

CASE REPORT

Unbalanced Chromosomal Translocation: A Cause of Recurrent Spontaneous Abortion

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Summary

Recurrent spontaneous abortion, defined as three consecutive abortions, occurs in approximately 1% to 2% of couples. Although the cause is unknown in up to 50% of cases, about 5% of these couples are found to be a balanced translocation carrier. We report a case in which the mother was identified to be a translocation carrier following the birth of a baby with multiple congenital abnormalities.

Key Words: Balanced translocation, Recurrent spontaneous abortion, Prenatal diagnosis

Case Report

The patient, a term female baby, had a spontaneous vaginal delivery; her birth weight was 2.38kg. Her mother who had a poor obstetric history had three previous pregnancies. The first child died at the age of two months secondary to septicaemia following ligation of patent ductus arteriosus; she also had underlying lung hypoplasia. The second pregnancy, which resulted in an intrauterine death at six months of gestation, had cleft lip and cleft, whereas the third pregnancy was a spontaneous abortion at two months of gestation. Antenatal ultrasonography, which was performed at 32 weeks for this patient, showed right lung hypoplasia with right hydronephrosis and hydroureter; she also had cleft lip and cleft palate. Amniocentesis and karyotyping at 33 weeks gestation revealed a structural abnormality involving chromosome 15. Following this, parental karyotyping was requested.

The baby required cardiopulmonary resuscitation at birth. Clinically, she had microcephaly with midline cleft lip and cleft palate. There was brachydactyly,

bilateral clinodactyly and a left transverse palmar crease. The carrying angle was wide and she had rockerbottom feet. There was hepatosplenomegaly; both hips were dislocated and there were petechiae over the inguinal region. There was a single umbilical artery and a sacral dimple. Cardiovascular examination showed gallop rhythm with an ejection systolic murmur at the lower left sternal edge. The first chest radiograph showed cardiomegaly and echocardiography confirmed a diagnosis of pulmonary atresia with ventricular septal defect. Ultrasound of the brain showed mild periventricular echodensity with partial agenesis of the corpus callosum. Abdominal ultrasound revealed a hydronephrotic polycystic left kidney; the pelvicalyceal system of the right kidney was dilated.

She remained clinically stable until day 3 of life when she was ventilated for increasing respiratory distress. She was treated for nosocomial sepsis; chest radiograph showed pneumonic changes with right middle lobe collapse. Her respiratory support was however changed to high frequency oscillatory ventilation (HFOV) in view of progressive respiratory acidosis and recurrent desaturations.

This article was accepted: 25 October 2005

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At day 5 of life the baby had seizures; she also developed coagulopathy as manifested by coffee ground aspirate, macroscopic haematuria and pulmonary haemorrhage. Intravenous ranitidine was started and blood products comprising packed cells, fresh frozen plasma and platelet concentrate were given. She was started on total parenteral nutrition. Tromethamine infusion was administered in view of persistent metabolic acidosis and noradrenaline infusion was added. Her general condition continued to deteriorate despite escalation of treatment and she progressed into renal failure. Both parents were counseled of the grave prognosis and despite all the supportive measures, she succumbed at day 7 of life.

The chromosomal analysis of cultured amniotic fluid cells showed an unbalanced translocation involving the short arms of chromosomes 10 and 15 which was derived maternally: 46, XX, der (15) t (10;15) (p11.2; p12). As a result of this translocation, the baby was trisomic for the short arm of chromosome 10 (from band p11.2 to pter) and monosomic for the short arm of chromosome 15 (from band p12 to pter). The mother's karyotyping was 46, XX, t (10;15) (p11.2; p12); she is a balanced translocation carrier.

Discussion

Spontaneous abortion is a common occurrence with a frequency of 1 in 8 pregnancies. With this in mind, it is usually recommended that further investigations are performed for cases in which at least three or more spontaneous abortions have occurred. Of this particular subset, after ruling out a possible gynaecological cause (e.g. anatomic, endocrine, immune – mediated and thrombophilic cause), approximately 5% of affected couples will be a balanced translocation carrier¹.

These carriers are usually phenotypically normal unless the translocation breakpoint disrupts a specific gene, which is rare. The main medical concern however, is related to reproductive health in that there may be associated infertility, recurrent abortions and offspring with physical and mental disabilities; our case illustrates the latter. This problem occurs because there is abnormal segregation of the derivative chromosomes during meiosis. To enable meiosis to proceed, the four chromosomes [chromosome 10, chromosome 15, derivative (10) and derivative (15)] must form a

complex pachytene structure and segregation of these chromosomes into the daughter cells can lead to either chromosomally balanced or unbalanced gametes. In our case, it is likely that all three previous pregnancies were the result of an unbalanced conception particularly the first two pregnancies. In view of this likelihood, amniocentesis was performed. Although amniocentesis can generally be done from 16 weeks onwards, as the mother was referred in the last trimester, amniocentesis was only done at 33 weeks. Had she been seen sooner, prenatal diagnosis (PND) could have been performed earlier and genetic counseling given to the couple.

Reciprocal translocation is relatively common, with an estimated incidence of 0.2% in the general population; however, the incidence increases to 9.2% in fertile couples with more than 3 first trimester abortions². As mentioned, the risk to the offspring depends on how the chromosomal rearrangement interferes with meiosis. The prevalence of unbalanced gametes in reciprocal translocation is within the region of 50 to 70%. In this couple, based on empirical data, a recurrence risk of approximately 20% was given; because of this high recurrence risk, not to mention the emotional turmoil encountered, PND is indicated for subsequent pregnancies¹.

Prevention through selective pregnancy management i.e. use of preimplantation genetic diagnosis (PGD) will help obviate the issue of termination of an affected pregnancy as only genotypically unaffected embryos will be transplanted following in – vitro fertilization. Of course, there are limitations even with PGD as balanced translocation carriers produce fewer normal gametes^{2,3}. At present, PGD is not available in Malaysia. Therefore, CVS or amniocentesis would still be the main options for now. In our case, the mother subsequently conceived spontaneously two years later. Early antenatal follow – up was made and detailed scan at 15 weeks was normal. No antenatal karyotyping was done. Postnatally, the baby boy is phenotypically normal and well. Postnatal karyotyping has been performed and the results are pending.

Although uncommon, autosomal translocation should still be sought as a possible cause of recurrent spontaneous abortions because of the significant risk of an abnormal liveborn offspring. Following this, the couple should ideally be referred for genetic counseling and prenatal diagnosis.

References

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