Prevention of rheumatic heart disease: Potential for change

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Jovita is a fourth year medical student (2011) from James Cook University with a great interest in research, mainly in the field of paediatric cardiology. She aspires to undertake an Honours project in the field of cardiology. After moving to the tropics and seeing cases of Rheumatic Heart Disease, Jovita became highly passionate in looking at its prevention. She believes that Rheumatic Heart Disease is still an important issue that should not be forgotten.

Rheumatic heart disease (RHD), an autoimmune reaction to an infection of rheumatogenic group A streptococcus bacteria, is characterised primarily by progressive and permanent heart valvular lesions, although other parts of the heart may be affected. Despite an overall decrease in the incidence of RHD in developed countries, it remains a pertinent health issue with high rates in developing countries and amongst certain Indigenous populations in industrialised countries. Primary, secondary and tertiary strategies for the prevention of rheumatic heart disease exist, as do numerous barriers to such strategies. A review of the literature, incorporating its epidemiology and pathophysiology, demonstrates that interventions at various stages of the disease may reduce the collective burden of disease.

Introduction

Rheumatic heart disease (RHD) is a chronic condition characterised by fibrosis and scarring of the cardiac valves and damage to heart muscle. It arises from an episode or recurrences of acute rheumatic fever (ARF), an immune-mediated multisystem inflammatory disease. ARF is caused by infection with rheumatogenic group A streptococcus bacteria. [1,2] One of the most serious manifestations of ARF is carditis, which is evident in approximately 30-45% of people with rheumatic fever. [3,4] Although the severity of rheumatic carditis varies widely between individuals, it is usually the main contributor to the morbidity and mortality of rheumatic fever. This is due to the permanent and progressive nature of damage it causes to the heart, ultimately leading to rheumatic heart disease. [3,5]

The diagnosis of rheumatic heart disease is most effectively determined through the use of echocardiography. The patient may present with various signs including pericardial rub, tachycardia, an apical systolic murmur consistent with mitral regurgitation, a basal diastolic murmur consistent with aortic regurgitation or severe congestive heart failure. [4,6] The most commonly affected valve is the mitral valve, affected in 65-70% of patients, followed by the aortic valve, affected in 25% of patients. Damage to the tricuspid valve is typically associated with mitral and aortic valvular lesions. Severe dysfunction of the cardiac valves can lead to congestive heart failure and death. [7,8]

The incidence of rheumatic heart disease is estimated at 15.6 to 19.6 million cases worldwide and it is responsible for over 233,000 deaths annually. [3,9,10] RHD is a major public health problem particularly in developing countries, which account for over 80% of cases of ARF and RHD. [11] Whilst the incidence of ARF and RHD has decreased in most developed countries, cases are disproportionately high amongst the Indigenous populations in these countries. [3,11] It may thus be concluded that this disease affects populations universally and is a pertinent issue to address and prevent. This review will explore different preventative strategies and barriers to these preventative measures.

Pathophysiology

Rheumatic heart disease is characterised by heart valve damage and is the consequence of rheumatic fever, an acute immune-mediated inflammatory disease triggered by untreated Group A streptococcal (GAS) pharyngitis. [12] Rheumatic fever causes permanent damage

to cardiac valves, particularly the mitral and aortic valves, leading to rheumatic heart disease. Pathological findings include thickening of the valve leaflets and chordae, mitral annular dilation and chordal dilation. [3,13] Multiple episodes of rheumatic fever cause additional damage to cardiac valves and exacerbate rheumatic heart disease. [14] It has been estimated that 60% of those with ARF will develop RHD. [11,15]

GAS is a gram-positive bacterium that attaches to the epithelial cells of the upper respiratory tract, eliciting an acute inflammatory response within three to five days. Patients typically present with a sore throat. [16] In 0.3-3% of cases, rheumatic fever occurs as a consequence of the infection and it is generally believed that only infections of the pharynx can cause rheumatic fever. [17,18] However, emerging studies have suggested that GAS impetigo could also lead to rheumatic fever. McDonald *et al.* [19] found that in some Indigenous Australian populations with a high incidence of ARF, there is a low incidence of GAS pharyngitis but a high incidence of GAS impetigo. In other high-incidence ARF populations, an absence of rheumatogenic M-serotypes of GAS may suggest that other serotyopes, including those causing GAS impetigo, may be involved. [11] Although it is widely accepted that only certain strains of GAS leads to rheumatic fever, the mechanism of how the initial infection develops into rheumatic fever remains unclear. [7,9]

