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CASE REPORT

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CHARGE syndrome with early fetal ear abnormalities: A case report

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Key Clinical Message

CHARGE syndrome is a rare genetic disorder characterized by several distinct features. The presence of fetal ear abnormalities could be the early indicator of CHARGE syndrome. Subsequent prenatal diagnosis is essential to confirm the disorder. This is significant because the patient may receive genetic counseling and appropriate disposal based on the accurate diagnosis.

Abstract

CHARGE syndrome is a rare genetic disorder with multiple specific clinical features. The prenatal diagnosis is crucial but rarely achieved. We report a fetus with fetal external ear abnormality detected by ultrasound at 22nd week of gestation. Postnatal examination revealed an external ear abnormality, a mild atrial septal defect, and other clinical signs of CHARGE syndrome. A de novo pathogenic nonsense mutation in the *CHD7* gene (c.406C > T, p.Q136X in exon 2) was identified to cause the disorder. Our study demonstrated that prenatal diagnosis and genetic testing were recommended to obtain a solid diagnosis of CHARGE syndrome when fetal external ear abnormality was detected by ultrasound examination.

KEYWORDS

CHARGE syndrome, *CHD7*, De novo mutation, ear abnormalities, ultrasound and prenatal diagnosis

Yu Liang, Sijie He and Liuqiao Yang contributed equally to this work.

1 | INTRODUCTION

CHARGE syndrome is an autosomal dominant disorder characterized by eye defects (C), heart problems (H), posterior nostril atresia (A), growth and/or central nervous system retardation (R), genitourinary abnormalities (G), and ear abnormalities (E), with no family history. The estimated incidence ranges from 1 in 8500 to 15,000 births.[1] The primary cause of CHARGE syndrome is a functional pathogenic mutation in the gene encoding chromodomain helicase DNA binding protein 7 (*CHD7*), which regulates a large number of developmental pathways. Mutations in the *CHD7* gene are frequently associated with complex developmental disorders affecting craniofacial structures, cranial nerves, and multiple organ systems. Parents and patients with CHARGE syndrome will face extensive medical needs requiring interdisciplinary medical and surgical intervention.[2] Therefore, improving the prenatal diagnosis of the syndrome at an early stage will be crucial.

The primary and secondary clinical diagnostic criteria for CHARGE syndrome were first published by Verloes[3] in 2005 and subsequently revised in 2015.[1] The presence of an abnormal external, middle, or inner ear and pathogenic *CHD7* mutations were the primary criteria, along with coloboma, choanal atresia, or cleft palate. Secondary criteria include cranial nerve dysfunctions such as hearing loss, dysphagia/feeding difficulties, structural brain abnormalities, developmental delay/ID/autism, hypothalamo-hypophyseal dysfunction (gonadotropin or growth hormone deficiency), genital abnormalities, cardiac or esophageal malformations, renal anomalies, and skeletal/limb abnormalities. Diagnosis of CHARGE syndrome requires the detection of at least two major criteria and any amount of minor criteria.[4–8] However, most of the requirements are difficult to meet in prenatal ultrasonography. Clinical examinations at birth revealed abnormalities in the inner and outer ear, with bilateral hearing loss in almost all cases.[9] The appearance of the external ear is a common result from this disease, namely a short, wide, cup-shaped ear that is low and posteriorly rotated with a triangular cone. The presence of an external ear abnormality is considered one of the key factors in the prenatal diagnosis of the syndrome.

In the present study, we detected external ear abnormalities by ultrasonography as early as the 22nd week of gestation. The fetus was normal except for the external ear abnormality, which could be an early sign of CHARGE syndrome, and then the syndrome was confirmed postnatally by genetic testing that revealed a mutation in the *CHD7* gene.

2 | CASE HISTORY

A gravida 2 and para 0 (G2P0) pregnant woman came to Shijiazhuang Fourth Hospital for prenatal examination. The ultrasound examination as well as other routine prenatal examinations were carried out. A preterm female infant was delivered at 35^{+6} weeks of gestation. The postpartum examination and follow-up were proceeded.

