

What is the outcome of rheumatic carditis in children with Sydenham's chorea?

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SUMMARY: Ekici F, Çetin İİ, Şaylan-Çevik B, Şenkon OG, Alpan N, Değerliyurt A, Güven A, Ateş C, Çakar N. What is the outcome of rheumatic carditis in children with Sydenham's chorea? Turk J Pediatr 2012; 54: 159-167.

We evaluated the echocardiographic features of 69 children diagnosed with Sydenham's chorea at the first attack of acute rheumatic fever. By echocardiography, carditis was detected in 71% of cases and silent carditis was shown in 28.9% of cases at initial presentation. Most patients had mild or moderate valvular regurgitation. Sixty-three cases were followed from 1-10 years. The improvement rate in valvulitis in cases with silent carditis (29.4%) was not different than in cases with clinical carditis (18.5%) ($p>0.05$). Persistence of valvular pathologies occurred in 72.2% of cases with carditis in the long-term follow-up (>2 years). Most patients (88.8%) complied with secondary prophylaxis, so relapse of carditis was exclusively prevented in our patients. Recurrence of chorea was identified in 20.6% of cases and was not associated with clinical or laboratory evidence for streptococcal re-infection.

Patients with chorea usually had mild carditis, and carditis showed resolution. Relapse of carditis in our population was exclusively prevented with secondary prophylaxis. Recurrence of chorea was not rare, despite regular treatment with benzathine penicillin.

Key words: Sydenham's chorea, rheumatic carditis, children, recurrence rate, adherence to secondary prophylaxis, prognosis.

Acute rheumatic fever (ARF) is relatively uncommon in developed countries, but is a common cause of heart disease in our country¹⁻⁴. Sydenham's chorea (SC) is a poststreptococcal, autoimmune disorder and is found in 6-14% of patients with ARF^{1,5-8}. It is a neuropsychiatric disorder consisting of both neurologic (choreic movement and hypotonia) and psychiatric signs. It has been reported that the prevalence of chorea has been increasing over the last decades⁹⁻¹².

It has been well known that chorea may accompany carditis. Carditis can cause permanent cardiac damage, and more than 60% of patients with ARF develop rheumatic heart disease (RHD)¹¹. Carditis also has a critical importance in determining the duration of antibiotic prophylaxis. There are very limited studies in our country evaluating the outcome of rheumatic carditis in patient with SC.

Both the severity of the initial carditis and RF recurrences strongly influence the prognosis and natural history of rheumatic carditis¹³. All patients with RF, especially those with cardiac involvement, are at risk for recurrence. The risk of recurrence and cardiac complications can be reduced by secondary antibiotic prophylaxis in children with ARF¹²⁻¹⁵. Poor compliance with secondary prophylaxis may limit the effective prevention of recurrence, which may lead to progressive RHD. The exact level of adherence to secondary prophylaxis required to prevent an episode of ARF has not been known exactly, and very few studies have reported whether or not patients complied with secondary prophylaxis¹⁶⁻²⁰.

In our study, we screened all patients diagnosed with ARF in our hospital between 1999 and 2011 and evaluated the echocardiographic characteristics of 69 children diagnosed with

SC at the first attack of ARF. To determine the frequency and outcome of carditis in patients with SC, we described their clinical and echocardiographic features at the initial and follow-up examinations. The persistence rate of valvular pathologies was assessed in 63 cases with carditis at first examination who were followed at least one year. The improvement rate of valvulitis in patients with silent carditis was compared with patients having clinical carditis. The frequency of patients who complied with penicillin prophylaxis and recurrence rate was also evaluated.

Material and Methods

We screened all patients diagnosed with ARF between 1999 and 2011 retrospectively. Among cases with ARF, only patients with new-onset acute chorea were included in our study. ARF was diagnosed according to the modified Jones criteria¹³. The patients' demographic, clinical, laboratory, follow-up, and imaging information were obtained from the medical records of each patient and entered into a standardized database. SC was diagnosed by two experienced authors (AG or AD) in the Department of Pediatric Neurology of the same hospital. Diagnosis of SC was made after exclusion of other etiologies. Patients were excluded when they had a previously recognized underlying neurologic disorder or RF. SC was classified as hemichorea or bilateral chorea.

