



CASE REPORT

Joubert Syndrome-Related Disorder: Report of Six Cases and Literature Review

Kareem Mohamed*¹ and Belal Awwad¹

1. Department of Radiology, KFCH, Jazan, Saudi Arabia

* **Corresponding author.** Contact: kareemam@moh.gov.sa

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Abstract

Background: The prevalence of Joubert syndrome in most Arab countries is unknown, yet it has an estimated prevalence of 1/5,000 live births in the United Arab Emirates. Geographic areas where consanguinity represent high percentage (40-60%) of marriages, similar prevalence might be expected.

Findings: In Case 1 (Figure 2), we found the neuroimaging features of classic JS in the form of MTS and mild vermian hypoplasia. In Case 2, (Figure 3) the imaging features included the appearance of persistent Blake's pouch cyst. In Case 3 (Figure 4), we found the additional imaging features of Dandy Walker malformation. Case 4 (Figure 5) revealed classic JS features of the posterior fossa but with partial dysgenesis of the corpus callosum. In Case 5 (Figure 6), we found the unidentified JSRD that would help in recognizing the prognosis and clinical outcome. Case 6 (Figure 7) demonstrated the associated small posterior fossa, dysplastic superior vermis, occipital meningocele, platybasia and compression of the cervicomedullary junction.

Conclusion: First, these cases emphasize the importance of raising the clinical suspicion in this diagnosis in newborns presenting with abnormal respiration. Second, it is essential for the radiologist to look for other posterior fossa anomalies in case of finding an entity before jumping to a certain or specific syndrome. Additionally, follow-up cases of hydrocephalus should be thoroughly searched again for congenital malformations.

Limitations: Our main limitation is the lack of genetic study of the presented cases due to outsourcing. That could help better classification of the Joubert syndrome in children.

Introduction

Joubert syndrome (JS) is a rare autosomal-recessive syndrome that manifests in the midbrain and hindbrain, with symptoms mainly including irregular neonatal breathing, ataxia, oculomotor apraxia, and hypotonia (1). It was first described by Joubert et al. in 1969 as a syndrome of episodic hyperpnea, abnormal eye movements, ataxia, and mental retardation (2).

The prevalence in most Arab countries is unknown, yet there is an estimated prevalence of 1 in 5,000 live births in the United Arab Emirates (3). In geographic areas where consanguinity represents a high percentage (40-60%) of marriages, a similar prevalence might be expected.

Joubert syndrome-related disorders (JSRDs) are a large group that includes, in addition to posterior fossa anomalies, craniofacial deformities and multiorgan abnormalities

such as liver fibrosis, retinopathy, nephronophthisis (NPH), polydactyly and cystic renal disease. (4)

A new classification of JSRD was introduced in 2008 based on additional secondary organ manifestations, which primarily includes three organs (eye, kidney, and liver) and resulted in six subgroups as follows: (1) pure JS; (2) JS associated with retinopathy; (3) JS with renal involvement (either NPH or cystic dysplastic kidneys); (4) cerebello-oculo-renal syndromes: comprising JS with both retinal and renal involvement; (5) cerebellar vermis hypoplasia, oligophrenia, ataxia, coloboma and hepatic fibrosis (COACH) syndrome; and (6) oral–facial–digital (OFD) VI syndrome. (5)

Molar tooth sign (MTS) (Figure 1) results from a malformation of the midbrain and hindbrain connection characterized by thickening and elongation of the superior cerebellar peduncle (SCP), deep interpeduncular fossa (IF), and narrowing of the pontomesencephalic isthmus. (5)

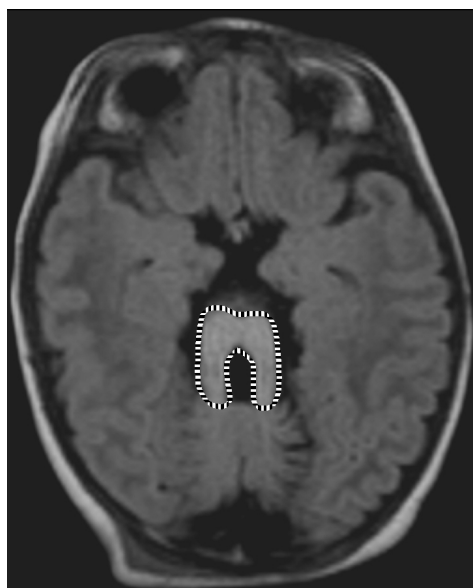


Figure 1. Midbrain region in axial FLAIR image with molar tooth sign.

