Distinctive Imaging in a Toddler with Joubert's Syndrome

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A 2-year-old boy firstborn to a nonconsanguineous couple brought with the concern of delayed attainment of developmental milestones since early infancy. He achieved a social smile at 5 months, able to sit with support, and did not have stranger anxiety. On formal development assessment by DASII, motor and mental development quotient of the child was 33 and 25, respectively (overall DQ-29). He also had a history of abnormal breathing patterns (intermittent episodes of fast breathing). Examination revealed development delay, microcephaly (occipitofrontal circumference-40.5 cm, OFC for age <-3 SD), intermittent horizontal gaze nystagmus, central hypotonia, and preserved deep tendon reflexes. He also had repeated head thrusting, with poor saccade initiation and episodic hyperpnea. An ophthalmic evaluation revealed horizontal nystagmus, oculomotor apraxia, and retinal pigmentary changes [Figure 1]. Ultrasonography of the abdomen was normal. Clinically he was suspected to have Joubert's syndrome because of ataxia, oculomotor apraxia, episodic hyperpnea, and pigmentary retinal changes. Magnetic resonance imaging (MRI) of the brain showed the characteristic "molar-tooth" sign of the midbrain and "batwing" shaped fourth ventricle [Figure 2]. Whole-exome sequencing detected compound heterozygous missense pathogenic mutations in the *AHI1* gene (c.1765C>T in exon 13 and c.2168G>A in exon 16) confirming the diagnosis of Joubert's syndrome. Both these mutations were found to be previously reported in patients with Joubert's syndrome. Both the variants were confirmed by Sanger sequencing and parents were carriers for one of the variants. The in silico predictions of the variant was also found to be possibly damaging by PolyPhen-2 (HumDiv) and damaging by SIFT, LRT, and MutationTaster2.

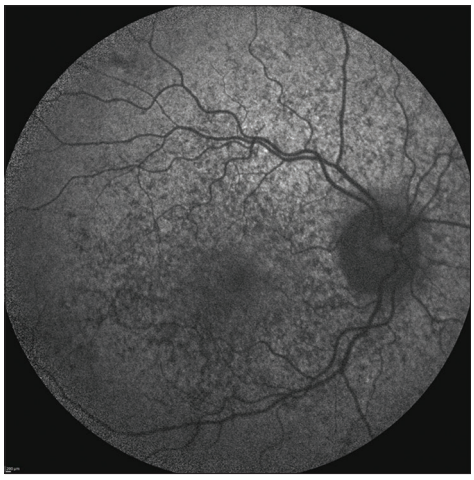

Figure 1: Fundoscopic examination of the child showing pigmentary retinal changes

Joubert's syndrome is a rare ciliopathy, first described in 1969 by Marie Joubert.[1] Joubert syndrome and related disorders (JSRD) are classified into six phenotypic subgroups: Pure JS, JS with ocular defect, JS with renal defect, JS with oculorenal defects, JS with the hepatic defect, and JS with orofaciodigital defects. JSRD is genetically heterogeneous. Mutations in the ten ciliary/basal body genes (*AHI, INPP5E, CEP290, NPHP1, ARL13B, MKS3, CC2D2A, TMEM216, TMEM67,* and *RPGRIP1L*) have been identified in JSRD patients, with variable clinical presentation and survival up to adulthood in the majority of patients.[1] Mostly JSRD follows autosomal recessive inheritance, except X-linked inheritance in rare cases. A broad spectrum of phenotypic findings has been reported with this syndrome, caused by abnormalities in the structure and/or function of the primary cilium. Distinctive clinical features include global developmental delays, ataxia, abnormal eye movements episodic, and hyperpnoea.[1] Nystagmus, oculomotor apraxia, and head thrusting to compensate for poor saccade initiation are common in these children. Nystagmus may be vertical, horizontal, or torsion, and characteristically has a pendular or see-saw pattern.[2] Retinitis pigmentosa is a less commonly detected ocular finding in children with JS and characteristic abnormalities detected are oculomotor apraxia, nystagmus, strabismus, and ptosis, apart from nystagmus. The characteristic imaging findings in Joubert's syndrome are a "molar-tooth" sign (formed by elongated, parallel, thickened, and horizontally oriented superior cerebellar peduncles) and "batwing" sign (due to severe hypoplasia of vermis).[3] Other features are enlargement of lateral ventricles, corpus callosum agenesis, and abnormal foliation and fissuration of the cerebellar hemisphere.[4] Associated anomalies with variable prevalence include polydactyly, retinal dystrophy, ocular coloboma, tongue tremors, and oral frenulae, cystic renal dysplasia, juvenile nephronophthisis, and congenital hepatic fibrosis. Renal anomalies demonstrate age-dependent penetrance and can be detected in at least 30% of affected cases.[1] Retinitis

