Cardiology in the Young (2015), **25**, 745–751
doi:10.1017/S1047951114000900

Original Article

Incidence and clinical features of acute rheumatic fever in Kayseri, Central Anatolia, 1998–2011

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Abstract *Background:* In developing countries, acute rheumatic fever is the most common cause of acquired heart disease in the paediatric and adolescent population. It is believed that vulnerability to developing acute rheumatic fever is associated with several factors such as socio-economic and living conditions. *Aim:* Determine the incidence and clinical characteristics of acute rheumatic fever in the Central Anatolia region of Kayseri within the last 14 years, and to make a comparison of two 7-year periods. *Material and methods:* We performed a retrospective analysis of 624 patients who were diagnosed with acute rheumatic fever at the Department of Pediatric Cardiology in the Medical Faculty of Erciyes University between January, 1998 and December, 2011. *Results:* The mean age of patients was 10.9 ± 2.7 years. The female/male ratio was 1.4. When patients were categorised according to age groups, the largest group represented 376 patients (60.3%) aged between 10 and 14 years. The estimated incidence rate of acute rheumatic fever was 7.4/100,000 in the Central Anatolia region of Kayseri. Among the major findings, the most common included carditis at 54%, arthritis at 35%, Sydenham's chorea at 25%, and subcutaneous nodules at 0.5%, respectively. No significant difference was found between the first 7-year period and second 7-year period in distributions of age, gender, and major findings. *Conclusion:* Although there has been socio-economic development in Turkey in the recent years, the incidence of acute rheumatic fever is still high in the Central Anatolia region of Kayseri.

Keywords: Acute rheumatic fever; Anatolia; incidence

Received: 30 July 2013; Accepted: 9 May 2014; First published online: 6 June 2014

ACUTE RHEUMATIC FEVER IS AN AUTOIMMUNE inflammatory and multisystemic disease secondary to pharyngitis and is caused by group A streptococcus. The diagnosis of acute rheumatic fever is made based on the modified Jones criteria. According to this method, the major criteria include carditis, polyarthritis, Sydenham's chorea, erythema marginatum, and subcutaneous nodule under the evidence of the prior group A streptococcus infection.[1] The first acute rheumatic fever attack occurs most frequently in children and adolescents aged between 5 and 14 years. It rarely occurs in children younger than 5 years of age, and in adults over 35 years of age.[2]

Its incidence has been reduced in developed countries with the development of antibiotics and improved socio-economic conditions since the 1950s. However, acute rheumatic fever, which is a severe cause of morbidity and mortality, as well as its sequela, rheumatic heart disease, is still common in developing countries. According to the data of the World Health Organization, each year ~0.5 million people acquire acute rheumatic fever all over the world, and it is estimated that 60% of these patients develop rheumatic heart disease. The majority of these cases are reported in the developing countries. The annual incidence of acute rheumatic fever has

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been reported to be about 150/100,000 in the underdeveloped countries. Among the industrialised countries, the annual incidence is reported as 10/100,000 cases in Eastern Europe and <1/100,000 in the United States.[3] It is believed that vulnerability for developing acute rheumatic fever is associated with several factors such as genetic predisposition, streptococcus virulence, socio-economic, and living conditions.[4]

The objective of the present study was to determine the incidence, clinical characteristics, and course of acute rheumatic fever in the Central Anatolia region of Kayseri within the last 14 years.

Patients and methods

Our centre is a tertiary hospital at Central Anatolia, Turkey. This hospital is a referral centre, serving to a population of ~3 million along with the surrounding cities, and is the only centre in the field of paediatric cardiology in Kayseri region. According to the Turkey National Institute of Statistics records, the total population of the Kayseri is 1,255,349, 35% of which is aged <20 years. We retrospectively evaluated the records of 624 patients who were diagnosed with acute rheumatic fever at the Department of Pediatric Cardiology, in the Medical Faculty of Erciyes University between January, 1998 and December, 2011. The patients who admitted from the Kayseri region were determined.

