



Acute rheumatic fever in children: Experience at the hospital Hassan II of Fez, Morocco



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ABSTRACT

Problem considered: Acute rheumatic fever (ARF) is a major problem of public health in developing countries like Morocco. This study was done to find out the clinical manifestations and laboratory features of patients with ARF in Fez city.

Methods: A retrospective study was conducted from 2009 to 2015 in the pediatric ward of the university hospital Hassan II of Fez. A total of 209 children (< 18 years) diagnosed ARF, based on modified Jones criteria, was included.

Results: The mean age of ARF cases were 11 years. The sex ratio male/female was 0.9. The most represented age class was the class between 5 and 15 years. Unschooled represented 2.9% and the most found was the primary level school (58.9%). Urban residence was found in 84.2% of cases and the majority of patients with and without carditis were admitted in winter and autumn respectively. Cases of ARF with carditis was documented in 53.1% and without carditis in 46.9%. In the two groups, arthritis was the major criterion most represented and arthralgia was the minor criterion most represented. History of sore throat was found in ARF with carditis cases (51.3%) more than ARF without carditis cases (35.7%). Penicillin A was the most antibiotic prescribed in the two groups. Commonest valvular lesions among ARF with carditis cases was mitral regurgitation (62.1%). There were 3 deaths among cases in this group.

Conclusion: ARF continues to occur in Morocco, despite the progress made in the socioeconomic development of the country, often associated with severe cardiac involvement.

1. Introduction

Acute rheumatic fever (ARF) is a major problem of public health in developing countries, because of the high prevalence of its main complication, rheumatic heart disease (RHD). According to the world health organization (WHO), between 15.6 and 19.6 million people have RHD in the world with 282000 newcases and 233000 deaths each year are directly attributable to ARF or RHD.^{1,2} In Morocco, around 4921 new cases of rheumatic heart disease are recorded in 2013.³ While in the developed countries, the current incidence of this pathology is weak, it's less than 2/100,000.⁴

The Jones criteria (arthritis, carditis, fever ...), represent the clinical standard to establish the diagnosis of acute rheumatic fever.^{5–7}

The most common risk factors among ARF cases in developing countries are poverty, undernutrition and overcrowded homes.⁸ For

the prevention of ARF and especially heart damage, a long-term managed with regular penicillin injections should be practice.^{1,9,10}

No studies have been conducted about the acute rheumatic fever and chronic rheumatic heart disease among children in Morocco. The purpose of this study is to describe the clinical manifestations and laboratory features of patients with ARF in Fez city.

2. Methods

2.1. Study design and setting

We conducted a retrospective study in the pediatric ward of the hospital Hassan II of Fez from January 1, 2009 to December 31, 2015. We included patients less than 18 years who diagnosed acute rheumatic fever based on Jones criteria.

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The data of patient were collected from the medical records and HOSIX software. The values of some variables, like erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level are not specified in all cases.

2.2. The jones criteria

It's divided into majors and minor criteria and evidence of recent streptococcal infections. The major ones being: polyarthrits, carditis, chorea, subcutaneous nodule. While the minor criteria consisted of arthralgia, fever, high ESR and/or CRP, and prolonged PR interval (11). For the acute rheumatic fever, diagnosis is recorded if 2 majors or 1 major criterion and 2 minor criteria associated with evidence of recent streptococcal infection: ASO elevated.¹¹

2.3. Participants and samples

We collected socio-demographic variables: gender; the age that we grouped in 3 classes (< 5 years; between 5 and 15 years and > 15 years); educational level (unschooling, koranic, primary, and secondary); residence (urban or rural); season (spring, summer, autumn and winter). Clinical data and health status: history of sore throat; jones criteria; prescription of antibiotics; prescription of penicillin; prescription of aspirin; prescription of non-steroidal anti-inflammatory drugs (NSAIDs); prescription of corticosteroids. Various laboratory investigations such as complete blood count; erythrocyte sedimentation rate (ESR); C-reactive protein (CRP) level, antistreptolysin O (ASO) dosage (categorized into normal, moderate and high according to age) were undertaken either on day 0 or day 1. Echocardiography (GE Vivid 7 Dimension Ultrasound, USA) was performed on all the patients by day 3 and interpreted by the cardiologist specifically trained in pediatric echocardiography.

