

Original Article

Subclinical rheumatic valvitis: a long-term follow-up

Cristina Costa Duarte Lanna, Edward Tonelli, Marcio Vinicius Lins Barros,
Eugenio Marcos Andrade Goulart, Cleonice Carvalho Coelho Mota

Division of Paediatric Cardiology, Department of Paediatrics, Hospital das Clínicas, Federal University of Minas Gerais, Belo Horizonte, Brazil

Abstract In order prospectively to investigate the frequency and evolution of subclinical valvitis, we selected 40 consecutive patients suffering their initial attack of rheumatic fever, seen in our clinic from 1992 to 1994, and followed-up until 2001, with a mean period of follow-up of 8.1 years, and a standard deviation of 0.6 year. We also assembled a matched control group of 37 healthy children and adolescents. We discovered a murmur of mitral regurgitation in 28 (70.0%) of the patients. In 3 (7.5%) of these patients, there was also a murmur of aortic regurgitation. In the group of 28 symptomatic patients, Doppler echocardiography showed mitral regurgitation in all, and aortic regurgitation in 17. In the group of 12 patients without clinical evidence of cardiac involvement, Doppler echocardiography identified mitral regurgitation in 2, isolated in one and associated with aortic regurgitation in the other. Thus, the frequency of subclinical valvitis was 16.7%. In patients with subclinical valvitis only the aortic regurgitation regressed during the period of follow-up. In the group of 28 symptomatic patients, mitral regurgitation disappeared in 6 (21.4%), aortic regurgitation in 7 of the 17 having this feature (41.2%), while 2 patients (7.1%) developed mitral stenosis. The sensitivity and specificity of cardiac auscultation were, respectively, 93.3%, with 95% confidence intervals between 72.3% and 97.4%, and 100%, with 95% confidence intervals between 65.5% and 100%, for the diagnosis of mitral regurgitation, and 16.7%, with 95% confidence intervals between 4.4% and 42.3%, and 100%, with 95% confidence intervals between 81.5% and 100%, for that of aortic regurgitation. We conclude that the Doppler echocardiogram is an important means of diagnosing and assessing the evolution of subclinical rheumatic valvar lesions, which are not always transient. We suggest that Doppler echocardiography should be performed in all patients with acute rheumatic fever. Subclinical valvitis should be considered as mild carditis, provided that strict criteria are observed in the differential diagnosis from physiological regurgitation, and Doppler echocardiographic findings are analyzed in the context of the other manifestations of the disease.

Keywords: Rheumatic fever; Doppler echocardiogram; subclinical valvitis

THE INCIDENCE AND PREVALENCE OF RHEUMATIC fever, and chronic rheumatic heart disease, have decreased sharply in North America, Europe, and Japan over the last 20 years. In developing countries, however, rheumatic fever is still a great challenge. Chronic rheumatic valvar disease, considered the main cause of acquired heart disease in those aged

from 5 to 24 years, impairs the quality of life of many young people, having significant social and economic impact.^{1,2} The degree of valvar involvement in the acute phase, and its worsening due to recurrences of the disease, are intimately related to the poor outcome. The necessity of surgery is another problem because of the use of prostheses and anticoagulants. The high morbidity reinforces the importance of early and accurate diagnosis, as does appropriate prophylaxis against recurrences.

In some studies, valvar regurgitation has been demonstrated by Doppler echocardiography in some

Correspondence to: Cristina Costa Duarte Lanna, Rua Juiz da Costa Val 65/402 – Santa Efigênia – 30 240-350, Belo Horizonte – Minas Gerais, Brazil. Tel: 55 31 3281 8190; Fax: 55 31 3221 1552; E-mail: lanna@medicina.ufmg.br

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Table 1. Comparative analysis between the 40 patients and their 37 controls.

