Third-trimester prenatal brain imaging for early diagnosis of glutaric aciduria type 1 in monochorionic diamniotic twins

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Case presentation

A 33-year-old primiparous Chinese woman presented for a 12-week ultrasound. Previous early ultrasound had confirmed monochorionic diamniotic twins. Her marriage was non-consanguineous. She had conceived spontaneously and had no family history of inborn errors of metabolism. The 12-week fetal scan revealed normal nuchal translucency in both twins, and non-invasive prenatal testing showed normal results.

Serial ultrasound examinations were performed every 2 weeks from 16 weeks onwards to monitor fetal growth and detect early signs of twin-twin transfusion syndrome or twin anaemia-polycythaemia sequence. Both fetuses followed the 10th percentile growth curve in abdominal circumference, head circumference, and femur length. Morphology scan showed no abnormalities, and there was no evidence of twin-twin transfusion syndrome or twin anaemia-polycythaemia sequence throughout the pregnancy. Routine targeted neurosonography at 32 weeks showed multiple bilateral germinolytic cysts and temporal cysts in both fetuses (Fig). Brain findings were almost identical in both twins. Although abdominal circumference and femur length remained at the 10th percentile, the head circumference of Fetus A exceeded more than two standard deviations above the mean, while that of Fetus B was at the mean. Fetal magnetic resonance imaging (MRI) at 33 weeks demonstrated normal brain structure with cystic findings consistent with the ultrasound findings and no signs of ischaemia. Amniocentesis at 34 weeks for chromosomal microarray and cytomegalovirus polymerase chain reaction tests yielded negative results. Trio whole-genome sequencing was arranged. At 35 weeks, the mother developed pre-eclampsia, and an emergency lower-segment Caesarean section was performed the following day. Whole-genome sequencing results, available on the day of delivery, revealed a homozygous pathogenic variant, c.1244-2A>C, in the *GCDH* gene (NM_000159.4) associated with glutaric aciduria type 1 (GA1). Both parents were found to be heterozygous carriers of this variant. Fetus A weighed 2.4 kg with Apgar scores of 7 at 1 minute and 8 at 5 minutes, while Fetus B weighed 2.2 kg and had Apgar scores of 9 at 1 minute and 10 at 5 minutes. Umbilical cord arterial pH was 7.35 for Fetus A and 7.29 for Fetus B. Both neonates were admitted to the neonatal unit and promptly started on intravenous L-carnitine supplementation and a specialised formula diet. No seizures have been observed to date. Postnatal brain MRI at 1 month of age showed unchanged cystic findings in both twins, with no evidence of white matter involvement.

Discussion

This case highlights the importance of comprehensive prenatal evaluation, including detailed neurosonography and fetal brain MRI, when unusual fetal brain findings are detected. The initial concern was for transfusion-related complications;

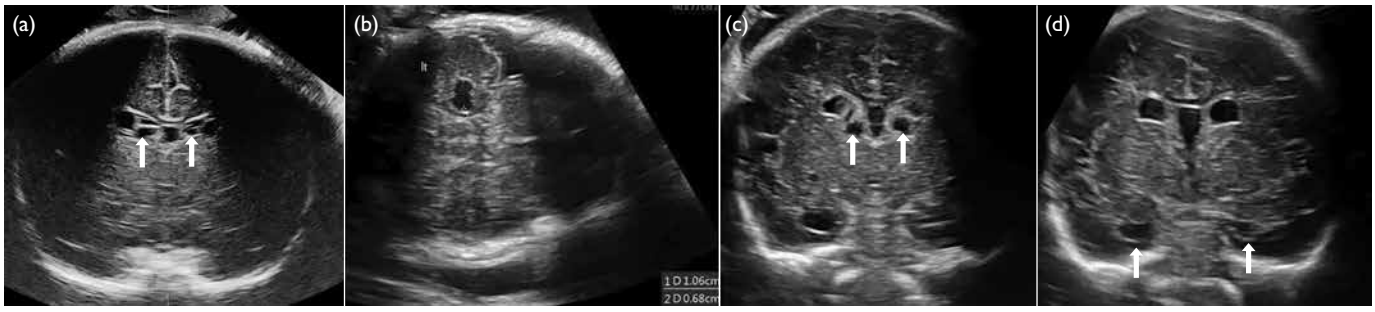

FIG. Ultrasound images of the fetal brain at 32 weeks of gestation. Twin 1: (a) multiple bilateral germinolytic cysts (arrows); (b) left temporal lobe cyst. Twin 2: (c) multiple bilateral germinolytic cysts (arrows); (d) bilateral temporal lobe cysts (arrows)

however, the absence of typical features prompted a broader differential diagnosis, ultimately leading to the diagnosis of GA1. Metabolic crises such as severe hypoglycaemia, hyperammonaemia, lactic acidosis, and permanent neurological or systemic complications can occur in patients diagnosed after the onset of symptoms. Early identification of GA1 enabled prompt multidisciplinary consultation and the initiation of appropriate treatment, including dietary management. Prenatal diagnosis of GA1 based on third-trimester brain features is possible and facilitates early postnatal management, enabling prompt treatment at birth and potentially improving long-term neurological outcomes.

Author contributions

Concept or design: IYM Wah.
Acquisition of data: All authors.
Interpretation of data: All authors.
Drafting of the manuscript: IYM Wah.
Critical revision of the manuscript for important intellectual content: All authors.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

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Ethics approval

The patient was treated in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

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