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Joubert syndrome: a Rare Radiological Case in Tertiary Care Hospital

Case Report

Borikar BY, Sable D and Tayade A

Department of Radiodiagnosis, Mahatma Gandhi Institute of Medical Sciences, Sevagram, Maharashtra, India

***Corresponding author:** Borikar BY, Department of Radiodiagnosis, Mahatma Gandhi Institute of Medical Sciences, Sevagram, Maharashtra, India Email: bhagyashri.4ever4u@gmail.com

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Abstract

Joubert syndrome is an unprecedented autosomal recessive neuro developmental disorder characterised via way of means of atypical respiratory styles composed of episodic tachypnea/apnea, hypotonia, ataxia, developmental delay, highbrow impairment, ocular impairment, renal cysts, and hepatic fibrosis.

We record the case of 17 months old boy who presented with fever with cough for 8 days with respiratory distress and rapid noisy breathing, Crepts, global developmental delay with audio-visual impairment and moderate to severe hearing loss, chronic kidney disease, hypotonia in all four limbs, and plantar extensors in bilateral lower limbs with pendular nystagmus. Magnetic resonance imaging showing molar teeth signal and a batwing look of the fourth and absence of the characteristic "focal red dot" deep within the interpeduncular fissure on colour-coded FA-maps.

Keywords: Case Report; Joubert Syndrome and related disorders; clinical and neurological signs; MRI; Diffusion tensor imaging

Introduction

Joubert syndrome (JS) is an autosomal recessive neurological sickness named after Marie Joubert in 1968 [1]. Joubert syndrome-associated disorders are assessed into six phenotypes [1,7]. Such entities encompass Joubert syndrome with renal defect, Joubert syndrome with ocular defect (natural JS), Joubert syndrome with oculorenal defects, Joubert syndrome with hepatic defects, and JS with oro-facio-digital defects [4]. It offers with unusual oculomotor findings, hypotonia, ataxia, breathing dysregulation, and developmental retardation as a result of abnormalities of the cerebellum and brainstem [3-5]. Classic JS is characterised via the triad of hypotonia, developmental delays, and pathognomic brainstem and cerebellar malformation known as the molar teeth sign (MTS) [1,6]. However, extra recently, the Joubert syndrome-associated disorders (JSRD) has been followed to explain formerly wonderful pathological entities with the neuroradiological characteristic of MTS at the same time as related to different organ systems. Based on organ involvement, The common age at prognosis is 33 months, and therefore, JS is to be taken into consideration a syndrome with various phenotypes accordingly making it hard to diagnose the correct subtype for the duration of the new child period [5].

Case presentation

A 4-year-old boy was offered to the radiology branch as a referred case from the branch of paediatrics, in which he turned into mostly admitted for cough and fever for 8 days, noisy breathing since 4-5 days, wheezing, bilateral nystagmus, and gaze instability. These signs and symptoms emerged at six months of age and steadily worsened. Further wondering the patient's mom discovered negative and not on time developmental milestones. He completed rollover at the age of 5 months and had no social smile till 1 year of age. He doesn't respond to the light but alerts on sound. His mother had premature rupture of membranes for 48 hrs and he was delivered through a normal vaginal delivery and weighed 2.5 kg at birth. Postnatally he was started on antibiotics because of premature rupture of membranes. USG was

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suggestive of bilateral echogenic kidneys with left inguinal hernia. Blood creatinine level 1.4, hence was referred to a higher centre for the pediatric surgeon's opinion. Review Ultrasonography was suggestive of bilateral polycystic kidney Disease with left inguinal hernia. Rest there was no records of cough, asthma, feeding issue, or respiration problems. On family history, there was no history of consanguineous marriage and he was the first child by birth. No different previous participants of their circle of relatives had been affected.

On bodily exam, the kid has a normal facial appearance and was thin and fragile. His weight was -2 to -3 Standard deviation (SD) and his height was at -2 Standard deviation (SD) at the pediatric increase chart for his age. His mid-upper arm circumference was 12.5 cm and he was classified as protein-energy malnutrition grade I. All relevant investigations sent. Reports were suggestive of Hemoglobin 9 mg/dl with iron deficiency anaemia and Vit D deficiency.