Cardiac Evaluation

Echocardiographic studies were performed by four experienced authors (FE or NA from 2001-2004 and FE and IİÇ from 2004-2011) in the Department of Pediatric Cardiology of the same hospital. Complete transthoracic two-dimensional, M-mode, continuous wave and pulsed wave Doppler and color Doppler echocardiographic examinations were performed in all cases followed by a thorough physical examination. Echocardiographic examination was performed using Vivid 7 (General Electric, Horten, Norway) and a 3 MHz multifrequency transducer. The diagnosis of "carditis" was based on the presence of pathological murmur considering valvular involvement, cardiomegaly, heart failure, or pericardial effusion¹³. Echocardiographic images were obtained according to a previously reported position by

the American College of Cardiology/American Heart Association Task Force on Practice Guidelines²¹. A positive echocardiographic finding considering valvular involvement (pathologic mitral/aortic regurgitation) was defined as meeting the following criteria mentioned below: 1) the jet should be >1 cm in length, 2) seen in at least two planes, 3) having a peak velocity >2.5 m/s, and 4) persisting throughout systole (mitral valve) or diastole (aortic valve)²². If there was clinical evidence of valvular disease, and positive echocardiographic findings, these cases were defined as "clinical carditis". If there was no clinical evidence of valvular disease with positive echocardiographic findings, these cases were defined as "silent carditis". A routine complete blood count and biochemical test, throat culture, erythrocyte sedimentation rate and C-reactive protein, rheumatoid factor, antinuclear antibody (ANA) and anti-DNA test, electrocardiography, and chest roentgenography were performed in all patients. Supportive evidence of preceding streptococcal infection, including antistreptolysin O (ASO) titer, history of streptococcal sore throat (within previous 45 days) and throat culture, was evaluated in our patients. To exclude the other etiologies of chorea, serum ceruloplasmin level, antiphospholipid antibodies (APA), anticardiolipin antibodies (ACA), cranial magnetic resonance imaging (MRI), and electroencephalography were performed in 24 cases.

During the acute inflammatory period of rheumatic carditis, patients were treated with steroid (2 mg/kg/day, max: 60 mg/day) until the normalization of acute phase reactants (APRs).

Patients with mild chorea were subjected to a quiet environment, and sedatives like oral phenobarbitone or diazepam were given if necessary. Haloperidol was given in most patients with SC. Alternatively, some patients were also managed with sodium valproate or carbamazepine. Cases with severe symptoms of chorea were treated with intravenous immunoglobulin. Treatment was continued for 2-4 weeks after clinical improvement.

Follow-Up

Patients were followed for 1-10 years (at least 1 year after the first attack). Cardiac

findings of patients at the first and the last echocardiographic examinations were compared:

- 1) Complete improvement rate of valvulitis (disappearance of valvulitis) in patients with silent carditis was compared with the improvement rate of patients with clinical carditis.
- 2) If patients who had carditis (either clinical or silent) at the first examination were followed up for a period of 1-2 years, they were classified as the short-term follow-up group. If patients with carditis at the first echocardiographic examination were followed up for a period of 3-10 years, they were classified as the long-term follow-up group.
- 3) The persistence rate of valvulitis was compared between patients in the short-term follow-up group and long-term follow-up group.

Secondary prophylaxis with benzathine penicillin G (intramuscular, IM) with a three-week interval was started in all patients after establishing the diagnosis of ARF. Patients were classified as “adherent” to therapy when they did not skip or delay more than one dose of benzathine penicillin G. If more than one

dose of benzathine penicillin G was delayed or missed during this period, patients were classified as “non-adherent”.

We classified a RF episode as recurrent according to standardized World Health Organization criteria²¹. Recurrence of RF was defined as presence of new signs of RF observed after at least two months from the last episode. When the recurrences of chorea were observed, AFRs and ASO titers were also repeated to assess the reactivation of RF. The mean age at the first presentation and gender predilection of patients with recurrence were compared to those patients without recurrence. The rate of recurrence in patients adherent to secondary prophylaxis was compared with the rate of recurrence in non-adherent patients.

