RESIDENT & FELLOW SECTION

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Clinical Reasoning: A tale of a hypotonic infant

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SECTION 1

An 11-month-old girl was referred to our center for evaluation of hypotonia and developmental delays. She was born at term via cesarian delivery because of breech presentation. Fetal movements were reduced during pregnancy. Delivery and immediate postnatal events were uneventful. Her birth weight was low (2.5 kg). However, at 4 hours of life, she developed respiratory distress requiring intubation. She had 2 brief episodes of right upper extremity twitching on day one following intubation without further recurrence. She was extubated after 4 days. She had significant swallowing dysfunction requiring nasogastric tube feeding. She was the only child of her parents and there was no family history of neurologic disorders or early unexplained death.

Questions for consideration:

1. What is the differential diagnosis of a hypotonic neonate?
2. What tests would you consider to help narrow your differentials in this case?

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SECTION 2

On reviewing medical records from the outside hospital, it was noted that she had generalized hypotonia, poor spontaneous movements of the limbs, and reduced tendon reflexes. She was initially lethargic but subsequently was more awake. She had swallowing dysfunction but there was no ptosis, extraocular movement abnormalities, or tongue fasciculations.

Evaluation of a floppy or hypotonic infant is challenging for a child neurologist. Hypotonia is broadly classified into 2 categories: central (suprasegmental) and peripheral (segmental/motor unit).[1] However, this distinction is arbitrary and frequently there is overlap of clinical features in a sick neonate. Sometimes follow-up examinations are very helpful to establish a diagnosis in a hypotonic child. Systemic illnesses such as sepsis, hypoxic-ischemic encephalopathy, cardiac failure, and electrolyte and metabolic disturbances are common causes of central hypotonia.[1] Other causes of central hypotonia are brain malformations, various genetic/metabolic disorders (e.g., Down syndrome, Pompe disease), and spinal cord injury.[1] The motor unit hypotonia involves disorders of the anterior horn cell, peripheral nerve, neuromuscular junction, and muscle (table).

There was no evidence of septicemia or gross electrolyte or metabolic abnormalities. She had an elective cesarian delivery and there were no immediate postnatal complications, making hypoxic-ischemic encephalopathy less likely. She had a normal ECG and echocardiogram ruling out cardiac involvement. The child was lethargic at birth, and brief episodes of right upper extremity twitching were concerning for seizures, so a central cause of hypotonia cannot be ruled out. EEG did not disclose any epileptiform activity. Poor spontaneous movements and reduced tendon reflexes, however, suggested more of a peripheral cause of hypotonia.

Creatine kinase (CK) is a very helpful screening test to detect myopathy in children with hypotonia. She had high CK (2,787 U/L; normal 30–279 U/L) on her second day of life. Among the peripheral causes of hypotonia with high CK at birth, congenital muscular dystrophy (CMD) tops the list of differentials.[1] Other myopathies associated with high CK at birth are congenital myopathies (typically CK values are not very elevated) and some metabolic myopathies (e.g., Pompe disease).[1] Some muscular dystrophies (dystrophinopathies and some forms of limb girdle muscular dystrophy) can also present with high CK at birth although they typically do not present with hypotonia in the neonatal period.[1] Brain MRI on the third day of life was reported as T2-weighted hyperintense signals in the white matter of both cerebral hemispheres with frontoparietal predominance, disorganized appearance of the inferior cerebellar folia, and abnormal sulcal gyral pattern in both the cerebral hemispheres. Malformations of cortical development or white matter changes on neuroimaging are common in children with certain variants of CMD (merosinopathies [merosin-deficient CMD] and dystroglycanopathies [Fukuyama, Walker-Warburg, muscle-eye-brain

Table Common causes of neonatal/infantile hypotonia

Type of hypotonia	Clinical conditions	Investigations
Central (suprasegmental) hypotonia	Systemic illness (sepsis, meningitis, electrolyte disturbances)	Workup for sepsis, blood count, cultures, electrolytes
Normal muscle strength	Hypoxic ischemic encephalopathy	Brain MRI, EEG
Preserved or brisk tendon reflexes	Inborn errors of metabolism	Blood, CSF, and urine tests for metabolic disorders
Altered sensorium	Cardiac failure	ECG, echocardiogram
	Brain malformations	Brain MRI
	Genetic syndromes (Down syndrome, Prader-Willi syndrome, and others)	Genetic studies
	Spinal cord injury	Spine MRI
Peripheral (segmental/motor unit)	Anterior horn cell disorder (e.g., spinal muscular atrophy type 1: Werdnig-Hoffmann disease)	EMG (neurogenic changes), genetic studies
Reduced muscle strength	Peripheral nerve disorders (e.g., hypomyelinating neuropathy, Dejerine-Sottas disease)	EMG (peripheral neuropathy), genetic studies
Diminished or absent tendon reflexes	Neuromuscular junction disorders (e.g., transient neonatal myasthenia, congenital myasthenic syndrome, infantile botulism)	EMG (repetitive nerve stimulation and single-fiber EMG studies), anti-acetylcholine receptor antibodies in transient myasthenia, genetic studies for congenital myasthenic syndrome, toxin assay in botulism
Normal sensorium	Muscle disorders (e.g., congenital myopathy, congenital muscular dystrophy, Pompe disease, congenital myotonic dystrophy)[2]	EMG (myopathic EMG), muscle biopsy, genetic studies