Rheumatic fever is mediated by molecular mimicry between beta haemolytic streptococci and host tissue epitopes. [19] There are many GAS antigens that are believed to be cross-reactive epitopes including the M protein and N-acetyl glucosamine. These antigens share epitopes with human cardiac tissue, including the alpha-helical cardiac proteins including myosin, laminin and vimentin. [3,11,20] Recent studies conducted on rats support the similarity between components of M proteins found in certain strains of GAS and human tissue epitopes. [9] The anti-streptococcal antibodies that are produced by B cell lymphocytes cross-react with the host tissue epitopes by binding to the endothelial surface, leading to inflammation, cellular infiltration and valve scarring. Peptide fragments from the bacteria are also presented to T cell lymphocytes via major histocompatability complex (MHC) molecules, generating an immune response. [3,20] Guilherme

et al. [20] found that 91% of heart tissue biopsies revealed cellular infiltration consisting predominantly of CD4+ T cells. In addition, upregulation of vascular cell adhesion molecule-1 (VCAM-1) and neovascularisation promote T cell migration and infiltration, thereby causing further damage to cardiac valves. [11,20]

Genetic predisposition has been suggested to play a role in the autoimmune response against GAS, with an estimated 3-15% of any population being genetically susceptible to ARF. [9] Autoimmune diseases have been associated with several human leukocyte antigen (HLA) class II alleles which are expressed on antigen presenting cells. The antigen presenting cells are in turn responsible for presenting pathogenic antigens to, and consequently activating, T and B lymphocytes. The allele most commonly found to be associated with ARF and RHD is HLA-DR7, which may associated with to the occurrence of multiple valvular lesions. [3,20] Additionally, the tumour necrosis factor-alpha (TNF-α) gene, which is located close to the HLA class II genes, is related to inflammatory responses. The presence of this allele suggests a link to the development of rheumatic heart disease. [20]

Epidemiology

Rheumatic heart disease causes an estimated 233,000 deaths per year with approximately 282,000 newly diagnosed cases annually. The first episode of ARF typically occurs in those aged five to fourteen years old. Of the 15.6 to 19.6 million cases of RHD worldwide, 2.4 million cases occur in this age group. [3,8] In many developing countries, RHD is the most common cause of acquired heart disease in children and young adults. However, it still affects developed countries, particularly the Indigenous populations of these countries. [11,21]

Developing Countries

ARF and RHD affect an estimated 20 million people in the developing areas of the world and are the leading causes of cardiovascular death in the first five decades of life. [12] Ninety-five percent of new cases and deaths due to RHD each year occur in the developing world. [10] Epidemiological data from developing countries is poorly documented. It may therefore be the case that case numbers are higher than those recorded in the data. Many studies conducted in these countries have used data from school-aged children. [8]

The estimated annual number of cases of ARF amongst children aged 5 to 14 years old is 374 per 100,000 population, with approximately 60% of these children going on to develop RHD. The highest prevalence of RHD among school children is in sub-Saharan Africa where it has been documented as 5.7 cases per 1,000 population. [8,17,21] Kyrgyzstan, located in Central Asia, has the highest prevalence of ARF and RHD of all the developing countries. Over the last ten years, mortality from ARF and RHD in Kyrgyzstan has increased by 150% among children, by 33% among adolescents and 27.5% among adults. [8] These high rates are due to factors such as low standards of living, the high number of GAS carriers and an increase in the population migrating to other areas. [21]

A study from Brazil revealed that the incidence of ARF in Brazil declined by 75% between 1992 and 2002. Despite an overall decrease in incidence, figures remain high with 5,000 new cases in 2002. [4,21] In some regions of Brazil ARF is regarded as endemic, and RHD is accountable for nearly 90% of early childhood valvular surgeries in the country. [20]

The global burden of RF and RHD amongst developing countries over the past century can be explained by the socioeconomic conditions, lack of hygiene, access to medical care and overcrowding. [22] As mentioned earlier, the possibility that GAS impetigo could also be responsible for ARF may explain the disparity between ARF in different communities; however there is no definitive evidence to support this. [17,22]

Developed Countries

Over the past 80 years, the incidence of ARF and RHD has decreased in the United States and other developed countries. [7] A systematic review of ten population-based studies, which investigated the worldwide incidence of ARF between 1967 and 1996, found the lowest incidence rates in American and Western European nations. [3] The prevalence of RHD in the United States is now less than 0.05 per 1,000 population. [7] The overall decline in these areas of the world is due to improvements in aspects of primary prevention such as access to healthcare, housing conditions and appropriate use of antibiotics. It has also been suggested that the decreased incidence of ARF in the United States over the past 50 years is related to the replacement of rheumatogenic strains by non-rheumatogenic strains in cases of streptococcal pharyngitis in children. However, the reason for the change in distribution remains unclear. [12,19]

