Hypotonia in the Newborn

16

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Introduction

A newborn presenting with abnormal muscle tone is often a diagnostic and therapeutic challenge to those caring for newborn babies in the general nursery. Hypotonia in a newborn infant can be best defined as the decrease in resistance to passive motion, ideally in an awake infant, as opposed to weakness, which is merely the decrease in active strength [1–3]. While recognizing hypotonia is fairly obvious, the underlying etiology is often not, since neurological dysfunction at various levels can cause hypotonia. Hypotonia without weakness is highly suspicious for central nervous system causes (brain and brain stem/upper motor neuron), while hypotonic infants with weakness tend to have a systemic etiology or a defect in the peripheral nervous system (spinal cord, anterior horn cells, lower motor neurons, neuromuscular junction, peripheral nerves, and muscles) [4]. Higher brain functions are not affected in disorders affecting the peripheral nervous system. In many cases, hypotonia in the newborn might be the initial presentation of a more serious underlying condition, which, if unrecognized, might lead to persistent long-term complications, including seizures, developmental delays, and/or death.

The clinical management of these infants varies from observation to immediate interventions based on the diagnoses identified. The nursery provider is tasked with identifying a possible etiology using a systematic approach, performing a timely workup, as well as transferring to a neonatal intensive care unit or referring to higher centers for treatment when necessary. It is of utmost importance to identify time-sensitive etiologies since they have the most response to therapy.

Case Presentation

You are called from the newborn nursery to evaluate a full-term newborn delivered 3 h ago for decreased activity noted on the nurse's initial assessment on admission to the nursery. The infant is a 4100 gram male at 38 2/7-week gestational age based on first trimester ultrasound. The mother is a 38-year-old primigravida African American woman with negative prenatal labs including human immunodeficiency virus (HIV), hepatitis B, syphilis, and rubella as well as group B streptococcus (GBS). Pregnancy was complicated by gestational diabetes managed with glyburide and preeclampsia managed with labetalol and magnesium sulfate prior to delivery. She

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presented with prolonged rupture of membranes for 20 h and was delivered via cesarean section for breech presentation.

Delivery of the infant was complicated by difficult extraction of the head with a nuchal cord, after delivering the rest of the body from the uterine incision. He was born with a weak spontaneous cry and required vigorous stimulation followed by brief CPAP via face mask with good response. He did not require any further resuscitation and was allowed to room in with the mother. Apgar score was 7 and 8 at 1 and 5 min. respectively (points taken off for tone and color). While in the recovery room, he attempted to breastfeed with some difficulty latching on.

The baby was just admitted to the nursery from the recovery room, and the admitting nurse is concerned that the baby is not very active. The infant's vital signs including heart rate, respiratory rate, oxygen saturations, and axillary temperature are within normal limits. On a brief exam, the baby has truncal hypotonia as evidenced by significant head lag and decreased tone on ventral suspension.

At this time you attempt to obtain a detailed history. What specific prenatal history would be highly suspicious for a congenital neuromuscular disorder in this infant?

1. History of maternal diabetes
2. Decreased fetal movements and abnormal presentation
3. Abnormal fetal heart tracing
4. Large for gestational age fetus

A detailed history and comprehensive neurological exam are the first steps in identifying the etiology of hypotonia in a newborn. A detailed medical history of the mother's general health (e.g., diabetes, hypertension, metabolic disorders, etc.) as well as specific neuromuscular conditions could suggest a possible congenital or genetic etiology (e.g., myotonic dystrophy, myasthenia gravis, seizure disorders, etc.) [5, 6]. Some of this information might not be available immediately and should be addressed when possible. Infants exposed to maternal drugs or medications (e.g., general anesthesia or maternal magnesium sulfate administration) may present with decreased muscle tone and, in severe cases, with respiratory failure. Maternal infections such as chorioamnionitis as well as toxoplasmosis, (Syphilis, etc.), rubella, cytomegalovirus and herpes (TORCH) infections can cause perinatally acquired systemic illness in the newborn. The affected infants may have other signs and symptoms of systemic illness, including abnormal vital signs, respiratory distress, desaturations, apnea, tachypnea, bradycardia, tachycardia, hypotension, decreased peripheral perfusion, hypothermia, as well as feeding intolerance. These infants warrant additional workup geared toward identifying and treating the underlying etiologies.

