

A large, stylized graphic of a hand in shades of purple and blue, positioned on the left side of the page. A smaller, stylized graphic of a hand in shades of orange and red is positioned on the right side, near the title.

EVALUATING NEONATAL HYPOTONIA

Considerations for differential diagnosis of
X-linked myotubular myopathy (XLMTM)
and other rare neuromuscular conditions

ABBREVIATIONS CK, creatine kinase; CNS, central nervous system; DMT1, myotonic dystrophy; EMG, electromyography; HIE, hypoxic-ischemic encephalopathy; MRI, magnetic resonance imaging; NCS, nerve conduction studies; NGS, next-generation sequencing; NMJ, neuromuscular junction; PWS, Prader-Willi syndrome; SMA, spinal muscular atrophy; TORCH syndrome, cluster of symptoms caused by congenital infection with toxoplasmosis, rubella, cytomegalovirus, herpes simplex, and other organisms; XLMTM, X-linked myotubular myopathy.

REFERENCES 1. Morton SU, et al. *JAMA Neurol.* 2022;79(4):405-413. 2. Karachunski PI, Kang PB (2024). The diagnostic approach to the hypotonic and weak infant. In: Walk D, et al. (eds) *Clinical Handbook of Neuromuscular Medicine*. Springer, Cham. 3. Bodamer O. Approach to the infant with hypotonia and weakness. UpToDate, updated Nov 25, 2025. 4. Prasad AN, Prasad C. *Semin Fetal Neonatal Med.* 2011 Apr;16(2):99-108. 5. North KN, et al. *Neuromuscul Disord.* 2014; 24(2):97-116. 6. Beggs AH, et al. *Muscle Nerve.* 2018;57(4):550-560. 7. Graham RJ, et al. *Arch Dis Child.* 2020;105(4):332-338. 8. Arnold WD, et al. *Muscle Nerve.* 2015;51(2):157-167. 9. Haliloglu G. *Eur J Paediatr Neurol.* 2022;38:A6-A11.

This Brochure is for Healthcare Professionals Only



EVALUATING NEONATAL HYPOTONIA

A diagnostic classification based on recent expert reviews¹⁻³

- Differential diagnosis of neonatal hypotonia ("floppy infant") is a critical gateway to identifying rare neuromuscular conditions such as XLMTM⁴

DEFINITIONS¹

Hypotonia: reduced resistance to passive range of motion (phasic tone), or loss of postural control

Weakness: a reduction in maximum voluntary power of the muscles

Neonate presents with hypotonia →

MEDICAL HISTORY (pre/perinatal, family)

CLINICAL EXAMINATION

(See Steps 1 to 6)*

Eliminate secondary acute/systemic causes
e.g. sepsis, acute infectious encephalopathies, hypoxic-ischemic encephalopathy (HIE), trauma, drug toxicities^{1,3,4}

Low muscle tone, normal or exaggerated deep tendon reflexes, and relative preservation of antigravity movements; decreased consciousness; possibly symptoms of encephalopathy^{1,2}

CENTRAL HYPOTONIA (CNS)⁵

Ancillary/confirmatory testing¹⁻³

- Electrodiagnostic (nerve conduction, EMG)
- Biochemical (CK and other lab markers)
- Imaging – MRI/ultrasound (brain, peripheral nerves, muscles)
- Histopathology (muscle and nerve biopsies)
- Broad molecular/genomic analyses (NGS) and/or confirmatory gene-targeted testing

Hypotonia (as the presenting symptom), absent or diminished deep tendon reflexes, absent neonatal reflexes, profound weakness; possibly joint contractures^{1,2}

PERIPHERAL HYPOTONIA (motor unit level^a), contractures⁵

Brain

- EXAMPLES**
- Down syndrome
 - Prader-Willi syndrome (PWS)
 - HIE

Spine

- Birth trauma (e.g. breech delivery)
- Syringomyelia

Anterior horn cell

- Spinal muscular atrophy (SMA)

Peripheral nerve

- Hereditary motor and sensory neuropathies
- Charcot-Marie-Tooth disease

Neuromuscular junction (NMJ)

- Myasthenia gravis
- Infantile botulism
- Aminoglycoside toxicity¹
- Magnesium toxicity³

Muscle

- Congenital myopathies
 - XLMTM
 - Nemaline, central/multicore
 - DM1
 - Muscular dystrophies

In XLMTM, in contrast to SMA, the clinical symptoms (muscular weakness, bulbar weakness, respiratory insufficiency) are already evident in the newborn⁵⁻⁸

*A stepwise diagnostic pathway ↓

STEP	Central Hypotonia	Peripheral Hypotonia
STEP 1: Assess alertness and responsiveness • Differentiates central vs peripheral hypotonia ²	Lethargic → Suggests central cause	Alert → Suggests peripheral cause
STEP 2: Observe body shape, dysmorphic features • Supporting clues for central vs peripheral ^{1,2,4}	Craniofacial features, abnormal head size/shape → Suggests central cause, brain disturbances (e.g. Down syndrome, PWS)	Long, thin extremities; frog-leg posture → Signs of low tone/movement in utero, suggests peripheral cause
STEP 3: Examine reflexes • Areflexia suggests lower motor neuron origin ^{2,9}	Brisk/Normal → CNS lesion (e.g. HIE, genetic syndrome)	Absent → Lower motor neuron disorder (e.g. SMA, XLMTM)
STEP 4: Evaluate muscle bulk and movement • Detects atrophy, hypertrophy, contractures, and movement quality ^{1,2,9}	Normal → Consider CNS or benign variant	Atrophy, Contractures, scoliosis → Congenital myopathies, muscular dystrophies
STEP 5: Check for respiratory effort, facial weakness, and feeding difficulty • Identifies respiratory and bulbar involvement ^{2,9}	Absent → Consider central or mild hypotonia (e.g. prematurity)	Present → Consider XLMTM, myasthenia gravis, DM1, SMA
STEP 6: Initiate targeted testing • Confirms diagnosis via genetic, metabolic, and imaging studies ^{1,2,5,9}	If central: - Brain MRI - Chromosomal microarray - Methylation testing (e.g. PWS) - Metabolic panel; TORCH screen	Peripheral: - CK levels - EMG/NCS - Muscle biopsy (if needed) - SMN1 gene (SMA) - DM1 genetic testing - MTM1 gene (XLMTM)

Immediate ventilatory dependence is a dominant feature of XLMTM^{5,7}

^a Peripheral hypotonia refers to hypotonia due to disorders of the motor unit including the lower motor neuron (anterior horn), peripheral nerves, NMJ, or muscle²

