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Echocardiography and genetic counselling in tuberous sclerosis

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Abstract

Objectives **– To assess echocardiography as an investigation for the detection of occult gene carriers in tuberous sclerosis.**

Patients **– Sixty parents of children with tuberous sclerosis who had been extensively investigated for signs of the disease and 60 age and sex matched controls.**

Procedure **– Blind study by two experienced echocardiographers and blind interpretation of video recordings by an adult cardiologist.**

Setting **– Cardiology department of a district general hospital.**

Results **– Two parents and three controls had bright echodense areas interpreted as possible rhabdomyomas.**

Conclusions **– In our hands echocardiography of adults is not an investigation with a high specificity for gene detection in tuberous sclerosis.**

Two dimensional echocardiography is a useful technique for the detection of primary heart tumours in infancy and childhood. Clinicopathological correlation for the abnormalities seen in children have been well established by echocardiography of cases before surgery or necropsy.[1-3]

Echocardiography of adults with tuberous sclerosis has led to the detection of echodensities, assumed to represent cardiac rhabdomyomas, the primary heart tumour associated with this disease.[4,5] Similar clinicopathological correlations for these abnormalities have not been established. The echodensities seen in adults have been invariably small and difficulties with their interpretation have been alluded to, in particular when bulky left ventricular papillary muscles are detected.[5] There has been no previous critical assessment of the use of echocardiography in this situation.

It has recently been suggested that echocardiography has a role in the assessment of parents for genetic counselling in tuberous sclerosis.[6] Giving accurate advice to parents of an apparently sporadically affected child about the risk of a second affected child remains a challenge to the clinical geneticist. The extent to which parents are investigated varies between different centres, largely because the significance of abnormal findings from some of these investigations remains in doubt. We have previously shown that renal ultrasound and skeletal survey will detect abnormalities the significance of which are unclear and that the most important aspect of counselling is a careful clinical examination of the parents.[7] Because of the paucity of published reports about the use of echocardiography for genetic counselling in tuberous sclerosis we have sought to evaluate its use in a blind controlled study.

Methods

Children with tuberous sclerosis thought to represent new mutations were identified through a prevalence study and by the Tuberous Sclerosis Association. Fifty-two parents of these children have been previously investigated by an extensive protocol including examination of skin, hair, and oral cavity, direct and indirect fundoscopy, cranial computerised tomography, renal ultrasound, and skeletal survey.[7] Eight further parents have had the same investigations excluding skeletal survey. None of these parents had evidence of tuberous sclerosis.

The 60 parents and 60 age and sex matched controls underwent transthoracic cross sectional echocardiography with an ATL ultramark 9 machine and a 3 megahertz phased array scanner. Two dimensional examinations were performed from parasternal, apical, and subcostal windows and recorded on videotape. Both echocardiographers had a minimum of five years experience of cross sectional echocardiography. Discrete, round, or oblong echodensities visible on two or more views were considered significant and the size of lesion determined from its maximum diameter. The papillary muscles and right ventricular trabeculations were viewed repeatedly in different views and standard M mode measurements were also taken. The echocardiographer was kept blind to the patient's status and the scans were interpreted blind by an adult cardiologist (RDT). Reproducibility was assessed by viewing a selection of the images on a second occasion. The study was approved by the hospital ethical committee and written consent obtained from all patients.

Table 1 Size and distribution of the abnormal echodense areas noted in six subjects.

	Sex	Age (y)	Site	Size (mm)	Echo	Cons
Controls	M	41	RV	5	?	+
	F	38	RV	8	?	+
	M	44	LV/IVS	10	+	+
Parents	F	41	RV	9	?	+
	F	32	RV	8	+	−
	F	43	RV	10	+	+

RV = right ventricle, LV = left ventricle, IVS = intraventricular septum, Echo = echocardiographer, Cons = consultant cardiologist, + = definite lesion, − = normal findings, ? = probable lesion.

