Case Report

Joubert syndrome: unusual story

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Received: 28 November 2021

Accepted: 29 December 2021

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ABSTRACT

Joubert syndrome (JS) is a rare autosomal recessive neurodevelopmental disorder characterized by hypotonia, ataxia, developmental delay, intellectual disability, abnormal eye movements and abnormal breathing pattern. It has a variable phenotype which makes it difficult to diagnose. We presented a case of a 14 month old girl with delayed developmental milestones and feeding difficulties. MRI brain of this patient in contrast to the classical molar tooth appearance showed only mild corticocerebral atrophy. Gene study revealed a heterozygous missense mutation in exon 1 of the INPP5E gene. Although our patient did not fulfil all three diagnostic criteria for JS, on gene sequencing, there was a missense mutation in one of the commonly found genes for JS. She was managed by a multidisciplinary approach including physical and speech therapy.

Keywords: Joubert's syndrome, Genetic disorder, Motor delay, Nystagmus

INTRODUCTION

JS is an autosomal recessive heterogeneously inherited neurological disorder named after Marie Joubert in 1969.¹ Only 200 cases have been reported worldwide with an prevalence of 1 in 80,000 to 1,00,000 live births.^{2,3} Classic JS is defined by the triad of developmental delay, hypotonia and characteristic brainstem and cerebellar malformation called the molar tooth sign (MTS) on radiological finding.^{1,4} It presents with abnormal oculomotor findings, hypotonia, ataxia, respiratory dysregulation and developmental delay owing to abnormalities of the cerebellum and brainstem. It presents commonly as delayed developmental milestones and hence, most of the cases may not be diagnosed till several months after birth.⁵ JS can be managed through a multidisciplinary intervention program including physical therapy, special education, occupational and speech therapy. The importance of early detection of the syndrome is important for appropriate interventions to be started as early as possible.

CASE REPORT

A 14 month old girl presented in our outpatient department with developmental delay and feeding difficulty. There was no history of seizure, abnormal breathing pattern or abnormal eye movements. She achieved neck holding at 7 months of age and could only sit with support. Her speech milestones were also delayed, she couldn't talk any words with meaning. She was born out of a non-consanguineous marriage via a caesarean section at 35 weeks of gestational age in view of maternal pregnancy induced hypertension. There was a history of NICU stay for low birth weight (1800 grams) without any other perinatal complications. Detailed family history was taken and revealed that no other members were affected.

On physical examination, child had low set ears and broad forehead. She weighed 7.7 kgs which was below 25th centile on WHO growth chart for age. She was playful and did not have any ocular abnormalities. She had hypotonia in all four limbs with normal deep tendon reflexes. She did not have abnormal oculomotor findings

or breathing pattern. Head circumference was below 25th centile (43.5 cm).

Magnetic resonance imaging (MRI) showed mild corticocerebral atrophy. Whole genome sequencing of patient displayed a heterozygous missense variation in exon 1 of the INPP5E gene and that of the father revealed a heterozygous condition of the same gene. Mother's report was normal. Brainstem auditory evoked response and ophthalmic examination were normal. Blood parameters like complete blood count, liver and renal function tests were within normal limits.

Figure 1: T1 weighted MRI brain showing mild corticocerebral atrophy.

Based on clinical and gene study findings, diagnosis of JS was made and parents were counselled. Physiotherapy, occupational therapy and speech therapy was advised. Follow up visit at 19 months of age revealed that she was able to walk short distances with support and had a decrease in feeding difficulties. Hypotonia had diminished with persistent speech delay without any meaningful words.

DISCUSSION

JS is a rare autosomal recessive disorder characterized by clinical and characteristic neuroradiological findings. The diagnostic criteria for JS included three primary findings: hypotonia, developmental delay and a distinctive cerebellar and brain stem malformation called the MTS.⁶ The most common features of JS were lack of muscle control (ataxia), abnormal breathing patterns (hyperpnea), sleep apnea, abnormal eye movements and low muscle tone. Many authors have reported the prevalence of some of these associated findings, which included polydactyly (8%), ocular coloboma (4%) and hamartomas of the tongue (2%), dysmorphic facies, microcephaly, tongue

protrusion, multicystic kidney disease, congenital heart disease, unsegmented midbrain tectum, retinal dystrophy and agenesis of the corpus callosum.⁷⁻⁹

Cilia are motile or non-motile organelles that transport proteins. A defect in ciliogenesis resulted in the abruption of various signalling pathways such as Wnt, sonic hedgehog, planar cell polarity and directional movement of which one transduction pathway played a vital role in regulating neuronal cell proliferation and axonal migration.¹ JS was known to have a genetic origin with an autosomal recessive pattern of inheritance. There were around 34 genes known to cause JS, 33 were autosomal recessive and one was X-linked.⁴ A defect in genes encoding for ciliary proteins resulted in the clinicopathological manifestations of JS.

