More Clinical Mimics of Infant Botulism

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Objective To ascertain the actual diagnoses of 76 patients (2005-2015) whose clinical presentations so closely resembled infant botulism that the patients were treated with Human Botulism Immune Globulin Intravenous (BIG-IV; BabyBIG), but whose illnesses subsequently were not laboratory confirmed as infant botulism ("clinical mimics" of infant botulism).

Study design The California Department of Public Health produces BIG-IV and distributes it nationwide as a public service (ie, not-for-profit) orphan drug to treat patients hospitalized with suspected infant botulism. During the study period, admission records and discharge summaries for all patients treated with BIG-IV but who lacked a laboratory-confirmed diagnosis of infant botulism were collected and abstracted. The patients' discharge diagnoses were identified, categorized, and compared with previously reported clinical mimics categories for 32 patients (1992-2005).

Results From 2005 to 2015, 76 clinical mimic illnesses were identified. These illnesses were distributed into the 5 categories previously reported of (1) probable infant botulism lacking confirmatory testing (26.3%); (2) spinal muscular atrophy (19.7%); (3) miscellaneous (15.8%); (4) metabolic disorders (11.8%); and (5) other infectious diseases (10.6%). Of the 76 clinical mimic illnesses, 15.8% had no alternate diagnosis established and were therefore categorized as undetermined.

Conclusions Over the 23 years 1992-2015, patients presenting with illnesses so clinically similar to infant botulism that they were treated with BIG-IV had actual diagnoses that were distributed into 5 main categories. These categories and their individual components constitute a working bedside differential diagnosis of infant botulism. *(J Pediatr 2018;193:178-82).*

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Since 1980, infant (intestinal toxemia) botulism has been the most common form of human botulism in the US, with approximately 100-140 infant botulism cases reported each year.[1] The disease has been recognized on all inhabited continents except Africa.[2] The clinical spectrum of this rare, life-threatening, flaccid paralytic illness ranges from mild, outpatient cases to fulminant, severe-onset cases that result in sudden death.[3,4] Most recognized cases of infant botulism require hospitalization and critical care support. Approximately 90% of cases have occurred in infants 6 months of age or younger, with an age range among US cases reported to date of 1.5 days to 1 year.[1,5]

Infant botulism results when swallowed spores of *Clostridium botulinum* (or rarely, toxigenic *Clostridium butyricum* or *Clostridium baratii*) germinate, temporarily colonize the large intestine, and there produce botulinum neurotoxin (BoNT). BoNT is then absorbed and carried by the systemic circulation to peripheral cholinergic synapses, where after internalization it cleaves intracellular proteins needed for release of acetylcholine.[6] Clinically, the neuromuscular junction is the most important peripheral cholinergic synapse, and BoNT intoxication results in flaccid paralysis. BoNT exists in 8 serotypes (A-H) that are distinguished by the inability of polyclonal antibodies raised against 1 toxin type to neutralize any of the other 7 toxin types in the standard mouse bioassay.[6-8]

Clinical manifestations of infant botulism include generalized weakness and hypotonia, lethargy, constipation, cranial nerve palsies, difficulty feeding, hypoventilation and occasionally, respiratory arrest. Features that help distinguish infant botulism from other causes of acute-onset weakness in infants include prominent bulbar palsies, sluggishness of the pupillary reflex, and fatigability with repetitive stimulation of muscle contraction.

