Joubert Syndrome among Two Related Children

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A seven-year-old Pakistani male presented with gross developmental delay. The child had delayed walking and speech. He had ataxic gait, head nodding to the left side and mild dysmorphic features.

Diagnosing Joubert syndrome (JS) requires clinical, radiological and genetic testing for final confirmation. Magnetic resonance imaging (MRI) study revealed Molar Tooth Sign (MTS) which is the hallmark, together with genetic testing, confirming the diagnosis of Joubert syndrome.

The manifestations of JS are variable and to keep into consideration the differential diagnoses of hypotonia and ataxia, delayed walking, speech and development.

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Joubert syndrome (JS) is a rare genetic heterogeneously inherited autosomal recessive disorder; it is a rare x-linked recessive[1,2]. It was first described by Marie Joubert 1969 [3,4].

The incidence is 1/80.000 to 1/100.000[5]. The cerebral vermis is affected with either aplasia or hypoplasia; the vermis controls balance, coordination and posture; in addition, the brain stem abnormality, which controls breathing, heart rate and temperature. The signs and symptoms are variable; however, the most common clinical manifestations are hypotonia, ataxia, dysmorphic features and intellectual disability[6].

Joubert syndrome is a multisystemic disorder with multi-organ involvement in some cases; they are labeled as Joubert Syndrome and Related Disorder (JSRD)[7]. During infancy, the manifestation may be only hypotonia and diagnosed as classic Joubert syndrome, but later in life, other multi-organ involvements begin to manifest, such as renal, liver and eye abnormalities, hence the term JSRD. Fascial features are distinctive for JS: a broad forehead, ptosis, hypertelorism, low set ears and arched eye brows[6]. MRI brain is the main diagnostic tool that clearly can show MTS[8].

The aim of this report is to present two cases of Joubert Syndrome which can be found within one consanguineous family having similar gene mutation.

THE FIRST CASE

AA is a seven-year-old Pakistani boy who presented with a history of delayed walking and speech. He began to walk independently and to speak the first word at the age of three years.

The gait had always been abnormal, swaying from side to side, taking rest in between to continue walking and avoid falling. His speech has improved, able to formulate a sentence of three to five words, but poorly intelligible.

He is a product of normal vaginal delivery with normal growth parameters; there was no antenatal, perinatal, or postnatal complication. He had meningitis at five months of age; his vaccination was up to date.

His parents were second-degree relatives, both are healthy. He has one younger brother, three years old, alive and healthy. The mother's niece has a similar history and was diagnosed as Joubert syndrome.

He had ataxic gait, head nodding to the left side, mild dysmorphic features broad forehead and a large head. Eye examination for coloboma or other retinal changes and ENT was normal.

Systemic examination detected no abnormality and there was no focal neurological deficit. The metabolic evaluation was normal. Renal ultrasound showed that the left kidney is not seen in the left fossa and does not appear to be ectopic, see figures 1 and 2. However, correlation with dimercaptosuccinic acid (DMSA) scan is advised to assess for the ectopic kidney. Unfortunately, it has not been performed. MRI brain undoubtedly showed (MTS) with mild vermian hypoplasia, see figure 3. The Whole Exome Sequencing (WES) confirmed the diagnosis of Joubert syndrome. Psychologist IQ testing revealed borderline delayed intellectual functions.

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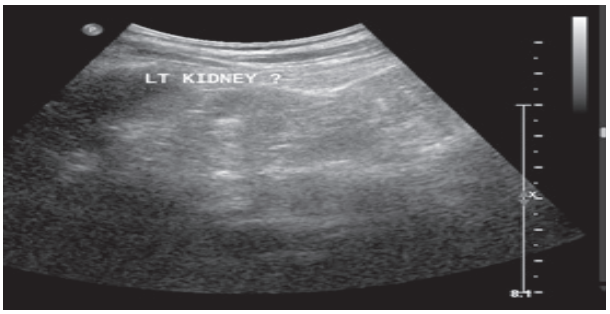

