Early Diagnosis of a Rare Genetic Syndrome by the First-trimester Ultrasound Combined with Exome Sequencing

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Dear Editor,

Arthrogryposis multiplex congenita (AMC) is a descriptive diagnosis. Fixed joints and fetal akinesia *in utero* may result from abnormalities of the central nervous system, muscle, and nerve development as well as connective, cartilage, and osseous tissue disturbances.[1] The etiology is highly heterogeneous, comprising 300–400 disease entities. The prognosis of AMC depends on the underlying causes. Presentation at an earlier gestational age frequently correlates with severity. Therefore, it is important to achieve an early detection of AMC and a definite etiology. Here, we report a prenatal case of *DYNC1H1*-associated AMC diagnosed in the first trimester.

A 33-year-old G1P0 woman, conceiving naturally, came to our unit for a routine first-trimester scan at 11 weeks of gestation. She was healthy and had a nonsignificant medical history or family history. The woman had a normal aneuploidy screening test based on maternal cell-free DNA at 9 weeks. At this time, the ultrasound measured a nuchal translucency of 2.9 mm with a crown-rump length of 48 mm. The fetal hands were fixed in front of the chest with a posture unchanged, and the knees were fixated and extended [Figure 1]. The fetal four limbs showed no movements with the same postures during the 20 min of the whole examination. AMC was the prospective diagnosis of the fetus. After genetic counseling, chorionic villus sampling was offered for etiological investigation. Considering that the fetus had a low risk of chromosomal abnormalities which would have been detected by cell-free DNA screening, exome sequencing (ES) was used as the first-line diagnostic test. Rapid trio ES with placental villi and parental blood samples detected a *de novo DYNC1H1* variant c.8389C>T (p. R2797C), which was classified as likely pathogenic according to ACMG. At 13 weeks with the ES result available, the pregnancy was terminated by the parents. The postmortem examination confirmed the prenatal sonographic findings [Figure 1].

DYNC1H1-related disorders are heterogeneous, affecting the development and function of either the central or peripheral nervous system or both.[2] The musculoskeletal spectrum includes foot abnormalities, spinal deformities, AMC, congenital hip dislocation/dysplasia, and perinatal fractures. Surprisingly, there has been no case report of fetal DYNC1H1-related disorders in the literature, let alone the diagnosis at the first trimester. Our case is the first one diagnosed *in utero*.

Guidelines for routine fetal ultrasound at 11–14 weeks usually include the nuchal translucency measurement, facial profile, the three segments of all limbs, and the detection of major organ anomalies.[3,4] Although there are no standards for the purpose of reliably detecting fetal contractures, persistent abnormal limb postures with reduced movements should alert AMC.[5] Indeed, the first trimester is the best time for assessing fetal limbs, with enough amniotic fluid and room needed for fetal movements. Early detection can promote further etiologic and diagnostic workup and offer families of making informed pregnancy choices. Our case presentation indicates that the first-trimester ultrasound can detect AMC, which can lead to early *in utero* diagnosis of rare genetic disorders when combined with advanced genetic testing such as ES.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent form. In the form the patient has given her consent for her images and other clinical information to be reported in the journal. The patients understand that her

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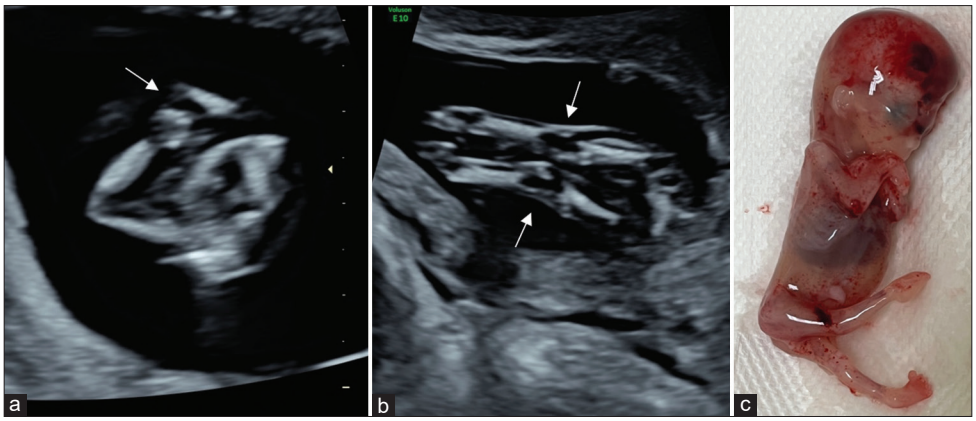

Figure 1: Fetal ultrasound performed at 11 weeks of gestation (a and b) and autopsy image of the 13-week fetus (c). (a) Fetal hands (arrow) fixed in front of the chest with a posture unchanged; (b) Fetal knees (arrow) were fixated and extended; (c) Upper limbs presented the same posture as *in utero*, and both knees were fixated in extension, with left club foot and right arthrogrypotic foot

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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