Maria et al. (6) reported the MTS as the characteristic neuroimaging finding of “pure” JS. However, MTS is seen also in other syndromes. MTS and vermis hypoplasia (VH) result in distortion and enlargement of the fourth ventricle, and together are essential manifestations of JSRD. Therefore, MTS and VH are considered mandatory diagnostic findings in neuroimaging of JSRD. (1)

Although MTS and VH have been well described, few studies demonstrate their anatomic variability. A recent study conducted by Poretti et al. (7) on 110 patients found complete agenesis of the cerebellar vermis in 1% of the cases, rendering this entity very rare.

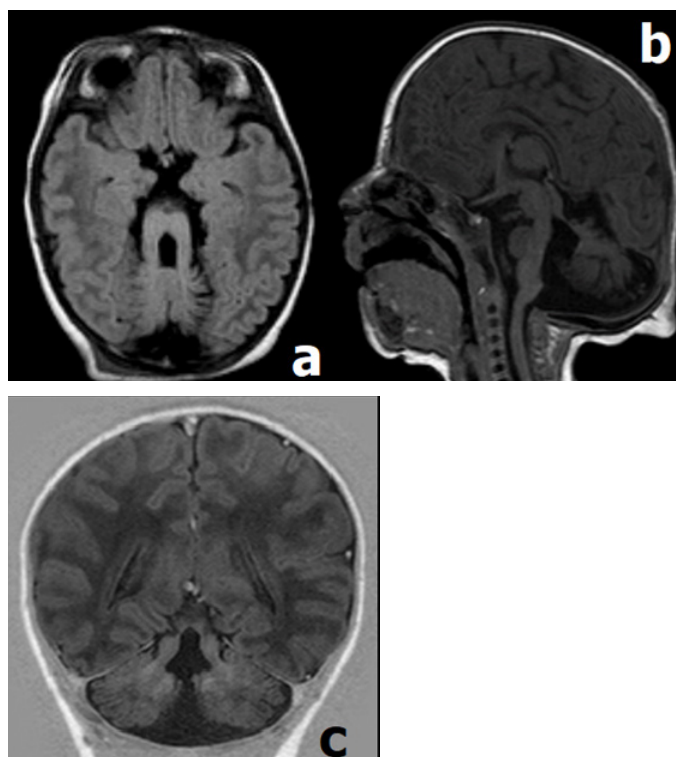
Here, we report six cases of Joubert syndrome and related disorders that were presented to our radiology department and referred from the outpatient clinic, emergency room (ER), and neonatal intensive care unit (NICU).

Case 1

A 2-week-old baby with mild dysmorphic features, low-set ears, and a low hairline was following in the genetic outpatient clinic. The baby was brought from home with a fever and a history of loose motions for two days, decreased breathing, and blue lips. In the ER, the pediatrician noticed two attacks of apnea. On examination, the temperature was 38.3 centigrade, and the patient looked dehydrated with a dry mouth and skin. CNS examination: active, with mild hypertonia, anterior fontanelle (AF): depressed. CVS: normal heart sounds, no murmur. Chest: clear, mild tachypnea. Abdomen: soft, lax. Blood CS: no growth. CSF CS: result in no growth. Urine culture: few pus cells, no organism seen.

The pediatric team consulted a pediatric neurologist for the recurrent attacks of apnea and an MRI examination was decided.

The diagnosis based on imaging findings (Figures 2a-c) was of classic Joubert syndrome.



Figures 2a-c. (a) Axial FLAIR image of the brain shows MTS of the midbrain with dysmorphic superior vermis. (b) Sagittal T1WI of the brain shows narrowing of the pontomesencephalic isthmus, hypoplastic vermis and prominent retrocerebellar CSF space. (c) Coronal T1 IR sequences shows thickening of the superior cerebellar peduncles.