Indigenous Populations

ARF and RHD are not endemic in developing countries alone. They also affect industrialised countries, particularly within certain population groups. Various studies have demonstrated that in developed countries, the rates of ARF and RHD are vastly higher in Indigenous populations including Aboriginal Australians, Maoris of New Zealand, Native Americans and Hawaiians in the United States. [5]

The highest documented rates of ARF and RHD in the world occur in Indigenous Australians living in the "Top End" of the Northern Territory. [14] Aboriginal and Torres Strait Islanders are 8 times more likely than non-Indigenous Australians to be hospitalised for ARF and RHD and nearly 20 times more likely to die from causes related to the disease. [23,24] The increased susceptibility is due to the socio-economic and health statuses of Indigenous Australians, which are generally lower than those of the non-Indigenous population. One study reported that in two different communities in the Northern Territory the median number of people per household was 14 to 17 and concluded that this was a contributing factor to the high rates of ARF and RHD. [22]

Prevention

Primary Prevention

The purpose of primary prevention is to avoid the initial development of RHD. RHD is a consequence of ARF and hence primary prevention should be focused upon preventing ARF through timely diagnosis and treatment of GAS infections. Over 50 years ago, during epidemics approximately 3% of untreated streptococcal sore throats resulted in rheumatic fever. The dramatic reduction in ARF and RHD in developed countries since then is thought to be the result of improvements in socioeconomic conditions such as hygiene, access to medical care and reduced overcrowding. [11,23] Another factor which has led to the decline of ARF in developed countries is the widespread availability and use of antibiotics to treat GAS infections, which greatly reduces the chance of developing ARF. [5] Poor socio-economic conditions in developing countries and amongst certain populations within developed areas result in an increased susceptibility to ARF. However, it is important to acknowledge that ARF is not a disease that only affects these populations, as there are microbiological, immunological and genetic factors involved. [3] A successful vaccine against rheumatic heart disease is yet to be developed but is a future prospect.

While improving the socioeconomic status of high-risk populations is beneficial in reducing the circulation of GAS, the main focus has been placed on treating GAS infections appropriately. An accurate diagnosis of GAS pharyngitis is vital and usually involves microbiological confirmation via a throat culture or a rapid antigen detection test (RADT). [12] A recent systematic review found that the risk of ARF was reduced by 70% if antibiotics were given to patients with sore throats and symptoms indicative of a streptococcal infection. The risk was further reduced by 10% if intramuscular penicillin was given. [17] The recommended guideline for managing an initial attack of ARF is a single intramuscular dose of benzathine benzylpenicillin as a prophylactic agent against recurrent episodes and for the eradication of Group A streptococcus if it is still present. [9]

A correct diagnosis of ARF is also imperative to prevent RHD from occurring. The diagnosis is based on clinical criteria, known as the Jones Criteria, shown in Table 1. These criteria have been suggested to result in the under-diagnosis of ARF in high-incidence populations due to their strict application, as reported by epidemiologists and clinicians working in developing countries and Indigenous populations in developed countries. A modified set of criteria targeted at high-risk groups has been proposed to increase sensitivity. [11]

Table 1. *Modified Jones Criteria for the diagnosis of ARF. [25] For the diagnosis of ARF: 2 major or 1 major and 2 minor manifestations plus evidence of a preceding GAS infection are required.*

Major manifestations	Minor Manifestations
Carditis	Fever
Migratory polyarthritis	Arthralgia
Sydenham's Chorea	Elevated acute phase reactants
Erythema marginatum	Prolonged P-R interval on ECG
Subcutaneous nodules	

Secondary Prevention

Secondary prevention of RHD involves preventing recurrent attacks of ARF and treating the disease in its initial stages to avoid further damage. Rajamanan *et al.* [8] suggest that medical therapies for patients in the early stages of RHD may slow the progression of RHD affecting the valves.

An individual with a history of rheumatic fever who develops GAS pharyngitis is at high risk of suffering from a recurrent attack of ARF. Recurrences of ARF can exacerbate the severity of RHD from previous attacks or, less commonly, may result in the new onset of RHD in individuals who have not experienced cardiac manifestations. A study conducted by Meira in Brazil observed a group of children and adolescents by clinical examination and echocardiography for 5.4 years after their initial episode of ARF. They found that one of the risks of developing chronic RHD was a history of recurrent episodes of ARF. Preventing recurrent attacks of ARF has been shown to be the most successful and cost-effective way of preventing RHD. [3,25]

