Clinical Spectrum and Long-term Follow-up of Isolated Mitral Valve Prolapse in 119 Children

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SUMMARY One-hundred nineteen children with isolated mitral valve prolapse were studied in order to elucidate the clinical, electrocardiographic, echocardiographic, angiographic, and exercise response manifestations and its natural history in childhood. The mean age at the time of diagnosis was 9.9 years, with a mean follow-up of 6.9 years. The diagnosis in 118 cases was based on characteristic auscultatory phenomena. Ninety-one percent (n = 84) of the patients undergoing echographic examination had documentation of mitral valve prolapse. The evaluation of these children also included routine ECGs (n = 116), thoracic roentgenograms (n = 106), cardiac catheterization (n = 16), and graded exercise testing (n = 43). Two patients required antiarrhythmic medication for supraventricular tachycardia. No progression of mitral incompetence was observed, and there were no sudden deaths. One patient developed infective endocarditis and one had a cerebrovascular accident. We conclude that the diagnosis of mitral valve prolapse can be made clinically by characteristic auscultatory phenomena and that “silent” mitral prolapse is rare in childhood. The prognosis of isolated mitral valve prolapse in children appears to be excellent.

THE CLINICAL FEATURES of mitral valve prolapse (MVP) have been well described in adults, but little attention has been given to the spectrum of isolated MVP in children. We identified 118 children with the characteristic auscultatory features of MVP and one child with echocardiographic manifestations of prolapse, but an absence of clinical findings. In this study we analyze the clinical, electrocardiographic, echocardiographic, angiographic findings, exercise response, and natural history in these patients with MVP.

Materials and Methods

One hundred eighteen patients seen at Children's Hospital Medical Center had auscultatory evidence of a late systolic murmur, apical systolic nonejection click, or both. This study group represents all of the children referred to our institution between 1956 and 1977 who were recognized as having isolated MVP. Auscultation was performed in every case with the patient in the supine, left lateral decubitus, standing and squatting positions. The timing and intensity of the murmur/click complex responded characteristically to various postural maneuvers. In every instance the patients were examined by one of the investigators. We excluded from the study all patients with hypertrophic cardiomyopathy, pericardial effusion, atrial septal defect (ASD), ventricular septal defect, obvious features of Marfan's syndrome or other associated cardiac defects.

The familial cases in the study group included two sisters and the female sibling of a 26-year-old male with documented MVP.

One hundred sixteen patients had standard 12-lead ECGs and 106 had posteroanterior and left lateral chest teleoroentgenograms. Forty-three underwent graded exercise testing using the method described by James et al. Patients were selected because of a history of chest pain and/or arrhythmias. In addition, some children were exercised randomly as a provocative test for ventricular arrhythmia. These tests were performed within 1 year of the initial diagnosis. The criteria for an abnormal ST-segment change during exercise have been described.

Ninety-two children underwent M-mode echocardiographic examination. All studies were performed with a Hoffrel ultrasonoscope Model 101 and recorded on an Irex multichannel recorder. Various transducers, both focused and unfocused, were used, ranging from 2.25-5 MHz. Recordings from the free edge of the mitral valve leaflets were performed with the transducer placed perpendicular to the chest wall along the left sternal border. We performed cephalad positioning and rocking of the transducer in different intercostal spaces, as described by Brown and Kloster, to assure the optimal recording position of the free edges of the mitral valve and to minimize spurious posterior movement. In every patient MVP was arbitrarily defined as any movement of the mitral valve leaflets posterior to an imaginary line (reference line) drawn parallel to the chest wall from the closure or C point (end-diastole) of the mitral valve echogram. This movement should occur after the onset of mechanical systole (as determined by aortic cusp opening), since some posterior movement may occur normally during isovolumic contraction (fig. 1).

Early in our experience we catheterized 16 un-
selected patients in order to verify the diagnosis of MVP. These studies were undertaken soon after the presumptive diagnosis was made. All had left ventricular cineangiography in the right anterior oblique (RAO) projection. Ten also had left ventriculograms performed in the left anterior oblique (LAO) projection.

