CASE REPORTS
(CC BY-SA)

UDC: 618.33-07
https://doi.org/10.2298/VSP180906173K

Unilateral, frontal polymicrogyria and supratentorial white matter microcysts in fetus with Joubert syndrome and related disorders: Prenatal diagnosis with magnetic resonance imaging

Unilateralna frontalna polimikrogirija i mikrociste supratentorijalne bele mase fetusa sa znacima Joubert-ovog sindroma i povezanih bolesti: prenatalna dijagnoza magnetno rezonantnim snimanjem

Katarina Koprivšek*†, Mladen Bjelan*†, Miloš Lučić*†, Olivera Šveljo‡, Dejan Kostić§‖, Duško Kozić*†

University of Novi Sad, *Faculty of Medicine, ‡Faculty of Technical Sciences, Novi Sad, Serbia; Institute of Oncology of Vojvodina †Diagnostic Imaging Centre, Sremska Kamenica, Serbia; Univeristy of Defence, §Faculty of Medicine of the Military Medical Academy, Belgrade, Serbia; Military Medical Academy, ‖Institute of Radiology, Belgrade, Serbia

Abstract

Introduction. Joubert syndrome (JS) and related disorders (JSRD) are a group of rare multiple congenital anomalies syndromes, defined by complex midbrain-hindbrain malformation that creates the "molar tooth sign" (MTS) on brain imaging and may be associated with multisystem organ pathology, mainly of the retina, kidney, liver and skeleton. Prenatal diagnosis of JSRD has proved difficult because of the rarity of the condition and low sensitivity of ultrasound in evaluation of the fetal posterior fossa (PF) in most affected fetuses. **Case report.** We presented an unusual case of JSRD, pure Joubert syndrome with unilateral frontal polymicrogyria and supratentorial white matter microcysts, diagnosed by magnetic resonance imaging (MRI), in fetus aged 30 gestational weeks. The distinctive MRI features of this rare ciliopathy were confirmed by 6-months postnatal MRI study. The postnatal outcome was poor; clinical follow-up in the first 6 months of life confirmed hypotonia, developmental delay, oculomotor apraxia and seizures. **Conclusion.** To the best of our knowledge, fetal MRI features of the coexistence of pure JS and supratentorial abnormalities leading to postnatal cerebellar dysfunction and epilepsy, have never been reported before. Presented case may contribute to the broadening of the spectrum of sparse prenatal features of JRSD, and support the stand that presence of neuronal migration abnormalities can affect the clinical outcome and prognosis of fetuses with JSRD.

Key words:
cerebellum; congenital abnormalities; diagnosis, differential; epilepsy; neurologic manifestations; growth disorders; prognosis.

Apstrakt

Uvod. Joubert-ov sindrom (JS) i povezane bolesti (*Joubert syndrome and related disorders* – JRSD) su objedinjena grupa retkih urođenih, razvojnih sindroma srednjeg i zadnjeg mozga, sa tipičnim neuroradiološkim „znakom kutnjaka", često udruženih sa multiplim anomalijama mrežnjače, bubrega, jetre i skeleta. Prenatalna dijagnoza JSRD je teška zbog veoma retke pojavnosti oboljenja i niske senzitivnosti i specifičnosti fetalnog ultrazvuka u proceni struktura zadnje lobanjske jame. **Prikaz bolesnika.** Prikazali smo neuobičajen slučaj JSRD sa unilateralnom, frontalnom polimikrogirijom i mikrocistama supratentorijalne bele mase, detektovane magnetnorezonantnom snimanjem (MRI) fetalnog mozga u 30. gestacijskoj nedelji. Prenatalno uočena morfologija je potvrđena MRI snimkom na uzrastu od šest meseci. Kliničkim praćenjem u prvih šest meseci života, uočeno je pogoršanje od rođenja prisutnih epileptičnih napada i neuroloških simptoma tipičnih za JSRD (hipotonija, razvojno zaostanje, poremećaji pokretanja očnih jabučica). **Zaključak.** Prema saznanjima autora, do sada nije objavljen slučaj prenatalno postavljene MRI dijagnoze JS udruženog sa supratentorijalnim razvojnim poremećajima, postnatalno manifestovanih cerebelookularnom simptomatologijom i epilepsijom. Smatramo da prikazani slučaj može proširiti uzak spektar neuroradioloških prezentacija JSRD u fetalnom

Correspondence to: Mladen Bjelan, , University of Novi Sad, Faculty of Medicine, Institute of Oncology of Vojvodina, Diagnostic Imaging Centre, Put dr Goldmana 4, 21 204 Sremska Kamenica, Serbia. E- mail: mladen.bjelan@gmail.com

i postnatalnom periodu i potvrditi mogući uticaj udruženih poremećaja neuronalne migracije na prognozu i klinički ishod u fetusa sa JSRD.

