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A RARE CASE OF JOUBERT SYNDROME WITH HEPATIC ABNORMALITY: COACH SYNDROME

Dr. Priyanka Borah*[1] and Prof. (Dr.) Parul Dutta[2], MD, DMRD

[1]Post Graduate Trainee, [2]Professor and Head of the Department,
Department of Radiology, Gauhati Medical College and Hospital, Guwahati Assam, India.

***Corresponding Author: Dr. Priyanka Borah**
Post Graduate Trainee, Department of Radiology, Gauhati Medical College and Hospital, Guwahati Assam, India.

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ABSTRACT
Joubert syndrome is a very infrequently found autosomal recessive neurological disorder characterized by complex brainstem malformation and hypoplasia of the cerebellar vermis. COACH syndrome, a rarer subtype, can affect multiple systems and lead to varied phenotypic spectra. We present a case of a 9-month-old girl, presenting to the pediatric outpatient department with developmental delay, abnormal eye movements, ataxia, hypotonia and episodes of hyperpnea-apnea. Hypoplasia of cerebellar vermis with thickened and elongated bilateral superior cerebellar peduncle gave rise to typical "Molar tooth" sign and "batwing" appearance of fourth ventricle on MRI. Based on typical imaging features of Joubert syndrome, positive family history and evidence of ocular and hepatic involvement along with genetic confirmation, a diagnosis of COACH syndrome was made. The typical clinicoradiological features of this rare disorder can guide us through the diagnostic dilemma to make an early diagnosis and help in taking a timely appropriate intervention.

KEYWORDS: Joubert syndrome, COACH syndrome, Molar tooth sign, Batwing appearance, Ciliopathy.

INTRODUCTION
Joubert Syndrome, also called Joubert-Boltshauser syndrome, was first described by Maria Joubert et al. in 1968.[1] It is an extremely rare developmental neurological disorder resulting in only 200 global reported cases till the year 2009. The prevalence of the disease is less than 1 in 100,000 worldwide.[2] Joubert syndrome is characterized by developmental delay, ataxia, hypotonia, irregular pattern of breathing, and abnormal eye movements including nystagmus and oculomotor apraxia. In majority of patients, the classical "molar-tooth" sign is found on brain MRI, which is considered as diagnostic hallmark of Joubert Syndrome.[3] COACH syndrome is a multisystemic subtype of Joubert syndrome, characterised by cerebellar vermis hypo/aplasia, oligophrenia, congenital ataxia, coloboma, and hepatic fibrosis, first described by Verloes et al. in 1989.[4] Even though it is a developmental disorder, due to these variable clinical manifestations, establishment of the early correct diagnosis based on radiological findings becomes very crucial. Implementation of genetic counselling and proper rehabilitation have a huge positive impact on the affected patient as well as family.

CASE HISTORY
A 9-month girl presented with developmental delay, abnormal eye movements, squint, ataxia, hypotonia, episodes of hyperpnea and apnea. She was born out of a non-consanguineous marriage at term of an uneventful pregnancy after LSCS with birth weight of 2.7 kg. She has a previous history of hospital admission with complaints of respiratory distress in the form of cough, shortness of breath and choking during feeding. After being treated as aspiration pneumonia the child was discharged as she received the complete course of antibiotic and supportive treatment on day 8 of hospital admission.

There was positive family history in the form of clinically and radiologically diagnosed Joubert Syndrome in an elder female sibling, who however had a sudden death 4 years back at the age of 5 months. The cause of death was presumed to be aspiration due to neurological deficit caused by cerebellar vermian hypoplasia. There is no other history of miscarriage or no other living sibling of the present case under study.

On examination, facial dysmorphic features were seen-mild frontal bossing, depressed nasal bridge, low set ears, low frontal hairline and mild degree of squint. Abnormal eye movements in the form of intermittent extremes of gaze were noticed. Weight, height and head circumference were normal for age.

Neurological examination revealed ataxia and generalized hypotonia. There was hepatomegaly. On auscultation, no respiratory and cardiac abnormalities could be seen.

Eye examination revealed squint on left eye (30 degree exotropia) with normal fundus.

