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Presenting Symptom: Generalized Weakness in an Infant

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Presenting Symptom: Generalized weakness in an infant

Appropriate Audience: Residents and practicing physicians

Learning Objectives: After completing this educational activity, participant will be able to (1) describe the differential diagnosis of a floppy baby, including that of new onset, (2) explain the physical findings in an infant with botulism, (3) explain the clinical course in an infant with botulism, (4) describe the electrodiagnostic approach in an infant with botulism, and (5) describe the electrodiagnostic findings in an infant with botulism.

History

A three-month-old previously healthy female infant presents for evaluation of generalized weakness and hypotonia. Her parents report that her weakness first involved her arms, then rapidly progressed over the course of 2 days to involve all limbs. The baby is described as "floppy." The infant is afebrile but is lethargic and irritable. There has been no witnessed seizure activity. She does have a difficult time breastfeeding with a poor suck and frequent coughing. Prior birth and past medical history are unremarkable. Parents report that the infant was developing normally and that her current status is a remarkable change from her usual state of health.

- *Prior to continuing, please develop a differential diagnosis and list each possible diagnosis in order of likelihood.*
- *Is there any additional information regarding the clinical history that might be helpful in clarifying your differential list or changing its order of priority?*

Commentary I

There is an extensive differential diagnosis for the "floppy infant syndrome." However, given a history of normal development with acute deterioration, the diagnostic possibilities are narrowed. In an infant of this age, systemic illness, such as sepsis, would be included in the initial diagnostic impression. Because the baby is also irritable and lethargic, investigation to rule out meningitis would also be warranted. Additional systemic conditions would include toxic exposures or a metabolic process. The temporal course, unremarkable birth history, past medical history and developmental history argue against the various disorders categorized as etiologies for cerebral hypotonia. There is also no history of trauma to suggest a spinal cord injury. The differential diagnosis should include lower motor neuron disorders with acute onset, such as acute inflammatory demyelinating polyneuropathy (AIDP), polymyositis, myasthenia gravis, and infantile botulism. Additional disorders of the motor unit that present with gradual onset of symptoms and differing features that are less consistent with this presentation include infantile spinal muscular atrophy and various myopathies.



History, continued

Further history reveals that the infant has no known recent toxic or infectious exposures. She is not receiving prescription or over-the-counter medications. Immunizations are reported to be up to date with no recent vaccinations administered. A family medical history of neuromuscular or endocrine disorders is denied. She regularly is breastfed without introduction of infant formula or cereal. The parents mention that the infant was constipated before the onset of her weakness and honey was given to alleviate the constipation without success.

- *If necessary, revise your differential diagnosis based on the additional clinical history.*
- *On which details of the physical examination should you focus at this point?*

Commentary II

Regarding the infant's regular diet, breast-feeding is proposed to be protective against botulism and could result in a less severe course. It is also theorized that formula or other foods have potential to alter the intestinal flora, changing susceptibility to botulism. Additional history focuses attention on the fact that the baby was given honey in attempts to alleviate constipation, which could be a mechanism for the introduction of *Clostridium botulinum* spores into the gastrointestinal tract. Examination should include evidence of cranial nerve involvement, bulbar signs, respiratory compromise, autonomic instability, and urinary or bowel retention.

Physical Examination

The patient is a female infant lying supine on the examination table with oxygen per nasal canula in no distress. She is afebrile with stable vital signs. Anterior fontanelle is soft. She has minimal facial movements, without dysmorphic features. Pupils appear dilated and are sluggish to react to light. Bilateral ptosis is appreciated, however extraocular muscle movements appear to be intact. There is a depressed gag reflex with weak cry. No spontaneous movement is observed in the upper limbs with the exception of trace finger movement bilaterally. A frog leg position is noted in the lower limbs with trace muscle movement proximally and at the knees and 2/5 strength at the ankles. No atrophy or fasciculations are noted. The infant demonstrates a weak cry in response to sensory testing. Muscle stretch reflexes are hypoactive throughout with plantar responses bilaterally. Both appendicular and axial tone is decreased. The baby was unable to support her head with her arms extended during pull from supine to sitting. Examination of the abdomen reveals decreased bowel sounds with slight distension but no guarding or rebound.