Age, gender, presenting complaints, major and minor findings, supportive findings, and the seasonal distribution of patients diagnosed with acute rheumatic fever were determined. All patients had been examined by at least one paediatric cardiologist. The results of complete blood count, erythrocyte sedimentation rate, C-reactive protein, and anti-streptolysin O titer were derived from laboratory findings. All patients had undergone a standard 12-lead electrocardiography, two-dimensional, and Doppler echocardiography.

The diagnosis of acute rheumatic fever was based on the Jones criteria as modified by the American Heart Association in 1992.[1] According to these modifications, major criteria include carditis, polyarthritis, Sydenham's chorea, erythema marginatum, and subcutaneous nodules. Minor criteria are arthralgia, fever, elevations in acute phase reactants such as erythrocyte sedimentation rate C-reactive protein, and electrocardiographic PR prolongation. The diagnosis of acute rheumatic fever was based on the presence of two major or one major, and two minor criteria, in the patient. Secondary prophylaxis with benzathine penicillin G (intramuscular), with a 3-week interval, was started in all patients after establishing the diagnosis of acute rheumatic fever. The World Health Organization criteria for carditis by echocardiography include length of colour jet >1 cm, colour jet identified in at least two planes, mosaic colour jet with a peak rate >2.5 m/second, and the presence of a signal, holodiastolic for aortic regurgitation, or holosystolic for mitral regurgitation.[5] Information about age, gender, major manifestations, and minor manifestations was collected from the hospital records, and compared for two consecutive 7-year periods.

Statistical analysis was performed using SPSS for Windows. During evaluations, descriptive statistical methods (mean, standard deviation, frequency) were used as well as the Student's t-test, χ^2, and Fisher's exact tests for comparison of qualitative data. The results were evaluated in a 95% confidence interval at a significance level of $p < 0.05$.

Results

The study included 624 patients who were diagnosed with acute rheumatic fever according to the modified Jones criteria over a period of 14 years. The maximum number of cases per year was 83 in 2008, whereas the minimum number was 16 in 2010 (Table 1, Fig 1). The mean number of patients per year was 44.5. A total of 435 patients (435/624; 70%) were admitted from the Kayseri region. The mean number of patients per year was 31 for the Kayseri region. According to the Turkey National Institute of Statistics records, the average population under 20 years were determined to be 420,000 between 1998 and 2011 in the Kayseri region. According to these data, the estimated incidence rate of acute rheumatic fever was 7.4/100,000.

Of these patients, 362 (58%) were female and 262 (42%) were male (female/male ratio 1.38). Patients were aged between 2.5 and 18 years of age

Table 1. Annual number of cases between 1998 and 2011.

Years	Number of cases	%
1998	45	7.2
1999	52	8.3
2000	33	5.3
2001	39	6.3
2002	26	4.2
2003	40	6.4
2004	60	9.6
2005	58	9.3
2006	48	7.7
2007	73	11.7
2008	82	13.1
2009	30	4.8
2010	16	2.6
2011	22	3.5

https://doi.org/10.1017/S1047951114000900 Published online by Cambridge University Press

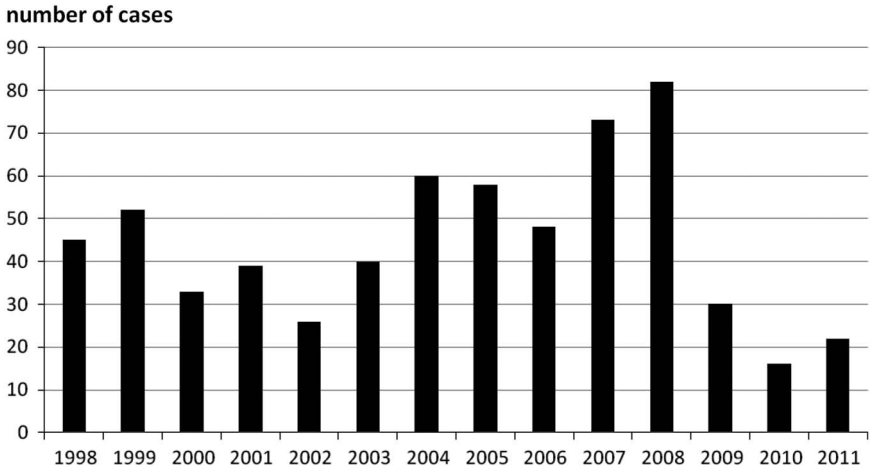

Figure 1.
Distribution of 624 patients diagnosed with acute rheumatic fever by years as graph.

