Prenatal diagnosis of bilateral congenital microphthalmia in two fetuses from the same parents

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Congenital microphthalmia (CM) is a rare anomaly of the fetal orbit, results from developmental defects of the primary optic vesicle, and is characterized by a reduced eyeball volume and axial diameter. Fetal CM cases have rarely been reported. Herein, we present a case of two fetuses with bilateral CM from the same parents, diagnosed using ultrasonography (US) and magnetic resonance imaging (MRI). We found that the antepartum US and MRI measurements were smaller than the postpartum ones. Genetic testing of the parents and fetuses revealed that GL12 gene mutation may be associated with CM.

Key words: Congenital microphthalmia, magnetic resonance imaging, prenatal diagnosis, ultrasonography

Congenital microphthalmia (CM), an eyeball defect, is caused by abnormal embryonic optic vesicle development and is characterized by a reduced eyeball volume and axial diameter. It is a rare congenital disease with an incidence rate of 0.7–1.9 cases per 10,000 persons, at birth, with an incidence rate of 0.22 per 10,000 persons for bilateral microphthalmia.[1-3] However, data concerning the diagnostic criteria for fetal CM remain limited. We present two rare cases of bilateral CM, involving the same parents, diagnosed using ultrasonography (US) and magnetic resonance imaging (MRI). Genetic testing was performed for both parents and fetuses.

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Case Report

This study was approved by the Ethics Committee of Beijing Tongren Hospital, Beijing, China (Approval no: TRECKY2018-005). A 31-year-old Chinese woman (gravida 1, para 0) at 22^{+1} weeks of gestation underwent abdominal US; bilateral CM of the fetus was suspected. Abdominal MRI (23 gestation weeks) was performed to confirm the diagnosis [Fig. 1a and b]. The pregnancy was terminated at parental request after MRI examination, the induced fetus (male) was examined, and CM was confirmed.

Eight months later, the woman became pregnant again. The abdominal US examinations during early pregnancy indicated fetal eye abnormalities. At 22 weeks of the pregnancy, based on abdominal US, bilateral CM was suspected. Abdominal MRI was performed to confirm the diagnosis. US (27^{+5} gestation weeks) and MR (26 gestation weeks) images are shown in Fig. 2a-d, respectively. The family received extensive counseling and decided on pregnancy termination at 27 weeks of gestation. The induced fetus (female) was examined and the diagnosis of CM was confirmed based on the following characteristics: short and narrow palpebral fissure length, shallow eye sockets, and small eyeballs [Fig. 3a and b]. With parental consent, binocular US and craniocerebral MRI were performed within an hour of induction [Fig. 3c and d].

Genetic testing in the parents and two fetuses involved extracting DNA from parental blood and fetal skin tissue, respectively, identifying a heterozygous mutation (c. 1532C > G; p.S511W) in *GL12*, derived from the father. The parents were healthy, and no maternal history of antenatal drug use or X-ray exposure was noted. The parents denied consanguineous marriage or family history of eye malformations. The babies did not show any systemic malformations, including cardiac defects, facial clefts, microcephaly, or hydrocephaly.

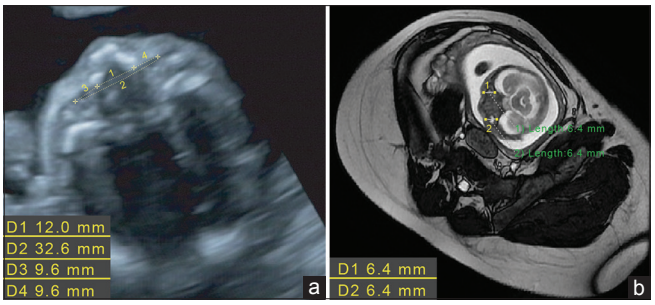

Figure 1: Prenatal ultrasonography (US) imaging of the first fetus. (a) Abdominal US: the inner canthal distance (D1) is long and the outer canthal distance (D2) is normal. The orbital margin diameters (D3 and D4) are small. (b) Abdominal magnetic resonance imaging: anterior–posterior ocular diameters (D1 and D2) are small

