ORIGINAL ARTICLE

Rheumatic fever presentation and outcome: a case-series report

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ABSTRACT

Objective: To assess the clinical characteristics and outcome of a rheumatic fever case-series from a referral hospital over the last 20 years. **Patients and methods:** Patients under the age of 18 years, diagnosed with rheumatic fever between 1986 and 2007 were retrospectively assessed to estimate the carditis and relapse rates, by use of descriptive and survival analysis. **Results:** Of 178 cases identified, 134 were included. During the acute phase, 66.4% had polyarthritis, 56.8% had carditis, 28.6% had chorea, 1.5% had subcutaneous nodules, and 1.5% had erythema marginatum. The association of carditis and arthritis occurred in 40%. Carditis and chorea were more frequent among female gender. High antistreptolysin-O titres were found in 58.3%, and family history of rheumatic fever, in 14.5%. Mean follow-up was 6.8 years (1.1 to 16.9). Relapse was observed in 15%, hospital admissions in 27.6%, and follow-up discontinuation in 47.4% after a mean of 5.1 years. Carditis and relapse probabilities were 17.5% and 13.2%, respectively, five years after the initial attack. **Conclusion:** The risk of carditis and relapse of rheumatic fever was higher within the first five years. Follow-up discontinuation was frequent, pointing to the need of measures to improve adherence to prophylaxis and follow-up.

Keywords: arthritis, chorea, outcome assessment (health care), rheumatic fever.

BACKGROUND

Rheumatic fever (RF) is a multisystem inflammatory disorder presenting with self limited migratory arthritis. It may be also accompanied or followed by carditis, and less frequently by chorea and skin involvement. It is related to post-infectious autoimmune mechanisms driven to group A streptococcus antigens. Jones criteria are the main diagnosis guidelines, by combining major and minor signs at presentation. There is no single biologic marker, and the disease course is characterized by relapse after re-exposure to streptococcal antigens.[1–6] There is no clear outcome predictor and the adherence to long-term penicillin prophylaxis is still challenging for these patients' care. It is estimated that carditis may occur in up to 60% of the cases.[5,6] Rheumatic valvular disease may be caused by a single severe attack, but it is often related to recurrent attacks. However, relapsing risks should be considered even for RF mild forms.

Penicillin is prescribed for the initial attack and for prophylaxis of new attacks and close follow-up surveillance is currently recommended by expert consensus.[1,5–7] Long-acting benzathine penicillin is the recommended treatment, with the first dose prescribed at diagnosis, followed by continuous 3-week interval age-appropriated dosing, according to WHO experts guidelines[5,6] and a multidisciplinary Brazilian expert committee.[7] Penicillin prophylaxis duration is still a matter of controversy. According to current expert guidelines it varies from a minimum of five years until 25 years, or even life-long duration depending on relapse risk.[7] Penicillin prophylaxis adherence is of major concern in low socio-economic population

layers.[8] Surveillance follow-up is recommended in order to keep updated records of the prescribed penicillin by filling a scheduled-chart, a common practice in most specialized clinics. RF causes high impact to the health system due to carditis and heart damage. Treatment costs are high, as estimated by Terreri et al.[9] in an urban Brazilian population, concerning medication, clinic visits, hospital admissions and parents-patients working day loss.

RF accurate diagnosis depends on physician experience and specialist training. After industrialization, the incidence declined in most of developed countries, but it is still endemic in developing countries.[5,6] There are many socio-geographic factors involved in the epidemiology; therefore, periodic evaluation of outcome is needed.

This study aimed to examine the presentation profile, overlap of clinical features and outcomes in a case-series from a specialized clinic over the last 20 years.

PATIENTS AND METHODS

Of 178 cases diagnosed from 1986 to 2007, 134 were selected, being retrospectively examined from the first to the last clinic visit. Case-notes review was conducted by a trained assessor (SMC), according to a standardized case-report form.

Inclusion criteria were: diagnoses established by fulfilling Jones criteria[4] for the first and relapsing attacks, age below 18 years, regular follow-up for at least one year, and complete clinical assessment in all visits. All cases were followed by one of the authors (CSM). Exclusion criteria were: age over 18 years old, presence of chronic arthritis, and less than one year of follow-up.

