Case Report

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Joubert's Syndrome

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Abstract

Joubert syndrome is a autosomal recessive disorder (ciliopathy) with significant genetic heterogenicity that is associated with cerebellar vermis hypoplasia and the pontomesencephalic molar tooth sign (a deepening of the interpeduncular fossa with thick and straight superior cerebellar peduncles). Clinically there is hypotonia, ataxia(as toddler), characterized by breathing abnormalities including episodic apnea and hyperpnoea (which improves with age), global developmental delay, nystagmus, strabismus, ptosis and oculomotor apraxia. Here we report a case of a 45 day female child brought by parents with complaints of: Feeding difficulty and poor sucking since birth and abnormal movements of upper and lower limbs since day 6 of life. On MRI Brain, there is seen caudal Vermian agenesis, thickening and elongation of the superior cerebellar peduncle with deepening of interpenduncular fossa giving a batwing appearance of the fourth ventricle – 'molar tooth appearance' typically seen in Joubert Syndrome.

Keywords: Hypotonia; Apraxia; Seizures; Joubert's Syndrome.

Introduction

Joubert's syndrome is a well-recognized entity for paediatricians and neonatologists and refers to an infant with generalized hypotonia presenting at birth or in early life. An organized approach is essential when evaluating a floppy infant, as the causes are numerous [1]. Muscle tone can be defined as the tension in a relaxed muscle due to involuntary contractions of its motor units. It is our muscles that exert sufficient force against gravity to pull us upright; and it is our muscles that enable our postural reactions to maintain this upright posture and so prevent us from being injured [2]. Hypotonia is described as reduced resistance to passive range of motion in joints; weakness is reduction in the maximum power that can be generated. A more useful definition of hypotonia is an impairment of the ability to sustain postural control and movement against gravity. Thus, infants with Joubert's syndrome exhibit poor control of movement, delayed motor skills, and hypotonic motor movement patterns [3]. Weak infants always have hypotonia, but hypotonia may exist without weakness. Some indications of CNS abnormality are because of poor state of alertness, lack of response to visual and auditory stimuli, inability to manage co-ordinated functions like swallowing and sucking noted that the earlier the onset, the more severe and precipitus the course [4].

Case Report

A 45 day female child with informant being mother with consistently reliable history was brought by parents with complaints of:

Feeding difficulty and poor sucking since birth and abnormal movements of upper and lower limbs since day 6 of life. Also irregular respiration and nystagmus. She is second issue of third degree consanguineous marriage, born by normal vaginal delivery at completed 9 months of gestation with birth

weight of 2.5 kg and cried immediately after birth. She was admitted in NICU for poor suck and feeding difficulty since birth and is on nasogastric tube feeding since birth. She started having abnormal movements of upper and lower limb since 6th day of life. She was admitted in private NICU for initial 40 days. Outside baby was started on single anticonvulsant of phenobarbitone. The seizures were under control till day 42 of life after which she started having recurrent seizures not responding to phenobarbitone. She has global developmental delay. She is not immunized.

On General Examination,

Anthropometry

	Observed	Expected
Weight	2.5 kg	2.5 kg
Length	48 cm	50 cm
Head circumference	34 cm	35 cm
Chest circumference	31.5 cm	33 cm

On head to toe examination she had dysmorphic facial features like:

- Widely open anterior fontanelle.
- Hypertelorism.
- Nystagmus episodes intermittently.
- Low set ears
- triangular mouth opening

Hypertelorism Low set ears

On systemic examination

Central system examination

1. Higher function: child lethargic, poor eye contact, not interested in surrounding
2. Sensory system: Cannot be assessed.
3. Cranial nerves : Poor suck and poor gag reflex
4. Motor examination:

- Generalized hypotonia and frog like posture.
- Ragged doll appearance on ventral suspension.
- Complete head lag on pull to sit.
- Square window sign positive.
- No arm recoil.
- Scarf sign positive.
- Increased angle of dorsiflexion

Frog like posture Scarf sign positive

Complete head lag Ragged doll appearence

Other system examination was unremarkable.

On investigations: Hb- 11.2 gm/dl

TLC-6800

N-46, L-46, E-5, M-6

Platelet- 5.81 lakh /cumm

S.sodium- 138 mg%

S.potassium – 4.5 mg%

S.calcium- 9.5 mg/dl

RBS -125 mg%

Blood culture: no growth.

CSF routine examination: proteins- 22 mg/dl, sugar: 92 mg/dl, ADA -3 U/L.RBC -1, polymorph- 0, lymphocytes- 6.