Statistical analyses were performed using SPSS 11.0 for Windows (Chicago, IL, USA). A “p” value of less than 0.05 was considered statistically significant. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to test for normality. According to the results, nonparametric tests were preferred. The differences in proportions between groups were compared by using chi-square or Fisher’s exact test, where appropriate. Continuous variables such as age at the first examination and follow-up period were compared using

Table I. Clinical and Demographic Features of Cases with Sydenham’s Chorea at the First Examination

FEATURES	Number of cases (%)
Age	
Mean (SD) (year)	10.5 (2.5)
Median (year)	11
Range	6-16
6-9 years	27 (39.1)
10-12 years	28 (40.5)
13-16 years	14 (20.2)
Gender	
Female	49 (71)
Male	20 (29)
History of family member with rheumatic fever	13 (18.8)
Neurological findings of chorea	
Involuntary movements of extremities	67 (97.1)
Changes in speech	18 (26.0)
Gait impairment	17 (24.6)
Changes in handwriting	16 (23.1)
Changes in behavior	10 (14.4)
Characteristics of Chorea	
Bilateral	35 (50.7)
Hemichorea	34 (49.2)

Mann-Whitney U test. To compare two ratios of recruitment among clinical and silent carditis groups, Z test was performed, and for inference, corresponding p values were used.

Results

Study Group

A total of 551 cases were diagnosed with ARF within the study period, and SC was established in 69 cases (12.5%). Clinical and demographic features of 69 cases with SC at the first attack of RF are shown in Table I. SC was remarkably more common in pre-adolescent girls. The female to male ratio was 2.45 (49 female, 20 male). Half of the patients had bilateral chorea at presentation. Chorea resolved in 52 (75.3%) of the cases within two months and in 17 (24.6%) cases between the 3rd and 8th months after the medication was started. Electroencephalography was performed in 13 cases and found normal in all cases. MRI was performed in 24 cases, and revealed minor intracranial abnormalities in 4 cases. None of these abnormalities could have been responsible for chorea. Serum ceruloplasmin level, APA and ACA levels were normal in 24 cases.

Clinical Examination

Pure chorea was detected in 39 cases (56.5%). Clinical carditis was diagnosed in 30 patients (43.4%), and they had murmurs consistent with carditis. Among cases with chorea and associated carditis, 7 patients also had arthralgia. As a rare clinical association of ARF, arthritis, carditis and chorea were observed in a 12-year-old girl. Erythema marginatum and subcutaneous nodules were not observed in any case.

Laboratory Work-Up

An elevated ASO titer was observed in 47 cases and positive throat culture was documented in only 1 case. At the initial diagnosis, elevation of APRs was recorded in 8 cases (11.5%), and they also had either arthritis/arthralgia or carditis. By electrocardiography, all had a sinus rhythm, and first-degree atrioventricular block was recorded in 13 (18.8%) of all cases. Serum APA and ACA were evaluated in 21 cases and found normal in all cases. Serum ANA and

anti-DNA antibodies were investigated in 31 cases and none of the patients had positive results.

Echocardiography

At the initial examination, 20 patients (28.9%) had a normal echocardiogram. The diagnosis of silent carditis was established in 20 (28.9%) cases, and clinical carditis was established in 29 (42%) patients (Fig. 1A). As a typical echocardiographic finding, pure mitral regurgitation was detected in 36 (73.4%) of the patients with carditis. Both mitral and aortic regurgitation was detected in 13 (26.5%) of the patients with carditis. Carditis was mild in 41 patients with carditis (83%). Moderate and severe carditis was observed in 7 cases and 1 case, respectively. Mild dilation of left cardiac chambers was detected in 8 cases. Except for 1 case with third-degree mitral and aortic regurgitation, all cases with carditis had mild or moderate valvular regurgitation, not exceeding second-degree valvular regurgitation.

Treatment

All patients received secondary prophylaxis with benzathine penicillin G (IM) at a three-week interval. During the follow-up period, 2 cases had experienced allergic reaction to penicillin, so they received prophylaxis with 250 mg oral erythromycin twice daily.

Antiinflammatory treatment: Steroids were given in 8 cases during the acute inflammatory period of RF.

Specific protocol for treatment of chorea: 8 patients (11.5%) with mild chorea did not receive medication. Haloperidol (0.25-0.5 mg/kg/d) was given in 52 (75.3%) cases. Sodium valproate (15 mg/kg/d) and carbamazepine (7-20 mg/kg/d) were given in 5 (7.2%) and 2 (2.8%) cases, respectively. Two cases with severe symptoms of chorea were treated with intravenous immunoglobulin.

Follow-Up

Sixty-three cases were followed-up for 1-10 years (mean (SD): 3.6 (2.7) years). Echocardiography was normal in 29 patients (49%) at the last examination. Silent carditis and clinical carditis were established in 12 (19%) and 22 (31.7%) patients, respectively (Fig. 1B).