In addition to the above, antenatal history of fetal malpresentation, decreased fetal movements, polyhydramnios, or oligohydramnios can hint congenital causes of hypotonia including certain genetic conditions [5, 7]. The decreased muscle tone and abnormal movements in these fetuses could result in malposition and malpresentation. Any abnormal swallowing mechanism in these fetuses could present with polyhydramnios [8]. Arthrogryposis is another condition associated with certain congenital neuromuscular disorders with decreased fetal movements and contractures [9].

The newborn's course at delivery and resuscitation history can often point to a possible etiology for systemic compromise in a newborn. While abnormal intrapartum fetal heart tracing is considered a marker for fetal compromise, it often does not point to the etiology. In addition, a need for resuscitation at birth, especially when prolonged, is a well-accepted marker for perinatal distress [10]. While it is not uncommon for an otherwise normal newborn to have delivery complicated by various factors leading to perinatal hypoxia, a newborn with a neuromuscular disorder might be much less able to tolerate the stress of labor and delivery and hence is at higher risk of developing perinatal hypoxia.

Answer: 2

Table 16.1 Key points on a detailed history in a newborn with hypotonia

Maternal medical history	Drug/medications: magnesium sulfate, general anesthetics, opioids Infections: chorioamnionitis, GBS, TORCH Neuromuscular illnesses: muscular dystrophies, myasthenia gravis
Family history	Neurological or metabolic disorders in family members, e.g., congenital myotonic dystrophy, spinal muscular atrophy, metabolic disorders, etc. Fetal and infantile deaths Developmental delays Seizure disorders Race/ethnicity/consanguinity
Pregnancy and delivery history	Prematurity Abnormal fetal presentation, decreased fetal movements Polyhydramnios, oligohydramnios Delivery mode, complications during delivery Resuscitation at delivery, APGAR score Cord gases
Nursery course	Abnormal cry, tone Decreased spontaneous activity Decreased alertness Feeding difficulties, especially poor latch during feeding

To summarize, an accurate history should focus on the key areas, given the broad list of differential diagnoses (Table 16.1).

Case Presentation Continued

Maternal history for this newborn was negative for myasthenia gravis, muscular dystrophies, or seizure disorders, with no known family history of genetic conditions. The infant did not have any risk factors for sepsis other than prolonged rupture of membranes. Information about decreased fetal movements during pregnancy could not be confirmed at this time, but there was reported suspicion of decreased fetal movements prenatally. In addition, the infant had history of polyhydramnios and was in breech position at delivery. The infant is now 3 h old with hypotonia and some difficulty with breastfeeding.

At this time, which one of the following statements is most applicable?

1. Brain imaging should be performed immediately.
2. Transient systemic causes of hypotonia must be ruled out.
3. Infant should obtain a full sepsis workup.
4. Electroencephalography (EEG) is recommended at this time.

The magnitude of differential diagnoses causing hypotonia in a newborn varies from a wide range of transient systemic causes, chromosomal (genetic) causes, inborn errors of metabolism, endocrine causes, as well as central and peripheral neurological and neuromuscular causes [3]. Since systemic causes are by far the most common etiology for hypotonia in a newborn, it is essential to identify the transient and reversible etiologies as soon as possible, given the risk of permanent neurological injury if untreated [11]. A detailed newborn physical exam includes a head-to-toe evaluation for general assessment, including Dubowitz assessment for gestational age (if unclear), evaluation for dysmorphic features, skeletal abnormalities, microcephaly, macrocephaly, as well as a complete neurological exam, including mental status, muscle tone, newborn reflexes, as well as deep tendon reflexes.

Poor perfusion may be seen in infants with hypovolemia, hypotension, hypoxia, and acidosis and can be easily identified on a quick general exam. Infants with transient electrolyte abnormalities like hypoglycemia, hypocalcemia, and hypermagnesemia often present with nonspecific clinical signs and symptoms in the newborn period requiring higher index of suspicion. Infants with sepsis are usually ill-appearing and could deteriorate rapidly if untreated. Hence it would be prudent to assume that a hypotonic infant is septic until proven otherwise [11, 12]. If the infant does not appear well, a sepsis workup is definitely warranted. Infants with a difficult delivery course and complicated resuscitation often have transient acidosis which can be identified on the cord or infant's blood gases. Although most units obtain routine cord blood gases at all deliveries, it is not always available. Cord blood gases, when available, may show evidence of acidosis as a surrogate marker for in utero hypoxia.

