Case Report

Adducted Thumb in the First Trimester of Pregnancy: An Early Clue to Prenatal Diagnosis of L1 Syndrome

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Abstract

A pregnant woman was revealed to have an unusual position of the fetal hand by a routine 12-week ultrasound. Bilateral adducted thumbs and a male phenotype were confirmed by another ultrasound at 14 weeks' gestation. A structural survey at 18 weeks revealed fetal hydrocephalus with severe bilateral ventriculomegaly. The pregnancy was terminated, and postnatal examination with trio exome sequencing detected a hemizygous deletion (1,511 bp in size) variant of L1CAM gene in the fetus, inherited from the mother. The fetus was diagnosed as L1 syndrome (X-linked hydrocephalus). A family study found that this was a familial mutant allele. This study demonstrates that fetal hand abnormalities can be identified in the first trimester. Adducted thumbs might indicate the maldevelopment of the fetal brain, and therefore, examination of fetal hands and fingers should be integrated into fetal anomaly scans.

Keywords: Adducted thumbs, first-trimester ultrasound screening, L1 syndrome, X-linked hydrocephalus

Introduction

L1 syndrome is an inherited, X-linked disorder occurring in males with a prevalence of approximately 1/30,000.[1] This syndrome represents a spectrum of disorders including X-linked hydrocephalus with stenosis of the aqueduct of Sylvius (HSAS); mental retardation, aphasia, shuffling gait, adducted thumbs; X-linked complicated hereditary spastic paraplegia type; and X-linked complicated corpus callosum agenesis. In this study, we report the prenatal diagnosis of L1 syndrome in a case due to the sonographic finding of adducted thumbs in the first trimester of pregnancy.

Case Report

A 24-year-old G1P0 woman came to our center for a routine first-trimester scan at 12 weeks' gestation. The ultrasound showed a viable fetus with a nuchal translucency of 1 mm and a crown-rump length of 60 mm. The examination of fetal limbs showed an unusual position of the thumbs which could not be seen extended during the 10-min scan. The angle of the genital tubercle appeared to be male. Bilateral adducted thumbs and a male phenotype were confirmed by another ultrasound examination at 14 weeks' gestation with a normal cranial appearance [Figure 1]. The lower limbs appeared normal. The movements of limbs were active. The couple was apparently healthy with no physical or n*europsychiatric* impairments. However, carefully inquired familial medical history revealed that the maternal sister (II-3) had an abnormal reproductive history. The sister had a 5-year-old healthy girl. Her first pregnancy ended with artificial interruption because of fetal hydrocephalus identified at 20 weeks gestation, with a normal chromosomal microarray of amniocytes. The maternal brother (II-5) was healthy with normal physical morphology. Based on these findings, the pregnant woman was explained that the fetus was at risk for X-linked hydrocephalus. Chorionic villus sampling was recommended for genetic testing but was declined.

A structural survey at 18 weeks revealed fetal hydrocephalus with severe bilateral ventriculomegaly [Figure 2] and bilateral adducted thumbs. No other abnormalities were noted.

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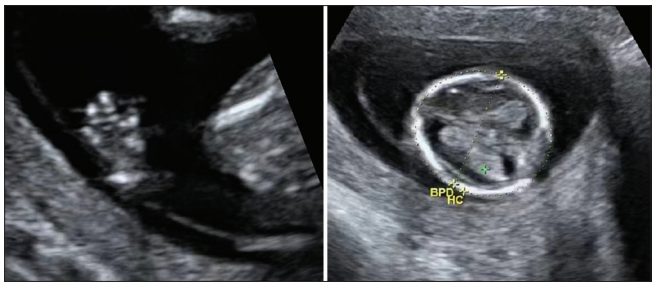

Figure 1: Sonographic examination showing adducted thumbs (left) and a normal cranial appearance (right) at 14 weeks' gestation

The parents opted for pregnancy termination. The aborted fetus showed bilateral adducted thumbs. Fetal autopsy was declined. With informed consent, the samples of fetal skin tissue and parental blood were sent for exome sequencing. This detected a hemizygous deletion variant of L1CAM gene in the fetus, inherited from the mother. Gap-polymerase chain reaction confirmed the large deletion and Sanger sequencing of the amplified fragment revealed accurately the breakpoints [Figure 3]. The deletion was 1,511 bp in size (chrX: 153,131,395–153,132,905), removing the whole exons 17/18 and partial exon 16 of L1CAM. The fetus was then diagnosed as L1 syndrome (HSAS). The family study found that the L1CAM variant was a familial mutant allele [Figure 4].

Discussion

Prenatal diagnosis of HSAS is usually suggested on ultrasound showing hydrocephalus in a male fetus. However, early diagnosis *in utero* is challenging for sporadic cases because hydrocephalus does not usually become apparent until late second trimester.[2,3] In this study, we identified adducted thumbs in a male fetus in the first-trimester which alerted us to consider X-linked hydrocephalus. Although adducted thumbs are not always observed in HSAS patients,[4] its presence is a clinical clue to genetic diagnosis. Verhagen *et al*.[5] surveyed 25 patients with adducted thumbs, and found that additional features were observed in 88% (22/25) of patients, including congenital hydrocephalus in 16 patients in whom *L1CAM* variants were identified in 25%. Gilboa *et al*. reported the pregnancy outcomes of six fetuses diagnosed prenatally with adducted thumbs.[6] Three fetuses had severe associated anomalies. However, no genetic information was available in that study. Our study further indicates that fetal adducted thumbs might represent the tip of a severe neurodevelopmental syndrome and therefore a follow-up search for signs related with central nervous system involvement should be performed.

