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Sonographic 'molar tooth' sign in the diagnosis of Joubert syndrome

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ABSTRACT

The characteristic imaging finding common to Joubert syndrome and related disorders is the 'molar tooth' sign. The prenatal diagnosis of Joubert syndrome using both ultrasound and fetal magnetic resonance imaging (MRI) in families with an affected child has been reported previously. We report two cases in which the molar tooth sign was identified by sonography at 26 + 4 weeks and at 20 + 6 weeks, respectively, prior to fetal MRI or genetic testing. In both cases the finding was subsequently confirmed on fetal MRI. As definitive prenatal genetic testing may not be conclusive in Joubert syndrome, the ability to identify the molar tooth sign sonographically before 24 weeks provides a valuable adjunct to prenatal diagnosis. Copyright © 2011 ISUOG. Published by John Wiley & Sons, Ltd.

CASE REPORT

Case 1

A 24-year-old nulliparous woman was referred for evaluation after a fetal cisterna magna measurement of 11 mm had been made on routine sonography at 22 + 2 weeks. Sonography at 17 + 3 weeks had noted a prominent cisterna magna. The couple was consanguineous (first cousins). Amniocentesis revealed a normal male karyotype. Sonographic evaluation at 26 + 4 weeks showed marked vermian hypoplasia (Figure 1), a deep cleft between prominent cerebellar peduncles and deficiency of the dorsal midbrain in the midline (Figure 2), consistent with the 'molar tooth' sign described on computed tomography (CT) and MRI in Joubert syndrome[1]. Postaxial polydactyly of both hands and one foot was also identified. Fetal MRI performed at 27 weeks confirmed the findings of vermian hypoplasia, absence of the primary fissure, midline cleft in the tegmentum and presence of the molar tooth sign (Figure 2).

A male infant, delivered at 41 + 4 weeks, was limp at birth and was intubated because of a lack of respiratory drive. Apgar scores were 3, 6 and 7 at 1, 5 and 10 min. Continuing episodes of apnea, desaturations and CO_2 retention required intubation for 25 days. Polydactyly was confirmed.

Cranial MRI showed a small vermis with abnormal vermian folia, dysplastic cerebellar hemispheres opposed in the midline and enlarged superior cerebellar peduncles with absence of decussation, consistent with the molar tooth sign (Figure 2). Clinical and radiological findings were consistent with Joubert syndrome; however, sequencing of the Joubert syndrome-associated genes (*AHI1, TMEM67/MKS3, CEP290, CC2D2A, RPGRIP1L, INPP5E, ARL13B* and *TMEM16)* showed no causative sequence changes, and there was no evidence of a homozygous deletion in the *NPHP1* gene.

Case 2

A 30-year-old woman presented in her second pregnancy at 20 + 6 weeks for fetal sonographic assessment. Her first child had been diagnosed with Joubert syndrome based on clinical features and MRI findings of the molar tooth sign. In this child, sequencing of the *CC2D2A* gene had revealed one copy of the c.351 T > G nucleotide change in exon 7 and one copy of the c.1519 A > G nucleotide change

