Familial Occurrence of Mitral Valve Prolapse in X-Linked Muscular Dystrophy

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SUMMARY A high incidence of mitral valve prolapse (MVP) has been reported in patients with X-linked Duchenne muscular dystrophy. In our study MVP was present in six of 22 Duchenne dystrophy cases (27%) followed in the Maryland General Hospital Muscular Dystrophy Clinic. In addition, seven carriers of Duchenne and X-linked benign (Becker) dystrophy had evidence of MVP. Autosomal dominant transmission of MVP was present in four families. The unusually high prevalence of MVP in families with X-linked muscular dystrophy may have potential value in the recognition of the carrier trait.

MITRAL VALVE PROLAPSE is common in healthy, asymptomatic people and in patients with a variety of cardiac and metabolic diseases. Familial occurrence is common, with an autosomal dominant mode of transmission. More recently a high incidence of mitral valve prolapse has been described in patients with two neuromuscular diseases: X-linked muscular dystrophy and myotonic dystrophy.

In our investigation of cardiac disease in patients with X-linked muscular dystrophy we found that a number of unaffected family members had auscultatory and echocardiographic evidence of mitral valve prolapse. The current study was designed to identify the association between mitral valve prolapse and the carrier state of X-linked muscular dystrophy.

Methods

We clinically evaluated propositi who had X-linked muscular dystrophy, either Duchenne or Becker type, for the presence of cardiac disease in the Muscular Dystrophy Clinic of the Maryland General Hospital. The diagnosis of neuromuscular disease had been confirmed by neurologic consultation. None were known to have a history of heart disease before the initial examination. We examined the patients for evidence of chest deformity, cardiac enlargement or decompensation, and abnormal auscultatory findings, and performed standard 12-lead electrocardiograms, chest X-rays and echocardiograms. We used a Unirad Sonograf D series system with a 2.25 MHz cardiac transducer to obtain echocardiograms. ECGs and echocardiograms were also performed on other family members available for study. Carriers of X-linked muscular dystrophy were defined according to the criteria of Thompson et al. Definite carriers had affected sons and affected brothers or uncles. Probable carriers had two or more affected sons, but no affected brothers or uncles. Possible carriers had affected sons or brothers. Two determinations of serum creatine phosphokinase (CPK) and aldolase were made on the carriers.

Echocardiographic criteria of mitral valve prolapse included late systolic or pansystolic posterior bowing of the posterior or both mitral valve leaflets > 2 mm. We used an average of five systolic cycles to assess the degree of mitral valve prolapse. The cardiac transducer was placed as perpendicular to the chest wall as possible.

Results

The pedigrees of four families are described in figures 1-4. In each family, muscular dystrophy was transmitted in an X-linked recessive pattern, while mitral valve prolapse was transmitted in an autosomal dominant pattern. There was auscultatory evidence of mitral valve prolapse in each of the mothers of the propositi, with subsequent identification in other family members. We confirmed the presence of mitral valve prolapse in each instance by echocardiography.

Clinical and auscultatory findings are summarized in table 1. In the first family, three male offspring were affected with the Becker type of X-linked muscular dystrophy (fig. 1). Each had been confined to a wheelchair for 10 years or longer at the time of initial study. Chest deformities were not present by clinical examination or chest x-ray. Auscultatory findings included a constant mid-systolic click along the lower left sternal border in two and an intermittent late systolic apical murmur in one. The mother and two possible carrier offspring had a constant systolic click and late systolic apical murmur. All three females had narrow anteroposterior chest diameters; none had clinical muscular weakness, although each had minimal elevation of serum CPK.

