PRENATAL FINDINGS IN CASES OF FAMILIAL AND SPORADIC 22Q11.2 DELETION SYNDROME (DIGEORGE SYNDROME/VELOCARDIOFACIAL SYNDROME)

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ABSTRACT

Background: To date, published information is lacking regarding the prenatal natural history of DiGeorge syndrome/velocardiofacial syndrome. Caused by the deletion of chromosome 22q11.2 in most cases, this syndrome is increasingly detected prenatally with the use of microarrays.

Objective: The authors hypothesized that current prenatal screening methods (such as nuchal translucency, maternal serum markers, and ultrasonography) may be useful as prenatal indicators for the early diagnosis of the 22q11.2 deletion syndrome (DS). The goal of this study was to identify characteristic findings, including sonographic abnormalities, in 22q11.2 DS to improve prenatal detection.

Methods: A single-center chart review comprising 26 years of prenatally or postnatally diagnosed cases of the 22q11.2 DS was performed. Prenatal records were available for 14 of 17 patients.

Results: Patients were categorized into 2 groups based on family history. Of those with no family history (n = 12), 50% were prenatally diagnosed by level II ultrasound with a heart defect and/or other anomalies. All 6 of those patients were diagnosed with 22q11.2 DS at amniocentesis by fluorescence in situ hybridization. Of the 12 patients, 11 (92%) were postnatally diagnosed with a heart defect. Tetralogy of Fallot (TOF) was the most common heart defect, detected in 6 of 12 cases. Two of 12 patients had abnormal maternal serum screens. Other sonographic findings included polyhydramnios (3/12), cleft lip/palate (2/12), and intrauterine growth restriction (6/9). Of those with a family history (n = 2), both mothers had confirmed 22q11.2 DS, yet neither received genetic counseling, level II sonography, or prenatal diagnosis at outside hospitals. Both had affected children with heart defects.

Conclusions: We found a higher frequency of TOF than previously reported in 22q11.2 DS. Polyhydramnios was associated with postnatally diagnosed velopharyngeal insufficiency.

Key words: 22q11.2 deletion syndrome, Tetralogy of Fallot, prenatal diagnosis, polyhydramnios.

BACKGROUND

With a prevalence of 1 in 4000, the 22q11.2 deletion syndrome (DS) is the most common human DS.[1,2] It is a contiguous gene DS with ~93% of cases resulting from a de novo mutation. The 22q11.2 DS has many names, including DiGeorge, velocardiofacial, CATCH 22, and asymmetric crying facies syndrome. Prenatal diagnostic testing for the 22q11.2 DS is possible using fluorescence in situ hybridization (FISH) as well as prenatal microarrays. In most cases, fetal cells are obtained through amniocentesis performed between 15 and 18 weeks of gestation or chorionic villus sampling performed between 10 and 12 weeks of gestation. The 2 available FISH probes, TUPLE1 and N25, have a similar detection rate, but neither is sensitive enough to identify small 22q11.2 deletions or point mutations.[3] In the future, noninvasive prenatal testing may be clinically available for 22q11.2 DS.[4] Fetuses can be evaluated between 18 and 22 weeks by echocardiogram and by high-resolution ultrasound for palatal and other physical anomalies. One of the hallmarks of the 22q11.2 DS is the variability of phenotypic expression: patients can present with developmental problems, hypotonia in infancy, feeding difficulties, impaired immune function, parathyroid dysfunction, psychiatric disorders, and an array of craniofacial, cardiac, neurologic, ocular, renal, and skeletal abnormalities.[2,3]

While there is no consensus regarding indications for prenatal testing, a few well-established indications do exist. These include (1) affected parent, as the risk of

transmission is 50% with each pregnancy; (2) previously affected child, owing to the possibility of germline mosaicism; and (3) prenatal detection of conotruncal cardiac defects, as the 22q11.2 DS is the most common cause of these defects.[5]

