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ORIGINAL ARTICLE

Prenatal Ultrasonographic Molar Tooth Sign: Case Reports and Review of Literature

Rinshi Abid Elayedatt[1] · **Basil Mathew**[1] · **Vivek Krishnan**[1]

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Abstract Joubert Syndrome and Related Disorders (JSRD) refers to all disorders presenting as "molar tooth sign" (MTS) on brain imaging. Fetuses with JSRD present with relatively nonspecific signs on prenatal ultrasound varying from increased nuchal translucency, enlarged cisterna magna, cerebellar vermian agenesis, occipital encephalocele, ventriculomegaly, renal disease and polydactyly. However, the hallmark sign in the diagnosis is MTS and MRI is the imaging modality of choice. We report two cases in which MTS was identified on prenatal ultrasound at 22 and 21 weeks (wk) of gestational age respectively. The other prenatal findings on ultrasound included polydactyly and anteroposteriorly enlarged 4th ventricle and vermian hypoplasia in both, and, aortic stenosis evolving to hypoplastic left heart in the former. Prenatal MRI was not done. Amniocentesis was done in the one with associated cardiac anomaly which was reported as normal. In both cases, the couple opted for termination of pregnancy and declined fetal autopsy and further mutation analysis. Only a few cases of JSRD diagnosed on prenatal ultrasound, have been reported. Due to the autosomal recessive inheritance (with 25% recurrence) JSRD has to be differentiated from Dandy-Walker malformation and cranio-cerebello-cardiac syndrome. As definitive prenatal genetic testing may not be conclusive in Joubert syndrome (JBTS) due to the large number of pathogenic variants and genetic heterogenicity, the ability to identify the MTS sonographically early provides a valuable adjunct to prenatal diagnosis.

Keywords Prenatal diagnosis · Molar tooth sign · Fetal ultrasound · Joubert syndrome · JSRD

Introduction

Joubert syndrome (JBTS; OMIM 213,300) is a rare, autosomal recessive disorder belonging to the group of ciliopathies [1] and was first described by Marie Joubert et al. in 1969 in four siblings [2]. It is characterized by intellectual disability, hypotonia, ataxia, tachypnea/apnea, and abnormal eye movements [3]. Other associations reported are psychomotor delay, and variable multi-organ involvement, mainly retinal dystrophy, renal involvement and congenital liver fibrosis [4].

JSRD shows a pathognomonic midbrain-hindbrain malformation, which on fetal MRI consists of hypoplasia of the midline cerebellar vermis and a characteristic appearance resembling a molar tooth on axial imaging at the pontomesencephalic level, called the molar tooth sign (MTS). This is characterised by an abnormally deep interpeduncular fossa and enlarged superior cerebellar peduncles (SCP) [5].

Prenatal diagnosis is rare, and currently, a diagnosis is commonly made after birth. A few cases of prenatal diagnosis by ultrasonography have been made, but these are likely to be misdirected because of nonspecific features that also manifest in other conditions like, DWM, cranio-cerebello-cardiac syndrome, and so on [6]. In this background, we report two cases of MTS detected on prenatal ultrasound.

✉ Rinshi Abid Elayedatt
rinshielayedatt81@gmail.com

[1] Division of Fetal Medicine and Perinatology, Amrita Institute of Medical Sciences and Research Centre, Kochi, Kerala 682041, India

Case Report

CASE 1—A 25-year-old second gravida with a previous healthy child, was referred to our perinatology department for a second opinion for ill-defined CSP and vermian defect at 22 wks of gestation. She denied consanguinity with her husband and had no history of teratogen exposure during or immediately preceding pregnancy. On ultrasound examination, a singleton viable intrauterine pregnancy was detected. Fetal biometric measurements were consistent with the period of gestation with bilateral prominent cerebral lateral ventricle (right- 9.4 mm, left- 9 mm), 4th ventricle index 0.7, hypoplasia of cerebellar vermis, vermian area of 0.5cm^2 (< 5th centile for the period of gestation), a deep cleft between prominent cerebellar peduncles and deficiency of the dorsal midbrain in the midline, the MTS. Bilateral postaxial polydactyly in both hands and feet were detected with ectrodactyly in the right hand and foot. There was syndactyly involving the index and middle finger of the right hand (Fig. 1). Fetal echocardiography revealed aortic stenosis (AS) with evolving hypoplastic left heart (HLHS), Amniocentesis for microarray was normal. A presumptive diagnosis of JSRD ciliopathy was made on demonstration of MTS and postaxial polydactyly. On genetics consultation, a Fetal MRI and panel testing for Joubert syndrome were advised. The couple opted out of further testing. Parental counseling was done and the family opted for pregnancy termination. Postnatal clinical examination revealed a female fetus weighing 520 g with postaxial polydactyly in both hands and left foot. A fetal autopsy was declined by the couple.

