Rheumatic fever: New ideas in diagnosis and management

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ABSTRACT

Rheumatic heart disease remains a major cause of disability and death in developing countries. Careful re-analysis of mid-20th century data as well as the juxtaposition of well-funded research units and populations at risk have generated information that resulted in radical departures from standard approaches to the prevention, clinical recognition and treatment of acute rheumatic fever. As a result, rheumatic heart disease may be eliminated in the future.

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INTRODUCTION

In the minds of many practitioners in the developed world, rheumatic fever is an old and vanishing disease. Diagnosis is framed in the revered Jones criteria and treatment rests with a simple drug that is difficult to buy in modern commercial pharmacies. In reality, rheumatic heart disease disables young adults and shortens their lives in many parts of the world. Sadly though, even in developing countries the clinical recognition of acute rheumatic fever can be inaccurate.[1]

T. Duckett Jones (whose criteria were first used in 1944) deserves credit for establishing a set of clinical rules that with relatively few modifications are still the gold standard for the diagnosis. These rules have a number of major weaknesses, one being their application to diagnose recurrences in areas of high prevalence of rheumatic heart disease. Another weakness is the lack of specificity in areas of low prevalence.

Why has a new diagnostic test for acute rheumatic fever not emerged yet? The pathological consequences of the process (typified by the Aschoff nodule) are remote and not easily accessible in the patient. The pathogenesis of the disease is not straightforward. However, increasing understanding of the process should lend itself to the development of biomarkers. ("Biological characteristics that can be objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention that refine the diagnosis of the disease".)[2]

Apparently there appear to be very few other processes that can damage the mitral or aortic valve of the younger patient. Established changes are relatively easy to recognise as being typical of rheumatic heart disease. However, there are consequences of under-diagnosis of cardiac involvement (inadequate duration of prophylaxis) or incorrect diagnosis (labelling congenital disease or physiological regurgitation as rheumatic heart disease). It remains equally important to be able to identify the patient with acute rheumatic fever without cardiac disease in the group of patients seen with febrile illnesses and arthritis.

What is the current understanding of the disease's pathogenesis? To paraphrase a recent publication:[3] A Group A streptococcus which is "rheumatogenic" has to affect a susceptible individual (genetic/environmental risks) and this is then followed by a complex immune process (again modulated by genetic influences).

The author of this paper have attempted to summarise current knowledge on the genetic susceptibility to acute rheumatic fever and rheumatic heart disease.

It is unclear whether some of the various genetic markers of risk such as HLA typing or B cell markers are epiphenomena or true

pointers to populations at risk. In other words, are these abnormalities (such as the increased incidence HLA DR 1 and 6 described in South Africans with rheumatic heart disease)[4] part of the pathogenesis of the disease or flags for other components of the complex pathogenesis?

Adding to this uncertainty, HLA markers vary from country to country. The D8/17 lymphocyte subset is said to be increased in most populations with rheumatic heart disease[3] but our own experience with the D8/17 B cell subpopulations in patients with rheumatic heart disease is totally different.[5] The pathogenesis of the acute stadium involves molecular mimicry and all components of the immune system. While the streptococcal pharyngitis is still regarded as the main triggering infection, streptococcal skin infections may also have some influence.[6]

Three percent of individuals who are exposed to pathogenic streptococci will develop rheumatic fever in their lifetime. Three percent of individuals with a symptomatic sore throat during epidemics will develop acute rheumatic fever. Carapetis et al.[7] point out that this rate is fairly similar to rates in North America at the start of the 20th century, thus the contributions of a "genetic" component to the development of rheumatic fever need to be judged in this light.

Anecdotally the number of patients admitted to facilities in Cape Town with acute rheumatic fever appears to be decreasing; yet rheumatic heart disease remains a problem. Why so? Is there a true decline in acute rheumatic fever or has the recognition of the condition become poorer during the recent AIDS epidemic?

Parks and colleagues were able to show (by retrospectively analysing patient records) that the recognition of acute rheumatic fever at primary care facilities in Fiji was very poor.[8] Their work is disturbing given the high prevalence of rheumatic heart disease in that area as well as the lack of other major epidemic illnesses which might be confused with rheumatic fever.

THE JIGSAW PUZZLE OF PATHOGENESIS: HOW COULD IT AID IN DIAGNOSIS AND MANAGEMENT?

