Clinical Reasoning: A neonate with micrognathia and hypotonia

Marissa M. Vawter-Lee,
MD
Shannon S. Seals, MD
Cameron W. Thomas,
MD, MS
Charu Venkatesan, MD,
PhD

Correspondence to
Dr. Vawter-Lee:
Marissa.Vawter@cchmc.org

SECTION 1

A female infant was delivered via cesarean section at 39 weeks' gestation to a 40-year-old mother. Pregnancy was notable for normal fetal movement and amniotic fluid indices. Apgar scores were 7 and 8 at 1 and 5 minutes. Shortly after birth, the infant developed respiratory distress and apnea that resolved with repositioning of her neck and trunk. General examination was remarkable for severe micrognathia, high arched palate, bitemporal wasting, and bilateral talipes varus (club foot) contractures. Neurologic examination showed intact mental status, facial diplegia, axial hypotonia

with vertical suspension, normal resting tone (knees and elbows were flexed when supine), normal strength (i.e., antigravity throughout her extremities), and normal infantile and deep tendon reflexes. She was transferred to our neonatal intensive care unit for evaluation of surgical options to correct her micrognathia.

Questions for consideration:

1. What is the differential diagnosis of neonatal hypotonia?
2. How do her physical examination findings narrow the differential diagnosis?

[GO TO SECTION 2](#)

From the Division of Neurology (M.M.V.-L., C.W.T., C.V.), Cincinnati Children's Hospital and Medical Center; and Department of Neurology (S.S.S.), University of Cincinnati Medical Center, OH.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

SECTION 2

A wide range of disorders present with hypotonia during the neonatal period. Important details to consider in the prenatal history include quality and quantity of fetal movements and presence of polyhydramnios, as these factors may suggest intrauterine hypotonia or central nervous system injury. Cesarean section due to breech presentation may also indicate decreased or ineffective fetal movement.¹ Neonatal hypotonia can be due to central, peripheral, or mixed causes (table 1). Central causes are most common in the neonate and include hypoxic ischemic encephalopathy, infections (sepsis, meningitis, encephalitis), chromosomal disorders (Down syndrome, Prader-Willi), and metabolic disorders.¹ Some central causes demonstrate hypotonia at birth (hypoxic ischemic encephalopathy and chromosomal disorders) whereas others may not manifest hypotonia for hours or days (sepsis and metabolic disorders). Peripheral processes include anterior horn cell disease (spinal muscular atrophy), motor/sensory neuropathies (Dejerine-Sottas), neuromuscular junction disorders (transient neonatal myasthenia, congenital myasthenia gravis, botulism), congenital myopathies (nemaline rod, central core, fiber-type disproportion), muscular dystrophies (congenital myotonic dystrophy [CMD] and congenital muscular dystrophy such as merosin deficiency), and several metabolic disorders (Pompe,

Zellweger, mitochondrial myopathy).¹ Combined causes (due to abnormalities of both the upper and lower motor neurons) include dystroglycanopathies (Walker-Warburg, Fukuyama, muscle-eye-brain disease), mitochondrial encephalomyopathies, congenital disorders of glycosylation, Pelizaeus-Merzbacher, and Canavan disease.²

Physical examination findings may differentiate between central and peripheral causes, although some disorders will have features of both (table 2). Not every central or peripheral cause will include all distinguishing features. Neonatal examination findings must always be considered in the context of the gestational age. Thorough general examination may reveal organomegaly, skin stigmata, or craniofacial and other somatic dysmorphisms that suggest specific genetic or metabolic diseases. Neurologic examination should then be performed with particular attention to features that may distinguish central and peripheral causes of hypotonia. Altered mental status should heighten concern for central causes of hypotonia (although there are genetic central causes in which mental status is preserved). Tone and strength are frequently assessed in tandem. Infants with central hypotonia often demonstrate relatively greater reduction in tone than in muscle strength (which is typically antigravity or better), whereas in peripheral disorders, weakness becomes more prominent. Reflex examination in central causes may show normal or

Table 1 Differential diagnosis of neonatal hypotonia

Central causes	Mixed central and peripheral causes	Peripheral causes
Hypoxic ischemic encephalopathy	Mitochondrial encephalomyopathies	Anterior horn cell disease (spinal muscular atrophy)
Infection (sepsis, meningitis)	Congenital disorders of glycosylation	Neuropathies (Dejerine-Sottas)
Chromosomal disorders (Down syndrome, Prader-Willi, etc.)	Pelizaeus-Merzbacher	Neuromuscular junction (transient neonatal myasthenia, congenital myasthenia gravis, botulism)
Metabolic disorders (inborn errors of metabolism)	Canavan disease	Congenital myopathies (nemaline, central core, fiber-type disproportion)
	Dystroglycanopathies (Walker-Warburg, muscle-eye-brain, Fukuyama)	Congenital muscular dystrophies (myotonic dystrophy, merosin deficiency)
		Metabolic (Pompe, Zellweger)

Table 2 Physical examination findings to differentiate central vs peripheral neonatal hypotonia

	Central causes	Peripheral causes
Mental status	Can be altered or normal	Normal
Strength	Normal	Decreased
Reflexes	Normal or increased	Decreased or absent
Other key exam findings	Dysmorphic features	Tongue fasciculations (e.g., spinal muscular atrophy)

hyperactive reflexes but may be decreased or absent in peripheral disorders. Contractures and arthrogryposis can be seen with either central (e.g., holoprosencephaly) or peripheral causes (e.g., spinal muscular atrophy). At times, as in the reported case above, infants may have features of both central and peripheral causes, increasing diagnostic uncertainty.