He regarded to be conscious but not interested in his surroundings. However, while instructed, he turned into not able to attention to his gaze on unique objects. The child was evaluated for developmental delay and audio and vision examination. An ocular exam discovered bilateral pendular nystagmus without myopia. With BERA, brainstem auditory evoked potential (BAEP) recording shows evidence of Vth wave formation at 60 dB Bilaterally, hence ENT opinion was taken and the child was found to be having moderate to severe hearing loss. The cardiovascular exam proved to be within normal limits. No presence of any type of murmur was recorded. A pulmonary exam showed expiratory wheeze with Crepts present on bilateral lower zones. Examination findings of the cranial nerves, other than the oculomotor nerve, were within normal limits. The motor examination discovered hypotonia in all four limbs, Deep tendon reflexes were not ellicitable in bilateral biceps, triceps, knee & ankle, plantar- Extensors noted in bilateral lower limbs.

A complete collection of Magnetic resonance imaging (MRI) scans had been performed at our radiology department for evaluation and to find out the cause of delayed milestones, hypotonia and bilateral nystagmus. We performed MR imaging using a 1.5 Tesla MR imaging unit (Simens magneton Avanto 1.5 T) and acquired the imaging with a standard 8-channel head coil. Before DTI measurement, we measured conventional sagittal and axial T2-weighted fast spin-echo and coronal T1-weighted spin-echo and FLAIR imaging sequences using standard departmental imaging protocols The axial T2-weighted MRI discovered overall aplasia of the cerebellar vermis with outstanding, thickened, and elongated advanced cerebellar peduncles forming a function molar tooth appearance. Furthermore, the fourth ventricle is regarded as enlarged and triangular, giving it a moderate batwing appearance (Figures 1-2). Based on those clinical findings, MRI scans, and family history, a prognosis of Joubert syndrome was made.

For fiber tractography (FT), we transferred the DTI data set to a personal computer. We performed fiber tractography using homemade routines based on commercially available image display software.

On DTI imaging, the fibers in the superior cerebellar peduncles were oriented horizontally as represented by a green colour coding on the FA-maps, instead of slight vertical orientation (blue colour coding) These fibers projected into the red nuclei and thalami without decussating. The transverse fibers were absent at the level of the inferior colliculi of the midbrain, with an absence of the characteristic "Focal red dot" deep within the interpeduncular fissure on colour-coded Fractional anisotropy (FA) maps. Failure of the superior cerebellar peduncles to decussate was also demonstrated by fiber tractography (FT).

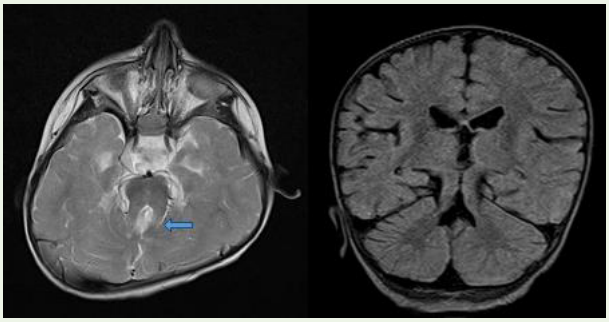

Figure 1: Axial T2W (a) and COR FLAIR (b) image shows thick and elongated superior cerebellar peduncles (blue arrow) imparting molar tooth appearance and aplasia of the cerebellar vermis. Bilateral cerebellar hemispheres appear normal.

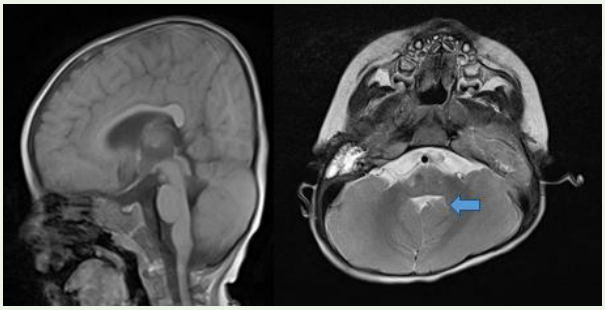

Figure 2: Batwing configuration of the fourth ventricle (blue arrows) with enlarged fourth ventricle.

