Infratentorial Magnetic Resonance Imaging Evaluation of Joubert Syndrome

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ABSTRACT

Introduction: Joubert syndrome is rare autosomal recessive/X-linked disorder involving the posterior fossa structures. It is often missed clinically and radiologically. However, vermian hypoplasia and 'molar tooth' sign on axial Magnetic Resonance Imaging (MRI) are key to the diagnosis of Joubert syndrome.

Aim: To identify and characterize the classical and associated brain, brainstem and cerebellar imaging findings in the patients of Joubert syndrome.

Materials and Methods: Clinical details and MRI details of 7 Joubert syndrome patients were collected from hospital medical record department and Picture Archiving and Communicating System (PACS). Existing images were evaluated retrospectively by two qualified radiologists.

Results: Vermian hypoplasia was seen in 85.7% of patients. Asymmetric thickening of bilateral superior cerebellar peduncles measuring more than 2 mm was seen in all the patients. Enlargement with distortion of the fourth ventricle with rounded roof and widening of foramina Magendie were seen in all patients.

Conclusion: Identification of hallmark findings-classic molar tooth sign and other posterior fossa abnormalities on MR imaging along with the clinical features can help to establish the diagnosis and to plan genetic counselling and prenatal screening for future pregnancies.

INTRODUCTION

Joubert syndrome is a rare disorder with severe vermian hypoplasia/aplasia, abnormally thickened superior cerebellar peduncles, dysgenesis of ponto-mesencephalic junction. Clinically, it is manifesting as severe hypotonia, ataxia, oculomotor apraxia, nystagmus, episodic apnoea and hyperpnoea and developmental delay [1-4]. This syndrome is an autosomal recessive or X-linked inheritance ciliopathy and 21 gene mutations have been identified, responsible for approximately 50% of patients with Joubert syndrome. Hence, phenotypic variability is common in the brain and in other organs [2-3]. Joubert syndrome cases have characteristic findings in the brain such as hypoplasia of vermis, fragmented spinal trigeminal and dentate nuclei, hypoplastic pontine nuclei, hypoplastic inferior olivary nuclei and non-decussation of cortico-spinal tracts. Non-decussation of superior cerebellar peduncles, enlarged arcuate nuclei, hypoplastic reticular formation, hypoplastic medial lemnisci, dorsal spinal cord disorganizations and dorsal cervico-medullary heterotopias are less commonly seen features [2].

However, vermian hypoplasia and 'molar tooth' sign on axial MRI are key to the diagnosis of Joubert syndrome [1,4-6]. The finding of deep inter-peduncular fossa, non-decussated horizontally oriented superior cerebellar peduncles and enlarged fourth ventricle gives molar tooth appearance [1-4]. Extra neural findings can also be seen in few patients which includes retinal dystrophy, hepatic fibrosis, cystic kidneys, endocrine abnormalities, encephalocoele and polydactyly [2].

MATERIALS AND METHODS

This retrospective hospital based study was done in SDM College of Medical Sciences and Hospital, Dharwad Karnataka, India after institutional ethical clearance. Six years of study duration from January, 2010 to December 2015 was taken for the study.

Inclusion Criteria: Study included 7 patients (4 males and 3 females) of age group 3 months to 50 months (mean age is 24 months) presenting with hypotonia, nystagmus, ataxia, episodic apnoea and hyperpnoea, developmental delay and MRI of brain showing molar tooth sign.

Exclusion Criteria: Patients whose MRI images did not show molar tooth sign.

Clinical details and MRI details of these seven Joubert syndrome patients were collected from Hospital Medical Record Department and Picture Archiving and Communicating System (PACS). Existing images were evaluated retrospectively

by two qualified radiologists.

Test was performed with a 1.5 Tesla MRI system using 8-channel phased array neurovascular coil (HDe signa, General Electric, Milwaukee) and included axial, sagittal, and coronal short TR and TE (500/10) (T1-weighted) and long TR and TE (400/110) (T2-weighted) spin-echo imaging sequences. In addition, axial fluid attenuation inversion recovery images (FLAIR), diffusion and gradiant echo images of entire brain was performed. The imaging components of Joubert syndrome and associated other brain morphological abnormalities were studied.

