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ORIGINAL ARTICLE

Evolutive Study of Rheumatic Carditis Cases Treated with Corticosteroids in a Public Hospital

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Abstract

Background: Rheumatic carditis is a challenge for treatment and secondary prophylaxis, due to severe valve sequelae.

Objective: To evaluate the cases of rheumatic carditis in patients under 18 years old treated with corticosteroids.

Methods: An observational, longitudinal and retrospective study was carried out on the profile of patients, in the period of 2000-2015. We selected those who received corticosteroid therapy at immunosuppressive doses, for the treatment of carditis and were aged 5 to 18 years. Data were extracted from medical records. Calculations of: averages, standard deviations, medians and interquartile ranges, ratios and 95% confidence intervals were obtained. Chi-square and Wilcoxon tests were applied for comparisons. The level of significance was 5%.

Results: Of the 93 cases, 93.53% developed moderate or severe carditis. Mitral regurgitation was detected in 100% of the sample. Pulse therapy was administered in 11.83%. Surgery was performed in 23.69% of patients: mitral, aortic and/or tricuspid valve repair or replacement. The evolution of the cases was favorable in 70.96%. There was a good response among those who received only clinical treatment and those who belonged to the surgical group. The comparison of the initial and posterior valve lesions to the corticoid use was statistically significant ($p < 0.001$). A difference between the ejection fraction medians was observed ($p = 0.048$). Hospitalization was required twice or more for 45.16% of the patients. The mortality rate was 5.38%.

Conclusions: The patients showed significant clinical improvement. The treatment was effective, reducing trivalvular impairment. (Int J Cardiovasc Sci. 2018;31(6)578-584)

Keywords: Myocarditis/physiopathology; Myocarditis/complications; Rheumatic Fever; Mitral Valve Insufficiency; Adrenal Cortex Hormones; Penicilin G Benzathine.

Introduction

Although rheumatic fever (RF) occurs all over the world, in developing countries (such as Brazil), it is still a major cause of acquired heart disease among children and adolescents, which unfortunately still remains underreported.[1-3]

According to the National Census conducted by the Brazilian Institute of Geography and Statistics (IBGE), some 10 million cases of streptococcal tonsillitis are diagnosed each year, of which 0.3 to 10% develop into RF.[1,4] This indicates that, around 15,000 people must live with carditis each year.[1,5,6] Rheumatic damage to heart valves accounts for 40% of valve replacement operations,[7] costing the nation an average of R$ 89 million (close to US$ 28 million) a year.[8] Information from Brazil Unified National Health System database (DATASUS), indicates a cardiac mortality rate of about 7.87% from chronic RF.[8]

The dissemination of projects, such as the Rheumatic Fever Prevention Program (PREFERE), by the Ministry of Health (MH), aims to raise awareness among medical

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practitioners and the population in general about the importance of prevention and early diagnosis of this disease.[1] However, secondary prophylaxis is prone to failure, due to poor treatment compliance by patients[9] and/or gaps in nationwide antibiotic distribution networks, particularly Penicillin G Benzathine, breaching the directive issued by this MH that ensures no-cost distribution of this medication.[10]

Due to the importance of this issue, we decided to evaluate the cases of rheumatic carditis in individuals under 18 years of age treated with corticotherapy, in a public hospital in Rio de Janeiro State, and to verify the results obtained in the long-term follow-up.

Methods

An observational, longitudinal and retrospective study was carried out in patients treated in the pediatric cardiology department of a tertiary hospital in the city of Rio de Janeiro, Rio de Janeiro State, Brazil, for 15 years (2000–2015). All cases had the RF diagnosis made according to the reviewed and revalidated Jones criteria, plus evidence of prior pharyngotonsillitis caused by Lancefield's group A beta-hemolytic *Streptococcus* (GABHS).[1,11,12]

The inclusion criteria were: children and adolescents between 5 and 18 years of age undergoing corticoid treatment. The treatment followed the guidelines issued by the World Health Organization (WHO) and the Brazilian Cardiology Society (SBC).[1,2,13]

Corticoid treatment consisted of oral Prednisone, given as a single daily dose of 1 to 2 mg/kg/day (milligrams per kilogram per day), for eight weeks in cases of mild carditis or nine to 11 weeks in cases of moderate and severe carditis.[1,2] The full dose was given for approximately three weeks, tapering off by 20 to 25% of the initial dose each week, in response to clinical and laboratory improvement.[1]

Pulse therapy involved the administration of venous Methylprednisolone, at doses of 30 mg/kg/day,[1,14,15] for two weeks, with each cycle lasting three days, for severe carditis or when emergency surgery was required.[1,16] Immunosuppression was then completed with full-dose oral corticoids.