- *At this point, review your differential diagnosis and revise as appropriate.*
- *Are there additional observations on physical examination that might be helpful in narrowing your differential list?*

Commentary III

The physical examination shows significant symmetric weakness of all limbs in addition to axial hypotonia. Reflexes are depressed and plantar responses are present, which in addition to hypotonia support a lower motor neuron process. The examination also confirms involvement of facial and bulbar muscles. The presence of dilated and sluggish pupils should specifically alert one to the possibility of a defect in neuromuscular junction transmission.



Commentary IV

Initial workup includes routine laboratory studies, including CBC with differential, and platelets, chemistry profile, liver enzyme profile, TSH level, CK and urinalysis, all of which are normal. Blood and urine cultures are also negative to date. Stool has also been sent for culture, including analysis for the presence of Clostridium botulinum or its toxin. The latter results may not be available for several weeks. Routine CSF studies obtained upon admission reveal a normal protein, glucose and cell differential count. CSF Gram stain is negative, and culture is pending at the time of electrodiagnostic testing. Head CT on admission is unremarkable, without evidence of a focal process. Empiric antibiotics that were started on admission have been discontinued. No aminoglycoside antibiotics were administered that could worsen a neuromuscular junction condition.

Electrophysiologic Data

SENSORY NERVE CONDUCTION									
nr = no response									
NERVE	LATENCY			AMPLITUDE (µV)			CONDUCT VEL (m/s)		
	R	L	Norm	R	L	Norm	R	L	Norm
Median antidromic (digit 3, wrist, 6cm)	1.8	-	1.7 at 6cm	15	-	16	-	-	35
Ulnar antidromic (digit 5, wrist, 5.5cm)	1.6	-	1.6 at 5.5cm	20	-	16	-	-	35
Sural antidromic (lateral malleolus, calf, 7cm)	2.1	-	2.0 at 7cm	11	-	12	-	-	35

Normal values from Parano et al. for median and sural nerve NCV in 1-6 month olds.



MOTOR NERVE CONDUCTION									
nr = no response									
NERVE	LATENCY (ms)			AMPLITUDE(mV)			CONDUCT VEL (m/s)		
	R	L	Norm	R	L	Norm	R	L	Norm
Median orthodromic (APB, wrist, 3cm)	2.2	-	2.2	0.3	-	7.4	35	-	34
Ulnar orthodromic (ADM, wrist, 3.5 cm)	2.1	-	2.2	0.4	-	7.4	37	-	34
Peroneal orthodromic (EDB, ankle, 7.6cm)	2.4	-	2.3	0.3	-	5.2	38	-	35

Normal values from Parano et al. for median and peroneal nerve NCV in 1-6 month olds.

ELECTROMYOGRAPHY										
N = normal incr = increased decr = decreased 0 = absent 1+ = minimal 4+ = maximal crd = complex repetitive discharge fasc = fasciculation potential myk = myokymic discharge myt = myotonic discharge nmt = neuromyotonic discharge p wave = positive sharp waves fib = fibrillation potentials recr = recruitment amp = amplitude dur = duration poly = polyphasic potential										
R/L	MUSCLE	INSERTION		SPONTAN		VOLUNTARY				
		activ	p wave	fib	other	recrt	amp	dur	poly	effort
R	Deltoid	-	2+	2+	-	-	decr	decr	-	-
R	Triceps	-	2+	2+	-	-	decr	decr	-	-
R	Extensor carpi radialis longus	-	1+	1+	-	-	decr	decr	-	-
R	First dorsal interosseous	-	1+	1+	-	-	decr	decr	-	-



R	Vastus lateralis	-	2+	2+	-	-	decr	decr	-	-
R	Anterior tibialis	-	2+	2+	-	-	decr	decr	-	-
R	Gastrocnemius	-	2+	2+	-	-	decr	decr	-	-

