

Clinical Spectrum and Considerations of Rheumatic Fever and Rheumatic Heart Disease: Call for National Disease Prevention and Control Programme in Saudi Arabia

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Abstract: Rheumatic fever (RF) and its sequel rheumatic heart disease (RHD) are considered to be preventable chronic diseases; however, they are still epidemic in developing countries. This study was designed to collect the clinical details and compliance with treatment from patient in the Northwest region in Saudi Arabia. Clinical records from patients referred to the paediatric cardiology unit between 2004 and 2016 were reviewed. The demographic, sociodemographic, clinical data, echocardiography and laboratory data were collected. A total of 297 children with RF/RHD were identified. Complete medical record was found for 248 patients. Of these, 86 patients with RF and 162 with RHD. RHD referrals are more from rural compared to urban areas. Arthritis was the major manifestation in RF group (69%), while carditis was the major manifestations in the RHD group (66%). Mitral regurgitation was the most common valvular lesions among RHD cases (42%). Compliance with secondary prophylactic treatment was found to be 43%. Family history of RHD was noted in 7 cases, which represent 4.3%. RF/RHD is still a burden in Saudi Arabia especially in rural areas and cause of hospital admissions. An initiative for control and prevention of RF/RHD, including public awareness activities, is needed across the country.

Keywords: RF; RHD; epidemiology; disease control & prevention; Saudi Arabia

Date of Submission: 20-02-2019

Date of acceptance: 06-03-2019

I. Introduction

Group A streptococcal (GAS) infection is the most common childhood illness, [1] which is associated with acute inflammation leading to an autoimmune disease, rheumatic fever (RF). [2] Recurrent episodes of RF with sustained and persistent inflammatory process cause heart valvular damage and lead to rheumatic heart disease (RHD) [3]. Even though standard antibiotic treatments are available, RHD is still one of the most common sources of acquired heart disease in young adults and children in many developing countries [4,5].

RF is presented with a range of symptoms, with a latency period of 2–5 weeks after the initial episode of infection. RF is manifested as a group of symptoms such as musculoskeletal, cardiac and neuropsychiatric [3]. The first presentation and the most common symptom of RF is arthritis. It is presented in 60–80% of the patients [6]. Knees, ankles, elbows, and wrists are mostly affected [7]. Patients may also be presented with a non-specific symptoms such as; elevated inflammatory markers, fever, abdominal pain and anaemia [6]. Sometimes, RF patients have asymptomatic episodes, and hence exposing the patients to develop more sever RHD [6].

Carapetis et al. estimated that, on a global scale, upper respiratory tract infection by GAS is among the most common human pathogens that cause morbidity and mortality and only exceeded by HIV, TB, and malaria [8]. Therefore, RHD has been recognized as a neglected tropical disease by World Heart Federation (WHF) [9] and the World Health Organization (WHO) [10]. Worldwide 50% of patients with RF exhibit carditis presented as valvulitis, pericarditis and myocarditis [3]. All of RF manifestations are tent to resolve except valvular damage which is permanent and significantly contribute to the morbidity and mortality of the disease [11].

During the last century great efforts from the WHO in collaboration with different countries was put to increase awareness and improve prevention strategies, which leads to significant decrease in the incidence of RF and RHD in developed countries. However, in Saudi Arabia, until now there is no prevention and control program in the country. In 1990, Al-Sekait et.al. assessed the prevalence of RHD among 9,418 school children in Western district of Saudi Arabia [12]. This cohort underwent full clinical and cardiac examination. They reported the prevalence of RHD in this cohort is 2.4 per 1000 children aged 6-15 years old. A decade later, a hospital based study from the capital Riyadh, covers period between 1994–2003, found that despite the progress made in the socio-economic development in Saudi Arabia, RF/RHD is still a serious complication especially in the rural area where medical attention and medical care is less [13]. Therefore the present study was designed to

update information on the frequency and pattern of RF/RHD patients, to verify the sociodemographic profile and compliance with treatment in the Northwest district region and compare it with other national and international data.

