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Hercules Baby - A Rare Case Presentation of Congenital Myopathy

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Abstract:- Congenital myopathies are a heterogeneous group of congenital neuromuscular disorders. Most of these disorders have subcellular abnormalities that can be only demonstrated by muscle biopsy and by means of histochemistry, immunocytochemistry and electron microscopy A genetic etiology is demonstrated in many of the congenital myopathies and molecular genetic testing from blood sample may confirm the diagnosis without muscle biopsy. These disorders have varied clinical presentation like dysphagia, respiratory insufficiency, cardiac insufficiency, global developmental delay. Here we report a case of a one month old male child ,born out of non- consanguineous marriage who presented with microcephaly, difficulty in feeding, difficulty in swallowing, respiratory distress, cyanosis and hypertrophy of all skeletal muscles including deltoid, biceps, triceps, gastrocnemius, hamstrings, adductors, muscles of abdomen sent was very high 2800IU/L.CT Brain done s/o diffuse cerebral hypodensity s/o ischemic changes .child was on ventilatory support so EMG and NCV could not be done. Whole exam sequencing sent s/o TPM3 heterozygous gene mutation which has been proven to play a very important role in muscle development and an important risk factor for development of congenital myopathies, hence a diagnosis of Congenital myopathies secondary to TPM3 tropomyosin gene mutation was made.

Keywords:- *Congenital Myopathy, Hypotonia, Developmental Delay.*

I. INTRODUCTION

Congenital myopathies are a rare group of heterogeneous neuromuscular disorders. Some of the specific congenital myopathies are central core disease, nemaline myopathy, myotubular myopathy (Centro nuclear myopathy), congenital fiber type disproportion. Most congenital myopathies are non-progressive condition, but some patients show slow clinical deterioration accompanied by additional changes in their muscle histology. IN some congenital myopathies such as severe neonatal nemaline myopathy, the clinical. Expression can life threatening because of dysphagia and respiratory or cardiac insufficiency. Cardiomyopathies develop in some patients with congenital myopathies. Most of the diseases in the category of congenital myopathies are hereditary, some as classical mendelian traits and others as sporadic or novel point mutations. Though clinical features including phenotype can raise a strong suspicion of a congenital myopathy ,the definitive diagnosis is determined by the histopathologic findings in the muscle biopsy specimen or by genetic testing in lymphocytes if a known specific mutation is present .The morphologic and histochemical abnormalities differ considerably from those of the muscular dystrophies ,spinal muscular atrophies and neuropathies but there may be co expression, exemplified by congenital muscle fiber type disproportion in infantile myotonic dystrophy .Many are reminiscent of the embryologic development of muscle thus suggesting possible defects in the genetic regulation of muscle development. Congenital myopathies often show closer genetic relationships than previously appreciated between entities that have quiet distinct pathologic phenotypes in the muscle biopsy and distinctiveness in clinical expression with a degree of overlap. Mutation of Tropomyosin 3 (TPM 3) gene is a well-known etiology of nemaline myopathy, but identical genetic mutation of this gene is also shown to be capable of causing isolated congenital fiber type disproportion without nemaline rods, cap myopathy, centronuclear myopathy and central core/minicore disease.

Clinical manifestations are varied such as fetal movements can decrease in late gestation, polyhydramnios is a common complication because of pharyngeal weakness of the fetus and inability to swallow amniotic fluid .at birth affected infants have a thin muscle mass involving axial, limb girdle and distal muscles, severe generalized hypotonia and diffuse weakness. Respiratory efforts may be ineffective requiring Ventilatory support. Gavage feeding may be required because of weakness of the muscles of sucking and swallowing. the testis is often undescended. Facial muscles may be weak, but infants do not have the characteristic facies . ptosis may be a prominent feature. ophthalmoplegia is observed in a few cases. The palate may be high. tendon stretch reflexes are weak or absent. Laboratory findings, serum creatine kinase can be high or normal. the muscle biopsy is diagnostic. electromyography does not show evidence of denervation, results are usually normal or show minimal nonspecific myopathic features in early infancy. Nerve conduction velocity may be slow but is usually normal. Most of these disorders have subcellular abnormalities that can be only demonstrated by muscle biopsy and by means of histochemistry, immunocytochemistry and electron microscopy A genetic etiology is demonstrated in many of the congenital myopathies and molecular genetic testing from blood sample may confirm the diagnosis without muscle biopsy.

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Only supportive and palliative treatment is presently available. Treatment remains largely supportive care for respiratory insufficiency and feeding and swallowing difficulties, but genetic approaches specific for identified mutations are being investigated and eventually may reverse some of the most disabling clinical deficits. administration of steroids as well as other antiinflammatory agents is not effective for congenital myopathies. Prognosis is poor. approximately 75 percent of severely affected neonates die within few weeks or months of life. survivors do not experience a progressive course but have major physical handicaps, rarely walk and remain severely hypotonic. Treatment by gene therapy may dramatically change this prognosis.