Case 2

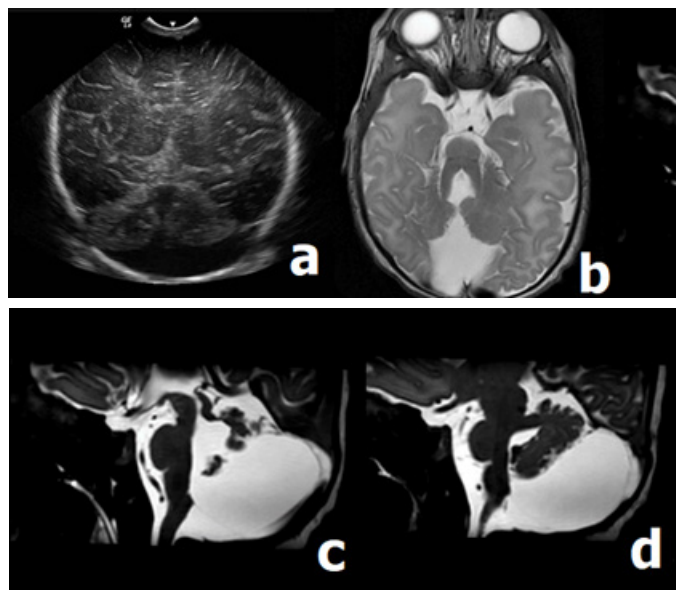
A live full-term baby boy, product of normal vaginal delivery (NVD), mother G8P7A1 with a history of fever. The mother was admitted to the hospital and received antibiotics due to urinary tract infection with fever.

On examination, baby grunting and distress on nasal cannula. Sat.: 96, Pulse 96. CNS: Baby active accepted tone and reflex, HC: 34.5 cm. Chest: mild retraction, mild distress. CVS normal S1, S2 with no additional sound or murmur. Abdomen: soft and lax.

Saturation is maintained on CPAP 6 FiO2 30. Lab.: PH 7.33, Pco2: 38, HCO3 22, WBC 12.9, HGB 8.8, PLT 229.

As prenatal fetal ultrasound seemed to indicate Dandy-Walker syndrome, post-natal transcranial ultrasound was done and revealed prominent retro cerebellar CSF space and an MRI was recommended for further evaluation of congenital malformation.

The diagnosis based on imaging findings (Figures 3a-d) was a Joubert syndrome-related disorder, as it was associated with aplastic cerebellar vermis and persistent Blake's pouch cyst.



Figures 3a-d. (a) Transcranial ultrasound coronal view shows prominent retrocerebellar CSF space. (b) Axial T2WI of the brain shows MTS with aplasia of the cerebellar vermis. (c) midline sagittal reformatted heavy T2WI shows narrowing of the pontomesencephalic isthmus, dilated posterior fossa CSF space with thin rim of low signal suggestive of persistent Blake's pouch cyst. (d) parasagittal reformatted heavy T2WI shows thickened superior cerebellar peduncle and more depiction of the wall of the Blake's pouch.

