CASE REPORT

Phenotypic extremes in liveborn monozygotic twins with mosaic Edwards syndrome

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SUMMARY

Mosaic trisomy 18 (Edwards syndrome) in monozygotic diamniotic liveborn twins is rare. We describe such a case involving preterm male infants. Although both infants had a low percentage of trisomy 18 cells in peripheral blood leucocytes, their varied phenotypic presentation of mosaic trisomy 18 resulted in one twin surviving, with the other twin's demise at 1 month of age. Despite the presence of trisomy 18 in peripheral leucocytes, further analysis of a buccal smear and skin biopsy of the surviving twin did not show evidence of trisomy 18. Establishing such diagnoses in a timely manner is imperative for the child, parents and clinicians. The clinical course of these twins reflects the unpredictable prognosis associated with the diagnosis of mosaic trisomy 18, and emphasises the challenges that can be encountered when counselling parents.

BACKGROUND

Trisomy 18, otherwise known as Edwards syndrome, is the second most common trisomy after trisomy 21. This syndrome, caused by an extra copy of chromosome 18, was first described in the literature by Edwards *et al* in 1960.^{1 2}

Mosaic Edwards syndrome occurs when two cell lines exist, whereby one cell line has a normal disomic chromosome 18 complement, while the other has three copies. Mosaic Edwards syndrome is associated with marked phenotypic variation, with some individuals appearing to have typical Edwards syndrome clinically, while others can appear largely phenotypically normal.³

In 2004, Irish Central Statistics Office figures estimated twin sets to make up 1.5% of live births. UK figures report monozygotic (MZ) twins accounting for approximately one-third of twin pregnancies.^{4 5} Previous literature review has revealed mosaic trisomy 18 in siblings, but no reports of Mosaic Edwards in MZ liveborn twins.⁶

MZ twins with trisomy 18 have previously been reported, as has a case of MZ twins with trisomy 18 in one twin and mosaicism in the other.^{7–14} Thus mosaic trisomy 18 in liveborn MZ twins is rare.

CASE PRESENTATION

A healthy couple, with one healthy 2-year old daughter, underwent in vitro fertilisation for subfertility from which a single embryo was successfully implanted. At the 12 weeks ultrasound scan, a monochorionic, diamniotic (MCDA) twin pregnancy was confirmed. Tetralogy of Fallot was suspected in both twins on a fetal echocardiogram

performed at 20 weeks gestation. Amniocentesis was offered to the parents at this time, but was declined. At 29+5 weeks gestation, an emergency caesarean section was performed due to premature rupture of membranes and fetal distress involving one of the twins.

At the time of delivery, twin 1 made good respiratory effort and was stable on nasal continuous positive airway pressure for the first 36 h. On day 2 of life, due to an increasing oxygen requirement, he was electively intubated so as to administer one dose of surfactant. He had small dysplastic ears, but no other dysmorphism. His birth weight was 1.25 kg lying just above the 25th centile for his gestation. A postnatal echocardiogram on day 2 of life showed an atrial septal defect (ASD), a ventricular septal defect (VSD) and patent ductus arteriosus (PDA). By 2 weeks of age he had successfully weaned off all forms of respiratory support. However, on day 14 of life he became acutely unwell due to necrotising enterocolitis, which was managed conservatively. He recovered without sequelae.

Twin 2 made no respiratory effort at birth. He required immediate respiratory support, subsequently including a period of high-frequency oscillatory ventilation as well as inotropic support. On examination, he had microcephaly, a large anterior fontanelle, microphthalmia with small palpebral fissures, micrognathia, clenched hands, a single palmar crease and a micropenis. His birth weight, at 1.09 kg, lay on the 9th centile for his gestation. An echocardiogram confirmed an ASD, VSD and PDA. An umbilical venous catheter was successfully placed. His umbilical arteries could not be accessed. On day 6 of life, meconium was noted to be passing from his umbilical cord, which was presumed to be due to a persistent vitellointestinal duct.

INVESTIGATIONS

Blood karyotyping of both twins was sent in view of twin 1 dysmorphic features.

