A CASE REPORT OF JOUBERT SYNDROME IN ADULT PRESENTING WITH SEIZURES

Ramla Nayaib Hashmi, Umm ul Kiram
Department of Neurology, Liaquat National Hospital, Karachi, Pakistan

Correspondence to: *Ramla Nayaib Email: ramlahashmi123@gmail.com*
Date of submission: *August 31, 2014,* ***Date of revision:*** *October 12, 2014,* ***Date of acceptance:*** *November 1, 2014*

ABSTRACT

Joubert syndrome (JS) is rare autosomal recessive condition characterized by hypotonia, ataxia, psychomotor delay, and variable occurrence of oculomotor apraxia and neonatal breathing abnormalitie,intellectual disability, and specific mid-hindbrain malformation (“molar tooth sign”, MTS) We reportthe case of Joubert syndrome in a 32 years old female patient presenting with intellectual impairment, breathing abnormal breathing patterns like tachypnea followed by apnea ataxia, and seizures. She was diagnosed on the basis of Magnetic Resonance Imaging (MRI) and clinical features. JoubertSyndrome should be considered in all patients presenting with hypotonia, ataxia, nystagmus, breathing abnormalities and developmental delay. Its neuroimaging hallmarks include molar tooth sign and batwing shaped fourth ventricle.Joubert syndrome and related disorders (JSRD) refers to individuals who have JS with additional findings such as eye, renal and hepatic problems. As JS is associated with multiorgan involvement, these patients should enter a diagnostic protocol to assess systemic abnormalities. Extreme caution should be taken while administering drugs in these patients as they are prone to respiratory depression.Early diagnosis of Joubert syndrome and related disorders (JSRD) is important for rehabilitation programmes, prognostic outcome and genetic consultation. Close follow-up is also necessary to identify potential complications of the disease

Key Words: molar tooth sign, intellectual impairment, magnetic resonance imaging

BACKGROUND

Joubert Syndrome (JS) is a rare autosomal recessive disorder characterized clinically by neonatal breathing dysregulation, developmental delay, intellectual disability, hypotonia, ataxia, nystagmus and facial dysmorphism. Approximately 212 cases have been reported so far [(1)]. We report a case of this uncommon syndrome in a 32 years old female diagnosed by Magnetic Resonance Imaging along with the clinical features and discuss the neuroimaging findings.

CASE REPORT

A 32 years old female presented to emergency department of our institute with multiple episodes of generalized tonic clonic seizures (GTCS). She had history of delayed milestones, intellectual impairment, ataxia, abnormal breathing pattern manifested as tachypnea followed by apnea along with generalized tonic clonic seizures since childhood. Previously, patient has been taking homeopathic medications for seizures. The patient remained undiagnosed until the age of 32 as no neuroimaging or other diagnostic evaluation was performed on her.On examination she was a young female of average height and weight,coarse facial features, unconscious,,no eye opening on pain, bleeding from mouth due to tongue bite due to seizures, pupils 2 to 3 mm bilaterally reactive to light,neck supple ,intermittent stiffening of all 4 limbs,slight flexion of limbs on pain without any verbal output.planter response was extensor bilaterally.Fundoscopy was normal.Her laboratory investigations showed Hemoglobin 11.5 g/dL, Platelet count 250 *109/L,WBC 24.3,electrolytes were normal; renal functions showed slightly elevated creatinine of 1.5 mg%; phosphorus was 0.6mg%. Coagulation profile showed PT of 19 second, APTT 26 seconds,INR of 1.8. Liver function tests were normal except SGPT 118 units/L. Cerebrospinal fluid (CSF) analysis showed sugar 84 mg/dL (blood sugar - 181mg/dL), protein 30 mg/dL, RBC nil, WBC 5. CSF herpes simplex virus PCR and CSF cytomegalovirus PCR, as well as CSF gram stain and culture were all negative. Blood, urine and tracheal cultures were also negative. HBsAG and Anti HCV were nonreactive. Abdominal ultrasound was normal.EEG showed generalized slowing.Magnetic resonance imaging (MRI) showed superior cerebellar peduncles appear thickened and elongated giving the midbrain a molar tooth appearence; cerebellar vermis appeared mildly deformed (figures 1 and 2). Hence, the diagnosis of Joubert syndrome was made based on pathognomonic neuroimaging and clinical features. No genetic testing was done due to nonavailability of this facility. The patient was kept on supportive treatment which consisted of antiepileptics, antibiotics for respiratory tract infection due to aspiration

airway protection and chest and limb physiotherapy. Patient seizures were controlled but no significant improvement in her mental status.Patient discharged home on nursing care. 1 month after discharge she was again brought to liaquat National Hospital emergency in gasping state due to severe respiratory tract infection and expired.

