

Acute rheumatic fever: 15-year single-center experience of a middle-income country in Latin America

Fiebre reumática aguda: 15 años de experiencia en un centro de salud de un país de ingresos medios en Latinoamérica

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Abstract

Objective: Acute rheumatic fever (ARF) is the leading cause of acquired heart disease in children and young adults in developing countries. The objective is to describe the clinical and epidemiological presentation of patients under 18 years of age with ARF in a pediatric hospital in Colombia over a period of 15 years (2006-2020), emphasizing cardiac involvement. **Methods:** Case series study of children with rheumatic fever for 15 years (2006 to 2020). **Results:** Seventy patients under the age of 18 with criteria for acute rheumatic fever were evaluated. Mean age was 10 years. Chorea was the most frequent manifestation ($n = 51$, 72.8%) followed by carditis ($n = 31$, 44.2%). Cases of ARF were proportionally more frequent from 2015 (43/70, 61.4%), as did the frequency of carditis (19/31, 61.2%) and subclinical carditis (7/11, 63.6%). Eight percent had a PR prolongation. **Conclusions:** The incidence in this study is high (moderate-risk). Chorea was the most frequent initial manifestation, which reflects the late diagnosis. The case frequency of acute rheumatic fever, especially for carditis and subclinical carditis, increased considerably beginning in 2015. Echocardiographic is transcendent because 35.4% of cases with carditis were subclinical.

Keywords: Acute rheumatic fever. Carditis. Subclinical carditis. Chorea. Arthritis.

Resumen

Objetivo: La fiebre reumática aguda (FRA) es la principal causa de enfermedad cardíaca adquirida en niños y adultos jóvenes en países en desarrollo. El objetivo es el de describir la presentación clínica y epidemiológica de pacientes menores de 18 años con FRA en un hospital pediátrico en Colombia en un período de 15 años (2006-2020), haciendo énfasis en el compromiso cardíaco. **Métodos:** Estudio de serie de casos de niños con FRA durante 15 años (2006-2020). **Resultados:** Setenta pacientes menores de 18 años con FRA. La mayoría de los pacientes con FRA fueron niñas (44/70, 62.9%). El promedio de edad fue de 10 años. De los criterios mayores, la corea fue la más frecuente (51/70, 72.8%), seguida de la carditis (31/70, 44.2%). Los casos de FRA fueron proporcionalmente más frecuentes desde 2015 (43/70, 61.4%), al igual que la frecuencia de carditis (19/31, 61.2%) y carditis subclínica (7/11, 63.6%). 8% tuvo prolongación del PR.

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Conclusiones. *La incidencia de FRA en este estudio es alta (riesgo moderado). La corea fue la manifestación inicial más frecuente, lo que refleja el diagnóstico tardío. La frecuencia de casos de FRA, especialmente de carditis y carditis subclínica, aumentó considerablemente a partir de 2015. La ecocardiografía es trascendental porque el 35,4% de los casos con carditis fueron subclínicos.*

Palabras claves: *Fiebre reumática aguda. Carditis. Carditis subclínica. Corea. Artritis.*

Introduction

Acute rheumatic fever (ARF) is a multisystemic, inflammatory immune-mediated disease which occurs in genetically predisposed people after an abnormal inflammatory process triggered by group A beta hemolytic streptococcal (GAS; *Streptococcus pyogenes*) tonsillopharyngitis¹⁻⁵. The disease affects the heart, joints, central nervous system and skin or subcutaneous tissue, with carditis being the most serious manifestation⁶⁻¹⁰. Acute rheumatic fever is the main cause of acquired heart disease in children and young adults in developing countries. There are approximately 450,000 new cases of ARF per year, 60% of which progress to rheumatic heart disease, causing 233,000-337,300 deaths every year¹¹⁻¹³. Acute rheumatic fever is diagnosed using the Jones criteria, which were revised in 2015. These latest criteria identified low and medium-high risk populations, with monoarthritis as a major criterion and monoarthralgias as a minor criterion for the latter group. This guideline emphasizes subclinical carditis as a major criterion and sets the Doppler echocardiography criteria for diagnosing valvulitis⁹.