CASE 2—A 29-year old woman was referred in her second pregnancy at 21wks of gestation for a second opinion on DWM. The couple was non-consanguineous with a previous normal child. Ultrasound showed bilateral prominent cerebral lateral ventricles of 9 mm each, 4th ventricle index was 0.66 with the separation of the superior cerebellar peduncles, consistent with the 'molar tooth' sign (Fig. 2), and vermian area of 0.6cm^2(< 5th centile for the period of gestation). There was also left-sided cleft lip & palate and postaxial polydactyly in both feet. Subsequently, amniocentesis and a genetics consultation were advised but the pregnancy was terminated and the autopsy was declined.

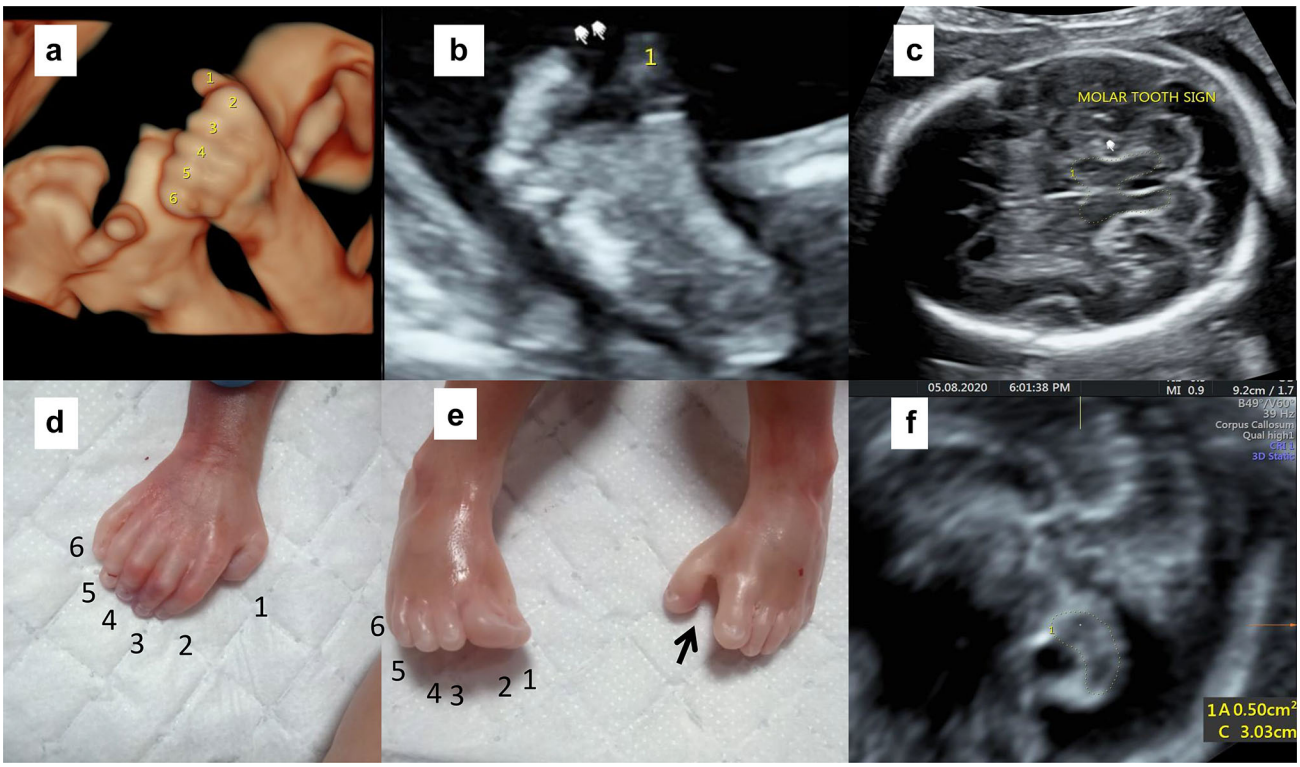

Fig. 1 **a** 3D surface rendering of hand showing polydactyly. **b** A 2D grayscale imaging of foot showing ectrodactyly. **c** An axial section of fetal head through the level of superior cerebellar peduncle showing MTS. **d** Postnatal picture showing polydactyly. **e** Postnatal picture showing bilateral polydactyly in both feet with syndactyly between the great toe and second toe on the right side and ectrodactyly in the left foot. **f** A 3D reconstructed sagittal section from an axial plane acquisition showing a vermian area < 5th centile for GA (vermian hypoplasia)