3 | METHODS

Ultrasound examinations were carried out at 22nd, 28th, 33rd, and 35th weeks of gestation. After delivery, physical examination, Apgar score evaluation, neonatal echocardiography, transcranial Doppler ultrasonography, and ophthalmologic examinations were applied. Genetic testing (whole exome sequencing) was also performed to confirm the disorder.

4 | CONCLUSION AND RESULTS

4.1 | Ultrasound during pregnancy

A gravida 2 and para 0 (G2P0) pregnant woman at the 22nd week of gestation attended her antenatal checkup. Two-dimensional (2D) ultrasonography exhibited an abnormal ear shape and in comparison to the three-dimensional (3D) determined an abnormal external ear structure (1.63 cm in length and 1.17 cm in width, resulting in an ear length/width ratio of 1.39). The normal c- or s-shaped structure of the external ear bilaterally was found absent in the fetus, showing a short, wide, markedly prominent antihelix (Figure 1A,B). Ultrasonography tests displayed no other major abnormality. The woman continued the pregnancy and declined invasive prenatal testing after genetic counseling. However, the following ultrasound tests at the 28th, 33rd, and 35th weeks of her gestation indicated the same results as that of the 22nd week.

4.2 | Postpartum examination

After 35 weeks and 6 days of gestation, the woman delivered a preterm female infant vaginally with a birth weight of 2200 grams. The Apgar score was 10 at both 1 and 5 min after birth. At birth, the newborn cried weakly, struggled to breathe and eat, and had impaired hearing. Both ears were presented short and wide, cup-shaped, with triangular conchae and small earlobes (Figure 1C). Neonatal