Results

Clinical Features

The youngest child presented at 2.5 years of age and the oldest patient was 22.2 years at the time of initial examination (mean 9.9 years). There were 82 females and 37 males (2.2:1 female: male ratio). The follow-up period was 756 patient-years. The shortest was a one-time visit and the longest was 21 years. Twenty-one (18%) have been followed for more than 10 years. The mean duration of continuous clinical observation was 6.9 years. Ten of the original 119 patients have been lost to follow-up. Of the remaining 109 patients, 101 have been followed more than 2 years.

Forty-one patients (34%) presented with a nonspecific febrile illness of short duration. All but three of these patients had been followed by the same physician for a minimum of 2 years, and 30 of the remaining 38 patients were noted by the same referring physician to have the positive auscultatory findings. A click, murmur or an unusual auscultatory examination were not previously noted in these 41 patients until they presented with this acute febrile reaction. Four of the 41 patients were referred to our institution because of a suspicion of pericarditis, based on auscultation. However, each of these patients subsequently was found to have typical features of MVP. Another 39 patients (33%) were initially referred for evaluation of a murmur or unusual auscultatory findings heard on routine physical examination. Twenty-one patients (18%) presented with a chief complaint of nonexertional, ill-defined chest pain. Eight (7%) developed MVP after an episode of acute rheumatic fever. Each of these eight patients initially had a holosystolic or late systolic murmur, and subsequently developed a nonejection click and late systolic murmur. Three patients (3%) were referred for evaluation after an arrhythmia was noted on physical examination, although only one complained of palpitations.

Chronic fatigue was the major reason for referral in three (3%) cases. Only one child presented with the chief complaint of dyspnea on exertion. Two patients were evaluated for a murmur in the presence of documented hyperthyroidism. The remaining patient with auscultatory features of MVP presented with a murmur heard during an evaluation of failure to thrive.

The single patient with “silent” MVP was a 17-year-old white female who presented with chest pain and fever. The pain was described as a nonspecific precordial ache that was intermittent and was not

\[ \text{FIGURE 1. Method for determining mitral valve prolapse. See text for discussion. PEP = preejection period. Reproduced with permission from Lea & Febiger Co.} \]

\[ \text{FIGURE 2. Mitral valve echogram (MV) demonstrating pansystolic prolapse (arrows). A corresponding electrocardiogram is included, demonstrating T-wave inversion in the inferior leads (II, III, aVf).} \]
relieved by aspirin. The cardiac examination was unremarkable. Because of persistence of the chest pain, accompanied by T-wave changes on the ECG, an M-mode echocardiographic examination was performed (fig. 2).

Physical Findings

Seventy-four patients (62%) presented with an apical nonejection systolic click, followed by a late systolic murmur. Twenty-eight patients (24%) had an isolated late systolic murmur. Sixteen (13%) of the children were noted to have an isolated apical click or series of clicks. Two (2%) of the above patients initially presented with a pansystolic murmur of mitral insufficiency. Both of these later developed a mid-systolic click along with a late systolic murmur. Of the 102 patients with murmurs, 31 had a "whooping," "honking," "squeaking," or a musical quality to the murmur.

Four (3%) of the patients were noted to have pectus excavatum on physical examination. One patient had bilateral hip dislocations, associated with scoliosis and spina bifida. One patient had severe kyphoscoliosis associated with a rib cage deformity.

One patient was beyond the ninety-seventh percentile for height and two were below the third percentile. All children were between the third and ninety-seventh percentile for weight.

Radiographic Findings

One hundred six of the 119 patients had posteroanterior and lateral chest radiographs. Eighty-three (78%) were normal; 12 (11%) had varying degrees of mild thoracic scoliosis, associated with pectus excavatum in one patient. Two patients had radiographic findings consistent with the straight-back syndrome. One patient had pectus carinatum. Eight patients (8%) had minimal cardiomegaly as judged by a cardiothoracic ratio greater than 0.60 but less than 0.70 on a radiograph taken during full inspiration.