RESULTS

MRI findings showed multiple infratentorial brain abnormalities in these patients with Joubert syndrome which are mentioned in [Table/Fig-1].

Vermian hypoplasia was seen in 85.71% of patients; in them disorganized folia and absent folia were seen in 71.42% and 14.28% patients respectively. Aplasia of vermis was seen in

Infratentorial Abnormalities			No. of Patients	Percent-age (%)
Cerebellar Abnormalities	Hypoplastic Vermis	Disorganized folia	5	71.42
		Absent folia	1	14.28
	Aplasia of Vermis		1	14.28
	Interhemispheric cleft size	< 1 mm	1	14.28
		1-2 mm	1	14.28
		> 2 mm	5	71.42
	Superior Cerebellar Peduncles	Thickening > 2 mm	7	100
		Orientation - Parallel	6	85.71
		Orientation - Curved	1	14.28
Fourth Ventricle Abnormalities	Level of Fastigium	Same level of ponto-mesencephalic junction	1	14.28
		Above the level of ponto-mesencephalic junction	6	85.71
	Distortion and enlargement		7	100
	Rounded Roof		7	100
	Foramina magendie widening		7	100
Other CSF Spaces	Giant cisterna magna		7	100
	Prepontine cistern Dilation		6	85.71
Brain Stem Abnormalities	Shallow ponto-mesencephalic junction		7	100
	Decussation of the superior cerebellar peduncles		0	0
	Ratio of widths of ponto-mesencephalic junction and interpeduncular fossa	> 1	0	0
		= 1	1	14.28
		< 1	6	85.71

[Table/Fig-1]: MRI findings in patients with Joubert syndrome.

14.28% of patients. Cerebellar inter-hemispheric cleft size measuring <1 mm, 1 to 2 mm and >2 mm were seen in 14.28%, 14.28% and 71.42% of patients respectively. Thickening of bilateral superior cerebellar peduncles, measuring more than 2 mm was seen in all the patients. Among them 85.71% were oriented in parallel and 14.28% were oriented in curve. Enlargement with distortion of the fourth ventricle with rounded roof and widening of foramina Magendie were seen in all patients. Level of fastigium of fourth ventricle was seen at same level and above the level of pontomesencephalic junction in 14.28% and 85.71% patients respectively. Giant cisterna magna was seen in all the patients and pre-pontine cistern dilation was seen in 85.71% patients.

Brain stem abnormalities were observed as shallow pontomesencephalic junction and absent decussation of the superior cerebellar peduncles seen in all the patients. Ratio of pontomesencephalic junction width and inter-peduncular fossa width less than one and equal to one were seen in 85.71% and 14.28% of patients respectively.
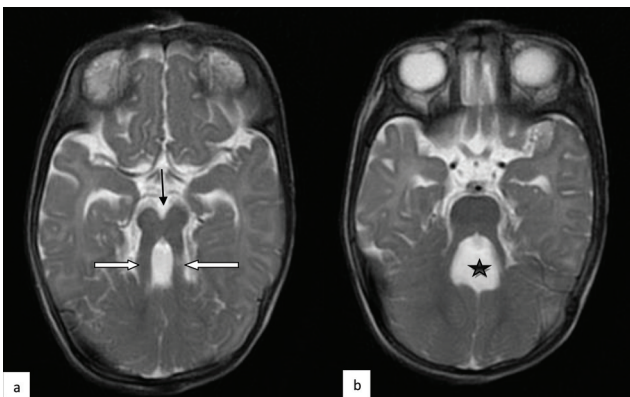
DISCUSSION

Joubert syndrome was first reported by Marie Joubert in 1969. A series of five patients who presented clinically with mental retardation, episode of rapid and deep breathing, abnormal eye movements and ataxia were reported and later the name Joubert syndrome was given to this entity [7].
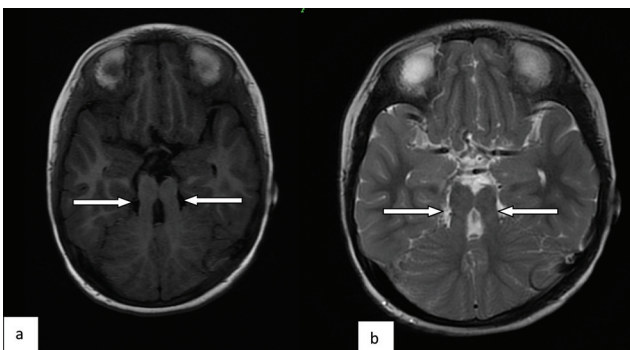
Joubert syndrome is inherited in an autosomal recessive or X-linked pattern. Diagnosis is usually made by MRI. Consistent findings on MRI include partial / complete absence of cerebellar vermis, thickened and abnormal orientation of superior cerebellar peduncles, and a deep inter-peduncular cistern with thinning of pontomesencephalic junction of brain stem. These findings produce the appearance of molar tooth, known as molar tooth sign - characteristic of Joubert syndrome [Table/Fig-2,3].

