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Classic Neuroimaging Features in a Case of Congenital Muscular Dystrophy [Fukuyama Variant] - a Rare Cause of Infantile Hypotonia in an Indian Male

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ABSTRACT

The aetiological diagnosis in an infant with hypotonia is a challenging task for a clinician due to variable and long list of differentials [1]. It could be due to an insult within the central nervous system (CNS) or less commonly result from a peripheral defect at neuro-muscular level and other miscellaneous causes (rickets, hypothyroidism) [2]. Most commonly it is a central hypotonia where the muscular weakness is absent or not profound. In Indian scenario, it is mostly idiopathic central hypotonia, followed by HIE (cerebral palsy) [2]. In cases of cerebral palsy, neuro-imaging reveals the severity of affliction. The peripheral aetiologies like congenital myopathies, congenital myasthenia, infantile botulism etc. are rather rare occurrences.

Infants with congenital muscular dystrophy have muscular dystrophy, central neural affliction and involvement of multiple systems (skeletal, cardiovascular, respiratory, ocular etc.). It is a rare disease with studies in Italian population showing point prevalence of 0.563 per 100,000 total population [3]. Unlike HIE, the affliction in CMD is multi-system and it is an inherited disease with variable penetration, the distinction between the two is important to a clinician for the management. CMDs generally have early fatal outcome. So, early diagnosis is important for prognostication, supportive treatment and genetic counselling. The neuro-imaging findings of CMD clearly stand out from the rest aetiologies and can guide a clinician to go in early , for an invasive test like muscle biopsy which is the gold standard diagnostic test .

Keywords: Infantile Hypotonia, Congenital Muscular Dystrophy, Cobblestone Lissencephaly, Fukuyama.

Abbreviations: CMD(congenital muscular dystrophy), HIE (hypoxic-ischemic encephalopathy), EEG (electroencephalogram), DGC (dystrophin-glycoproteins complex).

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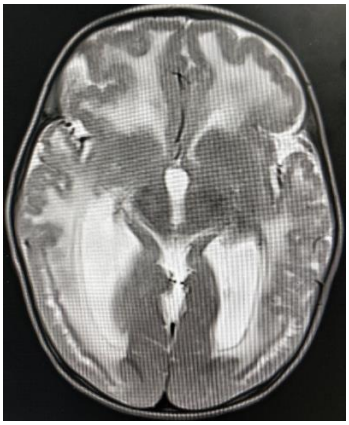
CASE REPORT-Here we report a case of CMD in an Indian male infant for the rarity of this disease. He presented with recurrent afebrile seizures, floppiness since birth and a small head size. He was the first issue of the mother, born from non-consanguineous marriage and delivered normally by vaginal route. The perinatal history revealed a low APGAR score of 06 at 5 minutes and frequent seizures since birth requiring hospital admissions. On examination he had a small head size (5^{th} centile) with hypotonic posture - limbs lying floppy on bed with an inability to sit in tripod with support at 8 months. The deep tendon reflexes were brisk, the muscle tone was reduced however the muscle bulk was normal. The infant also demonstrated a nystagmus. Rest of the systemic examination was unremarkable. Recurrent seizures and delayed motor milestones prompted a request for MRI brain.

The imaging findings revealed a cobblestone brain with areas of pachygyria and polymicrogyria (lissencephaly II). It also revealed gray matter spanning unmyelinated white matter at the posterior parieto-temporo-occipital cortex. There was ventriculomegaly with high arched corpus callosum, kinking of pons-midbrain junction (Z shaped configuration), vermian hypoplasia alongwith numerous small cerebellar cysts. These classic findings on MRI brain clinched the diagnosis CMD.



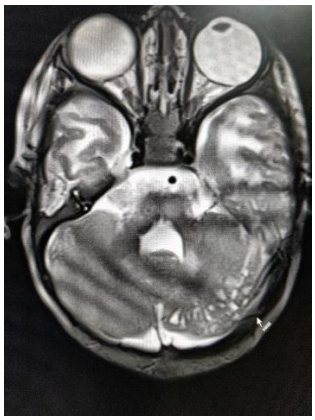


FIGURE 1 & 2– Axial T2 weighted MRI Brain images through third and fourth ventricles respectively of an infant reveal pachygyria in bilateral frontal and occipital lobe, polymicrogyria in bilateral temporal lobes, unmyelinated periventricu- lar white matter, a band of subcortical gray matter spanned by unmyelinated white matter, ventriculomegaly, absence of foliar pattern in cerebellar hemispheres and numerous small cysts in left cerebellar hemisphere.

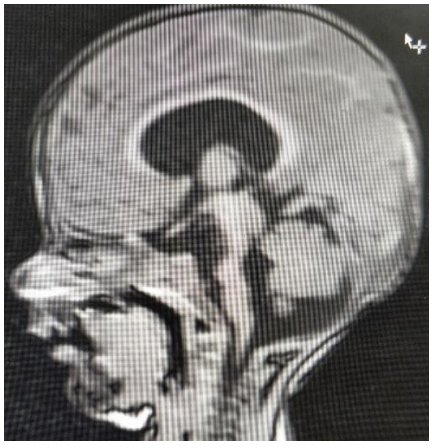


FIGURE 3 - Sagittal T1 weighted MRI Brain image shows Z configuration of ponto-medullary junction and high arched corpus callosum.

