ARTERIAL STIFFNESS ASSESSMENT IN ACUTE RHEUMATIC FEVER; A PILOT STUDY.

By

DR. HAYATI JAAFAR
MBCHB

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LIST OF ABBREVIATIONS

ARF	acute rheumatic fever
RHD	rheumatic heart disease
WHO	world health organization
PWV	pulse wave velocity
AIx	augmentation index
PSRA	post streptococcal rheumatoid arthritis
BMI	body mass index
ESR	erythrocyte sedimentation rate
CRP	c-reactive protein
VCAM-1	vascular cell adhesion molecule-1
FS	fraction shortening
IVS	intraventricular septum
ECG	electrocardiography
HLA	human leucocyte antigen
IL	interleukins
IMT	intima media thickeness

MMPs	matrix metalloproteases
TIMPs	tissue inhibitorsof MMPs
ROS	reactive oxygen species
TNFα	tumour necrosis factor alpha
NO	nitric oxide
SBP	systolic blood pressure
DBP	diastolic blood pressure
Th	T helper cell

ABSTRACT

Background and objectives:

Acute rheumatic fever and it sequelae rheumatic heart disease continue to be a significant health issue in developing country. The pathogenesis of this disease remains elusive but most accepted hypothesis is molecular mimicry triggered by streptococcal infection. Abnormal host immune response triggers cascade of immunological reaction leading to multi-organ inflammatory reaction causing its clinical manifestations. In recent years, many studies have been done to look at the risk factor for increase in arterial stiffness in children including inflammatory condition namely Kawasaki disease. Recent studies showed that Kawasaki disease has been associated with increase in arterial stiffness. We postulated that acute rheumatic fever which also associated with endothelial inflammation may cause increase in arterial stiffness in children. Having to establish this, future prediction of cardiovascular risk can be made and tackled appropriately as increase in arterial stiffness may lead to premature atherosclerosis. To our knowledge, there was no previous study done looking at arterial stiffness in rheumatic fever.

Methodology:

We conducted a prospective pilot study where we investigated arterial stiffness in patients with acute rheumatic fever with or without carditis and compared them to healthy controls. The assessment of arterial stiffness was by measuring the pulse wave velocity and augmentation index derived from pulse wave analysis. These measurements were done by

doing spyghmoCor assessment. There have been no previous studies using spyghmoCor to assess arterial stiffness in rheumatic fever. All data were analysed and expressed as median (interquartile range). A p-value of 0.05 was considered as statistically significant.

Results:

There were total of thirty-eight patients recruited for arterial assessment. Seventeen patients were included in rheumatic fever without carditis group; six patients were in rheumatic fever with carditis group and fifteen participants in the control group. All were between ten to sixteen years old. There was no significant different noted in pulse wave velocity comparing all three groups. We noted that the augmentation index were higher in rheumatic fever with carditis and rheumatic fever without carditis as compared to the control group. However these differences were not statistically significant. This study also showed that there was significant reduction of pulse wave velocity comparing acute phase of acute rheumatic fever to the chronic phase in the rheumatic fever with carditis group. This evolution of aortic stiffness was associated with resolution of inflammatory process evidence by reduction in inflammatory markers namely erythrocyte sedimentation rate (ESR).

Discussion:

This study showed that rheumatic fever with carditis patients have increase in arterial stiffness which occurs transiently. The temporary phenomenon is similar to many of other clinical features of acute rheumatic fever namely Sydenham chorea, erythema marginatum

and arthritis. As this is a pilot study, further investigation need to be done to clarify our findings.

ABSTRAK

Pengenalan dan objektif:

Demam reumatik akut dan penyakit jantung reumatik terus menjadi agenda kesihatan yang utama di negara-negara membangun. Patogenesis kepada penyakit ini masih belum diketahui secara sah dan terperinci tetapi hipotesis yang semakin diterima ramai adalah teori 'molecular mimicry'. Berdasarkan kajian yang dijalankan sebelum ini, teori ini mengandaikan bahawa penyakit demam reumatik akut adalah disebabkan oleh tindakbalas sistem immuniti badan yang tidak normal kepada serangan jangkitan kuman 'streptococcus'. Tindakbalas immuniti badan ini seterusnya menyebabkan rantaian tindakbalas immuniti yang mengakibatkan randangan di dalam pelbagai organ badan dan menyebabkan manifestasi penyakit demam reumatik akut.