Electrocardiographic Findings

Seventy-three (63%) patients had abnormalities on the resting tracing. Fifty-six (48%) of the 116 patients exhibited the classic pattern of T-wave inversion in the inferior leads. Eight (7%) presented with an isolated arrhythmia and nine had both arrhythmia and T-wave abnormalities. Of the 17 patients (15% of the total group) with arrhythmias, 10 had multiple unifocal premature ventricular contractions (PVCs), one patient had premature atrial contractions (PACs) associated with frequent paroxysmal atrial tachycardia, two had both PACs and PVCs, and three patients had intermittent junctional rhythm. The remaining patient developed intermittent supraventricular arrhythmias of several types (paroxysmal atrial tachycardia, atrial fibrillation, and accelerated junctional rhythm). Thirteen of the patients with electrocardiographic abnormalities had prominent midprecordial U waves. Forty patients (34%) were initially noted to have normal resting ECGs. The remaining three patients had miscellaneous abnormalities, including complete right bundle branch block, left-axis deviation and right atrial enlargement. Ten of the 116 children had first-degree atrioventricular block (PR interval > 0.20 second).

Of the 41 children presenting with an acute febrile illness and auscultatory signs of MVP, 14 (34%) had initial T-wave abnormalities on the ECG in the inferior leads, which subsequently improved or reverted to normal, despite persistence of the late systolic murmur/nonejection click auscultatory complex (fig. 3). The average heart rate on the initial tracing in the 14 patients was 99 beats/min. The average heart rate after the ECG normalized was 90 beats/min. Only four of these patients subsequently underwent graded exercise testing. All were performed after T waves

D.B. Age 10yrs. (♀)

Dec.

I

II

III

AVR

AVL

AVF

V1

V3

V6

April

I

II

III

AVR

AVL

AVF

V1

V3

V6

Figure 3. Characteristic pattern of T-wave inversion in the inferior leads (II, III, aVF) is demonstrated in the upper tracing (December). The lower tracing (April) indicates the reversion of T waves toward normal.
normalized. In three of the patients, the T waves remained normal with exercise. The remaining patient developed inverted T waves with hyperventilation and with exertion.

Exercise Electrocardiograms

Forty-three patients underwent graded exercise testing. Ten patients (23%) had ST-segment depression during exercise. Four (9%) demonstrated multiple, unifocal PVCs (without ST changes) during and after exercise. Five other patients (11%) had both ST-segment depression and PVCs during exercise. Two patients with frequent PVCs in the preexercise resting period developed regular sinus rhythm with exercise. Twenty-two of the 43 patients (51%) had no evidence of ST depression or cardiac arrhythmias.

Echocardiographic Features

Ninety-two patients with auscultatory evidence of MVP had echocardiograms performed. Eighty-four (91%) had echocardiographic features of MVP, based on the criteria previously described.18 Fifty-eight (69%) of the patients demonstrated midsystolic dipping of the mitral valve leaflets. The remaining 26 (31%) demonstrated pansystolic hammocking of the posterior leaflet or both leaflets.

Thirteen of our 16 patients with an isolated, or multiple clicks had midsystolic dipping of the mitral leaflets. None of these had left atrial or left ventricular enlargement. By contrast, in 23 patients with pansystolic hammocking, only two had an isolated click or series of clicks. Six of these 23 patients had minimal left atrial and/or left ventricular enlargement compatible with trivial mitral incompetence.

Angiographic Findings

Sixteen of the patients underwent cardiac catheterization. Fourteen of these patients had evidence of mild mitral insufficiency, as demonstrated by left atrial opacification during retrograde left ventricular angiography in the RAO position. In the remaining two patients technically satisfactory left ventricular angiograms were not obtained.

In the RAO projection, where satisfactory angiographic views were achieved, each patient demonstrated paradoxical movement of the mitral valve leaflets through the left ventricular–left atrial interface along the inferior margin of the mitral ring.

Although eight of the patients demonstrated the characteristic “ballerina-foot” contraction pattern of the left ventricle,14 no other abnormalities of contractility were noted. No patients demonstrated left ventricular cavity obliteration during systole.