Streptococcus eradication required the administration of a single dose of 1,200,000 IU (International Units) of Penicillin G Benzathine through deep intramuscular injection, for patients weighing 20 kg (kilograms) or more and 600,000 IU for those weighing less than 20 kg. The oral medication used was Penicillin V, at a dose of 50,000 IU/kg/day (International Units per kilogram per day) every eight hours, for 10 days. As an option, treatment in some cases consisted of Amoxicillin at a dose of 50 mg/kg/day every eight hours, for 10 days.[1]

Secondary prophylaxis, with Penicillin G Benzathine, began while patients were still hospitalized and continued after their release, with outpatient control, prescribed at the same doses and with an interval of 21 days.[1,12,17] Some cases were treated with oral antibiotics, by administering 400,000 IU of Penicillin V every 12 hours; or daily Sulfadiazine at a dose of 500 mg for patients weighing less than 30 kg and 1 g (gram) for those weighing 30 kg or more;[1,18,19] or 250 mg of Erythromycin every 12 hours.[1,19]

Based on their clinical evolution, patients were divided into two groups: A – cases treated only with corticosteroids at immunosuppressive doses; B – cases that also required surgery.

Statistical analysis

The Stata program version 13.0 (*Stata Corp*) was used. The level of statistical significance was set at 5% ($p < 0.05$) as the statistically significant difference for all analyses. The Shapiro-Wilk's test was used to test the normality of the variables. Continuous variables with normal distribution were represented by mean and standard deviation and, otherwise, by median and interquartile range. The 95% confidence intervals were calculated, and the chi-square test was applied for the difference between proportions. Wilcoxon's test was used to compare left ventricular ejection fraction (LVEF) before and after treatment.

Ethical aspects

This research was approved by the Research Ethics Committee (REC) of the institute – National Research Ethics Commission (CONEP) and obtained a CAAE registration number: 21608213.0.0000.5265, available at the following website: http://www.saude.gov.br/plataformabrasil. As a retrospective study, there was no need to obtain the Free and Informed Consent form.

Results

The number of diagnosed cases of RF treated at the institute between January 2000 and December 2015 included 174 patients. We selected 93 of them that required immunosuppression with corticosteroids.

Between the ages of 5 and 18 years, the mean age of these patients was 9.89 years old, of which 47 (50.54%) were females. No significant gender-related differences were observed (Table 1).

Of the total number of patients, 11 (11.83%) did not adequately respond to oral Prednisone and were consequently given pulse therapy with Methylprednisolone.

Six (6.47%) of them had mild, 36 (38.69%) had moderate and 51 (54.84%) had severe carditis, indicating that 93.53% of the cases had the moderate or severe form of the disease. All 93 patients (100%) also had mitral insufficiency.

An initial daily dose of 30 mg of Prednisone was administered to mild cases, whereas 40 to 60 mg a day were administered to moderate or severe cases (Table 2).

In group A, 71 patients (76.31%) received corticoids, with no surgical intervention. Among them, only two (2.15%) were lost to follow-up. Group B consisted of 22 patients (23.69%) who required surgery in addition to corticoid treatment. Among them, 17 (18.31%) had good outcomes (decreased pressure gradient and intracavitary volume, with left ventricular systolic function improvement). Five (5.38%) died. The team performed surgical corrections of the mitral, aortic and/or tricuspid valves through repairs or replacements (Table 3).

As shown in Table 3, eight patients (8.64%) underwent surgery in only one valve. Two patients (2.15%) underwent surgery twice for the same valve, at different

Table 1 - Baseline characteristics of the study population (n = 93)

Variables	Results
Female gender - n (%)	47 (50.54)
Male gender - n (%)	46 (49.46)
Age (years old) - mean ± standard deviation	9.89 ± 3.10

Table 2 - Distribution of treatment with Prednisone (in mg) in patients with rheumatic carditis (n = 93)

Initial doses	Total weeks	n	%	95% confidence interval	
				Lower	Upper
60	11	51	54.84	43.4	64.5
50	10	23	24.72	17.6	34.0
40	9	13	13.97	7.9	21.1
30	8	6	6.47	2.2	12.9

Table 3 - Surgical cases in patients with rheumatic carditis (n = 22)