The key distinguishing feature for this infant was bitemporal wasting, suggesting a specific peripheral cause for her hypotonia.

Question for consideration:

1. What imaging and laboratory workup should be done to evaluate neonatal hypotonia?

[GO TO SECTION 3](#)

SECTION 3

Evaluation of the hypotonic infant is directed by the clinician's suspicion for a central vs peripheral etiology. An etiology for hypotonia can be identified in 50% of hypotonic infants based on the history and physical examination alone.³ Laboratory and imaging evaluation can further refine the diagnostic process (table 3). Sepsis requires emergent evaluation and treatment; thus, clinical suspicion should prompt urgent acquisition of serum, urine, and/or CSF cultures. Investigation of central hypotonia usually begins with brain imaging, preferably MRI, to evaluate for structural, traumatic, or metabolic diseases. Magnetic resonance spectroscopy can provide additional information when there is concern for metabolic derangement. Additional workup can include genetic (karyotype, single nucleotide polymorphism microarray, exome) and metabolic evaluation (electrolytes, liver function, ammonia, serum amino acids, urine organic acids, lactate, pyruvate, and acylcarnitine). Investigation of peripheral hypotonia can also begin with imaging as many peripheral diseases have characteristic brain imaging findings. For example, congenital muscular dystrophies can have increased white matter signal intensity on brain MRI.² For investigation of mixed causes of hypotonia, MRI and additional testing should be guided by history and examination. Concern for muscle diseases should prompt measurement of serum creatine kinase (CK) levels, but one should interpret elevations in the first 1 to 2 days of life with caution and consider following trends as CK may be affected by birth trauma. Additional ancillary testing might include muscle biopsy and EMG and nerve conduction studies (NCS). Interpretation of neonatal EMG/NCS is confounded by a newborn's size (it is easy to costimulate nearby nerves), the enlarged endplate zone in neonatal muscles (which can lead to endplate spikes being interpreted as fibrillations), normal smaller motor unit action potentials (which may appear myopathic), and slower conduction velocities (due to newborn nerves having incomplete myelination).⁴

Our patient's electrolytes and liver enzymes were normal. Muscle CK was 177 U/L (normal 60–305). Brain MRI showed severe micrognathia, along with mild enlargement of the lateral ventricles, thin corpus callosum, and mild cerebellar hypoplasia (figure). Family history revealed that the infant's mother had undergone 3 jaw distraction procedures in her 30s. She also reported “freezing” of her hands when opening jars. Physical examination of the mother was remarkable for long, thin facial features, bitemporal wasting, and percussion myotonia.

The sum of the infant and maternal physical examinations, along with family history, prompted testing for CMD. This showed 1,500 CTG repeats on one allele of the *DMPK* gene (normal 5–34, asymptomatic 35–49, and >50 repeats abnormal), consistent with a diagnosis of CMD. Positive diagnosis is confirmed by CTG repeat number >200.

The multidisciplinary airway team at our hospital thought that the patient's severe micrognathia was contributing to her obstructive apnea. She therefore underwent mandibular distraction surgery. The surgery stabilized the apnea, and the infant was discharged home with nasal cannula oxygen support.

DISCUSSION CMD is an autosomal dominant condition caused by a defect in the *DMPK* gene on chromosome 19, resulting in an increased number of CTG trinucleotide repeats (OMIM #160900). Myotonic dystrophy can present at any age. A CTG repeat number >200 and clinical manifestation before 30 days of age are consistent with a diagnosis of CMD.⁵ CMD typically presents as hypotonia and respiratory distress present at birth. However, other neonatal findings might include raised hemidiaphragm, delayed gastric emptying, reflux, difficulty feeding requiring nasogastric or gastric tubes, cerebral ventriculomegaly, apnea, club feet, facial weakness, and tenting of the upper lip.⁵ Of note, the CTG repeat count does not correlate with severity of the phenotype. Some infants may have a high repeat count but

Table 3 Evaluation for central and peripheral causes of hypotonia

Central cause evaluation	Peripheral cause evaluation
1. Sepsis evaluation if appropriate	1. CK
2. Liver function testing	2. Brain MRI/MRS
3. Metabolic evaluation (serum amino acids, urine organic acids, lactate, pyruvate, acylcarnitine, ammonia) ^a	3. EMG/NCS
4. Brain MRI/MRS	4. Genetic testing (e.g., <i>SMN1</i> or CTG repeats)
5. Genetic testing (chromosomes, microarray, whole exome sequencing)	5. Muscle biopsy

Abbreviations: CK = creatine kinase; MRS = magnetic resonance spectroscopy; NCS = nerve conduction study; *SMN1* = survival of motor neuron 1.