Characteristics	Study group		Control group		p
	n	%	n	%	
Gender					
Male/female	17/23	42.5/57.5	20/17	54.1/45.9	0.4321*
Age (years)					
Mean	10.6 ± 2.7		9.5 ± 2.4		0.0743**
Minimum	5		6		
Maximum	15		14		
Body surface area					
Mean (m ²)	1.5 ± 0.23		1.10 ± 0.25		0.5400**

*Chi square; **Fischer exact test

patients with isolated arthritis or chorea and normal cardiac auscultation, a feature which has been called “subclinical valvitis”.^{3–16} The high sensitivity of the Doppler echocardiogram has also, however, revealed physiological valvar regurgitation in healthy children without any evidence of heart disease, with different characteristics from the regurgitant jets of rheumatic patients with valvar lesions. As a consequence, strict criteria must be used when differentiating these two conditions.^{17–20}

The frequency and evolution of subclinical valvitis are not well known in patients with chorea or polyarthritis. The information provided by the Doppler echocardiogram raises the question whether the Jones Criteria need modification to incorporate this technology. With this in mind, the objectives of our study were to investigate, prospectively, the frequency and late evolution of the first attack of rheumatic fever in patients with subclinical valvitis, and also in patients with clinical evidence of cardiac involvement, comparing the echocardiographic characteristics of the minor regurgitant jets seen in the patients with those found in a matched group of controls.

Methods

This prospective and descriptive controlled study was carried out with children and adolescents seen at the Clinic for Rheumatic Fever of the Division of Paediatric Cardiology, Hospital das Clínicas, Federal University of Minas Gerais, Brazil. Over the period from October 1992 through December 1994, we selected 40 consecutive patients seen during their first attack of acute rheumatic fever, submitting them to clinical and laboratorial follow-up until October 2001. The period of follow-up varied from 7.7 to 9.7 years, with a mean of 8.1 years, and a standard deviation of 0.6 year.

The diagnosis of rheumatic fever was determined according to the revised Jones Criteria of 1992.²¹ The acute phase of the disease was defined as starting

from the beginning of the symptoms, with alteration of at least one of the acute phase reactants. Patients with recurrence during follow-up, those with report of previous acute attacks, or those without any report of a previous acute phase, but with echocardiographic findings compatible with chronic valvar diseases, such as restriction of the mobility or “doming” of the valvar leaflets and presence of mitral or aortic valvar stenosis, were excluded, as well as those without regular compliance to the follow-up protocol. We also excluded those with chorea as an isolated manifestation whose acute phase reactants were normal.

To compare the characteristics of the pathological and physiological regurgitant jets, we assembled an equivalent control group of 37 health children and adolescents without murmurs, even innocent, without previous or current heart disease, or any other systemic disease. The variables used for matching the two groups were age, body surface area, and gender (Table 1).

For the definition of pathological regurgitation, we required the presence of turbulence with a reverse jet of posterior location and prolongation into the interior of the preceding chamber for varying distances, but greater than 1 cm beyond the valvar leaflets, with a duration longer than 200 ms, and maximum peak velocity of flow higher than 2.5 m/s as analysed by continuous Doppler. When assessing the mitral valvar jets, we analysed the pattern of the mosaic in at least two planes. The criteria used to classify the degree of valvar thickening were:

- Normal leaflets: up to 2 mm;
- Mild thickening: 3 to 5 mm;
- Moderate thickening: 6 to 8 mm;
- Severe thickening: more than 8 mm.

All the patients were examined from the initial to the last evaluation by the same two paediatric cardiologists, and submitted to laboratorial tests to confirm a preceding streptococcal infection and acute phase

Table 2. Comparison between patients in first attack of rheumatic fever, with and without diagnosis of carditis according to frequency of echocardiographic abnormalities.