Maria BL et al., conducted a study in patients with Joubert syndrome and found molar tooth sign in 85% of patients with Joubert syndrome and hence this sign is thought to be pathognomonic of this disease [8]. Valente et al., conducted a study and he concluded that molar tooth sign is the most consistent imaging feature in Joubert syndrome. However, molar tooth sign is also seen in other syndromes like Dekaban Arima syndrome, Senior-Løken syndrome. Hence, the term 'Joubert syndrome and related disorders' was coined. 'Joubert syndrome and related disorders' describe conditions that share the molar tooth sign and the clinical features of classic Joubert syndrome and have other organ system involvement [9].

The fastigium of the fourth ventricle is normally located approximately midway between the obex and colliculo-central point. In Joubert syndrome, rostral migration of fastigium is seen. Fourth ventricle is dilated and distorted with rectangular configuration of roof. On axial images, the dilated fourth ventricle shows a triangular configuration typically appearing as 'bat wing' [Table/Fig-2].

[Table/Fig-2a,b]: (a) T2-weighted axial MR images in patient with Joubert syndrome at the level of the midbrain showing deep interpeduncular cistern (black arrow) with a resultant narrow ponto-mesencephalic junction. Thick vertical superior cerebellar peduncles (paired white arrows) represent the roots of the tooth for the "molar tooth"; (b) Pons showing dilatation of the fourth ventricle (star) with a deformed roof and an anteriorly convex floor, taking the shape of a batwing or umbrella.
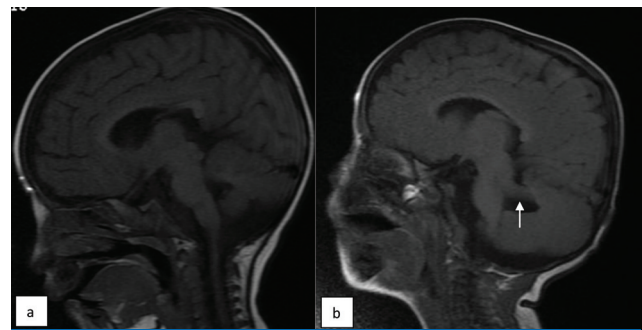

[Table/Fig-3a,b]: MR images in another patient with Joubert syndrome at the level of the midbrain (a) T1 weighted; (b) T2-weighted axial image showing thickened and parallel oriented superior cerebellar peduncles (white arrow) giving 'molar tooth' appearance.

foramina Magendie is larger with wide communication between the fourth ventricle and cisterna magna [1,4,7].

Superior cerebellar peduncles are normally oriented obliquely downwards and measuring 1-2 mm in thickness. But in Joubert syndrome these peduncles are thickened, dysplastic, elongated and oriented in parallel, 'A'-like, 'V'-like or in curve and directed horizontally and perpendicular to posterior surface of brain stem [1,4]. This feature is better appreciated on para median sagittal images [Table/Fig-4].
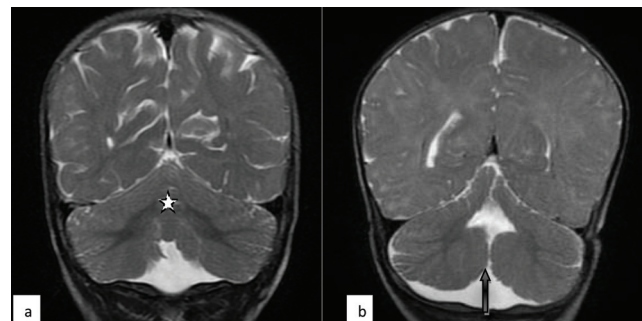
There may be asymmetric appearance of the superior cerebellar peduncles, one side being thicker than the other side when affected unequally.