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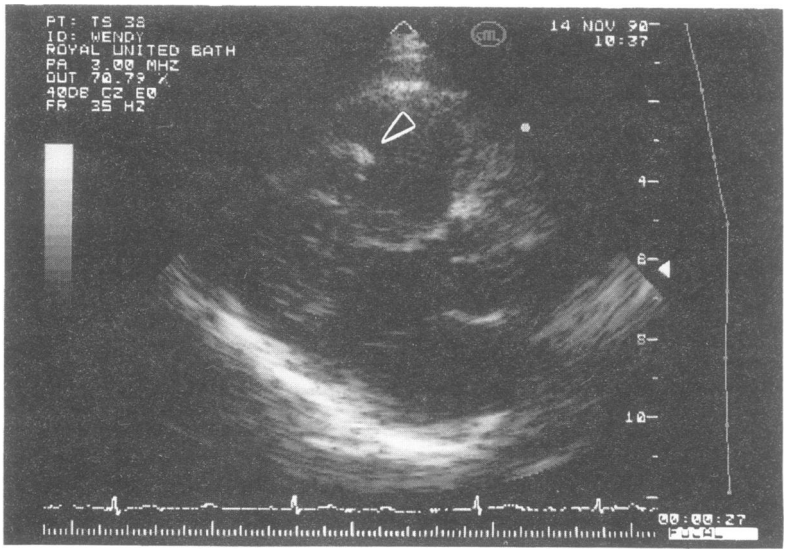

Figure 1 Long axis parasternal view of a control patient showing an echodense area in the apex of the right ventricle (arrowed).

Results

Mean maternal age was 41·4 years (range 22 to 76 years), and mean paternal age was 45·1 years (range 23 to 79 years). Mean age for control females was 39·2 years (range 21 to 63 years) and for control males 42·2 years (range 25 to 67 years).

Discrete echodense areas were detected on several scans. Three of these were thought to be definitely abnormal by the echocardiographer doing the scan (two parents, one control) and in a further three cases were felt to be probably abnormal (table 1). The cardiologist reviewing the scans reported five of these echodensities to be abnormal (two parents, three controls) and felt the findings in the sixth case were normal. Five patients had mitral valve prolapse (four controls, one parent); none of these had significant regurgitation as determined by colour flow doppler. Three subjects had asymptomatic atrial septal aneurysms (two parents, one control). Four scans were uninterpretable because of poor quality (three parents, one control) and the remainder were normal. The same abnormalities were identified when a selection of the scans was reviewed blind on a second occasion.

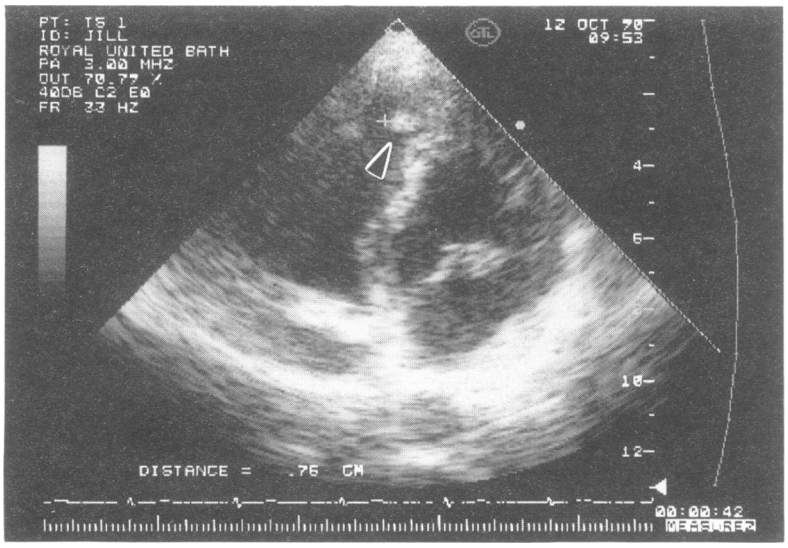

Figure 2 Short axis parasternal view of a parent showing an echodense area in the right ventricle (arrowed).