After case-selection, a comprehensive revision of clinic visits, hospital admissions, and time of relapse was carried out. Evidence of heart dysfunction, either by clinical or echocardiogram assessment, was recorded during all follow-up visits. Descriptive demographic and clinical data, including laboratorial and outcome variables, are presented by frequency for categorical variables and by descriptive statistics for continuous variables. The probabilities of relapse and carditis were examined by actuarial survival analysis, with one-year-interval censoring. The survival events were: documented clinical evidence of relapse by a recent RF attack, or clinical and/or echocardiogram evidence of carditis, all observed at diagnosis and at follow-up consultations and adjusted for one-year-intervals.[10]

The protocol was approved by the institutional Ethics Committee (protocol #142/08 on May 5th 2008), and for those still on follow-up, informed consent was signed by parents. Assent forms, when applicable, were signed by patients.

RESULTS

Subjects

Of 178 cases identified, 134 were selected. Forty four were excluded, being 39 for missing medical records, three due to follow-up less than one year and two developed chronic arthritis, being diagnosed with concomitant juvenile idiopathic arthritis. The proportion of diagnosed cases during the first 10 years was 86 (64%), and during the last 10 years it was 48 (36%). Patients were referred from 41 different towns in São Paulo state, Brazil. Age at onset varied from 4–14 years, median 9.5 years. Overall gender distribution was 65 (48.5%) females and 69 (51.5%) males. Family history of RF was described in 17 patients (14.5%).

Diagnoses were confirmed by retrieving clinical and laboratory data in the case-report form. The frequency of major and minor signs at onset is presented in Table 1. In 22 patients (17%), previous upper respiratory infection within two weeks from the diagnosis was recorded, and hospital admissions in 37 (28%), during either an initial attack or a relapse. There was concomitant arthritis and carditis in 52 patients (40%), chorea and carditis in 14 (11%), chorea and arthritis in six (4.5%) and chorea concomitant to arthritis and carditis in just two (1.5%) patients. Presentation of only one major sign, so-called isolated polyarthritis, occurred in 31 patients (23%), isolated chorea in 16 (12%), and isolated carditis in seven (5%) cases. There were two (1.5%) cases with subcutaneous nodules and two other ones (1.5%) with erythema marginatum; all of those had concomitant carditis. Isolated major signs were accompanied by at least two minor signs and all cases fulfilled Jones criteria.[4]

High erythrocyte sedimentation rate and C-reactive protein were observed in 58% (74 of 127) and 46% (56 of 122) of the patients, respectively. Antistreptolysin-O titres higher than 320 IU/mL were found in 71 of 121 cases (58%). It varied from 320 to 4,370 IU/mL, median 722 IU/mL.

Complete records describing an arthritis pattern were found in 80 of 131 case-notes. It was migratory in 58 (67%) and additive in 22 (25%). The first affected joint was as follow: ankle in 30 (37%) patients, knee in 24 (30%), hip in nine (11%), wrist in six (7.4%), shoulder in five (6.2%), and elbow in six (5%). Overall, the number of joints with arthritis varied from 3–20 and arthritis duration varied from 1–123 days, median 6 days, with an inter-quartile range of arthritis duration of 2–20. Only two subjects presented prolonged arthritis, with 83 and 123 days of duration.

Table 1
Frequency of major and minor signs during rheumatic fever presentation

Sign	Present sign/n of records§	Frequency
Fever	60/131	45.8%
Arthralgia	43/130	33.1%
Arthritis	87/131	66.4%
Carditis	75/132	56.8%
Chorea	38/133	28.6%
Subcutaneous nodules	2/133	1.5%
Erythema marginatum	2/132	1.5%
Increased P-R interval on electrocardiogram	1/72	1.4%
High antistreptolysin-O	71/121	58.7%
High C-reactive protein	56/122	45.9%
High erythrocyte sedimentation rate	74/127	58.3%

§ Percentage was corrected for missing data.

Carditis was diagnosed, considering the whole disease course, in 75 cases: 53 females (71%) and 22 males (30%). All were assessed at least once by a cardiologist. By the time of diagnosis, 61 patients (81%) underwent echocardiogram assessment. Of those, mitral regurgitation was diagnosed in 45 (74%), aortic regurgitation in one (1.6%) and aortic stenosis in one (1.6%), with normal exams in 14 patients (23%). Among those with acute carditis, 13 (17%) had congestive heart failure. For the only patient diagnosed with aortic stenosis, a congenital valve defect was suspected; however, there was no previous assessment for this patient. During follow-up, 85 had one or more additional echocardiogram exams. Persistent murmur and abnormal echocardiogram were considered for scoring carditis events in the survival analysis.