2.4. Data management and analysis

Data entry was done using excel. The socio-demographic characteristics and clinical manifestations and laboratory features of the sample were described. The chi-square and the T student test were used to study the association between ARF with and without carditis and variables of interest. The logistic regression was performed with ARF as the dependent variable. The explanatory variables were age, season and residence. Odds ratio (OR) with 95% confidence interval (95% CI) was determined for each variable. A $P < 0.05$ was considered as significant. Analyses were performed using the Epi-info software (version 7) elaborated by the United States Centers for Disease Control. Statistical tests were considered significant if the p value was less than 0.05.

2.5. Ethics

The approval of the hospital-university ethics committee of Fez has been obtained in May 2016 from the responsible of ethics committee professor. Hida Moustafa.

3. Results

During the 7- year period, the staff at hospital Hassan II of Fez admitted a total of 209 cases with a diagnosis of ARF that satisfied the modified jones criteria. All full records of 209 were analyzed.

In our sample, men represented 46.9% and the sex ratio (male/female) was 0.88. The mean age of children was 11.07 ± 3.15 years. Age class most frequent was the age between 5 and 15 years. They represented 90.9% of our sample. Unschooling represented 2.9% and the most found was the primary level school (58.9%). Urban residence was found in 84.2% of cases and the majority of patients were admitted in spring. (Table 1).

Table 1
Demographic characteristics of ARF in 209 children.

Characteristic	No. of cases	% of Total
Gender		
Male	98	46.9
Female	111	53.1
Class age		
< 5 years	5	2.4
[5- 15] years	190	90.9
> 15 years	14	6.7
Season		
Autumn	47	22.5
Winter	56	26.8
Spring	67	32.1
Summer	39	18.7
Residence		
Urban	176	84.2
Rural	24	11.5
Education level		
Unschooling	6	2.9
Koranic	1	0.5
Primary	123	58.9
Secondary	71	34.0

The major criterion from jones criteria was carditis. It was present in 53.1% of cases. Arthritis was found in 11.5% and chorea was found in 4.3%. None patient presented subcutaneous nodules in our study (Table 2).

In minor criteria, the most frequent was arthralgia. It was presented in 56.0% of cases. Fever was found in 15.3%, a high ESR level in 28.7% of cases and a high CRP level in 10.5% of cases. The ASO was positive in 34.0% of cases (Table 2).

In polytherapy, the most medicines prescribed was penicillin A. It was prescribed in 61.7% of cases. Acetylsalicylic acid was prescribed in 4.3% of cases and the other NSAIDs in 2.4%. Corticosteroids were prescribed in 30.1% of cases. The other antibiotics were prescribed in 12.4% of cases (Table 2).

3.1. Acute rheumatic fever with carditis

They represented 53.1% of our sample. The mean of age was 11.1 ± 3.2 years and the sex ratio male/female represented 0.9. The most represented age class was the class between 5 and 15 years. They represented 91.0% of patients. Majority of hospitalization was in winter (34.2% of cases). The majority of patients of this group (81.9%) lived in urban residence. Most than half was in primary level school (55.9%). We found 51.3% history of sore throat in this group (Table 3).

The major criterion of the Jones criteria most represented in this group was arthritis. It was presented in 12.6% of cases. The minor criterion most represented was arthralgia (58.6% of cases) (Table 3).

ASO were elevated (> 200 UI/ml) in 36.9% of cases and raised ESR were found in the first hour in 34.2% (Table 3).

Penicillin A was the most prescribed (58.6%). Corticosteroids were prescribed in 38.7% of cases (Table 3).

Of the 111 children of ARF with carditis, isolated valve lesions were found in 79 (71.1%) of which the commonest lesion was mitral regurgitation (MR) (62.1%). MR with aortic regurgitation (AR) was found in 30 cases (27.0%).

Out of the 111 ARF with carditis cases, 10 cases (9.0%) underwent surgical correction for the valve lesions. This included mitral valve repair in six cases, aortic valve repair in one case, and mitral valve and aortic valve replacement in three cases. We deplore three deaths; One died due to a massif aortic insufficiency, one due to a massif mitral insufficiency and one due the Combined of massif mitral and aortic insufficiency. No children had recurrences in this group.

Table 2
Clinical characteristic of ARF in 209 children and treatment received.

