Current Practice

Clinical approach to a floppy infant

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Introduction

A floppy infant is one with hypotonia at birth or early infancy[1]. Hypotonia is a common symptom associated with disorders of brain, spinal cord, nerves and muscles[2].

Muscle tone is maintained at the peripheral level by participation of the fusimotor system: pathways involving the muscle spindles that promote muscle contraction in response to stretch and the inverse myotactic reflex involving the Golgi tendon organ that provides a braking mechanism to the contraction of muscle[3]. A lesion interrupting the stretch reflexes at any level in the lower motor neuron (LMN) will result in a loss of muscle tone and stretch reflexes i.e. flaccidity[3]. The output of gamma motor neurons to the muscle spindle is influenced by supraspinal influences, which are predominantly inhibitory; thus lesions affecting the upper motor neuron (UMN) result in the reduction of these inhibitory influences, in turn causing an increase in excitatory output of the gamma motor neurons to the muscle spindle[4]. However, in early infancy, contrary to the expected increase in muscle tone, the response to an UMN lesion in the early stages is flaccidity and loss of muscle tone[5]. This pattern of hypotonia is usually associated with preserved or hyperactive reflexes and later evolves into spasticity[6].

Parents commonly complain to physicians that their baby is very passive, that it does not move its limbs like others, that its breathing pattern is abnormal or inquire why the baby cannot be weaned off the ventilator. Floppy babies in early infancy may present with abnormal posturing of limbs and body, diminished resistance of limbs to passive movement, abnormal range of joint movement and /or ventilator dependency[7,8]. When these babies pass through infancy the next concern of the parents would be the delay in the motor milestones. The differential diagnosis of hypotonia presenting in the newborn is shown in table 1.

Table 1: Differential diagnosis of hypotonia presenting in newborns[9]

Anterior horn cell disorders	*Congenital motor or sensory neuropathies*
Acute infantile spinal muscular atrophy	Hypomyelinating neuropathy
Hypoxic-ischemic myelopathy	Charcot-Marie-Tooth disease
Neurogenic arthrogryposis	Dejerine-Sottas disease
Infantile neuronal degeneration	Hereditary sensory and autonomic neuropathy
Metabolic and multisystem diseases	*Muscular dystrophies*
Acid maltase deficiency	Dystrophinopathies
Severe neonatal phosphofructokinase deficiency	Congenital muscular dystrophy with merosin deficiency
	Congenital muscular dystrophy without merosin deficiency
Severe neonatal phosphorylase deficiency/ Debrancher deficiency	Congenital muscular dystrophy with brain malformations or intellectual disability
Primary carnitine deficiency	Walker-Warburg disease
Peroxisomal disorders	Muscle-eye-brain disease
Neonatal adrenoleukodystrophy	Fukuyama disease
Cerebrohepatorenal syndrome (Zellweger)	Congenital muscular dystrophy with cerebellar atrophy /hypoplasia
Disorders of creatine metabolism	
Mitochondrial myopathies	Congenital myotonic dystrophy
Congenital myopathies	*Neuromuscular junction disorders*
Nemaline myopathy	Transient acquired neonatal myasthenia
Central core disease	Congenital myasthenia
Myotubular myopathy	Magnesium toxicity
Congenital fibre type disproportion myopathy	Aminoglycoside toxicity
Multicore myopathy	Infantile botulism

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Once an infant presents, the most important aspect is the history to guide one to a possible aetiological diagnosis. Antenatal, natal and postnatal histories are important aspects that need attention (table 2).