Propositi in the second through fourth families were affected with the Duchenne type of X-linked muscular dystrophy. Three male offspring, two affected and one unaffected, had auscultatory evidence of a constant mid-systolic click (fig. 2). One also had an intermittent late apical systolic murmur. Both affected males had marked kyphoscoliosis. A phonocardiogram and echocardiogram of the propositus is shown in figure 5. He developed clinical congestive heart failure and died 8 months later. Autopsy of the heart showed diffuse

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= male

= male affected with muscular dystrophy

= female

C = definite carrier
e = possible carrier

CPK = serum creatine phosphokinase

? = mitral valve prolapse

* = propositus

**Figure 1. Pedigree of family 1.**

/ = deceased

= unaffected male

= male affected with muscular dystrophy

= female

C = probable carrier

P = mitral valve prolapse

* = propositus

**Figure 2. Pedigree of family 2.**
Figure 3. Pedigree of family 3.

Figure 4. Pedigree of family 4.
Table 1. Summary of Clinical and Auscultatory Findings

<table>
<thead>
<tr>
<th>Family</th>
<th>Dystrophy type</th>
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<th>Murmur</th>
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Abbreviations: MVP = mitral valve prolapse; Abn AP = abnormal anteroposterior chest diameter.

cardiomyopathy involving the left ventricle and myxomatous change of the mitral valve leaflets. The carrier mother also had a late systolic apical murmur and echocardiographic evidence of mitral valve prolapse (fig. 6).

Figure 5. A) Phonocardiogram of the propositus in figure 2, showing a midsystolic click and late apical systolic murmur. B) Echocardiogram of the mitral valve in the same patient, showing pansystolic prolapse of both mitral valve leaflets. Autopsy correlation showed myxomatous degeneration involving both mitral valve leaflets. C = click; M = murmur; MVP = mitral valve prolapse; S₁ = first heart sound; S₂ = second heart sound.

Figure 6. Mitral valve echocardiograms of other family members of the propositus in figure 2. A) An 18-year-old brother with Duchenne muscular dystrophy; echocardiogram shows pansystolic prolapse of the posterior mitral leaflet. B) The mother carrier; echocardiogram shows late systolic prolapse of the posterior mitral leaflet.
The mother of the third propositus had a constant midsystolic click (fig. 3). One of the sisters of the propositus had clinical evidence of muscular weakness involving both upper and lower extremities, and significantly elevated serum CPK. She had experienced intermittent palpitations and had an intermittent late systolic murmur along the lower left sternal border. Echocardiograms of both mother and daughter were compatible with late systolic mitral valve prolapse only after amyl nitrite administration.

In the fourth family, the mother of the propositus had auscultatory evidence of a late systolic apical murmur (fig. 4). She had a narrow anteroposterior chest diameter and minor ST aberrations inferiorly on the ECG.

Discussion

Since Barlow’s original description, mitral valve prolapse has been reported in 2–17% of normal healthy middle-aged females, with a true mean incidence closer to 6% — and in 0.5% of normal males. Many were asymptomatic, while others experienced variable symptoms including chest pain and palpitations with or without associated arrhythmias. Familial occurrence has been described with an autosomal dominant pattern of transmission. Mitral valve prolapse has also been demonstrated in patients with a variety of connective tissue and metabolic disorders, including Marfan’s syndrome. Associated cardiac diseases have included congenital defects such as secundum atrial septal defect, coronary artery disease, and both congestive and hypertrophic cardiomyopathies.

Winter et al. described mitral prolapse in eight of 10 family members affected with myotonic dystrophy and showed autosomal dominant inheritance of both conditions. A high incidence of mitral valve prolapse has been reported in four of 17 patients with Duchenne muscular dystrophy. Mitral valve prolapse has been a common finding in our own experience with X-linked muscular dystrophy, occurring in six of 22 Duchenne dystrophy patients (27%) over the age of 14 years.

An association between mitral valve prolapse and chest deformities has been reported. Clinical evaluation of mitral valve prolapse was often difficult in our patients due to displacement of thoracic landmarks and the coexistence of pulmonary problems. Auscultatory findings were variable in the same patient, and at times difficult to elicit because the patients could not assume an upright posture. Echocardiography has been very useful in confirming mitral valve prolapse in these patients. We took special care in the perpendicular placement of the transducer on the chest because excessive inferior angulation produces mitral prolapse pattern artifactually. Although greater specificity of the late prolapse pattern vs pansystolic prolapse has been reported, we considered both patterns equally valuable in our series when correlated with auscultatory findings. Autopsy confirmation of myxomatous change of the mitral valve leaflets was made in two of our Duchenne dystrophy patients with previous clinical and echocardiographic evidence of mitral valve prolapse.