II. Materials and Methods

This study was conducted at Taibah University, Madina Maternity and Children Hospital (MMCH), Al-Madina, Saudi Arabia. MMCH is the main referral hospital for Northwest of Saudi Arabia and hosts the only paediatric cardiology clinic in the region. More than 300 small villages and 7 cities surround Al-Madina city in the Northwest Saudi Arabia. The study has two parts, retrospective from 2004 to 2012 and a prospective part from 2013 to 2016. The Maternity & Children Hospital ethics committees approved the study, and the authors followed the norms of the World Medical Association Declaration of Helsinki. All adult patients or their guardians (<18 years old) signed consent form approved by the committees.

RF/RHD diagnosis was based on evidence of recent streptococcal infection and according to the modified Jones criteria [14], which includes the major criteria, such as arthritis, carditis, subcutaneous nodules, erythema marginatum and chorea. The minor criteria includes high fever, high erythromycin sedimentation rate (ESR), C-reactive protein (CRP) and prolonged PR interval. Full clinical assessment and laboratory investigation were performed. Patients with high CRP, more than 20 (mg/L), and high ESR, more than 22 mm/hr for men and 27 mm/hr, were considered to have elevated acute phase reactants (APR). All patients underwent two-dimensional (2D) and Doppler echocardiography examination. Exclusion criteria were patients with other inflammatory conditions or heart complications. Sociodemographic information was collected from the clinical record or by direct phone call to patients or their guardians. Patients who did not miss more than one monthly prophylaxis injection per year were considered as compliant patient [15].

Statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS) version 17 (IBM Statistics, Chicago, IL, USA). Categorical variables were presented as the number and percentage and summarized in frequency tables. The appropriate chi square or Fisher's exact test was used.

III. Results

This section may be divided by subheadings. It should provide a concise and precise description of the experimental results, their interpretation as well as the experimental conclusions that can be drawn.

3.1. Incidence and demographics

During the 12-year period, a total of 276 children and adolescent with RF and RHD were referred to the Paediatric Cardiology unit at Children and Maternity Hospital from different hospitals in the Northwest district of Saudi Arabia. Of those, a complete medical record was found for 248 patients. Also, socioeconomic data was available for only 186 patients. The mean of age at diagnosis (age of onset) was 6.7 ± 2.2 years for RF and 7.9 ± 2.4 years for RHD. Age of last follow up was 17 ± 4.1 for RF and 19 ± 4.8 for RHD (Table 1). Males represented with slightly more but the difference was not significant in both groups, with 52% in RF group and 53% in RHD group (Table 1). Interestingly, referrals from rural areas were more than from urban in RF group, with 58% and 42% respectively. Similarly, RHD referrals are more from rural than urban areas, with 64% and 36% respectively (Table 1). We also studied the socioeconomic status for our patients and found that 48% of RHD referrals are form poor socioeconomic background and 34% of RF from the same group. We have found seven familial cases that have more than one individual affected with RHD in the same family.

Table 1: Sociological and demographic characteristics of rheumatic fever and rheumatic heart disease

	RF (N= 86)		RHD N=(162)	
	Count	%	Count	%
Gender				
Males	45	52	86	53
Females	41	48	76	47
Place of residence	(n=69)		(n=130)	
Urban	29	42	47	36
Rural	40	58	83	64
Socioeconomic status	(n=65)		(n=121)	
High	10	15	12	10
Middle	33	51	51	42
Poor	22	34	58	48
Mean age (mean \pm SD years)				
Age of onset at diagnosis	6.7 ± 2.2		7.9 ± 2.4	
Age at last follow-up	17 ± 4		19 ± 5	

3.2 Major clinical manifestation

A summary of the major clinical manifestations in our cohorts is shown in Table 2. Arthritis was the major manifestation in RF group (69%), while carditis was the major manifestations in the RHD group (66%). Sydenham chorea was presented in 14 patients with RF (16%) and 16 patients with RHD (10%). The duration of chorea ranged from one to five months. Erythema marginatum and subcutaneous nodules were rare events in both RF and RHD groups (Table 2).

Table 2: Major clinical manifestations

Manifestations	RF cases (n=86)	%	RHD cases (n=162)	%
Carditis	32	37	107	66
Arthritis	59	69	94	58
Chorea	19	22	26	16
Skin rash	6	7	5	3
Subcutaneous nodules	4	5	3	2

3.3 Minor clinical manifestations

The minor clinical manifestation of RF and RHD that were present are summarized in Table 3. There was no significant difference in minor clinical manifestations between the RF and RHD cohorts. High grade fever was reported in 57 RF patients (66%) and in 102 RHD patients (63%). Prolonged PR interval (more than 0.16s on ECG) was seen in 27 RF patients (31%) and in 58 RHD patients (36%). Raised erythrocyte sedimentation rate was reported in both RF and RHD groups as 78% and 76% respectively. Elevated C-reactive protein was found in 46.5% of RF patients and 49% of RHD patients (Table 3).