A better understanding of the disease (including the accurate identification of the disease-causing streptococci) could help in the following ways:

- By defining a group at risk, the use of primary prophylaxis and/or vaccination would be appropriate given the risks of unchecked antibiotic use and the theoretical risks of vaccine use. Similarly, these preventative regimens could be extended to family members of patients with rheumatic heart disease.
- Alternative concepts of the triggering of the disease, such as the role of skin infections as a primer could be tested and therapies directed specifically at those triggers.
- The combination of biomarker estimation, echocardiography and clinical criteria would allow the development of a set of "super criteria" for the diagnosis of acute rheumatic fever avoiding over-diagnosis in patients with arthritis and fever due to other illnesses or mild valvular prolapse and a febrile illness.
- The recognition of subgroups at risk for cardiac involvement during an acute attack would allow tailored secondary prophylaxis regimens to be instituted.
- The recognition of subtle cardiac involvement during an attack either using a biomarker or a tested echocardiographic screening protocol would also allow structured use of secondary prophylaxis regimens.
- An accurate model of the pathophysiology leading to cardiac and neurological structural damage would allow tailored treatment of carditis and chorea by immuno-modulatory therapies.

THE CURRENT STATUS OF PRIMARY PREVENTION AND VACCINATION

A successful vaccine against Group A streptococcal infection would have the benefit of decreasing the prevalence of rheumatic heart disease as well as other sequelae of infection such as invasive disease. Initial attempts at developing a vaccine against group A streptococcal infection failed when vaccinated subjects developed acute rheumatic fever after vaccination.[9] Despite a better understanding of vaccine design the authors of a recent paper expressed disappointment that only one vaccine has been studied clinically in the last 3 decades.[10] The accurate identification of the multiple serotypes causing acute rheumatic fever in various parts of the globe has raised concerns regarding the potential effectiveness of the current multivalent vaccine.[11]

The differentiation of a "strep throat" from an episode of viral pharyngitis remains difficult. Furthermore, confirmation by culture or other techniques remains unlikely in resource poor communities. Indeed, under recognition and underreporting of sore throats is probably responsible for the well-recognised lack of a history of

sore throat in patients with documented episodes of acute rheumatic fever as well as the presentation of young adults with established rheumatic heart disease and no preceding history of acute rheumatic fever.

The available evidence on penicillin treatment of all patients with pharyngitis with suspected streptococcal sore throat has been reviewed in a meta-analysis,[12] treatment was associated with a positive benefit in so far as episodes of acute rheumatic fever were prevented. It has been suggested from work in Costa Rica[13] and Cuba[14] that treatment of all patients with a suspected streptococcal sore throat with penicillin is beneficial. This is controversial.[15]

The existing body of work suffers from a lack of controlled trials, apart from a trial from New Zealand (see below) as well as clinical decision rules which vary from loose to strict in terms of deciding which patients had streptococcal sore throat.

A recent randomised control trial in New Zealand could not show any benefit in the nurse-led treatment of streptococcal sore throats in terms of the prevention of acute rheumatic fever.[16] Concern has been expressed that the control group in this study may not have been "pure" in terms of access to primary health care and oral penicillin therapy.[17]

The distinction of "streptococcal" from "viral" sore throats on clinical grounds is difficult. The use of clinical algorithms has be shown to reduce the unnecessary administration of antibiotics – even preventative programmes which use the weakest algorithms are likely to be successful.[18]

SECONDARY PREVENTION STRATEGIES

For the contemporary practitioner, each meta-analysis of past research yields surprises. The often-repeated criticism of these analyses is that past studies were not performed with modern rigour and that archaic forms of modern drugs were used. Nevertheless, standard practices are constantly being challenged.

For example: It is disappointing to realise that though there is evidence that secondary prophylaxis reduces the incidence of second attacks of acute rheumatic fever, the assumption that this reduction will coincide with a reduction in cardiac damage is probably not true.[19] The standard for prophylaxis is an intramuscular penicillin injection rather than oral prophylaxis.[20]

Although there is evidence that 2-weekly prophylaxis is more effective than 4-weekly treatments in some countries there appears to be little advantage in administering penicillin more frequently than every 4 weeks unless a patient has breakthrough attacks.[21] Intra-muscular penicillin is also recommended in some populations for patients taking oral anticoagulants.[22] Paradoxically, intramuscular penicillin is an orphan drug in some major centres in South Africa with preparations available in State facilities but not in private pharmacies. The incidence of anaphylaxis is very low.[23]

The injection however remains painful and continued adherence is facilitated by a close relationship between practitioner and patient. A recent study in the Pacific's Northern Mariana Islands confirmed that poor adherence to prophylaxis offers no advantage over no prophylaxis with respect to prevention of acute attacks.[24] Various culturally appropriate methods (lunar calendars for rural Australians, cell phone text message reminders for Fijians) are used in an effort to improve adherence.

The duration of secondary prophylaxis varies from country to country. World Health Organisation (WHO) guidelines for example suggest that prophylaxis should be continued until 25 years of age or ten years after the last episode of carditis occurred.[25] The New Zealand guidelines suggest that prophylaxis should be continued until the age of 30 years if carditis is present.[22] Guidelines for South African patients are currently being developed.