II. CASE REPORT

One month old male baby 3rd birth by order, born out of non-consanguineous marriage, preterm 35 week presented with complain of feeding difficulties like inadequate sucking reflex and difficulty in deglutition noted since birth. he also had complained of generalized muscular hypertrophy involving deltoid, biceps, triceps, abdominal muscles, quadriceps, hamstrings, calves which was not present on birth and gradually progressed over a period of month. He also had complained of cyanosis and respiratory distress which was intermittent. Distress was not present only while feeding. on examination microcephaly was present, generalized hypotonia present, deep tendon reflexes were diminished, neonatal reflexes such as swallowing, rooting sucking, moor reflex were weak, dysmorphic facies present. there was generalized muscular hypertrophy involving all the muscles of appendicular system and abdominal muscles also.

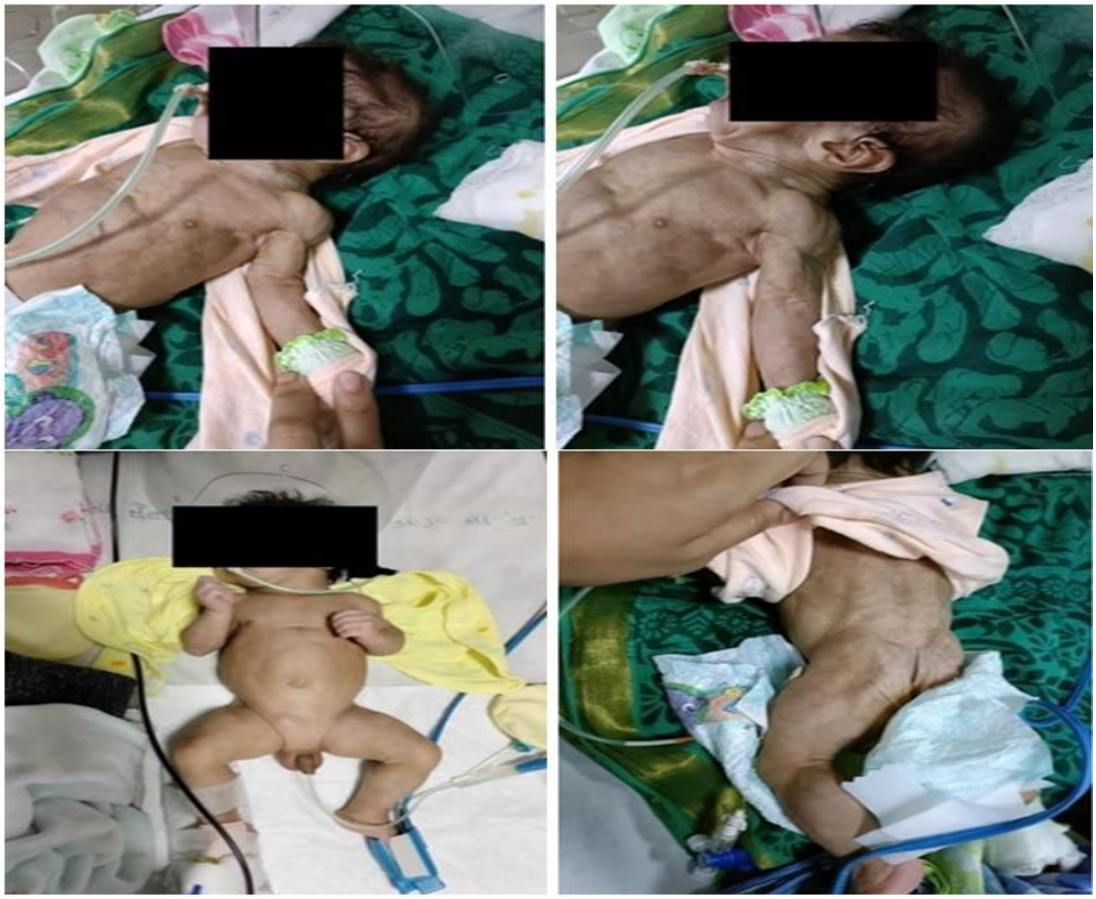

Fig 1 Generalised Muscular Hypertrophy With Hypotonia

III. INVESTIGATION

Complete hemogram s/o hemoglobin 8.2, white blood cell count 18400, platelet 248000/mm3.liver function test, renal function test were within normal limit.

- Reticulocyte count was very low 0.2
- Parvo virus Titer sent was very high 12.5 lakh IU/ml.
- Total CPK 2800IU/L
- 2d echo 1.8mm patent foramen oval with left to right shunt rest of the findings within normal limit.
- CECT brain showed diffuse cerebral hypodensities in bilateral cerebral hemisphere suggestive of ischemic changes.
- CECT thorax showed Diffuse bilateral lung parenchymal consolidation changes with air bronchogram suggestive of some infective etiology.