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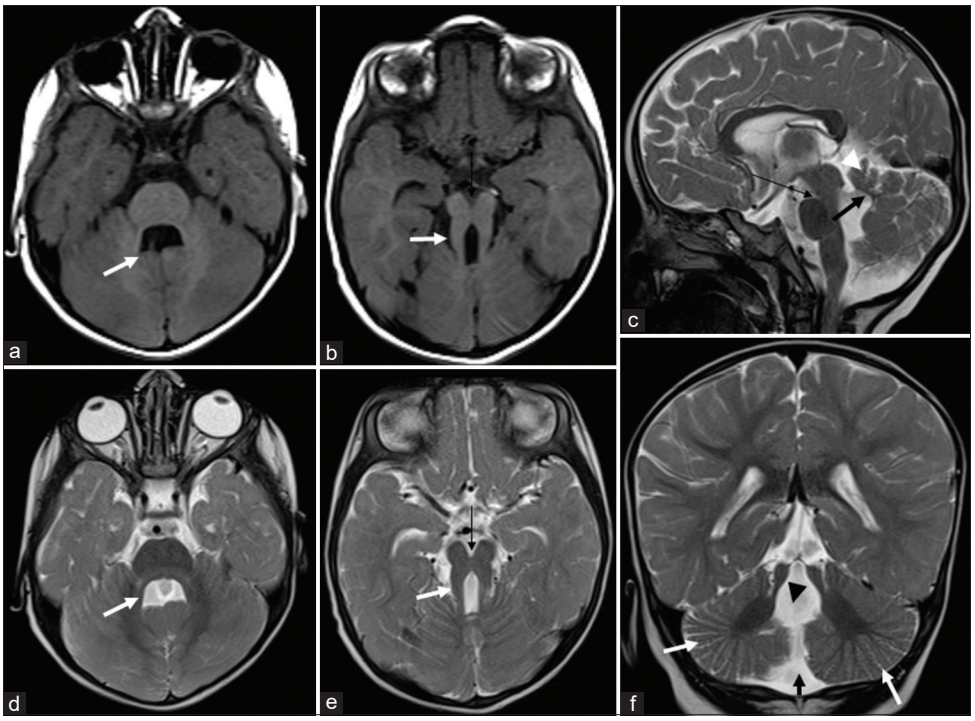

Figure 2: Magnetic resonance imaging of the brain of a child. T1-weighted (a, b) and T2-weighted (d, e) axial sequences show the typical "batwing" shaped fourth ventricle (arrow) (a, d) and elongated, parallel, thickened, and horizontally oriented superior cerebellar peduncles (white arrow) with a deepened interpeduncular fossa (black arrow) (b, e) suggestive of "molar tooth sign" of the midbrain. T2-weighted (c) sagittal sequence shows enlarged and distorted fourth ventricle with a rostral shifting of the fastigium (thick black arrow), vermian hypoplasia (arrowhead), and deepened interpeduncular fossa (thin black arrow). T2-weighted (f) coronal sequence demonstrates retrocerebellar CSF collection (black arrow), enlarged and distorted fourth ventricle (arrowhead), and abnormal foliation and fissuration of bilateral cerebellar hemisphere (white arrow).

pigmentosa occurs due to defect in the connecting cilia of the retinal photoreceptor cells and modified cilia of the outer segment. It typically manifests with the spotting of the retinal pigment epithelium, along with thinning and reduction of retinal vessels.[2] Nystagmus and ataxia in young children can be due to the wide spectrum of cerebellar pathology. In such cases apart from JSRD, clinicians need to consider the possibility of other ciliopathies like cerebellar-oculo-renal syndrome (CORS), Senior–Loken syndrome, Meckel–Gruber syndrome, Dekaban–Arima syndrome, COACH (cerebellar vermis hypo-/aplasia, oligophrenia, congenital ataxia, ocular coloboma, and hepatic fibrosis), orofacial digital syndrome, and Cogan-type congenital oculomotor apraxia. Among these, Meckel-Gruber syndrome is the closest associated ciliopathy for JSRD. Even, ataxia and retinitis pigmentosa may occur simultaneously in children due to several causes like NARP (neuropathy, ataxia, and retinitis pigmentosa) syndrome, Friedrich ataxia, neuronal ceroid lipofuscinosis, and spinocerebellar ataxia, but distinguishing features like episodic hyperpnea, when present, help pediatrician in suspecting Joubert's syndrome clinically.[5]

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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