Characteristic	Effective N = 209	% of Total
Clinical characteristics		
History of sore throat		
Yes	92	44.0
No	34	16.3
Carditis		
Yes	111	53.1
No	98	46.9
Chorea		
Yes	9	4.3
No	200	95.7
Arthritis		
Yes	24	11.5
No	185	88.5
Subcutaneous nodules		
Yes	0	0
No	209	100
Arthralgia		
Yes	117	56.0
No	20	9.6
Fever		
Yes	32	15.3
No	12	5.7
High ESR^a		
Yes	60	28.7
No	28	13.4
High CRP^b		
Yes	22	10.5
No	187	89.5
ASO positive titer^c		
< 200 UI/ml	7	3.3
200-600UI/ml	11	5.3
> 600UI/ml	60	28.7
Treatment received		
Penicillin A		
Yes	129	61.7
No	10	4.8
Acetyl salicylic acid		
Yes	9	4.3
No	200	95.7
Corticosteroids		
Yes	63	30.1
No	2	1
NSAIDs^d		
Yes	5	2.4
No	2	1
Other Antibiotics		
Yes	26	12.4
No	3	1.4

^a ESR – Erythrocyte sedimentation rate.

^b CRP – C-Reactive protein.

^c ASO – Antistreptolysin O.

^d NSAIDs – Non-steroidal anti-inflammatory.

3.2. Acute rheumatic fever without carditis

They represented 46.9% of our patients. The mean of age was 11.0 ± 3.1 years. The sex ratio male/female was 0.9. The class between 5 and 15 years was the most represented age class, (90.8%) and urban residence was the most frequent (86.7%). The primary school was the most found. It represented 62.2% of this group. We recorded most hospitalization in autumn (39.8%). History of sore throat was found in 35.7% of cases (Table 3).

The major criterion of Jones criteria was arthritis. It represented 10.2% of cases. The main minor criterion was arthralgia (53.0%) (Table 3).

ASO were positive (> 200 UI/ml) in 30.6% of cases and raised ESR were found in the first hour in 22.4% (Table 3).

The prescription was dominated by penicillin A (65.3%) followed by corticosteroids (20.4%) (Table 3).

Table 3
Univariate analysis between ARF and interest variables.

Characteristics	Acute Rheumatic fever with carditis (%) N = 111	Acute Rheumatic fever without carditis (%) N = 98	P
Gender			
Male	52 (46.8)	46 (46.9)	0.989
Female	59 (53.2)	52 (53.1)	
Class age			
< 5 years	2 (1.8)	3 (3.1)	0.860
[5–15]years	101 (91.0)	89 (90.8)	
> 15 years	8 (7.2)	6 (6.1)	
Season			
Spring	27 (24.3)	20 (20.4)	0.024
Summer	18 (16.2)	21 (21.4)	
Autumn	28 (25.2)	39 (39.8)	
Winter	38 (34.2)	18 (18.4)	
Residence			
Urban	91 (81.9)	85 (86.7)	0.187
Rural	14 (12.6)	10 (10.2)	
Education level			
Unschooling	2 (1.8)	4 (4.1)	0.544
Koranic	0 (0.0)	1 (1.0)	
Primary	62 (55.9)	61 (62.2)	
Secondary	39 (35.1)	32 (32.7)	
History of sore throat			
Yes	57 (51.3)	35 (35.7)	0.536
Major criteria			
Chorea	5 (4.5)	4 (4.1)	1.000
Arthritis	14 (12.6)	10 (10.2)	0.586
Minor Criteria			
Arthralgia	65 (58.6)	52 (53.0)	0.711
Fever	19 (17.1)	13 (13.3)	0.293
High ESR ^a	38 (34.2)	22 (22.4)	0.579
High CRP ^b	17 (15.3)	7 (7.1)	0.054
ASO positive titer^c			
< 200 UI/ml	5 (4.5)	2 (2.0)	0.849
200-600UI/ml	6 (5.4)	5 (5.1)	
> 600UI/ml	35 (31.5)	25 (25.5)	
Treatment received			
Penicillin A	65 (58.6)	64 (65.3)	0.329
yes			
Corticosteroids	43 (38.7)	20 (20.4)	0.111
yes			
Acetyl salicylic acid	2 (1.8)	7 (7.1)	0.087
yes			

^a ESR – Erythrocyte sedimentation rate.

^b CRP – C-Reactive protein.

^c ASO – Antistreptolysin O.