Ključne reči:
mozak, mali; anomalije; dijagnoza, diferencijalna; epilepsija; neurološke manifestacije; rast, poremećaji; prognoza.

Introduction

Joubert syndrome (JS) and related disorders (JSRD) are a group of rare developmental, multiple congenital anomalies syndromes, defined by complex midbrain-hindbrain malformation that creates the "molar tooth sign" (MTS) on brain imaging, associated with variable multiorgan pathology, mainly of the retina, kidneys, liver and skeleton [1]. MTS describes hypoplastic vermis, narrow mesencephalic isthmus, deep interpeduncular fossa and thick horizontally placed superior cerebellar peduncles, with consequent midline cerebellar cleft and dysmorphic fourth ventricle. The incidence of JSRD ranges between 1/80,000 and 1/100,000 live births, although these figures may represent an underestimate [2]. JSRD is thought to be part of ciliopathies, genetic disorders related to the disturbed development of primary cilia, organelles that play key roles in the development and functioning of retinal photoreceptors, neurons, kidney tubules and bile duct. JSRD are transmitted in autosomal recessive fashion, with the exception of rare cases following X-linked recessive inheritance [3]. JSRD are clinically heterogenous; the characteristic features include hypotonia, ataxia, oculomotor apraxia, neonatal breathing dysregulation, developmental delay associated with variable multiorgan pathology. Based on the main organ involvement and genotype-phenotype correlates, JSRD are classified in six phenotypic subgroups: pure JS and JS with ocular, renal, oculorenal, hepatic and orofaciodigital defects [1, 2]. Since the first Gleeson`s report in 2004, only five cases of JRS associated with neuronal migration anomalies have been described, but only based on postnatal imaging and/or autopsy findings [4, 5]. A single case of white matter cyst in JRSD detected by magnetic resonance imaging (MRI) was described by Senocak et al. [5]. To the best of our knowledge, prenatal imaging features of JSRD were described in the literature in only 17 fetuses, mostly examined by ultrasound (US) [6]. In all available prenatal imaging studies, MTS was noted as isolated finding, not a single case in conjunction with associated brain anomalies. We describe a unique JSRD case and fetal MRI features of the coexistence of MTS, cortical polymicrogyria (PMG) and white matter cyst.

Case report

A 37-year-old woman, (grav 2, para 1) with no relevant medical history, was referred to MRI unit, at 30 weeks of uneventful pregnancy, after previous US exam, performed two weeks earlier, suggested forth ventricle enlargement and vermian abnormality, as isolated findings. Fetal brain MRI was performed on a 1.5 T unit, with 3mm thick half Fourier single-shot fast spin-echo (760/104/1; TR/TE/excitations) T2-weighted images obtained in 3 reference planes. The fetal MRI study revealed MTS with vermian hypoplasia, bilateral horizontally oriented and slightly thicker superior cerebellar peduncles and deepened interpeduncular fossa. The forth ventricle was enlarged, with abnormally rounded fastigium. There were no abnormal MRI findings related to the PF size and cerebellar hemispheres. In the right frontal lobe, the gyral/sulcal pattern was abnormal with multiple irregular, shallow, cortical infoldings, consistent with polymicrogyria. Frontal white matter was slightly hyperintense with scattered punctiform zones, with signal intensity resembling cerebrospinal fluid (CSF). There were no abnormal MRI findings related to the cortex in the left cerebral hemisphere (Figure 1. A–D). Based on a presumptive diagnosis of JSRD, the parents were counseled that the fetus had a complex rombencephalic developmental abnormality combined with neuronal migration disorder, with expected developmental impairments and high risk of epilepsy. Due to religious beliefs, the family decided to continue the pregnancy.