Complications

Two children required digoxin and/or quinidine for control of supraventricular tachycardia. One of these patients also had multiple unifocal PVCs in association with dizzy spells. She later presented at age 10 years with an acute cerebrovascular accident characterized by a transient right hemiparesis. Infective endocarditis was excluded by multiple negative blood cultures and a normal erythrocyte sedimentation rate.

There was one episode of questionable infective endocarditis (L-form of a streptococcal organism). Sudden death has not occurred in our patient group, nor has a progression of mitral regurgitation been recognized in any patient.

Discussion

Since 1892, when Griffith16 first described the acoustic features of mitral incompetence confined to late systole, there has been a great deal of interest generated regarding the unique form of mitral apparatus dysfunction referred to as mitral valve prolapse. Although a generous portion of the literature in recent years has been devoted to the description of the clinical spectrum of MVP in adults, little attention has been focused on this syndrome and its clinical implications in childhood.

Many studies have alluded to the prevalence of this syndrome in females.2, 8, 16 Our female:male ratio of 2.2:1 correlates closely with the data of others. We have not recognized isolated MVP in an infant younger than 2 years of age.

The small number of familial cases detected in our study group provides little support for a genetic predisposition, although no relatives underwent physical examination or had echocardiographic studies performed.

The major indication for referral of patients in this study to our institution was a new murmur or click heard during a nonspecific febrile illness. Many of these patients had been followed by the same physician since birth, and the cardiac findings had not been previously noted. Admittedly, recognition of MVP during an acute febrile episode may be coincidental; however, an infectious etiology cannot be excluded. The transient T-wave changes could represent evidence of myocarditis associated with an intercurrent viral illness. The absence of progressive valvular disease, after the initial auscultatory complex was noted, may further support an infectious etiology, because the primary infection may be the only insult to the valvular apparatus.

The patients with well-documented rheumatic fever who subsequently developed MVP may also illustrate an inflammatory pathogenetic mechanism for this syndrome. Even though Sherman et al.17 could not demonstrate an inflammatory reaction in the mitral valve of children with "floppy valve syndrome," we suggest that myxomatous degeneration (myxoid change) is a nonspecific reaction to abnormal hemodynamic stress, and that this stress may have been triggered by an earlier reaction (possibly secondary to inflammation), which preceded fibrosis and collagenization. The role of acute rheumatic fever in the pathogenesis of MVP has been described by others.3, 18

Many reports have alluded to the spectrum of auscultatory findings of isolated MVP in adults.18-22
We concur with Jeresaty\textsuperscript{28} that the mid-late systolic, apical, nonejection click is the pathognomonic auscultatory feature of MVP.

In reviewing the nearly 4000 consecutive echocardiograms performed on children at our institution, including 182 normal subjects between 2 months and 15 years of age, using criteria described above, we have recognized only one case of “silent” MVP. This experience suggests a low incidence of “silent” MVP in the pediatric population. We recognize that minimal dipping of the mitral leaflets beyond the reference line (especially in the already equivocal diagnosis of pansystolic hammocking) may not be the sine qua non for diagnosis of prolapse. However, we believe that this echographic definition of MVP provides the clinician with a practical means of assessing the mitral valve echogram when it is applied in the context of the clinical picture.

Despite the fact that many authors have described a characteristic asthenic body habitus associated with MVP,\textsuperscript{24} we have not recognized a distinctive body build linked with isolated MVP. However, patients with associated morphologic syndromes, such as Marfan’s, were excluded from our study. Thoracic and skeletal abnormalities have been previously described by Bon Tempo et al.\textsuperscript{26} Although the thoracic bony abnormalities have been considered by many to be another characteristic finding in MVP, only 15 patients in our study were noted to have one or more of the frequently described skeletal abnormalities on routine chest radiographs.

