Fetal echocardiography in trisomy 18

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Abstract

**Background:** Previously reported pathological series suggest that cardiac malformations are universal in trisomy 18. We examined our experience of fetal echocardiography in trisomy 18 for comparison.

**Methods:** Of 255 fetuses detected in our centre between January 1999 and June 2004 with trisomy 18, 174 were evaluated by fetal echocardiography. Our results were compared to four previous echocardiographic and four autopsy series, comprising 89 and 110 patients, respectively.

**Results:** Of these 174, 114 were examined between 10 and 14 weeks and the remainder between 15 and 33 weeks. An increased nuchal translucency measurement was the reason for referral in the majority of the early cases, and extracardiac anomalies in the later cases. Images were non-diagnostic in 12 cases (7%), all examined at less than 15 weeks gestation. Abnormal cardiac findings were detected in 118 of the remaining 162 fetuses (73%), including 15 with functional anomalies. The types of heart malformation were varied and included ventricular septal defects, tetralogy of Fallot, left heart disease and atrioventricular septal defects. In all series used for comparison, a similar diversity of disease was seen. In pathological series of trisomy 18, structural heart malformations were found in all cases, but some had lesions which would not be detectable echocardiographically in the fetus.

**Conclusion:** Abnormal cardiac findings are detectable echocardiographically in the majority of cases of trisomy 18 examined in fetal life, but not in all. A wide spectrum of heart defects is seen. Diagnosis of heart malformations can be made reliably, even in the first trimester at the time of nuchal translucency measurement.
Introduction

Fetal echocardiography can reliably detect congenital heart disease (CHD), even as early as 12 weeks gestation, at the time of measurement of nuchal translucency (NT). The identification of increased NT is associated with a high incidence of chromosomal anomalies. It is well-recognised that the types of CHD seen in trisomy 18 are more varied than those associated with trisomy 21, but conventional wisdom from pathological series suggests that CHD is universal in trisomy 18. As this did not seem to be our experience in trisomy 18 using echocardiography, we examined our data to elucidate this.

Methods

Our database was searched for cases of trisomy 18 detected in our centre between January 1999 and June 2004. All patients seen in the department sign a consent form for data release, which has been approved by the Ethics committee. Of a total of 255 cases, 174 had a detailed cardiac evaluation, 162 of which were diagnostic. All patients were examined transabdominally using an Acuson Aspen (Mountain View, CA) with a 4-7mHz curvilinear transducer. Of these 174, 114 were examined between 10 and 14 weeks gestation (median=12) (crown rump length between 37.6 and 78.7mm), and the remaining 60 between 15 and 33 weeks, with the mean gestational age for the total group at the time of examination of 15 weeks. A study was considered diagnostic (of normality or abnormality) if the atrioventricular and ventriculoarterial connections could be defined and the relative sizes of the two atria, two ventricles, two great arteries, the transverse arch and duct could be determined. The reasons for referral for fetal echocardiography are shown in Table 1. The data described in four published echocardiographic series and four pathological series were combined for comparison with our data.

Table 1 Reason for referral for fetal echocardiography

<table>
<thead>
<tr>
<th>Gestational age</th>
<th>11-14 weeks</th>
<th>15-33 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased NT</td>
<td>106</td>
<td>2</td>
</tr>
<tr>
<td>Extracardiac abns</td>
<td>7</td>
<td>33</td>
</tr>
<tr>
<td>Suspected CHD</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Known T18</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>1</td>
<td>6</td>
</tr>
</tbody>
</table>

Abbreviations: NT= nuchal translucency, abns= abnormalities, CHD= congenital heart disease
Results

Current series
The gestational age was less than 14 weeks in 114/174 (66%). Images were considered non-diagnostic in 12 cases, all examined at <15 weeks. No abnormality of the heart was found in 44 cases, and there were abnormal findings in 118. A wide range of CHD was seen and this is illustrated in Table 2. According to an accepted cardiological method, each case was assigned only one “principal” cardiac diagnosis, considered the most fundamental from a cardiological standpoint. Some cases had what we grouped as “functional abnormalities”. These included isolated tricuspid regurgitation, an abnormal pattern of atrioventricular valve Doppler with a high E/A ratio or bi-directional flow in either great artery. The E/A ratio is the ratio of the velocity of the passive initial phase of ventricular filling to the active ventricular filling wave during atrial contraction. Normal values have been well described during fetal life.

Table 2 Comparison of the types of CHD found in the present series with the combined data of the four pathological and four echocardiographic series. Only the “principal” diagnosis was assigned to each case.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Present series</th>
<th>Combined Path series</th>
<th>Combined Echo series</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular septal defect</td>
<td>23 (14%)</td>
<td>58 (52%)</td>
<td>39 (44%)</td>
</tr>
<tr>
<td>Atrioventricular septal defect</td>
<td>29 (17%)</td>
<td>2 (2%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Double outlet right ventricle</td>
<td>5 (3%)</td>
<td>2 (2%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Coarctation</td>
<td>21 (13%)</td>
<td>21 (19%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Mitral Atresia</td>
<td>7 (4%)</td>
<td>4 (4%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>8 (5%)</td>
<td>11 (10%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Hypoplastic left heart</td>
<td>4 (2%)</td>
<td>1 (1%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Common arterial trunk</td>
<td>3 (2%)</td>
<td>4 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Tricuspid atresia</td>
<td>1 (1%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary atresia, IVS</td>
<td>2 (2%)</td>
<td>4 (4%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>0</td>
<td>0</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Double aortic arch</td>
<td>0</td>
<td>1 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Functional abnormalities</td>
<td>15 (9%)</td>
<td>2 (2%)</td>
<td>5 (6%)</td>
</tr>
<tr>
<td>No abnormality seen</td>
<td>44 (26%)</td>
<td>0</td>
<td>22 (25%)</td>
</tr>
<tr>
<td>Total</td>
<td>162</td>
<td>110</td>
<td>89</td>
</tr>
</tbody>
</table>
Of 156 with a known NT measurement, the mean measurement was 6.1 mm, with a range between 0.8 and 12 mm. There were 127/156 cases with NT over the 99th centile (81%), 10 between the 95th and 99th and 19 were within the normal range (12%). The mean NT in those with no detectable CHD was the same as the mean NT in those with CHD. Of the 174 patients, 161 proceeded to termination of pregnancy, there were 10 intrauterine deaths (gestational age range 12-37 weeks) and 3 neonatal deaths. There is no post-mortem data.