3.3. No deaths or recurrences were reported among this group

In the two groups: gender was not significantly associated with ARF. It was a significant difference between the ARF and season (P = 0.024). ARF with carditis was mostly found in winter and ARF without carditis in spring. Class age was not associated with ARF and the most touched by ARF with and without carditis was between 5 and 15 years. It wasn't a significant association between residence, school level, and history of sore throat, ASO and the prescription (acetyl salicylic acid, corticosteroid, penicillin A) with ARF (Table 3).

4. Discussion

The acute rheumatic fever (ARF) is an inflammatory disease of the heart that occurs two to three weeks after a pharyngeal infection of the group A beta-hemolytic streptococci (streptococcus pyogenes).¹² The disease usually affects school's children. Carapetis and al. estimate that there are at least 517000 deaths each year because of severe GAS, the most relevant being rheumatic heart disease.¹³

Acute rheumatic fever (ARF) is one of the leading causes of cardiac diseases or even cardiac deaths in developing countries.^{1,2} The global estimates reported 471,000 annual cases of ARF, with 336,000 of those

cases in children and adolescence aged 5–14 years of age (1). The prevalence of rheumatic heart disease is estimated at 5.1 for 1000 among school children in Egypt.^{14,15} There isn't a reporting about ARF in Morocco, however, the present study highlights our 7 years' experience at the pediatric ward of the hospital Hassan II of Fez. Our series indicate that the prevalence of ARF hospitalized knew a clear improvement between 2009 and 2013, however the prevalence seems to increase to stabilize in 2015. This stabilization in the number of cases of ARF admitted to our hospital is probably due to the primary prevention of ARF by early diagnosis of pharyngitis and the prescription of adequate antibiotic therapy.

The mean age on admission of RF patients in our study is the same as that is found in Turkey, which is 11.2 years, while it is higher than the one found in Tunisia and France (9.5 and 9 years respectively).^{16–18}

Approximately 2.5% of children with RF are younger than 5 years at diagnosis. This is confirming that we are a country of high endemicity.¹⁹

Children aged between 5 and 15 years have a higher risk to developed ARF. Because of over crowds and the bad ventilated schools that spread of streptococcal infection increase in school going children.²⁰ The proportions of female RF patients in this study are more than male, which is, according to the studies realized in France. However, in other studies, male patients are more than female.^{16,17,21}

The admission of patients with ARF to hospitals occurs throughout the year, especially in the autumn-winter period. This is in agreement with the seasonal variability of throat infections caused by group A beta-hemolytic streptococci that is also diagnosed in the winter and spring.^{22–25}

This study reports the majority of patients from urban areas. This is similar to the study done in Tunisia and South India (17,21). The increase of the frequency of cases from urban areas can be explained by the difficulties that patients from rural areas found to access to hospitals.

The family history of ARF is seen only in 2 cases. Our result is less than the one in South India and Tunisia (21.6% and 6.6% respectively).^{17,21} History family of ARF is weak, yet it can be an argument of a genetic disposition.

The results of our study shows that two thirds of cases have history of sore throat, one to four weeks before the onset of the manifestations of ARF, which is higher than the observations of other studies.^{16,17,21,26} The population exposed to frequent infection by streptococcus pyogenes and had insufficient treatment of initial pharyngeal infection lead to repeated ARF episodes and thus, increased risk of RHD development.

Polyarthralgia is the commonest clinical manifestation followed by fever among ARF patients in this study. The same observations are found in Tunisia,¹⁷ western Ukraine (23), and in Turkey's study (18). However, studies done in Saudi Arabia (26), South India²¹ and in literature¹ have reported polyarthralgia followed by fever as the commonest clinical presentation of ARF which is different from our results. Arthralgia was the main reason for medical consultations and an important sign of the diagnostic orientation. A fewer articulation sign in case of no cardiac involvement, especially when it is severe.

Arthritis is seen only in 12.6% of children, who are different from the observations of the other workers that described arthritis as the most common criterion (17,18,21,23,26). The low number of patients with arthritis is probably because that only patients with arthritis are included.

We diagnosed Sydenham's chorea in 4.3% of the cases either alone, or in combination with other major diagnostic criteria. This percentage is similar to the results of some series (16,20,24) and it is lower than reported in other series (21,23,26). In literature too, the prevalence of chorea in ARF has been found to vary considerably between populations going from < 2 to 30%.¹ Chorea in most severe cases is disabling as the affected individuals are incapable to execute activities of daily living and are at risk of injuring themselves (1).