Low Apgar scores (especially if prolonged) on the other hand have been linked to increased neonatal mortality and worse neurodevelopmental outcomes [13–16].

Hypoxic-ischemic encephalopathy (HIE) is the most common cause for hypotonia presenting in a newborn soon after birth, resulting from perinatal hypoxia [11], and is associated with other systemic causes like hypoglycemia, hypermagnesemia, hypocalcemia, hypovolemia, and acidosis. The reported prevalence of HIE in full-term infants with Apgar score of 0–3 at 5 min is as high as 70% [10]. Affected infants usually have early signs in the initial newborn period with abnormal cry, tone, activity, alertness, and feeding difficulties, to name a few. Altered mental status is usually noted in encephalopathies, including HIE which needs to be identified as soon as possible. The therapeutic intervention with hypothermia therapy is time-critical and needs to be started within 6 h of birth [17]. Infants with mild HIE present with mild hypotonia, irritability, increased alertness, and normal/increased deep tendon reflexes. The outcomes for these infants are usually favorable [17]. Moderate cases (Sarnat Stage 2 HIE) present with generalized hypotonia with depressed reflexes and depressed mental status. These infants may also present with seizures. Infants with Stage 2 HIE can improve significantly if treated with hypothermia in a timely manner. Infants with severe (Sarnat Stage 3) HIE are severely depressed with severe hypotonia and absent reflexes and may even present with posturing [17, 18]. The details of staging and management of HIE are discussed elsewhere in this book (Chaps. 1 and 17).

Although brain imaging is vital, transient and reversible systemic causes for hypotonia should be ruled out prior to obtaining imaging studies. Brain imaging and EEG are primarily indicated in newborns presenting with signs of focal neurological deficits, e.g., seizures, or if the infant has focal abnormality on neurological exam. Head ultrasound scan is usually the easiest to obtain and does not involve risk of radiation. A brain MRI is indicated if suspecting structural abnormality and is preferred to head CT due to high resolution and low risk of ionizing radiation [19].

Table 16.2 Transient causes of hypotonia and key diagnostic points

Etiology	Key points
Acidosis	Infant appears sick with depressed strength and reflexes Abnormal cord gases or infant's blood gases Any history of resuscitation at birth
Hypoglycemia	Variable newborn exam; usually subtle neurological findings Hypotonia, jitteriness, seizures in severe hypoglycemia Maternal history of diabetes
Hypermagnesemia	Depressed reflexes, respiratory distress, ileus Maternal treatment with magnesium sulfate
Hypocalcemia	Hypotonia, seizures, myoclonic jerks
General anesthesia	Neonatal hypotonia, respiratory distress/apnea
Congenital hypothyroidism	Hypotonia, decreased activity Large anterior fontanelle Poor feeding, constipation Jaundice
Infections/sepsis	Ill-appearing infant Acidosis, poor perfusion, risk factors present

Head CT may have better resolution than a brain ultrasound but not used as the first-line investigation due to risk of radiation and limited yield. Imaging may also be obtained to complete the diagnostic workup in infants with hypotonia of unknown etiology [11].

Answer: 2

The table above lists common transient systemic illnesses in a newborn with hypotonia with key diagnostic points (Table 16.2).

Case Presentation Continued

This infant did not require resuscitation and was stable in room air after delivery with a normal level of alertness. Upon review of the chart, you notice that the infant's cord arterial blood gas showed pH of 7.28, pCO_2 of 48, and pO_2 of 30 with a base deficit of 3. Cord venous blood gas

showed pH of 7.36, pCO_2 of 40, and pO_2 of 35, with a base deficit of −3.

While conducting a detailed exam, what laboratory testing would you order first in this infant?

1. Point-of-care glucose
2. Serum calcium
3. Complete blood count
4. Arterial blood gas

Infants with transient electrolyte abnormalities can be identified quickly with simple laboratory testing and can be managed with intravenous fluids and supportive care until the electrolytes normalize. Infants with nuchal cords at birth can present with acute hypovolemia with hypoxemia and acidosis from cord compression and can also present with generalized hypotonia. It is standard practice in many units to observe infants in the recovery room with the mothers after a cesarean section and transfer them to the nursery when the mother is sent to the postpartum floor. However, since this infant has no tachycardia as evidenced by normal vital signs as well as normal cord blood gases, the index of suspicion for hypovolemia and acidosis is low.

