Fetal Magnetic Resonance Imaging Demonstration of Central Nervous System Abnormalities and Polydactyly Associated With Joubert Syndrome

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A 33-year-old woman, gravida 2, para 1, was referred to hospital for prenatal imaging evaluation of the fetal brain and limbs at 27 weeks' gestation. The woman and her husband were healthy and non-consanguineous. Two years previously, she delivered a female baby at 26 weeks' gestation with Joubert syndrome (JBTS), Dandy-Walker malformation, ventriculomegaly, cerebellar vermian hypoplasia and polydactyly of the feet. JBTS was confirmed by magnetic resonance imaging (MRI). The infant's karyotype was 46,XX. During this pregnancy, cerebellar hypoplasia was noted at 17 weeks' gestation, and ventriculomegaly and polydactyly were noted at 18 weeks' gestation. Level II ultrasound examination at 27 weeks' gestation revealed a male fetus with a femur length and an abdominal circumference equivalent to 27 weeks, polyhydramnios with an amniotic fluid index of 24.07 cm. Macrocephaly was present with an increased biparietal distance of 7.9 cm, an increased head circumference of 28.82 cm, an increased lateral ventricle posterior horn width of 2.64 cm, an increased transcerebellar distance of 3.61 cm, an increased cisterna magna length of 2.10 cm, an increased head circumference to femur length ratio of 5.66 (all > 95th centile). Ventriculomegaly, vermian hypoplasia, postaxial polydactyly of the left hand and preaxial polydactyly of the hallux of the left foot were also present. A tentative diagnosis of recurrent JBTS was made. Fetal MRI examination at 27 weeks' gestation revealed the "molar tooth sign", Dandy-Walker malformation, ventriculomegaly

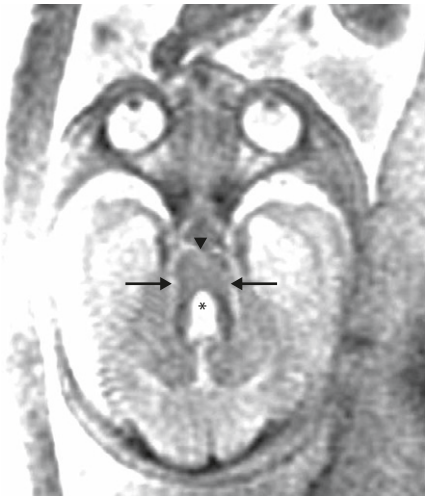

Figure 1. A male fetus at 27 weeks' gestation with abnormal magnetic resonance imaging findings suggestive of Joubert syndrome. Prenatal axial imaging at the pontomesencephalic junction shows the "molar tooth sign" with cerebellar vermian hypoplasia, a dilated fourth ventricle (*), thickened and elongated superior cerebellar peduncles (arrows), and a deep interpeduncular fossa (arrowhead).

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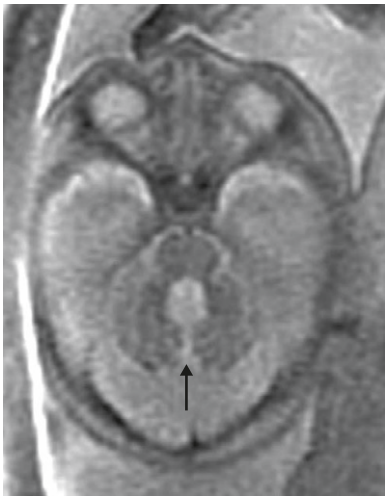

Figure 2. Prenatal axial imaging shows a vermian cleft (arrow).

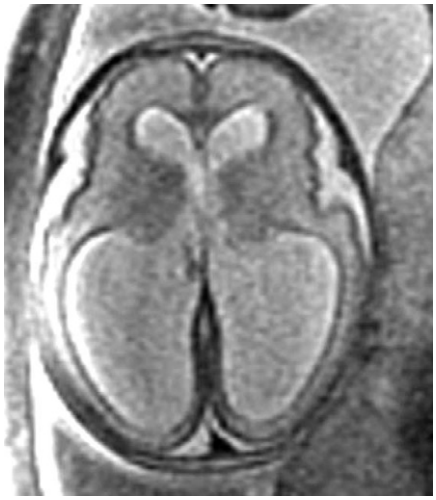

Figure 3. Prenatal axial imaging shows ventriculomegaly with dilation of the lateral ventricles.

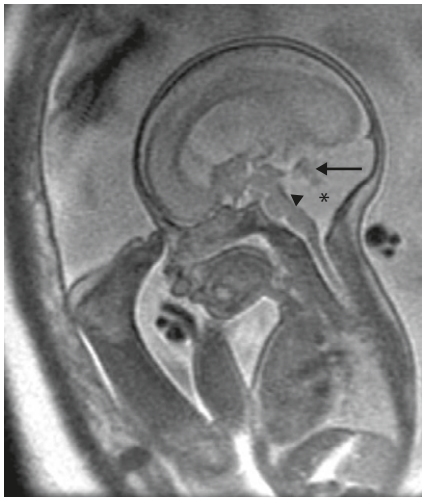

Figure 4. Prenatal sagittal imaging shows a dilated fourth ventricle (arrowhead) with a round roof, a hypoplastic cerebellum (arrow), and a large posterior fossa cyst (*).

