Joubert Syndrome with a Rare Ocular Phenotype: Coloboma with Retrobulbar Cysts – A Case Report

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Abstract
Joubert syndrome (JS) is a rare, autosomal recessive, genetic syndrome that derives from the defects in a sensory organelle, the primary cilia. It is a multiorgan disorder affecting the brain, kidneys, liver, and eyes. The most common presenting feature in the newborn period is hypotonia, abnormal eye movements, irregular breathing pattern, characterized by episodic hyperpnea and apnea, later on, ataxia, and developmental retardation. Besides, a range of highly variable, systemic and ocular features can be present. We report a case of 2-month-old female infant, the product of a consanguineous marriage, with a sibling affected by JS, presenting with intermittent hyperpnea, apnea, facial dysmorphism, strabismus, oculomotor apraxia, proptosis, retinal dystrophy, chorioretinal coloboma, and large retrobulbar cysts communicating with the coloboma. Magnetic resonance imaging of the brain revealed the characteristic neuroradiologic finding, the “molar tooth sign.” The child does not fix or follow the light, and the visual prognosis with all the ocular features of the syndrome present is extremely poor. In addition to adding to the diversity of ocular phenotypes, this case reiterates the importance of identifying the syndrome, understanding the varied ocular phenotypic presentations, need for further research on causative genes, prenatal diagnosis in affected families, interventions, and adequate genetic counseling.

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Introduction

Joubert syndrome (JS) is a rare autosomal recessive genetic syndrome, with a prevalence of 1 in 80,000 to 1 in 100,000 [1] and with an average age of diagnosis at 33 months (up to 25 years) [2]. The classical features of JS include the cerebellar vermis hypoplasia with complex brainstem malformation, molar tooth sign and hypotonia, developmental delay/mental retardation, cerebellar ataxia, abnormal eye movements, and irregular respiratory pattern. The radiological features include the “molar tooth sign” produced by increased depth and length of the interpeduncular fossa with a narrow isthmus, increased thickness of the cerebral superior peduncle, dilated and anteriorly deviated fourth ventricle with “batwing” appearance, and cerebellar vermis hypoplasia or dysplasia [3]. The other systemic clinical features include seizures, mental retardation, autism, and delayed psychomotor development.

The rest of the spectrum of clinical features, including occipital encephalocele, polymicrogyria, polydactyly, ocular coloboma, retinal dystrophy, cystic kidney disease, nephronophthisis, and hepatic fibrosis, are described under the subsets of JS termed JS and related disorders [4]. Ocular clinical features include horizontal nystagmus, strabismus, oculomotor apraxia, vertical gaze palsy, congenital retinal dystrophy, pigmentary dystrophy, fundus flavus, chorioretinal coloboma, perimacular and retinal blindness, oculomotor apraxia with compensatory head movements, and wink [5].

JS is grouped under “ciliopathies” as it affects the cells’ primary cilia, leading to altered development of the cerebellum, brainstem, and other organ systems. Genetic defects are found in only 50% of cases. More than 34 genes are known to cause the disease, including the AHI1 (chromosome 6) and CEP290 (chromosome 13) genes critical in the primary cilia function [5]. The other genes involved include the NPHP1 (JBTS4), CEP290 (JBTS5), TMEM67 (JBTS6), JBTS1, JBTS2, JBTS7, JBTS8, and JBTS9 genes. These genes are associated with the protein expressed in cilia and centrosomes. A high recurrence rate of about 25% is seen in families with autosomal recessively inherited JS, but not applicable to the X-linked inherited JS. The advancement in molecular genetics research leads to improved disease prediction and genetic counseling. Prenatal diagnosis is usually rare but is a potential area of early detection and possible early intervention in families with confirmed cases. The significance of early detection of the syndrome is stressed so that clinicians can start suitable measures as early as possible.

Case Report

Our institution’s pediatrician referred a 2-month-old baby girl for ophthalmic evaluation as a case of JS. Parents complained that the infant is visually inattentive. It was an uneventful full-term normal delivery. There were no untoward perinatal events reported, and the child cried immediately after birth. The Apgar scores were 8 and 10 at 1 and 5 min, and the birth weight was 2,975 g. She was born to first cousins, consanguineous parents. Systemic features included only intermittent tachypnea. Ocular examination showed that the child does not fix or follow a light source. There was no nystagmus, and on VOR testing (vestibulo-ocular reflex), the fast refixation phase was absent, indicating oculomotor apraxia. In the anterior segment, the left eye was proptosed inferonasally. The pupil was round and regular. Fundus examination revealed that the right eye has a pale disc, disc coloboma, and a salt and pepper dystrophic retina. The left fundus showed disc coloboma, and salt and pepper dystrophic retina. Both fundi showed attenuated vessels and chorioretinal colobomas as well.

MRI scan of the proband revealed dysplastic changes of the scanned cerebellar vermis, along with elongation of the superior cerebellar peduncles, showing characteristic molar tooth appearance and the batwing appearance of the 4th ventricle (Fig. 1–3). MRI brain and
orbits and the ophthalmic sonography showed bilateral retrobulbar mass, more prominent on the left side (as big as the eyeball), oval-shaped, well-defined, hypo-dense (near water density around 10 HU) cystic lesion measuring 19 × 14 × 23 mm along the maximal anteroposterior,
mediolateral, and caudo-cephalic diameters, respectively, inducing mass effect in terms of proptosis of the left eye and flattening of the posterior aspect of the left eye globe (Fig. 1, 4, 5).