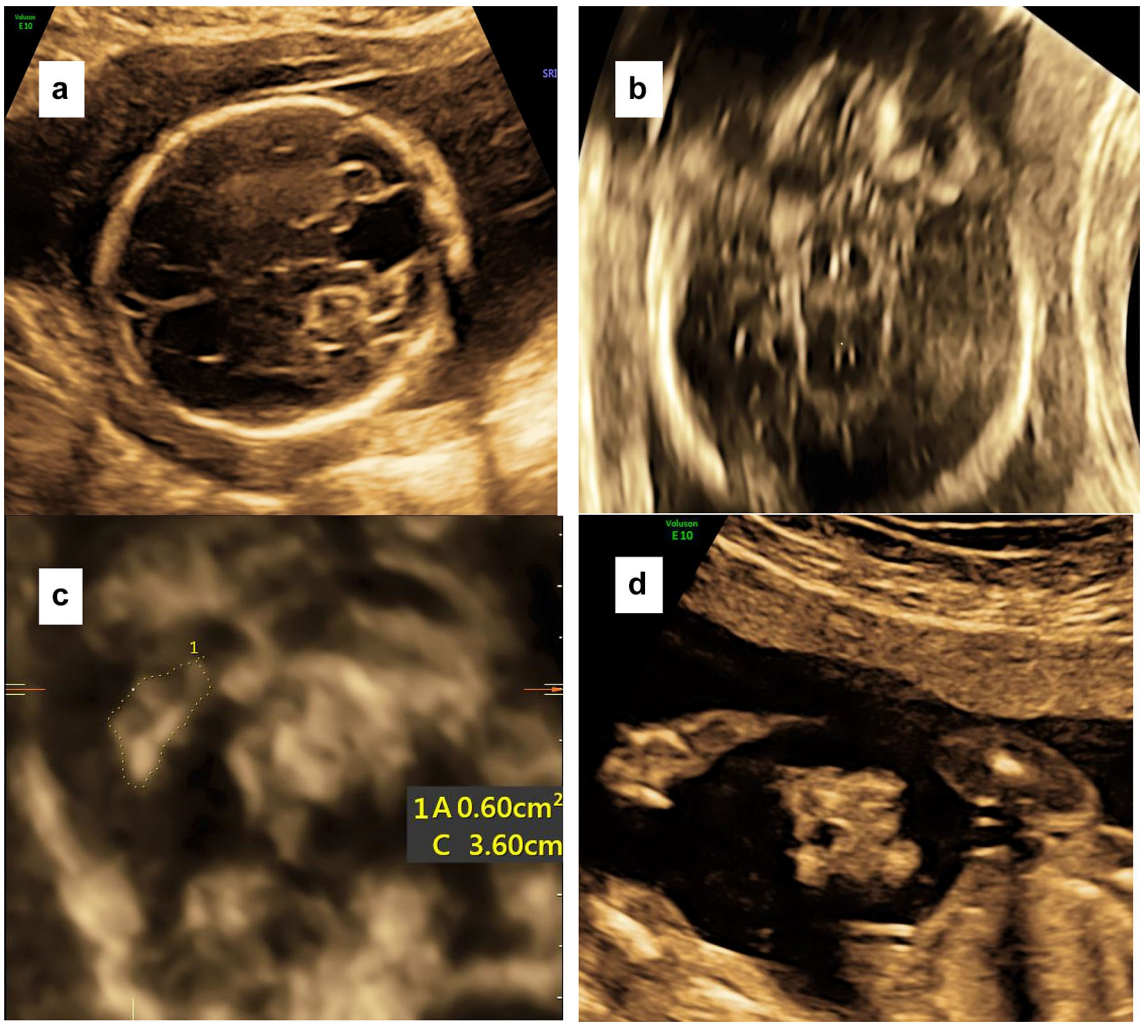

Fig. 2 **a** An axial section of the fetal head through the suboccipito-bregmatic plane, showing abnormal posterior fossa with dilated cisterna magna and an open 4th ventricle. **b** Coronal imaging of the fetal head showing the MTS. **c** 3D reconstructed sagittal section from an axial plane acquisition showing a vermian area < 5th centile for GA (vermian hypoplasia). **d** Coronal view of the face showing unilateral cleft lip

Discussion

JBTS was initially described as a triad of cerebellar vermis hypoplasia, oculomotor apraxia and intermittent hyperventilation [7]. JSRD include JBTS (also known as Joubert–Boltshauser syndrome), as well as other related conditions showing the pathognomonic MTS, such as cerebello–oculo–renal syndrome, Dekaban–Arima syndrome, COACH syndrome, Varadi–Papp syndrome (orofaciodigital type-VI), Malta syndrome, and a minority of cases with Senior Loken syndrome [8].