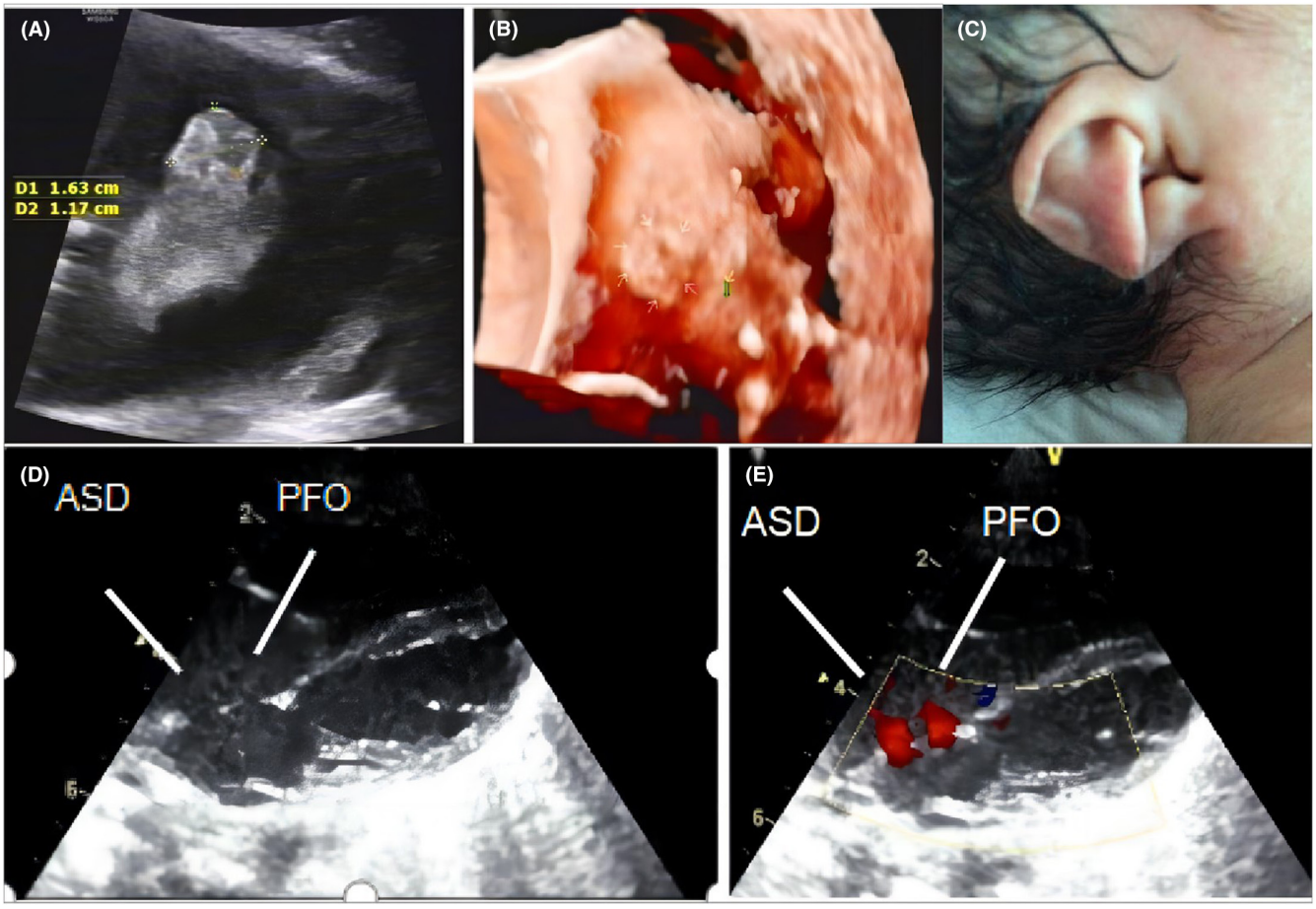

FIGURE 1 Clinical features of the patient. (A) The external ear length and width of the fetus was shown at the 22nd week of gestation in 2D ultrasound. (B) A markedly prominent superior anti-helix crus was displayed in 3D-Ultrasound with the abnormal fetal ear. (C) Image of the neonate's right ear, showing three typical ear morphological characteristics of CHARGE syndrome: absence of ear lobes, a triangular cymba conchae, and a prominent antihelix. (D) Two-dimensional and (E) color-flow Doppler neonatal echocardiography at the level of the xiphoid showing a small atrial septal defect (ASD) and a patent foramen ovale (PFO).

echocardiography showed an oval foramen and a small atrial septal defect (Figure 1D,E). Transcranial Doppler ultrasonography and ophthalmologic examinations did not find significant structural abnormalities. There was no evidence of any congenital anomalies within the reproductive system.

4.3 | Genetic analysis

To confirm the genetic disorder, a trio-whole-exome sequencing (Trio-WES) analysis was performed on the neonate and the parents. A de novo nonsense mutation chr8-61,654,397-C-T (GRCh37/hg19) in *CHD7* gene (ENST00000524602 c.406C > T, p.Q136X in exon 2) was identified in the neonate (Figure 2) but not in her parents. The mutation caused a very early truncation of the protein, which may suggest a serious functional impact. It was absent in public database (Genome Aggregation Database: http://gnomad.broadinstitute.org/) and predicted to be deleterious by CADD (https://cadd.gs.washington.edu/) and MutationTaster (https://www.mutationtaster.org/). Referring to the American College of Medical Genetics and Genomics (ACMG) mutation interpretation guidelines, this mutation was graded as pathogenic (PVS1 + PS2 + PM2). The variant was also recorded in Human Genome Mutation Database (HGMD ID: CM126591). According to the evidence above, we thought the mutation is responsible for the patient's abnormality.

4.4 | Follow-up

The neonate was treated with nutritional support for 1 month, and the disease continued to progress. Eventually, the parents refused any curative treatment and allowed for only supportive care.