Akhir-akhir ini, banyak kajian telah dilakukan untuk melihat factor-faktor risiko kepada ketegangan urat darah 'arterial stiffness' dikalangan kanak-kanak termasuklah factor penyakit radangan seperti penyakit 'Kawasaki'. Kajian sebelum ini menunjukkan bahawa penyakit 'Kawasaki' boleh menyebabkan ketegangan urat darah. Kami mengandaikan bahawa penyakit demam reumatik akut juga boleh mengakibatkan kesan yang sama kerana penyakit demam reumatik akut juga melibatkan radangan sel endothelium urat darah.

Dengan melihat kaitan antara ketegangan urat darah dan penyakit demam reumatik akut ini, kami boleh menjangkakan risiko pembentukkan aterosklerosis pramatang kerana ketegangan urat darah boleh menyebabkan fenomena ini. Menurut pengetahuan kami, tiada

kajian sebelum ini yang melihat kaitan antara demam reumatik akut dan ketegangan urat darah.

Prosedur kajian:

Kami telah menjalankan kajian awal melihat kaitan antara ketegangan urat darah dengan penyakit demam reumatik akut yang melibatkan keradangan jantung atau tanpa melibatkan kerandangan jantung. Kami membandingkan ketegangan urat darah pesakit-pesakit ini dengan individu-individu yang sihat.

Kajian tahap ketegangan urat darah dilakukan dengan menilai kelajuan gelombang nadi 'pulse wave velocity' dan indeks augmentasi yang didapati dari analisis gelombang nadi. Nilai-nilai ini didapati dengan melakukan ujian 'spyghmoCor' keatas pesakit. Setakat ini, tiada kajian sebelum ini yang menggunakan ujian 'spyghmoCor' untuk menganalisa ketegangan urat darah di dalam kes demam reumatik. Setiap data dianalisa dan dicatatkan sebagai 'median (interquartile range)'. Nilai statistik p kurang daripada 0.05 adalah dianggap meyakinkan.

Keputusan:

Terdapat tiga puluh lapan pesakit yang menjalani ujian tahap ketegangan urat darah ini. tujuh belas pesakit adalah di dalam kategori demam reumatik akut dengan keradangan jantung, enam orang adalah di dalam kategori demam reumatik akut tanpa keradangan

jantung dan lima belas sukarelawan di dalam kategori individu sihat. Semua yang terlibat adalah berumur diantara sepuluh hingga enam belas tahun.

Tiada perbezaan yang ketara mengenai ujian nilai kelajuan gelombang nadi ' pulse wave velocity' bilamana tiga kumpulan ini dibandingkan. Kami mendapati bahawa indeks augmentasi bagi kumpulan demam reumatik akut dengan keradangan jantung mahupun tanpa keradangan jantung adalah lebih tinggi berbanding dengan individu-individu yang sihat. Walaubagaimanapun, perbezaan ini tidak ketara secara statistiknya. Kajian ini juga menunjukkan bahawa terdapat pengurangan yang ketara dengan nilai kelajuan gelombang nadi bilamana ia dibandingkan di antara fasa akut penyakit reumatik dengan fasa kroniknya. Perubahan ini dilihat setara dengan resolusi proses keradangan seperti yang dilihat dengan penurunan penunjuk keradangan 'erythrocyte sedimentation rate' (ESR).

Perbincangan:

Kajian ini menunjukkan bahawa pesakit penyakit demam reumatik akut samada dengan keradangan jantung atau tanpa keradangan jantung, mungkin menghidap komplikasi ketegangan urat darah yang sementara. Fenomena yang sementara ini dilihat setara dengan manifestasi klinikal yang lain termasuk penyakit saraf 'sydenham chorea', ruam 'erythema marginatum', dan radangan sendi. Memandangkan kajian ini adalah kajian awal mengenai penyakit demam reumatik akut dan ketegangan urat darah, kajian lanjutan perlu dibuat untuk memastikan semula penemuan kami.