Biochemical investigation showed normal metabolic parameters except elevated liver enzymes (SGPT- 191 U/L, SGOT- 128 U/L) with normal bilirubin. On USG whole abdomen, hepatomegaly was seen along with mildly heteroechoic echotexture of liver.

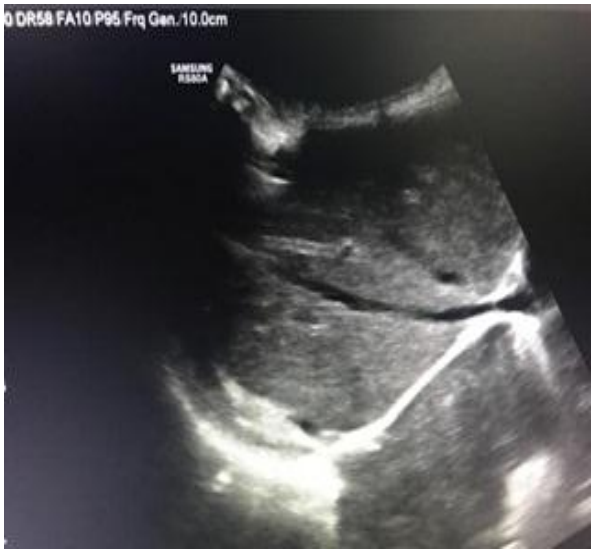

Figure 1: Ultrasound image showing increased liver span for age with mildly heteroechoic parenchymal echotexture.

Magnetic Resonance (MR) images showed Hypoplasia of cerebellar vermis with thickened and elongated bilateral superior cerebellar peduncle, giving typical "Molar tooth" appearance of the midbrain in axial sections. There is secondary distortion of Fourth ventricular shape giving rise to its typical "batwing" appearance. There was deepening of interpeduncular fossa and rostral shifting of the roof of fourth ventricle (Fastigium). The supratentorial structures and Corpus callosum were normally developed.

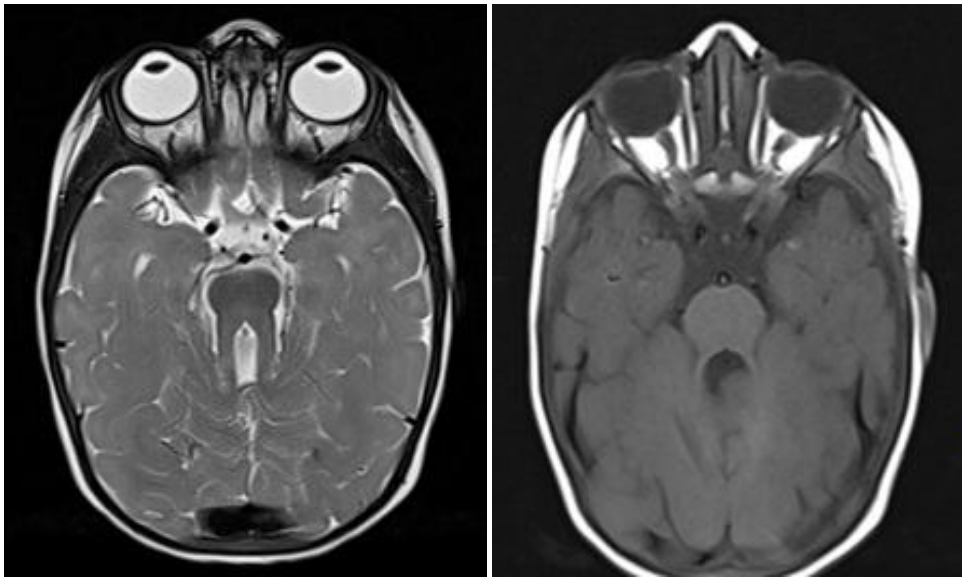

Figure 2 & 3: Axial section MR images showing "Molar tooth" appearance of midbrain and "Bat wing" configuration of fourth ventricle.