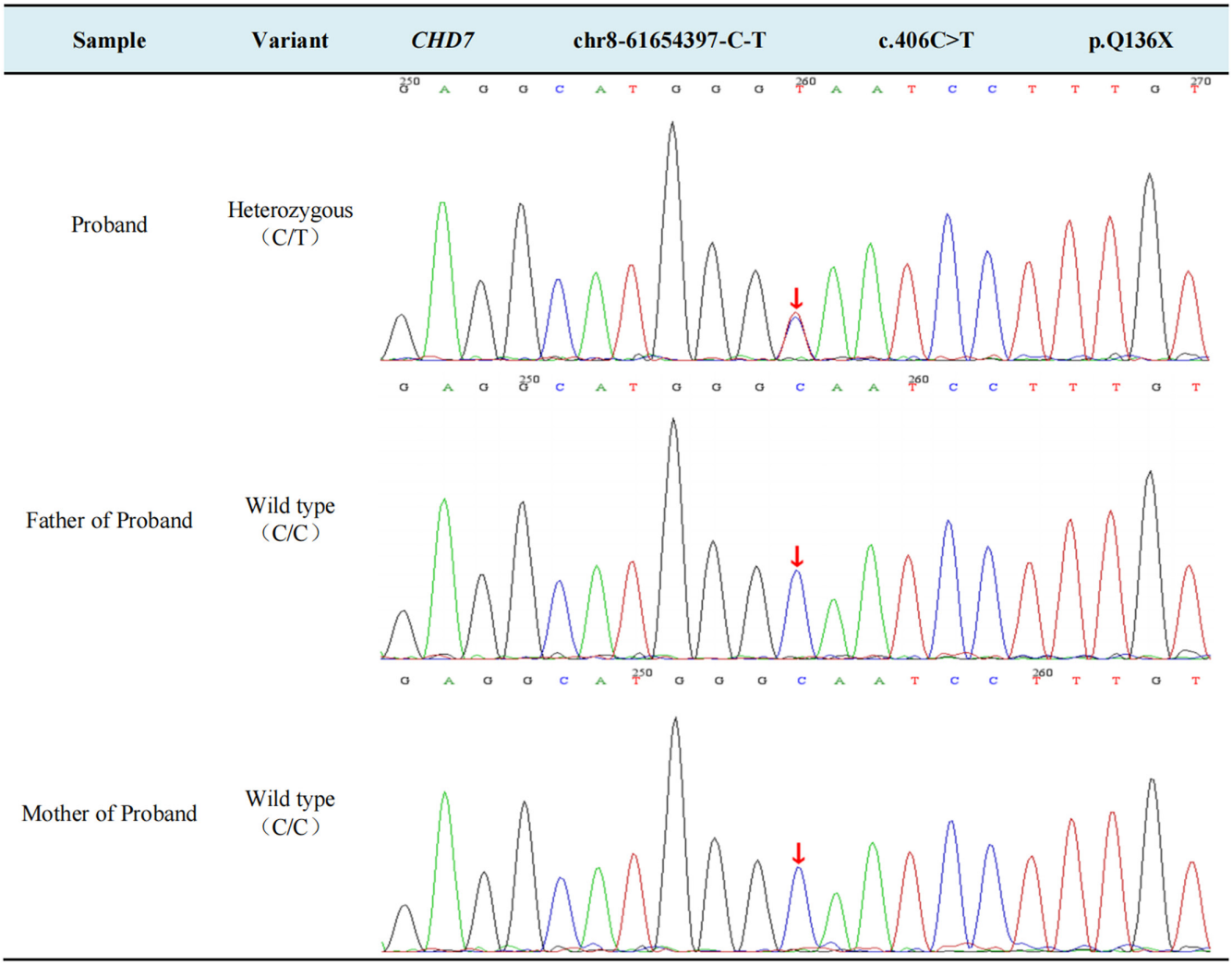

FIGURE 2 Sanger sequencing results. Trio-WES genetic analysis showing the presence of a nonsense mutation of *CHD7* gene in the neonate (c.406C > T, p.Q136X in exon 2) and the absence of mutation in the parents. The mutation location was marked by the arrows.

4.5 | Conclusion

CHARGE syndrome is multiple congenital anomalies with high mortality and possibly serious prognosis, which makes it imperative to be diagnosed at earlier prenatal stage. The external ear malformations are the only prominent prenatal manifestations in this case, suggesting that a thorough evaluation of the fetal ear by ultrasound should be performed between the 20th and 24th week of gestation to identify subtle ear abnormalities that are usually seen during this period. When the syndrome is suspected based on unusual ear shape, size, and/or location, molecular analysis of *CHD7* gene should be proposed. Early prenatal diagnosis of CHARGE syndrome will improve pregnancy outcomes and allow for appropriate management of neonatal care.