About 75% of patients diagnosed with this deletion have a congenital heart defect.[6] The conotruncal cardiac defects most associated with 22q11.2 DS are Tetralogy of Fallot (TOF), an interrupted aortic arch type B, ventricular septal defect, and truncus arteriosus, but double outlet right ventricle and transposition of the great vessels have also been detected.[2,7-9] Sonographic detection of polyhydramnios, skeletal, or renal anomalies in conjunction with a cardiac defect should raise suspicion for the 22q11.2 DS. Facial malformations such as cleft lip and palate are observed in 1% to 2% of patients with the 22q11.2 DS, but cleft palate alone is seen in 10% of patients with 22q11.2 DS and can be detected prenatally with advanced sonographic techniques.[3,10] The palatal anomaly noted most commonly in 22q11.2 DS is velopharyngeal insufficiency, which cannot be diagnosed prenatally. Isolated anomalies that are detected through prenatal ultrasound apart from cardiac defects are nonspecific and do not necessarily warrant further workup for 22q11.2 DS.[1,5] Facial dysmorphisms are subtle and include a long face with malar flattening, a broad nose, "hooded eyelids," hypertelorism, squared ears with overfolded helices, and microstomia.[11] Again, most of these findings would not be detected prenatally, even with 3D ultrasound.

Very little information has been published to date regarding the prenatal natural history of the 22q11.2 DS, but with increased use of prenatal microarray as a diagnostic tool, the syndrome is being diagnosed more frequently. We hypothesized that the currently used prenatal screening methods (such as nuchal translucency, maternal serum markers and ultrasonography) may be useful as prenatal indicators for the early diagnosis of the 22q11.2 DS. The objective of this study was to present our 26-year experience in prenatal and postnatal diagnosis of familial and sporadic chromosome 22q11.2 deletion in the hope of identifying characteristic findings, including sonographic abnormalities, to improve prenatal detection. Early detection will allow parents to receive important information regarding this syndrome. This in turn will facilitate pregnancy management and optimize postnatal care, thereby decreasing neonatal morbidity and mortality.

METHODS

A single-center retrospective chart review comprising 26 years of prenatally or postnatally diagnosed cases of the 22q11.2 DS at Tufts Medical Center, Boston, Massachusetts, was performed. Seventeen documented cases of 22q11.2 DS were identified, 14 of which had available prenatal records. Patients were categorized into 2 groups, those with a negative family history of the deletion (group A; n=12) and those with a positive family history (group B; n=2). The frequency of abnormal prenatal ultrasound findings was recorded.

RESULTS

In group A, 6 of 12 (50%) patients were prenatally diagnosed by level II ultrasound with a heart defect with or without other anomalies (**Table 1**). Eleven of 12 (92%) patients were postnatally diagnosed with a heart defect. TOF was the most common heart defect, seen in 6 of 12 cases. All (6/6) patients with prenatally diagnosed heart defects were diagnosed with 22q11.2 DS at amniocentesis by FISH testing. Other sonographic findings included polyhydramnios (3/12), cleft lip/palate (2/12), and intrauterine growth restriction (6/9) (**Table 2**). All 3 fetuses with polyhydramnios had velopharyngeal insufficiency diagnosed postnatally. Three patients terminated the pregnancy via induction; all required dilatation and curettage secondary to retained placenta. Two of 5 women had abnormal serum screens (increased risk for trisomy 18 and Down syndrome of 1:24). In group B, although both patients had confirmed 22q11.2 DS before pregnancy, neither received genetic counseling, level II sonography, or prenatal diagnosis at outside hospitals because of poor prenatal care. Both had affected children with conotruncal heart defects, neither diagnosed prenatally.