The incidence of ARF varies by geographical area, with a global average of 19 cases per 100,000 people. Western Europe and North America have the lowest incidence, while Eastern Europe, the Middle East, Asia and Australia may have higher frequencies¹⁴. Studies on ARF in Latin America¹⁵⁻¹⁷, and specifically in Colombia, are scarce^{18,19}.

The objective of this study is to evaluate the clinical presentation and epidemiology of patients under the age of 18 with ARF in a tertiary care pediatric hospital in Colombia (a middle-income Latin American country) over a period of 15 years (2006-2020), emphasizing cardiac involvement and the frequency of carditis before and after 2015.

Methods

Patients and data collection

This was a case series study of patients under the age of 18 diagnosed with ARF and seen between

January 2006 and December 2020 at a single pediatric tertiary care health center in Bogotá, Colombia (Fundación Hospital Pediátrico La Misericordia [HOMI]). The clinical variables included in the analysis were: age, sex, place of residence, frequency of the clinical signs (Sydenham's chorea, carditis, subclinical carditis, arthralgias/arthritis (location), erythema marginatum, subcutaneous nodules and fever). Also, the type and results of tests such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), strep A test, throat culture, antistreptolysin O (ASO) antibodies, electrocardiogram (EKG) abnormalities, carditis and other echocardiographic abnormalities, the need for and findings on neuroimaging studies and the different types of treatment. The patients were divided into two periods: the first group from January 2006 through December 2014 (nine years), and the second group from January 2015 through December 2020 (six years), in order to evaluate the clinical characteristics before and after the Jones criteria were revised in 2015⁹. The study was approved by the hospital's research and ethics committee prior to commencing.

Definitions

The diagnosis of ARF cases prior to 2015 was based on the 1992 Jones criteria and 2004 WHO (World Health Organization) criteria^{20,21}, while the cases after 2015 were determined according to the Jones criteria modified that year by the American Heart Association/American College of Cardiology (AHA/ACC)⁹. Carditis was defined as a new pathological heart murmur on physical exam and/or valvular regurgitation detected by echocardiography. The criterion used for mitral regurgitation was a systolic jet within the left atrium, and for aortic regurgitation was a diastolic jet within the left ventricular outflow tract. The degree of mitral regurgitation was measured by the ratio between the maximum jet areas corrected for atrial area, and the degree of aortic regurgitation was measured by the ratio of the width to the diameter of the left ventricular outflow tract using a longitudinal parasternal view^{9,22}. Subclinical carditis was defined as positive echocardiographic

findings without clinical manifestations. Antistreptolysin O antibodies were positive at levels greater than 200 IU/mL. An elevated CRP was defined as > 30 mg/L, and an elevated ESR was defined as ≥ 30 mm/h⁹.

Statistical analysis

The descriptive analysis of the quantitative data calculated the following for each variable: median, average, standard deviation, range and interquartile range (IQR 25-75), as applicable. The qualitative variables were presented as frequencies or percentages. The data were entered in an Excel spreadsheet. The differences between frequencies were evaluated using Chi square or Fisher's exact test, as applicable. The differential analysis used 95% confidence intervals (CI). All statistical tests were two-tailed, with $p < 0.05$ considered to be statistically significant. The data were analyzed using the SPSS version 24 (SPSS 24 Inc., Chicago, IL, USA) statistical package.