5 | DISCUSSION

The ear is a sensory organ that is vital for facial appearance. One in every 3800 newborns is found to have structural deformities and auricular malformations on the ear.[10] Various malformations, including the shape, size, position, orientation, and location of the fetal ear have been associated with CHARGE syndrome.[10,11] However, prenatal ultrasonography of the external ear is not performed often due to the rarity of ear malformations. Furthermore, it is still challenging to detect ear abnormalities on prenatal ultrasound, although fetal external ear ultrasonography tests could be performed to indicate CHARGE syndrome. Therefore, in some CHARGE cases reported previously, the condition was identified by ultrasound scans only when the fetus had

prenatal congenital heart disease with or without other malformations.[12] However, CHARGE syndrome is generally confirmed after birth, and it is unlikely to acquire a prenatal diagnosis.

In this case, the specific abnormality of the external ear structure was observed at a time as early as the 22nd week of gestation. In contrast to previously reported cases, prenatal ultrasound tests did not uncover other major abnormalities, which makes it more difficult to confirm the diagnosis of CHARGE syndrome based on ultrasound findings alone.[8] The external ear abnormalities are mostly short, wide, cup-shaped, triangular conchae, with the absence of earlobes. Only an adequate amount of knowledge on the shape, size, and position of the normal fetal ear can increase our confidence and sensitivity in identifying abnormal ears in utero. Normal fetal ears on ultrasound images have a distinctly clear bright-field C- or S-shape. Previous studies have shown that the length and width of the ear have a positive linear relationship with gestational age and have established a formula for objectively determining ear abnormalities.[13,14] Normal ears are located on the lateral surface of the head at eye level.[15] Abnormalities in the shape, size, and position of the fetal ear are often associated with syndromes caused by chromosomal abnormalities. One of the most common genetic disorders in neonates is trisomy 21, characterized by reduced ear length.[16] A lower ear position occurs frequently in Noonan syndrome.[17] Some ear abnormalities such as the absence of earlobes, a prominent antihelix, or a triangular cymbal conchae are prevalent in fetuses with CHARGE syndrome. However, the patterns of abnormalities in several syndromes overlap to a large extent, so they must all be taken into account in the differential diagnosis. The shape and location can be detected using both 2D and 3D ultrasound, and quantitative measurements of the external ear could determine the size of the abnormalities, these factors will facilitate the differential diagnosis.

Studies have shown that the detection rate of fetal external ear anomalies is negatively correlated with gestational age after 16 weeks of gestation.[18] Therefore, based on these studies and also in agreement with the results of this case study, we concluded that the optimal timing to detect external ear anomalies is between the 20th and 24th weeks of gestation. Thereafter, the detection rate of ear anomalies decreases due to the accumulation of amniotic fluid and changes in the fetal position. Our findings highlighted the importance of screening for ear anomalies at the appropriate gestational weeks. When special external ear abnormalities are found by ultrasound in utero, thorough scanning of other organs, such as the heart, eye, face, and genitourinary, is required to increase the prenatal diagnosis rate of the disease.

Additionally, prenatal diagnosis containing genetic testing was recommended and may also help. If the mutation in *CHD7* gene was identified during pregnancy, the family may have better therapeutic measures. Though the variant (*CHD7*, c.406C > T) detected in proband was not recorded in ClinVar, it was previously reported in large cohort studies,[19,20] which supported pathogenicity of the variant. And we have submitted the variant to ClinVar (SCV004231838). Unfortunately, the maternity refused to receive prenatal diagnosis. Besides, a non-stress test (NST) is recommended to assess fetal ear function of auditory perception after the detection of structural ear abnormalities, while magnetic resonance imaging (MRI) is to be done for inner ear evaluation to avoid exposure of the fetal brain to radiation.[12,21] However, in this case, the parents did not agree to receive an MRI for the newborn.

AUTHOR CONTRIBUTIONS

Yu Liang: Data curation; formal analysis; writing – original draft. **Sijie He:** Data curation; validation; writing – review and editing. **Liuqiao Yang:** Formal analysis; validation; writing – original draft. **Tao Li:** Conceptualization; funding acquisition; methodology; supervision; writing – review and editing. **Lijian Zhao:** Conceptualization; data curation; supervision. **Cong-xin Sun:** Conceptualization; funding acquisition; methodology; supervision.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

This study has been performed in accordance with the Declaration of Helsinki and has been approved by the Ethics Committee of Shijiazhuang Fourth Hospital (protocol code 20230159).

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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