disease]).[2] Based on the above findings, a provisional diagnosis of CMD was considered. Seizures can be a clinical manifestation in children with CMD due to underlying brain malformations. Swallowing assessment demonstrated a moderate to severe oral-pharyngeal dysphagia, with frequent laryngeal penetration and direct aspiration. Metabolic workup including thyroid function testing, serum amino acid profile, lactate, and acylcarnitine were normal.

Question for consideration:

1. What further testing would you consider to obtain a diagnosis?

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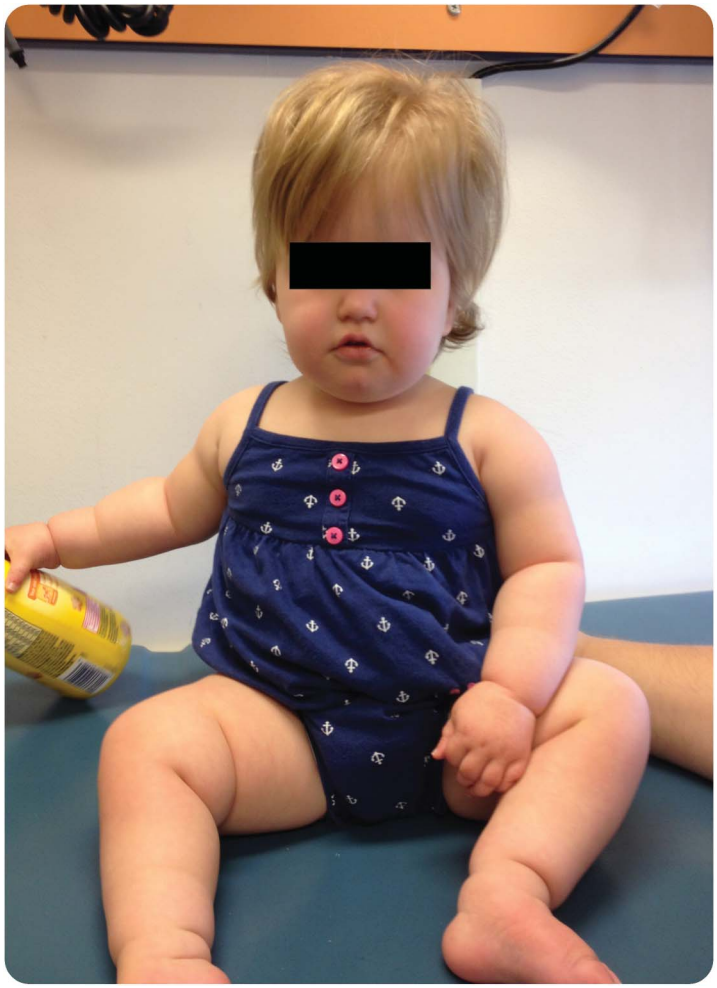
SECTION 3

EMG can be helpful in narrowing the differential diagnosis of peripheral causes of hypotonia, although neonatal EMG is technically challenging and sometimes difficult to interpret. Targeted genetic testing often identifies causative mutations, characteristic phenotype, or MRI appearance.[2] However, as there was no clear pattern in this case, the sequencing and deletion/duplication panel for CMD was sent, which did not detect any known pathogenic variants. The genes that will be of interest in this case with possible CMD, high CK, and brain imaging abnormalities are *LAMA2* (merosin-deficient CMD), Fukuyama CMD (*FKTN*), Walker-Warburg syndrome (*POMT1*, *POMT2*, *POMGNT1*, *FKRP*, *LARGE*), and muscle-eye-brain disease (*POMGNT1*, *FKRP*).[2] On follow-up neurologic evaluation at the outside hospital at 2 months of age, there were no obvious dysmorphic features; she continued to have diffuse hypotonia but her muscle strength improved. The child continued to have poor weight gain and swallowing dysfunction and underwent gastrostomy-tube placement at 7 months. At the same time, she had left vastus lateralis muscle biopsy, which did not show any evidence of myopathy or neurogenic atrophy. Subsequently, she was referred to us for further evaluation. At age 11 months, she had global developmental delays pertaining to motor, language, and social milestones. She started gaining weight after 8 months of life. Her weight was 10.1 kg (73rd percentile), height 71 cm (20th percentile), and head circumference 45.5 cm (66th percentile). She had dysmorphic facial features: almond-shaped eyes, upturned nose, tented and thin upper lip, and small chin (figure). She had mild diffuse hypotonia with good antigravity movements in the arms and legs and normal tendon reflexes. CK was checked and was found to be normal.