In clinical practice, the optimal gestational moment of the first-trimester anomaly scan is usually after 12 weeks when the fetal organ development is large enough to be clearly visualized by ultrasound. In our experience, the completion of the basic protocol regarding the assessment of the fetal limbs rarely requires an increased gestational age. The

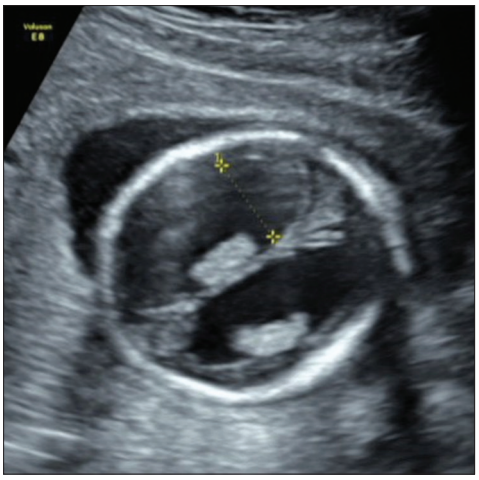

Figure 2: Sonographic examination showing hydrocephalus with severe bilateral ventriculomegaly at 18 weeks' gestation

fingers are relatively easy to assess in the first trimester because they frequently lie in the same ultrasound plane due to enough amniotic cavity space. The performance of routine screening for fetal limb abnormalities in the first trimester was reported satisfactory in a retrospective study,[7] where the vast majority of limb abnormalities detected prenatally were identified in the first trimester (82%). In a systematic review and meta-analysis of first-trimester ultrasound screening for fetal structural anomalies, detection rates ranged from 32% in low-risk groups to more than 60% in high-risk groups, demonstrating that first-trimester ultrasound has the potential to identify a large proportion of fetuses affected with structural anomalies.[8] The identification of fetal anomalies in early pregnancy will provide patients with more time to pursue counseling/genetic testing.

In the present study, the visualization of an abnormal position of the thumbs was the first sign to indicate a genetic syndrome. Because the adducted thumb is the most common concomitant feature of X-linked hydrocephalus,[9] a detailed family history, especially with searching for the reproductive history of hydrocephalus in maternal female relatives, should be collected. The information of a positive family history is very helpful to assess the fetal risk of suffering from X-linked hydrocephalus, even though in early gestation. When a woman is confirmed to be a carrier of *L1CAM* variant, the carrying status should be determined in familial female members. As evidenced in this study, the same variant was identified in the daughter and a sister of the pregnant woman. Genetic counseling regarding on recurrence risk and the choice of preimplantation genetic testing or prenatal diagnosis for future pregnancies should be offered to the family.

In summary, our study demonstrates that fetal hand abnormalities can be identified in the first trimester. Adducted thumbs might indicate the maldevelopment of fetal brain, and therefore examination of the fetal hands and fingers should be integrated into fetal anomaly scans. A first-trimester detection of an abnormal position of the thumbs in a male fetus should be

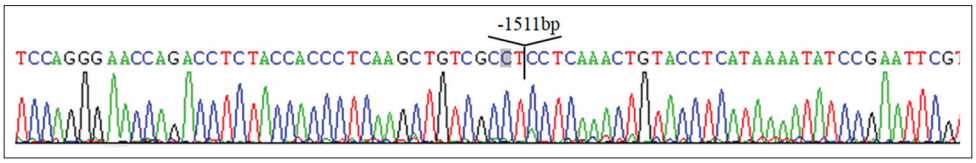

Figure 3: Chromatogram of the L1CAM variant by Sanger sequencing in the foetus showing the 1,511-bp deletion

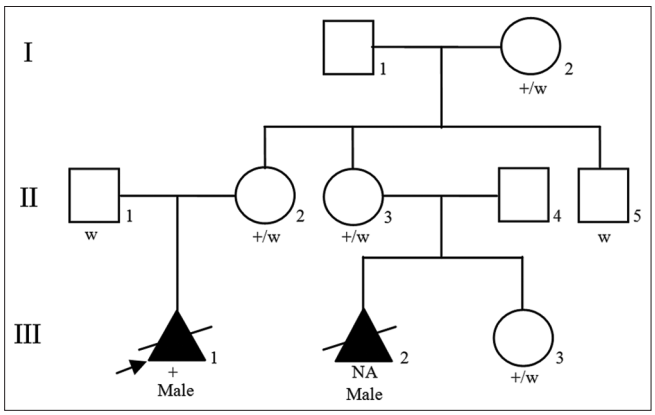

Figure 4: Family pedigree showing the L1CAM variant in the family members. NA: Not available, w: Wild allele, +: Mutant allele

followed closely by ultrasound to search for ventriculomegaly which is the early sign of X-linked hydrocephalus.

Declaration of patient consent

The authors certify that they have obtained appropriate patient consent forms. In the form, the patient has given the consent for the prenatal images and other clinical information to be reported in the journal. The patient understands that the 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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Nil.

Conflicts of interest

There are no conflicts of interest.

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