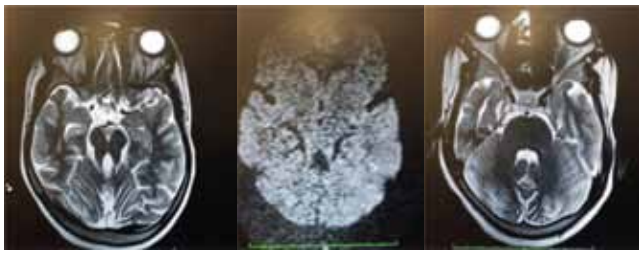

Figure 1,2: MRI T2W image and DWI showing thickened and elongated superior cerebellar peduncles giving molar tooth sign and mildly deformed cerebellar vermis. Figure 3 shows batwing shaped 4th ventricle

DISCUSSION

Joubert syndrome (JS) was originally described by Marie Joubertin 19682. The incidence of JShas been estimated between 1/80,000 and1/100,000 live births 3. Diagnostic criteria for JS include hypotonia, ataxia, global developmental delay, and the neuroradiological finding of MTS. In our patient all of these features were present.The term 'JSand related disorders' (JSRD) was introducedto refer to a group of pleiotropic conditions presenting the pathognomonic features of JSassociated with variable involvement of other organs and systems. These disorders have beenclassified as ciliopathies. Ciliary dysfunction can affect a single tissue or manifest as multi-organ involvement. The first gene for this condition was identified in 2004, andto date,21 causative genes have been identified, all encoding for proteins of the primary cilium or its apparatus. This is a subcellular organelle that plays key roles in development and in many cellular functions, making JS part of the expanding family of ciliopathies.

NPP5E,TMEM216,AHI1,NPHP1,CEP290,TMEM67,FTM (RPGRIP1L),ARL13B,CC2D2A,CXORf5 (OFD1),TTC21B,KIF7,TCTN1,TMEM237,CEP41,TMEM138,C5Orf42,TCTN3,ZNF423,TMEM231,TCTN2 (4)

Developmental impairment and intellectual disability are usually severe and present across a variety of domains, including behavior and motor, language and general development and it was present in our patient, she was mentally retarded, was unable to mobilize without support since childhood. The breathing pattern in JS is effortless hyperventilation, which is more conspicuous in the awake state and intensifies when the patient is stimulated, interspersed with central apnea. This abnormal breathing pattern is typically in the neonatal period and usually wanes with age. It was reported to be present in 71% cases in the study of Maria et al [5]. The CC2D2A gene was first identified in an extended consanguineous Pakistani family with autosomal recessive cognitive impairment with retinitis pigmentosa6.Our patient expired due to severe respiratory tract infection due to aspiration on readmission so Genetic study could not be done. Management is supportive and requires a multidisciplinary approach. Medication like opioids should be used with caution as these patients are sensitive to respiratory depressants, and anesthetic agents like nitrous oxide should be avoided. Cognitive and behavioral abnormalities should be dealt with adequate neuropsychological support and rehabilitation. Prognosis depends on the extent and severity of breathing dysregulation and systemic abnormalities [1,7,8].

CONCLUSIONS

Joubert Syndrome should be ruled out in all patients presenting with hypotonia, ataxia, nystagmus, breathing abnormalities and developmental delay. Its neuroimaging hallmarks include molar tooth sign and batwing-shaped fourth ventricle. As JS is associated with multi-organ involvement, these patients should undergo a diagnostic protocol to assess systemic abnormalities. Extreme caution should be taken while administering drugs in these patients as they are prone to respiratory depression

REFERENCES

1. Singh P, Goraya JS, Saggar K et al: A report of Joubert Syndromein an infant, with literature review. J PediatrNeurosci, 2011; 6(1):44–47
2. Joubert M, Eisenring JJ, Robb JP, Andermann F. Familial agenesis of the cerebellar vermis. A syndrome ofepisodic hyperpnea, abnormal eye movements, ataxia,and retardation. Neurology 1969; 19: 813-825.
3. Brancati F, Dallapiccola B, Valente EM. Joubert syndrome and related disorders. Orphanet J Rare Dis 2010; 5: 20.
4. Romani M, Micalizzi A, Valente EM. Joubert syndrome: congenital cerebellar ataxia with the "molar tooth".LancetNeurolsep 2013;12(9): 894-905.
5. Fabbri M, Vetrugno R, Provini F, Bosi M, Santucci M. Breathing instability in Joubert syndrome. MovDisord 2012; 27: 64.
6. Noor A, Windpassinger C, Patel M, et al. CC2D2A, encoding a coiled-coil and C2 domain protein, causes autosomal-recessive mental retardation

with retinitis pigmentosa. Am J Hum Genet 2008; 82: 1011-1018
7. Sarikaya B, Akpinar E, Karli-Oguz K et al: Joubert Syndrome:Magnetic resonance imaging findings. Neuroanatomy, 2004; 3: 30–31
8. Brancati F, Dallapiccola B, Valente EM: Joubert Syndrome and related disorders. Orphanet J Rare Dis, 2010; 5: 20

Conflict of interest: Author declares no conflict of interest.

Funding disclosure: Nil

Author's contribution:
Dr. RamlaNayaib Hashmi: Study concept and design, protocol writing, data collection, data analysis, manuscript writing, manuscript review
Dr.UmmulKiram: Data collection, data analysis, manuscript writing, manuscript review