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Neonatal hypotonia- A case series

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***Abstract*---**Floppy baby is a non-specific and potentially serious multisystem disorder in the neonatal period. Diagnosing hypotonia in a newborn is very difficult as many disorders could manifest with diminished tone. In most cases, medical history and laboratory tests are useful for diagnosis, but they still require advanced research such as whole exome sequencing. The objective of this study was to know the presentation and how we evaluated hypotonia by using basic investigations to comprehensive molecular genetics tests which provides the advantage of the rapidity and diagnostic specificity as a part of the workup. Methods: This study was conducted on infants hospitalised in NICU at a tertiary care centre (Niloufer hospital), Hyderabad, Telangana, India. Clinical presentations, clinical examinations, laboratory tests, imaging, and genetic studies were reviewed. Clinical assessment includes evaluation of muscle tone, primitive reflexes, deep tendon reflexes, resting postures, and maneuvers. We used images and molecular genetic tests in the required cases. Results: Ten babies with hypotonia were studied. The male to female ratio was 6:4. The most common complaint was poor feeding, and other presentations were seizures, tachypnea, and icterus. On examination, all cases had hypotonia with absent DTR, and a few cases had dysmorphism. CPK levels were raised in a few cases of peripheral hypotonia and mixed hypotonia. Thyroid function tests were normal in all cases. In motor neuron disorders such as

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SMA and myopathies, NCV and EMG were abnormal. MRI was abnormal in congenital myopathy and peroxisomal disorders. A muscle biopsy was done in suspected myopathies and revealed myopathic changes. TMS and GS-MS were normal in most of the cases. Molecular genetic tests were abnormal in SMA and metabolic causes of hypotonia. Conclusion: Neonatal hypotonia is not uncommon in NICU in our setup. Any baby presenting with hypotonia in the neonatal period should be evaluated thoroughly because of the serious potentially underlying disorder. Diagnosing a patient with hypotonia remains a diagnostic challenge even though investigations have progressed. In most cases, the diagnosis was ascertained by antenatal history and neurological examination. MRI, genetic and metabolic tests were also important in diagnosis. Whole-exome sequencing has emerged as a more cost-effective and time-saving way to diagnose patients with hypotension.

***Keywords*---**floppy baby, hypotonia, thyroid.

Introduction

The classic "floppy infant" presents with nonspecific clinical signs due to a variety of disorders with varying degrees of hypotonicity, which may be axial, appendicular, or both. Hypotonia can be a manifestation of conditions on the spine called central hypotonia or segmental conditions called motor unit hypotonia. We must first determine the location of the pathology in the nervous system and then determine whether hypotonia is associated with weakness in the assessment of congenital hypotonia. Hypotonia can be defined as a decrease in the resistance of skeletal muscles to passive movement, while weakness is a decrease in muscle strength. The clinician carefully examines the pregnancy and neonatal history to determine the location of lesions affecting any level of the nervous system, whether central or peripheral[1].

Clinically, central hypotonia is characterized by seizures, normal or increased deep tendon reflexes, microcephaly with developmental delay along with weakness, on the other hand, decreased tendon reflexes, fasciculations, and prolonged breathing difficulties are observed in peripheral hypotonia. Based on previous data, central hypotonia (60-80%) is more common than peripheral hypotonia in neonates. Although asphyxia at birth is the more common cause of central hypotonia, other differential diagnoses include cerebral malformations (13%), congenital metabolic defects (3%), and genetic disorders as well[2]. Common syndromes associated with dysmorphisms such as Down syndrome and Prader Willi syndrome also cause central hypotonicity. Peroxisomal (Zellweger syndrome) and storage disorders are rare metabolic causes of central hypotonicity[3,4]. Diagnosing congenital hypotonia is a tedious task because manifestations are caused by many disorders, therefore genetic studies are imperative for prognostic information and screening strategies in these disorders. Depending on the clinical context, neuroimaging, biochemical testing, and genetic testing, including karyotype analysis, microarray and in situ fluorescence hybridization, are mandatory diagnostic tools[5].

Prognosis is largely based on the underlying cause. Illnesses such as transient myasthenia gravis and neonatal botulism have a good prognosis because they have disease-modifying therapies, whereas spinal muscular atrophy and Pompe disease (classical neonatal form), can be cause premature death in life.