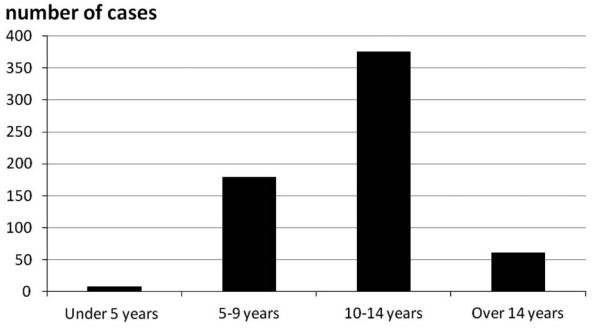

Figure 2.
Distribution of patients by age groups.

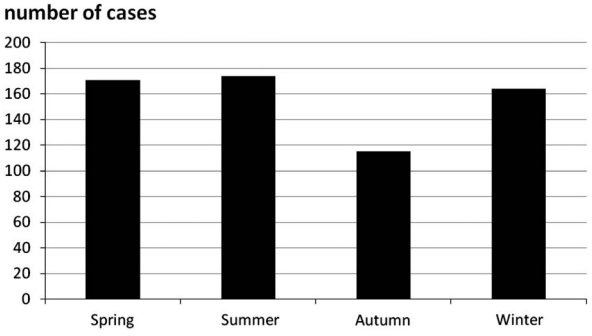

Figure 3.
Distribution of patients' presentation by season.

during the diagnosis (mean 10.9 ± 2.7 years). When the patients were categorised according to age groups (Fig 2, the largest group represented 376 patients (60.3%) aged between 10 and 14 years. There were eight patients (1.3%) under 5 years of age, and 61 patients (9.8%) over 15 years of age. Analysis of the seasonal distribution of acute rheumatic fever showed an incidence of 28% in summer, and 27% in spring (Fig 3). In 7.4% of patients, there was a family history of acute rheumatic fever, with no significant difference between genders. Of the patients studied, 22 (3.5%) had recurrence.

Arthralgia was the most common presenting complaint in 211 patients (34%). Interestingly, it was followed by involuntary movements in 157 patients (25%). The incidence of major findings was most common for carditis at 54%, which was followed by arthritis (35%), Sydenham's chorea (25%), and subcutaneous nodules (0.5%), whereas one patient had erythema marginatum. No significant difference was found in the incidence of carditis, arthritis, subcutaneous nodules, and erythema marginatum during the gender analysis of major findings. However, the incidence of Sydenham's chorea was 29% in female patients, and 20% in male patients, which represented a statistically significant difference. Analysis of distribution of major findings by age groups showed no significant difference. Minor findings were as follows: elevated sedimentation, 60%; C-reactive protein positivity, 45%; and fever, 17%. As evidence of the prior group, A streptococcus infection, the elevated anti-streptolysin O titer was 82% (Table 2). C-reactive protein positivity was observed as 53% in male patients and 38% in female patients. A significant difference was found in these minor criteria between genders. However, the distribution of other minor criteria was similar in both genders.

In patients who presented during an acute attack, the most common finding was combined carditis and arthritis at a rate of 22%. Patients who presented with chorea were routinely evaluated with echocardiographic examination. The combination of chorea and carditis was found in 16% of all the enrolled patients with acute renal failure. Of the minor findings, fever, arthralgia, C-reactive protein

https://doi.org/10.1017/S1047951114000900 Published online by Cambridge University Press

positivity, and elevated erythrocyte sedimentation rate were significantly lower in patients with chorea than in patients without chorea.

The most commonly affected joints in arthritic patients were those in the knees at 38%, ankles at 37%, and wrists at 14%, respectively. In arthritic patients, joint involvement was as follows: in one identical joint (45%), two different joints (35%), three different joints (8%), and four and more different joints (12%). Monoarticular arthritis was found in 8% of all arthritis patients.