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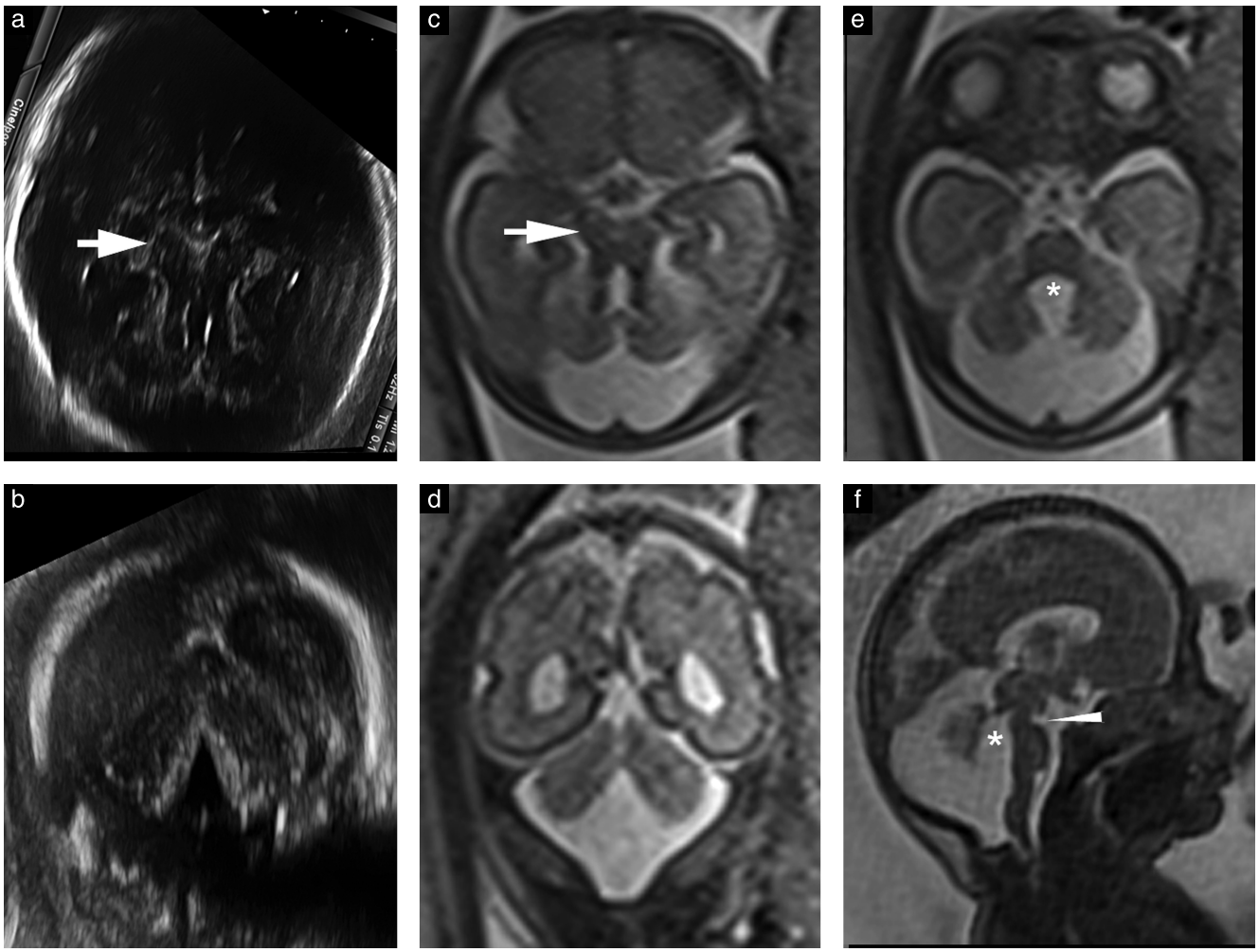

Figure 1 Images of the fetal brain in Case 1: ultrasound images at 26 + 4 weeks in axial (a) and coronal (b) planes, and fetal T2-weighted magnetic resonance images at 27 + 0 weeks in axial (c), coronal (d) and sagittal (f) planes, and in the axial plane at the level of the fourth ventricle (e). Axial ultrasound (a) and magnetic resonance (c) images show prominence of the interpeduncular fossa and a deep cleft in the midbrain between thickened cerebellar peduncles comprising the molar tooth sign (arrows). Ancillary findings include severe hypoplasia of the vermis (d,e,f) and steeply vertically oriented cerebellar folia as a result of the apposed hemispheres (b,d). Note the abnormally shaped fourth ventricle (*, e,f) and narrowing of the isthmus in the sagittal plane (arrowhead, f).

in exon 15. These have not been previously reported in patients with Joubert syndrome. The c.351 T > G change was predicted to result in the amino acid substitution p.Ser117Arg, thus predicted to have a damaging effect on *CC2D2A* protein function, while predictions for the c.1519 A > G nucleotide change effect were inconclusive. Both were interpreted as variants of unknown significance. Sequencing of the parental *CC2D2A* gene showed a maternal heterozygous c.351 T > G nucleotide change and a paternal heterozygous c.1519 A > G nucleotide change.