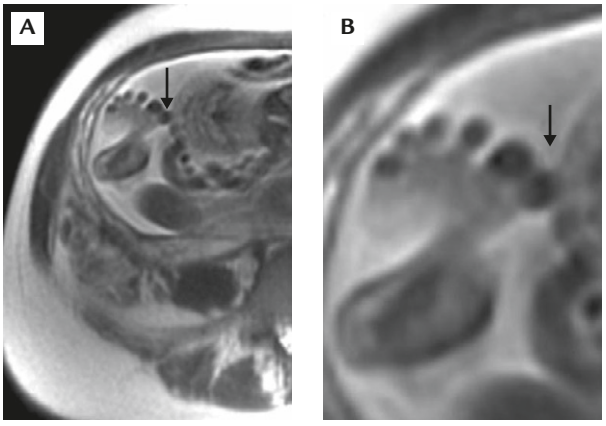

Figure 5. (A, B) Preaxial polydactyly (arrow) of the hallux of the foot.

and polydactyly (Figures 1–5). On the transaxial scan, there was a complex brainstem malformation consisting of cerebellar vermian hypoplasia, thickened and elongated superior cerebellar peduncles and a deep interpeduncular fossa, giving the appearance of the molar tooth sign which is pathognomonic for JBTS. The parents decided to continue the pregnancy. At 31^{+5} weeks' gestation, a 2,220 g live male baby was delivered with postaxial polydactyly of both hands, preaxial polydactyly of the left foot, and a 46,*XY* karyotype. The postnatal central nervous system findings were consistent with JBTS.

JBTS is a genetically heterogeneous disorder characterized by hypoplasia of the cerebellar vermis with a characteristic brainstem malformation and neuroradiologic molar tooth sign, intellectual disability, hypotonia, ataxia, tachypnea/apnea, and abnormal eye movements [1]. JBTS and related disorders (JSRD) is classic JBTS with variable features such as central nervous system anomalies including occipital encephalocele and corpus callosal agenesis, retinal dystrophy, ocular coloboma, oral frenulae, tongue tumors, polydactyly, cystic renal dysplasia, nephronophthisis, and congenital hepatic fibrosis [1]. JSRD is one type from the wide spectrum of ciliopathies known to be caused by aberrant function of the primary cilia [1–4].

In the case presented here, JBTS involved an affected female and an affected male from the same sibship and is likely inherited in an autosomal recessive pattern. To date, at least nine genes and one additional locus have been identified in patients with JSRD [1]. The nine genes include *INPP5E* on 9q34.3 (JBTS1), *AHI1* on 6q23.3 (JBTS3), *NPHP1* on 2q13 (JBTS4), *MKS4/CEP290* on 12q21.32 (JBTS5), *MKS3/TMEM67* on 8q21.13–q22.1 (JBTS6), *MKS5/RPGRIP1L* on 16q12.2 (JBTS7), *ARL13B* on 3q11.2 (JBTS8), *CC2D2A* on 4p15.3

(JBTS9), and *CXORF5* on Xp22.3 (JBTS10). The additional locus of *CORS2* has been suggested on 11p12–q13.3 (JBTS2). JBTS1–9 are inherited in an autosomal recessive pattern. JBTS10 is inherited in an X-linked recessive pattern [5]. Meckel syndrome (MKS) shares JBTS phenotypes [6,7]. Among the nine JSRD genes, three genes (*MKS3/TMEM67*, *MKS4/CEP290* and *MKS5/RPGRIP1L*) are also associated with MKS, indicating genetic complexity in JSRD. Both of the affected siblings in this case had polydactyly. Polydactyly is present in 8% [8] to 15% [9] of subjects with JSRD. Polydactyly has been shown to be present in cases with JBTS2, JBTS6 and JBTS7 but has rarely been described in other types of JSRD [1]. Polydactyly associated with JSRD is often postaxial, although preaxial polydactyly of the hands or large toes has been observed [1].

JSRD has an estimated prevalence of 1 in 100,000 live births [1]. Prenatal imaging of JSRD has rarely been described in the literature. To date, only 14 reports of prenatal imaging of JSRD have been described [10–23], most of which were examined by ultrasound and only three reports [21–23] were examined by fetal MRI. Prenatal sonographic findings in fetuses with JSRD are relatively nonspecific and include increased nuchal translucency, enlarged cisterna magna, cerebellar vermian agenesis, occipital encephalocele, ventriculomegaly, hypoplastic phallus, renal cysts, and polydactyly [20,21]. Prenatal ultrasound lacks sensitivity with regard to posterior fossa malformations. In contrast, fetal MRI is able to identify the characteristic molar tooth sign, which is the cardinal diagnostic imaging sign of JSRD. The molar tooth sign consists of cerebellar vermian hypoplasia, thickened and elongated superior cerebellar peduncles and a deep interpeduncular fossa, and midbrain dysgenesis is responsible for the molar tooth sign [24–26]. Fluss et al [22] identified the molar tooth sign at 27 weeks of gestation by fetal MRI in a fetus with JBTS. Saleem and Zaki [23] were able to identify the molar tooth sign associated with JSRD as early as 22 weeks of gestation by fetal MRI. We suggest that fetal MRI should be considered in pregnancy with a previous JSRD-affected child and/or documented posterior fossa malformations with associated anomalies suspicious of JSRD.

Acknowledgments

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