Surgery performed	Affected valve	n	%	95% confidence interval	
				Lower	Upper
Single repair	Mitral	1	1.08	0.0	13.6
Double repair	Mitral and Tricuspid	2	2.15	0.0	22.7
Repair / biological prosthesis	Mitral / Aortic	1	1.08	0.0	13.6
Repair and biological prosthesis two years later	Mitral	1	1.08	0.0	13.6
Repair and metal prosthesis in the same year	Mitral	1	1.08	0.0	13.6
Repair / biological prosthesis	Tricuspid / Mitral	3	3.23	0.0	31.8
Repair / metal prosthesis	Tricuspid / Mitral	1	1.08	0.0	13.6
Repair / double metal prosthesis	Tricuspid / Mitral and Aortic	2	2.15	0.0	22.7
Single biological prosthesis	Mitral	4	4.30	4.5	36.4
Single biological prosthesis	Aortic	1	1.08	0.0	13.6
Double biological prosthesis	Mitral and Aortic	3	3.23	4.5	27.3
Single metal prosthesis	Aortic	2	2.15	0.0	22.7

times. In 12 cases (12.90%), surgery was required for two or three valves damaged by carditis.

The median follow-up time in our service was 5 years.

During outpatient follow-up, we observed that secondary prophylaxis with Penicillin G Benzathine was administered on a regular basis to 55 patients (59.14%) and irregularly to 38 (40.86%) others.

As a result of one episode of carditis, 44 patients (47.31%) had only one hospitalization and five (5.38%) were maintained in outpatient control only. All of these were free of surgery.

There were indications of two to three subsequent hospital admissions for 31 patients (33.33%) and four to five or more returns to hospital for another 11 (11.83%).

In 12 cases (12.90%), the diagnosis was rheumatic carditis with bacterial endocarditis, using the modified Duke criteria.[20] Among them, three patients (3.23%) required surgery, of which one (1.08%) died after a double valve replacement using mitral and aortic biological prostheses. Evidence of vegetation at the two-dimensional Doppler echocardiogram was found mainly in the mitral valve (MV) of 10 patients (10.75%). In two others (2.15%), one showed damage to the aortic valve (AoV) only, while the other had mitral-aortic injury.

Microorganisms were identified through blood cultures in six patients (6.47%), as follows: two (2.15%) with coagulase-negative *Staphylococcus*; one (1.08%) had community-acquired methicillin-resistant *Staphylococcus aureus* (CA–MRSA); one (1.08%) had *Streptococcus pneumoniae*; one (1.08%) had *Streptococcus thermophilus*; and another (1.08%) had *Klebsiella pneumoniae*.

The initial clinical status of carditis related to arthritis or arthralgia was found in 63 cases (67.74%). Other 12 patients (12.90%) also showed an association with Sydenham's chorea (SC).

In terms of clinical evolution: improvement was observed in 66 patients (70.96%); one (1.08%) showed worsening; 19 (20.43%) showed no change in the clinical picture; two (2.15%) were lost to follow-up and did not return for control visits; and five (5.38%) died. Consequently, we currently have 86 patients (92.47%) still undergoing outpatient follow-up.

We observed good outcomes in the 49 patients (52.65%) who received clinical treatment only (valve regurgitation improvement) and the 17 (18.31%) submitted to successful surgical procedures (decreased pressure gradient and intracavitary volume, with an improvement in left ventricular systolic function).

After corticotherapy, echocardiography showed that of the 52 cases (55.91%) with an initial lesion in three heart valves, 36 (38.69%) had a favorable evolution, with regression to univalvular disease and only 16 (17.20%) remained with the trivalvular involvement (mitral, aortic and tricuspid). Therefore, at the end of the treatment, we demonstrated that most patients showed a decrease in the carditis intensity. Comparison of the frequencies of the initial and final lesions (triple, double and single) showed a reduction in the number of patients with trivalvular involvement, with a significant difference (p value < 0.001 and chi-square 34.7473).

LVEF determination by conventional transthoracic echocardiography (TTE) was performed before and after treatment was instituted. Subsequently, we verified the median ejection fraction (EF) values (Table 4).

It was observed that in both the echocardiographic study at the acute phase and in the final evolution assessment, the EF was preserved, although a statistical significance was found in the comparison between these LVEF medians (p value = 0.048). Only two patients (2.15%) showed ventricular systolic dysfunction (LVEF < 50%) and died. These were male patients with an initial estimated mean LVEF of 33.50% and final LVEF of 27.00%.

Table 4 - Median initial and final left ventricular ejection fraction (LVEF) in patients with rheumatic carditis (n = 93)

EF	n	Median	p value*	Interquartile range	
				Lower	Upper
Initial	93	69.0	0.0484	40	81
Final	93	71.0		66	76
Female gender					
Initial	47	69.0	0.0408	60	73
Final	47	71.0		66	77
Male gender					
Initial	46	69.0	0.4475	61	74
Final	46	71.5		67	75

Wilcoxon's test.

