



Serial Clinical and Echocardiographic Evaluation in Children with Marfan Syndrome

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OBJECTIVE

To describe the clinical cardiac manifestations and temporal evolution of Marfan syndrome in children; to estimate the incidence of annuloaortic ectasia and mitral valve prolapse; and to evaluate tolerability and efficacy of beta-blockers in these patients.

METHODS

During one year, 21 children with Marfan syndrome underwent serial clinical and echocardiographic examinations. Echocardiograms assessed: the presence of mitral valve prolapse, aortic root diameter, mitral and aortic valves regurgitation, and aortic enlargement during beta-blocker therapy. Eleven patients had two measurements of the aortic root taken one year apart.

RESULTS

The children were asymptomatic throughout the study. Mitral prolapse was found in 11 (52%) children. Annuloaortic ectasia occurred in 16 (76%) patients and found to be mild in 42.8%, moderate in 9.5%, and severe in 23.8%. One of these patients underwent aortic valve replacement and repair of the ascending aorta by the Bentall-De Bono technique, with good results. Heart rate decreased by 13.6% (from 85 to 73 bpm; $p < 0.009$) with the use of beta-blockers; however, aortic root diameter increased by 1.4 mm/year ($p < 0.02$). One child could not be given beta-blockers due to bronchial asthma, and no significant side effects were observed in the remaining children, including one who also had bronchial asthma.

CONCLUSION

The children remained asymptomatic throughout the study, the use of beta-blockers led to a significant decrease in heart rate, and no significant adverse effects were observed. Contrary to the literature, incidence of annuloaortic ectasia was high among the study population, greater than that of mitral valve prolapse, even during beta-blocker therapy.

KEYWORDS

Marfan syndrome, thoracic aortic aneurysm; mitral valve prolapse; Doppler echocardiography

The Marfan syndrome is named after Antoine Marfan, a French pediatrician who in 1896 presented the case of a 5-year-old girl to the Société Médicale des Hôpitaux in Paris¹. Clinical characteristics and natural history of the disease were described for the first time, in an ordered manner, by McKusick in 1955². Marfan syndrome is an inherited autosomal dominant disorder of the connective tissue, with variable expression, which affects primarily the skeletal, ocular and cardiovascular systems. Its prevalence is estimated at about 1/10,000 individuals. However, other estimates suggest higher figures ranging from 4 to 6/10,000 individuals³. Marfan syndrome results from mutations in the fibrillin 1 gene (FBN1)⁴. The primary cardiovascular changes are annuloaortic ectasia and mitral valve prolapse. Owing to these changes, life expectancy of patients with Marfan syndrome just a few years ago was up to the third or fourth decade of life⁵, but a greater knowledge of the disease and the advent of surgical techniques in the last years led to a significant improvement in prognosis⁶.

Most papers published in the literature describe adult patients^{2-7,8}; however, pediatric population is not free from complications. Therefore, the aim of the present study is threefold: to describe the clinical cardiac manifestations and temporal evolution of Marfan syndrome in children; to estimate the incidence of annuloaortic ectasia and mitral valve prolapse; and to evaluate tolerability and efficacy of beta-blockers in these patients.

METHODS

Between January 1999 and November 2000, 21 children with Marfan syndrome - 13 (62%) boys and 8 (38%) girls - were prospectively evaluated. Using the reviewed criteria, the syndrome was confirmed in all the patients⁹. Ages ranged from nine months to sixteenth years (median 10 years). Patients' body weight ranged from 8 to 70 kg. The study protocol was approved by the Institutional Research Ethics Committee, and written informed consent was obtained from all legal guardians of the children for their inclusion in the study.

The same examiner performed all serial clinical and echocardiographic examinations. A chest radiograph was taken on the first visit and an electrocardiogram on each follow-up visit. All patients were maintained on beta-blocker medication, except those with any contraindication; younger children received propranolol, and the others received atenolol. Systemic blood pressure could not be obtained in all children, and dosage of beta-blocker was based solely on heart rate, that is to say, the necessary dosage to maintain heart rate at around 60 bpm or the maximum dosage of the drug for body weight. All school-age children were instructed not to engage in competitive physical activities.