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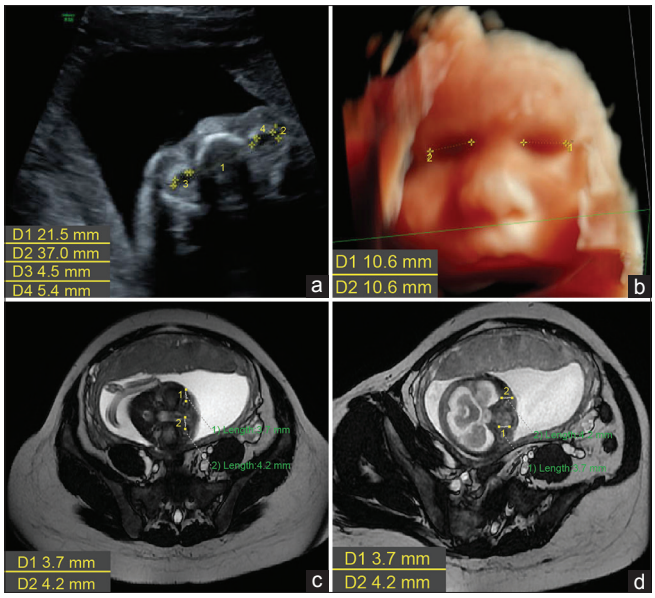

Figure 2: Prenatal ultrasonography (US) imaging of the second fetus. (a) Abdominal US: The inner canthal distance (D1) is long, and the outer canthal distance (D2) is normal, and the transverse ocular diameters (D3 and D4) are significantly small. (b) Three-dimensional abdominal US: the palpebral fissure lengths (D1 and D2) are significantly short. (c) Abdominal magnetic resonance imaging (MRI): the transverse ocular diameters (D1 and D2) are significantly small. (d) MRI examination: the anterior–posterior ocular diameters (D1 and D2) are significantly small

Discussion

This is a report of two fetuses with bilateral CM, from the same parents, diagnosed using US and MRI. To date, the universal diagnostic criterion for neonatal CM is an axial length of ≤20.0 mm.[4] However, data concerning the diagnostic criteria for fetal CM remain limited. Denis *et al*.[5] analyzed 108 "normal" fetuses from spontaneous and therapeutic abortions and obtained the mean palpebral fissure length, inner and outer canthal distances, and the axial length of the eyeball (11.71 ± 1.02 mm at 23–25 weeks) at different weeks of gestation. According to the current international US protocols, a diagnosis of CM is rendered when the axial diameter of the eyeball is less than 2 standard deviations below the mean using prenatal US.[6] The eyeball size of the two aborted fetuses was significantly smaller than that observed in gestational age-matched normal fetuses.

CM can have serious effects on orbitofacial development.[7] An ocular examination of the second fetus revealed a short palpebral fissure length, long inner canthal distance, and an outer canthal distance within the normal range, consistent with the ophthalmic features of children with CM. The axial lengths of bilateral eyeballs of the first (23 gestational weeks) and second (27 gestational weeks) fetuses were similar, suggesting that eyeball development of fetuses with CM occurs at early gestational ages. Eyeball development was retarded or inactive at the middle and late gestational ages.

Chromosomal abnormalities, mutations, infection, and antenatal drug exposure are the common underlying causes of CM.[5,8] Bilateral CM has an incidence rate of 0.22 per 10,000 persons. CM is usually associated with systemic abnormalities (50%–90%)[6] and differential diagnoses of CM include anophthalmos, microcornea,