Discussion

Most of the cases already had severe carditis, as previously shown. Of the 93 patients assessed by this study, more than half developed triple valvular injury, indicating the severity of the disease during the initial examination. However, there was a predominance of preserved LVEF. In the study by Rocha and Silva et al.,[21] most patients underwent repairs at an advanced stage of valve damage, being in functional class IV of congestive heart failure (CHF), according to the criteria established by the New York Heart Association (NYHA). The MV surgical approach was performed in a large number of patients, due mainly to mitral insufficiency (MI). Most of the monitored children showed satisfactory responses to MV reconstruction. In the study by Travancas et al.,[22] more than half of the replacement surgeries were focused on this valve. In our sample, surgical valve repair occurred mainly in the MV, as mentioned above. Patients undergoing surgery at the ideal time evolved well and death occurred in those treated at the later stages, who already showed compromised myocardial function.

In our group, valve replacement was performed due to device deformity, being in agreement with the literature. According to Rocha and Silva et al.,[21] one of the causes of mitral repair failure was the advanced inflammatory process of the valve. In the study carried out by Travancas et al.,[22] patients with severe valve damage required surgical prosthesis implantation. It was also stressed that biological prostheses were appropriate, for children and adolescents, in case of difficulty resulting from the prescription or maintenance of laboratory control over anticoagulant use. Inadequate control of the international normalized ratio (INR) might lead to hemorrhagic or thrombo-embolic complications.

This study showed that, of the total number of cases with vegetation image, preferably in the MV, 50% had the bacteriological isolation of the triggering microorganism of infective endocarditis (IE), with the coagulase-negative *Staphylococcus* being the main pathogen identified. Similarly, the results of Torbey et al.,[23] showed that the mitral valve was predominantly affected, accompanied by significant regurgitation, and that *Staphylococcus* had been isolated, especially in newborns and patients with prosthetic valves.

In some of our patients, treatment with oral corticoids was not effective initially, requiring the introduction of intravenous Methylprednisolone. The protocol followed for intravenous immunosuppression continued to be used in severe cases, of which importance has been underscored in certain publications.[15,24] However, pulse therapy was not widely used in our sample, probably due to prior treatment optimization with oral medications.

Our clinical control and monitorization through the echocardiography series showed lesion improvement in most of the severe carditis cases treated with oral and/or intravenous immunosuppression and in those who remained in outpatient control with regular administration of secondary prophylaxis. This outcome was similar to that found in the follow-up study by Herdy et al.,[25] which showed that even critically-ill patients had achieved a satisfactory evolution.

Secondary prophylaxis failed in some of our adolescent patients. Adherence difficulty was observed regarding the systematic use of periodic injections of Penicillin G Benzathine, which has also been previously reported.[9,26] In the study by Herdy et al.,[25] carditis reappeared in 49% of the cases, due to secondary prophylaxis disregard. Furthermore, recent failures in the free distribution of medication in some parts of the country and at certain times, resulted in higher RF recurrence rates, constituting a serious national public health problem.

Our outpatient follow-up drop-out rate was lower than the initially expected one, comprising only two patients (2.15%). In the study carried out by Muller et al.,[6] 10.8% of the patients gave up on treatment. The drop-out rate and loss of follow-up in the group studied by Herdy et al.,[25] reached a considerably high rate of 51%. This difference of results may be explained through the efforts of our multi-disciplinary team to get patients and their families to understand the disease severity and the need to prevent further RF flare-ups, stressing the importance of prevention.

Limitations of the study

Due to the retrospective nature of the study, we considered the possibility of limiting the sample size, because it is time-defined.

Additionally, the data collection was restricted to a single hospital, not representing the entire State of Rio de Janeiro.

Conclusions

We observed a favorable clinical evolution in most cases of severe carditis treated through immunosuppression with corticoids and periodic outpatient follow-up. The

treatment proved to be effective, decreasing damage in the three valves.

Author contributions

Conception and design of the research: Lemos FMCF, Herdy GVH, Valete COS, Pfeiffer MET. Acquisition of data: Lemos FMCF. Analysis and interpretation of the data: Lemos FMCF, Herdy GVH, Valete COS, Pfeiffer MET. Statistical analysis: Valete COS. Writing of the manuscript: Lemos FMCF, Herdy GVH, Valete COS, Pfeiffer MET. Critical revision of the manuscript for intellectual content: Lemos FMCF, Herdy GVH, Valete COS, Pfeiffer MET.

Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Instituto Estadual de Cardiologia Aloysio de Castro under the protocol number 21608213.0.0000.5265. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. As a retrospective study, there was no need to obtain the Free and Informed Consent form.

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