In contrast to the high prevalence (48\%) of the characteristic electrocardiographic pattern of posteriorinferior myocardial ischemia noted in our patients, Pocock and Barlow\textsuperscript{4} noted only a 9\% incidence of T-wave changes in their adult patients. However, in a more recent study, Lardani et al.\textsuperscript{28} detected a 36\% incidence of T-wave changes in the inferior leads in adults.

Although the transient T-wave changes in the 14 patients with an acute febrile illness may have been rate-related, three of the four patients in this group undergoing graded exercise testing continued to have normal T waves during exercise.

Various arrhythmias have also been reported in adults with MVP, including atrial fibrillation, paroxysmal atrial tachycardia, atrial flutter, ventricular tachycardia, and ventricular fibrillation.\textsuperscript{3} In our patients arrhythmias were documented in 17 instances. The most common rhythm disturbance was unifocal ventricular ectopic beats (59\%). Although first-degree atrioventricular block has been noted by others,\textsuperscript{26} adults reported with this ECG finding were receiving digitalis preparations, whereas none of our patients with this finding were taking digoxin.

The results of graded exercise studies in adults have been variable. Sloman et al.\textsuperscript{27} found that 60\% of patients with MVP had ST-segment depression with exercise. Gooch et al.\textsuperscript{29} found no ST-segment depression in 24 patients with MVP undergoing graded treadmill exercise tests, and Nutter et al.\textsuperscript{28} also noted a low incidence (8\%) of ischemic changes in adults with MVP during maximal treadmill exercise tests.

Although there were no children in our study group with ST depression on the resting ECG, there was an increased incidence of ST depression (35\%) during exercise compared with our own control population. The mechanisms for these changes are not clear. Since overt coronary artery disease was not present in our children, this increased incidence of positive electrocardiographic findings of “ischemia” during stress implies a functional alteration in myocardial blood supply. Perhaps this could be attributed to impaired left ventricular contractility, which may be a primary abnormality, or may be secondary to distortion of the papillary muscle and adjacent myocardium, resulting from the abrupt stress of the prolapsing mitral valve. Exercise-induced arrhythmias, noted in 21\% of our patients, may reflect latent myocardial instability, which was unmasked by maximal stress. However, the prognostic implications of these findings remain obscure.

The echocardiographic spectrum of isolated MVP has been discussed in detail by others.\textsuperscript{30, 31} In our patients, interventions such as the Valsalva maneuver, standing and inhalation of amyl nitrite did not unmask positive echographic features. If patients did not demonstrate echographic evidence of MVP in the supine position, provocative measures were not helpful in substantiating the diagnosis of prolapse. An isolated midsystolic click is apparently rarely associated with significant mitral regurgitation; none of our patients with a click or series of clicks had echographic evidence of left atrial or left ventricular enlargement.

Left ventriculography in the RAO projection as reported by others is the optimal view for angiographic demonstration of MVP.\textsuperscript{3, 32-34} This projection permits visualization of the mitral annulus in profile during its anterior excursion from end-diastole to end-systole. The mitral ring moves anteriorly as the long axis of the left ventricle shortens. Although a certain degree of normal “inflation” of the cusps occurs during systole, the normal mitral leaflet is held in apposition, and tethered by the papillary muscle-chordal apparatus, thus preserving the left ventricular–left atrial interface. Abrupt, paradoxical, midsystolic movement of the prolapsing mitral leaflets through the left ventricular–left atrial interface produces the characteristic deformity on the left ventriculogram.