Table 3: Minor clinical manifestations

Investigations	RF cases (N=86)	%	RHD cases (N=162)	%
Fever	57	66	102	63
Prolonged PR interval (>0.16 s on ECG)	27	31	58	36
Raised erythrocyte sedimentation rate	67	78	123	76
Elevated C reactive protein	40	46.5	79	49

3.4 Classification of valvular heart lesions in RHD

There were 162 patients registered as having been diagnosed with RHD between 2004 and 2016. Echocardiography findings were available for 153 patients. Table 4 summarize the valvular heart lesions classification in RHD patients. Isolated valve lesions were found in 64 patients (42%) and the commonest lesion was mitral regurgitation (MR). Aortic Regurgitation (AR) and mitral stenosis (MS) were found less common, 11% and 6.5% respectively (Table 4).

Table 4: Classification of valvular heart lesions in rheumatic heart disease (RHD) patients (n =153)

Type of lesion	Count	%
Mitral regurgitation (MR)	64	42
Aortic regurgitation (AR)	17	11
Mitral stenosis (MS)	10	6.5
MR+AR	45	29.5
MR+MS	14	9
MR, MS, Tricuspid Regurgitation	3	2

3.5 Treatment

Isolated arthritis or carditis was treated with aspirin in most cases (79%). Prednisolone and aspirin was used for all sever carditis and heart failure. In line with our practice, Benzathine Penicillin injection was given once monthly as secondary prevention in most cases. Oral antibiotics were used in remaining cases. However, patients compliance with secondary prophylaxis were only 43%. Sydenham chorea cases were treated with Valproic acid and haloperidol.

IV. Discussion

There are few studies regarding the clinical spectrum of RF and RHD from Saudi Arabia, however, this is the largest hospital based study conducted at the only paediatric cardiology clinic that covers the Madina city and the surrounding villages, hence providing data on the spectrum and the frequency of RF and RHD in the Northwest region of Saudi Arabia. Such data has substantial implications for future management and control of RF and RHD in the country. In our 12-year hospital based study we identified 276 RF/RHD cases. Al-Qurashi [13] did similar study and identified 112 acute RF patients admitted to Suleimania Children's Hospital, in the capital Riyadh, during the period of 1994–2003. In addition, we observed a reduction in respect to age of onset for RF patient (6.7 years), which is less than the mean age reported by other studies from Saudi Arabia. We

believe that the apparent high incidence rate reported in younger children in our region is more likely due to improved recognition of RF/RHD, especially the use of echocardiography examination in recent years as a diagnostic tool for RHD [16]. In addition, our paediatric cardiology unit, as the only unit in the region, receives referrals from all Northwest districts in Saudi Arabia, which has more rural areas compared to the capital city Riyadh. These rural areas are still in need for more clinical attention and care. Also, we noticed that there is no significant difference in proportions of male and female patients. This is in contrast to other findings of several studies where more female patients were reported [17]. However, study from India reported higher male proportion, [18] therefore, its gender difference is still not obvious in the disease.

Clinical manifestations in our cohorts are almost comparable to findings from worldwide reports, especially hospital based studies. In our RF group we reported 69% arthritis and 37% carditis. We reported higher carditis in our RHD group 66%, which is similar to study from the Southern region in Saudi Arabia, [19] and in a cohort from Riyadh [13]. However, recent study from India reported less carditis rate compared to studies from Saudi Arabia [18]. Our study was conducted in the main paediatric cardiology clinic in the region. Therefore, as highly specialized tertiary center we receive more complicated cases with heart involvement. Among children with RHD, the commonest isolated valvular diseases were mitral regurgitation and aortic regurgitation. This profile is similar to national and international published data [4]. However, in some studies such as from India and Ethiopia, mitral stenosis is the most common valvular disease [18,20]. The reason for the discrepancy between populations is still unknown; however, environmental and genetic factors may play a role in the predispositions to valvular diseases in RHD. Sydenham Chorea was present 22% and 16% in RF and RHD groups respectively, which is similar to worldwide studies ranging from 8.8% in Africa to 28% in Brazil [4]. Regarding the minor Jones criteria, the frequencies of fever, elevated CRP and elevated ESR in our groups were in line with previous findings by others [4].