- *On the basis of both the clinical and electrophysiologic evaluations, formulate your diagnostic impression. List the most likely diagnosis first and follow in order with the other possibilities that are not excluded by the data. Eliminate those diagnoses not supported by the data.*
- *Are there additional electrophysiologic data that you feel would further delineate the diagnosis? (Remember, collecting data that are not needed for the diagnosis is costly and uncomfortable for the patient.)*

Electrophysiologic Data, continued

Repetitive Nerve Stimulation

- Stimulus delivered via surface electrodes and arm board utilized for immobilization of wrist/hand.
- Temperature monitored periodically throughout examination with thermistor, and baby wrapped in blanket to maintain body temperature >34 oC.
- Recording from APB with right median nerve supramaximal stimulation of 0.1 msec duration
- No change at 2Hz stimulation (n=10)
Incremental response with post-tetanic facilitation to 115% (20Hz stimulation for 1 sec)
- Recording from ADM with right ulnar nerve supramaximal stimulation of 0.1 msec duration
- Mild decrement of 7% at 2 Hz stimulation (n=10)
- Incremental responses with post-tetanic facilitation to 130% (20 Hz stimulation for 1 sec)
- *Make the final revisions of your diagnostic impression(s).*

Diagnostic Impression

History and physical examination findings, with the addition of electrodiagnostic test results, support the diagnosis of infant botulism. The presence of post-tetanic facilitation is very specific for a presynaptic defect of neuromuscular transmission.

- *What other diagnostic procedures (laboratory tests, etc.), if any, are needed?*
- *What treatment would you recommend?*

Commentary V

This patient presents with rapid loss of strength in all limbs in a descending pattern with axial hypotonia and hyporeflexia. In addition, there is cranial nerve involvement, pupillary



change, and a history of constipation. In an infant of this age, the possibility of a systemic illness, central nervous system infection, or toxic exposure should be considered. Initial diagnostic testing did not support sepsis or meningitis, and the focus of the investigation shifts towards various lower motor neuron disorders that can present with sudden onset of generalized weakness. Included in the differential diagnosis are AIDP, polymyositis, myasthenia gravis, and infantile botulism. As mentioned previously, the temporal course of this presentation, with a history of normal development thus far, makes conditions such as spinal muscular atrophy, congenital myopathies and congenital dystrophinopathies unlikely.

Electrodiagnosis proves to be extremely useful in elucidating the specific area of involvement within the lower motor neuron. In the infant, electrodiagnosis can be challenging. The examiner should have a logical approach formulated before the test begins so that useful information can be obtained in a time-efficient manner that will either support or eliminate the contemplated diagnoses. Indications for performing repetitive nerve stimulation (RNS) include ocular or bulbar signs and symptoms and low amplitude compound muscle action potentials (CMAP) on nerve conduction studies, or myopathic-appearing MUAPs on EMG (Jones, 1990). Single-fiber EMG (SFEMG) as a means of assessing neuromuscular transmission is not generally practical in the infant due to lack of cooperation, but stimulated SFEMG can be performed in an infant or others who are unable to specifically cooperate.

Electrodiagnosis in this case helps to exclude the diagnosis of AIDP, which can also present with cranial nerve and bulbar involvement in addition to generalized weakness and hyporeflexia. In contrast to infantile botulism, AIDP usually presents with a history of ascending paralysis and is characterized by an elevated CSF protein level. Additionally, electrodiagnosis in classic AIDP would reveal segmental demyelination with evidence of conduction block and temporal dispersion, prolonged or absent F waves, and absence of post-tetanic facilitation with repetitive nerve stimulation.

Poliomyelitis, whether sporadic or associated with live vaccine (in the past), could also be entertained in the differential diagnosis for this case presentation, however it is very rare. Polio may have facial and bulbar weakness with constipation. History and physical findings vary from infant botulism in that weakness follows a febrile illness with typically asymmetric motor involvement and CSF showing pleocytosis. On electrodiagnosis, CMAP amplitudes are reduced with preservation of nerve conduction velocities. EMG shows neuropathic recruitment with denervation two to three weeks after onset of weakness. Decrement on RNS has been described but there is no post-tetanic facilitation (Dumitru).