Preeclampsia, maternal diabetes, and perinatal stress are associated with increased risk of hypocalcemia early in the neonatal period. Hypocalcemia in the early neonatal period (<3–4 days of life) is largely asymptomatic and is diagnosed incidentally unless severe. In severe hypocalcemia (calcium <7 mg/dL or ionized <4 mg/dL), infants may present with signs of neuromuscular irritability, myoclonic jerks, jitteriness, exaggerated startle, and seizures [20].

Although all the above choices are correct, the most time-critical choice at this time would be a point-of-care test for glucose. Untreated hypoglycemia could rapidly progress to cause neurological injury which may present with worsening hypotonia and seizures. It is vital to monitor for hypoglycemia in a large for gestational age infant of a mother with gestational diabetes, especially in the first 24 h of life [21]. Point-of-care glucose testing can identify hypoglycemia which can then be managed appropriately.

Answer: 1

Case Presentation Continued

The infant's glucose was 65 mg/dL, and serum calcium is 9.2 mg/dL, which are within normal limits.

You then send a serum magnesium level on this infant. What do you expect to find on neurological exam if the baby presented with elevated serum magnesium?

1. Hypotonia with decreased level of alertness
2. Hypotonia with intact level of alertness

Infants born to mothers with preeclampsia or eclampsia who received magnesium sulfate can have hypermagnesemia, presenting with generalized hypotonia, apnea, bradycardia, feeding difficulty, and, in severe cases, respiratory distress and may even mimic septic shock. Magnesium is known to inactivate acetyl choline at the neuromuscular junction, especially in the respiratory muscles, and does not affect the brain directly [22]. Hence the infants' clinical presentation would be similar to peripheral neurological disorders, with intact alertness.

Answer: 2

Case Presentation Continued

The infant's electrolyte panel is normal including a serum magnesium level. Workup has been sent to rule out sepsis and is in progress. The infant was large for gestational age (97th percentile) and measured appropriately for weight, length, and head circumference. On exam, this patient was awake, warm, well perfused, and otherwise well appearing.

You continue to perform a detailed exam on the infant. Which of the following can be best used to differentiate peripheral and central causes of hypotonia?

1. Decreased strength
2. Decreased tone
3. Decreased reflexes

Hypotonia can be caused by neurological dysfunction anywhere from the brain all the way down to the muscles. Central hypotonia results from a defect arising from the brain, brain stem, or spinal cord above the anterior horn cells (AHC), while peripheral causes are the result of a defect anywhere from the AHCs, peripheral nerves, neuromuscular junction (NMJ), and muscles. Central neurologic causes of hypotonia are more common than peripheral causes and account for about 60–80% of the cases, while peripheral causes are seen in 15–30% of the cases with a neurological etiology [11, 23]. It is essential to differentiate the two and narrow down the differential diagnosis.

Central causes affect the brain and brain stem and are associated with altered mental status with a depressed level of consciousness, while peripheral nervous system causes for hypotonia tend to have an intact mental status with normal sleep-wake patterns. The evaluation of higher mental functions in a newborn is limited to alertness and wakefulness. In an older infant, normal sleep-wake cycles should be established. In a newborn however, sleep-wake cycles are not fully established [24].

A complete neurological exam begins with an assessment of the infant's resting posture and tone. Infants with normal tone have flexed posture of all four limbs with active movements of the extremities. Hypotonic newborns do not have the usual flexed posture of all limbs. Instead they tend to present with abducted and extended limbs [25]. Evaluation of axial tone in a newborn is done best by suspending the infant horizontally and vertically. During horizontal (ventral) suspension, the hypotonic infant drapes over the hand of the examiner like an inverted "U" with the head and legs dangling on the side. Poor axial tone also causes these infants to have a significant head lag when pulled to sit off the bed and a positive "shoulder slip-through" sign when picked up vertically by grasping under the arms [24].

Newborns with central hypotonia have predominantly axial hypotonia with intact strength. Strength is more preserved than tone in central lesions, while peripheral lesions tend to present with profound hypotonia and weakness. While hypotonia is described as reduced resistance to passive movements, weakness is the reduction in maximum power [1–3]. Additionally, asymmetry in muscle tone is a red flag and requires further investigation to identify focal neurological lesions, e.g., neonatal ischemic stroke, traumatic myelopathy, brachial plexus injuries, etc. Deep tendon reflexes are usually exaggerated in central lesions, including clonus, while they are normal/depressed in peripheral disorders. Higher brain functions are usually not affected in disorders affecting the peripheral nervous system [24, 26].