Echocardiograms were performed using ATL HDI 1500, ATL 5000, or Phillips SD-800 machines equipped with a 2.5 or 5 MHz electronic, multifrequency

transducers. Heart cavities and aortic root measurements (in the Valsalva sinuses area) were performed by two-dimensional guided M-mode echocardiographs; only one patient had aortic root measurement taken in two-dimensional mode using the parasternal long-axis view at end-diastole.

Mitral valve prolapse was defined by echocardiographic examination using Freed et al' criteria¹⁰ (superior displacement of one or both mitral leaflets by more than 2 mm above the mitral annular plane during ventricular systole on the parasternal long-axis view).

Mitral and aortic valve regurgitation was further divided into two groups: mild or minor and significant (moderate and severe) After gain adjustment and maximum increase of Nyquist velocity, reflux severity was assessed visually and subjectively, taking into account morphological changes of mitral valve, cavities measurements and regurgitant jet into the left atrium¹¹. Later, interobserver analysis for the quantification of mitral regurgitation was performed. Two experienced and independent examiners reviewed images of ten examinations recorded on VHS tape and, using the same method, determined the degree of valve regurgitation.

Aortic regurgitation was estimated by the ratio of jet width to the left ventricular outflow tract on color flow mapping¹¹.

Annuloaortic ectasia grading was based on reference values used by the Echocardiography Department (adapted from Roge et al)¹² and was established by weight range following the criterion below: a) up to 20%, mild enlargement; b) between 20 and 40%, moderate enlargement; c) above 40%, major enlargement.

Both measurements were performed using the paired Student's t-test for correlated samples, in this case, comparison of aortic root enlargement and heart rate behavior during beta-block administration after one year, where $p < 0.05$ was considered significant. Interobserver variability of mitral regurgitation was assessed by Kappa test.

RESULTS

All children remained asymptomatic during the one-year follow-up, with no evidence of heart failure, including the few with significant valve regurgitation. No asymmetries were found on peripheral pulse palpation. A two-year-old child underwent replacement of the ascending aorta by the Bentall-De Bono technique, due to severe annuloaortic ectasia with rapid enlargement of the ascending aorta and worsening of aortic regurgitation.

Annuloaortic ectasia occurred in 16 (76%) patients and found to be mild in 42.8%, moderate in 9.5%, and severe in 23.8% (five children) (fig 1). Eleven (52%) children had two measurements of the aortic root taken one year apart. Mean annual increase of aortic diameter was 10%, meaning 1.4 mm/year ($p < 0.02$) (tab I). Only three children (14.2%) had aortic valve regurgitation, with a mild regurgitation at the initial evaluation; however,

Table I - Ages in months (m) or years (y); gender: male (M) or female (F); weight in kilograms; aortic diameter (at Valsalva sinuses); and heart rate in beats per minute

Patient	Age	Gender	Weight	Aorta 1st meas.	Aorta 2nd meas.	Heart Rate 1	Heart Rate 2
1	9m	M	8	26 mm	31 mm	150	100
2	7y	F	22		54 mm	80	72
3	11y	F	45	36 mm	37 mm		55
4	6y	M	20	27 mm	28 mm	80	88
5	6y	M	27		30 mm	66	55
6	10y	M	52		45 mm	66	58
7	12y	F	43		23 mm	56	54
8	10y	M	70		34 mm		75
9	10y	M	26	28 mm	26 mm	80	70
10	14y	F	49	44 mm	46 mm		64
11	12y	M	42		34 mm	98	58
12	16y	M	69	38 mm	39 mm	67	48
13	13y	M	38	34 mm	36 mm	55	60
14	5y	F	20		21mm	80	
15	1y	M	20	25 mm	26 mm	118	110
16	14y	M	38	43 mm	44 mm		115
17	10y	F	23		43 mm	75	
18	10y	M	24	25 mm	27 mm	90	86
19	2y	M	16	20 mm	21 mm	120	100
20	15y	F	47		32 mm	70	54
21	8y	M	25		27 mm	90	

in one child the regurgitation evolved to a moderate-to-severe degree.

