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Cardiac abnormalities in the fragile X syndrome

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SUMMARY Twenty three patients with fragile X syndrome underwent cardiovascular assessment. Echocardiography showed dilatation of the aortic root in 12 (52%) and mitral valve prolapse in five (22%), four of whom had an apical mid-systolic click on auscultation.

Patients with fragile X syndrome have cardiac defects similar to those seen in other disorders of connective tissue such as Marfan's syndrome and Ehlers-Danlos syndrome. These, and other somatic features, suggest an underlying connective tissue dysplasia.

The fragile X syndrome is the commonest inherited cause of mental retardation and it affects approximately one in a 1000 males.[1 2] It is so called because there is a fragile site on the long arm of the X chromosome in affected patients.[3] Common somatic manifestations include a long face, large and prominent ears, prognathism, and macroorchidism. Other associated findings such as hyperextensible finger joints, pectus carinatum, a high-arched palate, and flat feet suggest an underlying connective tissue dysplasia.[4] Previous reports of mitral valve prolapse and aortic root dilatation in patients with fragile X syndrome support this proposition.[5 6]

This study was performed to establish the frequency of cardiac abnormalities in a population of patients with fragile X syndrome who underwent voluntary cardiac assessment.

Patients and methods

PATIENTS

We studied 23 men (aged 18–80, mean 51) with proven fragile X syndrome. Most were moderately or severely mentally handicapped. A few were living in the community while most were resident in a hospital for the mentally handicapped. They were drawn from a group of 28 patients identified by cytogenetic examination in a prospective survey of an inpatient population. Five patients did not consent to examination.

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METHODS

Each patient underwent clinical examination of the cardiovascular system. Special note was made of the clicks of mitral valve prolapse and murmurs of mitral and aortic valve regurgitation. All patients had a chest *x* ray, an electrocardiogram, and Doppler echocardiography. Cross sectional and M mode echocardiography were performed to look for mitral valve prolapse and aortic root dilatation; and continuous wave, pulsed wave, and colour Doppler were used to detect mitral and aortic regurgitation.

Mitral valve prolapse was diagnosed if there was systolic leaflet billowing into the left atrium in the parasternal long axis view and the point of coaptation of the mitral valve leaflets was displaced to above the atrioventricular ring.[7 8] The aortic root dimensions were compared with the normal values based on age and body surface area reported by Feigenbaum.[9]

Results

CLINICAL EXAMINATION

Auscultation of the heart was normal in 17 patients. An isolated apical mid-systolic click was heard in two patients, and a classic mid-systolic click and late systolic murmur in two others, one of whom also had an early diastolic murmur in the aortic area. Two patients had an apical late systolic murmur without a click.

CHEST *X* RAY

Four patients had cardiomegaly (cardiothoracic ratio > 55%) but only one had clinical signs of mitral valve prolapse with mitral and aortic regurgitation. The chest *x* ray was normal in the remainder, although many patients showed poor inspiratory effort.

Table *A comparison of fragile X, Marfan's, and Ehlers-Danlos syndromes and homocystinuria*

Syndrome	*Clinical manifestations*	*Mental retardation*	*Cardiac abnormalities*	*Inheritance*	*Gene defect*
Fragile X	SJ	+	ARD/MVP	X linked	Unknown
Marfan's syndrome	SJE	−	ARD/MVP	Dominant	Unknown
Ehlers-Danlos syndrome	SJE	−	ARD/MVP	Dominant or recessive	Specific gene defect in some subgroups
Homocystinuria	JE	+	—	Recessive	Specific enzyme deficiency

ARD, aortic root dilatation; E, eyes; J, joints; MVP, mitral valve prolapse; S, skin.

ELECTROCARDIOGRAMS

One patient was in atrial fibrillation with a ventricular rate of 90/min (not on any medication). Two others, who were brothers, had sinus tachycardia with nodal bigeminal extrasystoles; another patient had sinus arrest with nodal escape beats. The remaining 19 electrocardiograms were normal.

ECHOCARDIOGRAPHY AND DOPPLER ULTRASOUND

In five patients (22%) cross sectional echocardiography showed mitral valve prolapse, and two also had mitral regurgitation on Doppler examination. No abnormality was shown in the two patients with isolated apical late systolic murmurs. Otherwise echocardiographic findings correlated well with auscultatory findings in that all four patients with clicks had echocardiographic prolapse, and both with clicks and murmurs had Doppler evidence of mitral regurgitation.

Twelve patients (52%) had dilated aortic roots, with the diameter being above the 95th centile for age and body surface area. There was no correlation between age and aortic root dimension. One patient had associated aortic regurgitation, and another had aortic valve stenosis and regurgitation. Four of these patients had mitral valve prolapse, two also had mitral regurgitation, and three had cardiomegaly on the chest *x* ray.

Discussion

Little is known about the life expectancy of patients with fragile X syndrome. Although they have cardiac abnormalities similar to those seen in patients with other types of connective tissue dysplasia, it is not clear whether the cardiac lesions are progressive or influence the prognosis.

Loehr *et al* examined 40 patients with fragile X syndrome.[6] Twenty two (55%) had evidence of mitral valve prolapse diagnosed by both auscultation and M mode echocardiography; 80% of men over the age of 18 years had mitral valve prolapse. Their criteria for echocardiographic diagnosis of prolapse were not strictly defined. It may be that more stringent recent echocardiographic criteria have led to fewer false positive diagnoses, thus explaining the lower frequency of mitral valve prolapse in our study. However, although we used a cross sectional echocardiographic definition of mitral valve prolapse, the frequency of abnormalities would have been no higher had we used M mode recordings alone.

Loehr *et al* found that only seven (20%) of 34 male patients had aortic root dilatation, but their patients were aged nine months to 31 years.[6] We found a higher frequency of aortic root dilatation (52%), but the wide age range of our patients and the lack of correlation between age and aortic root dimension suggest that the lesion is not progressive.

The influence of these cardiovascular abnormalities is not known. None of our patients had symptoms and none had received antibiotic prophylaxis against infective endocarditis. We are not aware of any deaths related to cardiovascular disease or sudden unexplained deaths in our population of patients; but ours was not a longitudinal study. Although the similarities with Marfan's syndrome suggest that patients with fragile X syndrome are potentially at risk, it is not yet known whether these cardiac lesions carry the same risk of sudden death as in Marfan's syndrome.

Examination of our patients did not include detailed assessment of the joints, skin, or other physical manifestation of the syndrome but, in view of the extensive phenotypic heterogeneity, it would be interesting if any phenotypic pattern was shown to be consistently associated with mitral valve prolapse.

Patients with fragile X syndrome have a fragile site on the X chromosome. The gene responsible for the phenotype is probably related to the fragile site. Although a specific abnormality of connective tissue has not yet been shown, the prevalence of mitral valve prolapse and aortic root dilatation, together with some of the physical manifestations of the syndrome, suggest that there is an underlying connective tissue dysplasia, perhaps similar to that seen in Marfan's syndrome, Ehlers-Danlos syndrome, and homocystinuria (table). The precise relation between these conditions awaits definition of the basic biochemical defect in the fragile X and similar syndromes.

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