On the other hand, a newborn with severe hypotonia, weakness, and intact higher mental functions – e.g., alert, with normal sleep-wake patterns – tends to have a peripheral neurological cause affecting the lower motor neuron and motor unit as well as muscular disorders [27]. Spinal muscular atrophy (SMA) is a good example of a peripheral neuromuscular disorder where a third of the patients can present as early as the neonatal period and eventually progress to develop respiratory failure later in infancy. The SMAs consist of a group of disorders with progressive loss of spinal AHCs, leading to muscular atrophy and weakness. Since the problem is distal to the brain and brain stem, these infants have significant hypotonia and generalized weakness and absent deep tendon reflexes, but the higher functions are spared, giving the classic presentation of alert facies with significant distal weakness. Fasciculations of the tongue are often seen in infants with SMA as weakness starts to develop [5]. Albeit rare, other common peripheral causes include congenital myotonic dystrophies and congenital myopathies, which also present with profound hypotonia and weakness. The rest of the exam should be geared toward identifying additional clues to the etiology and localizing the site of defect (Table 16.3).

Hence, while there are many ways to differentiate central from peripheral causes of hypotonia, intact alertness and decreased strength out of proportion to the degree of hypotonia are strongly suggestive of peripheral hypotonia. However, it is important to note that the level of alertness is

Table 16.3 Key clinical features in hypotonic infants based on site of lesion

	Central hypotonia		Peripheral hypotonia			
	Congenital	Acquired (injury)	Anterior horn cell	Peripheral nerve	Neuromuscular junction (NMJ)	Muscle
Strength	Normal	Normal (decreased in early severe cases)	Decreased	Decreased	Decreased	Decreased
DTRs	Normal	Normal/ increased (decreased in severe cases)	Decreased/ absent	Decreased/ absent	Decreased/normal	Decreased/ absent
Alertness	Decreased (with exceptions)	Decreased (with exceptions)	Intact	Intact	Intact	Intact
Examples	Chromosomal disorders (e.g., PWS), cerebral dysgenesis	HIE, metabolic disorders	SMA, hypoxic-ischemic myelopathy	Hereditary sensory and autonomic neuropathy, congenital hypomyelinating neuropathy	Transient acquired neonatal myasthenia, hypermagnesemia	Muscular dystrophy syndromes, metabolic myopathies

Adapted from Peredo and Hannibal [11]

variable depending the degree of involvement and might not be enough to differentiate congenital and acquired causes of hypotonia in the early newborn stage.

Answer: 1

Case Presentation Continued

A detailed neurological exam was performed and was significant for generalized moderate hypotonia as evidenced with a prominent head lag and hypotonia on ventral suspension, with symmetric muscle tone on all extremities. No focal defects or seizures were identified. However the infant was able to move his limbs against gravity and did not have any obvious weakness on active movements. Deep tendon reflexes were normal.

Which specific findings on exam would you look for in a newborn if you suspect congenital central hypotonia?

1. Dysmorphic features
2. Level of alertness
3. Decreased strength

It is often difficult to differentiate congenital central causes of hypotonia from acquired causes of central hypotonia (e.g., injury). Central causes affect higher brain functions with possible seizure from cerebral cortical involvement. Infants with central hypotonia may be noted to have with dysmorphic features, scissoring of the legs on vertical suspension, as well as fisting of the hands [24]. On the other hand, if the brain stem and cranial nerves are involved, the newborn may present with abnormal or irregular breathing pattern, apnea, and abnormal eye movements. These babies could present with hypotonia and weakness along with depressed deep tendon reflexes. The features of hypotonic infants with central disorders vary with the etiology and, in some cases, with the timing of assessment in relation to the injury. Strength is usually preserved in central causes and cannot differentiate congenital from acquired causes. A focused exam with imaging might be necessary to identify the underlying etiology. Another special group is premature infants who tend to have generalized hypotonia, but reflexes and strength are spared. Since their muscle tone is gestational age dependent, it is

important to compare to a normal preterm infant of appropriate gestation.