Results

Throughout the 15 years of the study (January 2006 through December 2020), 70 patients under the age of 18 were diagnosed with ARF (65 children had a first episode and five a recurrence), for an average of five patients diagnosed per year. Forty-seven of these patients were seen as inpatients (67.1%) and 23 as outpatients (32.9%). The years with the highest number of ARF reports were 2015 and 2016 with nine and eight cases per year, respectively. The ARF cases were proportionally greater after 2015 (43/70, 61.4%), compared with those prior to this year (27/70, 38.6%) (Fig. 1). During the study period, a total of 231,265 patients between the ages of 3 and 15 were seen at the hospital (115, 839 in the first period [2006-2014] and 115,426 in the second period [2015-2020]), from which a cumulative incidence of 30 cases of ARF per 100,000 children was calculated. Most of the patients were from urban areas (30/37, 81.1%), with Bogotá being the main place of origin (24/37, 64.8%); seven patients were from rural areas (18.9%).

Most of the ARF patients were female (44/70, 62.9%). The patients' average age was 10 years \pm 2.9 years (range 3-15 years), with no significant difference in means between the two study periods ($p = 0.56$). Most of the patients were 9-12 years old (41.4%). Regarding manifestations according to the major criteria, chorea was the most frequent (51/70, 72.8%), followed by carditis (31/70, 44.2%), arthritis (19/70, 27.1%), subclinical

carditis (11/70, 15.7%), subcutaneous nodules (4/70, 5.7%) and erythema marginatum (4/70, 5.7%) (Table 1). For minor manifestations, both fever and arthralgias occurred in 24.2% ($n = 17$) (Table 1). Elevated CRP was found in 22.4 % (11/49) (average CRP 29 mg/L, median 10 mg/L, IQR 1.9-26.5 mg/L, range 0-192 mg/L). Elevated ESR was present in 33.3% (16/48) (average ESR 23.9 mm/h, median 17.5 mm/h, IQR 9.2-40 mm/h, range 0-83 mm/h). Five patients had a prolonged PR interval on the electrocardiogram (5/59, 8.4%); four had first-degree atrioventricular block and one had second-degree Mobitz type I atrioventricular block. One patient had a right bundle branch hemiblock. Altogether, 97.7% of the ASO titers (42/43) were elevated and 29.2% of the *Streptococcus pyogenes* tests were positive (12/41). There were no positive throat cultures for *Streptococcus pyogenes*.

Carditis

Carditis was the second most common manifestation, found in 70 patients ($n = 31$, 44.2%), with a greater frequency in males ($n = 16$, 51.6%). There was no significant sex difference between the two periods ($p = 0.37$). The mean age at onset was 10 years \pm 3 years (range 3-15 years). The most frequent age groups were 9-12 years and 13-15 years ($n = 11$, 35.4%, each). There was a significant difference in age distribution ($p = 0.008$). Most of the carditis cases were mild (83.9%) (Table 2). There was no statistically significant difference between the study periods in the severity of the carditis ($p = 0.77$). Beginning in 2015, there were proportionally more carditis cases compared with previous years (19/31, 61.2%), as well as subclinical carditis cases (7/11, 63.6%) (Fig. 1). There was no statistical difference in the presentation of carditis ($p = 0.98$) and subclinical carditis ($p = 0.86$) between the study periods. Regarding the presentation of carditis together with other major manifestations: 20 patients had carditis and chorea (28.5%), 12 had carditis and arthritis (17.1%) and three patients had carditis, chorea and arthritis combined (4.2%) (Table 1). For the 31 cases with carditis, the most commonly affected valve was the mitral valve ($n = 29$, 93.5%), followed by the aortic valve ($n = 17$, 54.8%) and both the mitral and aortic valves ($n = 15$, 48.3%). Of the 29 cases with mitral regurgitation, most were mild ($n = 18$, 62.1%) (Table 2). Subclinical carditis occurred in 11 of the 31 patients with carditis (35.4%). Of the 31 carditis cases, 48.3% required anticongestive therapy, 16.1% (corresponding to the moderate to severe cases) required