Figure 1: Absent Left Kidney

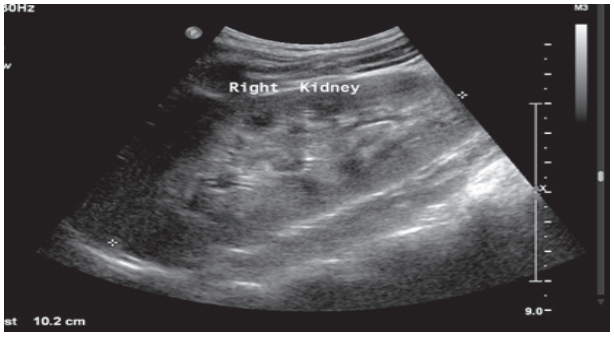

Figure 2: Solitary Right Kidney with Compensatory Hypertrophy

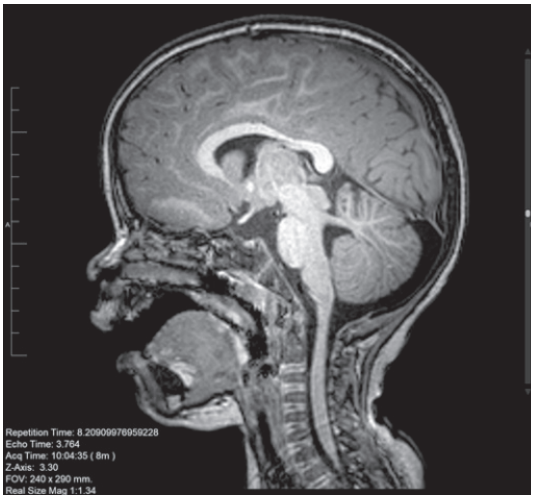

Figure 3: Hypoplasia of Vermis

THE SECOND CASE

AW is a three-year-old girl and a cousin of AA; she was referred for neurological assessment at the age of eighteen months because of her developmental delay. She started walking at the age of two years. Currently, she can say many words but still could not form sentences. She is not yet toilet trained. She can follow simple commands. No perinatal complications or other antecedent events were reported.

On examination, she was attentive, following simple commands, subtle coarse facial features, head circumference was 48 cm, extraocular movements were full, but she showed multi-directional, gaze-evoked nystagmus; fundoscopy was unremarkable. The rest of the cranial nerves were intact; motor evaluation revealed mild hypotonia, but her gait was unsteady. There was an element of dysmetria affecting the upper limbs. MRI brain revealed Molar Tooth Sign (MTS), see figures 4-6. Renal ultrasound study was unremarkable, see figure 5. Whole Exome Sequencing (WES) confirmed the diagnosis of Joubert syndrome similar to her cousin's mutation, AHI1gene, stage 1.

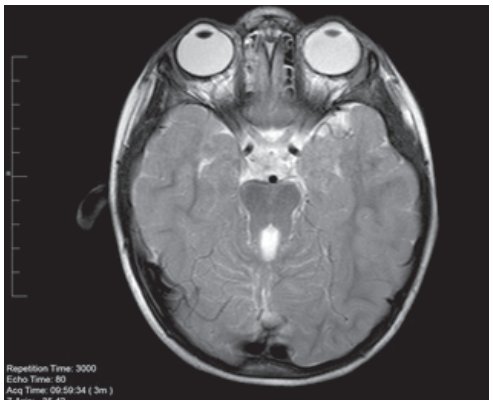

Figure 4: MRI T2 Axial Showing Typical Molar Tooth Appearance. Thick Elongated Superior Cerebellar Peduncles

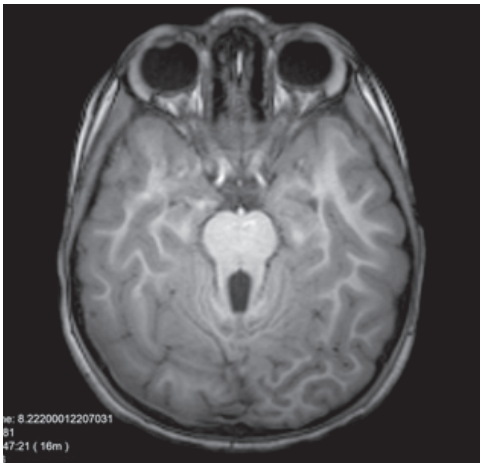

Figure 5: Molar Tooth Appearances (Axial T1W MRI Sequences)