Table 2
History taking in a hypotonic infant

Prenatal
Quality and quantity of fetal movements
Breech presentation
Poly or oligohydramnios
Natal
Birth trauma
Birth asphyxia
Delivery complications
Low cord pH and Apgar
Breech presentation
Postnatal
Neonatal seizures and an encephalopathic state
Dislocation of hips

The incidence of breech presentation is higher in fetuses with neuromuscular disorders as turning requires adequate fetal mobility. Documentation of birth trauma, birth anoxia, delivery complications, low cord pH and Apgar scores are crucial as hypoxic-ischaemic encephalopathy remains an important cause of neonatal hypotonia. Neonatal seizures and an encephalopathic state offer further proof that the hypotonia is of central origin. Onset of the hypotonia is also important as it may distinguish between congenital and acquired aetiologies. Family history is another important component in the history with consanguinity of parents and siblings with a similar illness. Early deaths / stillbirths and drawing a family tree / pedigree would be helpful for future genetic counselling

The clinical distinction between an UMN and LMN lesion provides a rationale for investigations based on localization of the lesion in the pathway of motor control (central vs. peripheral hypotonia). Weakness with hypotonia is unusual unless in acute situations in UMN lesions and profound weakness usually suggests a LMN lesion. Assessing power in an infant is generally limited to inspection. Useful indicators of weakness are:

1. Ability to cough and clear airway secretions (‘cough test’). Apply pressure to the trachea and wait for a single cough that clears secretions. If more than one cough is needed to clear secretions, this is indicative of weakness.
2. Poor swallowing ability as indicated by drooling and oropharyngeal pooling of secretions.
3. Character of the cry — infants with consistent respiratory weakness have a weak cry.
4. Paradoxical breathing pattern — intercostal muscles paralysed with intact diaphragm.
5. Frog-like posture and quality of spontaneous movements — poor spontaneous movements and the frog-like posture are characteristic of LMN conditions

Further confirmation of the last indicator can be obtained by means of informal neurological examination in the test positions. When traction is delivered to the arms, excessive head lag will be evident on ‘pull to sit’. Minimal support, with a sensation of ‘slipping through the hands’ during vertical suspension, and an inverted ‘U’ position on ventral suspension, are further indicators. Most hypotonic infants demonstrate a characteristic posture of full abduction and external rotation of the legs as well as a flaccid extension of the arms.

Weakness can be detected in the presence of a low-pitched cry / progressively weaker cry, readily distinguished from the vigorous cry of a normal infant. There is a paucity of antigravity movements in the weak and hypotonic infant. In addition, infants with neuromuscular disease are visually quite alert in comparison to those with central nervous system (CNS) involvement where depressed level of consciousness is present. The presence of characteristic patterns of regional weakness is noted in certain aetiologies. In central hypotonia, axial weakness is a significant feature. Preservation of muscle power with hypotonia and hyperreflexia favours a central origin to the hypotonia, while the combination of weakness in the antigravity limb muscles and hypo/areflexia together favour a neuromuscular disorder. A clear distinction, however, may not always be possible and features may overlap in conditions where the pathology affects both the CNS and the peripheral nerve[6].

The presence of a typical ‘myopathic’ facies and paucity of facial expression are common in hypotonic infants. A high arched palate is often noted in infants with neuromuscular disorders, while the tongue may be large in storage disorders (acid maltase / Pompe disease). The presence of tongue fasciculation suggests anterior horn cell disorders. Examination of eye movements may provide clues to the presence of ptosis and external ophthalmoplegia may suggest a myasthenic syndrome. Examination of the limbs and joints may show presence of arthrogryposis. Arthrogryposis refers to the fixed position and limitation of joint mobility affecting both proximal and distal joints. The main feature shared by these disorders appears to be the presence of severe weakness in early fetal development, which immobilizes joints, resulting in contractures. This can be a feature encountered in both neurogenic and myopathic disorders.

Neurogenic disorders are associated with a higher incidence of other congenital anomalies. The infants with myopathic features are less likely to be associated with other defects[8,9]. Visceral enlargement (hepatosplenomegaly) suggests storage disorders. The other disorders that should be suspected in an infant with hypotonia are peroxisomal disorders, congenital defects of glycosylation and sulphite deficiency[10,11, 12, 13].