A male neonate was born at 39 gestational weeks, *via* uncomplicated spontaneous vaginal delivery. At first day of life neonate manifested apnea spells and hypotonia, accompanied with oculomotor apraxia and seizures in the form of epileptic spasms. Physical examination at birth was unremarkable. Karyotype testing was not revealed chromosomal abnormalities, unfortunately; genetic testing (whole exome sequencing and/or targeted panels) was not performed. Clinical assessments in the following six months of age, revealed aggravation of cerebello-occular symptoms, an increase in number of epileptic attacks and significant developmental delay. Despite neurological deterioration, infant's respiratory abnormalities progressively improved with age, disappearing around the beginning of fourth month. An abnormal interictal EEG was recorded at six months, with electroencephalographic pattern of focal frontal spikes in the right central frontal region.

Postnatal brain MRI scan was obtained at 6 months of life, by using the same system of the prenatal studies. The MRI study confirmed prenatal MRI diagnosis; MTS was present with pathognomonic appearance, associated with midline cerebellar cleft in the place of the hypoplastic vermis, deep interpeduncular fossa and enlarged, "bat wing" shaped fourth ventricle on the axial scans. The unilateral PMG in the entire right frontal lobe was confirmed, without the gradient of severity in anteroposterior (AP) direction. Supratentorial white matter had slightly increased signal intensity on T2 sequence, suggestive of mild myelination delay. Multiple white mater microcysts were detected in frontoparietal regions bilaterally, more pronounced on the right side. Supratentorial ventricles, corpus callosum, basal ganglia and the cerebral cortex in the left hemisphere, appeared to be normal (Figure 1, E–H).

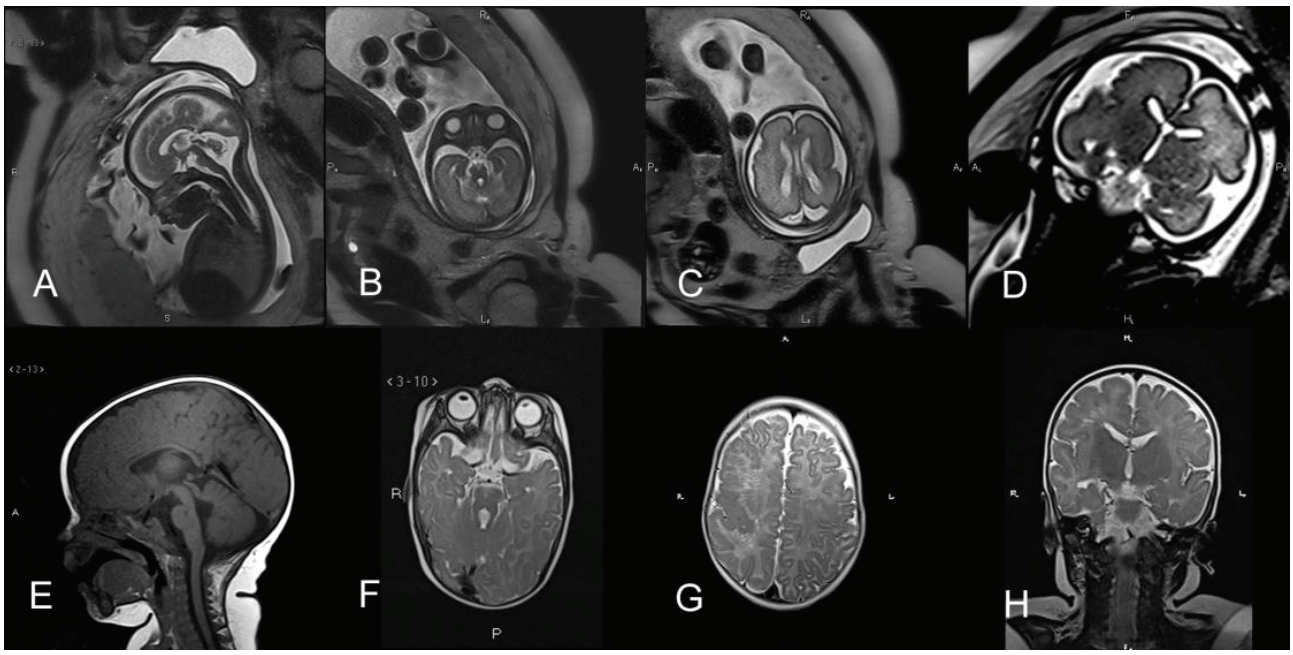

Fig. 1 – Fetal and postnatal magnetic resonance imaging features of Joubert syndrome and related disorders with unilateral polymicrogyria and white matter microcysts.