Recently, the term JS-related disorders (JSRD) had been adopted to describe previously distinct pathological entities with the neuroradiological features of MTS while involving other organ systems.¹ The new classification system divided JSRD into six sub-groups based on genotype-phenotype correlation.¹ These included pure JS, JS with ocular defect (JS-O), JS with renal defect (JS-R), JS with oculorenal defects (JS-OR), JS with hepatic defect (JS-H) and JS with oro-facio-digital defects (JS-OFD).^{1,10}

On examination, facial dysmorphic features including macrocephaly, prominent forehead, rounded eyebrows, epicanthal folds, ptosis, upturned nose and low-set tilted ears were seen.⁵ Hypotonia and intellectual disability were common features of JS along with hyperventilation that worsened on stimulation, followed by periods of apnea.¹¹ Respiratory abnormalities were known to be prominent during the neonatal period and reduced by six months of age.¹² Abnormal eye movements manifested due to underlying oculomotor dysfunction.⁵ Oculomotor apraxia was the most frequent eye finding which manifested as inability to track smooth pursuits and failure of the vestibulo-ocular reflex.¹ Other associated eye findings included retinal abnormalities, nystagmus, strabismus and ptosis.^{1,5} Renal involvement occurred in 25% of patients with the most common finding being nephronophthisis resulting in thickening of the basal membrane of the tubular epithelium, interstitial fibrosis and small cysts at the corticomedullary junction.¹ These patients generally present with polydipsia and polyuria with chronic renal insufficiency manifesting in the second decade of life. Hepatic subtype of patients tend to present with hepatosplenomegaly, portal hypertension, cirrhosis, oesophageal varices and elevated liver function tests.¹

On radiological investigation, MTS was seen consisting of midline hypoplasia of the cerebellar vermis, incomplete fusion of the halves of the vermis, abnormally deep interpeduncular fossa and thick superior cerebellar peduncles.^{1,2,4} The batwing or umbrella sign can also be seen due to the hypogenesis of the cerebellar vermis

resulting in dilatation of the fourth ventricle.^{11,13} Other findings included corpus callosum dysgenesis and moderate lateral ventricular enlargement.¹⁴ A detailed clinical history comprising the classical triad of JS and characteristic MTS sign on MRI were sufficient to confirm or exclude the disease after which investigation for possible multiorgan involvement should be done. Ocular investigations included evaluation of visual acuity, ocular motility, slit lamp examination, fundus oculi and electroretinogram.¹ Urine analysis with significance on urine specific gravity must be considered. An abdominal ultrasound can rule out hepatic fibrosis and evidence of renal structural changes.¹

In pregnant females, a diagnosis of JS was made possible prenatally by serial ultrasound imaging starting at 11 to 12 weeks gestation followed by an evaluation of cerebellar and foetal anatomy till 20 weeks of gestation and foetal MRI imaging at 20 to 22 weeks of gestation.¹¹ Genetic counselling had been recommended as one of the important measures to prevent JS. Prenatal diagnosis of JS can be done through chorionic villus sampling at about 11 weeks of gestation.¹⁵

Management strategies included supportive and symptomatic treatment. Special care was needed to manage respiratory and feeding problems and cognitive difficulties required appropriate rehabilitation strategy and regular follow up.¹ The sensitivity to the respiratory depressant effects of anaesthetic agents such as opiates and nitrous oxide were well known and hence, apnoea monitoring was required for them.¹⁴ Patients with delayed language and motor skills required special schooling to learn specific job skills and to work in a protected environment.⁵