DISCUSSION

Hypotonia is reduced resistance to passive stretch [4]. Typical presentation of a hypotonic infant reveals an inability to sustain posture or perform motion against gravity. The causes of a hypotonic child can be classified as - central origin, attributable to central nervous system (CNS) abnormalities, or peripheral origin -abnormalities of motor unit, neuro-muscular junction, muscles or peripheral nerves. and other miscellaneous causes (rickets, hypothyroidism). Common central causes of hypotonia in a child are hypoxic-ischemic insult, intracranial haemorrhage, infectious diseases, metabolic disorders, chromosomal genetic diseases and congenital syndromes.

The evaluation of a hypotonic child involves a step wise detailed history and physical examination which help in narrowing down the probable differentials for a hypotonic child attributing it to one of the central neural cause or peripheral neuro-motor defect [5]. Perinatal history of TORCH infections, maternal drug use/ alcohol abuse, low APGAR scores at birth and any significant hospital admissions during neonatal life are the leading enquiries which strongly favour a CNS involvement. Consanguinity, stillbirth and prematurity should be enquired for chromosomal anomalies and genetic causes such as Prader Willi syndrome. General physical examination is done for evaluation of head size, facial dysmorphism and ocular abnormalities. Developmental assessment for a discordant motor development as compared to language and social skills also point out CNS involvement. Poor muscle tone with normal social and language development indicates peripheral neuro-motor defect. A feeble cry, easy fatiguability during feeding and extra-occular muscle weakness (ptosis) points to a motor unit affliction [6]. Visceral organomegaly during abdominal examination rai- ses the suspicion of lysosomal/ glycogen storage disorders [7]. Musculoskeletal examination in a normal well fed, awake and alert infant should reveal spontaneous active limb movements and reaching out and lifting up of objects. Muscular weakness manifests as a limp infant lying in frog-leg position with bare attempts at reaching out to an object . Vertical and horizontal suspension tests are performed to look for truncal and nuchal tone. Deep tendon reflexes can be absent in a lower motor neuron disease and brisk or clonus is seen in central neural problems. One must also assess muscle bulk and symmetry.

Whenever a CNS involvement is suspected an EEG and MRI brain is useful followed by invasive tests like muscle biopsy and special staining or specific genetic tests for Spinal muscular atrophy, Prader willi etc, if needed. Electromyography and nerve conduction velocity (NCV) are difficult to carry out and interpret in infants. However, reduced amplitude of action potential can point to a peripheral cause.

After a through physical examination, sorted biochemical workup including Liver function test, urine and serum for amino acid, urine for organic acids / ammonia can pick up abnormalities indicating a metabolic disorder or a dystrophic pathology. If a dystrophic process is considered a raised serum creatine kinase aldolase, ALT and AST is seen. Muscle biopsy is an invasive test, but electron microscopy and immunohistochemistry are utmost important in distinguishing between various types of congenital muscular dystrophies [8].

Infantile hypotonia is present in - congenital myotonic dystrophy, early spinal muscular atrophy as well as in congenital myasthenic syndromes, congenital myopathies and congenital muscular dystrophy. Neuroimaging comes in as a handy non-invasive investigation which may reveal classical findings of congenital muscular dystrophy. An invasive muscle biopsy can then be carried out if neuro-imaging suggests CMD.

Congenital muscular dystrophies (CMDs) are a relatively rare cause of central hypotonia and manifest similarly as congenital hypotonia, delayed motor milestones and progressive muscle weakness as other causes but with histological features of significant muscle fibre dystrophy. There have been many advances in molecular basis of these diseases. However, the basic pathogenesis involves a dysfunction of DGC in

the sarcolemma. The constant features of this syndrome include variable extent of lissencephaly (type II -cobble stone appearance), cerebellar malformation, retinal abnormalities and muscular dystrophy. The overall incidence is unknown. No incidence studies have been done on Indian population till date. The use of molecular analysis for classifications of CMDs has resulted in knowledge of its numerous types. In the above dystroglycanopathy - Fukuyama CMD. Other important dystroglycanopathies in this group inclular muscular syndrome (Muscle-Eye-Brain disease).

DIAGNOSIS- Neuro-imaging findings in the clinical setting of congenital hypotonia, afebrile seizures and motor developmental delays strongly suggested this rare form of CMD. Muscle biopsy from the patient revealed dystrophic changes with absent laminin alpha-2 staining confirming the diagnosis.

CONCLUSION- Classic neuro-imaging findings in appropriate clinical setting of a hypotonic child point towards the diagnosis of CMD and serve as a steering force in guiding investigations in the correct direction seeking aetiological diagnosis from amongst a plethora of differentials of a hypotonic infant, eventually aiding genetic counselling for future pregnancies.

The authors declare no conflict of interest.

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