In the current pregnancy, as the two CC2D2A variants were not known to be causative, amniocentesis was timed to follow imaging studies. Ultrasound examination at 20 + 6 weeks showed enlargement of the cisterna magna, vermian hypoplasia and a midline cleft of the midbrain with prominence of the superior cerebellar peduncles, consistent with the molar tooth sign (Figure 3).

Subsequently, sequencing of the *CC2D2A* gene in fetal cells confirmed nucleotide changes identical to those of the sibling with Joubert syndrome. Fetal MRI performed at 21 + 4 weeks confirmed vermian hypoplasia and abnormal lobation, sagittal clefting of the tegmentum, thickened cerebellar peduncles and molar tooth sign (Figure 3). The pregnancy was terminated and autopsy was declined.

DISCUSSION

Joubert syndrome is characterized by hypotonia, abnormal ocular movement, hyperpnea, developmental delay, hypoplasia of the cerebellar vermis and brainstem malformation. Variable features, including cystic kidneys, nephronophthisis, retinal dystrophy, ocular colobomata, occipital encephalocele, polydactyly, ataxia and hepatic fibrosis[1–6], have led to broader classifications, such as Joubert syndrome and related disorders[7]. The characteristic finding common to all forms of Joubert syndrome is the molar tooth sign, first described in 1997[4], consisting of a triad of malformations including (i) a deepened