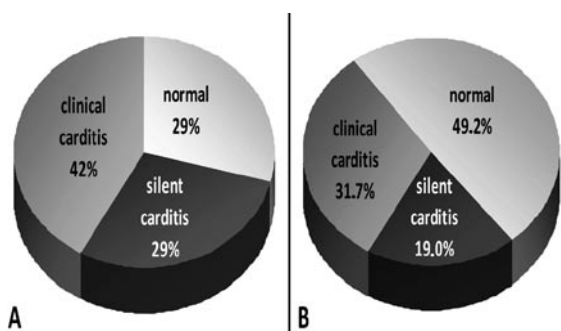


Fig. 1. Clinical and echocardiographic findings of patients at the initial (A) and the last examination (B).

Valvular regurgitation completely disappeared in 10 of 44 cases (22.7%) who had carditis at the initial echocardiographic examination. The degree of valvular regurgitation decreased in 6 of the cases with clinical carditis at the initial diagnosis. Although the complete improvement rate of carditis in patients with silent carditis was found higher than the rate in patients with clinical carditis, no statistically significant difference was found between the groups (29.4% vs 18.5%, $p=0.73$; 95% confidence interval: 2.20-3.63) (Table II). No new valvular involvement or increases in the degree of valvular pathologies were encountered in any case.

Twenty-nine cases were followed up for the short-term period. Among them, 26 cases had carditis at the first examination, and persistence of carditis was detected in 21 of the 26 cases (80.7%). Long-term follow-up information was available in 34 cases. Among them, 18 cases had carditis at the first examination, and persistence of carditis was detected in 13 of the 18 cases (72.2%). The persistence rate of carditis tended to decrease in patients with a long follow-up period; however, there was

no statistically significant difference between the groups (80.7% vs 72.2%, $p=0.72$; 95% confidence interval: 2.5-3.8).

Recurrence: Seventeen recurrences were identified in 13 of 63 cases (20.6%) and all had a reactivation of chorea. Interestingly, we did not encounter any patient who had a relapse of carditis during the follow-up period.

Only 1 recurrence was observed in 10 cases (76%). One patient had 3 relapses and 2 cases had 2 relapses of chorea. The time of the relapse (between the first attack and last recurrence of SC) ranged from 2 months to 9 years (Fig. 2). Fifty-eight percent of recurrent attacks occurred between the 2nd and 24th months after the first attack. Except in 1 case, relapse of chorea resolved in all cases within 3 months (mean (SD): 1.9 (1.4) months). One case had jerking, and it persisted up to 2 years after the first presentation. Recurrence of chorea was not associated with laboratory evidence for active RF in any case. Clinical features of patients with recurrent episodes of SC are shown in Table III.

Although the median age of patients without recurrence of chorea was found higher than patients with recurrence of chorea, no statistically significant difference was found between the groups (median ages: 11 years vs 9 years, $p=0.09$). The female to male ratio in patients with recurrence was 3.3 (10 female, 3 male). This ratio was 2.3 (35 female, 15 male) in patients without recurrence. There was no difference between the groups ($p=0.74$).

Adherence to secondary prophylaxis with benzathine penicillin G was remarkably high and recorded in 57 cases (88.8%). Among patients with recurrence of chorea, 2 cases were not adherent to secondary prophylaxis.

Table II. Echocardiographic Findings in 63 Patients with Sydenham's Chorea Followed Up at Least One Year

Echocardiographic evidence of carditis	Initial diagnosis n (%)	Follow-up examination n (%)	Improvement n (%)
ABSENT	19 (30.2)	29 (46.1)	-
PRESENT	44 (69.8)	34 (53.9)	10 (22.7)
Clinical Carditis	27 (42.8)	22 (34.9)	5 (18.5)*
Silent Carditis	17 (27.0)	12 (19.0)	5 (29.4)*
Total	63 (100)	63 (100)	10 (22.7)

* $p>0.05$

(*) Improvement rate of carditis in patients with silent carditis was compared with the ratio in patients with clinical carditis.

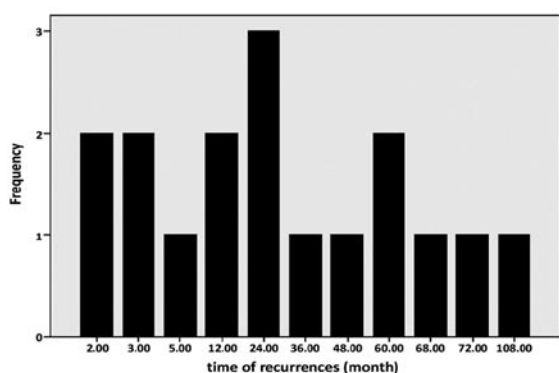


Fig. 2. Distribution of the frequency and time of recurrent episode of SC (between the first attack and last recurrence of RF) within the study period.