Methods and Meterials

This study was conducted after the chart review and access to publications were approved by the Institutional Review Board of Niloufer Hospital, Osmania Medical University in Hyderabad, Telangana, India. Diagnosis depends on detailed medical history, family history, and clinical and developmental assessment of the baby. This is because about 50% of cases of hypotonia can be identified by detailed medical history and physical examination[6]. Clinical assessment was performed by examining muscle tone, primitive reflexes, reflexes of deep tendon, and resting posture. Infants can be evaluated in four ways. 1) Vertical suspension, 2) Horizontal suspension, 3) Scarf sign and 4) Pull to sit [7].

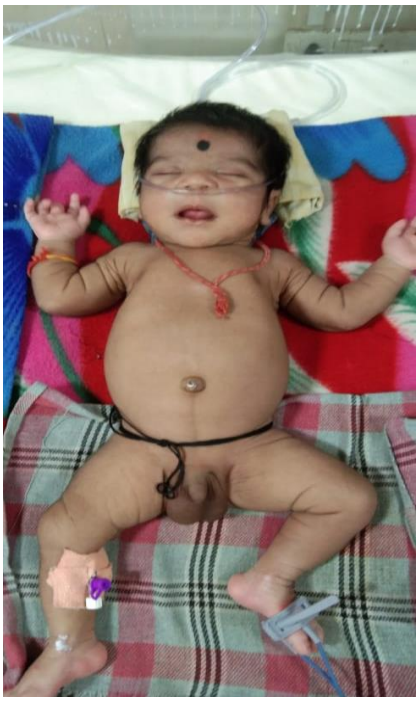
We excluded sepsis, hypoxic encephalopathy, and intracranial hemorrhage although these were the most common causes of hypotonia in the neonatal period. Basic blood tests and standard cultures (blood, urine, CSF) were performed to diagnose the infection. Specific laboratory tests were considered, including thyroid function tests to rule out hypothyroidism and screening for creatine kinase (CK). The potential for inborn errors of metabolism may be supported by baseline chemical acidosis, hyperammonemia, and persistent unexplained hypoglycemia. MRI of the brain and spine can rule out the CNS structural etiology of hypotonia if laboratory tests suggest the location of the CNS[8]. Whole-Exome Sequencing (WES) is also a popular tool on the market and is clinically useful for assessing multiple systemic diseases[9].

Cases Discription

Case 1:

A term male baby with dull activity, icterus, and decreased feed acceptance was brought in. The baby had low tone and neonatal reflexes.Antenatal history was normal. On pulling to sit, a baby had head lag, no resistance, and no flexion of the upper limbs, but some palmar grasp was present. On ventral suspension, the head falls forward in-plane with the rest of the body momentarily. In the prone position, the pelvis is not raised and the knees are not flexed. Power was diminished and DTR was absent. The sepsis screen was normal. Thyroid function and CPK levels were normal. The MRI was normal. TMS and GC-MS were normal.
Whole exome sequencing:

Table 1 : Variant of unknown significance							
Gene	Genomic Position	Variant change	Zygosity/ Inheritance	Seq. Depth	Variant type	Exon	Associated Disorders
*HSD17B4**	chr5: 118813159-118813160	c.398delC p.Ala133Glufs*6	Homozygous/ Autosomal Recessive	4x Ref=0 Alt=4 *(Low depth)*	frameshift deletion	7	D-bifunctional protein deficiency



Case 2:
A term (7-day old), male baby was admitted to the hospital due to difficulty feeding and dull activity. There was improvement in the level of consciousness, but the feeding difficulty and lack of vigorous spontaneous movement persisted. Antenatal and natal history were insignificant except for gestational diabetes. The O/E baby is comfortably sleeping with lower limbs abducted at the hips with partial flexion at the knees and elbows. On pulling to sit, head lag, no resistance, and no flexion of the upper limbs, but some palmar grasp are present. On ventral suspension, the head falls forward in-plane with the rest of the body momentarily. In the prone position, the pelvis is not raised and the knees are not flexed. DTR and neonatal reflexes were absent. The CPK level was -104 and the thyroid profile

was normal. TMS for amino acid disorders was normal. NCV had shown distal sensory-motor axonal neuropathy.