Clinical patients with carditis had echocardiographic demonstration of pathological valve regurgitation. The most commonly affected valve was the mitral valve alone (63%), followed by a combined aortic valve and mitral valve (32%), and the aortic valve alone (5%), respectively. During the echocardiographic diagnosis, severity of mitral regurgitation was mild in 72%, moderate in 25%, and severe in 3% of patients, whereas severity of aortic regurgitation was mild in 91% and moderate in 8% of patients, with only one patient having severe aortic regurgitation. The improvement in valve regurgitation after 1 year, as determined during the first diagnosis, was 51% for the mitral valve and 20% for the aortic valve. During follow-up, 18 patients underwent mitral or aortic valve replacement for an indication of cardiac insufficiency associated with valve regurgitation, despite anticongestive treatment. No death was observed during the acute period or after development of rheumatic heart disease.

Table 2. Major and minor manifestations in 624 patients with acute rheumatic fever.

	n	%
Major manifestations		
Carditis	339	54.3
Arthritis	218	34.9
Chorea	158	25.3
Subcutaneous nodules	3	0.5
Erythema marginatum	1	0.2
Two (or more) major manifestations		
Carditis and arthritis	137	21.9
Carditis and chorea	98	15.7
Carditis, arthritis, and chorea	7	1.1
Carditis, arthritis, and subcutaneous nodules	3	0.5
Minor manifestations		
Fever	109	17.4
Elevated C-reactive protein	280	45
Elevated erythrocyte sedimentation rate	376	60.3
Prolonged PR	108	17.4
Elevated anti-streptolysin O	508	81.5

Data on the age, gender, and major and minor findings of patients were compared for two 7-year periods (Table 3). The number of patients diagnosed with acute rheumatic fever was 295 (47%) during the first 7-year period, and 329 (53%) during the second 7-year period. No significant difference was found between the two periods in distributions of age and gender. There was no significant difference in the distribution of major findings. Of the minor criteria, fever and electrocardiographic PR prolongation were higher during the first 7-year period. No significant difference was found between the two periods in the distribution of age, gender, and number of joints involved in patients with arthritis. There was no significant difference between the two periods in the distribution of age, gender and affected valves, degree of valve involvement, and incidence of pericarditis (1.8% versus 1.2%) in patients with carditis.

Table 3. Comparative analysis of age, gender, major, and minor findings of patients during two 7-year periods.

	1998–2004 [295 patients (47%)]	2005–2011 [329 patients (53%)]	Statistical difference ($p < 0.05$)
Mean age	11.0 ± 2.7	10.6 ± 2.9	–
Gender (female/male ratio)	1.41	1.35	–
Major manifestations			
Carditis	56.6%	52.2%	–
Arthritis	36.6%	33.4%	–
Chorea	27.4%	23.1%	–
Subcutaneous nodules	1%	0%	–
Erythema marginatum	0%	0.3%	–
Minor manifestations			
Fever	19.6%	15.5%	+
Arthralgia	35.2%	32.5%	–
Elevated CRP	48.2%	41.1%	–
Elevated ESR	62.4%	57.2%	–
Prolonged PR	21.5	13.5	+
Elevated ASO	80.7%	82.4%	–

ASO = anti-streptolysin O; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate

https://doi.org/10.1017/S1047951114000900 Published online by Cambridge University Press

Discussion

Acute rheumatic fever and its subsequent complication, rheumatic heart disease, remain a major public health problem in low- and middle-income countries.[6] As primary prevention helps to prevent development of the disease, it is important to make an early diagnosis of group A streptococcal pharyngitis and introduce appropriate treatment strategies. It has been shown that secondary prophylaxis by monthly injections of penicillin is a very effective and economic approach in preventing recurrence of acute rheumatic fever and reducing the burden of rheumatic heart disease in the population.[5–7]