A detailed exam should help identify congenital central causes from an acute injury, an ongoing injury, and a static or progressive developmental disorder. The best example is HIE which can present with a mild, moderate, or severe encephalopathy [28]. The onset is usually acute, presenting with hypotonia. These infants could progress to develop hypertonia and hyperreflexia in the future as signs of cerebral palsy become more apparent [29]. Congenital developmental causes of central hypotonia tend to have unchanged or worsening hypotonia as in most genetic syndromes [2, 30], while injury-induced central causes develop hypertonia overtime as seen in cerebral palsy [3, 11]. Congenital causes may have associated dysmorphic features specific to the underlying condition as listed in Table 16.4 (e.g., Down syndrome, Prader-Willi syndrome (PWS), etc.).

Answer: 1

Alternative Scenario What would you do if this infant had no dysmorphic features, has severe hypotonia, decreased DTRs and has normal sleep-wake patterns?

1. Obtain EEG
2. Obtain creatine phosphokinase levels
3. Send for neuromuscular testing

A baby in this alternative scenario has features consistent with peripheral causes of hypotonia, narrowing down the defect to the level of the peripheral nerves, neuromuscular junction, or muscles. An EEG would not help in this situation, since this is not a suspected central neurological lesion. Serum creatine phosphokinase (CPK) levels are helpful to further localize the lesion. Significant elevation in CPK levels are often seen in congenital muscular dystrophies, while congenital myopathies and spinal muscular atrophy may have a normal CPK level. Anterior horn cell diseases can have mild elevation in CPK levels [5]. If inconclusive, the next step is to obtain electrophysiological studies for neuromuscular testing using electromyography (EMG) or nerve conduction studies. A normal EMG usually suggests central origin for hypotonia with some exceptions. Muscle biopsies are reserved for differentiating muscular dystrophies and myopathies. If biopsy

Table 16.4 Common findings in selected syndromes presenting with hypotonia

Syndrome	Hypotonia	Other common features
Achondroplasia	Mild	Macrocephaly, prominent forehead, short limbs, low nasal bridge
Acrocallosal syndrome	Mild	Absence of corpus callosum, polydactyly
Cerebro-oculo-facio-skeletal syndrome	Generalized	Neurogenic arthrogryposis, microcephaly, microphthalmia, cataract (later onset)
Down syndrome	Moderate/severe	Congenital heart disease (murmur), flattened facial profile, brachycephaly, short nasal bridge, epicanthal folds, single palmar crease, clinodactyly, loose nuchal folds
Myotonic dystrophy syndrome	Variable/severe	Variable onset from prenatal to adulthood; decreased activity, difficulty swallowing, muscle atrophy, hypogonadism
Organic acidemias, urea cycle defects	Variable	Abnormal odor; findings are variable depending on specific condition
Prader-Willi syndrome	Moderate/severe	Hypogonadism (undescended testes, hypoplastic labia), dysmorphic facial features (almond-shaped eyes with up slanting palpebral fissures, prominent forehead, narrow face, small mouth, thin upper lip, and micrognathia)
Zellweger syndrome	Moderate/severe	Murmur (PDA/septal defects), high forehead, flat facies, hepatomegaly (seen later in infancy and beyond)

shows specific abnormalities on immunohistochemical staining and electron microscopy, it may be indicated to do specific gene testing for definitive diagnosis. It is important to remember that CPK levels may be elevated transiently following these procedures and hence should be checked before the procedures if peripheral neuromuscular disorders are being considered.

Answer: 2

Case Presentation Continued

You complete examining the infant. In addition to the abnormal neurological findings, he was noted to have undescended testes and subtle dysmorphic features including a prominent forehead and a small mouth.

Does the newborn require genetic testing?

1. Yes
2. No

Karyotyping is indicated when multiple specific dysmorphic features are noted to identify any cytogenetic defects. Down syndrome and Prader-Willi syndrome are among the most common genetic conditions that present with hypotonia in the newborn period. This patient has generalized hypotonia with suspicion for a congenital central etiology and warrants a consult with a geneticist as well as focused testing. However given the delivery course, other transient causes of hypotonia had to be ruled out first.

Infants with hypogonadism (undescended testes) on exam with moderate to severe hypotonia and feeding difficulties are highly suspicious for Prader-Willi syndrome. Newborns with Prader-Willi syndrome tend to have typical facial features, including a prominent forehead, narrow face, almond-shaped eyes, small mouth, thin upper lip, and micrognathia [31]. Although older children with Prader-Willi syndrome are often noted to be obese, the infants might not necessarily be large for gestational age at birth. A vast majority of infants with Prader-Willi syndrome have feeding difficulties, leading to failure to thrive until 8–11 months of life. These infants however go on to develop severe hypotonia, insatiable appetites, obesity, and short stature later in infancy [7, 11]. Karyotype testing alone is inadequate for Prader-Willi since the genetic defect involves imprinting defects, affecting a small portion of chromosome 15 (15q11.2). The specific diagnostic tests include comparative genomic hybridization, DNA methylation studies, and fluorescence in situ hybridization (FISH) for Prader-Willi syndrome.