^aFurther metabolic testing can include CSF analysis (cell count, protein, glucose, amino acids, lactate, pyruvate, neurotransmitters) and very long chain fatty acids.

Figure Brain MRI of patient with hypotonia and micrognathia

The T2 axial (A) image shows mild enlargement of the lateral ventricles. The T2 sagittal (B) image shows a thin corpus callosum, cerebellar hypoplasia, and micrognathia.

have minimal symptoms, whereas some infants with a lower CTG repeat count have severe CMD.⁵

Respiratory distress is a prominent feature of CMD. In the past, infants with CMD who required early ventilator support were thought to have a poor prognosis; however, recent research questions this conclusion.^{5,6} A 2013 surveillance study in Canada followed a cohort of patients with CMD and showed that although the neonatal period is often tenuous and may involve prolonged intubation and ventilator support, this does not correlate with the infant needing lifelong invasive oxygen support.⁵ The need for supplemental oxygen support and tracheostomy did not correlate with increased mortality or morbidity.^{5,6} The majority of infants with CMD do not have long-term supplemental oxygen needs.

This case highlights the importance of maintaining a high index of suspicion for neonatal neuromuscular disorders. Neonatal neuromuscular conditions should be considered in any infant who presents with respiratory distress and hypotonia, regardless of the severity of symptoms. Detailed physical examination

may reveal subtle signs of CMD including bitemporal wasting, tented upper lip, or club feet. Hypotonia in an infant should also trigger a more thorough family history, and when appropriate, targeted physical examination of the parents to evaluate for subtle signs of myotonic dystrophy or myasthenia gravis. Due to genetic anticipation, it is not uncommon for a parent to be diagnosed with myotonic dystrophy after their infant has been diagnosed with the condition.

AUTHOR CONTRIBUTIONS

M.V.-L., S.S., and C.V.: design of the study, drafting and revising of the manuscript for intellectual content. C.T.: drafting of the manuscript and revising of the manuscript for intellectual content.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Institutional review board approval from Cincinnati Children's Hospital Medical Center was obtained for this study. Go to Neurology.org for full disclosures.

REFERENCES

1. Peredo DE, Hannibal MC. The floppy infant: evaluation of hypotonia. *Pediatr Rev* 2009;30:e66–e76.
2. Lisi EC, Cohn RD. Genetic evaluation of the pediatric patient with hypotonia: perspective from a hypotonia specialty clinic and review of the literature. *Dev Med Child Neurol* 2011;53:586–599.
3. Paro-Panjan D, Neubauer D. Congenital hypotonia: is there an algorithm? *J Child Neurol* 2004;19:439–442.
4. Preston D, Shapiro B. *Electromyography and Neuromuscular Disorders: Clinical-Electrophysiologic Correlations*, 3rd ed. London: Elsevier Saunders; 2013.
5. Campbell C, Levin S, Siu VM, Venance S, Jacob P. Congenital myotonic dystrophy: Canadian population-based surveillance study. *J Pediatr* 2013;163:120–125.e3.
6. Keller C, Reynolds A, Lee B, Garcia-Prats J. Congenital myotonic dystrophy requiring prolonged endotracheal and noninvasive assisted ventilation: not a uniformly fatal condition. *Pediatrics* 1998;101:704–706.

Neurology®

Clinical Reasoning: A neonate with micrognathia and hypotonia
Marissa M. Vawter-Lee, Shannon S. Seals, Cameron W. Thomas, et al.
Neurology 2016;86:e80-e84
DOI 10.1212/WNL.0000000000002397

This information is current as of February 22, 2016

Updated Information & Services	including high resolution figures, can be found at: http://n.neurology.org/content/86/8/e80.full
References	This article cites 5 articles, 1 of which you can access for free at: http://n.neurology.org/content/86/8/e80.full#ref-list-1
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): Clinical neurology examination http://n.neurology.org/cgi/collection/clinical_neurology_examination Muscle disease http://n.neurology.org/cgi/collection/muscle_disease Neonatal http://n.neurology.org/cgi/collection/neonatal Trinucleotide repeat diseases http://n.neurology.org/cgi/collection/trinucleotide_repeat_diseases
Permissions & Licensing	Information about reproducing this article in parts (figures,tables) or in its entirety can be found online at: http://www.neurology.org/about/about_the_journal#permissions
Reprints	Information about ordering reprints can be found online: http://n.neurology.org/subscribers/advertise

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2016 American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.