

Prenatal diagnosis of 22q11 deletions: a series of five cases with congenital heart defects

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Abstract

We report a series of five patients with congenital heart defects in whom a prenatal diagnosis of 22q11 deletion has been made. The accurate cardiac and cytogenetic diagnoses were made between 20 and 23 weeks' gestation in all cases and the cardiac findings were all confirmed postnatally. The cardiac abnormalities included tetralogy of Fallot with absent pulmonary valve, pulmonary atresia with VSD, common arterial trunk, and left atrial isomerism with double outlet right ventricle. The problems of genetic counselling in these cases are discussed. A recommendation is made to test all fetuses with conotruncal heart abnormalities detected prenatally for a 22q11 deletion, whereas guidelines for other congenital heart disease types are less clear.

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A consensus is emerging that the incidence of 22q11 deletion syndrome is approximately 1 in 5000-10 000 births.^{1,2} This makes 22q11 deletion syndrome one of the more common genetic diseases in the population. As a high proportion of people with 22q11 deletion have heart abnormalities, an important way in which fetuses with 22q11 deletion will present is through the detection of congenital heart disease. With the advent of high resolution ultrasound and specialist fetal cardiology, accurate and early prenatal diagnosis of cardiac abnormalities is now possible.

We report a series of five fetuses in whom an early prenatal diagnosis of a specific cardiac defect was made between 20 and 23 weeks' gestation and in whom a submicroscopic deletion within chromosome 22q11 was identified. On the basis of this series we provide initial guidelines for testing for 22q11 deletion in fetuses with congenital heart disease.

Case reports

CASE 1

This was the fourth pregnancy of non-consanguineous parents. The mother was referred for a fetal cardiology opinion following the detection of a cardiac abnormality on a routine anomaly scan at 20 weeks of pregnancy. Detailed fetal echocardiography confirmed congenital heart disease, with a large ventricular septal defect, overriding of the

aortic valve, and pulmonary atresia. The left kidney was also absent.

Amniocentesis was performed and a fetal karyotype of 46,XX was established using conventional G banding. A microdeletion of 22q11 region was detected using fluorescent in situ hybridisation (FISH) with Oncor N25 probe, which maps within the DiGeorge critical region at D22S75.³ This had arisen de novo.

Postnatal echocardiography and angiography confirmed the prenatal cardiac findings. No central pulmonary artery confluence was found and pulmonary blood supply was via four major aortopulmonary collateral arteries (MAPCAs). The baby is now 2 years of age with developmental delay. She crawls but is not walking and there are no intelligible words. There are severe feeding problems and she is fed through a gastrostomy as oral intake is so poor largely because of difficulty in swallowing. The degree of failure to thrive is out of proportion to her cardiac disability. Height and weight are 78.5 cm and 9 kg respectively (below the 3rd centile).

CASE 2

This was the first pregnancy of non-consanguineous parents who were referred for fetal cardiology assessment following the suspicion of a cardiac defect on a routine anomaly scan at 20 weeks of pregnancy. The fetal echocardiogram showed a complete atrioventricular septal defect (AVSD) with a double outlet right ventricle. In addition, there was fetal bradycardia and the inferior vena cava was interrupted. A prenatal diagnosis of left atrial isomerism was made.

In view of the cardiac findings the parents elected to terminate the pregnancy before the karyotype results. At necropsy, the prenatal ultrasound findings were confirmed and, in addition, there was polysplenia, malrotation of the bowel, absent thymus, and a multicystic left kidney. The atrial appendage morphology confirmed left atrial isomerism.

Amniocentesis was performed and the fetal karyotype of 46,XX was established but with a 22q11 deletion detected by FISH. Paternal blood was unavailable and therefore a de novo or inherited deletion could not be distinguished.