Initial laboratory evaluation of the hypotonic newborn is directed at ruling out systemic disorders. Routine studies should include evaluation for sepsis (blood culture, urine culture, cerebrospinal fluid culture and analysis); measurement of serum electrolytes, liver functions, ammonia, glucose, calcium, magnesium, and creatinine; a complete blood count; and a urine drug screen.

If the hypotonia is considered to be central, the patients should be investigated with magnetic resonance imaging (MRI) of the brain/computer tomography (CT) brain. These are helpful in the identification of structural malformations, neuronal migration defects (e.g. lissencephaly), altered signal and characteristics of white matter (e.g. laminin deficiency). Signal abnormalities in the basal ganglia (e.g. mitochondrial cytopathies), as well as the detection of brain stem and cerebellar abnormalities (e.g. Joubert syndrome, pontocerebellar hypoplasia), are findings that may be pathognomonic for specific disorders.

A karyotype is indicated when several significant dysmorphic features are present e.g. Down syndrome and can disclose any obvious cytogenetic defects. Array comparative genomic hybridization study, methylation study for 15q11.2 (Prader-Willi/Angelman) imprinting defects, and testing for known disorders with specific mutational analysis are now available. Molecular genetic testing provides the advantage of diagnostic specificity. These tests should be chosen according to the clinical presentation of the infant.

If the clinical evaluation suggests a multisystem involvement, screening for inborn errors of metabolism is indicated. If acidosis is present, plasma amino acids and urine organic acids (aminoacidopathies and organic acidaemias), serum lactate (disorders of carbohydrate metabolism, mitochondrial disease), pyruvate, ammonia (urea cycle defects), and acylcarnitine profile (organic acidaemia, fatty acid oxidation disorder) should be measured. Very long-chain fatty acids are specific for the evaluation of a peroxisomal disorder.

To evaluate causes of peripheral hypotonia, creatine kinase concentrations should be measured. This is significantly elevated in muscular dystrophy but not in spinal muscular atrophy or in many myopathies. Specific DNA testing can be performed for myotonic dystrophy and for spinal muscular atrophy.

Other potentially useful screening tools include electrophysiologic investigations such as electromyography (EMG) and nerve conduction studies which show abnormalities in nerves, muscles and disorders of the neuromuscular junction. It must be stated that electrophysiological studies in a newborn and an infant are difficult due to technical and interpretation difficulties and are best performed by an experienced person. EMG is very accurate in spinomuscular atrophy (SMA)[11] and is often used as supportive evidence in establishing the diagnosis of SMA. Myopathic findings include low amplitude compound muscle action potentials (CMAPs) and small polyphasic motor unit potentials. Slow nerve conduction velocity (NCV) and conduction block favour peripheral nerve involvement. The EMG can also be useful for the diagnosis of a disorder of the neuromuscular junction (botulism, congenital forms of myasthenia gravis). The presence of a decremental response at 2–3 Hz rates of stimulation in at least one muscle is very suggestive of defective neuromuscular transmission in congenital myasthenic syndromes.

Investigations in a hypotonic infant are shown in table 3.

Differentiating features with the investigations according to the site of involvement are shown in table 4.

Table 3: ***Investigations in a hypotonic infant***

Rule out sepsis	If central hypotonia is suspected	If peripheral hypotonia is suspected
Blood culture	MRI brain/CT brain	Electromyography (EMG)/Nerve conduction studies (NCS)
Urine culture	Karyotyping	Muscle biopsy for staining with different reagents and electron microscopy
Cerebrospinal fluid culture	Molecular genetics	Creatine kinase (CK) level
Full blood count	Very long chain fatty acids (VLCFA)	Toxin assay i.e. Botulism
C reactive protein	Serum/Urine amino acids	Auto antibody levels
Erythrocyte sedimentation rate	Urine organic acids	
Serum electrolytes, calcium, magnesium	Blood/CSF lactate	Specific DNA testing
Serum glucose	Carnitine/acylcarnitine levels	
Liver functions/Ammonia	Serum ammonia	