The incidence of acute rheumatic fever has decreased worldwide since the 1970s. It rarely occurs in the industrialized countries, with an incidence of 0.5–3/100,000 cases. The annual incidence of acute rheumatic fever has been reported to be about 150/100,000 cases in the underdeveloped countries. The annual incidence rate reported is 54/100,000 cases in South Central Asia, 20/100,000 cases in Latin America, 21/100,000 cases in China, and 10/100,000 cases in Eastern Europe.[3] A literature review covering 10 countries by Tibazarwa et al[8] reported that the mean incidence rate of acute rheumatic fever was 19/100,000 cases worldwide. It is estimated that every year there are 471,107 new cases of acute rheumatic fever worldwide, and 60% of these new cases are most likely to develop rheumatic heart disease. The worldwide prevalence of rheumatic heart disease is estimated to be 15.6–19.6 million cases, and every year 1.5% of these cases die because of complications associated with rheumatic heart disease.[3]

We retrospectively evaluated the records of 624 patients diagnosed with acute rheumatic fever over a period of 14 years. According to the analysis, the estimated lowest incidence rate of acute rheumatic fever was 7.4/100,000 in the Kayseri region. Kayseri, which is in the Central Anatolia region, is a developing city. However, it has low socio-economic neighborhoods. In other studies carried out on the incidence rate of acute rheumatic fever in Turkey, Saraclar et al[9] found a rate of 20/100,000 between 1972 and 1976, whereas Beyozova et al[10] reported 56.6/100,000 cases between 1970 and 1973, and then 36.7/100,000 cases after 15 years. Orun et al[11] reported 37, 60, and 21 cases per 100,000 children for every decade between 1980 and 2009, respectively.

Group A streptococcal pharyngitis and subsequent acute rheumatic fever most frequently occur in children and adolescents aged 5–15 years.[11–17] In the present study, the age of the patients ranged from 2.5 to 18 years (mean, 10.9 ± 2.7 years), which is consistent with the literature. Furthermore, the rate of patients aged from 5 to 15 years was 89%. Of the patients aged <5 years (1.3%), eight were diagnosed with acute rheumatic fever. The rate of patients aged fewer than five with an acute rheumatic fever diagnosis was reported as 5% by Tani et al[18] in a study on 541 patients, as 20% by Miyake et al[4] in 503 patients, and as 14% by Breda et al[12] in 88 patients. Orun et al[11] reported a rate of 1.7% in 1115 patients, which is in keeping with our finding.

Many publications report that acute rheumatic fever occurs equally in both sexes.[11,13–15] Some studies indicate that it occurs 1.4 times more often in males.[12,16] In the present study, females were dominant, although there was no statistically significant difference (female/male ratio 1.38).

Acute rheumatic fever, which occurs 2–5 weeks following the group A streptococcus pharyngitis attack, is most common during the winter and spring months.[6] Although we had similar seasonal distribution rates, the incidence rate was slightly higher than half at 54% during the winter and spring months.

It is already known that acute rheumatic fever develops as a result of mutual interaction among group A streptococcus, a genetically vulnerable host and environmental factors. It has been previously demonstrated that there is a significant difference between the development of acute rheumatic fever and different ethnic groups living under the same socio-economic conditions and geography.[19–21] We did not about study ethnic groups, but we discovered a positive medical record of 7% in questioning about family history for genetic vulnerability.

Carditis has been reported to be around 30–45% in previous studies.[22,23] Our most common major finding was carditis with a rate of 54%. Orun et al[11] from Central Anatolia found the rates of carditis as 67%. Karaaslan et al[14] from central Anatolia reported the rates of carditis as 50%. This situation could be related to the increased use of echocardiography, or genetic predisposition may be a factor for development of carditis.

It is already known that mitral regurgitation is the most common cardiac anomaly, with a rate of ~95% in patients with acute rheumatic carditis.[6] In our study, 95% of patients with carditis had mitral valve involvement, of which 63% was isolated. Isolated aortic regurgitation represented in only 5% of the patients with rheumatic carditis; this was previously reported as 5%.[24]

Arthritis is migratory and polyarticular, often involves the large joints, and has been reported as the most common major finding in 60–80% of patients.[25] In our patients, arthritis was the second most common finding with a rate of 32%. Acute rheumatic fever arthritis is traditionally migratory and involves the large joints. In our series, arthritis was most commonly observed in the knees, ankles,

and wrists, respectively, which is consistent with the literature.