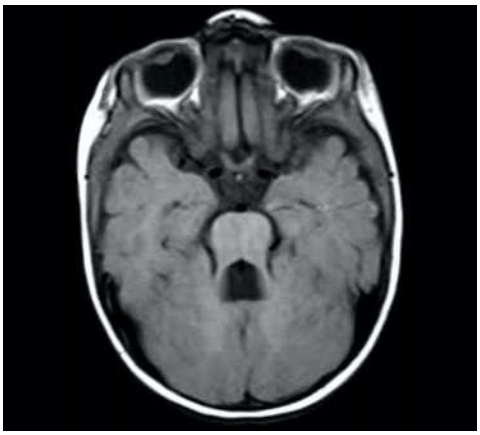
CSF culture: no growth.

2D ECHO: showed mild concentric left ventricular hypertrophy with dilated coronary sinus.

EEG: no abnormality detected.

On MRI Brain, there is seen caudal Vermian agenesis, thickening and elongation of the superior cerebellar peduncle with deepening of interpenduncular fossa giving a batwing appearance of the fourth ventricle – 'molar tooth appearance' typically seen in Joubert Syndrome.

Symmetrical white matter hyper intensities are seen in fronto-temporo-parietal-occipital region. No diffusion restriction is seen. Imaging differentials of Joubert syndrome are Hypoxic Ischemic Encephalopathy/ Metabolic Disorder-Inborn Error of Metabolism.



Molar tooth sign

Discussion

Joubert syndrome is a autosomal recessive disorder (ciliopathy) with significant genetic heterogenicity that is associated with cerebellar vermis hypoplasia and the pontomesencephalic molar tooth sign (a deepening of the interpeduncular fossa with thick and straight superior cerebellar peduncles). Joubert syndrome is estimated to affect between 1 in 80,000 and 1 in 1,00,000 newborn. Only 200 cases have been reported worldwide. However this incidence may be low because Joubert syndrome has such a large range of possible features and is likely under diagnosed [5].

Joubert syndrome is caused by mutation in at least 10 genes. The proteins produced from these genes are known or suspected to produce cell structures called cilia. Cilia are microscopic, finger like structures involved in chemical signaling and are important for function of neurons and certain cells of kidney and liver. It has a autosomal recessive pattern of inheritance. Rare cases of Joubert syndrome are inherited in an X linked recessive pattern [6]. Pathological studies in these patients have shown that the cerebellar vermis is hypoplastic and dentate nucleus is fragmented. The ponto-mesencephalic junction is dysplastic with abnormal decussation of the superior cerebellar peduncle and elongation of rostral fourth ventricle.

Clinically there is hypotonia, ataxia(as toddler), characterized by breathing abnormalities including episodic apnea and hyperpnoea (which improves with age), global developmental delay, nystagmus, strabismus, ptosis and oculomotor apraxia. Although the diagnostic criteria for Joubert syndrome has not been established, the clinical features mentioned for the diagnosis of classic JS include:

1. Hypotonia.
2. Developmental delay.
3. Irregular breathing.
4. Abnormal eye movements [7].

Our patient had all of the above clinical features. Associated supratentorial anomalies are uncommon but cerebral cortical dysplasia and gray matter heterotopias have been reported. Moderate lateral ventricular enlargement due to atrophy has been described in 6 to 20 % cases.

There may be associated systemic features (Joubert syndrome and related disorders) including progressive retinal dysplasia (Leber congenital amaurosis), coloboma, congenital heart disease, microcystic kidney disease, liver fibrosis, polydactyly, tongue protrusion and soft tissue tumors of tongue.

This syndrome is classified into two groups on basis of presence or absence of retinal dystrophy. Patients with retinal dystrophy have higher prevalence of multicystic renal disease and decreased survival rate. Besides JS, cerebellar vermian anomalies have been reported with other disorders like Dandy-Walker syndrome and rhombencephalosynapsis. Joubert syndrome and related disorders (JSRD) are categorized into six phenotypic subgroups: Pure JS, JS with ocular defect, JS with renal defect, JS with oculorenaal defect, JS with hepatic defect and JS with orofacialdigital defect. Developmental outcome is variable in JS.

Once a diagnosis of JS is made in a neonate or infant, the diagnosis of this syndrome can be made by looking for specific imaging findings at ultrasound during a subsequent pregnancy. Renal and retinal dysfunction can be progressive.

Symptomatic management is the only available treatment option [8,9].

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