CASE 3

This was the first child of non-consanguineous parents and congenital heart disease was detected on an anomaly scan at 20 weeks of pregnancy. The prenatal echocardiogram showed tetralogy of Fallot with absence of the

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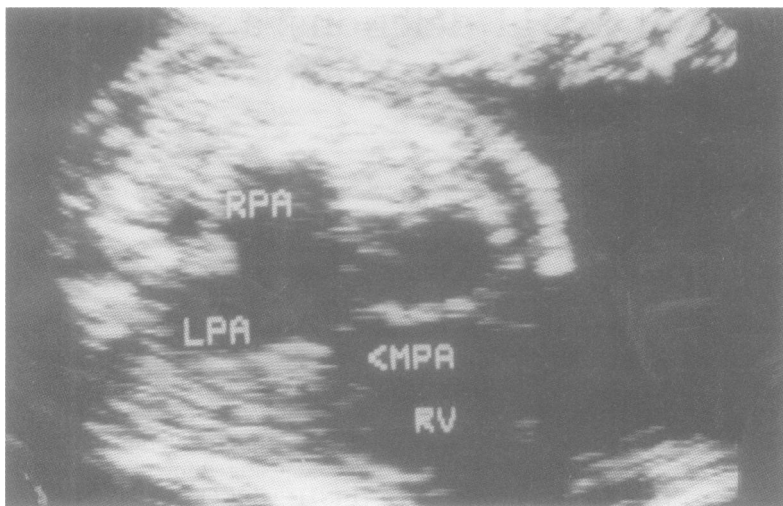


Figure 1 Prenatal echocardiographic findings in tetralogy of Fallot with absent pulmonary valve. This is a transverse echocardiographic view of the fetal thorax, at the level of the pulmonary arteries, showing the striking dilatation of the main and branch pulmonary arteries which is characteristic of the condition. RPA=right pulmonary artery, LPA=left pulmonary artery, MPA=main pulmonary artery, RV=right ventricle.

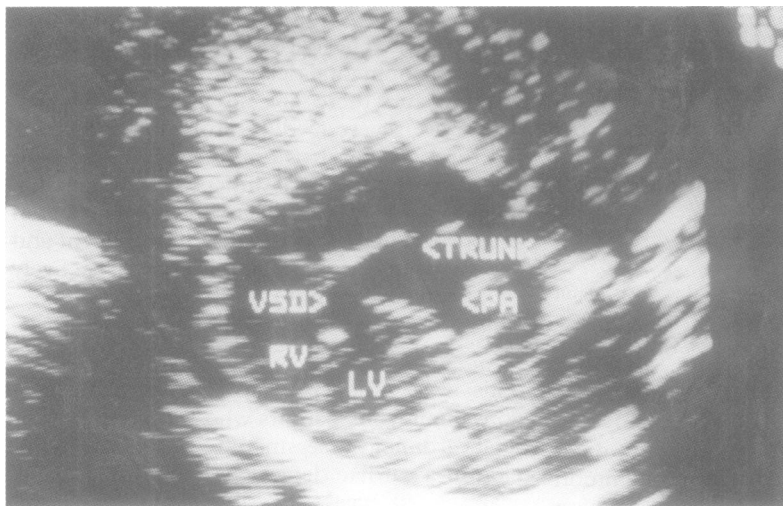


Figure 2 Prenatal echocardiographic appearances of a common arterial trunk. The common arterial trunk arises astride a ventricular septal defect. One of the branch pulmonary arteries can be seen arising from the common arterial trunk. RV=right ventricle, LV=left ventricle, VSD=ventricular septal defect, Trunk=common arterial trunk, PA=branch pulmonary artery.

