Case Report

Recurrent First-trimester Cystic Hygroma with Normal Chromosomes Identified in Two Cases with a Recessive Genetic Syndrome

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Abstract

First-trimester cystic hygroma (CH) was a frequent finding in a general obstetric screening program for fetal aneuploidy. Chromosomal abnormalities can be diagnosed in most cases with CH, especially common trisomies and Turner syndrome. For first-trimester CH with a normal array result, management choices are limited except for waiting for serial ultrasounds to detect structural anomalies. We report two cases with a recurrent diagnosis of fetal first-trimester CH in two subsequent pregnancies. In both cases, detailed anatomic surveys in the second trimester showed structural anomalies. After excluding chromosomal abnormalities, trio-exome sequencing (ES) revealed two pathogenic variants, P3H1:c.1032T >A and c.1927_1930delinsGCTT in Case 1, and two pathogenic variants, KIAA1109:c.5788del and c. 3055C >T in Case 2. These findings were associated with two recessive genetic syndromes, osteogenesis imperfecta type VIII and Alkuraya-Kucinskas syndrome, in the two cases, respectively. Our study showed that the recurrence of fetal CH with a normal karyotype strongly indicates the existence of an autosomal recessive type of genetic disorder. For such cases, health providers should be alerted to this possibility, and early application of ES should be considered before the presentation of fetal structural anomalies which are usually present in second-trimester anatomic scans.

Keywords: Cystic hygroma, exome syndrome, first trimester, genetic syndrome, prenatal diagnosis

Introduction

First-trimester cystic hygroma (CH) was a frequent finding in a general obstetric screening program for fetal aneuploidy, with a prevalence of 1/285.[1] Chromosomal abnormalities can be diagnosed in most cases with CH, especially common trisomies and Turner syndrome. A large body of evidence has shown that CH is also associated with an increased risk of structural anomalies, intrauterine, or neonatal demise.[2] In current clinical practice, for first-trimester CH with a normal karyotype, management choices are limited except for waiting for serial ultrasounds to detect structural anomalies. We here report two families with a recurrent diagnosis of fetal first-trimester CH in two subsequent pregnancies, which were detected by exome sequencing (ES) to have genetic syndromes.

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Case Reports

Case 1

A 27-year-old woman, G2P0A1, showed fetal CH at 12 weeks gestation [Figure 1]. Both partners were healthy and unrelated and had nonsignificant family histories. Chorionic villus sampling (CVS) with chromosomal microarray analysis (CMA) reported no genomic imbalance. The follow-up ultrasound at 16 weeks found normal fetal morphology with a nuchal fold of 6.0 mm. However, the routine scan at 21 weeks showed severe shortening and bowing of long bones [Figure 1]. Further etiologic investigation with trio ES detected two variants in *P3H1*, c. 1032T >A (p. Tyr344Ter) and c. 1927_1930delinsGCTT

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(p. Pro643_Gln644delinsAlaTer), in the fetus, inherited from the mother and father, respectively [Figure 1]. Both variants were classified as pathogenic according to the American College of Medical Genetics guidelines. Variants of *P3H1* are the cause of recessive osteogenesis imperfecta (type VIII).[3] The pregnancy was terminated at 21 weeks. Physical examination of the male fetus showed short extremities. Their first pregnancy was terminated at 13 weeks because of CH, and the abortus showed a normal CMA test. The archived fetal DNA sample of the first pregnancy was obtained, and target testing confirmed the presence of the two variants.