Midline sagittal T2W image (A) in a 30-week old fetus shows vermian hypoplasia, an enlarged forth ventricle with abnormally rounded fastigium, and horizontalized and thickened superior cerebellar peduncles. Axial T2W image (B) at the level of pontomesencephalic junction reveals deep interpeduncular fossa and dysmorphic fourth ventricle suggestive of MTS. Axial T2W scan, at a supraventricular level (C), shows the abnormal gyral and sulcal pattern in the right frontal lobe, consistent with polymicrogyria. Note the hyperintense signal of the supratentorial white matter, with scattered punctiform zones, resembling cerebrospinal fluid signal intensity (F). Postnatal brain MRI in sagittal (E), axial (F, G) and coronal planes (D), obtained at 6 months of life show presence of dysmorphic rhombencephalon, unilateral, frontal polymicrogyria, white matter microcysts and delayed myelination.

Discussion

Prenatal diagnosis of JSRD has proved difficult because of the rarity of the condition, the US limitations in evaluation of the fetal posterior fossa and the relatively nonspecific US features reported in most affected fetuses [6, 7]. The prenatal diagnosis of JSRB could be suspected in all fetuses with US findings of abnormal cerebellar vermis, either as isolated findings or associated with additional central nervous system or multisystem malformations. On the US scans of the fetal posterior fossa, MTS frequently remains unrecognized or overlooked. In our opinion, low sensitivity of US in detection of MTS could be caused by technique's inability to obtain clear transversal posterior fossa scans, perpendicular to clival line at the level of the pontomesencephalic junction.

Although MRI overcomes disadvantages of US in evaluation of the fetal rhombencephalon, its sensitivity in JSRD has not been systematically evaluated. Fetal MRI reports of JSRD are scarce and they do not reflect disease heterogeneity, describing only posterior fossa abnormalities. MTS was not detected in two of eight reported cases. Doherty et al. [8] reported only vermian hypoplasia, without being able to demonstrate MTS. We agree with current opinions that for fetal diagnosis of MTS, all pathological elements should be visualized on MRI scans and that coronal planes are dedicated for visualization of cerebellar cleft, axial planes for midbrain isthmus and fourth ventricle [9]. But, according to our study, fetal morphology of horizontalized and thickened superior cerebellar peduncle is better displayed in sagittal rather than in recommended axial plane.

It is not expected that MTS, as the neuroradiological hallmark of JSRD, changes its appearance, but according to Porreti et al. [10], rhombencephalic abnormalities could exhibit different degrees of hypoplasia or dysplasia (mild, moderate, severe). This can partially explain why mild forms of JSRD could be overlooked or misdiagnosed as isolated vermian hypoplasia or malformation from the Dandy-Walker spectrum. In order to enhance fetal MRI accuracy in diagnosing of JSRD, Saleem and Zaki [11] proposed quantification of morphologic changes at pontomesencephalic junction by measurements of AP diameters of interpeduncular fossa, isthmus and forth ventricle and calculation of the ratio of AP diameters. The reliability of the obtained parameters is not statistically verified. It is calculated in three cases, and we still do not know the normative values for healthy fetuses at different gestational age.

Although prenatally diagnosed infratentorial malformations in JSRD have been described sporadically in the radiological literature, coexisting supratentorial structural brain abnormalities were not reported at all. [8, 11]. It is possible that lack of data on supratentorial abnormalities is caused by moderate sensitivity of fetal MRI in detecting disorders at an early gestational age (less than 26 gestational weeks) and low conspicuity of the supratentorial abnormalities in JSRD

affected fetuses (e.g. hippocampal malrotation, mild midline defects, hypothalamic hamartomas and malformations of cortical development). According to our best knowledge, this is the first reported case of fetal JSRD with neuronal migration anomalies as associated supratentorial malformation [12]. Even though, our case is specific not only due to PMG being unilateral and exclusively localized in the frontal lobe, which sets it apart from two previously published pediatric cases of JS with bilateral, mostly perysilvian malformation, but due to the fact, that it is associated with delayed myelination and white matter cysts [13]. It is also of note, that the prenatally diagnosed right frontal lobe lesion represents a focal epileptic zone in concordance with postnatal seizure semiology and EEG findings. Unfortunately, clinical and imaging diagnosis in our patient was not confirmed by genetic/molecular data. According to Vilboux et al. [14], causative gene could be identified in 94% of JSRD patients, with significant genotype/phenotype correlation and high percent of unique potentially pathogenic gene variants linked to unusual clinical/imaging JSRD cases.