On the other hand, Down syndrome (Trisomy 21) is the most common chromosomal defect causing developmental delay in newborns. Typical newborn presentation includes hypotonia, congenital heart defects, and dysmorphic features. The most common dysmorphic features include flattened facial profile, brachycephaly, short nasal bridge, epicanthal folds, single palmar crease, clinodactyly, as well as loose nuchal folds [11, 32]. Testing for Down syndrome involves karyotype analysis, which is usually diagnostic. In mosaic cases of Down syndrome, FISH testing might be required.

Answer: 1

Case Summary

This is a case of a full-term infant with Prader-Willi Syndrome. The infant in this vignette presented with hypotonia in the early newborn period. The approach to this infant began with a comprehensive history and physical exam. Detailed physical exam of this infant showed a large for gestational age infant (97th percentile) with undescended testes. A hypotonic infant like this case demands a comprehensive neurological exam including a detailed assessment of tone, strength, reflexes, as well as higher mental functions.

The infant in this case had prenatal concerns for congenital etiology, due to abnormal fetal presentation and suggested decreased fetal movements with no other explanation. The presence of dysmorphic features is also suspicious

for a congenital/genetic etiology. Despite having a nuchal cord at delivery, the infant did not require any resuscitation, and the cord blood gases did not show any acidosis and hence not likely to have resulted from hypoxic insult. The next course of action involved ruling out transient systemic causes. Given the history of maternal diabetes, the infant was screened with point-of-care glucose testing, which was normal. A baseline electrolyte panel was also normal including normal calcium and magnesium levels. Given the history of normal cord gases, absence of hypoglycemia, and normal calcium and magnesium levels, including the history of lack of resuscitation at delivery, hypotonia in this infant was less likely to be secondary to a transient systemic etiology.

While transient causes of hypotonia were being ruled out, the infant underwent a detailed general and neurological exam to identify the location of neurological dysfunction. On examination, the infant had moderate hypotonia with intact strength as evidenced by normal strength during movements, which was suggestive of central etiology. The next steps involved identifying congenital versus acquired etiology for hypotonia. The infant was awake, alert, and responsive to stimulation. He did not have any clinical features of HIE barring isolated hypotonia. Decreased alertness is not always seen in newborns with Prader-Willi, and some newborns can have intact alertness [33]. Despite the presence of intact alertness in the early newborn period, this infant is suspicious for a congenital central cause of hypotonia.

Absence of any history suggestive of acidosis without encephalopathy goes against acquired causes like HIE. In addition, absence of asymmetric decreased movements ruled out any brachial plexus injuries. Presence of normal DTRs in this infant was also suggestive of possible congenital etiology. To be positive, however, this infant would require close follow-up to monitor the progression of muscle tone or lack thereof. Infants with Prader-Willi syndrome often tend to have significant hypotonia during the newborn period, with significant feeding challenges at times, even requiring tube feedings. Genetic testing with comparative genomic hybridization, DNA methylation studies, and FISH are diagnostic for Prader-Willi syndrome.

Infants with Prader-Willi syndrome are usually normal in birth weight and have poor weight gain in early infancy. However, they go on to develop insatiable appetites later in infancy and develop obesity between 6 months to 6 years. The infant in this vignette was LGA, which is not uncommon in the setting of maternal diabetes. Since these babies are at high risk of feeding problems, it is essential to monitor feeding closely and provide supportive care as needed until their feeding improves later in infancy.

An overview of the approach to a newborn with hypotonia is presented in Fig. 16.1. For the purposes of flow of case discussion, a review of systemic causes was discussed before clinical examination. It is important to note that in most situations, history is being reviewed and point-of-care assessments are done simultaneously, while the newborn is being examined. A detailed history and physical exam can identify up to 50% of the diagnoses without any additional testing. Imaging studies, evaluation by geneticist, and genetic testing can further diagnose about 25% of hypotonic infants [23]. Infants with normal tone at birth and subsequently developing hypotonia could have inborn errors of metabolism usually presenting after at least 1–2 days of life, once the baby accumulates the affected metabolites. These include disorders of carbohydrate metabolism, organic acidemias, urea cycle defects, fatty acid oxidation disorders, and various miscellaneous defects. The remaining infants require expanded biochemical testing for metabolic disorders, neuromuscular testing (EMG, muscle biopsy with immunohistochemical staining, etc.) and other miscellaneous tests. A small portion of these infants with hypotonia remain undiagnosed despite extensive workup. The importance of a detailed history and physical exam cannot be overstated when attempting to diagnose a newborn with hypotonia.

