Case Report

Development Delay in a Child with Microcephaly and Birth Asphyxia: Explore Diagnosis beyond Hypotonic Cerebral Palsy

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We describe a case of a 2-year-old female child who presented as emergency with acute gastroenteritis and severe dehydration. In this patient, there was a history of severe birth asphyxia, and the developmental milestones were delayed. The child was managed as hypotonic cerebral palsy elsewhere with antiepileptic drug and nutritional supplements. However, persistent abnormal pattern of breathing after adequate hydration and noncontributory metabolic profile raised the suspicion of alternate etiology. Later, the diagnosis of Joubert syndrome was established on contrast-enhanced magnetic resonance imaging of brain with findings of “molar tooth sign” appearance along with vermian hypoplasia. We present this case to alert the clinicians to explore all the differential diagnoses carefully whenever a child presents with the developmental delay associated with multisystem involvement.

**Keywords:** Birth asphyxia, cerebral palsy, development delay, molar tooth sign, polydactyly

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**How to cite this article:** Singh J, Dalal P, Rattan KN. Development delay in a child with microcephaly and birth asphyxia: Explore diagnosis beyond hypotonic cerebral palsy. J Pediatr Neurosci 2021;16:283-8.
showing weight gain, and seizures were controlled. Phenobarbitone was continued, and neuroimaging along with electroencephalogram were planned. But unfortunately, the child did not turn up for a follow-up visit. She started treatment elsewhere at a peripheral health unit at her native place, and she was managed as hypotonic cerebral palsy (CP) till present admission. On the present visit, the level of consciousness improved gradually after 2 days of treatment. The preliminary investigation revealed random blood sugar level as 76 mg/dL, hemoglobin 8 g, total leukocyte count (TLC) 24,000/mm³, serum sodium 146 meq/L, potassium levels 4.2 meq/L, and serum calcium level 9.1 meq/L. Renal and liver function tests were normal. Serum C-reactive protein (CRP) level was 46 mg/L. After adequate hydration, the patient was shifted to oral feeds and antiepileptic therapy was continued. But, the respiratory efforts were showing an episodic irregular pattern, and chest auscultation and radiograph findings were non-contributory. Because of hypotonia, creatine kinase enzyme levels were performed, which come out normal. The CSF analysis was also in the normal range. Ultrasound abdomen revealed normal hepatobiliary system and small cystic lesions in kidneys. Magnetic resonance imaging (MRI) brain revealed classical “molar tooth sign” and cerebellum vermis hypoplasia along with holoprosencephaly [Figures 2 and 3]. Bilateral frontal temporoparietal encephalomalacia with massively dilated ventricles and bat’s wing appearance of posterior fourth ventricle was also evident on neuroimaging, and diagnosis of Joubert syndrome (JS) and severe encephalomalacia was established. Electroretinogram findings were normal. There was no history of similar symptoms in other family members. The gene analysis (TMEM67) for JS diagnosis was planned but could not be done due to financial constraints. Appropriate physiotherapy and rehabilitation with the involvement of both parents and genetic counseling were planned.

**DISCUSSION**

Described first by Marie Joubert in 1969, JS is a rare autosomal-recessive condition with a reported incidence of 1 in 80,000–100,000 live births. It is characterized by cerebellar vermis agenesis, abnormal ophthalmic movements with nystagmus, irregular respiratory pattern, development delay, and retinal pigment abnormalities. Brain stem malformation and cerebellar vermis hypoplasia or agenesis are thought to be underlying pathology leading to the aforementioned symptoms. Because of varying clinical presentations with different phenotypes, the term “JS and related disorders” (JSRD) had been coined for the disorders comprising pathognomonic features of JS along with multiple systemic congenital abnormalities. Many gene mutations (e.g., TMEM67, AHI1, CEP290, and CC2D2A) had been identified for different pleiotropic phenotypes, all of them coding for abnormal ciliary protein. Owing to allelic and locus heterogeneity seen in JSRD, the clinical manifestations and associated medical conditions vary considerably. Our patient shared many features of JS with orofacial digital (JS-OFD) variant. The accurate diagnosis of JS is of prime importance as it may have therapeutic and prognostic implications. Moreover, as recurrence of JS had been also reported in subsequent pregnancies, genetic counseling and advanced prenatal screening may be offered to parents.

Hypotonic CP at 2 years of age is a great masquerader, and often children with cerebellar disorders present as hypotonic CP. Owing to overlapping clinical features, the diagnosis of JS can be delayed. Dekair et al. had reported a similar presentation of JS labeled as hypotonic CP in an 18-month-old child. Gunzler et al. and Atsumi et al. had described two cases of JS that were misdiagnosed as hypotonic CP, and the correct diagnosis was established by an MRI brain at the age of 48 and 25 years, respectively. In a report from India, Kumar and Singh described an 8-month-old girl who was being managed as hypotonic palsy.

**Figure 1:** Postaxial polydactyly in hand
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**Figure 2:** Contrast-enhanced MRI brain showing “molar tooth sign” (arrow) along with severe encephalomalacia

**Figure 3:** Contrast-enhanced MRI brain showing semilobar holoprosencephaly and vermian hypoplasia
and was diagnosed as JS later on with MRI of brain. Other disorders such as Dandy–Walker syndrome and rhombencephalosynapsis may share the radiological finding of cerebellar vermis hypoplasia and need to be differentiated from JS. Hydrocephalus is more commonly seen with Dandy–Walker syndrome, and it may pose a diagnostic challenge when associated with JS. The association of prenatal hydrocephalus with JS is a rarely reported occurrence in literature. Exact etiology is obscure, but it may be attributed to posterior fossa and CSF abnormalities. In Dandy–Walker malformation, the fourth ventricle is enlarged and communicates with a posterior fossa cyst. In rhombencephalosynapsis, a midline cerebellar cleft is absent. In a difference from JS, superior cerebellar peduncles are normal in both Dandy–Walker malformation and rhombencephalosynapsis. Other close differential diagnoses of hypotonia and developmental delay include congenital cytomegalovirus infection and congenital muscular dystrophies. They can be differentiated with prenatal history, family member involvement, radio imaging, immunological profile, and electromyography.

MRI of brain is the investigation of choice for the diagnosis of JS. On prenatal ultrasound screening, cerebellar vermis hypoplasia can be detected at the 20–21 weeks of gestation. If other findings are suggestive of JS (e.g., history of affected previous pregnancy, polydactyly, and occipital encephalocele), a fetal MRI scan is warranted to confirm the diagnosis. As there are 25% chances of recurrence in subsequent pregnancies, genetic counseling and prenatal screening form the important pillars of management.

**Conclusion**

JS is a rare clinical entity presenting with developmental delay, hypotonia, and ataxia and episodic respiratory dysregulation. Because of its rare occurrence and nonspecific presenting features, the accurate diagnosis may be delayed. Whenever a child presents with development delay and multisystem involvement, a genetic etiology should be kept as differential.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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