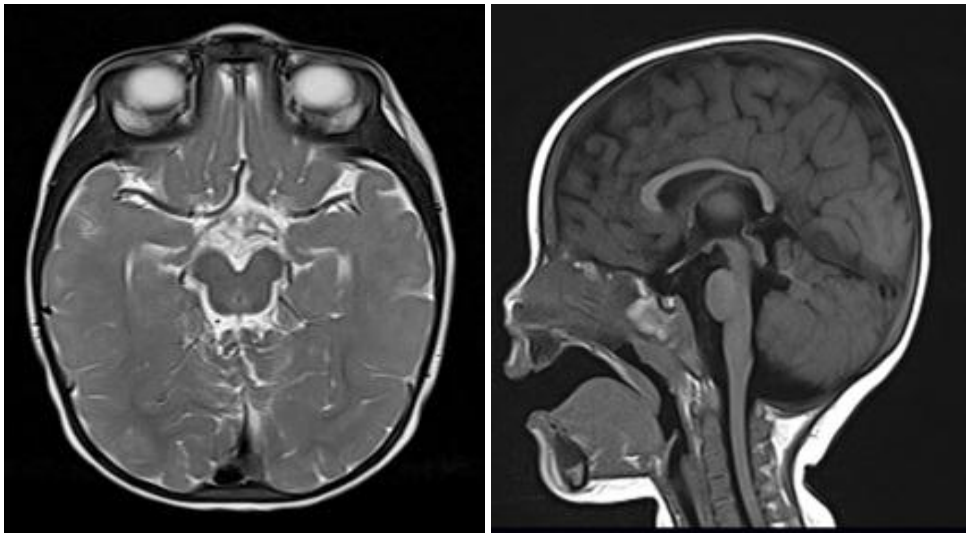

Figure 4 & 5: Axial and sagittal MR images showing deepening of interpeduncular fossa with rostral shifting of Fastigium.

DISCUSSION

Joubert syndrome belongs to a rare genetically and phenotypically heterogeneous group of ciliopathies in which specific mutations encode for faulty primary cilia proteins and result in defective functioning of cilia.[5] The diagnostic hallmark "Molar Tooth Sign" on an axial MRI section of brain through midbrain-hindbrain junction is caused by an abnormally deep interpeduncular fossa; elongated, thickened and maloriented superior cerebellar peduncles and hypo/aplastic cerebellar vermis. Joubert syndrome is mainly divided into two main types- pure JS and JS and related disorder (JSRD). In addition to neurologic manifestations, other features seen in association with Joubert syndrome e.g. liver fibrosis, renal disease, polymicrogyria, ocular coloboma, retinal dystrophy and polydactyly suggests a common pathogenesis with other ciliopathies.[6] All these disorders are categorized under Joubert Syndrome Related Disorders (JSRD). The examples of such syndromes are the COACH syndrome, Dekaban-Arima syndrome, Varadi-Papp, Senior-Loken, Joubert with polymicrogyria, and Malta syndromes.[7]

COACH syndrome is a subgroup of Joubert syndrome with hypoplasia of cerebellar vermis, oligophrenia, congenital ataxia, coloboma, and hepatic fibrosis. Hepatic dysfunction of COACH is due to the embryonic ductal plate malformation.[8] MKS3/TMEM67 mutations are responsible for a major percentage of COACH Syndrome.[9] In our case, positive family history, characteristic clinicoradiological signs of Joubert syndrome along with ocular signs and symptoms, hepatomegaly, early hepatic parenchymal changes and raised liver enzymes were found suggesting COACH syndrome. The patient had strabismus and nystagmus out of all other possible ocular abnormalities in COACH syndrome i.e. nystagmus, amblyopia strabismus, ptosis, and pigmentary retinopathy etc. Hepatic involvement in COACH syndrome can range from deranged liver function test to features of portal hypertension.[10] After confirmation of COACH Syndrome on genetic testing, parents were counselled and proper management including rehabilitation was done. On follow up after 6 months, signs of improvement were seen as evidenced by reduction of hypotonia. Early detection and timely intervention in the form of genetic counselling, physiotherapy, occupational and speech therapy can show significant reduction of risks and debilitation in patients and families of Joubert syndrome and its related disorders (JSRD) including COACH syndrome.

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