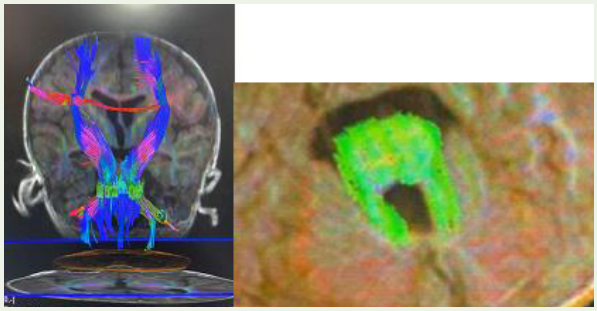

Figure 3: a) Color-coded FA-maps of the decussation of the pyramidal tracts. Fiber tractography displays the course of the pyramidal tracts (blue encoded) in a coronal projection. No crossing fibers could be identified with a parallel course of pyramidal tracts within the caudal medulla. A group of the noncrossing fibers within the superior cerebellar peduncles are also displayed on the left side.
b) Colour Coded FA maps showing the absence of "Focal Red Dot" at the level of the inferior colliculi of the midbrain. The fibers within the superior cerebellar peduncles that connect the dentate nucleus with the nucleus do not cross and remain ipsilateral.

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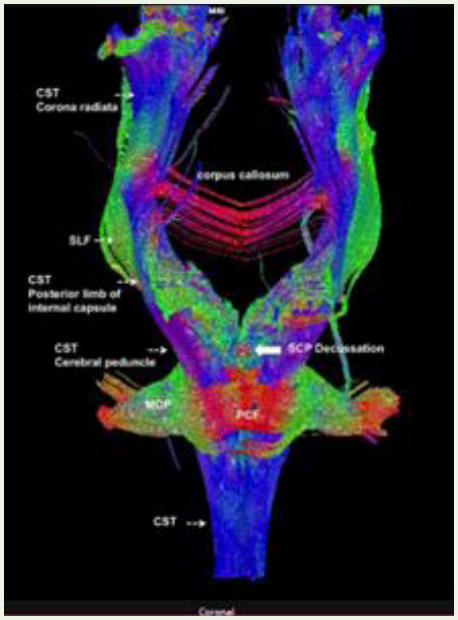

Figure 4: Diffusion tensor imaging (DTI) and tractography in a normal subject depicting the decussation of the superior cerebellar peduncle (SCP). **Abbreviations:** CST (corticospinal tract), SLF (superior longitudinal fasciculus), MCP (middle cerebellar peduncle), PCF (pontocerebellar fibres).

Table 1: Joubert syndrome (A new classification system of JSRD is based on more practical, a clinical-genetic classification which includes six sub-types primarily based on genotype-phenotype correlation) [3].

Clinical Subtype	Clinical Features
Pure JS	Hypotonia, ataxia, Develeopmental delay, molar tooth sign
	No retinal or liver involvement
	No major gene associated with the phenotype
JS with occular defect	Molar tooth sign, neurological features
	Retinal dystrophy and Leber's congenital amaurosis
	AH1 gene most common mutated (20 % cases)
JS with renal defect	Molar tooth sign
	Nephronopthisis
	Absence of renal involvement
	NPHP1 and RPGRIP1L genes commonly mutated
JS with hepatic defect	JS features
	Congenital hepatic fibrosis, chorioretinal or optic nerve colobomas, and Nephronopthisis
	TMEM67 gene mutated in 70% of cases
JS with oculorenal defect	Neurological signs
	Retinal dystroph, Nephronopthisis
	CEP 290gene mutated in50% of cases
JS with oro-facio-digital defects	Neurological features of JS
	Lobulated tongue, multiple oral frenul, mesoaxial polydactyly with y-shaped metacarpals, cleft lip/palate
	Hypothalamic hamartoma or comgenital absence of pituitary gland.

JS: Joubert syndrome; AHI 1: Abelson helper integration site 1; NPHP 1: Nephrocystin 1; TMEM 67: Transmembrane protein 67; CEP 290: Centrosomal protein 290; RPGRIP1L gene: RPGRIP 1 like protein gene.

Discussion

Joubert syndrome is underreported and the incidence ranges between 1/80000 to 1/100000 live births. JS was originally described by Marie Joubert in 1968 [1]. Later, Joubert Syndrome-related disorders (JSRD) were defined based on associated multi-organ involvement (retinal dystrophy, nephronophthisis, hepatic fibrosis and polydactyly) [4]. Until 2009, about two hundred instances of Joubert syndrome were pronounced worldwide, with an additional 12 instances being pronounced to date. Most cases are sporadic, but some families may show a recessive pattern of inheritance. The correct diagnosis was often delayed months or years after birth because of its due to its variable phenotypes, the correct diagnosis of disease was delayed by months or years even after manifesting the disease at the neonatal period [3,4].