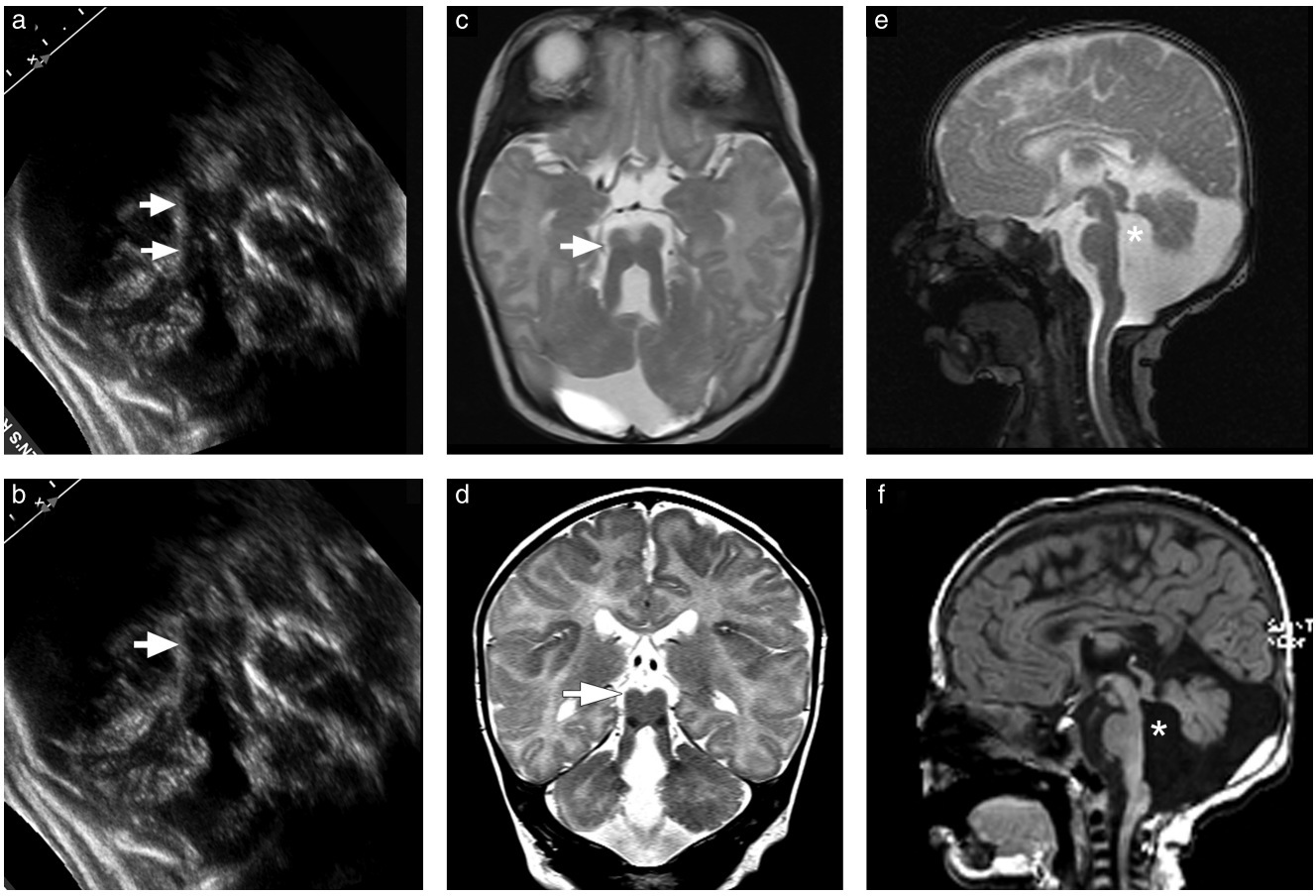

Figure 2 Case 1: prenatal axial ultrasound images at 36 + 5 weeks (a,b) and postnatal T2-weighted (c,d,e) and T1-weighted (f) magnetic resonance images in axial (c), coronal (d) and sagittal (e,f) planes on day 21. The molar tooth sign is indicated by arrows. Note the abnormally shaped fourth ventricle (*, e,f) in the sagittal plane.

interpeduncular fossa with narrow isthmus, (ii) thickened, elongated and horizontally oriented superior cerebellar peduncles as a result of the absence of normal decussation and (iii) a variable degree of vermian hypoplasia, creating an appearance which mimics a molar tooth on axial MR images[4,5]. A deep midline cleft in the superior vermis and rostrally displaced fourth ventricular fastigium[8] may give a bat-wing or umbrella shape to the fourth ventricle[9]. Other imaging features include an abnormal vermian foliar pattern and increased craniocaudal length of the pontomesencephalic junction[1,4,5,9,10]. Autopsy studies have shown reduction or absence of decussation of the superior cerebellar peduncles, severe hypoplasia of the cerebellar vermis and absence of decussation of the medullary pyramids (corticospinal tracts)[5,10–12].

Although there are reports of prenatal imaging findings using both ultrasound and fetal MRI in families with Joubert syndrome-affected children, to our knowledge there has been no previous report of the molar tooth sign being identified on 2D ultrasound imaging prior to fetal MRI. However, a recent Abstract describes the use of three-dimensional (3D) ultrasound to identify the molar tooth sign in two fetuses with enlarged cisterna magna prior to fetal MR diagnosis[13]. Sonographic abnormalities after 32 weeks, but not the molar tooth sign, have been described in a family that did not have a previously affected child[14]. The second of our cases demonstrates that identification of the molar tooth sign on ultrasound imaging, and thus the diagnosis of Joubert syndrome and related disorders, can be made as early as 20 + 6 weeks.

Mutations in nine genes have been implicated in Joubert syndrome to date: *TMEM67/MKS3, AHI1, CC2D2A, CEP290, RPGRIP1L, ARL13B, NPHP1, INPP5E* and *TMEM216*[15]. However, as in our first case, genetic testing may not find a mutation in a gene linked to Joubert syndrome, or, as in our second case, the presence of a mutation may not have been conclusively associated with Joubert syndrome. Therefore, clinical genetic testing may not be effective in all suspected cases. As in many locations termination of pregnancy is not a readily available option after 24 weeks' gestation, the ability to identify the molar tooth sign on prenatal sonography before 24 weeks presents a valuable adjunct to prenatal diagnosis for families known to have a 25% recurrence risk, as well as in couples who are not known to be mutation carriers. The sonographic detection of the molar tooth sign therefore expands the potential for early diagnosis of Joubert syndrome and related disorders.