DISCUSSION

In the present study, most patients with 22q11.2 DS had a congenital heart defect, confirming the very high correlation between congenital heart defects and the 22q11.2 DS.[6] A higher frequency of TOF (6/12; 50%) was found in those with the 22q11.2 DS than in the 11% to 30% reported in recent studies.[2,6,12] In concordance with other authors, we strongly advocate that prenatal detection of heart defects should prompt consideration of diagnostic studies for 22q11.2 DS.[13] Aside from

Table 1. Prenatal and Postnatal Findings in 12 Fetuses With a 22q11.2 Deletion

Case	Family History	Prenatal Cardiac Findings	Other Prenatal Findings	Postnatal Findings	Time of Diagnosis
1	None	TOF		TOF	Prenatal
2	None	Normal fetal ECHO	Cleft lip/palate; polyhydramnios	Normal postnatal ECHO; cleft lip/ palate	Postnatal
3	None	TOF		TOF; hypocalcemia	Prenatal
4	None	Complex heart defect		Not available	Prenatal
5	None	Normal ultrasound		Right-sided aortic arch; hypoparathyroidism	Postnatal
6	None	Truncus arteriosis	Severe polyhydramnios	Truncus arteriosus; velopharyngeal insufficiency	Prenatal
7	None	TOF	Borderline polyhydramnios; abnormal cavum septum pellucidum	TOF	Prenatal
8	None	Echogenic intracardiac focus	Cleft palate	Cleft palate; VSD; PDA; PFO	Postnatal
9	None	TOF with pulmonary atresia	Polyhydramnios	TOF; velopharyngeal insufficiency	Prenatal
10	None	Normal fetal echo		VSD	Postnatal
11	None	Echogenic focus on kidney		TOF	Postnatal
12	None	Pulmonary atresia;VSD		TOF	Postnatal
13	Mother with 22q11.2 deletion and developmental delay	None		TOF; pulmonary atresia	Postnatal
14	Mother and maternal grandmother with 22q11.2 deletion	None		TOF; absent thymus	Postnatal

Abbreviations: ECHO, echocardiogram; PDA, patent ductus arteriosus; PFO, patent foramen ovale; TOF, Tetraology of Fallot;

Table 2. Prenatal Sonographic Findings in Cases of 22q11.2 Deletion Syndrome

Sonographic Finding	n/N, %
Congenital heart defect	6/12 (50%)
Polyhydramnios	3/12 (25%)
Cleft lip/palate	2/12 (17%)
Intrauterine growth restriction	6/9 (67%)

aneuploidy and 22q11.2 DS, the differential diagnosis for the etiology of prenatally diagnosed cardiac defect should include isolated structural malformation, gestational diabetes, other genetic syndromes, and teratogen exposure.[5]

Bretelle et al proposed an algorithm for prenatal 22q11.2 DS testing according to ultrasound findings. This included fetal thymic measurements along with conotruncal anomalies as a relatively strong indication for prenatal testing. In that study, 2 of 8 fetuses had an absent or hypoplastic thymus noted prenatally. The dataset in the present study did not include information regarding prenatal thymic measurements, but thymic measurements may prove to be useful in the prenatal detection of 22q11.2 DS.[13] Other prenatal ultrasound findings that have been proposed as markers for 22q11.2 DS include shortened fetal ear length and 3D ultrasound for facial dysmorphology, though facial differences are usually subtle.[11] Of interest in the present study was that all the fetuses with polyhydramnios had velopharyngeal insufficiency diagnosed postnatally (3/3). Velo-pharyngeal insufficiency cannot be diagnosed prenatally, but polyhydramnios may be a marker for velopharyngeal insufficiency or submucosal clefts, which also cannot be diagnosed prenatally. Further studies to understand this relationship are needed. Additional anomalies that may be seen prenatally include polydactyly, central nervous system abnormalities including neural tube defects, and renal abnormalities.[14]