In this study, none cases of subcutaneous nodules has been found

and only one patient with erythema marginatum. These low rates are reported in some studies, and in literature as well,^{23,27} while the study released in South India had seen a higher number of cases than our observations (21).

Carditis seen in 53, 1% of ARF cases in this study is similar to that observed by other series,^{16,17,26} however, it is higher in others series.²³ The use of Doppler echocardiography helps improve the detection of carditis. The commonest valvular lesion among RHD cases is mitral regurgitation; it is essentially isolated, but also was combined with aortic regurgitation. The profile of ARF regarding the relative frequency of valvular involvement in this series is same to that observed by other workers.^{17,20,21,24,28,29}

ASO titre was left as the only available tool for confirming a preceding streptococcal infection. The increased ASO in our results is comparable with other studies (17,18,23,26). This raised levels of antistreptococcal antibodies are not specific only for beta-hemolytic streptococcus group A, but can also be seen during infections caused by other types of streptococci such as streptococcus group C and G, which do not lead to ARF.³⁰ Throat culture for Group A beta-hemolytic streptococci are not realized in our study.

Elevated levels of ESR (> 60 mm in the first hour) and C-reactive proteins (> 3 mg/L) observed in this study has also been supported by other studies (11,21,23,26).

In the present study, arthritis is mostly treated with associated between penicillin and corticoïd which is in nocampliance to the findings of other studies that treated with acetyl salicylic acid (20,21). It has been proven that steroids controlled more promptly than salicylates the acute process of ARF.

Patients with carditis were given lifelong penicillin prophylaxis which is the most common antibiotics used for treatment in this study. this has been also observed in other studies (20,21). In this research, just 12.9% patients had been on oral antibiotics wich could be a reason for the compliance observed of this study. 90% of children how diagnosed ARF continues to follow in our unity and none of them had recurrences. Previous studies have found that patients who were compliant and who took regular penicillin prophylaxis did not have recurrence of ARF^{29,31}, while the study realized in Arabia Saudi found that 23% of children had recurrences.²⁶ Consequently, patients and their family members need to be educated and sensitized about this disease, emphasizing the importance of the secondary prophylaxis if carditis is present and also providing information about the need for antibiotic prophylaxis against endocarditis for dental and surgical procedures.

Surgical treatment in this study is done in 9% of RHD cases. This is lower than the observations made by other studies.^{20,21,32} Delay in treatment probably increased RHD cases that required surgical interventions in this study. On the other hand, there might be RHD cases whose poverty are added to the delay in timely surgery because of high expenses, lack of education and sometimes patient reluctance.³³

The mortality rate of 2.7% observed here among RHD is lower in other studies,^{18,19,27} however, a Saudi Arabia study reported no mortality from ARF cases.²⁴ The commonest cause of mortality in our study is a massif mitral insufficiency and/or a massif aortic insufficiency. This is can be caused by retardation diagnosis of carditis and consequently delay of surgical treatment.

4.1. Study limitations

This was a record based on study and includes information pertaining to patients referred to a university hospital center. Hence, these results may not be applicable to the general population because of a referral bias. However, as the study settings were major hospital in Fez, the observed findings in this study can be a good approximation of the disease scenario in the region. Also, important information such as Socioeconomic level and reason for noncompliance with treatment was not mentioned in the records and hence could not be analyzed. Some

data are not mentioned in the files of the patients. It was shown only after the integration of HOSIX software in 2013.

5. Conclusion

Acute rheumatic fever (ARF) continues to occur in Morocco. Despite the progress made in the socioeconomic development of the country, it's often associated with severe cardiac involvement. As long as this condition is not well reported, it is the main source of morbidity and mortality.

The significant incidence of misdiagnoses in ARF children during admission to the hospital, especially the interpretation of joint syndrome indicates that physicians need extra awareness. Its diagnosis is made difficult by the lack of specific clinical signs of rheumatic carditis. A revised version of the Jones criteria (2015) for the diagnosis of ARF can improve the detection of carditis.

This treatment remains mainly preventive, insisting especially the parents on the interest in the preventive treatment of the preceding streptococcal infection and the dangers incurred by his arrest.

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Declaration of competing interest

None.

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