pills etc). Obsessive compulsive behavior may develop in many patients.[18]

**Some manifestations** like fever, arthralgia, anorexia and malaise can be prominent but not very specific and may occur in many other situation. Fever occurs in almost all rheumatic attacks at the onset but rarely lasts more than several weeks. Arthralgia without objective findings is common in RF. The pain usually involves large joints, may be mild or incapacitating and may persist for days or weeks.[3] Prolonged episodes of ARF (> 8 months) may occur in 5-10% of patients with spontaneous recurrence, unrelated to intervening streptococcal infection and mimic the initial episode. [8]

**Erythrocyte sedimentation rate (ESR) and serum C-Reactive Protein (CRP)** are sensitive tests but nonspecific and can be elevated in any inflammatory condition.The ESR is often high ie > 30 mm / h in about 40-60% of cases and CRP was found high (> 6 ml/ dL) in 18-35% patients. [4] As CRP rises and falls faster than ESR, a normal CRP may confirm that inflammation is resolving in a patient with prolonged ESR elevation after acute symptoms have subsided (3-5 months) in uncomplicated cases of carditis.[19]

The evidence of a previous streptococcal infection has been given special consideration in the

diagnosis of ARF. A preceding GAS infection (pharyngitis ) is suggested by a recent history, positive throat culture, an increase in the antistreptolysin O (ASO) titre or a rapid antigen test. [20] Often a history of pharyngitis is not very reliable and throat culture is negative at the time ARF manifests.[12] It is positive in 30- 40 % of cases in our center. Again, it is difficult to say whether the positivity is because of a true infection or a carrier state considering the fact, that the prevalence of Group A beta haemolytic streptococcal (GABHS) sore throat is quite high (10-18%) in our population. [21]

The estimation of streptococcal antibodies such as **antistreptolysin O (ASO)** and **anti DNase B** gives a reliable indicator of previous of GABS infection but there is an over reliance on ASO titre for the diagnosis of ARF. About 60-80 % of the healthy population may show an elevated ASO titre (>300 IU/ml in children) in developing countries like ours. [22] Hence, one must remember that single raised ASO titre does not equate to ARF, so paired sera collected at an interval of 4-8 weeks with 2- fold increase or decrease gives a more meaningful interpretation. Similarly, a negative ASO titre does not exclude the diagnosis of ARF.[23] Interpretation of ASO must be done in concurrence with other clinical findings, especially because 20-30 % of systemic onset of Juvenille Idiopathic Arthritis (JIA) also have elevated ASO titre. Anti DNase B antibody level has good reproducibility and should be obtained if possible. The **antigen detection** for group A streptococci is a specific test but with a very low sensitivity, thus hampering its utility.[24]

Though a number of dilemmas in the diagnosis of acute rheumatic fever (ARF) have been discussed. An over diagnosis at the initial phase of the illness and starting appropriate treatment earlier is always better in the prevention of serious cardiac morbidity and mortality, than missing the diagnosis altogether.[8]

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