Although recurrence in patients without adherence to prophylaxis was more prevalent than in patients with adherence to prophylaxis, no statistically significant difference was found between the groups (28.6% vs 19.6%, $p=0.44$) (Table IV).

Discussion

Cardiac involvement occurs in 44-70.5% of cases with chorea^{2,3,11,23,24}. Subclinical “silent

carditis” also occurs in 8-75% at the first episode of ARF^{2-4,9,16,18,25}. In our study group, carditis was observed in only 42% of cases by auscultation alone, and 28.9% of cases had silent carditis. Many researches also indicate that subclinical valvulitis demonstrated by echocardiography should be accepted as a major finding for the diagnosis of carditis^{4,16,24}.

Both the severity of initial carditis and RF recurrences strongly influence the prognosis and natural history of rheumatic carditis. Recognition of associated silent carditis is critical for preventing morbidity and mortality related to RF¹³. Figueroa et al.¹⁸ reported that valvar lesions of patients with silent carditis were not a transitory entity, with persistence of valvar illness being demonstrated in at least 60% of their patients with subclinical carditis after five years of follow-up evaluation. Caldas et al.¹⁹ observed that echocardiographic alterations persisted in 86.9% of patients with clinical carditis and in 72.7% of cases with silent carditis in the follow-up period. In a study from Turkey, Özkutlu et al.⁴ reported

Table III. Characteristics of Patients with Recurrent Episodes of Sydenham’s Chorea

No	Age (years)/ Gender	Rheumatic fever findings at the initial diagnosis	Treatment	Number of relapses	Time interval between first attack and recurrence of chorea	Follow-up period (years)
1	6/F	Hemichorea	Haloperidol	3	3 rd , 8 th , 9 th year	10
2	10/M	Chorea and carditis	Haloperidol	2	3 rd month and 2 nd year	6
3	9/F	Hemichorea and carditis	Sodium valproate	2	1 st and 2 nd year	4
4	10/M	Chorea and carditis	Haloperidol	1	2 nd month	2
5	9/M	Pure chorea	Haloperidol	1	6 th year	6
6	9/F	Hemichorea and carditis	Haloperidol	1	4 th year	6
7	10/F	Hemichorea and carditis	Haloperidol	1	2 nd year	8
8	14/F	Hemichorea and carditis and arthralgia	Haloperidol	1	5 th month	1
9	8/F	Chorea and carditis	No treatment	1	5 th year	6
10	12/F	Hemichorea and carditis	Haloperidol	1	4 th month	1
11	11/F	Hemichorea and carditis	Haloperidol	1	2 nd month	1
12	6/F	Pure chorea	Haloperidol	1	1 st year	10
13	8/F	Hemichorea and carditis	Haloperidol	1	5 th month	6

that persistence of carditis was detected in 40% of cases with silent carditis in the short-term follow-up. Panamonta et al.¹⁷ reported that the persistence of a mitral regurgitation murmur and of pathologically significant valvular regurgitation by echocardiography were seen in 33% and 60% of cases, respectively, at the one-year follow-up, but the persistence of both was 25% in the five-year follow-up. They also reported that the incremental benefit beyond five years after the initial attack might be minimal. In our study, the improvement rate of valvulitis in patients with silent carditis was not different from that in patients with clinical carditis. Similar to the results of Panamonta et al.¹⁷ and Caldas et al.¹⁹, we observed that carditis persisted in 72.2% of cases after two years of follow-up, and they had no evidence of reactivation of carditis.

Recurrence can cause new valve damage evident by echocardiography in a patient with pure SC who had previous subclinical valvulitis, so a longer duration of secondary prophylaxis is recommended to prevent a recurrence of RF in these patients¹⁷. In our study, most of our cases had mild carditis without recurrence and they showed resolution. The proportion of patients with ARF who developed RHD has decreased during the penicillin era¹³. IM administration of benzathine penicillin (1.2 million units and every 4 weeks) is the most effective secondary prophylaxis regimen in many areas, but in areas where RF is endemic, as in our country, administration of benzathine penicillin every

three weeks is preferable. Spinetto et al.²⁶ reported that 28-day long-acting penicillin prophylaxis is effective for patients with no or mild cardiac disease by auscultation, and non-adherence to prophylaxis was responsible for 55% of recurrences in their patients. In our study, 21-day long-acting penicillin prophylaxis was effective for patients with mild cardiac disease, and no new valvular involvement was observed in patients without carditis at the initial attack.

