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Tetralogy of Fallot in the fetus in the current era

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ABSTRACT

Objectives *To compare the spectrum of tetralogy of Fallot detected recently in fetal life with that in previous reports of prenatal and postnatal experience.*

Methods *All cases of tetralogy of Fallot, including those with pulmonary atresia, diagnosed between 1998 and 2005 inclusive were identified. Additional data for the 129 cases were collected, including associated congenital heart malformations, nuchal translucency measurement, karyotype and outcome.*

Results *The most common reason for referral was a suspicion of heart malformation at the routine obstetric ultrasonography scan and referrals increased during the study period. The mean gestational age at diagnosis was 20.6 weeks. The nuchal translucency measurement was above the 95th centile in 37 (47%) of the 78 fetuses in which it had been measured, and in 19/37 of the chromosomally normal fetuses. Of 112 fetuses with chromosomal analysis, 55 (49%) had anomalies, including 22q11 microdeletion in 15. There were additional extracardiac malformations in 65/129 cases (50%) and additional cardiac malformations in 73 (57%). In 70/129 (54%) cases, the parents chose termination of pregnancy. Overall survival to date in the continuing pregnancies is 77%.*

Conclusions *Tetralogy of Fallot is increasingly recognized during routine fetal obstetric scanning. However, the spectrum of disease detected in the fetus remains biased towards those cases with extracardiac malformations and those with complex disease. As a result, even in the current era, the prognosis for the whole group of fetal cases under the diagnostic heading of tetralogy of Fallot continues to be much less favorable than would be expected of a postnatal series. Copyright © 2007 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Tetralogy of Fallot is a common form of congenital heart disease (CHD), found in about 1/3600 live births and 3.5–7% of infants with CHD[1]. The key anatomical features result from an anterosuperior displacement of the outlet septum. The aorta arises astride an outlet ventricular septal defect (VSD) and there is some degree of right ventricular outflow tract obstruction, classically in the subpulmonary (infundibular) region. The neonate with the classical form, where there is pulmonary stenosis rather than atresia, is usually asymptomatic at birth and presents with a murmur or increasing cyanosis over the first month of postnatal life. Surgical repair of these typical cases is usually undertaken at around 4–6 months of age, and is performed at low risk. Pooled data from national UK statistics for 2001 reported a 97% survival rate at 1 year[2]. Of the survivors, 98% would be expected to be alive at 20 years[3]. More severe forms of Fallot's tetralogy, such as those with pulmonary atresia or absent pulmonary valve syndrome, are acknowledged to have a worse outcome. Previous reports of fetal series of tetralogy of Fallot have highlighted the surprisingly poor outcome when this diagnosis has been made prenatally[4,5]. This was found to be due to the severe spectrum of tetralogy preferentially detected prenatally, and to an unexpectedly high rate of associated extracardiac and chromosomal anomalies found in the fetal series.

METHODS

Our database was reviewed for cases with a diagnosis of tetralogy of Fallot seen between 1998 and the end of 2005. The videotaped record of each case was reviewed. Details of the cardiac findings, extracardiac abnormalities, karyotype, nuchal translucency measurement and outcome were recorded.

RESULTS

Of 129 cases identified, 59 were referred with a suspicion of CHD, 25 because of extracardiac anomalies, 30 for an increased nuchal translucency measurement, four for a family history of CHD and 11 for other reasons. The diagnosis was made increasingly during the study period, from a low of six cases in 1999, to a high of 28 cases

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during 2004. The mean gestational age at diagnosis was 20.6 weeks, with a range of 12–40 weeks. There were seven cases (5%) of absent pulmonary valve syndrome, nine (7%) with an additional diagnosis of atrioventricular septal defect, 38 (29%) with pulmonary atresia and 34 (26%) with a right aortic arch.

In four cases, the diagnosis of tetralogy of Fallot could not be clearly distinguished from a common arterial trunk. Of these four, one pregnancy resulted in intrauterine death and three were terminated. None had postmortem examination. Two of the four were known to have trisomy 13. In one further case, there was an outlet VSD with aortic override at 20 weeks with a normally sized pulmonary artery and right aortic arch. It was anticipated that this case would evolve into tetralogy of Fallot with advancing gestation. However, no right ventricular outflow tract obstruction developed and the infant required VSD repair only. This was our only known false-positive diagnosis.

Among 92 fetuses in which full chromosomal analysis was performed, 55 anomalies were identified including 15 cases of 22q11 microdeletion. A further 20 fetuses had a normal karyotype but 22q11 microdeletion was not sought. These are listed in Table 1. Of the 27 fetuses with a right-sided aortic arch that had chromosomal analysis, 16 had chromosomal anomalies.