**Previous echocardiographic series**
There were 89 cases studied echocardiographically in four published series. In two of the series, comprising 57 cases, examination took place in fetal life at gestational age range of 14-23 weeks. In the remaining 32 cases, echocardiography took place after the livebirth of an affected infant. Diagnostic categories were grouped and compared to our series as far as was possible and are shown in Table 2.

**Previous pathological series**
There were 110 cases studied at autopsy in 4 published series. Three of the series (total 86 cases) described cases which were late stillbirths or born alive. The remaining series of 24 cases was a study of fetal material of less than 16 weeks gestation. Diagnostic categories were grouped and compared to our series as far as was possible and are shown in Table 2.

**Discussion**
Increasingly widespread application of nuchal translucency screening is presenting the fetal cardiologist with a new high-risk group, who have a high incidence of chromosomal anomaly and who are being referred for evaluation at much earlier gestations. In this series, the majority of patients were referred at the time of the finding of an increased NT, and the NT was generally markedly increased. A smaller group were evaluated at 20 weeks or later, either because of a more modestly increased NT or because of the detection of fetal abnormalities at routine scanning. In 12% of cases, the NT was within the normal range, a finding which has been previously reported. Unfortunately from the point of view of auditing our diagnoses, post-mortem analysis was not available in any case. This is because nearly all of the patients were referred from other hospitals and had the termination procedure locally after the chromosome result became available.

In some of the papers used for comparison with this series, sufficient detail was not given in order to make an accurate comparison, but an attempt at as fair a comparison as possible was made. CHD was designated in a hierarchical fashion according to the cardiological convention of connection abnormalities taking precedence over additional anomalies, such as ventricular septal defect, and abnormal connections at the atrioventricular junction taking precedence over an abnormal great artery connection. Pathological series in trisomy 18 suggest that CHD is invariable, but close examination of the details in published series show that in some cases only minor CHD, which are not likely to be detectable prenatally, was found. No abnormality was found in the heart in 27% of our series. It is possible that some examples of minor CHD were overlooked,
particularly in the first trimester fetus, but a normal heart was found in 9/60 (15%) examined in the second trimester, where echocardiography is known to be more accurate. In the two other fetal echo series, no cardiac abnormality was found in 17% and 55%, respectively. Although large or even moderately sized ventricular septal defects can be detected or excluded in the early scans, smaller defects most certainly would be overlooked. In the two postnatal echocardiographic series, valvar dysplasia and/or a ventricular septal defect was reported in all cases, although the septal defect size was sometimes small, and valvar dysplasia mild, or confined to one valve. In the only pathology series where the findings are reported in sufficient detail to analyse, it appears that 9/41 (22%) cases had abnormalities which would not be detectable echocardiographically prenatally, such as a persistent arterial duct, an atrial septal defect or a small ventricular septal defect. In addition, valvar dysplasia was commonly described pathologically but only occasionally appreciable echocardiographically, both in this and in the other fetal series. It was more likely to be noticed as an additional finding in the later fetus, rather than in the first trimester fetus, which made up most of our cases. However, some of the functional anomalies, such as tricuspid regurgitation, which were found in the early fetus, may reflect valvar dysplasia. Some of the functionally abnormal findings found in our series seemed to be specific for trisomy 18, such as bi-directional flow in the arterial duct and pulmonary artery or an increased E/A ratio of the atroventricular valve Doppler, which is abnormal at early gestations.

One reason for any difference between our series and the pathological series in particular, was the timing of examination in gestation. In our series, most patients were studied in the first trimester of pregnancy and, as is known in trisomy 18, many would have resulted in intrauterine death. In contrast, in 3 of the 4 pathological series, autopsy followed late stillbirth or took place after a livebirth. This may be an explanation for the higher incidence of atrioventricular septal defects, for example, in our early fetal series than in the pathological series, and the higher incidence of more minor disease such as small ventricular septal defects in those examined in later pregnancy or after livebirth.

In summary, congenital heart disease is commonly detected echocardiographically in the fetus with trisomy 18, but not in every case, as suggested by pathological series. The forms of CHD which occur in this setting are widely varied with ventricular septal defects, atrioventricular septal defects, left heart disease and tetralogy of Fallot being the most frequent. In practical terms, what has been learnt from this series is that almost any form of complex heart malformation can be associated with trisomy 18. Conversely, a fetus with extracardiac malformations may have trisomy 18 despite the absence of detectable CHD.
Competing interests
There is no conflict of interest for any of the authors.

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