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Case Report

Neonatal presentation of Joubert syndrome

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ABSTRACT

Joubert syndrome is a rare genetic disorder with autosomal recessive or rarely X-linked recessive inheritance. Authors are reporting a case of a newborn girl with Joubert syndrome who presented with respiratory distress, hypotonia, hyporeflexia, abnormal eye movements, and facial dysmorphism. Brain MRI revealed vermian hypoplasia, "molar tooth sign" with "bat wing appearance" of the fourth ventricle, deepened interpeduncular fossa, and elongated superior cerebellar peduncles. The clinical diagnosis of this syndrome is difficult due to its variable presentation and non-specific presentation. Magnetic Resonance Imaging (MRI) has an important role in the diagnosis of Joubert syndrome. This not only helps in early diagnosis but also helps in appropriate counseling and proper rehabilitation of the baby.

Keywords: Joubert syndrome, Magnetic resonance imaging, Nystagmus, Prenatal diagnosis, Ultrasound

INTRODUCTION

Joubert syndrome (also known as cerebello-oculo-renal syndrome or cerebellar vermis agenesis or Joubert-Boltshauser syndrome or cerebello parenchymal disorder) is characterized by cerebellar vermis dysgenesis (brain part responsible for control and coordination) and brainstem malformation.[1] It was named after Dr. Marie Joubert in 1969 who first described the syndrome in a family where 4 of 6 children were affected with the same syndrome.[2] It is characterized by respiratory abnormality, hypotonia, ocular abnormalities, and developmental delay.

The reported incidence of Joubert's syndrome is 1/80000 to 1/100000 live births.[3] It is a genetic disorder that occurs due to mutation in the gene which affects cilia responsible for appropriate function of various body cell types like neurons, liver, and kidney cells. It also affects various senses like vision, hearing, and smell. Inheritance is mostly autosomal recessive and rarely X-linked recessive.[4]

Here we present a case of Joubert syndrome. This article aims at highlighting important aspects in the diagnosis and management of Joubert syndrome.

CASE REPORT

A 30-year-old patient, third gravida with previous two vaginal delivery presented to the out-patient department of a government hospital at 37 weeks period of gestation with complaint of pain abdomen. This was her first hospital visit. She did not undergo any antenatal investigations throughout her pregnancy. She gave the history of the neonatal death of her first child. Two years back, she delivered a full term live born girl. This baby had a poor cry and hypotonia at birth. This baby was admitted in neonatal ICU due to respiratory difficulty. Her MRI brain was suggestive of vermian agenesis. The

baby expired after 18 days of life due to respiratory distress and pneumonia. Unfortunately, no autopsy of the baby was done because parents did not give consent. There is no other significant family history or history of consangious marriage. Family pedigree given in (Figure 1).

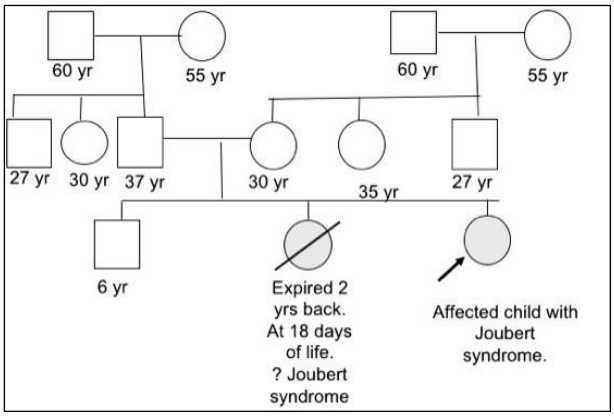

Figure 1: Family pedigree of index case.

On admission, her vitals were stable. Her abdominal and vaginal examination were suggestive of false labour as there were no contractions or cervical change. As a part of hospital protocol all routine antenatal investigations were done. The ultrasound was suggestive of vermian hypoplasia. All other antenatal work-up was normal. Genetic counselling was done, and patient was asked to follow up to the genetic clinic after delivery. She went into spontaneous labour at 39 weeks period of gestation and delivered a live born baby girl of 2.8 kg. Baby had a weak cry at birth and decreased tone. The birth APGAR was 5,6,7 at 0,5, and 10 minutes of life. She was admitted in neonatal ICU in view of moderate birth asphyxia. She was managed conservatively. She was kept on CPAP for 48 hours.