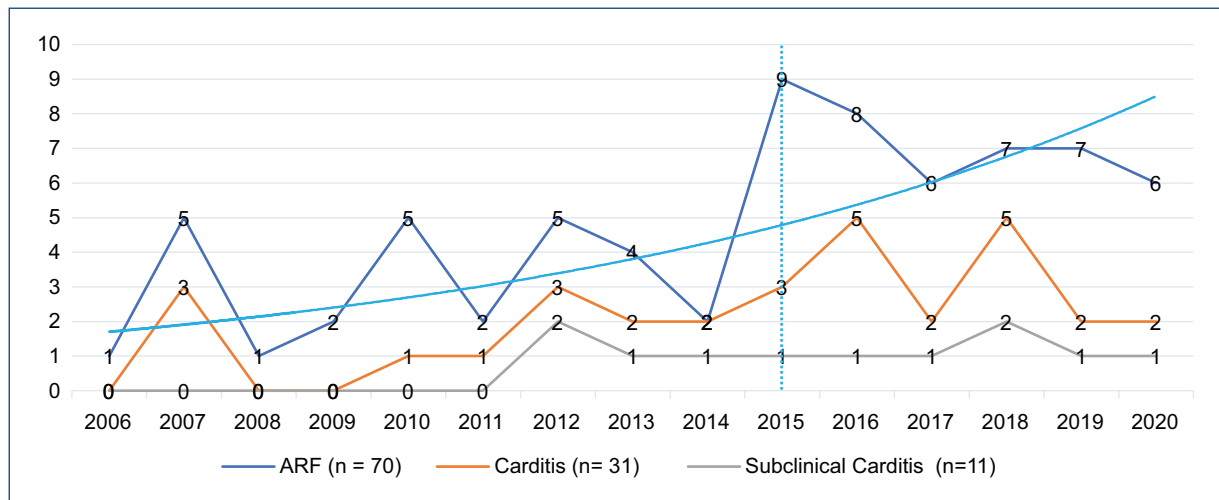


Figure 1. Distribution of AFR, carditis and subclinical carditis per year.

Table 1. Clinical features of cases with ARF (n = 70)

AFR Features	Total (n = 70)	First period (2006-2014) (n = 27)	Second period (2015-2020) (n = 43)	p
Mean age				
3-5 years	6 (8.6%)	4 (14.8%)	2 (4.7%)	0.09
6-8 years	17 (24.3%)	4 (14.8%)	13 (30.2%)	
9-12 years	29 (41.4%)	9 (33.3%)	20 (46.5%)	
13-15 years	18 (25.7%)	10 (37.1%)	8 (18.6%)	
Gender (female/male)	1.7 (44/26)	1.7 (17/10)	1.7 (27/16)	0.98
Major manifestations				
Chorea	51 (72.8%)	18 (66.7%)	33 (76.7%)	0.35
Carditis	31 (44.2%)	12 (44.4%)	19 (44.1%)	
Subclinical carditis	11 (15.7%)	4 (14.8%)	7 (16.3)	
Arthritis	19 (27.1%)	7 (25.9%)	12 (27.9%)	
Poliarthritits	17 (24.2%)	7 (25.9%)	10 (23.2%)	
Monoarthritits	2 (2.8%)	0	2 (4.6%)	
Erythema marginatum	4 (5.7%)	0	4 (9.3%)	
Subcutaneous nodules	4 (5.7%)	0	4 (9.3%)	
Two or more major manifestations				
Carditis/chorea	20 (28.5%)	8 (29.6%)	12 (27.9%)	0.87
Carditis/arthritis	12 (17.1%)	2 (7.4%)	10 (23.2%)	
Carditis/erythema marginatum	3 (4.2%)	0	3 (6.9%)	
Carditis/subcutaneous nodules	3 (4.2%)	0	3 (6.9%)	
Carditis/chorea/arthritis	3 (4.2%)	0	3 (6.9%)	
Minor manifestations				
Fever	17 (24.2%)	7 (25.9%)	10 (23.2%)	0.80
Arthralgia	17 (24.2%)	6 (22.2%)	11 (25.5%)	
Prolonged PR interval	5/59 (8.4%)	0	5/33 (15.1%)	0.75
Elevated CRP	11/49 (22.4%)	4/15 (26.7%)	7/34 (20.6%)	
Elevated ESR	16/48 (33.3%)	7/16 (43.5%)	9/32 (28.1%)	0.27
<i>Streptococcus pyogenes</i> exposure				
Elevated ASLO titer	42/43 (97.7%)	14/15 (93.3%)	28/28 (100%)	0.34
Positive strep A test	12/41 (29.2%)	4/16 (25%)	8/25 (32%)	

ARF: acute rheumatic fever, ESR: erythrocyte sedimentation rate; CRP: c-reactive protein; ASLO: antistreptolysin O.

