J. Fetal Med. (March 2019) 6:41–43
https://doi.org/10.1007/s40556-019-00195-w

BRIEF COMMUNICATION

Joubert Syndrome: Two Different Prenatal Ultrasound Presentations

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Received: 9 January 2019 / Accepted: 14 February 2019 / Published online: 26 February 2019

Abstract Joubert syndrome is a rare brainstem malformation characterized by hypoplastic vermis, thickened and elongated superior cerebellar peduncles, abnormally shaped 4th ventricle which may be associated with renal, ocular, hepatic orodigitofacial and cranial abnormalities and can be diagnosed on prenatal ultrasound and now is considered a part of Joubert syndrome and related syndromes (JSRD). Two prenatally detected cases of JSRD presented here expand the spectrum of sonological signs which should prompt a fetal medicine specialist to suspect JSRD.

Keywords Prenatal · Ultrasound · Joubert syndrome · Molar tooth sign · Fetal · TCTN1 · Vermian hypoplasia

Joubert syndrome is a rare brainstem malformation characterized by hypoplastic vermis, thickened and elongated superior cerebellar peduncles, abnormally shaped 4thventricle which may be associated with renal, ocular, hepatic orodigitofacial and cranial abnormalities and can be diagnosed on prenatal ultrasound [1, 2]. The genes attributed are TMEM216, AHI1, NPHP1, CEP290, TMEM67, RPGRIP1L, ARL13B, CC2D2A, CXORF5, TTC21B, KIF7, TCTN1, TMEM237, CEP41, TMEM138, C5ORF42, TCTN3, ZNF423, TMEM231, CSPP1, PDE6D, KIAA0586 TCTN2, CEP104, KIAA0556, B9D1, MKS1, TMEM107, ARMC9, CEP120, SUFU, PIBF1, B9D2 and ARL3 [2]. Postnatally, they present with hyperpnea or apnea, ataxia, ocular abnormalities and developmental delay [1, 2]. Joubert syndrome (JS) is now considered a part of Joubert syndrome and related disorders (JSRD) which are spectrum of disorders that exhibit molar tooth sign on imaging studies [2]. Another classification divides JS into simplex JS, JS with renal abnormalities, JS with ocular abnormalities, with oculorenal abnormalities, hepatic abnormalities, and JS with orofaciodigital abnormalities, based on the associated abnormalities [3]. JS usually has autosomal recessive inheritance with 25% recurrence in each pregnancy [2, 4, 5].

Below presented are two cases of Joubert syndrome which were suspected/diagnosed on prenatal ultrasound in absence of family history on routine exam.

Case 1 was a primigravida with non consanguineous marriage and poor socioeconomic background, presented for the routine growth scan at 32 weeks gestation wherein abnormal shape of 4th ventricle and its communication with the cisterna magna was noted on axial plane. On a detailed neurosonogram, the shape of 4th ventricle appeared elongated in anteroposterior direction on axial plane and quadrangular on sagittal plane. The vermis was hypoplastic (SI diameter 16 mm, trace 56 mm, both less than 5th centile for gestation) and abnormal in shape. Molar tooth sign due to thickened superior cerebellar peduncles, anteroposteriorly elongated 4th ventricle and hypoplastic vermis was demonstrated (Fig. 1). Fetal movements appeared decreased and the kidneys appeared enlarged for gestation. The parents decided to continue the pregnancy and a female weighing 2.5 kg, born out of vaginal delivery at 39 weeks was severely apneic and expired. Autopsy and genetic analysis was denied by the parents.

Case 2 was a 12 weeks pregnant lady, second gravida, non consanguineous marriage with previous missed miscarriage at 7 weeks gestation. On the routine NT scan, occipital encephalocele, polydactyly and cystic, enlarged

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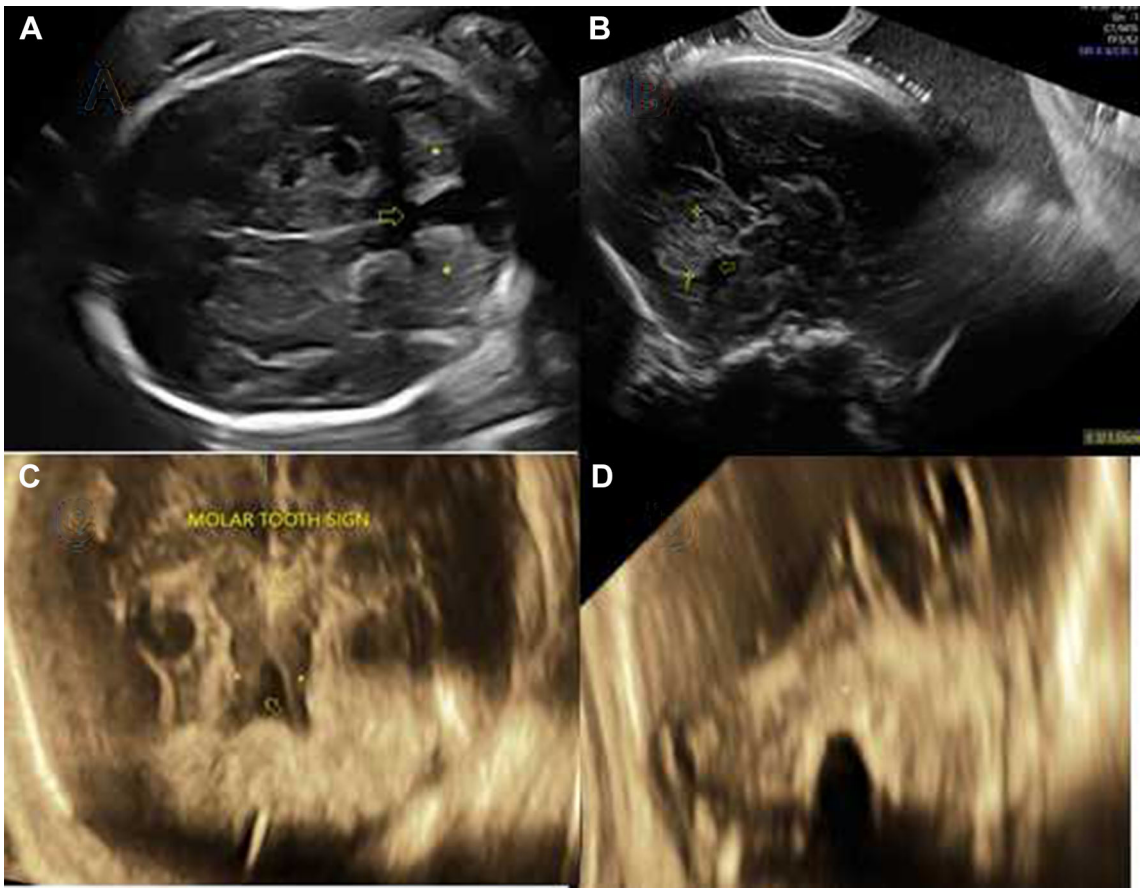