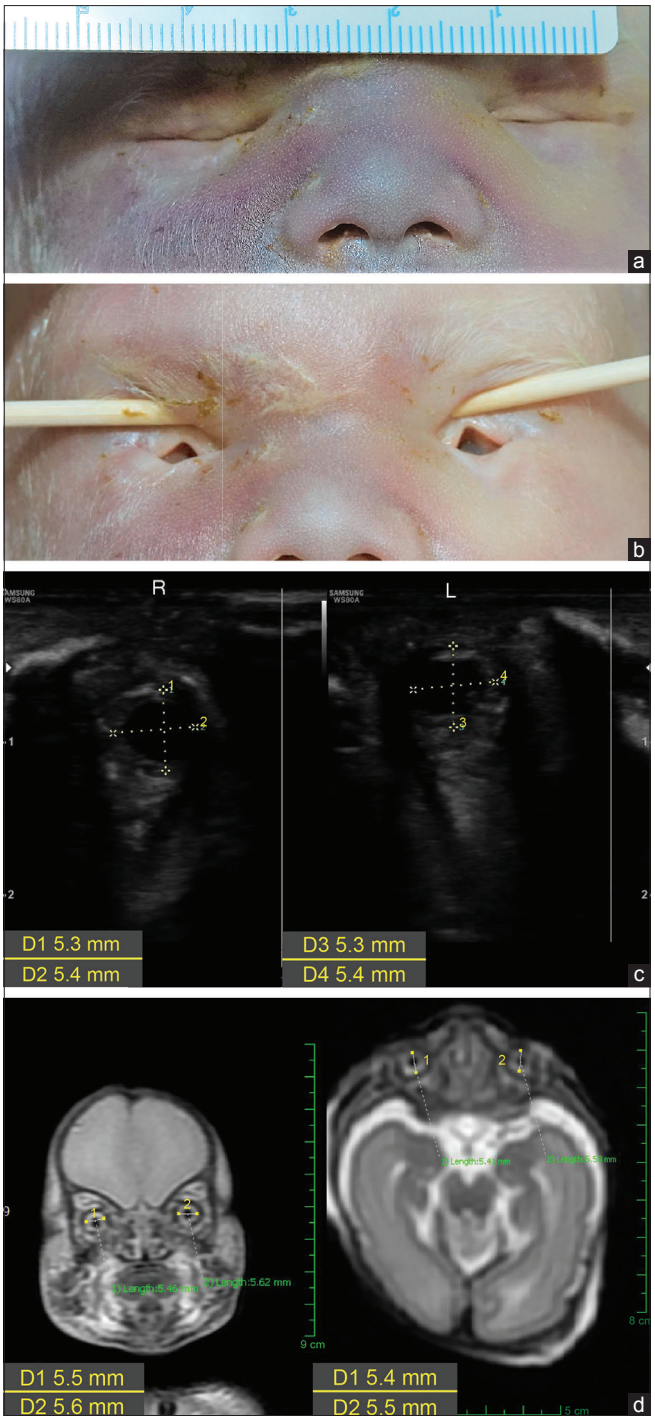

Figure 3: Ocular images of the second induced fetus. (a) The palpebral fissure length (9.0 mm) is significantly short, the inner canthal distance (23.0 mm) is long, and the outer canthal distance (46.0 mm) is normal. (b) Shallow eye sockets with small eyeballs. (c) US showing smaller eyeballs (D1, D2, D3, and D4). (d) Magnetic resonance images confirm the diagnosis of CM (D1, D2, D3, and D4)

and eyeball atrophy. In the present case, imageological examination and autopsy revealed isolated bilateral microphthalmia without any systemic malformations in the infant siblings. Moreover, the father and the two fetuses had a heterozygous mutation in *GL12*. Although previously unreported, our results reveal that *GL12* mutation may be associated with CM.

Prenatal abdominal US is useful for screening fetal CM. However, its accuracy may be affected by gestational age, fetal position, movements, or other factors. MRI is considered safe in the second and third trimesters;[9] unaffected by gestational age, fetal position, or amniotic fluid; and provides more detailed images for detecting ocular abnormalities. Thus, a detailed, targeted MRI with a specific focus on the orbital region should be offered for cases presenting with abnormal prenatal abdominal US. Fetal CM diagnosed with MRI can form a basis for pregnancy termination with mutual consent of the spouses.[10] In our case report, repeated abdominal US during the second trimester of pregnancy were suggestive of CM. Consequently, considering the health of the mother, early pregnancy termination was recommended; however, the parents were hesitant. Both cases were confirmed by MRI, and the parents ultimately made the decision to end the pregnancy. Therefore, clear MR images are conducive to diagnosing CM. The antepartum US and MRI measurements were approximately 25% smaller than the postpartum measurements, suggesting that antepartum measurements must be adjusted for more accurate estimation of eyeball size.

Conclusion

This study revealed that prenatal US screening combined with MRI is a reliable method for diagnosing fetal CM.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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