Joubert syndrome is classified under ciliopathies and to date, 10 causative genes have been discovered. Mutations in the AHI1 and CEP290 genes are causal in 10-15% and 10% of cases, respectively. Homozygous deletion of the NPHP1 gene results in 1-2% of cases (2 of original). For normal development and functioning of several cell types, including retinal photoreceptors, neurons, kidney tubules and bile ducts, the primary cilia play an important role (Joubert Syndrome and related disorders)

The clinic-pathological manifestations of Joubert syndrome and Joubert syndrome and related disorders are caused by a defect in genes encoding for cilium proteins [1,3]. Cilia are either motile or non-motile organelles that, via ciliogenesis, deliver proteins in both directions. A defect in ciliogenesis results in the abruption of various signaling pathways like Wnt, sonic hedgehog, planar cell polarity, and directional movement.]. Clinically, it is characterized by intellectual impairment, hypotonia, ataxia, abnormal eye movements, and abnormal breathing patterns.

Ocular investigations include visible acuity, ocular motility, slit lamp exam, fundus oculi, and electroretinogram [1]. Standard urine evaluation with an emphasis on urine unique gravity must be taken into consideration. An unusual urine unique gravity warrants a project to take a look at to evaluate the urine concentrating ability. A belly ultrasound can rule out hepatic fibrosis and proof of renal structural changes [1]. Though the respiratory dysregulation is more prominent during the neonatal period diminishing by six months of age [4,8]. Other findings consist of corpus callosum dysgenesis and slight lateral ventricular growth [4]. The essential clinical features of Joubert syndrome are infantile hypotonia, developmental delay, and one or both of the following: abnormal eye moment and/or respiratory dysregulation [5,6].

Of the 34 genes regarded to motive Joubert syndrome, 33 are autosomal recessive, and one is X-linked [6]. The term JS is reserved for people who meet the diagnostic standards of developmental delay, extraordinary ocular movements, radiological proof of molar teeth sign, and cerebellar vermis changes [7]. The terminology JSRD refers to conditions that have clinical features and radiological signs of Molar tooth sin along with the involvement of other systems and organ apart from the central nervous system [7,8].

Radiological findings mainly include characteristic molar tooth

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signs which help guide the diagnosis of Joubert syndrome [6]. Midline hypoplasia of the cerebellar vermis, incomplete fusion of the halves of the vermis, abnormally deep interpeduncular fossa, and thick superior cerebellar peduncles leads to molar tooth sign [4,6-8].

The pontomesencephalic junction is dysplastic with abnormal decussation of the superior cerebellar peduncle with a marked decrease in the neurons of the basis pontis and reticular formation [5]. Histopathological research has shown that the gross appearance of the brainstem and cerebellum is because of the fragmentation of the dentate nucleus. Another radiological finding is called a buttock signal formed due to the absence of the posterior vermian lobe, leaving the cerebellar hemispheres separated by a cleft. The hypogenesis of the cerebellar vermis resulting in dilatation of the fourth ventricle giving batwing or umbrella sign [4,7,8].

Hypotonia and intellectual disability are consistent features of Joubert syndrome. The altered breathing pattern includes hyperventilation worsened by stimulation, followed by periods of apnea or episodic hyperpnea [7]. The physical examination shows facial dysmorphism including a large head, prominent forehead, rounded eyebrows, epicanthal folds, ptosis, upturned nose with evident nostrils, and low-set tilted ear [9]. However, abnormal respiration is only seen in 68% of cases studied by Pellegrino et al., and 44% of that Kendall et al. [10,11]. Underlying oculomotor dysfunction results in abnormal eye movements [9]. Involvement of the retina leads to fundus flavus, congenital retinal dystrophy, chorioretinal coloboma, and perimacular and retinal blindness [9]. Other eye findings consist of nystagmus, strabismus, and ptosis. 25% of patients suffer from renal involvement. These patients have symptoms of polydipsia and polyuria followed by chronic renal insufficiency manifesting till the second decade of life.