INTRODUCTION

CHAPTER 1

INTRODUCTION

Acute rheumatic fever (ARF) and its sequel of chronic valvular rheumatic heart disease (RHD) remains a major public health problem in developing countries and imposes a considerable burden of morbidity and mortality affecting young adults in these countries including Malaysia.

The diagnosis of rheumatic fever is based on combinations of clinical manifestations and laboratory evidence of previous streptococcal infection based on modified Jones criteria 1992 and WHO criteria (2003). There is no definitive laboratory test for rheumatic fever.

The clinical profiles and echocardiography of patients presenting with rheumatic fever in developing countries has been suggested to be different as supposed to developed countries (Agarwal and Agrawal, 1986). This is likely due to different socioeconomic background with poor access to medical care, poor nutrition and overcrowding population leading to more severe presentation of rheumatic fever. The threshold in diagnosing rheumatic fever is indeed lower in developing countries as compared to developed countries (Carapetis and Currie, 1996).

The pathogenesis of acute rheumatic fever is still unknown; however, immunological and epidemiological evidence clearly implicates the group A β-hemolytic

streptococcus in the initiation of the disease (Guilherme *et al.*, 2006). Outbreaks of ARF usually follow epidemics of streptococcal pharyngitis. Molecular mimicry theory holds that antibodies directed against group A streptococci cross-react with host tissue leading to cascade of inflammatory processes and its clinical manifestation (Fae *et al.*, 2006).

The development of pressure sensitive tonometer and high-resolution ultrasound technique has given the advantange in non-invasive assessment of arterial stiffness in the pediatric population (Aggoun *et al.*, 2005). Arterial stiffness can be measured using the pulse wave velocity (PWV) and augmentation index (Oliver and Webb, 2003). PWV measures the velocity of the pressure wave along a specific arterial segment. The velocity of the pressure wave along the artery is dependent upon the stiffness of the artery. Aortic augmentation index (AIx) is another parameter used to assess arterial stiffness. It is obtained by performing pulse wave analysis. Stiffer artery will results in faster pulse wave velocity and higher augmentation index.

In recent years there is growing interest looking at risk factors associated with parameters arterial stiffness in children. Among them is Kawasaki disease where the pathogenesis is believed to involve immunological process. Studies showed that Kawasaki disease is associated with increased arterial stiffness (Cheung *et al.*, 2004; Schack-Nielsen *et al.*, 2005; Senzaki *et al.*, 2005). To my knowledge, there is no studies has been done to look at the association of rheumatic fever with arterial stiffness. In this pilot study, we investigated the arterial stiffness of patients with rheumatic fever, as rheumatic fever is also caused by inflammatory process much like Kawasaki disease.

LITERATURE REVIEW

CHAPTER 2

LITERATURE REVIEW

2.1 RHEUMATIC FEVER

2.1.1 Epidemiology

A previous study in General Hospital Kuala Lumpur (GHKL) had looked at the cardiothoracic surgical burden (which had indirectly assessed what morbidity rheumatic heart disease had imposed to the nation's health). In this review of open-heart operations carried out from April 1982 until February 1987, it was noted that valvular surgery made the largest group accounting for 303 out of 1110 cases, and almost all the valvular lesions were caused by rheumatic heart disease (Awang *et al.*, 1987). Rheumatic heart disease accounted for 20.6% of cardiology cases in GHKL (Jamal *et al.*, 1994). While another study also revealed the morbidity this disease had imposed to the population of kelantan; of all new referrals to adult cardiac clinic in Hospital Sains Malaysia between 1991 until 1992, the commonest diagnosis made was rheumatic valvular heart disease (Ibrahim and Rahman, 1995). Mortality rate due to rheumatic heart disease from the WHO figures are 233,000 deaths each year (Carapetis and Currie, 1996). This is probably under reported because of poor collection of audit cases from some countries in the world.