Table 2. Description of the epidemiological and echocardiographic features in children with carditis (n = 31)

Echocardiographic/epidemiological features	No. cases/No. patients with carditis (n = 31)	First period (2006-2014) (n = 12)	Second period (2015-2020) (n = 19)	p
3-5 years	2 (6.5%)	2 (16.7%)	0	0.008
6-8 years	7 (22.6%)	0	7 (36.8%)	
9-12 years	11 (35.4%)	3 (25%)	8 (42.1%)	
13-15 years	11 (35.4%)	7 (58.3%)	4 (21.1%)	
Gender (male/female)	1.1 (16/15)	0.7 (5/7)	1.4 (11/8)	0.37
Carditis	31 (100%)	12 (100%)	19 (100%)	0.98
Mild	26/31 (83.9%)	11/12 (91.7%)	15/19 (79%)	0.77
Moderate	3/31 (9.7%)	1/12 (8.3%)	2/19 (10.5%)	
Severe	2/31 (6.4%)	0	2/19 (10.5%)	
Subclinical carditis	11 (35.5%)	4 (33.3%)	7 (36.8%)	0.86
Mitral regurgitation	29 (93.5%)	11 (91.7%)	18 (94.7%)	0.92
Mild	18/29 (62.1%)	4/11 (36.4%)	14/18 (77.8%)	0.07
Moderate	8/29 (27.6%)	5/11 (45.5%)	3/18 (16.7%)	
Severe	3/29 (10.3%)	2/11 (18.1%)	1/18 (5.5%)	
Aortic regurgitation	17 (54.8%)	6 (50%)	11 (57.9%)	0.75
Mild	15/17 (88.2%)	6/6 (100%)	9/11 (81.8%)	0.51
Moderate	2/17 (11.8%)	0	2/11 (18.2%)	
Mitral and aortic regurgitation	15 (48.3%)	5 (41.7%)	10 (52.6%)	0.63
Pericardial effusion	5 (16.1%)	1 (8.3%)	4 (21%)	0.64
Dilated left atrium	18 (58.1%)	5 (41.7%)	13 (68.4%)	0.27
Dilated left ventricle	18 (58.1%)	5 (41.7%)	13 (68.4%)	0.27

glucocorticoids (prednisolone, average 1 mg/kg/day), and 70.9% required aspirin (average 65 mg/kg/day) (Table 3).

Joint involvement

Nineteen cases had arthritis (27.1%), two developed monoarthritis and 17 had polyarthritis (Table 1). Seventeen patients had arthralgias (24.2%). The mean age at onset in the arthritis cases was 10 years \pm 2.6 years (range 5-14 years). Most arthritis cases were males (n = 11, 52.6%), being significantly more common in males than females (p = 0.028). The most commonly affected joints were: knees (n = 14, 73.6%), ankles (n = 13, 68.4%), elbows (n = 7, 36.8%), wrists (n = 6, 31.5%), small hand joints (n = 6, 31.5%) and hips (n = 2, 10.5%).

Chorea

Chorea was found in 51 patients (69.8%), most of whom were females (n = 36, 70.5%), being significantly

more common in females than in males (p = 0.028). The mean age at onset was 10 years \pm 3 years (range 5-15 years). The average duration was 6.2 weeks (median 4 weeks, range 1-30 weeks, IQR 2.7-6 weeks). Twenty of the 51 chorea cases also had carditis (39.2%). Thirty-eight of the 51 patients with chorea underwent nuclear magnetic resonance imaging of the brain as part of the workup for abnormal movements, ruling out any other organic cause in the central nervous system which would explain the neurological manifestations of ARF. Most of the cases with chorea occurred during the second period (43/51, 84.3%). There was no significant difference in the frequency of chorea between the two periods (p > 0.05).