Table 4: Differentiating features with the investigations according to site of involvement[14]

Site of involvement	EMG	Muscle biopsy
Central	Normal	Normal
Anterior horn cell	Fasciculation/fibrillation	Denervation pattern
Peripheral nerve	Fibrillation	Denervation pattern
Neuromuscular junction	Decremental/incremental	Normal
Muscle	Short duration small amplitude potential	Characteristic

Muscle biopsy with immunohistochemical staining and electron microscopy is the method of choice for differentiating myopathies and certain muscular dystrophies, although it is more invasive. If biopsy shows specific abnormalities, it can be an essential initial step in guiding the DNA studies to be performed in the affected infant.

The most common clinical condition, although a diagnosis of exclusion, is benign congenital hypotonia. This non progressive neuromuscular disorder presents at birth with delays in achieving developmental milestones. Benign congenital hypotonia improves with the maturity of the central nervous system. Characteristics include generalized symmetric flaccidity of muscles and hypermobile joints. Because this is a diagnosis of exclusion, the history must not suggest any neurologic or metabolic disorders. Muscle stretch reflexes are normal or only slightly exaggerated and routine laboratory test results are within normal limits. Parents must be counselled about this condition. An increased incidence of intellectual disability, learning disability, or other sequelae of cerebral abnormality is often evident later in life, despite the recovery of normal muscle tone. A high familial incidence also is reported.

The cause of hypotonia in most affected patients is central. The greatest diagnostic yield starts with a detailed medical history and examination, including a neurologic evaluation and the search for dysmorphic features. The selective use of neuroimaging, genetic studies, and biochemical investigations can contribute to a diagnosis in an additional subset of patients. Invasive studies with EMG and muscle biopsy only contribute to a small fraction of diagnoses[15] (Table 5).

Table 5: Diagnostic yield[15]

Method of diagnosis	% successfully diagnosed
History and physical examination (Step 1) Family history Pregnancy and delivery Clinical and neurologic examination	50%
Imaging study (Step 2) Computed tomography or magnetic resonance imaging Magnetic resonance spectrography	13%
Clinical genetic evaluation (Step 3)	09%
Genetic testing (Step 4) Karyotype Fluorescence in situ hybridization Comparative genomic hybridization	06%
Biochemical evaluation (Step 5) Amino acids, organic acids, peroxisomes, carnitine Congenital disorder of glycosylation test	06%
Neuromuscular testing (Step 6) Creatine kinase Electromyography Nerve conduction velocity DNA for spinal muscular atrophy and congenital muscular dystrophy Muscle biopsy	06%
Follow up testing Some tests repeated Further tests	07%

Treatment of the infant who has hypotonia must be tailored to the specific responsible condition. In general, therapy is supportive. Rehabilitation is an important therapeutic consideration, with the aid of physical and occupational therapists. Nutrition is of primary importance to maintain ideal body weight for the age and sex which is often achieved through the nasogastric route or percutaneous gastrostomy. It is important to maximize muscle function and minimize secondary crippling anatomic deformities. Regular orthopaedic review for scoliosis and hip subluxation / dislocation is an important aspect of management. Vigorous therapy for respiratory tract infections and annual flu vaccinations are advised in affected patients.

In certain conditions (muscular dystrophies, central core disease) anaesthetic complications such as malignant hyperthermia and difficulty in reversing muscle paralysis may be an issue; hence if these patients are undergoing anaesthesia, it is imperative that the anaesthetist is informed in advance.

Genetic counselling is an important adjunct for the family. Once a definitive diagnosis is available discussing among professionals is of paramount importance and discussing with parents and family members about the disease and prognosis is an important step. Weaning off the ventilator may be an issue as there may be social and ethical considerations involved. Counselling on family planning and future pregnancies with appropriate genetic diagnosis would be helpful.

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