	Clinical examination/ECG/Chest X-ray					
	Patients without carditis (n = 12)		Patients with carditis (n = 28)		Total (n = 40)	
	n	%	n	%	n	%
Echocardiogram						
Mitral regurgitation	2	16.7	28	100	30	75.0
Aortic regurgitation	1	7.7	17	60.7	18	45.0
Tricuspid regurgitation	1	7.7	11	39.3	12	30.0
Pulmonary regurgitation	0		1	3.6	1	2.5
Mitral valvar thickening	2	16.7	28	100	30	75.0
Aortic valvar thickening	0		3	10.7	3	7.5
Mitral valvar prolapse	1	7.7	7	25.0	8	20.0
Pericardial effusion	0		3	10.7	3	7.5

reactants (erythrocytic sedimentation rate, C-reactive protein, white blood cell count, mucoprotein and electrophoretic protein study), as well as electrocardiography, chest X-rays and echocardiographic evaluation by M-mode, cross-sectional, color flow Doppler, pulsed and continuous wave Doppler. The echocardiographic studies of all the patients were performed during the first four weeks of the acute phase by the same cardiologist, who knew neither the clinical conditions of the patients nor whether they belonged to the study or to the control groups. The images were acquired with Siemens CF Plus and Toshiba 270 machines, with 3 and 5 MHz transducers.²²⁻²⁴

All the patients included in this study were evaluated prospectively, in agreement with the established protocol. During the acute phase, the clinical examinations were carried out at weekly intervals, and in the chronic phase the patients were appraised every 6 months. The first Doppler echocardiogram was done during the week of the first clinical exam in nine-tenths of the patients. The examinations were repeated at one, three, and six months, starting from the first visit, and then annually. The secondary prophylaxis instituted for all patients was benzathine penicillin, given at a dose of 1,200,000 international units every 21 days. The patients with a diagnosis of carditis, including those with subclinical valvitis, were treated with prednisone at a dose of 1 to 2 mg/kg/day.

Statistical analysis

Categorical variables of equivalence between the two groups were examined using Chi square analysis or Fisher's exact test, and the comparison of Doppler echocardiographic measurements were analysed using Student's t-test. The indexes of association, sensitivity and specificity, were calculated by the Fleiss method,

using an interval of confidence of 95%. A p value of less than 0.05 was considered as statistically significant.

Results

Having evaluated the 40 patients enrolled in our study, arthritis was diagnosed in 29 patients (72.5%), carditis in 28 (70.0%), chorea in 9 (22.5%), and subcutaneous nodules and erythema marginatum in 1 (2.5%) patient. Carditis, as based on the clinical, radiographic and electrocardiographic features, was diagnosed in 28 patients. Of these, tachycardia, with a heart rate of more than 100 beats per minute, was found in 14 (50.0%), congestive cardiac failure in 8 (28.6%), a murmur of mitral regurgitation in all, a murmur of aortic regurgitation in 3 (10.7%), and the Carey-Coombs murmur in 10 (37.0%). In one of these patients, mitral regurgitation had been registered by Doppler echocardiography two weeks before the murmur had been identified by cardiac auscultation, on the 37th day after the beginning of the disease.

The electrocardiogram was normal in all the patients without clinical evidence of cardiac involvement, and also in 11 of the patients with carditis. In the other 17 with a diagnosis of carditis, alterations were seen only suggestive of changes in the left chambers. Enlargement of the left ventricle represented the most frequent alteration, present in 15 patients (55.0%), being isolated in 7 and associated with enlargement of the left atrium in 8. There was an increase of the QTc interval in 5 patients (18.5%), and only 1 (3.7%) had first-degree atrioventricular block. The chest radiograph was normal in 31 patients (77.5%), these being all those without carditis, and 19 of those with clinical evidence of cardiac involvement.

The first Doppler echocardiographic evaluation, performed during the acute phase (Table 2), identified some type of valvar lesion in all the 28 patients with

carditis, and also in two of the 12 patients without clinical evidence of cardiac involvement (16.7%). Thickening of the mitral valve was the most frequent finding, being found in 30 (75.0%) individuals, in contrast with the thickening of the aortic valve, registered in only three patients. The second most common alteration was left ventricle dilation, present in 18 patients (45.0%), 11 of whom presented an associated enlargement of the left atrium. In one of these patients, no abnormalities had been detected in the clinical examination. Prolapse of the mitral valve, and pericardial effusion, was only found in patients with clinical manifestation of cardiac involvement. The ejection fraction, and shortening fraction of the left ventricle, was normal in all the patients.