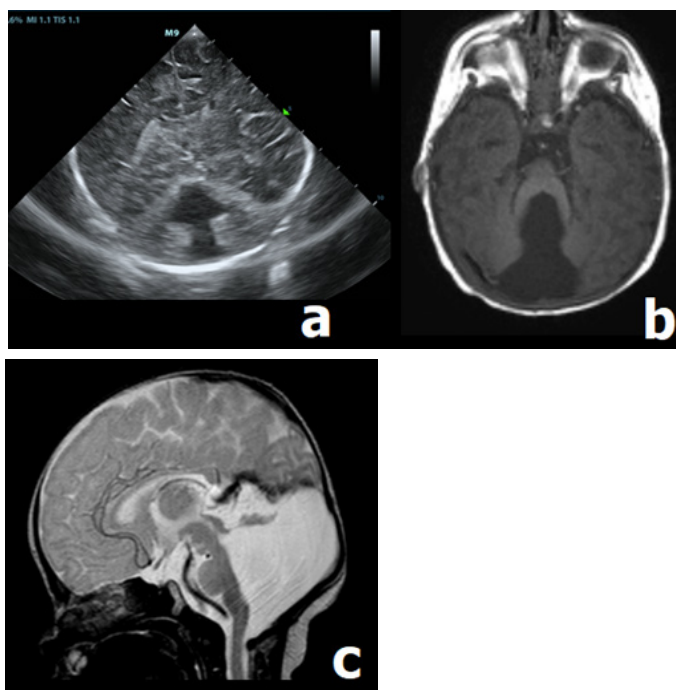
Case 3

Newborn full-term 2H female baby, the product of NSVD to mother G2P1 admitted to NICU for tachypnea, RR =100.

On examination: connected to CPAP, fairly active, mild hypotonia. Chest: marked tachypnea. Systemic examination: NAD. The provisional diagnosis was transient tachypnea of newborn (TTN) versus respiratory distress syndrome (RDS). On the second day postnatal, oxygen saturation was maintained normally in room air but the periodic tachypnea persisted. Echocardiography: normal. EEG: normal.

A routine transcranial ultrasound was done and revealed prominent retro cerebellar CSF space, so congenital malformation was suspected, and the decision was made to proceed with an MRI.

The diagnosis based on imaging findings (Figures 4a-c) was Joubert syndrome-related disorder with features of Dandy Walker malformation.



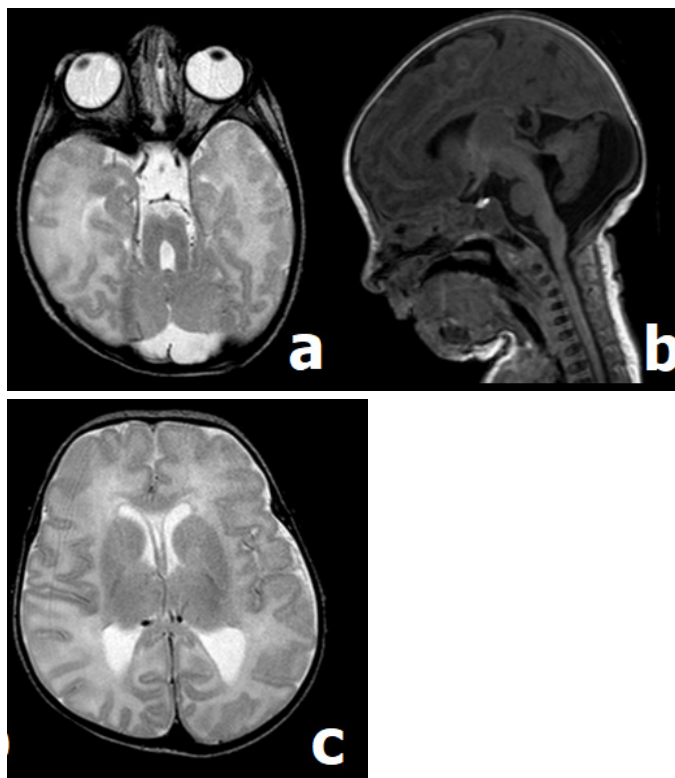
Figures 4a-c. (a) Transcranial ultrasound coronal view shows prominent retrocerebellar CSF space with absent vermis. (b) Axial T1WI shows MTS with agenesis of cerebellar vermis. (c) Sagittal T2WI shows enlarged posterior fossa, vermian aplasia with elevation of the torcula herophilii.

Case 4

Full-term baby outcome of elective CS, mother G3P1 with a previous history of gestational cholestasis. The baby needed initial steps only. The mother noticed the baby was not active. Assessment by an attending physician revealed tachypnea, O2 sat. 75, RBS: normal, so the baby was admitted to NICU on CPAP 6 FiO2 30. The initial diagnosis was TTN versus CHD. Echocardiography revealed no abnormality. Facial dysmorphic features (depressed nasal bridge, low set ears, box-shaped head) were noticed.

The mother gave a history of hydrocephalus on an antenatal ultrasound, so the decision was to have an MRI examination.

