Prenatal diagnosis of chromosomal abnormalities in fetuses with abnormal cardiac ultrasound findings

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Abstract
Objectives: To assess the frequency of karyotype abnormalities among fetuses with abnormal cardiac ultrasound findings. Methods: We carried out retrospective analysis of karyotype abnormalities diagnosed between January 2008 and March 2013 in the Department of Perinatology and Gynecology, Poznan University of Medical Sciences, among fetuses with abnormal cardiac ultrasound findings (n = 92). Only 32 included patients signed informed consent of the invasive prenatal genetic Testing. Results: Out of the 92 pregnancies with abnormal cardiac ultrasound findings, karyotyping revealed a chromosomal abnormality in 50% (16/32) of the cases. Classical autosomal aneuploidies (trisomy 21, 18 and 13) were the most frequent chromosomal abnormalities diagnosed in 43.8% (14/32) of the cases, followed by structural chromosomal rearrangements in 3.1% (1/32) of the cases and one triploidy (69,XXX) in 3.1% (1/32) of the patients. Sex chromosome aneuploidies (45,X or 47,XXX/46,XX) were not diagnosed. Conclusions: Patients with congenital heart defects (CHDs) require multidisciplinary care. Their families deserve up-to-date genetic information, as it is related to their child’s prognosis and to the kindred’s risk for future inheritance of genetic abnormalities associated with cardiac defects.

Key words: ultrasound, congenital heart defects, chromosomes, karyotype

Introduction
With an estimated prevalence of 4 to 50 per 1000 live births, congenital heart defects (CHDs) are the most common birth defects [1]. Chromosomal imbalances are a frequent cause of CHDs, especially when they are associated with the growth and developmental delay, the malformations affecting a second organ, dysmorphic features, or both [2]. Congenital heart defects represent one of the most common ultrasound findings in the prenatal diagnosis, but knowledge of their genetic basis is still limited. Generally, once chromosomal abnormalities have been ruled out in a fetus with CHDs, its etiology usually remains unexplained, making familial genetic counseling difficult [1, 3]. Fetal karyotype analysis by means of conventional cytogenetic methods such as G-banding after chorionic villus sampling (CVS) or amniocentesis (AC) has been the standard method for prenatal cytogenetic diagnosis for more than 40 years [4]. Such conventional cytogenetic analysis can identify all chromosomal aneuploidies and chromosomal aberrations that are microscopically visible. These include deletions, duplications or balanced and unbalanced chromosomal translocations, typically involving chromosomal segments of at least 4 to 5 megabases (Mb) in size [5]. For prenatal diagnosis traditional karyotyping is still considered as the gold standard, essentially because the interpretation of some variants of uncertain clinical significance is still challenging [6-9].

The aim of the present study was to investigate the prevalence of karyotype abnormalities among fetuses with abnormal cardiac ultrasound findings.

Material and methods
Patients
A total number of 92 patients in singleton pregnancies with CHDs were admitted to the Department of Perinatology and Gynecology, Poznan University of Medical Sciences, during the period from January 2008 to March 2013 and they were included to this study. Only 32 included cases decided to undergo invasive prenatal genetic testing. CHDs were diagnosed by means of fetal echocardiography using a VolusonW E8 ultrasound machine (GE Healthcare, Wauwatosa, WI, USA) at our tertiary referral centre. Diagnosis of CHDs was made by maternal-fetal medicine specialists. Fetuses underwent also a routine anatomy scan at the time of fetal echocardiography or prior. Gestational age was calculated based on last menstrual period or, in equivalent cases, on results of fetal biometry assessed by ultrasound. Appro
val for this study was obtained from the ethics commit-

The frequencies for the different types of CHDs are
given in Table 1. In 36 of the 92 (39.1%) cases more
than one cardiac pathology was found. In 45 of the 92
(48.9%) patients, ultrasound examination also revealed
extracardiac anomalies and/or ultrasound markers of
chromosomal abnormality. Mean gestational age, when
the invasive procedure was performed, was 26 ± 4 (range
from 14 to 33) weeks.

Cytogenetic analysis

Prenatal samples were karyotyped according to
standard procedures for amniotic fluid (n = 23) or fetal
blood cells (n = 9). When a chromosomal rearrangement
was diagnosed, parental karyotype testing was carried
out on peripheral blood lymphocytes to determine
whether the rearrangement was de novo or inherited.
Twenty G-banded metaphases from each sample were
analyzed using the G-banding Wright-staining method.

Results

Among the 92 pregnancies with CHDs and/or car-
diac ultrasound markers detected on ultrasound exa-
mination, conventional karyotyping revealed a chromo-
somal abnormality in 50% (16/32) of the patients (Table
2). The incidence of chromosomal abnormalities was
6.4% (3/47) in pregnancies with apparently isolated
heart ultrasound findings and 35.6% (13/45) in those
presenting with extracardiac malformations and/or ultra-
sound markers. Classical autosomal aneuploidies (tri-
somy 21, 18 and 13) were the most frequent chromo-
somal abnormalities diagnosed in 43.8% (14/32) of the
cases, followed by structural chromosomal rearran-
gements in 3.1% (1/32) of the patients and one triploidy
(69,XXX) in 3.1% (1/32) of the cases. Sex chromosome
aneuploidies (45,X or 47,XXX/46,XX) were not diagno-
sed. The chromosomal abnormalities and ultrasound
findings observed in these cases are presented in Table
2.