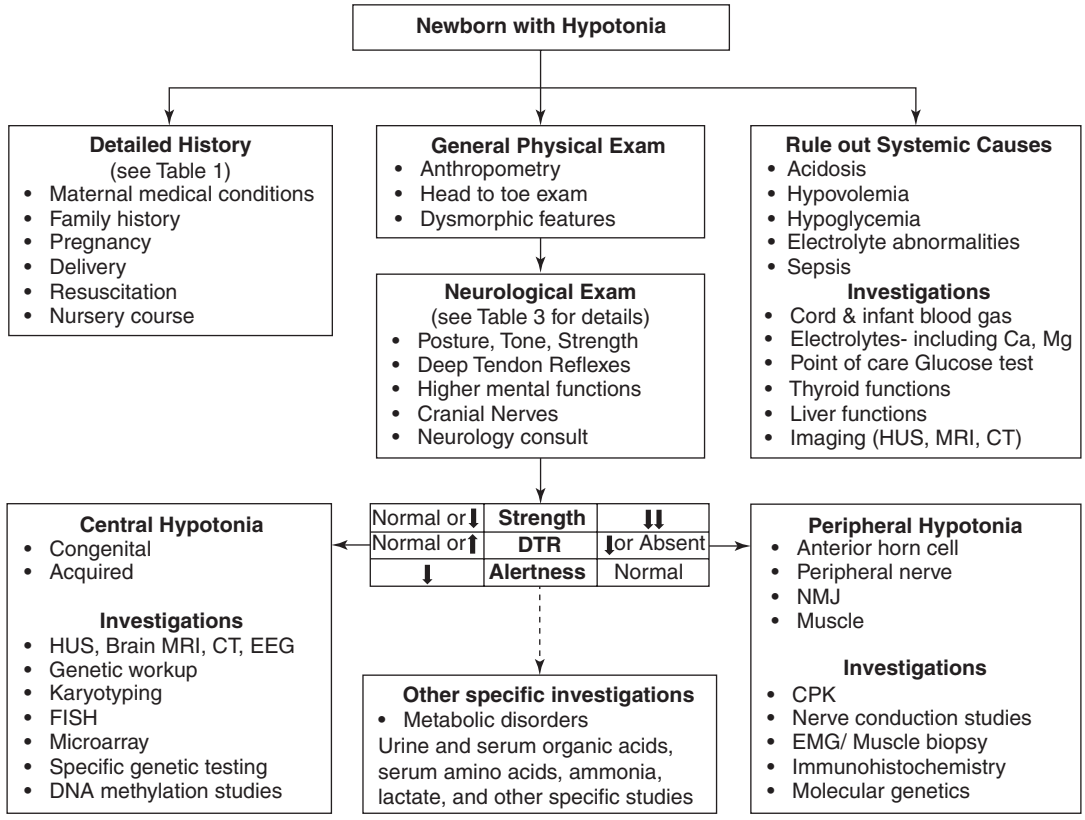

Fig. 16.1 Suggested approach for evaluation of a newborn with hypotonia

Clinical Pearls

1. Infants presenting with hypotonia should be assessed for posture, tone, and strength using ventral suspension, vertical suspension, and pull to sit by traction. It is essential to be able to differentiate normal from abnormal.
2. A detailed history and physical exam can yield a diagnosis in about half of the infants with hypotonia.
3. History of decreased fetal movements, malpresentation, and polyhydramnios are suspicious for congenital neuromuscular disorders. Family history of congenital neuromuscular disorders needs to be investigated.
4. Systemic causes of hypotonia need to be ruled out using history and physical exam of the newborn.
5. Central causes of hypotonia may present with decreased alertness, abnormal sleep-wake patterns, hypotonia, and normal or elevated DTRs, but strength is relatively preserved; peripheral causes of hypotonia present with intact alertness, profound weakness, significant hypotonia, and low or absent DTRs.

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