The prognosis depended on the type and extent of organ involvement, patients who survived had persistent developmental delay and visual/motor deficit and some had developmental quotients that fall within the mildly delayed range (70 to 80).⁵ Annual screening as per diagnostic protocol was recommended for such individuals. Renal and retinal dysfunction can be progressive so the renal function should be monitored regularly and ultrasonography should be done to detect cystic renal disease.⁴ The prognosis of JS cases may be good, if diagnosed in early childhood and managed early through a multidisciplinary intervention program including physical therapy, special education, occupational and speech therapy.⁴

CONCLUSION

Through this scientific article we would like to emphasize the need of genetic sequencing in all patients that present with developmental delay and hypotonia irrespective of fulfilling the diagnostic criteria for JB. We also highlight and promote awareness regarding disabilities of the child and improvement of developmental milestones, balance

and walking with a multidisciplinary team approach started early after diagnosis.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

REFERENCES

1. Brancati F, Dallapiccola B, Valente EM. Joubert syndrome and related disorders. Orphanet J Rare Dis. 2010;5:20.
2. Nuovo S, Bacigalupo I, Ginevrino M, Battini R, Bertini E, Borgatti R, et al. Age and sex prevalence estimate of Joubert syndrome in Italy. Neurology. 2020;94(8):797-801.
3. Boltshauser E, Isler W. Joubert syndrome: episodic hyperpnea, abnormal eyemovements, retardation and ataxia, associated with dysplasia of the cerebellar vermis. Neuropadiatrie. 1977;8(1):57-66.
4. Parisi MA. Clinical and molecular features of Joubert syndrome and related disorders. Am J Med Genet C Semin Med Genet. 2009;151(4):326-40.
5. Akcakus M, Gunes T, Kumandas S, Kurtoglu S, Coskun A. Joubert syndrome: report of a neonatal case. Paediatr Child Health. 2003;8(8):499-502.
6. Parisi M, Glass I. Joubert Syndrome. Seattle (WA): University of Washington; 2003: 1993-2021.
7. Egger J, Bellman MH, Ross EM, Baraitser M. Joubert-Boltshauser syndrome with polydactyly in siblings. J Neurol Neurosurg Psychiatry. 1982;45(8):737-9.
8. Aslan H, Ulker V, Gulcan EM, Numanoglu C, Gul A, Agar M, et al. Prenatal diagnosis of Joubert syndrome: a case report. Prenat Diagn. 2002;22(1):13-6.
9. Chance PF, Cavalier L, Satran D, Pellegrino JE, Koenig M, Dobyns WB. Clinical nosologic and genetic aspects of Joubert and related syndromes. J Child Neurol. 1999;14(10):660-6.
10. Singh P, Goraya JS, Saggar K, Ahluwalia A. A report of Joubert syndrome in an infant, with literature review. J Pediatr Neurosci. 2011;6(1):44-7.
11. Elhassanien A, Alghaiaty HA. Joubert syndrome: clinical and radiological characteristics of nine patients. Ann Indian Acad Neurol. 2013;16(2):239-44.
12. Arora R. Joubert syndrome: imaging features and illustration of a case. Pol J Radiol. 2014;79:381-3.
13. Incecik F, Hergüner MÖ, Altunbaşak Ş, Gleeson JG. Joubert syndrome: report of 11 cases. Turk J Pediatr. 2012;54(6):605-11.
14. Dahman HA, Mubaireek AH, Alhaddad ZH. Joubert syndrome in a neonate: case report with literature review. Sudan J Paediatr. 2016;16(1):53-7.
15. Saraiva JM, Baraitser M. Joubert syndrome: a review. Am J Med Genet. 1992;43(4):726-31.

16. Nuovo S, Bacigalupo I, Ginevrino M, Battini R, Bertini E, Borgatti R, et al. Age and sex prevalence estimate of Joubert syndrome in Italy. *Neurology*. 2020;94(8):797-801.
17. Boltshauser E, Isler W. Joubert syndrome: episodic hyperpnea, abnormal eye movements, retardation

and ataxia, associated with dysplasia of the cerebellar vermis. *Neuropaediatric*. 1977;8(1):57-66.

Cite this article as: Patil SS, Rajagara SS, Vatkar AJ, Chakurkar SS. Joubert syndrome: unusual story. *Int J Contemp Pediatr* 2022;9:211-4.