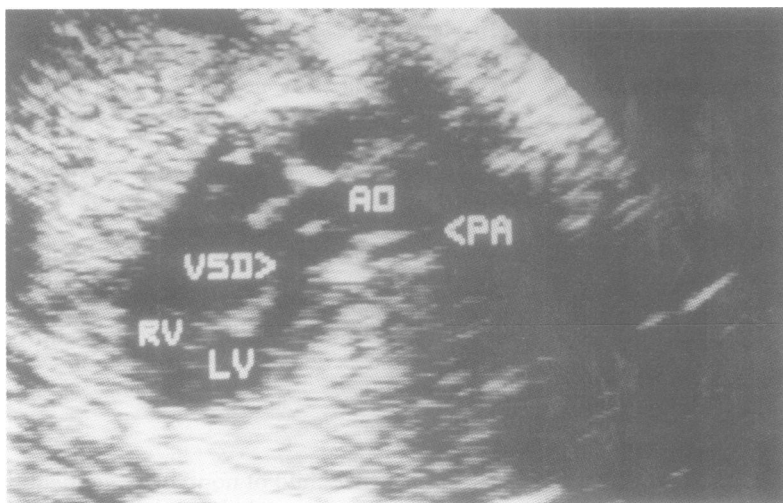


Figure 3 Prenatal echocardiographic findings of pulmonary atresia with a ventricular septal defect. The aorta overrides a ventricular septal defect. The main pulmonary artery is hypoplastic and may be seen just to the right of the aorta. RV=right ventricle, LV=left ventricle, VSD=ventricular septal defect, Ao=aorta, PA=main pulmonary artery.

pulmonary valve. The severe dilatation of the branch pulmonary arteries is shown in fig 1.

Amniocentesis was performed and the fetal karyotype was 46,XX with a de novo 22q11 deletion. The parents elected to continue the pregnancy and the baby was born at term following induction of labour. The baby was intubated and ventilated shortly after birth. Postnatal echocardiography confirmed the prenatal findings and the chest x ray showed "air trapping" which was attributed to the grossly distended pulmonary arteries. Surgical repair of the defect, including VSD closure and plication of the pulmonary arteries, was performed on day 5 but the child died later the same day.

CASE 4

Referral for a detailed fetal echocardiogram was made at 22 weeks' gestation following a suspicion of congenital heart disease on a routine ultrasound scan. The cardiac findings were of a common arterial trunk with separate origins of the pulmonary arteries (truncus arteriosus, type 2). Fig 2 shows the fetal echocardiographic findings.

Amniocentesis was performed and the fetal karyotype was 46,XX with a de novo 22q11 deletion. The baby was delivered at 38 weeks' gestation, and the postnatal echocardiogram confirmed the prenatal findings. This baby is clinically well at the age of 1 week with hypocalcaemia and reduced T cell numbers and is awaiting corrective surgery.

CASE 5

This was the first pregnancy of non-consanguineous parents who were referred for a fetal cardiology opinion at 22 weeks' gestation. The prenatal echocardiogram showed a large ventricular septal defect with overriding of the aortic valve and pulmonary atresia. Confluence of the pulmonary arteries was seen prenatally. The fetal echocardiogram is shown in fig 3.

Amniocentesis was performed and the fetal karyotype was 46,XY with a de novo 22q11 deletion by FISH. Labour was induced at 39 weeks and the cardiac findings were confirmed by postnatal echocardiography and angiography. Cardiac catheterisation showed small but confluent central pulmonary arteries and the lungs were supplied with blood by four MAP-CAs. The baby had dysmorphic facial features characteristic of the 22q11 deletion syndrome, generalised hypotonia, considerable feeding difficulties, and reduced T cell numbers. At 3 months, he was admitted for management of cardiac failure, and at 5 months, for repair of a right inguinal hernia. At that time, a laparotomy was performed because of persistent vomiting and adhesions around the duodenum were found and released. Feeding difficulties have continued and contrast studies have shown gastro-oesophageal reflux. At 13 months his height and weight are well below the 3rd centile (67 cm and 6 kg respectively). He is fed nasogastrically and requires total parenteral nutrition (TPN). He remains normocalcaemic. His T cell populations are

reduced; in particular CD3, 4, and 8 populations are below normal levels. Developmentally he is delayed and is not yet sitting independently. He also has few words.