Chorea predominated in females, affecting 24 (63%) of 38 cases. Duration of chorea symptoms varied from two weeks to 1.4 years, median 3.3 months. Full description of presenting symptoms was: involuntary movements of extremities in 36 patients (95%) dysartria in 26 (68%), hand writing disturbances in 24 (63%), poor coordination and balance in 30 (79%), easy-crying in 13 (34%), recent behavioral changes in 13 (34%), and sleep disturbance in three (8%). There was no description of tics, attention deficit disorders or obsessive-compulsive symptoms, either at onset or at follow-up.

Rheumatic fever outcome

Of 134 cases followed over 1.1–16.9 years (median, 6.9 years), two cases had severe carditis, with heart surgery performed, and one deceased shortly after surgery. Of the 133 on regular follow-up, 53 (40%) accomplished scheduled penicillin prophylaxis up to 18 years of age, being discharged after heart damage was ruled out. Seventeen (13%) were still on follow-up, but surprisingly, 63 (47%) went lost to follow-up. For those who discontinued follow-up, its duration varied from 1.7–13.7 years (median, 4.7 years). All patients who discontinued follow-up had updated penicillin schedule during the recorded follow-up visits and no heart damage was identified until the last visit. The reason for discontinuation remains unknown.

Twenty patients (15%) had at least one relapse. Only one patient had two relapsing RF attacks, both with arthritis. Another patient had three relapsing episodes of chorea, despite regular penicillin prophylaxis. Therefore, it was questioned if it was a true RF relapse or a relapsing course of chorea.

Survival analysis of carditis and relapse is presented on Figure 1A and 1B, respectively. The complementary value of the probability for each event (1-p) is represented on y-axis. Carditis probability was 17.5% at five years (Figure 1A). The overall probability of relapse was 13% at five years after disease onset (Figure 1B).
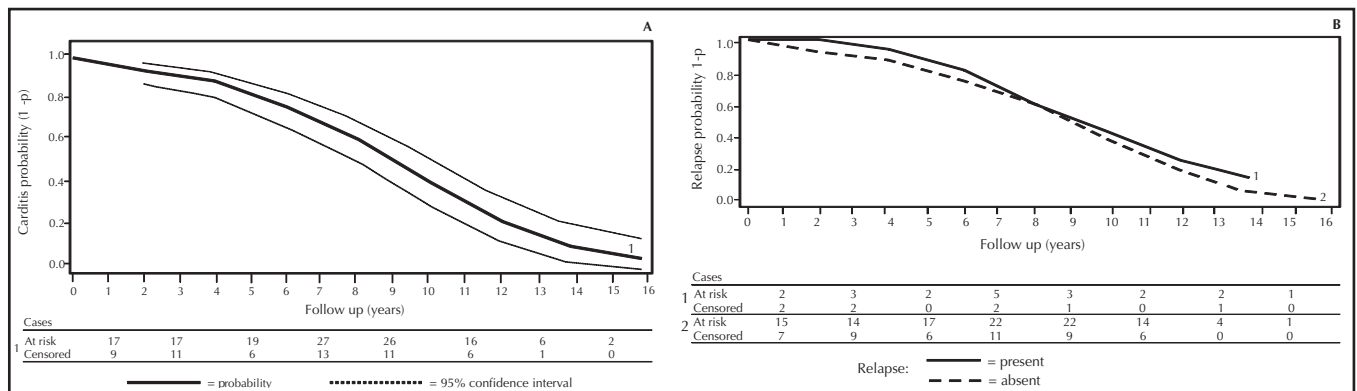
Figure 1
Rheumatic fever survival curve with complementary value probability [1-p] of carditis (1-A) and relapse (1-B).

DISCUSSION

RF is a public health concern due to carditis and heart damage, which may be aggravated by late diagnosis and poor penicillin prophylaxis adherence. A systematic evaluation of patients care is important to define further strategy for disease control and treatment.

A systematic comparison of the present series with previously published series[11–18] is presented in the Table 2. Onset age was comparable. RF family history was also comparable to a multicenter study in the state of São Paulo, the only study that addressed the familial history of RF.[11]

Arthritis was the most frequent major sign, followed by carditis in the present series. In another Brazilian series from the state of Acre,[14] as well as others reported from Liban[12] and Canada,[17] carditis was the most frequent major sign. Arthritis had migratory or additive pattern in most of our cases, affecting predominantly large joints as described originally in the 1950's.[4] Interestingly, the migratory pattern predominated in lower limbs. Presentation with symmetric small joints, neck, and hip arthritis involvement, as well as longer duration, as described in another Brazilian series from a single center,[18] was not observed. Prolonged arthritis with more than six weeks duration was observed in only two cases. Small joints, cervical spine involvement and longer arthritis duration need a differential diagnosis with post-streptococcal reactive arthritis,[19,20] but in the pediatric age range this feature is still a matter of controversy, where it possibly represents an atypical RF profile.