A major limitation of prenatal diagnosis of 22q11.2 DS is the inability to anticipate postnatal phenotypes because of low genotype-phenotype correlation.[15] This provides a challenge for health care providers, as it is not possible to predict the degree to which the individual will be affected. In addition to the variability seen in the physical manifestations, a wide range of cognitive and behavioral outcomes also exists. While severe intellectual disability is rare, developmental delays and learning disabilities are commonly associated with 22q11.2 DS. Psychiatric disorders are also reported to be one of the most common features associated with this deletion, including generalized anxiety disorder, major depression, attention deficit disorder, and obsessive-compulsive disorder. Current estimates suggest that 20% to 25% of individuals will develop schizophrenia or related psychiatric disorders.[16,17] One study showed a decrease in reproductive fitness in individuals with 22q11.2 DS that is significantly correlated to the severity of neuropsychiatric phenotype.[18] Developmental delays, psychiatric disorders, and facial dysmorphisms should also prompt the prenatal provider to consider this syndrome in mothers who may be undiagnosed. With the increased utilization of prenatal microarray, the number of prenatally diagnosed cases of 22q11.2 DS is expected to increase. It will be increasingly important for health care providers to have an understanding of the variability of this diagnosis to provide families with accurate information. Additionally, long-term follow-up is needed for individuals who receive a diagnosis of 22q11.2 DS prenatally.

Limitations notwithstanding, there are many benefits to prenatal testing. First, it provides couples with an accurate diagnosis. This allows parents and involved health workers to prepare to meet the needs of the infant during delivery and beyond.[19] Decisions about whether to deliver at a tertiary care center can be considered, as well as management of hypocalcemia, immune deficiencies, and feeding difficulties in the perinatal period. These patients require the expertise of various specialties including cardiology, otorhino-laryngology, genetics, immunology, plastic surgery, dentistry, and ophthalmology, along with the investment of substantial resources. For this reason, ensuring early, efficient, and accurate diagnosis of this syndrome is essential. Early detection allows for the coordination of multiple specialists, early intervention, and efficient allocation of resources. It also allows parents to make informed decisions regarding pregnancy termination.

Proper diagnosis lets couples determine their recurrence risk and risk to relatives. Once a fetus is found to have the deletion, the parents should be offered testing with the option of genetic counseling and psychological support, as expression of the deletion can be mild and varied, and ~7% of cases are inherited from an affected parent.[13] Patients with a positive family history of 22q11.2 DS should be offered genetic consultation, prenatal diagnosis, targeted anatomy survey, and fetal echocardiogram because of the 50% recurrence risk.

CONCLUSIONS

In the absence of a family history, detection of a fetal conotruncal anomaly is considered the best indication for prenatal 22q11.2 DS testing.[3,5,20] However, knowing

which sonographic findings should prompt testing for the deletion in fetuses with no detected heart defect is less clear. Our findings support the notion that any one of the minor signs (cleft lip/palate, polyhydramnios, intrauterine growth restriction, renal abnormalities, absent or hypoplastic thymus) in isolation may not warrant testing for the 22q11.2 DS. However, when these findings are detected in the presence of a heart defect or in conjunction with other minor signs of the deletion—especially cleft palate or polyhydramnios, which may be a marker for velopharyngeal insufficiency—the level of suspicion for the 22q11.2 DS should be very high. Microarray analysis should be considered in the presence of a major structural anomaly and a normal karyotype. If prenatal testing is performed, a normal karyotype should prompt consideration of obtaining a microarray in the setting of a major anomaly.[21]

Further studies are needed regarding the maternal serum screening abnormalities observed in this syndrome. One of our cases showed an increased risk for trisomy 18 and one showed an increased risk for trisomy 21. A previous case report was published of 3 patients with fetuses affected with 22q11.2 who all had an increased risk for trisomy 18 by maternal serum screen. Those investigators suggested that patients having prenatal diagnosis because of an increased risk of trisomy 18 be offered FISH for 22q11.2.[22] Data on retained placentas and abnormal placentation in pregnancies with fetuses affected with 22q11.2 are lacking as well. Because the number was small, it is possible that the 3 patients who terminated via induction of labor had retained placentas because of early gestational age (<24 weeks). We hope that early detection of this syndrome through observation of characteristic sonographic findings will allow couples to receive more information to improve pregnancy management and optimize postnatal care, thereby decreasing neonatal morbidity and mortality.

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