Cerebellar hemispheres are usually less affected in this disorder. They bulge under the fourth ventricle to come in contact in the midline due to absence or hypoplasia of the vermis. On axial images they are separated only by a thin cleft or groove [1,4]. Normally, it is not expected to see the cerebellar hemispheres in the midline sagittal plane. But due to vermian hypoplasia/

[Table/Fig-4a,b]: Paramidline sagittal T1-weighted MR image of a normal subject. (a) It is difficult to identify the superior cerebellar peduncles partly because of their smaller size (normal 1–2 mm) and partly because of partial volume averaging. They are normally oriented obliquely downward relative to the dorsal mesencephalon; (b) Patient with Joubert syndrome showing thick superior cerebellar peduncles (white arrow) oriented almost at right angles to the posterior surface of the brain stem.

aplasia in Joubert syndrome there is visualization of cerebellar hemispheres in the midline sagittal plane. On coronal images, the cerebellar hemispheres are separated only by a midline cleft due to absence of the posterior portion of vermis. This is known as "buttock sign" [Table/Fig-5].

[Table/Fig-5a,b]: T2-weighted coronal MR image of (a) a normal subject showing cerebellar hemispheres, which are separated by vermis (star); (b) A patient with Joubert syndrome showing the cerebellar hemispheres are seen to come together in the midline, being separated only by a sagittal cleft containing cerebrospinal fluid (black arrow), due to dysgenesis/agenesis of the vermis. This appearance is known as the "buttock sign."

Ponto-mesencephalic junction is the region of brain stem located below the inferior colliculi and above the pons where, decussation of superior cerebellar peduncles seen. Normal antero-posterior diameter of ponto-mesencephalic junction is greater than the dimension of the interpeduncular fossa. However, in Joubert syndrome, ponto-mesencephalic junction is thinner due to the failure of decussation of superior cerebellar peduncles and its dimension is less than that of interpeduncular fossa [1,4]. This feature is better assessed on axial images [Table/Fig-2].

Other disorders such as Dandy-Walker-syndrome and rhomboencephalo-synapsis have cerebellar vermian anomalies but Joubert syndrome can be easily distinguished from these disorders. A large cystic abnormality of the posterior fossa with

enlarged posterior fossa is seen in Dandy-Walker syndrome. The cerebellar hemispheres are fused in rhombonencephalo-synapsis with absent midline cerebellar cleft [1,4,10-12].

The supratentorial brain features in Joubert syndrome include disorders of neuronal migration, midline defects (agenesis or dysgenesis of corpus callosum, absence of septum pellucidum), fusion of fornices, mal rotation of hippocampus, enlargement of the lateral ventricles without signs of increased intracranial pressure and hypothalamic hamartoma [1,4].

Joubert syndrome is a ciliopathy disorder and multisystem involvement is common. Polydactyly and midline oro-facial defects are more commonly associated with the Joubert syndrome. Retinal dystrophy, renal defects (nephronophthisis or cystic dysplastic kidneys), congenital liver fibrosis, endocrine abnormalities, skeletal dysplasia or Hirschsprung's disease can be associated rarely with Joubert syndrome [1-3].

Prognosis is certainly poor in Joubert syndrome due to severe mental and motor hindrance, and symptomatic treatment, genetic counselling and mental and motor rehabilitations are being the main modes of management.

LIMITATIONS

Limitations of this study are absence of clinical follow-up and genetic workup.

CONCLUSION

There is significant overlap in many of the findings in posterior fossa malformations. One rare clinical and radiological entity among them is Joubert syndrome. MRI remains the most important diagnostic tool in the detection of this abnormality. It also helps to differentiate from other disorders like rhombencephalo-synapsis, Dandy-Walker syndrome which can simulate this disorder clinically. Being mainly an autosomal recessive disorder, there is a risk of 25% with subsequent pregnancies. Hence, recognizing the classic molar tooth sign

and other posterior fossa abnormalities on MR imaging along with the clinical features can help to establish the diagnosis and to plan genetic counselling and prenatal screening for future pregnancies.

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