

Prenatal diagnosis of cri-du-chat syndrome: importance of ultrasonographical markers

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ABSTRACT

Cri-du-chat syndrome is a chromosomal abnormality involving a 5p deletion and is characterised by a cat-like cry, mental retardation, microcephaly and abnormal facial features. We report a case of prenatally-diagnosed cri-du-chat syndrome. Although PAPP-A was low at first trimester screening (FTS), the combined risks of trisomies 21, 18 and 13 were low. Amniocentesis was, however, carried out following the ultrasonographical observation of a severely hypoplastic nasal bone, cerebellar hypoplasia, choroid plexus cyst and a single umbilical artery during the second trimester. This case report highlights the importance of careful examination of basic and extended foetal biometry and structures, as well as soft markers for the detection of rarer chromosomal abnormalities that may be missed at FTS.

Keywords: antenatal ultrasonography, cerebellar hypoplasia, cri-du-chat syndrome, first trimester screening, hypoplastic nasal bone, pregnancy-associated plasma protein A, prenatal diagnosis

Singapore Med J 2009;50(5):e181-e184

INTRODUCTION

Cri-du-chat syndrome is a rare chromosomal abnormality that is characterised by a deletion in the short arm of chromosome 5 (5p-). Its incidence is one in 20,000–50,000 live births. It was first described by Lejeune et al in 1963 as being characterised by a high-pitched cat-like cry, mental retardation, microcephaly and abnormal facial features.⁽¹⁾ These specifically include a round face, hypertelorism, micrognathia, epicanthal folds and low set ears. In addition, it causes low birth weight in newborns, as well as hypotonia and severe psychomotor and mental retardation in young children. Many of these features cannot be diagnosed prenatally on ultrasonography (US), and hence, the majority of such cases have been diagnosed postnatally. We report a case in which cri-du-chat syndrome was diagnosed via amniocentesis, when



Fig. 1 Sagittal US image of a severely hypoplastic nasal bone that measures only 2.4 mm.

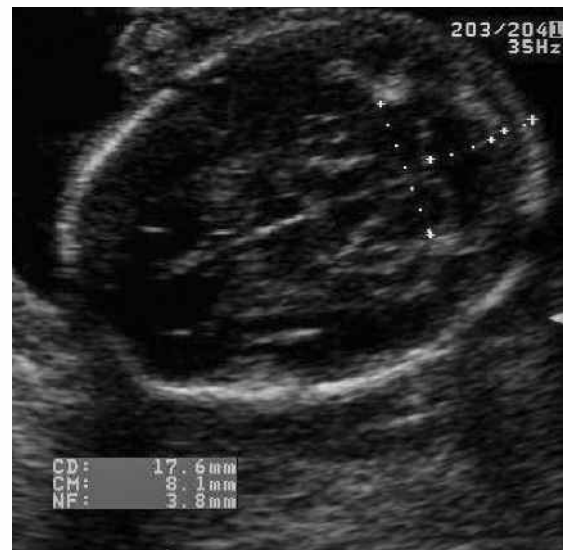


Fig. 2 Axial US image of a hypoplastic cerebellum with a transcerebellar diameter of 17.6 mm.

a second trimester screening US detected a multitude of US markers including a severely hypoplastic nasal bone (NB), cerebellar hypoplasia, choroid plexus cyst and a single umbilical artery, despite low risks of trisomies 21, 18 and 13 on first trimester screening (FTS).

CASE REPORT

A 32-year-old gravida 2 para 1 woman with one

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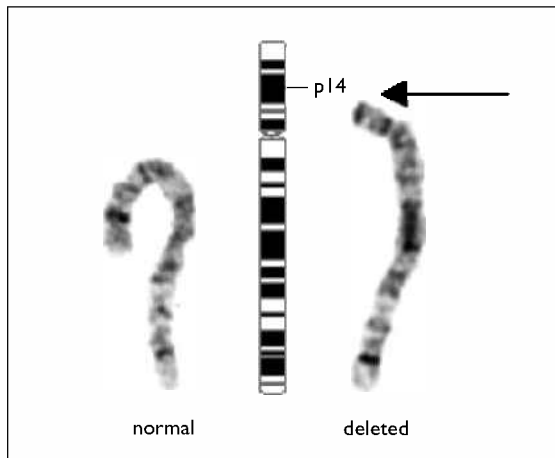