Case 2

A 27-year-old G3P0A2 woman had fetal CH at 12 weeks [Figure 2]. CVS performed at other clinics reported a normal CMA result. She came to our center at 20 weeks for a structural scan. A detailed ultrasound showed nuchal CH, a flat face, bilateral ventriculomegaly (17.4 mm/16.8 mm), micrognathia, cleft palate, scoliosis, clenched hands, and clubfeet [Figure 2]. The pregnancy was terminated. Physical examination of the female fetus showed facial dysmorphism, CH, clenched hands, overlapping fingers, diffuse fixed contractures, and clubfoot. Trio ES with fetal skin tissue and parental blood detected two pathogenic variants in *KIAA1109*, c. 5788del (p. Val1930CysfsTer2) and c. 3055C >T (p. Arg1019Ter), in the fetus, inherited from the mother and father, respectively [Figure 2]. Her first pregnancy ended with an early miscarriage without embryonic karyotyping. Her second pregnancy was interrupted at 13 weeks because of CH, and fetal tissue showed a normal karyotype. Both partners were not dysmorphic and had nonsignificant family histories. Target testing of the archived fetal DNA of the second pregnancy confirmed the presence of the two variants of *KIAA1109*, which are associated with autosomal recessive Alkuraya-Kucinskas syndrome.[4]

Discussion

The most common etiologic factors associated with fetal CH are reported to be chromosomal abnormalities, especially common trisomies and Turner syndrome, and structural malformations. For this reason, prenatal karyotyping with CVS and detailed anatomy scans are mandatory for first-trimester CH. Recurrence of fetal CH in subsequent pregnancies is rare. It strongly suggests the existence of an autosomal recessive type of genetic disorder. Some monogenic syndromes may present prenatally as CH. For example, Schreurs *et al*.[5] reported a retrospective study of 185 singleton pregnancies with a first-trimester diagnosis of fetal CH, and Noonan syndrome was diagnosed in 6 (3.24%) cases using testing for RASopathies. The existence of a form of Noonan syndrome that is inherited in an autosomal recessive pattern has been

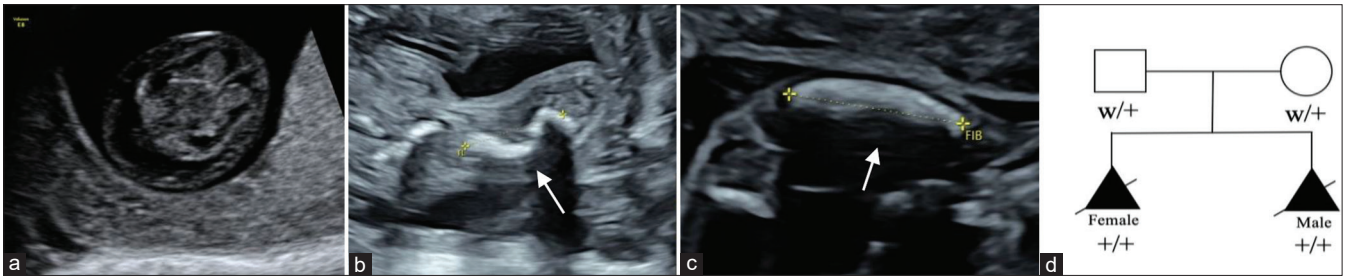

Figure 1: The case of recurrent cystic hygroma with *P3H1*-related osteogenesis imperfecta. (a) First-trimester cystic hygroma; (b) Short and bowed femur (arrow); (c) Short and bowed tibia (arrow); (d) Family pedigree. +: Mutant allele; W: Wild allele