Twin 1 blood G-banded metaphase karyotype showed mosaic trisomy 18 in 8 of 50 metaphases analysed. Four of 50 cell lines in twin 2 peripheral blood had an extra chromosome 18.

A buccal smear from twin 1 showed no evidence of trisomy 18 in 200 cells, using interphase FISH with a BCL2 probe, which maps to 18q21. Analysis of fibroblasts from a skin biopsy, taken from twin 1 at the time of hernia repair, also showed no trisomy 18 in 280 cells, using interphase FISH with the BCL2 probe. Analysis of a second blood sample

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from twin 1, using interphase FISH with the BCL2 probe, showed trisomy 18 in 21 of 200 leucocytes.

Extended G-banded karyotyping in twin 2 showed 4 of 50 cells with trisomy 18. Analysis of a buccal smear from twin 2 using interphase FISH with the BCL2 probe showed trisomy 18 in 51 of 86 cells (59%).

Microarray analysis of uncultured lymphocytes using a 60 K Agilent platform confirmed mosaic Edwards syndrome in both twins, at a level of 10–20%, estimated by log ratios. No further chromosome event was detected in either twin.

Twin 1 had a normal eye examination with no retinopathy of prematurity and a normal hearing screen. His cranial ultrasound scan showed mild prominence of extra axial fluid but was otherwise normal. Twin 2 cranial and renal ultrasound scans were normal. He did not undergo retinal or hearing screening.

DIFFERENTIAL DIAGNOSIS

Prior to establishing a diagnosis, based on clinical features, Edwards syndrome was the most likely diagnosis in twin 2.

Two other potential diagnoses to consider are:

- ▶ Patau syndrome (trisomy 13): the third most common trisomy.
- ▶ Pena-Shokeir syndrome: also known as pseudo-trisomy 18.

TREATMENT

Following his recovery from necrotising enterocolitis, twin 1 did well. He developed bilateral inguinal hernias. There was initial reluctance to intervene due to twin 1 genetic diagnosis, however, given his remarkable recovery, resilience and clinical stability, his inguinal hernias were successfully repaired. Although he was initially in cardiac failure, due to intracardiac (ASD and VSD) and extracardiac (PDA) shunts, his PDA closed spontaneously. The ASD and VSD were controlled medically and also resolved over time, averting the need for surgical intervention.

Twin 2 required increasing respiratory and inotropic support, and remained ventilated from birth. No surgical intervention was undertaken for the persistent vitellointestinal duct, as this resolved spontaneously.

OUTCOME AND FOLLOW-UP

Twin 1 was discharged home in the care of his parents on day 79 of life (corrected 41+1). At 6 months of age (6 weeks corrected for prematurity), his length was on the 0.4th centile and his weight was on the 2nd centile. His neurodevelopmental outcome remains guarded in view of underlying mosaicism.

At 1 month of age (33+5/40 corrected for prematurity) twin 2, although mosaic for trisomy 18 on cytogenetic analysis, had the clinical appearance of full trisomy 18 syndrome. He remained ventilator dependent, which was in part secondary to caffeine-resistant centrally mediated apnoea complicated by left to right shunt heart failure from the PDA, VSD and ASD. Following discussion with his parents compassionate care was instituted, respiratory support was withdrawn, and he died in his parents' arms.

DISCUSSION

Although full trisomy 18 has been reported in MZ twin pregnancies, to the best of our knowledge, this is the first reported case of mosaic trisomy 18 in liveborn MZ twins. This report is of interest from a diagnostic consideration, including the karyotyping challenges with mosaicism, the extremes of phenotype presentations and ethical considerations.

It has been proposed that fetal loss associated with trisomy 18 is estimated at 80%, and that having monozygotic twins with trisomy 18 is associated with even further fetal loss.^{7 15} An antenatal diagnosis of full or mosaic trisomy 18 may lead to termination of the pregnancy in up to 86% of cases.¹⁶ Furthermore, other case reports have shown that, because of the phenotypic variation of presentations, there may be a delay in diagnosis even beyond 1 year of age.⁶ These factors may explain why mosaic trisomy 18 in MZ liveborn twins has not, to the best of our knowledge, been previously reported. This report may assist others in prenatal and postnatal counselling.