<table>
<thead>
<tr>
<th>Cardiac ultrasound findings</th>
<th>Number of patients</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septal defect</td>
<td>51</td>
<td>55.4</td>
</tr>
<tr>
<td>Conotruncal defect</td>
<td>20</td>
<td>21.7</td>
</tr>
<tr>
<td>Right-heart defect</td>
<td>15</td>
<td>16.3</td>
</tr>
<tr>
<td>Left-heart defect</td>
<td>16</td>
<td>17.4</td>
</tr>
<tr>
<td>Other</td>
<td>21</td>
<td>22.8</td>
</tr>
</tbody>
</table>

Table 2. Chromosomal abnormalities diagnosed by conventional karyotyping in 32 pregnancies
with fetuses presenting abnormal cardiac ultrasound findings

<table>
<thead>
<tr>
<th>Chromosomal abnormality</th>
<th>n (%)</th>
<th>Cardiac ultrasound findings</th>
<th>Other ultrasound findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classical autosomal aneuploidies:</td>
<td>8 (50.0)</td>
<td>AVSD, VSD, CoA</td>
<td>Pielectasis, cystic hygroma, polyhydramnion, shortenes of long bones, “double bouble”</td>
</tr>
<tr>
<td>Trisomy 21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>5 (31.4)</td>
<td>TGA, DORV, VSD, AVSD, atresia MV</td>
<td>Diaphragmatic hernia, feet malposition, choroid plexus cysts, micrognatia, hyperechogenic jejuni</td>
</tr>
<tr>
<td>Trisomy 13</td>
<td>1 (6.2)</td>
<td>HLHS, unspecified</td>
<td>Holoprosencephalia, abnormal facial profile</td>
</tr>
<tr>
<td>Structural chromosomal aneuploidies:</td>
<td>1 (6.2)</td>
<td>VSD</td>
<td>Dandy-Walker syndrome, IUGR, ventriculomegaly</td>
</tr>
<tr>
<td>46,XX add(18)(q23)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triploidy:</td>
<td>1 (6.2)</td>
<td>unspecified</td>
<td>IUGR</td>
</tr>
<tr>
<td>69,XXX</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Discussion

Several specific aspects of CHDs such as relatively high population incidence, low concordance rate of heart lesions within individual families, and recurrence risks lower than expected in Mendelian inheritance, have puzzled scientists for years. More recently, the importance of genetic factors has become more apparent. Advances in human molecular genetics have contributed to a better understanding of causative mechanisms of CHDs. In recent years, separate environmental and genetic causes have been identified. Classic Mendelian transmission of congenital heart defects in some families has been described in the literature. In the past decade, molecular genetic studies have exploited these observations of families with multiple affected individuals and have provided insights into the genetic basis of several forms of CHDs [10].

Prenatal series of fetuses with CHDs and/or cardiac ultrasound markers and their relation to chromosomal abnormality were presented in this report. The study analyzed the frequency and nature of the cytogenetically visible chromosomal rearrangements detected among fetuses with cardiac ultrasound findings admitted to our center over a 4-year period.

The detection rate of chromosomal abnormalities by conventional karyotyping in fetuses with CHDs and/or cardiac ultrasound markers was 50% (16/32) (6.5% if only CHDs were considered). Both frequencies are consistent with previously published detection rates (22-56.3% and 5.4%, respectively), and corroborate a strong association between chromosomal abnormalities and cardiac defects [11-13].

The most common cardiac defects occurring in the trisomy 21 were septal defects; the atrioventricular septal defect (AVSD), the ventricular septal defect (VSD) whereas in trisomy 18 we mainly found: AVSD, VSD, the transposition of the great arteries (TGA) and the double outlet right ventricle (DORV). Our results were similar to the results presented in the literature [14-18]. In Pateau syndrome the hypoplastic left heart syndrome (HLHS) was diagnosed. Moreover, often in the case of this syndrome ASD, VSD, the patent ductus arteriosus (PDA) and laterality defects were observed [19-20].

Our results also show that the likelihood of diagnosis of a chromosomal abnormality increases four-fold with the presence of extracardiac anomalies. Congenital heart defects often occur in the setting of multiple congenital anomalies, including abnormal facial features, or in association with limb anomalies, other organ malformations, developmental abnormalities, or growth abnormalities [17, 20-26].

Conclusions

For individuals with CHDs and their families, identification of a genetic cause is highly beneficial. This allows the physicians to explain the exact genetic mechanisms to the family. It also alerts the clinicians to investigate other organ systems that may be involved in the syndrome and broadens the context of evaluation from the individual to other family members. Genotyping may be very useful for stratifying “asymptomatic” family members into groups, who should have cardiac evaluations and those for whom it is not necessary. Obstetricians will have involvement in these issues if prenatal echocardiography demonstrates CHDs. Pediatricians require knowledge about these issues in taking care of multiple organ systems in children with genetic syndromes which include CHDs. As children grow into adulthood, internists, obstetricians, cardiologists, and thoracic surgeons will step in to care for CHDs as it is superimposed on adult medical issues.

References

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