In all the 28 patients with a diagnosis of carditis, mitral regurgitation was confirmed by the Doppler echocardiogram, being mild in 14 (50.0%), moderate in 9 (32.0%), and severe in 5 (18.0%). The diagnosis of aortic regurgitation was registered by cardiac auscultation in 3 (10.7%) individuals, being mild in 2 and moderate in 1, but the Doppler echocardiogram identified aortic regurgitation in 17 (60.7%), mild in 14 and moderate in 3 patients. Of the 28 patients with diagnosis of carditis, 8 (28.6%) developed cardiac failure during the acute phase. Of the 12 patients without abnormalities by cardiac auscultation, the Doppler echocardiogram demonstrated mitral regurgitation in 2, both with thickening of the leaflets of that valve, one being of mild to moderate degree (Fig. 1), and the other of mild degree associated with mild aortic and tricuspid regurgitation. Regarding clinical manifestations in these two patients, the one with mild to moderate degree of mitral regurgitation presented chorea, and the other presented polyarthritis. The frequency, therefore, of Doppler echocardiographic abnormalities of the mitral valve, isolated or associated with aortic

regurgitation, was 16.7%, which corresponds to the frequency of subclinical valvitis (Table 2).

In the evaluation of the 28 patients with carditis, in addition to the concordance between auscultatory and echocardiographic findings of valvitis-mitral regurgitation in all and aortic regurgitation in 3 of 28, the echocardiogram identified associated pathological minor aortic jets without any corresponding murmur at the clinical examination in 14 of the 28 (50%) patients.

Considering the Doppler echocardiogram as the gold standard for the diagnosis of mitral and aortic regurgitation in the acute phase, the sensitivity, specificity, positive and negative predictive value of cardiac auscultation, complemented by the electrocardiogram and the radiographic chest exam, are demonstrated in Tables 3 and 4, respectively.

In the evaluation of the 37 healthy children and adolescents that constituted the control group,

Table 3. Clinical diagnosis of mitral regurgitation in our 40 patients considering the Doppler echocardiogram as the gold standard.

Mitral regurgitation (cardiac auscultation)	Mitral regurgitation (Doppler echocardiogram)		Total
	Yes	No	
Yes	28	0	28
No	2	10	12
Total	30	10	40

Sensitivity = 93.3% (28/30) (CI 95%: 76.5% to 98.8%)

Specificity = 100% (10/10) (CI 95%: 65.5% to 100%)

Positive predictive value = 100% (28/28) (CI 95%: 85.0% to 100%)

Negative predictive value = 76.9% (10/12) (CI 95%: 50.9% to 97.1%)