Discussion

Acute rheumatic fever is the main cause of acquired heart disease in children and young adults, especially in middle or low-income regions²³. Tibazarwa et al¹⁴. reported a global ARF incidence between 5 and 51 per

Table 3. Treatment of patients diagnosed with ARF (n = 70)

Condition	Treatment	No. (%)
Prophylaxis (n = 70)	Benzathine penicillin	69 / 70 (98.6%)
	Erythromycin	1 / 70 (1.4%)
Carditis (n = 31)	Enalapril	15 / 31 (48.3%)
	Enalapril + diuretic	6 / 31 (19.3%)
	Prednisolone	5 / 31 (16.1%)
	Aspirin	22 / 31 (70.9%)
Chorea (n = 51)	Haloperidol	36 / 51 (70.1%)
	Valproic acid	7 / 51 (13.7%)
	Haloperidol + Valproic acid	3 / 51 (5.8%)
	Prednisolone	9 / 51 (17.6%)
Arthritis (n = 19)	Naproxen	11 / 19 (57.8%)
	Aspirin	11 / 19 (57.8%)

100,000 people 5-15 years old, with fewer than 10/100,000 cases in North America and Western Europe, and more than 10/100,000 cases in Eastern Europe, the Middle East, Asia and Australia. The cumulative incidence of ARF in this study was 30 cases per 100,000 children seen per year (moderate risk), much greater than what has been reported in other Latin American countries. However, the incidence of ARF in Colombia is unknown, and studies in Latin American populations are still scarce, despite being a region with a significant risk¹⁵⁻¹⁹. The average age (10 years) and age group with the highest occurrence (9-12 years) were similar to those found by other authors^{17,24,25}. Most ARF cases were in females, similar to what has been reported in studies in low and middle-income studies²⁵, and contrary to the higher proportion of males in high-income countries²⁴.

The occurrence of major manifestations shows that carditis and arthritis are the most frequent worldwide (50%-70% and 35%-66%, respectively) (9, 24, 26, 27); however, in our study, chorea was the most frequent major manifestation (72.8%), much more common than what has been described globally (10%-30%)⁹. Our institution is a national referral center, and the more complex cases (including those with chorea) could explain this higher proportion. Other authors have described ARF cases diagnosed late by the presence of chorea²⁸. Late diagnosis of the disease in the initial

healthcare facilities and delayed consultation would also explain this high proportion of chorea cases. Demiroren et al.²⁹ recorded 70.5% valvular involvement in 65 patients with chorea, a higher percentage than we found in our study (39.2%). This suggests that at least one to two thirds of cases with chorea already have affected valves.

Carditis was the second most common manifestation with 44.2%, lower than the 57.1% reported by Fabi et al. in Italy³⁰, and close to what has been found in other countries in the region, such as the 48.2% reported by Caldas et al. in Brazil¹⁷. In our study, the incidence of carditis increased over time parallel to the general increase in the incidence of ARF, especially after 2015 (the second study period). This is probably explained by the application of the 2015 updated criteria which implemented greater sensitivity in diagnosing the disease. The carditis cases had a slight male predominance (57.1%), which coincides with what other authors have described³⁰. The combined presence of carditis and chorea (28.5%) and carditis and arthritis (17.1%) in this study was not insignificant and is similar to what Caldas et al.¹⁷ reported, with 10.7% and 25%, respectively. Subclinical carditis was significantly more common after 2015, and the fundamental role of echocardiography should be highlighted, as at least one third of the patients with carditis had subclinical carditis (35.4%). As for the degree of carditis, the mild form was most common (83.9%), similar to what was described by Erdem et al.²⁴ in Turkey. Mitral regurgitation was the most frequent lesion (93.4%), with mostly mild involvement (62.1%). These percentages are greater than those reported by Fabi et al.³⁰, with 87.5% and 36.7%, respectively. Pericardial effusion was documented in 16.1%, more than what was reported by Erdem et al.²⁴, at 5.7%. This same author reported combined mitral and aortic involvement in 51.7%, very close to our study's figure of 48.3%, which makes it necessary to look for combined valve involvement. Fabi et al.³⁰ reported a 16.1% frequency of left atrial dilation and a 17.9% frequency of left ventricular dilation, much lower than what we found in this study (58.1% for both conditions), possibly explained by the large percentage of mitral/aortic valve involvement.