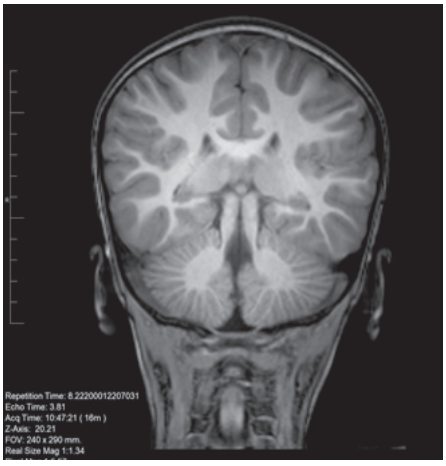

Figure 6: MRI T1W Coronal, Thick Elongated Superior Cerebellar Peduncles

DISCUSSION

Joubert syndrome is a rare genetic disorder of the brain development with an autosomal recessive mode of inheritance in the majority of cases and a small fraction inherited as sporadic or x-linked recessive in a few reported cases[9].

The syndrome is called classic or pure Joubert syndrome when only a few signs and symptoms manifest, but when there is major organ involvement, it is termed Joubert Syndrome and Related Disorder (JSRD); they may have retinal dystrophy, liver fibrosis/cirrhosis, kidney disease and polydactyl[7].

The typical history of classic Joubert starts in infancy with hypotonia and eventually the other manifestations become more obvious and represent JSRD.

During infancy, they suffer from hypotonia, episodic hyperpnea/panting like a dog, sleep apnea, abnormal eye and tongue movements[10].

Eye abnormalities such as retinal dystrophy, iris defect (coloboma), out deviation of one eye (strabismus), involuntary eye movement (nystagmus), drooping or falling of the upper eyelid, and oculomotor apraxia(OMA) causing difficulty moving the eyes from side to side to visualize objects in the peripheral visual field[9]. This condition is similar to what is seen in our report when trying to look around, the patient is forcefully tilting and nodding his head to one side to focus at a certain point[11].

Delayed gross motor milestones are the main affected part starting with infantile hypotonia progressing to ataxia and poor balance control. Intellectual disabilities are also common ranging from mild to severe and in some cases normal intellectual function[12].

There are ten genetic anomalies identified causing Joubert syndrome and the most common gene mutation, AHI1(JBTS3) is responsible for 11% of affected families. There are few case reports of homozygous AHI1 gene mutation in a consanguineous family with Joubert syndrome[13].

Our patient was diagnosed as autosomal recessive Joubert syndrome type 3 and the gene mutation AHI1. There are different mutations with variable organ involvement. NPHP1 mutation (JBTS4) have renal abnormalities like polycystic kidney disease termed as nephronophthisis[14,15].

It is important to mention that the molar tooth sign and the clinical signs/symptoms seen in Joubert syndrome are also found in few other syndromes, such as Coach syndrome, Cogam oculomotor apraxia, Dekaban Arima syndrome, severe retinal dysplasia, Senior Loken syndrome and Varadi-Papp syndrome.

Other clinical syndromes can have similar symptoms, such as Meckel syndrome, Dandy-Walker malformation and Oral-Fascial-Digital syndrome. The criteria to diagnose classic Joubert Syndrome must have the following three: molar tooth sign, infantile hypotonia with later development of ataxia and developmental delays/intellectual disability[16].

There is no specific treatment for Joubert syndrome. Physical occupational plus speech therapies are essential. They should be approached by a multidisciplinary team including geneticist, neurologist, ophthalmologist and nephrologist, liver and retinal assessment should be performed at regular intervals[17,18]. In case they develop any complications, the treatment is symptomatic and supportive.

CONCLUSION

Joubert syndrome is a rare autosomal recessive genetic disorder, mainly characterized by aplasia or hypoplasia of the cerebellar vermis and abnormal brain stem. The disorder manifests in infancy with delayed gross motor milestones like walking and eventually ataxic gait with poor balance. Joubert Syndrome and Related Disorders (JSRD) is the diagnosis used to describe JS with additional findings, such as retinal dystrophy, liver, kidney and skeletal involvement. The treatment of JS is symptomatic and supportive.

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