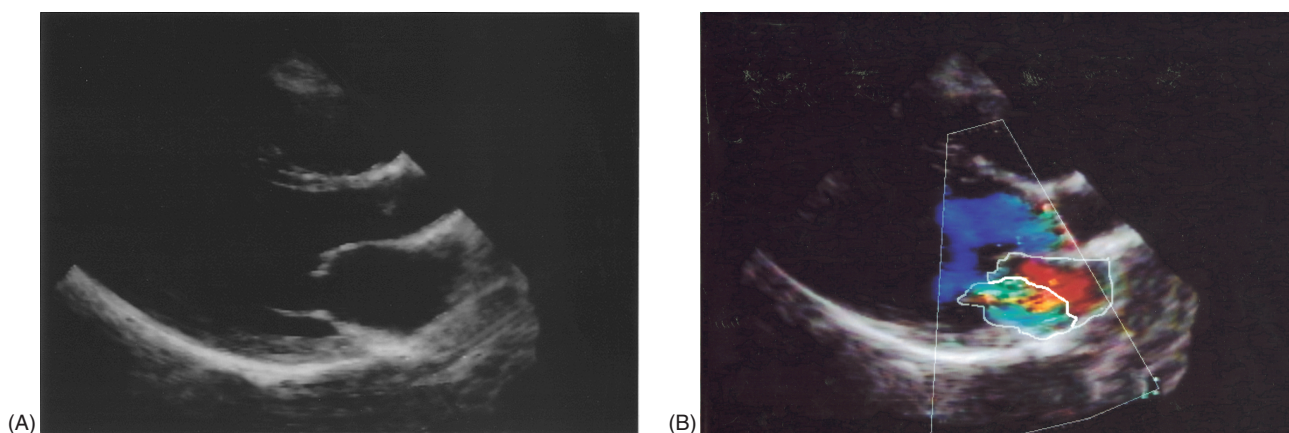


Figure 1.

A 9-year-old girl with subclinical rheumatic valvitis. (A) cross-sectional echocardiogram showing mild thickening of the aortic leaflet of the mitral valve. (B) Mild mitral regurgitation revealed by color flow Doppler.

following the established criteria, cardiac auscultations, and the M-mode and cross-sectional echocardiograms, were normal. The pulsed, continuous and color flow mapping Doppler registered physiological mitral regurgitation in 4 (10.8%), and physiological tricuspid regurgitation in 17 (45.9%). Aortic regurgitation was not found. As for the dimensions of the cardiac chambers and systolic function, there were no statistically significant differences between the controls and the group of rheumatic patients without alterations detected by the cardiovascular clinical exam, including the two patients with subclinical valvitis (Table 5).

During the period of follow-up from 7.7 to 9.7 years, with a mean of 8.1 years and a standard deviation of 0.6 year, the auscultation normalized in 6 of

the 28 patients with carditis. As judged from the Doppler echocardiograms, the thickening of the leaflets of the mitral valve persisted in 12 of 28, mitral regurgitation disappeared in 6 of 28, aortic regurgitation in 7 of 17, and 2 patients developed mitral stenosis. Of the 8 patients with prolapse of the mitral valve, 3 maintained the lesion. In the 2 patients that presented subclinical valvitis, thickening of the leaflets of the mitral valve persisted without modification, as well as the characteristics of the regurgitation jet in that same valve, both patients having had valvar lesions of mild degree. The jet of aortic regurgitation disappeared, as did the enlargement of the left atrium.

Discussion

The introduction of a new technique permitting both morphological and functional evaluation of cardiac diseases – the Doppler echocardiogram – has added important information on the type and the degree of cardiac abnormalities. Starting in the 1980s, several studies have been published about the use of this technique in the investigation of patients with acute rheumatic fever. The literature is also abundant with studies on the clinical and laboratorial characteristics of acute attacks of rheumatic fever.^{25–30} Studies on the echocardiographic analysis of the first attack, however, are fewer in number, mainly those that deal with late evolution of subclinical valvitis.^{14–16}

Although the electrocardiogram and the chest radiograph are of considerable clinical benefit, these tests are characterized by low sensitivity and specificity when compared with the Doppler echocardiogram,

Table 4. Clinical diagnosis of aortic regurgitation in our 40 patients considering the Doppler echocardiogram as the gold standard.

Aortic regurgitation (cardiac auscultation)	Aortic regurgitation (Doppler echocardiogram)		Total
	Yes	No	
Yes	3	0	3
No	15	22	37
Total	18	22	40

Sensitivity = 16.7% (3/18) (CI 95%: 4.4% to 42.3%)

Specificity = 100% (22/22) (CI 95%: 81.5% to 100%)

Positive predictive value = 100% (3/3) (CI 95%: 31.0% to 100%)

Negative predictive value = 59.5% (22/37) (CI 95%: 42.2% to 74.8%)

Table 5. Comparison of echocardiographic measurements between our 10 patients without valvar lesion and the 37 individuals of the control group.