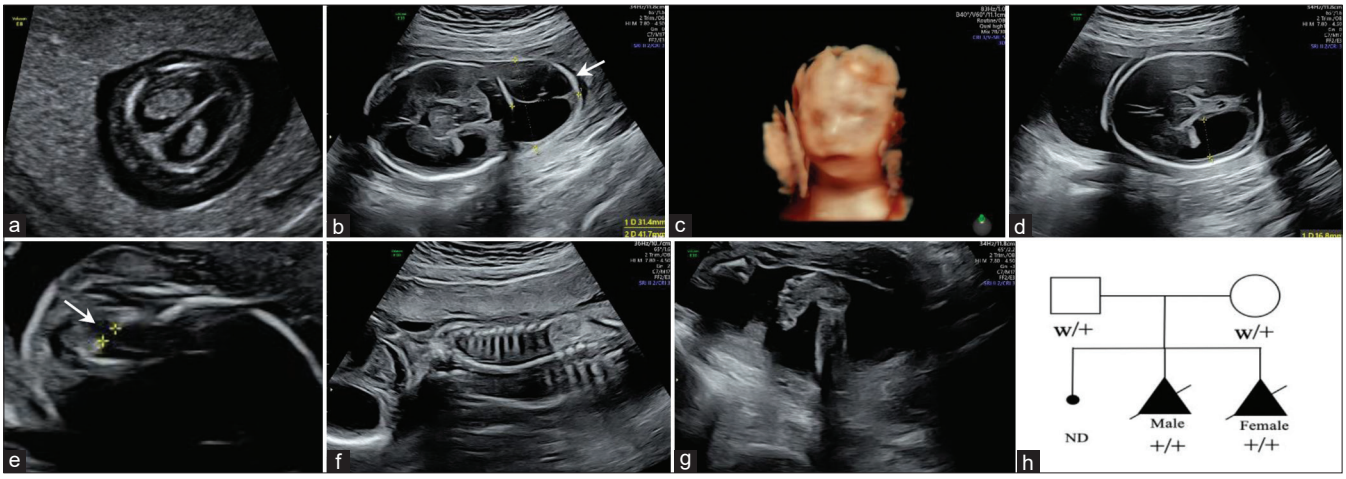

Figure 2: The case of recurrent cystic hygroma with Alkuraya-Kucinskas syndrome. (a) First-trimester cystic hygroma; (b) Second-trimester cystic hygroma (arrow); (c) Flat face and micrognathia; (d) Ventriculomegaly; (e) Cleft palate (arrow); (f) Abnormal alignment of the vertebral column; (g) Clubfoot; (h) Family pedigree. ND: Not detected, +: Mutant allele, W: Wild allele

reported with biallelic mutations in *LZTR1* or *SPRED2*.[6,7] Due to their rarity, the real prevalence of first-trimester CH in osteogenesis imperfect or Alkuraya-Kucinskas syndrome has not been reported. However, the association of CH with these two conditions has been described in case reports.[4,8] Our two cases further confirmed this association. Therefore, health providers should be alerted to the possibility of a recessive genetic condition in the cases of recurrent CH when chromosomal abnormalities have been excluded.

Thanks to the routine use of NT screening in prenatal care, the diagnosis of CH is now made in early pregnancy for the majority of cases. The prognosis of a fetus with a CH will largely depend on whether or not the fetus develops any other structural anomalies or carries a genetic defect. Malone *et al*.[1] reported that in 410 cases of CH diagnosed before 14 weeks of gestation, only 39% had normal chromosomal status; among these, 13% had a significant structural fetal abnormality, including 7 cardiac and 12 noncardiac abnormalities. Overall, the perinatal loss was 62%; the total survival rate in the setting of euploid CH without structural abnormality was 84%. Therefore, for first-trimester CH with a normal karyotype, the main management choice includes follow-up ultrasounds to detect structural anomalies. As evidenced in the present study, significant structural anomalies are expected to be identified in late pregnancy in the case of the coexistence of a genetic condition. In clinical practice for genetic counseling when a fetus is found to have a current CH, emphasis should not only be on fetal karyotyping but also detailed obstetric history and the possibility of recessive monogenic conditions in the family. With comprehensive pretest counseling, early application of ES should be offered as an option before the presentation of fetal structural anomalies which usually are identified in second trimester anatomic scans.

Prenatal ES has now been performed with increasing frequency in fetuses with structural anomalies and normal chromosomal analysis.[9,10] It is a very promising and additional tool for clinicians to adequately counsel parents of fetuses with nonspecific anomalies detected on prenatal ultrasound. The primary advantage of early prenatal diagnosis is earlier genetic information of the fetus. This knowledge provides patients with the opportunity to seek counseling for potential genetic or developmental issues, early referral to pediatric subspecialists, or earlier and safer pregnancy termination if the result-related condition is poor.

Declaration of patient consent

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

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Conflicts of interest

There are no conflicts of interest.

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