Figure 2: A) A child with Joubert syndrome with broad forehead, hypertelorism, slightly arched eyebrows, and broad nose and depressed nasal bridge. B) Same child with low set ears.

Baby was alert but had characteristic facial dysmorphic features like broad forehead, ptosis, hypertelorism, slightly arched eyebrows, broad nose, depressed nasal bridge, and low set ears (Figure 2). Cleft lip/cleft palate, and polydactyly were absent. Her weight and height were below the third centile. No neurocutaneous markers were noted.

On day 6 of life, horizontal nystagmus was noted. On neurological examination, generalized hypotonia and hyporeflexia was present. Incomplete Moro's reflex was demonstrated. Rest systemic examination was within normal limits.

Laboratory investigations like complete blood count, random blood sugar, liver, and renal function test, serum electrolytes, thyroid profile, and C-reactive protein were within normal limits. Ultrasound abdomen was done to rule out liver and renal abnormality, which was normal. 2D Echo was done, which was normal. Her brain MRI was done which revealed vermian hypoplasia, "molar tooth sign" with "bat wing appearance" of the fourth ventricle, deepened interpeduncular fossa, and elongated superior cerebellar peduncles (Figure 3).

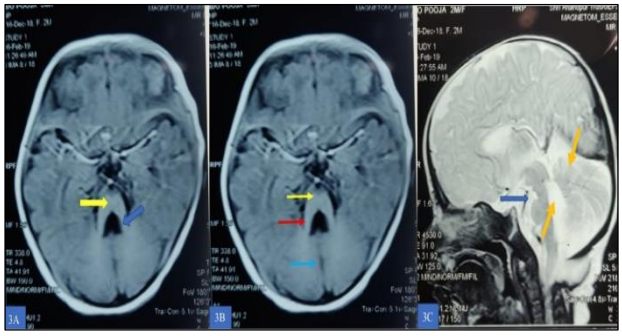

Figure 3: A) Axial T1w image showing "molar tooth sign" (yellow arrow) with "bat wing appearance" of the fourth ventricle (blue arrow). B) Axial T1w image showing deep interpeduncular fossa (yellow arrow), elongated superior cerebellar peduncles (red arrow), and cerebellar vermis hypoplasia (blue arrow). C) Saggital T2w showing deep interpeduncular fossa (blue arrow) and vermian hypoplasia (yellow arrow).

On ophthalmological examination, blinking response to light and normal pupillary response was noted. She could not follow light or any target. Horizontal nystagmus was present. Fundus examination was within normal limits. BERA (Brainstem Evoked Response Audiometry) was done at 1 month of life. Baby failed the test. The parents were counselled to follow up for a repeat test at 3 months.

The baby was referred to the genetic for genetic work up for which the reports are awaited. Baby came for follow up visit at one and a half month of life. Social smile was present, but neck holding was only partial.

DISCUSSION

The presentation of Joubert syndrome is variable. The diagnosis of "classic" Joubert syndrome is based on the presence of three primary criteria: molar tooth appearance

on MRI, hypotonia in infancy which later progresses to ataxia, and developmental and intellectual disability. Additional features include abnormal breathing patterns (alternating apneic /tachypneic episodes) and abnormal eye movements.[3] All these features were present in the present case, thus confirming the diagnosis of Joubert syndrome.