Echocardiographic measurements (M-mode and cross-sectional)	Study group without valvar lesion (n = 10)	Control group (n = 37)	p
Aortic root diameter (mm)			
Mean	24.9 ± 3.2	22.8 ± 3.1	p = 0.0648*
Left atrium (mm)			
Mean	29.6 ± 4.4	27.5 ± 3.8	p = 0.1320*
Ventricular septum (mm)			
Mean	6.2 ± 0.8	6.0 ± 0.9	p = 0.5382*
Ventricular posterior wall (mm)			
Mean	6.1 ± 0.7	5.6 ± 0.9	p = 0.1445*
Left ventricle – diastole (mm)			
Mean	42.6 ± 4.2	39.6 ± 4.6	p = 0.0694*
Left ventricle – systole (mm)			
Mean	27.0 ± 2.8	26.2 ± 4.2	p = 0.5948*
Fractional shortening of left ventricle (%)			
Mean	35.3 ± 5.0	5.6 ± 3.1	p = 0.7821*
Ejection fraction of left ventricle (%)			
Mean	65.0 ± 6.0	65.7 ± 3.8	p = 0.6584*

* Student's t-test

which is particularly useful in identifying the minor degree of valvar involvement. The prolongation of PR interval has been described as a common finding in acute rheumatic fever.^{31,32} In contrast, we detected first degree atrioventricular block in only one patient (3.7%), a lower frequency when compared with the increase of QTc interval (18.5%). These results are in agreement with a previous study among our patients. The investigation of 109 children in first attack of rheumatic fever showed the same pattern, with frequencies of 11.8% and 25.0%, respectively.³³ Hilário et al.¹⁴ did not detect any conduction disturbance in their investigation of 22 children also in the early stage of the first episode of rheumatic fever. These findings might reflect the stage of the inflammatory process, rather than the degree of repercussion, since asymptomatic patients can also present with disturbances of conduction.

Great variation exists in the frequency of subclinical carditis in the studies consulted, varying between involvements of two-fifths to nine-tenths, probably because of the different methodological approaches used. Few authors have used a control group of healthy children for comparison between the characteristics of physiological and pathological valvar jets and a blinded analysis by the Doppler echocardiogram.^{3,5,7-9,12,14-16}

The identification of the valvar lesion by the Doppler echocardiogram at a time prior to the detection of the murmur by cardiac auscultation, as occurred in one patient in our study, and two in the investigation of Abernethy et al.,¹¹ draws attention to the importance of the serial clinical examination, at weekly or biweekly intervals, during the acute phase of rheumatic fever. Considering that the murmurs can appear late, their absence in the initial phase of the acute episode does not rule out a diagnosis of carditis. Together with better knowledge of the echocardiographic pattern of physiological valvar regurgitation, and the elaboration of stricter criteria for the differential diagnosis of pathological regurgitation, the absence of a systematized clinical follow-up in the acute phase could also explain the wide variation in frequency of the subclinical valvitis registered in the literature.

In the present study, the identification, by Doppler echocardiography, of thickening of the leaflets of the mitral valve in all the patients with valvar lesions during the acute phase is an important finding, because it can aid in the differential diagnosis between pathological lesions and physiological regurgitation. The low sensitivity and specificity of cardiac auscultations for the diagnosis of aortic regurgitation in this research, in accordance with Wilson et al.¹² reinforces the difficulties of the diagnosis of the mild lesions, probably due to the characteristics of the

murmur, habitually of low intensity, even in lesions of greater severity. We would emphasize that the association of mitral and aortic lesions, frequent in rheumatic fever, is an additional characteristic in the context of diagnosis, besides the different prognostic implications, when compared to the presence of only one valvar lesion.

As regards the profile of presentation and evolution of the two patients with subclinical valvitis, some points must be emphasized. Although the small number of patients with subclinical valvitis constitutes a limitation for conclusions, there is similarity with the valvar lesions diagnosed by clinical examination considering the type of valve affected, the valvar morphology, and the pattern of regression of the lesions, demonstrating further, a larger percentage of regression of aortic as opposed to mitral regurgitation.