The recognition of the carrier state of X-linked muscular dystrophy by clinical, enzymatic, electromyographic and histochemical criteria remains suboptimal. It has been estimated that only 60–70% of Duchenne carriers and 50% of other X-linked dystrophy carriers have elevated serum CPK. More sophisticated serum and erythrocyte enzyme studies by Roses et al. have shown significant abnormalities in probable Duchenne carriers with normal serum CPK.

The high incidence of mitral valve prolapse in carriers of X-linked muscular dystrophy presented in this study has not previously been described. As in other studies, autosomal dominant inheritance of mitral valve prolapse was present in these four families. Identifying mitral valve prolapse is clinically important in the management of possible associated arrhythmias and the prophylaxis of infective endocarditis.

Should investigation of larger numbers of families with X-linked muscular dystrophy confirm our findings, the presence of mitral valve prolapse may be useful in identifying the coexistence of the dystrophy carrier trait.

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Effects of the Valsalva Maneuver on Myocardial Ischemia in Patients with Coronary Artery Disease

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SUMMARY The influence of the Valsalva maneuver (VM) on myocardial ischemia was evaluated in 24 patients with coronary heart disease. Clinical and hemodynamic responses to the VM were studied during acute ischemia manifested by angina pectoris with transient left ventricular (LV) dysfunction and compared with responses during nons ischemic intervals.

In the absence of evidence for acute ischemia (angina and increased LV end-diastolic pressure), six patients had abnormal hemodynamic responses to the VM. Five had lack of systolic pressure overshoot and in one, systolic pressure did not decline during pacing. When the VM was performed during an ischemic episode, 14 patients had abnormal responses (12 with lack of overshoot in phase IV and two with lack of systolic pressure decline in phase II). In 18 patients a prompt decline in LV end-diastolic pressure occurred with the disappearance of angina during the VM. These changes uniformly occurred during the latter part of straining (VM phase II) as cardiac size and systolic pressure declined. No adverse effects occurred when a VM was performed during acute ischemia.

Our observations suggest that the VM abruptly reduces determinants of cardiac oxygen demand, relieving acute ischemia without harmful effects.

STRAINING CAUSES exaggerated increases in intrathoracic pressure, frequently during various daily activities. The influence of maneuvers that increase intrathoracic pressure on myocardial ischemia has not been completely determined. For example, the Valsalva maneuver (VM) has been suggested as one of the few nonpharmacologic measures effective in relieving angina pectoris. The basis for this potentially beneficial response on manifestations of ischemia is not completely clear, and others have suggested that this maneuver may cause arrhythmias and "bedpan deaths." These clinical associations were implied because of the important reduction of venous return that occurs during straining, resulting in decreased aortic pressure and cardiac output. Although direct measurements of coronary flow were not made, Gorlin and Storaasli concluded that the VM may reduce blood flow, since it increases the transcoronary circulation time. In a recent study, Benchimol and co-workers implied that the velocity of coronary flow was reduced in patients with and without coronary disease during straining. They estimated unidirectional velocity changes by the Doppler technique, and suggested that reduced flow velocity was secondary to reduced cardiac output and could predispose patients to potentially lethal arrhythmias. If so, improvement in myocardial oxygenation, implied by relief of clinical findings of acute ischemia, is difficult to interpret. Furthermore, the systolic pressure "overshoot" after a VM might induce angina or increase ischemia in some patients. Since this maneuver is performed so frequently, a better understanding of its effects on the coronary circulation may be important.

In the present investigation we studied left ventricular (LV) hemodynamic and clinical responses to a VM in patients with coronary artery disease during acute ischemia. Angina pectoris and a transient rise in LV end-diastolic pressure were considered evidence for ischemia. Emphasis was placed on hemodynamic

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