Diagnosis based on clinical and imaging features (Figures 5a-c) was Joubert syndrome-related disorder as it was associated with corpus callosum dysgenesis.

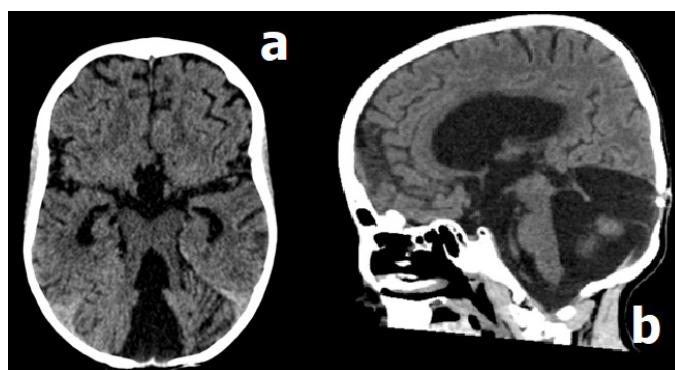


Figures 5a-c. (a) Axial T2WI shows MTS and prominent retrocerebellar CSF space. (b) shows narrowing of the pontomesencephalic isthmus with prominent retrocerebellar CSF space and deficient splenium of corpus callosum. (c) Axial T2WI of the brain at the ventricular level shows mild colpocephaly.

Case 5

A 9-year-old boy known for spastic CP (Dandy-Walker syndrome after shunting) presented to the ER with a five-day history of fever (not relieved by medication) associated with vomiting with each feeding, along with a three-day history of watery diarrhea. On examination, the boy looked dehydrated and vitally stable. Chest: EBAE. CVS: Normal S1, S2. Abdomen: soft, lax. CNS: spastic. On laboratory investigation: WBC: 5000 c/HPF, HGB: 6.6 g/dL, PLT: 175 c/HPF, Na: 155 mEq/L, K 3.4 mEq/L, Creatinine: 505 nmol/L, Urea: 40 mg/dL. The initial diagnosis was acute renal failure due to dehydration. CT was done to evaluate the VP shunt function and exclude the central cause of the vomiting.

The diagnosis based on imaging (Figures 6a-b) was Joubert syndrome-related disorder with Dandy Walker malformation and hydrocephalus.



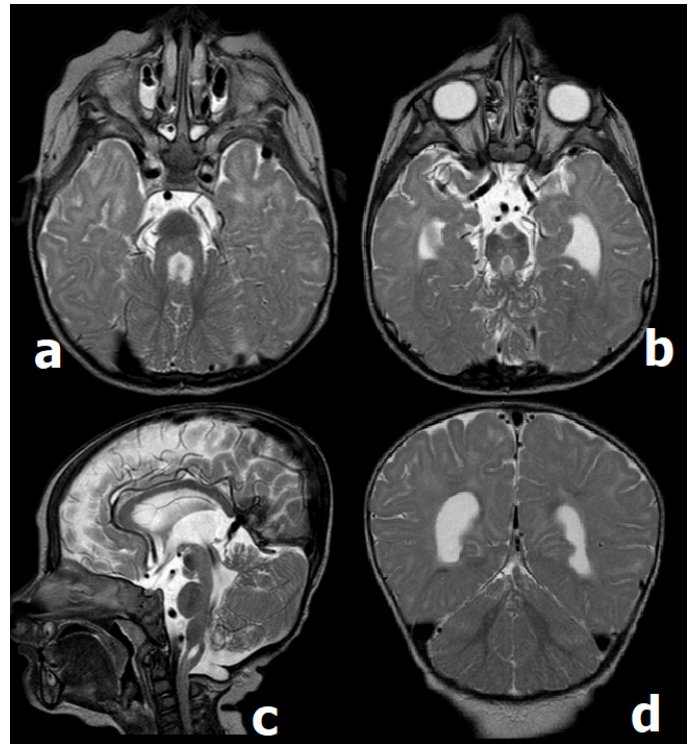
Figures 6a-b. (a) Axial CT of the brain shows MTS with absent cerebellar vermis. (b) Sagittal reformat of CT brain shows agenesis of cerebellar vermis with widened posterior fossa CSF space and upward tilting of the tentorium cerebelli and occipital burr hole of the shunt.