Family history of RHD was noted in 7 cases, which represent 4.3% in this study. RHD has been found to occur frequently in more than one individual in an affected family (some cases). Interestingly, a meta-analysis of twin studies found that heritability in rheumatic fever is around 60%, [21] which is higher than some other well characterized autoimmune diseases. [22] The involvement of genetic factors underlying RHD became more evident when several studies reported the association of the disease with different genes including human leukocyte antigen (HLA) and non-HLA genes [23,24]. The most commonly reported allele is HLA-DR7 in Mediterranean and Asian populations [23]. HLA-DR4 was reported in Caucasian-Americans and HLA-DR2 in African Americans [23]. To date, there is no genetic investigation conducted to elucidate the role of HLA alleles in Saudi RHD patients, except for one serological study published in 1987 which associates HLA-DR4 with the disease [25]. However, this association could not be replicated by a molecular study published in 1997 [26]. Non-HLA association, especially with immune genes have been reported from different populations. We found association with ACE, IL10 and MIF genes with RHD patients from Saudi Arabia [27–29]. Also, we found that different valvular diseases are associated with different genes [30]. Data on RHD genetic predisposition is scarce and requires continued research efforts to elucidate high risk individuals for better prevention strategies.

Compliance with secondary prophylaxis was only 43% among our RF and RHD patients. This rate indicates that over 50% of RF history patients may be at risk to develop RHD. High level of compliance is required for successful secondary prophylaxis outcome [31]. In six-study meta-analyses it was concluded that treatment of streptococcal pharyngitis in schools and community clinics with Penicillin could reduce expected acute RF cases by about 60%. [32] A nurse-led RF secondary prophylaxis programme from New Zealand reported 79 – 100% level of adherence in three different centres [33]. This high level of adherence was achieved by community health workers. A study from Jamaica reported only 48.7% adherence which is similar to our finding [34]. In Australia, a national consortium of researchers launched END RHD CRE (End RHD Center for Research Excellence) at the University of Sydney in August 2015 [35]. Their mission is to eliminate RF/RHD as a devastating disease among Australian people. Similar programmes were launched in Africa and other countries [17]. In Sept 2014 a global movement, called RHD Action, was established under WHF and WHO with aims to minimize RF/RHD mortality worldwide by the year 2025 (<http://rhdaction.org/>).

Worldwide economic constraints are the main obstacle for successful prevention and control programmes [17]. However, in the current study it was obvious that rural areas and poor understanding and knowledge are the main factors. Studies examining health literacy among our patients and their parents and level of community awareness is immediately required across the country. Moreover, establishing a regional register for RF/RHD will allow for better follow up and disease management. In addition, high level of awareness among primary healthcare providers is needed.

This is a cross sectional hospital based study of children referred to tertiary paediatric cardiology clinic in Al-Madina, Saudi Arabia. Being a hospital study, it may not represent the true prevalence of the disease in the country. Also, as our hospital covers a large area of small villages, there could be bias in the children profile who

could reach the hospital. Although our cohort is small, it is the largest RF/RHD cohort reported from Saudi Arabia with detailed cardiac assessment.

V. Conclusions

In conclusion, RHD is still the major acquired heart disease in Al-Madina region. This study highlight the need to create national movement supported by the government and private initiatives to establish a successful RF/RHD prevention and control programme with international cooperation with WHF and WHO. The programme should focus on education and secondary prophylaxis.

Author Contributions: KMA reviewed the clinical records, collected data, performed statistical analysis and wrote the manuscript.

Funding: Please add: This research was supported by Deanship of Research & Higher Education, Taibah University.

Acknowledgments

The author is grateful to all nurses who helped in collection patients data. I gratefully acknowledge the help from Dr Atiyeh M. Abdallah and Dr Mohamed M. Morsy for reviewing the manuscript.

Conflicts of Interest: The author declares no conflict of interest.

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Khalid Al-Harbi. “Clinical Spectrum and Considerations of Rheumatic Fever and Rheumatic Heart Disease: Call for National Disease Prevention and Control Programme In Saudi Arabia.” IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), vol. 18, no. 3, 2019, pp 37-42.