Case 3:
A full-term female baby was brought in with complaints of boredom and feeding difficulties. During the 8 months of GA, there was a h/o decrease in foetal movements. The baby is dull, in a supine position with the limbs extended. On pulling to sit, there was head lag (+), no resistance, and no flexion of the upper limbs, but some palmar grasp was present. On ventral suspension, the head falls forward in-plane with the rest of the body momentarily. In the prone position, the pelvis is not raised, and the knees are not flexed. DTR and neonatal reflexes were absent. CRP: elevated and treated with antibiotics. The thyroid profile was normal. CPK and S.Lactate were normal. The CT brain scan was normal. In TMS, ornithine is increased (263 micromol/L).

Case 4:
A 21-day old female baby was referred to Nioufer hospital in v/o feeding difficulties, poor activity. On examination, the baby had a dolicocephalic head with a retracted forehead and facial dysmorphism. Hypotonia manoeuvres showed hypotonia. Reflexes were absent. Thyroid and metabolic screening tests were normal.

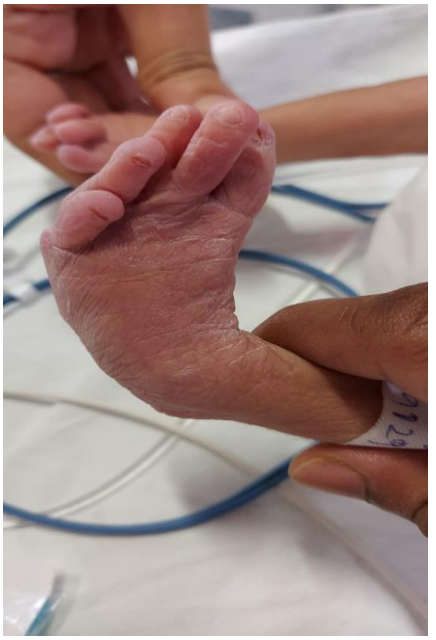
Case 5:
A 24 month old male term baby was brought in with complaints of not gaining weight and dull activity.H/O two sibling deaths in the neonatal period are present. The baby is dull and is in a supine position with the limbs extended. On pull to sit, there was head lag +, no resistance, and no flexion of the upper limbs, but some palmar grasp was present. On ventral suspension, the head falls forward in-plane with the rest of the body momentarily. In the prone position, Pelvis is not raised, and the knees are not flexed. DTR and neonatal reflexes were absent. Tongue fasciculations are present. The thyroid profile was normal. CPK levels were elevated and S.Lactate levels were normal. EMG showed motor and sensory axonal neuropathy. Finally, SMN gene analysis confirmed SMA.

Case 6:
A term male 27-day old baby presented with poor feeding. On examination, the baby was dull, and hypotonia was present. DTR and neonatal reflexes were present but sluggish. Blood gas has shown metabolic acidosis. The thyroid profile was normal. CPK and S.Lactate were normal. TMS was normal. MRI revealed hyperintensity in the b/l thalami and basal ganglia with frontal lobe white matter changes s/o mitochondrial myopathy. A congenital myopathy was diagnosed after a muscle biopsy revealed ragged red fibers.

Case 7:
A term 19 days old, the male baby was admitted with continuous seizure activity. Antenatal and natal history were insignificant. On examination, the baby is dull, with lower limbs abducted at the hips with partial flexion at the knees and elbows, indicating hypotonia. DTR and neonatal reflexes were absent. CPK levels were elevated and the thyroid profile was normal. The LFT was abnormal. 2decho

revealed cardiomegaly. EMG is associated with myopathic changes. A muscle biopsy revealed evidence of acid maltage deficiency.

Case 8:
At the age of 13, the baby presented with poor feeding and seizures. On examination, the baby was dull, with a weak cry and severe hypotonia present. DTR and neonatal reflexes were absent. Dysmorphic facies are present. The LFT was abnormal. The thyroid profile was normal. CPK and S.Lactate were normal. TMS was normal. Plasma VLCFA levels were raised and suggestive of peroxisomal disorder. An MRI revealed white matter changes.