Fig. 3 Chromosomal analysis shows abnormal chromosome 5. Foetal karyotype was 46,XX,del(5)p14, where the area of deletion is shown by the arrow.

previous normal child and no significant family history, underwent a routine FTS for chromosomal abnormalities. US scan at 13 weeks' gestation showed the following measurements: crown-rump length at 68.0 mm, nuchal translucency (NT) at 1.6 mm and a NB that was present and measured 1.8 mm. Maternal serum reflected normal free β -human chorionic gonadotrophin (bhCG) of 1.095 multiples of median (MoM) and a low pregnancy-associated plasma protein A (PAPP-A) of 0.335 MoM. Using the algorithm provided by Foetal Medicine Foundation, the term risk for trisomy 21 was low at 1:1,759 (1:7,023 based on NT and NB, and 1:159 based on biochemistry), while that for trisomies 18 and 13 was 1:29,360.

She had routine second trimester screening US at 20 weeks' gestation. During the US examination, there was a multitude of ultrasonographical markers present, including a severely hypoplastic NB, measuring only 2.4 mm, which was < fifth centile and short, even allowing for ethnic differences (Fig. 1), cerebellar hypoplasia with a transcerebellar diameter of 17.6 mm, which was < fifth centile (Fig. 2), a right-sided choroid plexus cyst, and a single umbilical artery. There was no thickened nuchal fold, echogenic bowel, or short humeral or femoral lengths. The basic measurements were otherwise within the normal limits. The couple was counselled extensively and offered an amniocentesis despite the reassuring FTS risk, in view of the presence of multiple prenatal markers. Amniocentesis was performed five days later. Chromosomal culture revealed a foetal karyotype of 46,XX,del(5)p14 (Fig. 3). The couple opted to have the pregnancy terminated. The parental karyotypes were later analysed and found to be normal.

DISCUSSION

There are 27 reported cases of prenatally-diagnosed cri-du-chat syndrome,⁽²⁻¹⁰⁾ including the current case. In 13 cases, the indication for genetic testing was a parent, previous child or family members with 5p translocations. In four cases, chromosomal analysis was carried out due to advanced maternal age, with three of these cases being associated with abnormal US features on further investigation. The remaining ten cases were diagnosed following abnormal maternal serum tests and/or US features. The abnormal prenatal findings that have been associated with cri-du-chat syndrome are summarised in Table I. These include high hCG > 95th centile / 2 MoM (n = 3), low hCG (n = 1), high alpha-foetoprotein > 2 MoM (n = 1), choroid plexus cyst (n = 2), intrauterine growth restriction (n = 2), single umbilical artery (n = 2), cardiac anomalies (n = 2), hydrops foetalis (n = 2), cerebellar hypoplasia (n = 3), ventriculomegaly (n = 1), microcephaly (n = 1), encephalocele (n = 1) and absent or severely hypoplastic NB (n = 2).⁽¹¹⁻²²⁾

It is important to routinely detect and measure the NB on US in the second trimester, and it should be measured in all cases as it is the best soft marker for chromosomal abnormalities. Where the foetal position is not optimal for measurement of the NB, another scan should be rescheduled to complete this if it is feasible. The association between an absent or severely hypoplastic foetal NB measuring < 2.5 mm in the second trimester, and trisomy 21 and other chromosomal abnormalities, has been reported by Cicero et al and others.⁽²³⁻²⁵⁾ A recent case (Table I) and our case demonstrate clearly that an absent or severely hypoplastic NB (Fig. 1) is also associated with cri-du-chat syndrome. Earlier reports have not reported the association of absent NB as a marker for cri-du-chat syndrome, as the detection of the NB was not routinely performed in most centres prior to Cicero's report in 2001.⁽²⁶⁾