The exact level of adherence to secondary prophylaxis required to prevent an ARF episode is not known; however, reducing the recurrence rate of ARF can be achieved with maintaining an adherence rate above at least 85%²⁷. Low adherence can lead to high rates of recurrence^{15,20,26,27}. Seckeler et al.²⁰ reviewed 144 patients with ARF. Recurrence of ARF was recorded in 38% of their study population. However, the mean level of compliance with secondary prophylaxis was remarkably low in their population.

Age and gender also influence prognosis, as rheumatic carditis resolves more frequently in boys. Pelajo et al.¹⁴ reported that the patients with a recurrent episode of RF were younger, more frequently males, and less adherent to secondary prophylaxis than patients without RF recurrence. Adherence to secondary prophylaxis and a recurrent episode of RF were detected in 65% and 16.5% of their patients, respectively. 54.5% of their patients who had a recurrence were non-adherent to secondary prophylaxis.

Table IV. Comparison of Recurrence Rate of Chorea in Patients With and Without Adherence to Secondary Prophylaxis

RECURRENCE	Adherence to secondary prophylaxis	Non adherence to secondary prophylaxis	TOTAL	P
ABSENT				
Number of cases	45	5	50	
% within group	80.4	71.4	79.4	
% of Total	71.4	7.9	79.4	
PRESENT				
Number of cases	11	2	13	0.44
% within group	19.6*	28.6*	20.6	
% of Total	17.5	3.2	20.6	
TOTAL				
Number of cases	56	7	63	
% within group	100.0	100.0	100.0	
% of Total	88.9	11.1	100.0	

(*) Recurrence rate in patients with adherence to secondary prophylaxis was compared with the ratio in patients without adherence to secondary prophylaxis.

Recurrent attack of chorea is observed in 8.5-30% of cases with SC^{1,14,23,24}. In our study, a recurrent episode of chorea was detected in 20.6% of cases. Although the median ages of patients without recurrence of chorea was found higher than in patients with recurrence of chorea, no significant difference was found between the groups. The female to male ratio in patients without recurrence was also not different from patients with recurrence of chorea.

Adherence to secondary prophylaxis was remarkably high in our study population. We also observed that recurrence of chorea in patients with non-adherence to prophylaxis was more prevalent than in patients with adherence to prophylaxis. We did not encounter relapse of carditis during the follow-up period, and benzathine penicillin G (at 3-week intervals, IM) was found highly effective on recurrence of rheumatic carditis.

Since most patients with chorea in our study were treated with haloperidol, response to treatment and risk factors for recurrence of chorea could not be evaluated in the different treatment groups. Despite regular treatment with benzathine penicillin, recurrence of chorea was not a rare complication in some patients in the follow-up period. Recurrence of chorea was not associated with clinical or laboratory evidence for streptococcal infection. Because of the retrospective nature of our study, we were unable to determine serum levels of penicillin in these patients; compliance was assessed according to the information from patients and parents. As seen in our study, Terreri et al.²⁴ reported that some of their patients with chorea presented recurrence of chorea despite regular treatment with benzathine penicillin. They examined 86 patients who presented chorea at the first attack. Twenty-five of them (29%) had 32 recurrences, of which 24 were of chorea. They observed a predominance of chorea (63%) in the recurrences, which proves the tendency of chorea to mimic its first attack. Sixty-one children (71%) had no failure in the secondary prophylaxis, while 25 (29%) were not compliant. Of the 17 patients who presented recurrence, 9 (53%) cases showed good compliance. ASO titer was found to be normal in all of them. These observations led us to think that non-streptococcal stimuli or a neuropathogenetic mechanism may be responsible for re-exacerbation of chorea.

In conclusion, patients with chorea usually had mild carditis, and the carditis showed resolution. Most patients complied with secondary prophylaxis, so relapse of carditis was exclusively prevented in our patients. Some of our patients with chorea presented recurrence of chorea despite regular treatment with benzathine penicillin. Non-streptococcal stimuli or a neuropathogenetic mechanism may be responsible for the relapse of chorea.

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