Concomitant arthritis and carditis was reported in high proportion of our cases, as well as in other series.[11,15] It was the second most frequent major sign, and mitral regurgitation was the most frequent valve involvement. During long term re-assessments, our survival analysis revealed 17.5% of carditis probability over five years. There is only one study addressing long term outcomes,[21] however only carditis cases were evaluated in this series and the outcome was carditis severity. We could not assess carditis severity with more refined assessment tools, like echocardiograms by the same observer or systematic accurate echocardiogram re-assessments, because these data were obtained during standard practice, and the exams were indicated at the discretion of the physician. There are no other reports about longitudinal assessment addressing all features of RF. It is important noting that, although carditis has more impact on morbidity and mortality, the diagnosis or RF itself implies in risk of relapse that may result in higher risk of carditis.

Frequency of chorea (28%) was higher than that reported in the international literature,[2,4,6] with 15%–20% estimates, but was similar to the results reported in the Brazilian series,[11,14,22] nearly 30%. Chorea is characterized by involuntary movements of extremities, muscular hypotonia, dysartria, gait disturbance, and tics, as well as behavioral manifestations. Symptoms are usually self-limited and with variable duration, and subtle cognitive dysfunction may persist into adult life,[23] what reinforces the need of long term surveillance, and more refined tools are desirable for surveillance. Cutaneous signs are of low frequency; this was confirmed in our series, where concomitant carditis was reported.[1–4]

An important clue for diagnosis ascertainment is high or rising titres of antistreptolysin-O. In our series, only 58.2% had high antistreptolysin-O titres. A comparison with previous reported series described in Table 2,[11–18] in addition to a

Table 2

Frequency of RF diagnostic parameters and comparison with previously published series

	SP, Brazil, 1999[11]	Liban, 2000[12]	India, 2003[13]	AC, Brazil, 2005[14]	SP, Brazil, 2006[15]	Turkey, 2006[16]	Canada, 2007[17]	SP, Brazil, 2011
Fever	58%	62%	___	___	___	___	41.8%	45.8%
Arthralgia	43.5%	55%	___	___	___	___	32.7%	33.1%
Arthritis	57.6%	39%	___	21.4%	70.5%	61.4%	37.8%	66.4%
Carditis	50.4%	93%	42%	69.7%	50.8%	46.1%	72.4%	56%
Chorea	34.8%	2%	18.8%	6.1%	35.2%	6.9%	49%	28.6%
Subcutaneous Nodules	1.5%	___	1.2%	___	2.1%	0.2%	3.1%	1.5%
Erythema marginatum	1.6%	4%	1.6%	3%	2.6%	2.5%	23.5%	1.5%
High ASO	63.5%	82%	___	58.8%	68.1%	___	81.4%	58.2%
High CRP	___	83%	___	24%	___	___	28.2%	45.9%
High ESR	63.2%	___	___	___	___	___	66.7%	58.3%

ASO: antistreptolysin-O; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; ___: data not available.

systematic review recently published by Costa et al. [24] comparing all Brazilian series published since the 1980's, indicated a wide variation, 48.7%–84.5%, from different studies in many parts of the country. Antistreptolysin-O rising titres in RF cases from our unit were previously examined, stressing the importance of serial determination over the first two months.[25] The tests of acute phase response indicated high erythrocyte sedimentation rate in 58.3% and C-reactive protein in 45.9%, and again a wide variation is observed in the published series.[11–18,24] It is possible that different laboratory techniques might have influenced these results in the same way for antistreptolysin-O, but it was not possible to reach a conclusion, due to the retrospective approach.

We could not control other socio-demographic variables in our series. Perhaps the long term risks of relapse were underestimated by the subjects' parents and this may be one of the factors related to the discontinuation or follow-up. Pelajo et al.[26] recently reported poor adherence to penicillin prophylaxis in a Brazilian cohort, observed in 35%–42% during follow-up appointments and 33.5% of their patients lost appointments during prolonged follow-ups.

In spite of all the above limitations of a retrospective study, this represents our current practice for patients care. Our study reinforce the need for early diagnosis and long term surveillance, in order to get better disease control to prevent heart damage.

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