Cerebellar hypoplasia is not a common feature of chromosomal abnormalities, though it has been previously reported with some cases of trisomy 13, trisomy 18, trisomy 21, cri-du-chat syndrome and other chromosomal abnormalities. All three reported cases of prenatally-diagnosed cri-du-chat syndrome associated with cerebellar hypoplasia were found in conjunction with other markers such as hydrops foetalis, cardiac anomalies, short index fingers, microcephaly, hypoplastic NB, choroid plexus cyst and single umbilical artery (Table I). The isolated finding of choroid plexus cysts or single umbilical artery is rarely associated with chromosomal abnormalities. However, when combined with the presence of a severely hypoplastic

Table 1. Summary of prenatal markers associated with foetal cri-du-chat syndrome.

Features	No. detected (screened)*	Study
Serum markers		
High hCG (> 95th percentile or > 2 MoM)	3 (6)	Fankhauser et al ⁽¹¹⁾ Muller et al ⁽¹²⁾ Sherer et al ⁽¹³⁾
Low hCG	1 (6)	Weiss et al ⁽¹⁴⁾
High alpha-foetoprotein (> 2 MoM)	1 (5)	Stefanou et al ⁽¹⁵⁾
Low PAPP-A	1 (1)	Current case
Ultrasound markers		
Cerebellar hypoplasia	3 (NA)	Aoki et al ⁽¹⁶⁾ Chen et al ⁽¹⁷⁾ Current case
Absent/severely hypoplastic nasal bone	2 (2)	Sherer et al ⁽¹³⁾ Current case
Choroid plexus cyst	2 (13)	Fankhauser et al ⁽¹¹⁾ Current case
Intrauterine growth restriction	2 (13)	Sarno et al ⁽¹⁸⁾ Chen et al ⁽¹⁹⁾
Single umbilical artery	2 (13)	Hutcheon et al ⁽²⁰⁾ Current case
Cardiac anomalies	2 (13)	Hutcheon et al ⁽²⁰⁾ Aoki et al ⁽¹⁶⁾
Hydrops foetalis	2 (13)	Tullu et al ⁽²¹⁾ Aoki et al ⁽¹⁶⁾
Ventriculomegaly	1 (13)	Stefanou et al ⁽¹⁵⁾
Microcephaly	1 (13)	Chen et al ⁽¹⁷⁾
Encephalocele	1 (13)	Bakkum et al ⁽²²⁾
Short index fingers	1 (NA)	Aoki et al ⁽¹⁶⁾

* No. screened refers to the number of patients where the particular feature had been or was likely to have been documented at the time of examination.

NA: Unable to ascertain

NB and cerebellar hypoplasia, they clearly increase the risk of a chromosomal abnormality. As seen in other reported cases, these features have also been reported in association with cri-du-chat syndrome (Table 1).

While the serum screening performed in the first trimester did not show a high bhCG, the low PAPP-A level and the ensuing high risk for trisomy 21, based on biochemistry alone, was seen retrospectively to be possibly a significant association. As our case is the first case report where an FTS had been performed in cri-du-chat syndrome, future case reports may further strengthen any association between a low PAPP-A level and cri-du-chat syndrome. If foetal cri-du-chat syndrome has been diagnosed, it is important to investigate parental karyotypes as slightly over 10% of cases are associated with parental translocations. Appropriate genetic counselling should be offered to carriers of balanced translocations involving 5p, who have a 8.7%–18.8% risk of producing offspring with unbalanced translocations.⁽²⁷⁾

This case report serves as a reminder that not

all chromosomal abnormalities are detected by FTS. Even during second trimester US examination, such abnormalities might not be easily detected. Hence, it is important that patients are counselled accordingly. It is also crucial to carry out careful examination of basic and extended foetal biometry and structures, as well as soft markers to allow the detection of rarer chromosomal abnormalities that may be missed at FTS.

ACKNOWLEDGEMENT

We would like to thank Thomson Medical Centre Prenatal Diagnostic Laboratory for providing the image of the karyotype.

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