Neonatal myasthenia usually is observed in the setting of maternal placental antibody transfer and presents in the neonatal period immediately after birth. In infants who are hypotonic from birth with ocular and bulbar weakness that persists, electrodiagnosis may support the diagnosis of congenital myasthenia. Decrement >10% is observed on low frequency repetitive stimulation without post-tetanic facilitation. A repetitive response to single stimulation is highly suggestive of congenital myasthenia. Polymyositis would not cause this rapid onset of weakness. A normal CK on admission would also argue against this diagnosis.

Electrodiagnostic evaluation in an infant suspected to have botulism begins with routine sensory and motor nerve conduction studies. One would anticipate normal sensory responses, variable reduction in CMAP amplitude depending upon disease severity, and preserved conduction velocities. Proceeding next to repetitive nerve stimulation, initial low-rate stimulation at 2-3 Hz can produce either a decrement, increment, or no change. The



diagnosis of infant botulism is supported by the classic finding of post-tetanic facilitation with incremental response on high-rate stimulation, indicative of a presynaptic defect. Other possibilities with similar findings on RNS include hypermagnesemia in infants born to mothers treated for eclampsia, and infants who have received aminoglycoside antibiotics. There are differing opinions about the existence of Lambert-Eaton myasthenic syndrome in infancy. Although this type of neuromuscular transmission defect would have post-tetanic facilitation, it is only observed briefly. In contrast the post-tetanic facilitation observed in botulism can persist for several minutes. It should be noted that up to a 20% increment has been observed in newborn infants following tetanic stimulation; therefore, caution should be made when interpreting the results of RNS (Cornblath, 1983). In Cornblath's study, post-tetanic facilitation was present in 23 cases of 25 infants with botulism proven by culture, with a mean increment of 73% and range of 23-313%. This same study revealed that the majority of cases of infant botulism may demonstrate facilitation with only 20 Hz stimulation, but the examiner should utilize 50 Hz stimulation when no increment or equivocal findings are seen at the lower stimulation frequency. Dumitru proposes utilizing 50 Hz stimulation for several seconds from the beginning. No uniform recommendation of the total duration of high-rate stimulation necessary to observe post-tetanic facilitation has been made. Disease severity, which is proportional to the amount of circulating toxin, may also impact the results of RNS. As an illustration, post-tetanic facilitation may be more frequently observed in infant botulism where toxin is slowly synthesized and released over time as compared to adult food-borne botulism where a large amount of preformed toxin is consumed at once. In fact, botulinum toxin is not routinely isolated from the serum of infants with disease for this reason. Although post-tetanic facilitation is "classic" evidence of a presynaptic defect, normal RNS results do not exclude the diagnosis. With a high degree of neuromuscular blockade, RNS at even 50 Hz may be insufficient to boost acetylcholine release.

Electromyography of the limb muscles in botulism may be normal in early or mild disease. The diagnosis is supported by the presence of short-duration, low amplitude MUAPs. Evidence of denervation, including positive waves and fibrillation potentials, is a variable finding and indicative of a severe course. Return to normal neuromuscular transmission requires new terminal sprouting to establish motor end plates.

Infant botulism is the most common type of botulism now reported in the United States. Types A and B are the most frequently implicated. It typically presents between the ages of 2 and 6 months of age with almost all patients demonstrating generalized weakness with limb involvement and hyporeflexia. Constipation is also frequently observed. Less consistent findings are facial and bulbar weakness, sluggish pupils, autonomic instability, and respiratory compromise. Honey should not be given to children less than one year of age as the intestinal flora of infants is susceptible to colonization with *Clostridium botulinum*. Management of infantile botulism is mainly supportive in nature with close attention to pulmonary care and respiratory status. Some patients do require mechanical ventilation and tracheostomy placement. There has also been recent development of a human-derived botulism immune globulin, which shows promise in hastening resolution of symptoms.

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