Francesco et al. in 2010 made a nosology to divide JSRD into 6 clinical subtypes, including pure JBTS, JBTS with ocular defect, JBTS with renal defect, JBTS with oculorenal defects, JBTS with hepatic defect, and JBTS with orofaciodigital defects [9]. Each of the subtypes corresponded to different genotypes, and 1 specific gene mutation caused different subtypes [1]. Our cases belonged to the last subtype. In 2012, Paprocka and Jamroz [10] divided JBTS into four different subgroups. The estimated incidence of JSRD ranges between 1/80,000–1/100,000 live births [4]. Only a few cases have been described prenatally [8].

Prenatal sonographic findings in fetuses with JSRD are relatively nonspecific and include increased nuchal translucency, enlarged cisterna magna, cerebellar vermian agenesis midbrain defects, agenesis of the corpus callosum, occipital encephalocele, ventriculomegaly, flat sulcus, polymicrogyria and other malformations of cortical development, retinal colobomata, hypoplastic phallus, renal cysts, and polydactyly [11, 12]. Our case showed vermian hypoplasia as evident from a vermian volume of < 5th centile for GA in both cases. JSRD are extremely pleiotropic conditions and other varied manifestations

reported are, median line defects (tongue or oral soft tumors, multiple frenula, cleft lip and/or palate, notched upper lip), situs inversus and congenital heart defects [13]. Congenital heart defects are not a typical association with JSRD but have been reported occasionally as stated by Emlali et.al in 2007 [14]. Our case also showed congenital heart disease (AS evolving to HLHS) in one case which is a rare association as per literature. Cleft lip was also seen in one of our cases. The two different kidney manifestations described are prenatal cystic dysplasia and juvenile nephronophthisis [15]. Saraiva et al. reported renal abnormalities in 30% of cases [16]. However, both our cases did not have any renal involvement. It could be due to the fact that renal disease may be progressive and can be detected in postnatal life as quoted by Ramadevi et al. in 2020 [17] or because it is associated more with certain mutations and absent in certain mutations and, consequently, normal renal imaging in utero cannot be used for reassurance[18]. Prenatal ultrasonography is considered a poor predictor of kidney involvement in JBTS [5]. The most reported skeletal abnormality is postaxial polydactyly (8–16%) [10]. Bilateral postaxial polydactyly was noted in both our cases. Also, associated ectrodactyly was noted unilaterally in both the left hand and foot and syndactyly was noted in between the index and middle finger of the left hand and between the great toe and the 2nd toe of the right foot. Scoliosis may appear with age [10].

The typical presentations of patients with JBTS are postnatal hypotonia, severe delay in gross motor milestones in early infancy and later ataxia [19]. A variable clinical course with rare mild forms has also been reported and most children with this condition surviving infancy and reaching adulthood have also been described by Kareena et al. [12]. As per the JBTS diagnosis revised criteria, the three cardinal features in diagnosis are intellectual disability, hypotonia, and MTS [17]. All cases of cerebellar vermis hypoplasia or dysgenesis without the MTS on MRI are to be considered as the differential diagnosis: DWM, X-linked cerebellar hypoplasia, congenital disorders of glycosylation, cranio-cerebello-cardiac syndrome, the pontocerebellar hypoplasia/ atrophies, oro-facial-digital syndromes II and III and Meckel-Gruber syndrome [20].

The characteristic finding common to all forms of JSRD includes a triad of malformations causing MTS on axial MRI: (i) a deepened interpeduncular fossa with a narrow isthmus, (ii) thickened, elongated and horizontally oriented SCP as a result of the absence of normal decussation and (iii) variable degree of vermian hypoplasia [5]. Saleem and Zaikai measured the ratio of AP diameters of interpeduncular fossa to midbrain/isthmus, and the ratio of the AP to transverse diameters of the 4v in axial sections at the pontomesencephalic junction on MRI in a 22wks fetus, and all measurements were significantly higher in JSRD fetuses [21].