Despite significant morbidity and mortality rheumatic fever can impose, sadly the incidence of this disease has remains significant in developing countries. According to the

World Health Organization (WHO) about 0.5 million individuals acquire acute rheumatic fever each year and most are in developing countries where the incidence of acute rheumatic fever exceeded 50 per 100,000 children (2004). It is primarily a disease of children and adolescents. First attacks are uncommon in the very young (under the age of 5 years) with the peak incidence occurring in those aged five to fifteen with a decline thereafter and are rare in adults over the age of 35 years. Recurrent attacks are most frequent in adolescence and young adulthood and are diagnosed infrequently after the age of 45 years.

A study in University Malaya between January 1981 to December 1990 reported the incidence of ARF of 21.2/ 100,000 pediatric admissions per year (Omar, 1995). In Kelantan, a study done from January 1987 to June 1994 documented a total of 158 hospital admission with diagnosis of ARF (Ibrahim and Rahman, 1995). The documented age range was from 1 year to 35 years old with the peak incidence between aged 6 to 15 years old. This study also showed that male and female were equally affected. A Prevalence study of rheumatic heart disease in Kelantan between august 1988 to December 1990, had a prevalence rate of 11 per 100,000 children (Ibrahim and Rahman, 1995). Much higher rates of 80–500 per 100,000 children have been documented in careful studies in the indigenous populations of Australia and New Zealand (Carapetis and Currie, 1997)

Environmental factors also have been implicated for the reason of high incidence and prevalence of rheumatic fever including malnutrition, poor hygiene, overcrowding population and poor access to medical care (1992b; 2004).

2.1.2 Diagnosis

The diagnosis of rheumatic fever are based on both clinical manifestations and laboratory evidence of streptococcal infection based on modified Jones's criteria 1992 and WHO criteria 2003. There is no definitive laboratory test for ARF. (1992a; 2004)

Criteria for diagnosis of acute rheumatic fever are divided into major criteria and minor criteria. Major criteria are carditis, arthritis, chorea, erythema marginatum and subcutaneous nodules. Minor criteria are arthralgia, fever, raised inflammatory markers include erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), and prolonged PR interval in ECG.

The diagnosis of first episode rheumatic fever based on modified Jones criteria requires two major criteria or one major and two minor criteria, together with evidence of antecedent group A β-streptococcal infection. Evidence of preceding streptococcal infection can be demonstrated by increase or rising anti-streptococcal antibodies or a positive throat swab culture for group A β-hemolytic streptococci (1992a).

There has been concern that strict application of the Jones criteria may result in under-diagnosis particularly in the case of recurrent episodes and in area where the incidence rate is high as in developing country (2004). During recurrence of rheumatic activity in a patient with pre-existing RHD, the carditis may present as heart failure but diagnosis of rheumatic fever may be difficult due to lack of information on previous cardiac findings or because of valve replacement surgery has been performed. Thus, WHO has

suggested new recommendation in making diagnosis of rheumatic fever (2004). WHO criteria stated that; in the present of Chorea and indolent carditis, diagnosis of ARF does not require other criteria or evidence of antecedent group A streptococcal infection. For the diagnosis of recurrent episode of ARF without established rheumatic heart disease, the diagnosis is made as for first episode of ARF. For the diagnosis of recurrent episode of ARF with establish rheumatic heart disease; it only requires two minor manifestations with evidence of antecedent streptococcal infection. Some authors have also suggested that it is acceptable for clinical judgment to be used and to supersede guidelines especially in areas where ARF remains very common (Carapetis *et al.*, 2005).

2.1.3 Clinical Manifestations and laboratory investigation

Carditis is the most important component of t he disease in determining the prognosis. Clinical manifestations may vary. It may present with heart failure, cardiac murmur without heart failure or pericardial effusion without much of valvular involvement. Pericarditis may manifest as pericardial pain and pericardial rub on auscultation. Auscultation may reveal new murmur or changing murmurs. The commonest valvular lesion is mitral regurgitation manifested as an apical pan-systolic murmur. Other valvular lesions are aortic regurgitation and tricuspid regurgitation, or a combination for example mitral and aortic regurgitation. Stenotic lesions are uncommon in the early stage of the disease. Severe carditis may lead to life-threatening heart failure (Carapetis *et al.*, 2005).