Conclusion

Presented case supports the claim that JSRD should be considered as a highly heterogenous malformation, with a variable degree of severity and clinical outcome. The prenatal MRI has to be mandatory part of prenatal diagnostic algorithm in fetuses with suspected JSRD, to confirm posterior fossa anomalies and detect the presence of associated supratentorial abnormalities. Presented MRI features contribute to the broadening of the prenatal neuroimaging spectrum, and could aid in prenatal prediction as to which JSRD affected fetus could develop epileptic seizures in the postnatal period.

REFERENCES

1. *Brancati F, Dallapiccola B, Valente EM.* Joubert syndrome and related disorders. Orphanet J Rare Dis 2010; 5: 20.
2. *Parisi MA, Doherty D, Chance PF, Glass IA.* Joubert syndrome and related disorders (OMIM 213300). Eur J Hum Genet 2007, 15: 511–21.
3. *Coene KL, Roepman R, Doherty D, Afroze B, Kroes HY, Letteboer SJ,* et al. OFD1 is mutated in X-linked Joubert syndrome and interacts with LCA5-encoded lebercilin. Am J Hum Genet 2009, 85(4): 465–81.
4. *Gleeson JG, Keeler LC, Parisi MA, Marsh SE, Chance PF, Glass IA*, et al. Molar tooth sign of the midbrain hindbrain junction: occurrence in multiple distinct syndromes. Am J Med Genet A 2004, 125A(2): 125–34 ; discussion 117.
5. *Senocak EU, Oğuz KK, Haliloğlu G, Topçu M, Cila A.* Structural abnormalities of the brain other than molar tooth sign in Joubert syndrome-related disorders. Diagn Interv Radiol 2010; 16(1): 3–6.
6. *Zhu L, Xie L.* Prenatal diagnosis of Joubert syndrome: A case report and literature review. Medicine (Baltimore) 2017; 96(51): e8626.
7. *Iskender CT, Tarim E, Alkan O.* Joubert syndrome and related disorders, prenatal diagnosis with ultrasound and magnetic resonance imaging. J Turk Ger Gynecol Assoc 2012; 13(2): 135–8.
8. *Doherty D, Glass IA, Siebert JR, Strouse PJ, Parisi MA, Shaw DW,* et al. Prenatal diagnosis in pregnancies at risk for Joubert syndrome by ultrasound and MRI. Prenat Diagn 2005; 25(6): 442–47.
9. *Poretti A, Snow J, Summers AC, Tekes A. Huisman TAGM, Aygun N,* et al. Joubert syndrome: neuroimaging findings in 110 patients in correlation with cognitive function and genetic cause. J Med Genet 2017; 54(8): 521–9.
10. *Poretti A, Huisman TA, Scheer I, Boltshauser E.* Joubert syndrome and related disorders: spectrum of neuroimaging findings in 75 patients. AJNR Am J Neuroradiol 2011; 32(8): 1459–63.
11. *Saleem SN, Zaki MS.* Role of MR imaging in prenatal diagnosis of pregnancies at risk for Joubert syndrome and related cerebellar disorders. AJNR Am J Neuroradiol 2010; 31(3): 424–9.
12. *López Ruiz P, García García ME, Dicapua Sacoto D, Marcos-Dolado A.* Uncrossed epileptic seizures in Joubert syndrome. BMJ Case Rep 2015; 2015. pii: bcr2014207719.
13. *Nagaraj UD, Hopkin R, Shapiro M, Kline-Fath B.* Prenatal and postnatal evaluation of polymicrogyria and bend heterotopia. Radiol Case Rep 2017; 12(3): 602–5.
14. *Vilboux T, Doherty DA, Glass IA, Parisi MA, Phelps IG, Cullinane AR,* et al. Molecular genetic findings and clinical correlations in 100 patients with Joubert syndrome and related disorders prospectively evaluated at a single center. Genet Med 2017; 19(8): 875–82.

Received on September 6, 2018.
Revised on October 9, 2018.
Accepted on October 12, 2018.
Online First October, 2018.