In pregnant females, a prognosis of Joubert syndrome is made feasible prenatally with the aid of using serial ultrasound imaging beginning at 11 to 12 weeks gestation. This must be observed with the aid of using an assessment of cerebellar and fetal anatomy through 20 weeks of gestation and fetal MRI imaging at 20 to 22 weeks gestation [7].

Lee et al showed thickened superior cerebellar peduncles but did not demonstrate the absence of decussation of the superior cerebellar peduncles. Lee et al and Widjaja et al applied diffusion tensor imaging (DTI), a relatively new MR imaging technique that allows examination of the course and integrity of white matter tracts in vivo [12].

Diffusion-tensor magnetic resonance (MR) imaging (DTI) and fiber tractography (FT) is new methods that can demonstrate the orientation and integrity of white matter fibres in vivo [14].

Diffusion tensor imaging (DTI) is an MRI technique that uses anisotropic diffusion to estimate the axonal (white matter) organization of the brain. **Fibre tractography (FT)** is a 3D reconstruction technique to assess neural tractsusing data collected by diffusion tensor imaging [14].

MRI are sufficient to confirm or exclude the disease depending on the detailed clinical history comprising the classical triad of JS and characteristic MTS sign-on After diagnosing with JS/JSRD, the child must also be evaluated for other organs/system involvement to rule out multiorgan involvement.

On DTI imaging there shows an almost complete absence of pyramidal tract decussation in the caudal medulla and abnormal decussation of the superior cerebellar peduncles with failure of the superior cerebellar peduncles to decussate in the mesencephalon.

Colour-coded FA-maps are used to evaluate the presence or absence of a “focal red dot” within the anterior mesencephalon adjacent to the interpeduncular fossa. The absence of the “focal red dot” is noted in the absence of decussation of the fibre tracts within the superior cerebellar peduncles, respectively, as an absence of the decussation peduncular cerebellarium superior. Similarly, also caudal medulla oblongata was studied for a “focal red dot” corresponding to the decussation of the corticospinal tracts. FT was performed to confirm the findings of colour-coded FA maps and identify a possible aberrant course of the studied tracts.

Management mainly includes supportive and symptomatic treatment. Special emphasis should be given to managing respiratory and feeding. Cognitive problems require a suitable rehabilitation strategy, and normal follow-up [3]. Due to excessive sensitivity to the respiratory depressant effects of anaesthetic agents such as opiates and nitrous oxide these patients require apnea tracking for intensive care management [4]. The prognosis mainly depends on the type and extent of organ involvement. Hence, Developmental outcomes may vary and can result between (a) patients who die young, (b) patients who survive with developmental delay and visual/motor deficit, (c) patients whose developmental quotients is in the mildly delayed range (70 to 80) [9]. Language and motor skills are also delayed in JS/JSRD patients hence special schooling to learn specific job skills and to work in a protected environment are also needed. [9]. Annual screening as per diagnostic protocol is advised for such individuals.

Our affected person provided with significant findings of hypotonia manifested as trouble with neck holding and posture. However, in our patent, there was no history of parental consanguinity which is supposed to have a role in the epidemiology of JS as reported in a study done by İncecik et al. at a rate of 63.6% [8]. Also, he is presented with bilateral nystagmus and oculomotor dysfunction with respiratory pattern dysregulation which may or may not worsen with advancing age. Also, other findings which are consistent with the diagnosis of Joubert syndrome were the MRI findings of molar tooth appearance, the batwing appearance of the fourth ventricle, and hypoplasia of the cerebellar vermis. The patient also presented with bilateral polycystic kidney disease and bilateral moderate to severe hearing loss, the diagnosis of JSRD was taken into consideration.

Conclusion

Joubert syndrome clinically presents with respiration dysregulation, infantile hypotonia, developmental delay, nystagmus, oculomotor disturbance, and intellectual impairment. The variability in clinical phenotypes often leads to delayed diagnosis. Diagnosis of Joubert syndrome requires essential diagnostic criteria in clinical history along with MRI findings, and a multi-gene panel. The main

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MRI finding is a molar tooth appearance with concomitant cerebellar vermis hypoplasia and a batwing configuration of the fourth ventricle. Management of such cases essentially includes easing respiratory and feeding difficulties, along with rehabilitation for cognitive and behavioural difficulties.

Other Diferentials of Joubert syndrome could be Joubert syndrome-related disorders (JSRD), Pontocerebelar dysplasia, cerebellar hypoplasia syndrome,Congenital Disorders of Glycosylation.

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