The recommendation for preventing recurrent attacks ARF is a continuous dosing regime of intramuscular benzathine benzylpenicillin every four weeks, and every three weeks in high-risk populations. This strategy has been shown to lead to regression of existing heart valve lesions and reduce RHD mortality. [25] Studies in Taiwan have shown that three-weekly instead of four-weekly injections reduced the number occurrences of ARF; however compliance with such frequent dosing is poor. American, Australian and New Zealand guidelines recommend four-weekly injectable benzathine penicillin G with three-weekly injections for patients who have a recurrent episode despite adherence with the four-weekly regime. [11] It is suggested that prophylaxis should be continued for at least five years after the initial attack as the chance of recurrence is the highest during this time period. However, more recent guidelines suggest a continuing with the regimen for a minimum of 10 years or until the age of 21, depending on which time length is longer. [3,11] Although the risk of RHD increases with multiple previous attacks of ARF, it decreases as the interval since the most recent attack lengthens. [12]

For early treatment of RHD, an accurate diagnosis must be made promptly. The diagnosis of RHD was previously made on the basis of clinical history and physical findings. However, echocardiography has since been introduced as the diagnostic standard following several reports showing that clinical examination alone lacks sensitivity in detecting RHD in high-risk populations. [26] Shiffman [27] revealed that despite 50 years of technological and methodological advances in medicine, echocardiography along with new antibody testing are the only new components of knowledge that have influenced the diagnosis of ARF. Studies conducted on children in Cambodia and Mozambique by Marijon *et al.* found that echocardiography detected ten times the number of cases of RHD compared with clinical examination alone. [5,27,28] Carapetis *et al.* [29] found that auscultation missed 54% of those with RHD and an accurate diagnosis of RHD was significantly higher if echocardiography was used after an abnormal murmur was detected through clinical examination. [3,29]

Tertiary Prevention

Tertiary prevention of RHD is achieved through monitoring and managing the disease. Once the heart valves have been damaged, tertiary prevention may prevent further damage from occurring. This can be accomplished by patients having regular health check ups and undergoing surgery if appropriate.

Surgery is recommended in adults who have symptoms of severe mitral incompetence or if they have reduced left ventricular function or a left ventricular end systolic diameter of 40mm or greater. There are various interventions for mitral stenosis including closed mitral valvotomy, open mitral valvotomy and interventional mitral valvotomy, although such procedures are not curative. [2] Valve repair has been demonstrated to be more effective than valve replacement due to the risk of complications of prosthetic valves, including thromboemboli, bleeding, teratogenic events associated with warfarin administration and the poor durability of bioprosthetic valves in younger patients. [17]

Barriers

Barriers exist to the effective prevention of rheumatic heart disease. Firstly, at least one third of episodes of ARF result from asymptomatic streptococcal infections, making it difficult to detect and appropriately treat the disease. [12] This may be partly attributable to a lack of access to medical care. Further, as previously suggested, an accurate diagnosis is necessary to treat GAS pharyngitis. This may be challenging in developing countries due to limited resources.

If diagnosed correctly, there are challenges to ensuring correct treatment and compliance. [11] Whilst primary prevention programs aim to educate at-risk populations about the importance of early presentation and treatment compliance along with health professional awareness, there are problems with sustaining such programs over a long period of time. [5] Barriers to secondary and tertiary prevention of RHD include the availability of medication, monitoring tests, cardiothoracic surgery and intervention facilities. [11] As the disease progresses to a chronic stage, continued medical and surgical treatment becomes costly for the patient, their family and society. [10] In addition, as emerging studies have suggested that GAS impetigo may also play a role in the pathogenesis of ARF, changes to primary prevention strategies which currently focus on GAS pharyngitis would need to be made.

Future possibilities for prevention

Clinical trials for an effective GAS vaccine have been conducted, as this would prevent GAS infection and thus the development of ARF and RHD. [9] Although multivalent M type specific vaccines have shown evidence of safety and immunogenicity, they may have limited efficacy due to the existence of numerous rheumatogenic M protein serotypes. [11,17]

Conclusion

It is evident that RHD poses as a pertinent issue across certain populations in developing and developed countries, including Australia. Hence, it is a disease that is of relevance on a global level. This review investigates the primary, secondary and tertiary prevention strategies that are most beneficial for RHD. It also outlines the pathophysiology of RHD to aid with the understanding of how the disease occurs and progresses as well as to emphasise the magnitude of the problem by examining its epidemiology. Treatment of RHD has not changed significantly over the past fifty years; however, the current treatment of streptococcal infections should remain while other strategies are being trialed. It is essential for research to continue in this area,

particularly for the development of a cost-effective vaccine, in order to greatly reduce the burden of RHD globally.

Conflict of interest

None declared.

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