Extracardiac anomalies occurred in 65 cases, and in 22/37 cases in which chromosomal abnormality had been excluded. The associated defects were varied in type and severity, and included talipes, tracheo-esophageal fistula, cleft lip, abdominal wall defects, ventriculomegaly, single umbilical artery and renal anomalies. Some associated syndromes, such as the VACTERL syndrome, were suspected, but not clearly identifiable as such until after birth.

The nuchal translucency measurement was known in 78/129 cases and was above the 95th centile in 37/78 (47%). Of the 37 cases that were chromosomally normal, the nuchal translucency was increased in 19 (51%).

Termination of pregnancy took place in 70 cases (54%), and there was an intrauterine death in five, neonatal death in five and childhood death in three cases. Two patients were lost to follow-up, leaving 44 live births, five with known chromosomal anomalies. Successful reparative surgery has been performed in 29 infants. Thus, of the 57 continuing pregnancies for which the outcome is known, there was a 22.8% mortality rate during follow-up ranging from 6 months to 8 years (mean, 2.9 years). Table 1 also compares the karyotypes found in fetuses undergoing termination of pregnancy and those who died, with those of survivors. With the exception of one fetus, all those that were terminated, or who died pre- or postnatally, had either complex forms of tetralogy, a chromosome anomaly or significant extracardiac defects.

Table 1 Karyotype anomalies found in association with tetralogy of Fallot and related to outcome

Chromosome complement	*Total*	*TOP*	*Died*	*Alive*	*Lost to F/U*
22q11 deletion	15	8	3	4	
Trisomy 21	18	15	1	2	
Trisomy 13	9	7	2	0	
Trisomy 18	9	8	1	0	
Miscellaneous chromosomal anomalies	4	4	0	0	
Unknown, apparently normal baby	17	7	5	4	1
Normal, not 22q deleted	37	11	1	24	1
Normal, 22q unknown	20	10	0	10	
Total	129	70	13	44	2

F/U, follow-up; TOP, termination of pregnancy.

DISCUSSION

Tetralogy of Fallot is a common prenatal diagnosis, accounting for 6% of our total series of cardiac anomalies over the 8-year period of study. Nearly half of the cases were referred because of the suspicion of a heart malformation at a prior obstetric scan, 18% were referred because of extracardiac anomalies and 23% as a result of increased nuchal translucency measurement. There was strong association between an increased nuchal translucency measurement and the diagnosis of tetralogy of Fallot, even in the absence of chromosomal anomaly, with almost half of the cases for which the nuchal translucency was known showing this association.

Although the rate of 22q microdeletion of 10–15% is the same in postnatal series as in the present series, it was not known in 37/129 cases and may indeed be higher than this, even when the infant appears superficially normal. The rate of other chromosomal anomalies of 30% is higher than that reported in a recent large postnatal series, in which there was an incidence of 27% of all genetic syndromes[6]. As described previously, a higher incidence of chromosomal anomalies, extracardiac malformations and complex forms of tetralogy was seen in our fetal series than would be encountered in postnatal life. As a result, the outcome for the fetal cohort is much less good than is commonly believed for this diagnosis, although similar to that in a population-based study of natural history dating from 1981 to 1985[7]. It is important to be aware that many reported surgical series, such as that from the Central Cardiac Audit Database[2], exclude complex forms of tetralogy such as those with pulmonary atresia and cases considered inoperable. Cases may be deemed inoperable either because of the complexity of the cardiac anatomy or because of overriding extracardiac malformations. Such cases are not only included in the fetal series, but are over-represented.

Thus, when the diagnosis of tetralogy is made in fetal life, karyotype and a detailed anatomical survey should be offered in every case. Complicating features of the cardiac diagnosis, such as a common atrioventricular valve or right aortic arch, should be specifically sought. If there are no detectable extracardiac abnormalities, and there is forward flow in the pulmonary artery with good-size confluent branch pulmonary arteries, therefore an

uncomplicated 'classical' case of tetralogy, counseling can be fairly optimistic. Among 33 such cases, in which the chromosomes were normal including exclusion of 22q deletion and no significant extracardiac malformations were found on detailed anomaly scanning, there was one termination of pregnancy and one patient lost to follow-up. Thirty-one are alive after successful surgical repair, or are suitable for and awaiting reparative surgery. However, the fetus should be assessed sequentially to monitor pulmonary artery growth, which has been shown in previous studies to be not only variable but unpredictable in fetal life[8,9]. Loss of forward flow in the pulmonary artery should also be sought, as pulmonary atresia can develop with advancing gestation. In addition, it is important to look for associated extracardiac anomalies throughout pregnancy, as some may not be evident until later pregnancy or even until after birth.

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