Twin 2, phenotypically, had Edwards syndrome, but by analysis of peripheral leucocytes, only 4 of 50 metaphases showed trisomy 18. However, FISH analysis of buccal smear cells showed a high level (59%) of trisomy 18 mosaicism, in keeping with his clinical findings.

In contrast, despite a similar level of mosaicism for trisomy 18 in the peripheral blood of twin 1, no evidence of mosaic trisomy 18 was seen in either buccal cells or skin fibroblasts in twin 1. These findings were in keeping with his relatively mild phenotypic effects of mosaic trisomy 18, and emphasise the importance of analysing tissues in addition to analysing blood in chromosomal mosaicism.³ In fact, the percentage of trisomic cells present in an individual having mosaicism is not a useful prognostic indicator.¹⁷

As these twins arose from a single implanted embryo, they are monozygotic, and would have divided soon after implantation. However, as both twins had mosaic trisomy 18, we assumed that the initial embryo had full trisomy 18, and that at blastocyst stage some cells lost the additional chromosome 18, leading to mosaic trisomy 18 in both twins, which would have been present prior to separation.¹⁸

Discordant phenotypic expression in MZ twins is well known. A literature review of 33 cases of mosaic Edwards syndrome reflected on the variable prognoses of mosaicism.³ Both infants in the present case report had an ASD, VSD and PDA, which are among the most common cardiac anomalies seen in children with trisomy 18, along with polyvalvular disease.^{19 20} Twin 1 was phenotypically normal apart from slightly dysplastic ears, with normal hearing screening responses. Twin 2 had typical Edwards syndrome. The diagnosis of mosaicism made by microarray does not provide greater clarity with regard to prognoses when counselling parents.

These twins highlight the ethical dilemma often faced by neonatologists. A US poll reported that 55% of neonatologists would not resuscitate a neonate following delivery with a diagnosis of trisomy 18 and a VSD.²¹ In contrast to the medical profession's pessimistic attitude towards these children, Dr Anne Janvier of the University of Montreal found that almost all families of children with trisomy 13 and 18, reported that their time together was happy and rewarding, overall. They reported that over 97% of the parents interviewed considered that their child was happy, and the child's presence enriched the life of the family and the parent's life as a couple regardless of longevity.²² Although, in this case, the phenotypically normal twin 1 was managed conservatively for necrotising enterocolitis and surgical intervention was not required, we believe it could have been a complex surgical referral based on general attitudes of non-intervention in Edwards syndrome. Later, however, when he was off the ventilator and breathing spontaneously, his inguinal hernias were successfully repaired. We were unable to wean the second twin off the ventilator due to central mediated apnoea and heart failure. Extensive discussions were held with his parents and subspecialists including neonatologists, a

geneticist and paediatric cardiologists, following which palliative care was instituted. The medical practitioner has a role to play as advocate for patients. This role may extend to persuading colleagues of clinical stability for certain interventional procedures on a background of a potentially life-threatening genetic diagnosis. Statistics report 5–8% patients with trisomy 18 living to 1 year of age without specialist care, and cases of mosaic Edwards syndrome surviving as adults have also been reported.^{1 6} While many cardiac centres have not offered cardiac surgery to children with Edward syndrome in the past, societal attitudes are changing.²²

Our cases highlight the heterogeneous nature of mosaicism and the importance of performing genetic investigations in both monozygotic twins, although they may not appear phenotypically similar. The paradoxical nature of the ratio of normal versus abnormal cells in peripheral leucocytes, and the phenotype in twin 2, was unexpected. This correlates with previous reports and highlights the phenotypic variation typical of mosaicism.^{3 6 23}

Learning points

- ▶ Mosaic Edwards syndrome in monozygotic twins is rare.
- ▶ When counselling parents it is important to take into consideration the patient's clinical condition when relaying important results.
- ▶ The heterogeneity of mosaicism continues to intrigue clinicians, as phenotypic extremes can be seen even in monozygotic twins.
- ▶ Awareness of stigmatisation.

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