Case 6

A 2-year-old boy was presented to a pediatric neurology clinic for developmental delay. The parents described the infant as unable to sit or walk with delayed speech. An examination revealed moderate hypotonia with hyporeflexia in all four limbs, so the decision was made to complete an MRI assessment.

The diagnosis based on imaging findings (Figures 7a-d) was Joubert syndrome-related disorder, as it was associated with multiple other posterior fossa anomalies.

Figures 7a-d. (a) Axial T2WI: shows MTS. (b) Axial T2WI: shows interpeduncular heterotopia with dysplastic superior vermis. (c) Sagittal T2WI: shows severely hypoplastic cerebellar vermis, narrowing of the pontomesencephalic isthmus, abnormal orientation of the cerebellar folia with impending fusion, small occipital meningocele, platybasia, compression of the cervicomedullary junction with small syrinx formation. (d) Coronal T1WI shows the abnormal orientation of the cerebellar folia, dilated cerebral ventricles.



Discussion

Joubert syndrome is characterized by hypotonia, ataxia, ocular motor apraxia, neonatal breathing dysregulation, and intellectual disability of variable severity. (8)

The “molar tooth sign” is the diagnostic criterion for Joubert syndrome and consists of elongated, thickened, and horizontally oriented superior cerebellar peduncles; a deep interpeduncular fossa; and vermian hypoplasia. (8)

In Joubert syndrome, the spectrum of neuroimaging findings extends beyond the molar tooth sign and vermian hypoplasia and dysplasia, thereby confirming the heterogeneity of Joubert syndrome, not only from the clinical and genetic but also from the neuroimaging perspectives. (8)

In Case 1, we found the neuroimaging features of classic JS in the form of MTS and mild vermian hypoplasia.

However, in Case 2, the imaging features were more complex and included severe vermian hypoplasia, cystic dilatation of the posterior fossa, and upward displacement of the fastigium, all of which are features of Dandy-Walker continuum with a thin hypointense rim indicative of persistent Blake’s pouch cyst.

Poretti et al. (7) reported that enlargement of the posterior fossa, presence of a retro cerebellar cerebrospinal fluid collection and vermian aplasia were noted in 42%, 20%, and 1%, respectively, of the 110 patients in the study and these were essential parts of Dandy-Walker continuum syndrome.

A classic Dandy-Walker malformation has a midsagittal appearance of a hypoplastic uplifted vermis, and the fourth

ventricle is identifiable and freely communicating with a cystically dilated posterior cranial fossa (9). There is also the elevation of the torcula with subsequent torcula-lambdoid inversion (9). Yet in Case 2, we found the presence of Blake’s pouch cyst which, to our knowledge, was reported only once as a case report by Hafeez et al. (10)

In Case 3, we found the imaging features were more consistent with Dandy Walker malformation, of course with the MTS of Joubert syndrome only lacking the supratentorial ventricular dilatation.

Case 4 revealed classic JS features of the posterior fossa but with a supratentorial malformation that happened to be partial dysgenesis of the corpus callosum. This case demonstrates the need to look thoroughly for all intracranial malformations and not to fall into the trap of search satisfaction once the finding that explains the clinical question has been found.

Case 5 demonstrates the problem of not identifying MTS of Joubert syndrome in cases of severe hydrocephalus. This child was treated with a cystoperitoneal shunt after the diagnosis of Dandy-Walker malformation was made at another hospital to relieve the hydrocephalus. When presented to our hospital, we found the unidentified JSRD that would help in recognizing the prognosis and clinical outcome. This issue was previously reported by Sartori et al (11). Therefore, we encourage the radiologists to not be satisfied with the initial diagnosis and to look again for other cerebral malformations.