A UNIFIED STRATEGY TO REDUCE ACUTE RHEUMATIC FEVER

Several experts[15,22] have argued that the incidence of acute rheumatic fever and rheumatic heart disease have decreased in populations after the application of a comprehensive set of strategies including both primary and secondary prevention and education. Unfortunately, many areas of the world ridden with rheumatic heart disease, there are no statistics on the incidence of acute rheumatic fever as well as the prevalence of rheumatic heart disease. Efforts to establish a series of worldwide registries (to remedy the lack of data) are currently underway.

It is sobering to note that the decline in acute rheumatic fever deaths in the United States that occurred in the early part of the twentieth century occurred without the use of penicillin. This

could probably be ascribed to an improvement in the average living conditions and a decline in the virulence of the causative organisms.[26]

THE ACUTE EPISODE – DIAGNOSIS IN 2010

The Duckett Jones criteria have been revised several times to track the drop in the occurrence of acute rheumatic fever in the USA.[27] Paradoxically the tightening of criteria has potentially decreased the diagnosis of acute rheumatic fever in high risk populations. Modifications of the 1992 revision have been adopted by the WHO to allow for the diagnosis of a recurrence of rheumatic fever in patients with established rheumatic heart disease as well as the diagnosis of indolent carditis.[25] The WHO guidelines below (Figure 1) explains the modifications by themselves as well as the Australian Health Assocation (AHA) in graphical form.

In the Australian experience, decreasing the threshold for the definition of fever to 38° instead of 39° increased the sensitivity of the diagnosis.[28]

In recent years it has been suggested that higher "local values" for abnormal ASO and anti-DNAse B titres should be established given the assumption that poorer populations were more often exposed to streptococcal infections. This belief has been challenged by the work of Steer and his colleagues in Fiji, suggesting that the "upper limits of normal" for such titres are not markedly different between populations. (For example, a "cut-off" value of 276 IU/ml for ASOT and 499IU/ml for anti-DNAse B for the age range of 5-15 years is suggested).[29]

The widespread use of echocardiography in patients with acute rheumatic fever has resulted in the recognition of subclinical carditis in up to 16% of patients.[30] In Australia and New Zealand, subclinical carditis has been added to the major criteria.[22] Standards for the diagnosis of carditis using echocardiography have been developed in New Zealand;[31] there are, however, differences reported in the literature as to the extent of documented valvular damage in patients with subclinical carditis. Subclinical carditis is being associated with more florid valvular change in patients from the Indian subcontinent.[32] "Echo-detected" carditis has not been