Case 9:
A term 19 days old, the male baby was admitted with respiratory distress. There was a history of decreased foetal movements in utero. On examination, the baby was looking well and had respiratory distress with retractions. Generalized hypotonia was present.DTR and neonatal reflexes were absent. Cpk levels were mildly elevated and the thyroid profile was normal. 2decho revealed cardiomegaly. EMG studies revealed fibrillations. NCV was normal. Molecular genetic testing suggested spinal muscular atrophy.

Case 10:
A term 4-day-old female baby was admitted with respiratory distress. There was a history of polyhydramnios and reduced foetal movements. On examination, the baby had respiratory distress. Generalized muscular hypotonia and lower limb contractures are present. DTR and neonatal reflexes were absent. CPk levels were elevated, and the thyroid profile was normal. EMG changes associated with myotonia.

Results

Ten babies with hypotonia were studied. The male to female ratio was 6:4. The most common complaint was poor feeding, and other presentations were seizures, tachypnea, and icterus. On examination, all cases had hypotonia with absent DTR, and a few cases had dysmorphism. CPK levels were raised in a few cases of peripheral hypotonia and mixed hypotonia. Thyroid function tests were normal in all cases. In motor neuron disorders such as SMA and myopathies, NCV and EMG were abnormal.MRI was abnormal in congenital myopathy and peroxisomal disorders. A muscle biopsy was done in suspected myopathies and revealed myopathic changes. TMS and GS-MS were normal in most of the cases. Molecular genetic tests were abnormal in SMA and metabolic causes of hypotonia.

Discussion

Various degree of Hypotonia is a common sign of multiple disorders in newborns that may be caused by a lesion at any level of the neuronal axis. Most of the parents brought their babies with complaints of poor feeding, dull activity, and respiratory distress rather than weakness. The diagnosis of hypotonia is well ascertained by antenatal history and neurological examination. We had significant abnormal fetal movement in peripheral hypotonia[10]. Generally, the proportion of central hypotonia is much more than the peripheral type. Dysmorphism was noticed in a few patients, although it is observed in many cases of central hypotonia. Our study found that weakness was associated with all cases, especially peripheral and mixed hypotonia. Deep tendon reflexes, muscular weakness, and axial hypotonia have been substantially correlated with the scientific sort of hypotonia. Absent deep tendon reflexes were observed in Peripheral hypotonia and mixed hypotonia[10].

Metabolic studies are of little diagnostic use in neonatal hypotonia, but they are useful to aid in the final diagnosis. Creatine kinase is the first biochemical test if a peripheral cause of hypotonia is suspected and is most correlated with peripheral hypotonia. They are useful in diagnosing muscle disorders such as congenital muscular dystrophy and congenital myopathy. The neuroimaging choice was MRI in the case of central hypotonia and we observed abnormal CNS changes in the metabolic etiology of hypotonia. Cranial and spinal neuroimaging research are beneficial withinside the identity of structural malformations and pathological adjustments of mitochondrial abnormalities and metabolic sicknesses that may be visible in neuroimaging. In order to evaluate diseases that affect lower motor units such as SMA, Nerve conduction studies and electromyography have been used.

We did muscle biopsy in two cases and the yield was very low in diagnosis. Immunohistochemical staining and muscle biopsies using electron microscopy are the best ways to differentiate between myopathy and muscular dystrophy. Spinal muscular atrophy (SMA) was diagnosed by Molecular genetic tests (deletion of SMN gene). Molecular genetic testing such as single gene testing and whole -exome sequencing has been recommended in the assessment of neonatal hypotonia.

Conclusion

Neonatal hypotonia is not uncommon in NICU in our setup. Any baby presenting with hypotonia in the neonatal period should be evaluated thoroughly because of the serious potentially underlying disorder. Diagnosing a patient with hypotonia remains a diagnostic challenge even though investigations have progressed. In most cases, the diagnosis was ascertained by antenatal history and neurological examination.MRI, genetic and metabolic tests were also important in diagnosis. Whole-exome sequencing has emerged as a more cost-effective and time-saving way to diagnose patients with hypotension.

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