Discussion

In a blind study of echocardiography we have found suspicious echodense areas in parents of children with tuberous sclerosis and in age and sex matched controls (figs 1 and 2). None of the controls had a family history of tuberous sclerosis.

This study highlights the difficulties associated with interpretation of non-invasive imaging. Echocardiography depends on the differentiation by the human eye of shades of grey on a two dimensional image. Qualitative differences of tissue reflectivity are difficult to see in this situation. Added to this are the not infrequent difficulties of achieving adequate image quality in adults. False negative results may occur because atrial rhabdomyomas are rarely seen at echocardiography but are present in about a third of cases of tuberous sclerosis at necropsy and small rhabdomyomas (1 to 2 mm) also described at necropsy may be below the lower threshold of resolution for echocardiography; this has been found for cardiac vegetations to be 3 to 5 mm.[8] False positive results may occur because of reflective areas in normal myocardium. The study of Smith *et al*[5] of patients with tuberous sclerosis refers to difficulties with interpretation of the left ventricular papillary muscle.[5] We have found greater difficulty with the area of the right ventricular apex along the tricuspid papillary muscle. A colour coding technique to colour code the grey scale image on echocardiography has been described by Allan *et al*.[9] This allows better visual separation of the tissue boundaries and might prove helpful in circumventing some of the difficulties of interpretation.

There were three cases of atrial septal aneurysm in this study. While this is a higher number than one would expect from a sample of this size,[10] the abnormality has not previously been described in tuberous sclerosis and as two of the cases were parents and one a control this is thought to be a coincidental finding.

Al-Gazali *et al*[6] performed echocardiography on 40 parents of apparently sporadically affected children with tuberous sclerosis and found evidence suggesting to them that five mothers had cardiac rhabdomyomas. Four of the mothers had no clinical evidence of the disease and one mother had hypomelanic macules. Two of the affected children did not fulfil accepted diagnostic criteria.[11,12] The findings are surprising for a number of reasons. There are only three histologically proven cardiac rhabdomyomas in adults reported in English publications and only five in non-English publications since their first description in 1862.[13] There is mounting evidence from ultrasound follow up of the course of these hamartomas and from our own observations (work in progress) that they regress during

Table 2 Distribution of lesions found in adults at echocardiography compared with the necropsy findings of 36 subjects who had cardiac rhabdomyomas.

Reference	No	M:F	Multiple (%)	LV (%)	RV (%)	VS (%)	VS alone (%)	Atria (%)
16	36	2:1	92	100	81	20	0	30
6	5	0:5	40	80	0	60	40	0

LV = left ventricle, RV = right ventricle, VS = ventricular septum.

childhood and adolescence.[5 14 15] The distribution of lesions found on echocardiography of adults with tuberous sclerosis has differed from the post mortem findings in patients with cardiac rhabdomyomas (table 2). This might be accounted for if all the cases at necropsy died as a direct result of their rhabdomyoma; however, in a large pathological study one third of the cases died for other reasons and the distribution in this group did not differ from the group as a whole.[16] Finally, one would expect a higher number of second affected subjects in families where the parents are clinically normal but have not had echocardiography. None of the parents in the study by Al-Gazali *et al*[6] had two affected children, although there were only seven sibs in the five families.

None of the lesions detected in our study were of large size (> 15 mm) and if a large pedunculated echodensity was found this would be strong, although not unequivocal, evidence for that parent being affected. However, it is far more likely, as this study shows, that one would rarely be able to give definitive genetic advice to parents of a child with tuberous sclerosis based on echocardiography and that if used routinely it would frequently create dilemmas of interpretation. The situation is different in young infants and children at risk of tuberous sclerosis where echocardiography should be performed as early as possible to avoid missing lesions that will very likely regress with time.[5]

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