The interpretation of the left ventriculogram is still controversial and may account for the reported association of MVP with secundum ASD.\textsuperscript{35, 36} Schwartz et al.\textsuperscript{4} initially described the prevalence of false-positive left ventriculograms in patients with secundum ASD. In reviewing the left ventriculograms performed in 58 patients with secundum ASD, 16 patients (26\%) had apparent MVP. However, upon direct inspection of the mitral valve at the time of intracardiac repair, only three of these children demonstrated the typical changes in the mitral valve leaflets, and each had clinical evidence of MVP. None of the remaining 13 patients had echographic or auscultatory features of MVP, and the mitral valve
was normal when visualized at surgery in each case. The echocardiogram in the patient with a secundum-type ASD appears to offer an advantage over the cineangiogram. When using anteroposterior and lateral views in visualizing a clockwise-rotated heart, the spurious nature of the prolapse can be realized. However, the echocardiographic transducer placement uses the mitral valve position relative to the left ventricular structures regardless of the cardiac rotation. Therefore, a combination of physical examination and echocardiography should provide more reliable indications of MVP. Somerville et al.\(^\text{37}\) subsequently detailed the spurious nature of the angiographic appearance of the mitral valve commonly noted with secundum-type ASD. We suggest that when the left ventricle is displaced by a volume-overloaded right ventricle (e.g., ASD), the distorted geometry of the “underloaded” left ventricle produces a prominence of the mitral valve on the left ventriculogram resembling MVP. Thus, in the absence of clinical and echographic evidence of MVP, subtle degrees of what appears to be MVP on left ventriculography may represent normal systolic inflation of the mitral valve leaflets.

Our studies indicate that in childhood, isolated MVP is a relatively benign disease. The growth and development patterns as judged by clinical examination have been normal, and all patients are living relatively normal lives without activity restrictions. The long-term prognosis and complications of MVP have been widely reported.\(^{2, 38-42}\) These complications have included infective endocarditis, rupture of chordae tendinae, ventricular arrhythmias, cerebrovascular accidents, progressive mitral insufficiency, refractory chest pain and sudden death. Depending on selection factors, studies in adults have reported significant morbidity and mortality associated with MVP. In a follow-up of 40 patients over a 10-year period, Koch et al.\(^\text{41}\) reported six instances of sudden death, two patients with progressive mitral insufficiency and no episodes of infective endocarditis. Allen et al.\(^\text{40}\) reported 62 patients followed 9–22 years and noted five cases (8%) of bacterial endocarditis and 10 instances of minimal progression of mitral insufficiency. The threat of infective endocarditis has been noted by many others, but this complication occurred in only one of our patients. However, we have advised the parents of most of our patients of the need for subacute bacterial endocarditis prophylaxis; therefore, to the best of our knowledge this represents a protected group. The true incidence of subacute bacterial endocarditis in an unprotected population with MVP is not known, and therefore, the need for prophylaxis in patients with an isolated click has not been established. There have been no prospective long-term studies with regard to the effectiveness of antibiotic prophylaxis in this syndrome, so we believe that all patients with clinically recognized MVP, especially those with mitral insufficiency, should receive antibiotic prophylaxis for the prevention of infective endocarditis. This opinion is based primarily on the fact that infective endocarditis has been reported in adults with MVP.\(^{43, 44}\)

One patient developed physical signs of a cerebrovascular accident, unassociated with bacterial endocarditis. Stroke as a complication of MVP was described by Kostuk et al.\(^{45, 46}\) but it appears to be uncommon in children.

Long-term management of children with MVP should present few problems. Since the diagnosis of MVP can be made on clinical grounds with a high degree of accuracy (based on the excellent correlation between echocardiographic findings and clinical examination), we suggest that the initial evaluation of an asymptomatic child presenting with classic auscultatory findings of MVP should include a resting ECG and an echocardiogram if there is doubt concerning the diagnosis. Chest radiographs have demonstrated the associated skeletal anomalies, but have not added diagnostic information concerning the cardiac disease.

The role of graded exercise stress testing in the evaluation of these patients is presently under study. Children with arrhythmias detected on routine ECG, or who have a history of syncope or palpitations, require continuous ambulatory Holter monitoring.

In summary, our experience with 119 children with isolated MVP indicates that the diagnosis can be made clinically by characteristic auscultatory phenomena and verified by the echocardiogram. Although “silent” MVP represents an important form of presentation in the adult population, we detected a very low incidence of this entity in children. The etiology of the syndrome remains obscure and is probably multifactorial. In addition to previously suggested etiologic factors, we postulate a possible infectious (viral) etiology in many children. In contrast to the clinical course of MVP in adults, in whom morbidity and mortality are significant, the prognosis of isolated MVP is excellent during childhood and adolescence.

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