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IV. WHOLE EXAM SEQUENCING

Table 1 Exom Sequencing Report

Gene	Chromosomal Coordinates	Ex on	Variant*	Zygosity	Condition group	Significance (ACMG Classification)	Inheritence
CACN A1A	chr19:13409571:CG ATGACGT:-NM_001127221.2	19	c.2871_2879delACGTCATCG p.Arg958_Arg960del	Heterozygous	Developmental and epileptic encephalopathy 42	Variant of Uncertain Significance (VUS)	Autoso mal Domina nt
MAP2 K1	chr15:66779584:G:A NM_002755.4	3	c.914G>A p.Arg305Gln	Heterozygous	Cardiofaciocutneous syndrome 3	Variant of Uncertain Significance (VUS)	Autoso mal Dominant
TPM3	chr1:154131467:G:A NM_001043352.2	8	c.722C>T p.Thr241Met	Heterozygous	Myopathy, congenital, with fiber-type disproportion	Variant of Uncertain Significance (VUS)	Autoso mal Dominant

V. TREATMENT

Largely supportive care was given for respiratory insufficiency, feeding difficulties. Baby had respiratory distress, initially child was on 02 by prongs, distress progressed over a period, child was shifted from 02 by prongs to non-invasive ventilation and then gradually invasive ventilation was required. Child had weak sucking reflex, so child was fed through orogastric tube. Mainly supportive care was given in the form of oxygenation, nutrition, and palliation.

VI. DISCUSSION

Congenital myopathies describe a set of genetic diseases that predominantly affect the muscles. the classification of congenital myopathy has been evolving from a primary pathologic diagnosis to one with a genetic basis. The typical features of congenital myopathy include early-onset muscle weakness, often associated with features of low muscle bulk and tone. While these features are typically found in neonates and infants, children or even adults can present with milder forms of congenital myopathy. In certain cases, patients can have normal strength and tone but be at risk of rhabdomyolysis and/or malignant hyperthermia. Due to the early weakness, dysmorphic features such as contractures, a high arched palate, and facial dysmorphisms can be seen. Other clinical manifestations due to weakness are feeding difficulties, respiratory insufficiency, developmental delay. The classification of congenital myopathies has evolved to no longer be a pure pathologic diagnosis but rather relying more on genetic data. Diagnosis should be a combination of genetic, phenotypic, and, if needed to confirm, pathologic, electro diagnostic. The congenital myopathies can be divided into 6 pathologic categories. [1, 2]

- nemaline myopathy (subtypes: rod, core-rod, cap, and zebra body myopathy)
- core myopathy (subtypes: central core and multimonitor myopathy)
- Centro nuclear myopathy (subtypes: myotubular myopathy and autosomal centronuclear myopathy)
- congenital fiber-type disproportion myopathy
- myosin storage myopathy
- nonspecific myopathic changes

The true incidence of congenital myopathies is unknown as no large population-based studies have been conducted. However, there are a varied number of studies that demonstrate a relative incidence of the diseases. Of hypotonic infants due to neurologic causes, approximately 60%–80% were from a central cause and 12%–34% were from a peripheral cause. [3, 4] In the children with a peripheral cause of hypotonia, less than 50% of the cases were due to congenital myopathy. [3, 4] The frequency of symptom onset was in the neonatal period in 76% of cases in one cohort study. [5] largest cause of morbidity and mortality is related to muscle function loss resulting in respiratory and/or feeding failure.

According to the study by Colombo et al 5 at birth, neonates with congenital myopathy required respiratory support and nasogastric feeding in 30.4% and 25.2% of cases, respectively. Of note, in the study cohort 12% of patients died within the first year, whereas 74.1% achieved independent ambulation with 62.9% being late walkers. There is no cure, and management is mainly supportive and symptomatic. survivors are usually wheelchair dependent and unable to overcome gravity. Both proximal and distal muscle are involved. Congenital arthrogryposis and fractures can occur and predict a poor prognosis. gastrostomy may be needed for chronic dysphagia. special attention to respiratory function in patients presenting with scoliosis and axial involvement is important to recognize early signs and symptoms of nocturnal hypoventilation

syndrome. In the juvenile form, patients are ambulatory and can perform most tasks of daily living. Weakness is not usually progressive, but some patients have more difficulty over time or enter a phase of progressive weakness. cardiomyopathy in an uncommon complication. Death usually results from respiratory insufficiency with or without superimposed pneumonia. Based on preclinical data in a mouse model.

ACTA1 related nemaline myopathy, a variety of pharmacologic compounds and supplements, including L thyroxine have been tested with nemaline myopathy and has been found to be beneficial. Treatment targeting the neuromuscular junction are another option, a single patient with KLHL 40 related nemaline myopathy had a sustained beneficial response to pyridostigmine. Drugs targeting thin filaments and their interactions, myostatin inhibitors to promote muscle growth and cardiac aloha actinin upregulation are being investigated (6). Despite recent advances in our understanding of pathophysiologic concepts and efforts for therapy, genetic counselling and prenatal diagnosis should be considered in families with an index patient and a precise genetic diagnosis.

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