The acronym "Joubert Syndrome and Related disorder" (JSRD) is used for the patients with Joubert syndrome with additional features like retinal dystrophy, ocular coloboma, occipital encephalocele, renal disease, liver fibrosis, polydactyly, and/or other abnormalities.[5] Facial dysmorphic features like broad forehead, arched eyebrows, depressed nasal bridge, widely spaced eyes (hypertelorism), ptosis, and facial hypotonia have also been associated with Joubert syndrome.[6] These were also noted in the index case. It is seen that many patients present as classic Joubert syndrome at infancy and develop additional features eventually.[3]

Joubert syndrome is caused by mutations in various genes which are responsible for regulating the function of cilia. These ciliary projections have a role in signaling in many cells, like neurons, liver, and kidney cells. Cilia also regulate the function of vision, smell, and hearing. Mutation in these genes disrupt the function of these cells.[7]

Joubert syndrome is a genetic disorder with autosomal recessive or rarely X-linked recessive inheritance.[5] Various genes are associated with Joubert syndrome. However, these are identified in only about 50% of the affected patients. So, genetic testing is usually not required for the diagnosis of Joubert syndrome. However, if the gene responsible for Joubert in a particular family is identified, it will help in planning future pregnancies.

Genetic counseling is an essential aspect in managing such patients. The family history of these patients should be thoroughly evaluated, and they should be explained about the risk of recurrence in future pregnancies. Genetic testing should be offered in the affected child. All the siblings and relatives should be offered genetic screening in a family where the pathognomic variant is identified.[4]

These parents should be clearly explained about the importance of genetic risk determination, and availability of prenatal and preimplantation diagnosis while planning future pregnancies.[8] They should be clearly informed about their carrier status. An option of DNA banking for future use can also be given.[5]

In patients when the genetic evaluation has not been done, other options are also available for prenatal diagnosis. Serial perinatal ultrasound screening starting at 11 to 12 weeks with a detailed evaluation of cerebellar and fetal anatomy at 18- 20 weeks' gestation is possible.[9] Further, confirmation can also be done by fetal MRI at 20 weeks'.[10]

Joubert syndrome is associated with renal involvement in at least 30% of the patients.[1] The various associations include renal cystic dysplasia and juvenile nephronophthisis.[5] So, these patients should be followed with ultrasound for early detection of these abnormalities.

Hepatic involvement is seen in about 9% of affected children.[11] Hepatic fibrosis, portal hypertension resulting in uncontrolled bleeding has been associated with the syndrome.[12] these patients should be followed up with periodic liver function tests and ultrasound.

A broad of ophthalmological involvement in the form of nystagmus, strabismus, amblyopia, ptosis, retinal dystrophy, and coloboma of choroid or retina have been associated with Joubert syndrome.[13] These patients should be followed up periodically for ophthalmological and fundus examination. In case of any abnormality VEP (visual evoked potential) and ERG (electroretinogram) should be done.[14] Authors plan to get VEP and ERG for this baby also.

Skeletal abnormalities like cone-shaped epiphysis, polydactyly, and scoliosis have been associated with Joubert syndrome.[5] So, detailed skeletal survey should be done in these patients.

These patients usually have speech apraxia. Authors plan to get an opinion of a speech therapist regarding the oromotor function.[4]

Endocrine abnormalities like growth hormone or thyroid hormone deficiency or sometimes pan-hypopituitarism have been associated with the syndrome.[5] So, these children should be monitored for the same.

No reliable distinguishing features to predict the onset of complications of Joubert syndrome are available. So, these patients require periodic follow up several times a year. During these follow-up visits, growth monitoring, neurological evaluation, assessment of sexual maturation, respiratory symptoms, and evaluation of motor function should be done.[11] Regular evaluation of developmental and neuropsychologic assessment with age-appropriate tools should be done.[15] These babies require early intervention through occupational, speech, and physical therapy. They should receive individualized educational assessment and support to maximize their performance.[15] Monitoring of liver and renal dysfunction should be done with ultrasound and blood investigations.

CONCLUSION

Joubert syndrome is a rare genetic disorder. Diagnosis is often delayed due to its variable and non-specific presentation. MRI has an important role in its diagnosis. Thus, it is very important to be aware about the clinical

and radiological findings of Joubert's syndrome. This will not only help in early diagnosis but will also help in ensuring appropriate counselling and proper rehabilitation of the baby.

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