Fig. 1 (**a**) Axial view showing abnormally shaped and open 4th ventricle (arrow) and widely separated cerebellar hemispheres (aesterisk). (**b**) Sagittal image showing hypoplastic vermis with abnormally shaped 4th ventricle (arrow). (**c**) Molar tooth sign comprising of elongated and thickened superior cerebellar peduncles (aesterisk) and anteroposteriorly elongated 4th ventricle (arrow) and deep interpeduncular fissure. (**d**) Coronal view showing steeply vertically oriented cerebellar folia

kidneys were noted which raised a suspicion of Meckel Gruber syndrome (MGS) or Joubert syndrome related ciliopathy (Fig. 2). The parents opted for termination of pregnancy. The genetic analysis suggested homozygous four base pair duplication in exon 1 of TCTN1 gene. Both parents were heterozygous for c.26_29dupTCCT (chr12: 111052013_111052016dupTCCT). The variant has been known to cause frameshift and premature truncation of the protein 72 aminoacids downstream to codon11 (p. Val11-ProfsTer72) in Joubert syndrome 13 [2].

Due to advance ultrasound equipment and improved expertise, JSRD is now diagnosable on prenatal ultrasound and its pathognomonic sign is molar tooth sign (MTS). Though there are reports describing increased intracranial

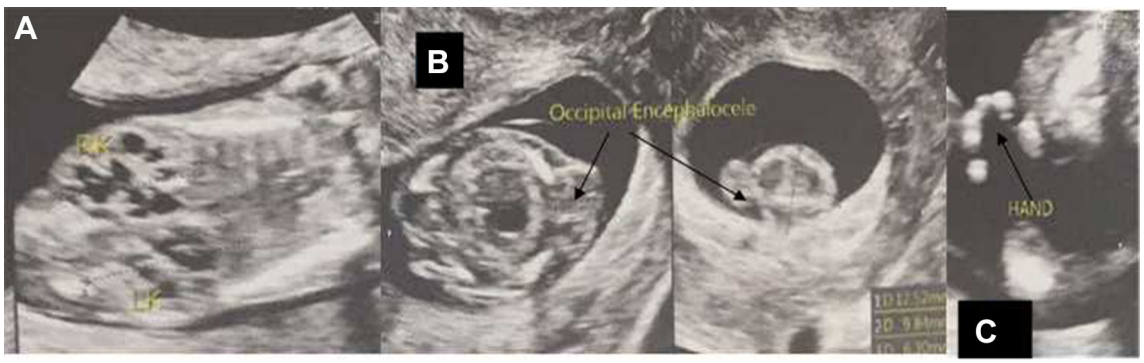

Fig. 2 Case 2 (**a**) cystic and enlarged kidneys (**b**) occipital encephalocele (**c**) postaxial polydactyly in hand

translucency, dilated posterior fossa and molar tooth appearance of cerebellar peduncles in first trimester [4], these are not always demonstrable in low risk pregnancies. In such cases, signs of ciliopathy like that described in case 2 (cystic kidneys, encephalocele and polydactyly) which overlap in many ciliopathies (e.g. MGS) can prompt inclusion JSRD in differential diagnosis. Genetic testing in such cases can help to reach for a specific diagnosis. TCTN1 forms a complex with multiple ciliopathy proteins associated with Meckel–Gruber and Joubert syndromes which explains the overlapping sonological features presented in Case 2 [5]. Thus, in a low risk pregnancy, signs of ciliopathy, abnormal 4th ventricle, hypoplastic vermis and molar tooth sign, should prompt a fetal medicine specialist to suspect JSRD.

Compliance with Ethical standards

Ethical Approval All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the 1975 Declaration of Helsinki, as revised in 2008.

Informed consent Patients' informed consents were obtained.

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