Mitral valve heart murmur was heard in six (28.6%) children, three of which were considered intense. Mitral click was heard in 13 (61%) patients. On echocardiographic examination, 11 (52%) patients had valve prolapse and 3 (14%) patients had significant mitral regurgitation, one of which was deemed severe and the other two moderate. In the interobserver analysis performed later for assessment of mitral regurgitation, a Kappa value of 0.635 was calculated, and as can be seen in the corresponding table (table II), most differences occurred in trivial regurgitation.

Beta-blocker therapy was attempted in all patients, including two children with history of bronchial asthma; this was tolerated by only one of them. Discontinuation of therapy would be made only if necessary, such as in case of bronchospasm. After beta-blocker therapy was introduced, a decrease in mean hear rate was observed, from 85 bpm to 73 bpm ($p < 0.009$) (table I).

DISCUSSION

Marfan syndrome is a hereditary disease caused by a mutation in the gene for fibrillin located on chromosome 15. In 1972, Murdoch et al⁵ demonstrated the early mortality of patients with Marfan syndrome between the third and fourth decade of life. Moreover, the number of deaths of patients under twenty years of age was not at all negligible (25% of the total number of deaths of the studied population). Cardiovascular death occurred in 93% of patients, most often secondary to aortic rupture, dissection or insufficiency. Later, other studies showed a

significant improvement in survival afforded by advances in diagnosis, clinical treatment and, especially, surgical techniques.⁶ Recently, Gott et al¹³, emphasized the importance of elective surgery for annuloaortic ectasia, with low operative mortality rates. Conversely, emergency surgery was associated with a much higher mortality rate.

Although all patients of our series have remained asymptomatic, a two-year-old child with neonatal Marfan syndrome, the most severe form of the disease, required replacement of the ascending aorta with a valved tube (Bentall-De Bono technique)¹⁴. This child had already presented for initial evaluation with a 26-mm aortic root (the upper limit of normal for the child's body weight should be 17 mm) and mild aortic regurgitation. In a single year the aortic root diameter increased 5 mm (19%), reaching 31 mm, followed by a worsening of aortic regurgitation. Albeit asymptomatic, the child required surgical correction, due to the impending risk of aortic rupture or dissection. Currently, the child is in general good condition and taking acetylsalicylic acid as the anti-platelet agent, because of the mechanical aortic prosthesis.

Four other children with severe annuloaortic ectasia are waiting for surgery. One of them required a concomitant mitral valve repair for significant mitral regurgitation.

Earlier studies showed an incidence of mitral valve prolapse of up to 100%¹⁵⁻¹⁶, yet rates are around 70% in most publications¹⁷. In the present study, the incidence of mitral prolapse was 52.4% (11 patients). This may be partly explained by the stricter criteria used in our protocol. Significant mitral regurgitation was detected in only 3 (14%) patients, and a single one was severe. The incidence of annuloaortic ectasia was 76% (16 patients), of which 23% was severe and, therefore, potentially more

serious. While mitral regurgitation is usually progressive, annuloaortic ectasia, despite also increasing over time, can complicate abruptly once a significant degree of dilation is reached, leading to catastrophic outcomes, such as dissection or rupture. Eleven (52%) children had two measurements of the aortic root taken one year apart. Mean annual increase of aortic diameter was 10%, or 1.36 mm/year (p value $p < 0.02$).

In the study by Shores et al,¹⁸ which included adults and adolescents, the ratio of aortic enlargement (measured diameter divided by expected diameter) was 0.023 in the treated group versus 0.084 in the control group. The study showed an increase of 2.1 ± 1.6 mm/year in the non-treated group versus 0.7 ± 1.8 mm/year and 1.1 ± 1.1 mm/year in two groups of patients treated with atenolol or propranolol, all of them with $p < 0.05$ ¹⁹.

The faster rate of aortic root enlargement in our group may be partly explained by the age range of the population studied, since relative aortic root enlargement is higher during childhood and adolescence than in adulthood, and partly because, in our group, a child with the neonatal form of Marfan syndrome accounted, alone, for a 5-mm enlargement, representing 19% of the initial diameter.