Although monoarticular arthritis is rarely reported in patients with acute rheumatic fever, three recent studies reported an incidence rate of monoarticular arthritis ranging from 3.5 to 17%.[26–28] Harlan et al published a report that shows monoarticular arthritis as a finding of acute rheumatic fever.[29] Olguntürk et al[13] indicated a rate of 33% monoarticular involvement in rheumatoid arthritis attacks. When our higher rates of monoarticular involvement (8%) and the above-mentioned studies are taken into consideration, we believe that acute rheumatic fever must be considered in the presence of findings suggesting clinical carditis, particularly in places where acute rheumatic fever is endemic in arthritic patients with one joint involvement.

The latent period between group A streptococcus pharyngitis and onset of chorea is 1–6 months. Sydenham's chorea was observed in 158 children (25%) alone or combined with other major diagnostic criteria, which was higher compared with previous reports. Other series reported a range from 7% to 21%.[11,13,15,16] The female/male ratio with chorea was 1.38. In patients diagnosed with acute rheumatic fever, 29% female and 20% male had chorea. Chorea was generalised in 91 patients (58%) and was one-sided in 67 children (42%). The incidence of chorea was higher, and it was the only major finding showing a gender difference. Demiroren et al[30] reported a female/male ratio of 1.7, and hemichorea in 22% of patients.

No cases of subcutaneous nodules or erythema marginatum have been reported in many series.[15,16] Breda et al[12] reported erythema marginatum in 11.4%, and subcutaneous nodules in 4.6% of patients. In studies with a larger number of cases, Olguntürk et al[13] indicated erythema marginatum in 2.5%, and subcutaneous nodules in 0.2% of patients. In our patient population, only three patients had subcutaneous nodules, and one of the patients had erythema marginatum.

Among the major findings of acute rheumatic fever, the most common was combined carditis and arthritis, which was followed by combined carditis and chorea. This result was related to the higher incidence of chorea in our patient population compared with previous studies. We had 10 patients with a combination of three major findings. Of the 10 patients, seven were diagnosed with carditis, arthritis, and chorea, with three patients having a combination of carditis, arthritis, and subcutaneous nodules. Some studies reported carditis to be more common in the younger age group, and arthritis in the elder age groups. However, there are some studies showing no difference in relation to distribution by age.[13] We also had similar findings when the distributions of major findings by age groups were evaluated.

Analysis of two 7-year periods of showed no significant difference in the distribution of patients by age and gender. A comparison of the age, gender, and clinical characteristics of patients presenting with arthritis between the two periods showed no difference. Similarly, no difference was found in a comparison of the age, gender, and clinical characteristics of patients presenting with carditis between the two periods. These results suggest that the presentation mode of the disease with both arthritis and carditis remained the same over the years.

For valve regurgitation detected during the initial diagnosis, the improvement achieved was 51% in the mitral valves, and 20% for the aortic valves, at the end of 1 year. Despite anticongestive treatment during follow-up, 18 patients underwent mitral or aortic valve replacement for an indication of cardiac insufficiency associated with valve regurgitation. The mortality rate in acute rheumatic fever attack was reported to be 0.5% by Orun et al.[11] There was no mortality during the acute period in the series of Ozer et al.[15] In our series, no death was observed during the acute period or after development of rheumatic heart disease.

In conclusion, acute rheumatic fever and its subsequent complication rheumatic heart disease remain a major public health problem, and are still common in Turkey. Primary prevention against group A streptococcus pharyngitis may prevent development of the disease, whereas secondary prevention against rheumatic heart disease may reduce the burden of disease in populations. Vaccine programmes being developed against group A streptococcus will mark a milestone in the struggle against the disease. Disease control and prevention strategies, such as elimination of difficulties in accessing health care, implementation of personal hygiene rules, urbanisation in accordance with international standards, improvement in socio-economic conditions, and the optimisation of primary and secondary preventions, may help in reducing the incidence of acute rheumatic fever and prevalence of its sequelae, rheumatic heart disease.

Acknowledgment

All authors contributed extensively and equally to this work.

Financial Support

This research received no specific grant from any funding agency, commercial, or not-for-profit sectors. All authors contributed extensively and equally to this work.

Conflicts of Interest

None.

Ethical Standards

The ethical aspects were respected and the research was approved by the Committee of Ethics and Research of Erciyes University.

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