To our knowledge, evolutionary analysis of subclinical valvitis involving the persistence of lesions after eight years of follow-up, as demonstrated in our study, has not previously been registered in the literature. Recently, Özkutlu et al.,¹⁶ during an investigation with a follow-up time of 1 to 10 months, observed disappearance of the lesions in 4 of 12 patients with silent valvar insufficiency. Considering the frequency of regression of the subclinical valvitis reported by these authors, the persistence of valvar involvement in all of our patients is probably due to the reduced size of our group, and reflects one of the limitations of the study.

Normal left ventricular systolic function was observed in all the patients, including those with cardiac failure. This fact is in agreement with recent observations that show a stronger correlation of congestive cardiac failure with the degree of valvar injury than with dysfunction of the myocardium. Corroborating this hypothesis, the low frequency of congestive cardiac failure in the first attack, unlike the recurrences of the disease, results from the small number of significant valvar lesions during this phase. The investigation of ventricular function exclusively by an echocardiographic study at rest, and through the transthoracic window, is also recognized as a limitation of our study.

The contribution of Doppler echocardiography to the diagnosis of valvar lesions of rheumatic origin, therefore, is valuable, as valvar involvement in 2 of our patients was identified only by that method. It is important to emphasize that mitral regurgitation persisted during the 8 year period of follow-up. The diagnosis of subclinical valvitis indicates that the heart may be affected very early in the acute phase, even in the absence of clinical manifestations. As these lesions are not very significant, and are usually seen in the absence of enlargement of chambers, pericarditis or prolapse of the mitral valve, the characteristics of

the jet and thickening of valvar leaflets must be considered the focus for the diagnosis. The comparison of characteristics of the regurgitation in patients with mild valvar involvement with the equivalent control group of healthy patients showed that differences, although unobtrusive, were found. Strict criteria, therefore, should be observed in this analysis to differentiate pathological from physiological regurgitations, because discrete valvar leaks are found in individuals with structurally normal hearts. The high prevalence of physiological regurgitation in children makes the knowledge of their characteristics by the Doppler echocardiogram of paramount importance, in order to avoid under or over diagnosis of subclinical valvitis. In addition, the Doppler echocardiogram does not provide the definition of the etiology. For a more precise diagnosis of rheumatic valvar lesions, therefore, the interpretation of the echocardiographic findings should always be made together with the evaluation of the clinical aspects, other laboratorial abnormalities and the evolution of the findings. The significance of the evolution, and the frequency of resolution of subclinical valvitis, will become apparent only after the follow-up of a larger series of patients.

Even in patients with later clinical manifestation of valvar involvement in the acute phase, as happened with one of the patients of this study, the earliest diagnosis through the Doppler echocardiogram allows a more appropriate control of the therapeutic procedures such as bed rest. In addition, the diagnosis of subclinical valvitis is useful in those patients with isolated polyarthritis of atypical evolution, a condition in which the diagnosis of rheumatic fever is more difficult.

In conclusion, subclinical rheumatic valvitis is not a transient condition. It can persist for a prolonged time, which extends the exposure of patients to the potential risks of increasing the degree of valvar lesions with recurrences. These patients, therefore, should receive preventive attention similar to that given to patients with clinically diagnosed valvar lesions, mainly regarding the longer duration of the secondary prophylaxis and the additional protection for endocarditis. Based upon the current knowledge of diagnosis and evolution of subclinical valvitis, we suggest that Doppler echocardiogram should be carried out in all patients during the acute phase of rheumatic fever, independently of the presence of cardiac abnormalities in the clinical examination. We also suggest that subclinical valvitis should be accepted as evidence of mild carditis, provided that strict criteria have been followed so as to distinguish this finding from physiological regurgitation. Doubts about the benign nature of subclinical valvitis remain, and complementary investigations are essential safely to define the best approach for these patients.

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