Echocardiographic image of annuloaortic ectasia is typical of Marfan syndrome ("pear-shaped"), with a greater degree of dilation at the Valsalva sinuses and extending to the sinotubular junction). Progressive dilation can compromise the remainder of the ascending and the aortic arch. Aortic root dilation also predispose both to a failure of central coaptation and aortic valve regurgitation²⁰.

Although other authors also have reported changes in the ascending aorta as the most serious lesions of Marfan syndrome in children⁷⁻²¹⁻²⁴, many textbooks on cardiology still suggest that mitral valve lesions are the most important in this pediatric group²⁵, to some degree because the research material included data of the time in which the echocardiogram was not available²⁶ as a routine method to assess the aortic root. It is known that plain chest radiograph alone does not allow a complete evaluation of that portion of the aorta²⁷. Several studies pointing toward the mitral valve as the primary cause of morbidity and mortality in the pediatric group were

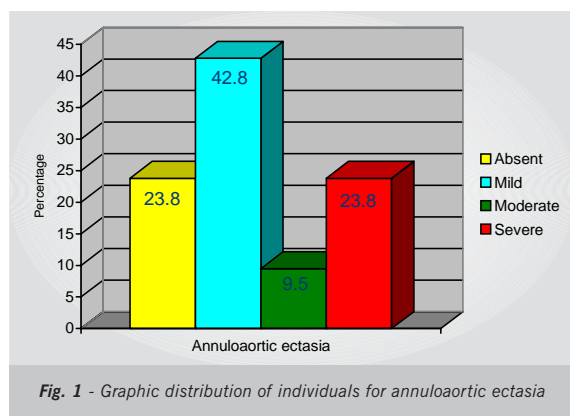


Table II - Interobserver analysis of the degree of mitral regurgitation in 10 patients. A high level of agreement is observed, with Kappa statistics of 0.635

	Mitral Regurgitation		
	Examiner	Observer 1	Observer 2
1	Absent	Absent	Absent
2	Absent	Absent	Absent
3	Severe	Severe	Severe
4	Mild	Mild	Mild
5	Moderate	Mild	Moderate
6	Minimal	Absent	Absent
7	Minimal	Minimal	Absent
8	Mild	Mild	Minimal
9	Absent	Absent	Absent
10	Minimal	Minimal	Minimal

conducted in children with the more severe, neonatal form of the disease²⁸, in which mitral valve prolapse with severe regurgitation and intractable heart failure is more frequent²⁹.

The beta-blocker used was atenolol, due to its easy dosage regimen. Only a one-year-old child with a history of bronchial asthma was given propranolol initially. The bradycardiac response was both variable and unpredictable. Some patients responded satisfactorily with a heart rate around 60 bpm, whereas others, including those on maximum dosage, got only modest results. An asthmatic child tolerated beta-blocker therapy, with discontinuation of medication only during bronchospasm episodes. Even so, there was a decrease in average resting heart rate, which dropped from 84 bpm to 73 bpm ($p < 0.009$); minimum heart rate also dropped from 55 bpm to 48 bpm, and maximum heart went from 155 bpm to 115 bpm.

Some limitations of the study should be noted, such as the relatively small number of patients included in the sample and of those in whom two evaluations could be made at a one-year interval, time that could be considered too short; however, as children usually grow fast, the variations observed may reflect the actual progressive involvement of the aortic root in children with Marfan syndrome. The mean enlargement of aortic root of 1.4 mm/year, though statistically significant to the group, should be considered carefully, because variations about 1 mm may be observed in daily practice, with no clinical significance. Nevertheless, it should be emphasized that, at study conclusion, 76% of the patients had annuloaortic ectasia, reference value for body weight considered.

Regardless of the limitations mentioned, the children remained asymptomatic throughout the study, the use of beta-blockers led to a significant reduction in heart rate, and no significant adverse effects were observed. Contrary to the literature, the incidence of annuloaortic ectasia was high (72%), greater than that of mitral valve prolapse (52.4%), and an enlargement of 1.4 mm/year was observed even during the effective use of beta-blockers.

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