Discussion

There has been, to our knowledge, only one previous report of prenatal detection of a chromosome 22q11 deletion in a family where a previous child had a common arterial trunk (truncus arteriosus) and DiGeorge syndrome.⁴ This is the first reported series of patients in whom prenatal diagnosis of 22q11 deletion has been made following the prenatal detection of cardiac defects. The cardiac and cytogenetic diagnoses were made between 20 and 23 weeks of gestation in all cases, and the cardiac findings were all confirmed postnatally. Four of the five cases had cardiac abnormalities within a conotruncal heart disease group, which has been seen previously in patients with 22q11 deletion.⁵⁻⁷ We confirm the high incidence of aortopulmonary collateral vessels, observed in pulmonary atresia with ventricular septal defect, in patients with a chromosome 22q11 deletion.⁸ Furthermore, one of our cases had no confluent central pulmonary arteries, which is not uncommon in patients with a 22q11 deletion, but is rare in the absence of a deletion.⁸ The one unusual case of left atrial isomerism with double outlet right ventricle has been reported elsewhere.⁹

Devriendt *et al*¹⁰ prospectively analysed 150 patients with conotruncal heart disease and suggested that a recognisable 22q11 deletion accounts for at least 12.8% of all cases of conotruncal disease diagnosed postnatally. This represents a significant number of patients in whom a cause for a congenital heart disease can be found. Detection of conotruncal abnormalities can be technically difficult prenatally but detailed echocardiography can show them. At this centre we currently detect approximately 20-25 new cases per year.

With the increasing availability of specialist fetal cardiology services, prenatal diagnosis of deletion 22q11 will become more commonplace and should be offered. The challenge to clinical geneticists is to provide appropriate and accurate genetic counselling for this condition. At present, the most useful guide to prognosis is a review of 120 patients with velocardiofacial syndrome.¹¹ This study, however, is limited as the sample size was small, not all the patients had proven 22q11 deletion by FISH, and they were ascertained by virtue of their palatal or pharyngeal problems. The patients described here, who have been diagnosed prenatally, represent a different clinical spectrum ascertained by virtue of their congenital heart disease. The degree of learning difficulties in this group of patients is not known. Currently, we provide the best available information when counselling patients but there is a clear need for more long term prognostic information about 22q11 deletion syndrome. In particular, parents are most concerned about the possible learning difficulties and psychiatric problems reported in velocardiofacial syndrome. A matched longitudinal

study of children with the same cardiac defect with or without 22q11 deletion is needed as only then can the additional load of 22q11 deletion on children with major cardiac defects be fully assessed. Once established, more accurate information can be given to parents when a 22q11 deletion is detected prenatally. One out of five sets of parents elected to terminate the pregnancy and this was entirely on the basis of the abnormal cardiac findings. The termination was in fact performed before the results of the karyotype were available. In this series, therefore, the presence or absence of 22q11 deletion did not greatly influence the parents' decision to continue with or opt for a termination of pregnancy. However, the additional information gained about the prognosis of children with 22q11 deletion may well be helpful to parents when coming to terms with and preparing to care for a child with substantial medical problems. All our parents, except the father of case 2 who was unavailable, were tested and found to be negative for 22q11.2 microdeletions. Also, detection of *de novo* 22q11 deletion in a fetus helps in counselling in future pregnancies. In these cases, the recurrence risk is extremely low, although a case of germinal mosaicism has been reported.¹² Without this information the couple would usually be given a 3-5% recurrence risk for all cardiac defects.¹³

On the basis of this series various recommendations for clinical practice can be made. Firstly, as conotruncal heart defects can be detected prenatally and as approximately 13% are thought to result from deletions in chromosome 22q11,¹⁰ testing all fetuses with conotruncal defects for 22q11 deletion would seem appropriate. Detecting a 22q11 deletion has important implications in the clinical management of the baby postnatally.

It is not known, however, what proportion of other types of congenital heart disease have 22q11 deletion and indeed one of the cases in this series had a complex heart arrangement not previously associated with 22q11 deletion. Until a detailed prospective study to establish the incidence of 22q11 deletion in prenatally detected congenital heart disease is complete, it will not be possible to provide clear recommendations for prenatal screening of other groups of congenital heart disease.¹⁴

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