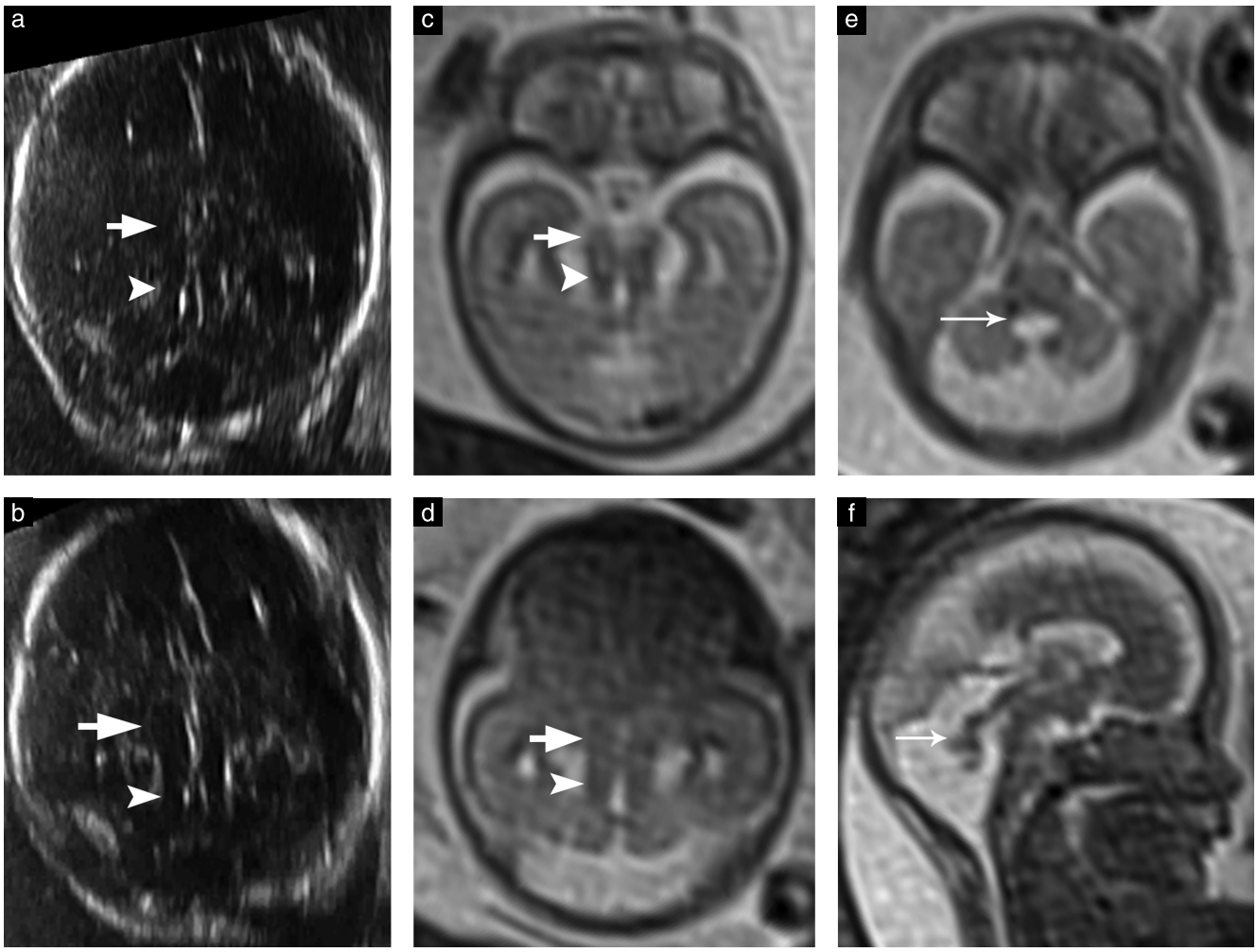

Figure 3 Images of the fetal brain in Case 2: axial ultrasound images at 20 + 6 weeks (a,b) and T2-weighted magnetic resonance images at 21 + 4 weeks in axial (c–e) and sagittal (f) planes. Arrows indicate the molar tooth sign and arrowheads indicate thickened cerebellar peduncles separated by a deep midline cleft in the midbrain. Thin arrows (e,f) show the abnormally shaped fourth ventricle and severely hypoplastic vermis.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Videoclip S1 Axial ultrasound views of the fetal brain in Case 1 at 29 + 4 weeks showing a deep cleft in the midbrain between thickened cerebellar peduncles and prominence of the interpeduncular fossa, comprising the molar tooth sign.

Videoclip S2 Axial ultrasound views of the fetal brain in Case 1 at 36 + 5 weeks showing a deep cleft in the midbrain between thickened cerebellar peduncles and a prominent interpeduncular fossa, consistent with the molar tooth sign.