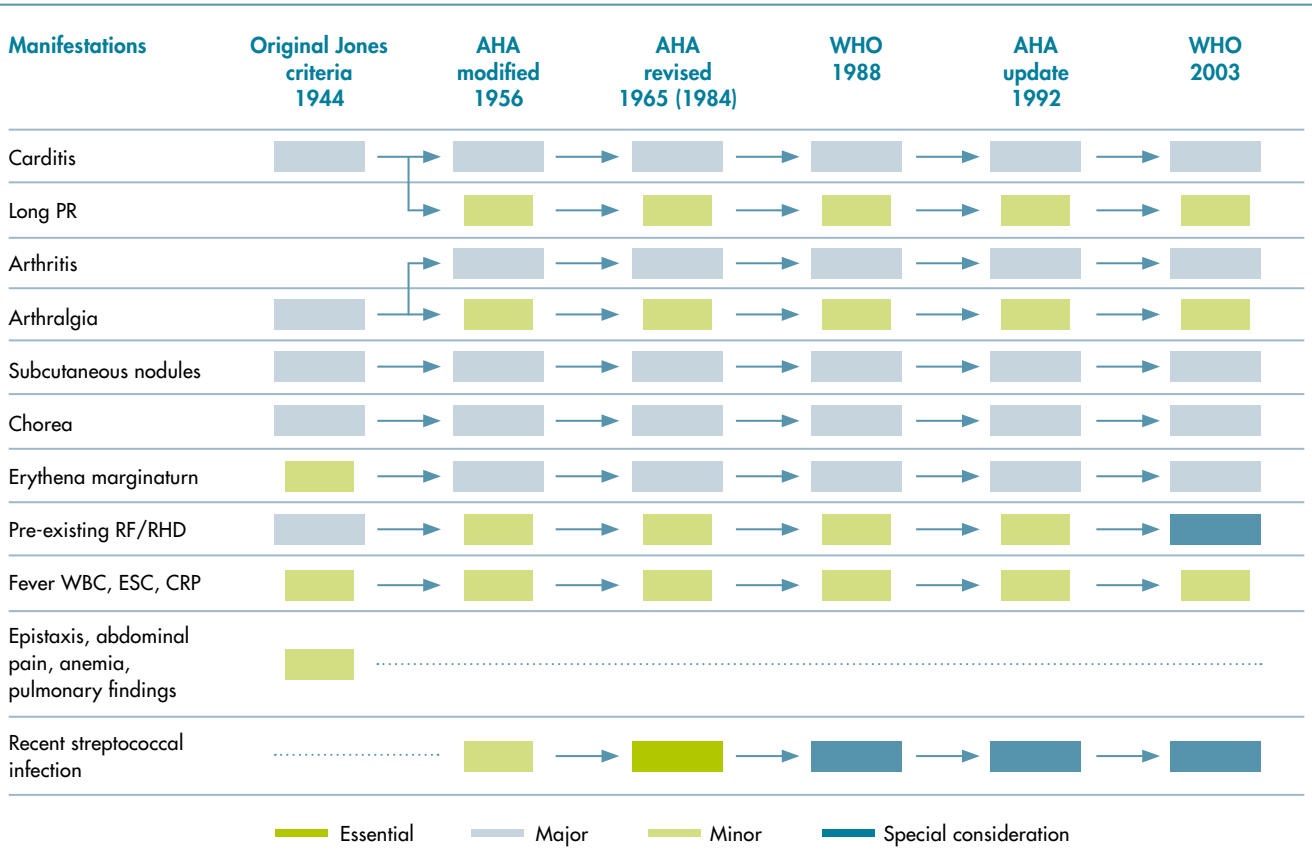

FIGURE 1: Changes in the Jones criteria following review from AHA and WHO

PR: PR interval in the electrocardiogram, WBC: leukcoytosis, ESR: erythrocyteseyimontation rate, CRP: C-reactive protein.

added to the proposed South African standards for the diagnosis of acute rheumatic fever.

New Zealand patients with mono-arthritis are considered to have the arthritis of acute rheumatic fever if they have used non-steroidal anti-inflammatory agents to relieve pain. (Practitioners are encouraged to use paracetamol rather than NSAIDs to treat patients with mono-arthritis).[33]

In populations with a high prevalence of disease, doubt has been expressed as to the existence of isolated arthritis following a streptococcal infection as well as to the existence of a separate category of neurological conditions known as PANDAS (paediatric auto-immune neuropsychiatric disorder).[33]

The existence of a separate myocarditis in patients with carditis has been disproved using sophisticated echo techniques as well by measuring serum troponin levels.[34,35] BNP measurement has been helpful to differentiate those patients with carditis from those without valvular involvement.[36] QT dispersion is also abnormal in those with carditis.[37]

Chorea has classically been regarded as an isolated phenomenon; however in our own patients chorea is associated with carditis in half of the patients.[38]

MANAGEMENT OF AN EPISODE OF ACUTE RHEUMATIC FEVER

Revisiting older literature has cast doubts on standard aspects of acute care such as bed rest and aspirin use.[39] In my opinion, bed rest is a useful surrogate for warmth, good food and freedom from the household chores and challenges that typify life for a poor child. Recent work from Turkey documented differences in bio-elements and vitamins with antioxidant functions between patients with acute rheumatic fever and control groups, thus the possibility exists that dietary manipulation might modify outcomes.[40]

There is no evidence that aspirin and corticosteroids play any role in the management of the inflammatory component of acute rheumatic fever.[41] Aspirin as an analgesic for arthritis is still recommended therapy, yet we do not use aspirin in other forms of arthritis. There is some data to suggest that naproxen is an effective agent to relieve joint pain.[42] Corticosteroids used in other diseases such as myocarditis are used in desperation despite lack of evidence for efficacy.

In patients with carditis and severe valvular involvement, standard anti-failure therapy including the use of modern vasodilators is recommended. A trial of immunoglobulin therapy had a negative outcome.[43] Valve replacement in severely affected individuals may be life saving. Recent work from New Zealand indicated that good valve repairs are possible in the aftermath of an acute attack but that the durability is affected by the presence of endocardial inflammation.[21]

The results of a trial of immunoglobulin therapy in chorea from our own institution are pending; this study and other data have reinforced our impression that chorea is a potentially debilitating and chronic condition and that the effective treatment of this condition is tricky. For example: Significantly reduced doses of haloperidol than recommended in the standard texts should be used to avoid extra-pyramidal side effects. (Starting dose: 0.025 mg/kg/day in divided doses increased slowly to a maximum of 0.05mg/kg/day.) Alternatives include sodium valproate or pimozide. The practitioner treating the patient with Sydenham's chorea must remember to eradicate the streptococcus as well.

CONCLUSION

The application of modern scientific techniques has destroyed the apparent simplicity of approaches to the prevention and management of acute rheumatic fever and its sequelae developed in the 20th century. Current practice should aim to improve the recognition of streptococcal sore throat at primary care level. It should ensure that both primary and secondary prophylaxis occurs in populations at risk in an effective manner while considering local circumstances. International cooperation both in terms of the establishment of registries as well as multicentre trials should be encouraged.

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