Arthritis was the third most common manifestation, and while the larger joints were most affected, the diagnosis should not be ruled out when the small joints or hips are the ones involved. Tal et al.²⁷ found that the knees (63%) and ankles (57%) were most frequently affected and, less frequently, the small hand joints (28%) and the hips (21%), very similar to what we found

in this study (73.6%, 68.4%, 31.5% and 10.5%, respectively). Beginning in 2015, the Jones criteria⁹ were modified and the monoarthritis presentation was included in the medium and high-risk population, alerting to a possible ARF diagnosis even without multiple joint involvement. Our study had a small but not insignificant percentage of monoarthritis (2.8%) for clinical suspicion of the disease.

Regarding minor criteria, fever and arthralgia were each present in 24.1%. Tal et al.²⁷ and Marino et al.²⁶ reported a higher frequency of fever (32%-46%) and arthralgias (50-75%). Elevated acute phase reactants have been reported in more than half of the cases (17,25-27); however, in this study, they occurred in less than one third. This could be explained by the fact that most of the cases had chorea, when the inflammatory response is not as high as it is at the beginning of the illness. Conduction disorders have been reported in 10-15% and should be diligently sought as soon as there is a clinical suspicion of ARF. Faby et al.³⁰ showed grade I atrioventricular block in 7.3% and Agnew et al.³¹ in New Zealand, reporting transient atrioventricular conduction disorders in 8.5%. In our study we found prolonged PR interval in 8.4%. As far as treatment, while there is still limited evidence for using anti-inflammatory medications (glucocorticoids) for carditis³², many guidelines include these medications in severe cases³³. In Malaysia, Patel et al.³⁴ described the use of prednisolone in moderate to severe carditis cases (76.9%) more frequently than in our study (16.1%). The use of glucocorticoids in cases with chorea has been described by other authors (26,35), and in our study they were used in nine patients with severe chorea (17.6%). Twenty-two patients with carditis and 11 with arthritis received aspirin, in line with the most current guidelines³³.

Our study has some limitations. The results obtained in this study will be valid for the population in which it was conducted, but the hypotheses generate. We recognize as a strength that, to our knowledge, this study represents one of the few and the largest documented in Colombia, with findings that could bring us closer to the general epidemiological behavior of the disease in this country.

Conclusion

The incidence of ARF cases seen in this study shows a moderate-severe risk presentation of the disease according to the latest revision of the Jones criteria (2015), with a frequency even greater than that of other Latin American countries. The large percentage of

cases with chorea indicates a delayed ARF diagnosis, as this is a late-onset manifestation, which should alert us to a timelier identification of the disease. The proportion of monoarthritis, as well as the involvement of small joints and hips, was not insignificant. Therefore, these should direct the search towards other manifestations which would support an ARF diagnosis. The number of ARF cases, as well as the number of carditis cases, increased proportionately after 2015, probably due to greater sensibility of the diagnostic criteria which were modified that year. Echocardiography was critical, as subclinical carditis was found in at least one third of the cases. This study alerts us to the importance of suspecting this disease early, to avoid confirming the disease with late manifestations when the heart has already been affected, since this is the main cause of acquired heart disease in children and young adults in developing countries (as most Latin American countries are, including Colombia).

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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