Case 6 demonstrates the more complex nature of Joubert syndrome being associated with relatively small posterior

fossa, interpeduncular heterotopia, inferior vermian hypoplasia, dysplastic superior vermis, the abnormal orientation of the cerebellar folia with impending fusion, occipital meningocele, platybasia and compression of the cervical-medullary junction with small syrinx formation. All these features cannot be categorized under a single disease entity or syndrome, emphasizing that the association is essentially due to complex embryologic processes occurring at simultaneous fetal age.

Conclusion

We report these cases of Joubert syndrome for various reasons. First, to emphasize the importance of raising the clinical suspicion in this diagnosis in newborns presenting with abnormal respiration such as periodic tachypnea or apnea, especially in a full-term baby who is unlikely to have RDS, and in countries or districts that have a high rate of consanguineous marriage.

Second, it is essential for the radiologist to look for other posterior fossa anomalies in case of finding an entity, and to be accurate in describing the malformations before jumping to a specific syndrome, because the wide difference in the genetic basis of Joubert syndrome makes the phenotypical presentation very different.

Additionally, follow-up cases of hydrocephalus should be thoroughly searched again for congenital malformations as they may be masked in the previous imaging study.

We also conclude that further research on the embryologic and genetic basis of posterior fossa malformations could help understand the complexity and variety of these lesions.

Acknowledgments

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Conflicts of Interest

The authors report no conflicts of interest.

References

- Poretti A, Huisman TAGM, 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. Available from: <https://doi.org/10.3174/ajnr.A2517>
- Joubert M, Eisenring J, Robb JP, Andermann F. Familial agenesis of the cerebellar vermis. a syndrome of episodic hyperpnea, abnormal eye movements, ataxia, and retardation. *Neurology*. 1969;19(9):813-825. Available from: <https://doi.org/10.1212/WNL.19.9.813>
- Al-Gazali L & Ali BR. Genetic disorders in the United Arab Emirates. In: Teebi A, editor. *Genetic disorders among Arab populations*. Berlin, Heidelberg: Springer; 2010. p. 639-76. Available from: https://doi.org/10.1007/978-3-642-05080-0_22
- Ben-Salem S, Al-Shamsi AM, Gleeson JG, Ali BR, Al-Gazali L. Mutation spectrum of Joubert syndrome and related disorders among Arabs. *Hum Genome Var*. 2014;1(1):14020. Available from: <https://doi.org/10.1038/hgv.2014.20>
- Brancati F, Dallapiccola B, Valente EM. Joubert syndrome and related disorders. *Orphanet J Rare Dis*. 2010;5(20). Available from: <https://doi.org/10.1186/1750-1172-5-20>
- Maria BL, Hoang KBN, Tusa RJ, Mancuso AA, Hamed LM, Quisling RG, et al. "Joubert syndrome" revisited: key ocular motor signs with magnetic resonance imaging correlation. *J Child Neurol*. 1997;12(7):423-30. Available from: <https://doi.org/10.1177/088307389701200703>
- 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):521-529. Available from: <https://doi.org/10.1136/jmedgenet-2016-104425>
- Bosemani T, Orman G, Boltshauser E, Tekes A, Huisman TAGM, Poretti A. Congenital abnormalities of the posterior fossa. *Radiographics*. 2015;35(1):200-20. Available from: <https://doi.org/10.1148/rg.351140038>
- Choudhri AF, Cohen HL, Siddiqui A, Pande V, Blitz AM. Twenty-five diagnoses on midline images of the brain: from fetus to child to adult. *Radiographics*. 2018;38(1):218-235. Available from: <https://doi.org/10.1148/rg.2018170019>
- Hafeez M, Galal MA, Khan A, Kodavooru GA, Adamjee Burhani HZ, Morsy El Saba YH, et al. Joubert syndrome-related disorders associated with Blake's pouch cyst. *Hamdan Med J* 2020;13:235-8. Available from: https://doi.org/10.4103/HMJ.HMJ_65_19
- Sartori S, Ludwig K, Fortuna M, Marzocchi C, Calderone M, Toldo I, et al. Dandy-Walker malformation masking the molar tooth sign: an illustrative case with magnetic resonance imaging follow-up. *J Child Neurol*. 2010;25(11):1419-1422. Available from: <https://doi.org/10.1177/0883073810370477>