Blood investigations including FBC, liver enzymes, thyroid hormones, urea, creatinine, and blood sugar were reported normal. An abdominal ultrasound was performed, which showed normal visceral organs, including the liver and kidneys. VEP was performed, which shows normal latency and amplitude of P100 in the right eye and normal latency but grossly reduced amplitude of P100 in the left eye.

The proband has one 13-year-old female sibling with cerebellar atrophy confirmed with MRI. She has mild mental retardation and difficulty in speech. The sibling’s ocular examination revealed normal vision in each eye, a normal fundus but with torsional, jerky nystagmus.

Whole-genome sequencing of the proband was performed, which revealed a homozygous variant in the coiled-coil and C2 domains containing the protein 2A gene (CC2D2A gene) (c.1466 + 4A>C chromosome 4 [GRch37] g.15530353 A>C). CC2D2A gene is mutated in JS and can interact with the ciliopathy-associated basal body protein CEP290. This variant was found in the heterozygous state in both the parents and in the homozygous state in the affected sister of the index case. The CC2D2A gene is highly variable and is linked to classic JS or JS with retinitis pigmentosa or encephalocele to the COACH phenotype with the liver involvement and coloboma [6]. Considering the patient’s genotype and phenotype, genetic diagnosis confirms JS type 9.
Discussion

A review of the recent literature indicates ocular motor apraxia as the most frequent ocular feature in patients with JS (80% of patients), followed by strabismus (74%), nystagmus (72%), ptosis (43%), retinal dystrophy (38%), chorioretinal coloboma (30%), and optic nerve atrophy (22%) [5]. Ocular and oculomotor anomalies are widespread in JS and support the diagnosis [7]. The retina is one of the most critical organs frequently involved in JS, either in retinal dystrophy or colobomas. Retinal dystrophy occurs due to progressive degeneration of the photoreceptor cells [8–10], whereas colobomas can be unilateral or bilateral and usually affect the posterior segment of the eye. Although colobomas signify a periodic basis of visual impairment in all JS clinical subgroups, the highest frequency of coloboma is in the JS-with-hepatic-defect subgroup, which is over 30%. JS is further classified into two groups based on the presence or absence of retinal dystrophy [11]. Patients with retinal dystrophy are known to have a higher prevalence of multicystic renal disease. These patients appear to have decreased survival rates compared with those without retinal dystrophy.

Our present case has almost all the ocular features mentioned above. An additional rare part of our case is the presence of bilateral retrobulbar cysts, the left one being as big as the eyeball, communicating with the vitreous cavity. Retrobulbar cysts as an ocular feature in JS have been reported sparingly in the literature so far [12, 13].

Despite the remarkable spurt in gene retrieval by Sanger next-generation sequencing techniques, the genetic basis for JS is still not well understood. Of late, 34 causative genes have been identified, showing either an autosomal or X-linked recessive inheritance pattern [14]. The implicated genes encode proteins that localize to the primary cilium; that is why JS has been classified as ciliopathies. The primary cilium is a nonmotile cilium that is found in nearly every cell of the body. Photoreceptors have a primary cilium identified as the connecting cilium, a slender structure connecting the outer and inner segments. In addition to its structural role, the photoreceptor cilium also provides a critical transport function [8]. Several genes (AHI1, INPP5E, ARL13B, and CC2D2A) are nearly exclusively mutated in patients presenting with either pure JS or JS with retinal involvement [10, 14]. AHI1 is required for the repair of outer segments of photoreceptors, as it enables the accurate maintenance of polarized vesicular movement to the cilia. The absence of AHI1 is causing retinal degeneration in mice.

There are reports of prenatal imaging findings of subsequent pregnancies using both ultrasound and fetal MRI in families with JS-affected children, proposing an ultrasound at 11 weeks to look for increased nuchal translucency, karyotyping at less than 18 weeks, if not already done, and evaluation of posterior fossa abnormalities by ultrasound at less than 20 weeks and with MRI at 20–22 weeks [15].

Conclusions

The case we reported is an example of JS with systemic features and the extreme ocular involvement causing blindness. Besides, this case constitutes a rare ocular phenotype of JS, presenting with the retrobulbar cysts, adding to the diverse range of ocular features. JS with retrobulbar cysts has been reported very few in the literature so far, and we are hopeful that our report will add valuable data to the existing literature on JS and its ocular phenotypes. The proband in the case reported has a sibling affected with JS with less serious ocular manifestations, reiterating the possibility of the extreme range of ocular manifestations in the affected families and warrants concerted action from the clinicians’ side. It cannot be overemphasized that the presence of an affected child in the family should prompt appropriate
genetic counseling, prenatal diagnostic tests like ultrasound, MRI, karyotyping, and well-informed clinical advice for subsequent pregnancies.

**Statement of Ethics**

Written informed consent was obtained from the parent of the patient for publication of the details of their medical case and any accompanying images. We have obtained Dubai Scientific Research and Ethics Committee approval for reporting this case. As formal application in the prescribed form was not necessary for case reports, only email communication was obtained on February 20, 2021.

**Conflicts of Interest Statement**

The authors have no conflicts of interest to declare.

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**Author Contributions**

Salam Chettiankandi was involved in the initial evaluation of the patient, initiation of the paper, writing of the manuscript, communication with the ethics committee, and parent’s approval for publication. This fulfills the current ICMJE criteria for authorship. Gazala Afreen Khan has contributed to the research and writing of the genetics part of the paper in addition to helping with the writing and formatting of the main manuscript. This fulfills the current ICMJE criteria for authorship. Hayat Ahmad Khan was involved in the clinical examination of the patient and writing of the manuscript. This fulfills the current ICMJE criteria for Authorship.

**Data Availability Statement**

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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