The first case of JBTS based on sonographic MTS on 2D ultrasound was reported by Pugash et al. 2011 [5] at 20 + 6wks gestation. The earliest prenatal detection of MTS on fetal MRI was at 17–18 wks by Saleem et al. in two unrelated fetuses with history of siblings with JSRD [22] in 2011. The second case reported on the detection of the MTS on sonography was in 2014 provided still earlier depiction at 18 + 3wks, although a definite diagnosis could not be made then, but was strongly suspected of a midbrain anomaly with a midbrain cleft separating the cerebellar peduncles, suggesting an MTS [11]. Quarello et.al in 2009 described the use of three-dimensional (3D) ultrasound to identify the MTS in two fetuses with enlarged cisterna magna prior to fetal MR diagnosis [23]. However, MTS reported earliest in pregnancy on ultrasound was in the first trimester by Quarello in 2016 in a case with a previous history of termination for vermian dysplasia and hyperechoic kidneys as features of JSRD [24]. The MTS was first identified prenatally by MRI [9], and by ultrasound [5] in the 3rd trimester. Most cases are identified by features of a vermian abnormality or with a positive family history [25]. Other indirect signs are abnormal anteroposteriorly elongated 4v morphology when compared to latero-lateral measurement in axial imaging [12], enlarged and quadrangular 4v, and flat fastigium on sagittal views [26]. Biometry and lack of the primary and secondary fissures [12], a 'keyhole' communication between the 4v and the cisterna magna at 20 weeks or the absence of the cerebellar vermis at 22 weeks associated with a smooth cortex and ventriculomegaly [27] also denote vermian dysplasia. Before 18 weeks when the cerebellar vermis is still developing and when the vermis may not yet cover the 4v, it may be difficult to separate normal from abnormal resulting in a potential false-positive diagnosis [28]. Autopsy studies in JSRD have shown reduction or absence of decussation of the SCP, absence of decussation of the medullary pyramids (corticospinal tracts), and severe vermian hypoplasia [29]. Pugash et al. [5] and Spampinato et al. concluded that the lack of superior cerebellar commissural fibers in JBTS accounted in part for the classic MTS observed in patients with the disorder [30]. The sonographic detection of the MTS, therefore, expands the potential for early diagnosis of Joubert syndrome and related disorders.

To date, pathogenic variants in 34 genes are known to cause JBTS; 33 of these are autosomal recessive and one is X-linked recessive [20] which is the subtype 10 (JBTS10) caused by OFD1 mutations [31]. A molecular diagnosis of JBTS can be established in about 62%-94% of individuals with a clinical diagnosis. Due to autosomal recessive inheritance, there is a 25% chance of being affected, a 50%

chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Whole exome sequencing significantly increases the yield for molecular diagnosis [20, 31].

Once the pathogenic variants have been identified in an affected family member, carrier testing for at-risk family members, prenatal testing for pregnancies at high risk, and pre-implantation genetic testing are possible. For pregnancies known to be at increased risk for JBTS, prenatal diagnosis by ultrasound examination with or without fetal MRI has been successful [20]. Given the fact that these groups of disorders are genetically heterogeneous [32], causative genes of Meckel–Gruber syndrome, MKS3, have also been found recently in patients with classical JBTS and CORS. And, as not all the causative genes are identified, the molecular prenatal diagnosis in JSRD is a challenge and only for research purposes. Amniocentesis and chorionic villus sampling (CVS) are not helpful in JSRD because DNA and protein markers for most types are not widely available on a clinical basis. It has been reported that currently identified genes account for an estimated 50% of causative mutations in JSRD [33]. To date, diagnostic genetic testing is available only for a few genes, while selected laboratories offer molecular testing of known genes on a research basis [9].

The 5-year survival rate in JBTS is about 50% [10]. Many of them have a life expectancy below one year. The remainder being neurologically impaired, prenatal diagnosis is necessary and prenatal counseling regarding the generally poor prognosis is extremely important especially in those with a positive family history [11].

Conclusion

Even with positive family history, a prenatal diagnosis through CVS/amniocentesis is possible only when the molecular defect has been previously identified in the proband. Despite molecular diagnosis in the proband, the prenatal diagnosis is still limited to a subset of families. To date, mutation screening of known genes have allowed the identification of mutations in only less than half of JSRD patients [34]. Hence in these families, a prenatal diagnosis of this severe disease may rely exclusively on imaging. A pre-implantation genetic diagnosis cannot be offered unless a molecular diagnosis has been made. Therefore, adding early prenatal sonography to the diagnostic tool kit for JBTS enhances management and counseling with regard to decisions for such cases at risk [11].

In India, as in many other countries, termination of pregnancy at a late gestation is not an available option. Early sonographic identification of MTS is, therefore, a valuable adjunct to prenatal diagnosis for couples who are known carriers of JSRD with 25% recurrence. This may also facilitate informed reproductive choices, reduce anxiety through reassurance, or enable preparations for the birth of an affected child.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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