Question for consideration:

1. What diagnostic testing will confirm the diagnosis?

Figure Patient photograph.



Dysmorphic facial features: almond-shaped eyes, upturned nose, tented and thin upper lip, and small chin.

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SECTION 4

Salient points in her history and examination at this point were global developmental delays, low birth weight, failure to thrive followed later by increased weight gain, significant swallowing dysfunction, hypotonia with preserved strength and tendon reflexes, and dysmorphic facial features. With the above features, a central cause of hypotonia was high on the differential. Given her dysmorphic facial features, Prader-Willi syndrome (PWS) was strongly considered. A methylation study demonstrated loss of the paternally imprinted 15q11-13 region consistent with a diagnosis of PWS.

DISCUSSION PWS is a multisystemic complex genetic disorder due to lack of expression of genes on the paternally inherited chromosome 15q11.2-q13 region.[3]

It has an estimated prevalence of 1/10,000 to 1/30,000. There are 3 main genetic subtypes of PWS: paternal 15q11-q13 deletion (accounting for 65%–75% of cases), maternal uniparental disomy 15 (accounting for 20%–30% of cases), and the remaining (1%–3%) due to an imprinting defect.[4] DNA methylation analysis using Southern blot or methylation-specific PCR identifies PWS in 99% of cases, although it does not provide information about the molecular type of the disease.[5]

Severe hypotonia is nearly universal at birth and during the neonatal period, so PWS should be considered in the differential diagnosis of unexplained neonatal hypotonia.[4] Hypotonia is manifested during antenatal life as reduced fetal movements, and atypical presentation at delivery sometimes requiring assisted delivery and cesarean delivery.[6] Also, infants with PWS are lethargic and have reduced spontaneous movements. They frequently have weak cry, poor suck, and failure to thrive.[4]

One confounding factor in our case was elevated CK, which led to the presumptive diagnosis of CMD. We do not have a clear explanation of high CK after birth in this case as CK is usually normal in children with PWS.[7] EMG is also normal in most children with PWS with few cases exhibiting increased insertion activity and neuropathic or myopathic changes.[7] Muscle biopsy is typically normal in PWS with few cases demonstrating atrophic fibers and increased interstitial adipose tissue. However, on electron microscopy, ultrastructural abnormalities were demonstrated although they were not specific.[7] So there is no convincing evidence of lower motor neuron involvement in PWS.

Other features of PWS are hypogonadism, short stature unless treated with growth hormone, hyperphagia leading to morbid obesity beginning during early childhood (hypothalamic involvement), developmental delay, intellectual disability, speech articulation defect, autistic spectrum disorder, behavioral issues, including obsessive-compulsive disorder, and sleep disorders including sleep apneas.[4] Characteristic facial features include almond-shaped eyes, prominent nasal bridge, high narrow forehead, thin upper lip, and downturned mouth. The dysmorphic facial features are noted in 80% of cases[4] and may not be apparent early in life.

Brain MRI frequently reveals an intracranial morphologic abnormality, predominantly ventriculomegaly, although these changes are nonspecific and MRI is not routinely performed in a child with PWS.[8] The MRI changes that were observed in our case have not been described, and we did not repeat MRI after the diagnosis of PWS was confirmed.

PWS is a classic example of a central cause of hypotonia, which can mimic peripheral hypotonia in the neonatal and early infantile period. Swallowing dysfunction and respiratory difficulties are common features of this syndrome and can mimic other neuromuscular disorders. Dysmorphic facial features can be missed in early life. This diagnosis should be considered in a hypotonic neonate with significant swallowing dysfunction. Early diagnosis can avoid unnecessary investigations and initiate appropriate management and provide genetic counseling for the family.

AUTHOR CONTRIBUTIONS

Dr. Partha S. Ghosh: study concept and design, critical revision of the manuscript for important intellectual content, study supervision. Dr. Fouad Al-Ghamdi: acquisition of data. Dr. Fouad Al-Ghamdi and Dr. Partha S. Ghosh: analysis and interpretation.

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DISCLOSURE

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