Treatment of infant botulism consists of meticulous supportive care and the botulinum antitoxin, Human Botulism Immune Globulin Intravenous (BIG-IV; BabyBIG). BIG-IV was developed, produced, and is now distributed nationally and occasionally internationally[9-11] by the California Department of Public Health

BIG-IV	Human Botulism Immune Globulin Intravenous
BoNT	Botulinum neurotoxin
CDPH	California Department of Public Health
EMG/NCS	Electromyography and nerve conduction studies
SMA	Spinal muscular atrophy

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(CDPH).[12,13] BIG-IV is approved in the US for the treatment of infant botulism caused by toxin type A or B in patients less than 1 year of age. Approximately 99% of US infant botulism cases (1976-2015) have been caused by BoNT type A or type B.[1] Early treatment with BIG-IV maximally shortens hospital stay; thus, the decision to treat should be based on the bedside physician's clinical diagnosis of infant botulism and not delayed for laboratory confirmation.[13]

Following completion of the 1992-1997 pivotal clinical trial of BIG-IV in California, CDPH began open-label distribution of BIG-IV in California in 1997 and nationwide in 1998 under Treatment Investigational New Drug authorization.[12] Nationwide distribution continued following licensure of BIG-IV in 2003.[13] Our previous report categorized the diagnoses, termed "clinical mimics," of 32 patients whose symptoms so closely resembled those of infant botulism that the patients were treated with BIG-IV, but who did not have subsequent laboratory confirmation of the diagnosis.[14]

We have now categorized patients with clinical mimic diagnoses who were treated from July 1, 2005 through December 31, 2015 to identify new clinical mimic diagnoses, if any, and to compare rates of BIG-IV treated-negative cases with the prior reporting period. An augmented list of diagnoses clinically mimicking infant botulism may aid medical providers in differential diagnosis and in appropriately diagnosing and treating patients suspected of having infant botulism and its clinically similar illnesses.

Methods

Approximately 94% of patients during the study period had laboratory-confirmed infant botulism with the diagnosis established by identification of BoNT or *C botulinum* or both in feces at a qualified state health department laboratory or by the US Centers for Disease Control and Prevention. Definitive laboratory testing for the presence of BoNT or *C botulinum* or both occurred after BIG-IV treatment was administered for all patients except one, for whom a diagnostic stool specimen was not submitted.

We collected and abstracted hospital admission records, discharge summaries, and laboratory reports for diagnostically relevant information for all patients treated with BIG-IV from July 1, 2005 through December 31, 2015 for whom the diagnosis of infant botulism was not laboratory confirmed. We then identified the patient's diagnosis at discharge or at subsequent follow-up postdischarge. We defined the actual diagnoses determined for these patients to be clinical mimics of infant botulism.[14] For patients for whom the diagnosis was not clearly stated in the discharge summary, we contacted the patients' physicians postdischarge to obtain additional clinical information and the diagnosis, if any, established by subsequent evaluation. Clinical mimic diagnoses were assigned to the following categories: probable infant botulism, spinal muscular atrophy (SMA) type 1, miscellaneous, metabolic disorders, infectious disease, and undetermined. Patients in the probable infant botulism category had clinical features consistent with infant botulism, but as records review confirmed, lacked sufficient laboratory evidence to meet the case definition. For these patients, postdischarge follow-up with their subspecialist or primary care physician confirmed that recovery remained consistent with the known recovery course of patients with infant botulism. Patients in the undetermined category did not have a diagnosis established for their illnesses.

Results

In the 10.5-year study period, a total of 1226 patients were treated with BIG-IV. Seventy-six (6.2%) of these patients did not have laboratory-confirmed infant botulism, and an alternate diagnosis was established for 44 (57.9%) of the 76. These alternate diagnoses were distributed into the following 4 major categories of SMA type 1 (n = 15); miscellaneous diagnoses (n = 12); metabolic disorders (n = 9); and other infectious diseases (n = 8). Of the remaining 32 patients without an alternate established diagnosis, 20 were classified as probable infant botulism lacking laboratory confirmation, the fifth category defined in the first report.[14] Twelve patients' diagnoses were categorized as "undetermined," the sixth major category of this reporting period (**Table I**).

SMA type 1 was the most common single diagnosis that mimicked infant botulism (**Tables I** and **II**). The 15 patients with SMA presented at a median age of 49 days (range 31-134 days). At the time of hospitalization, the majority of these patients had absent deep tendon reflexes, sparing of extraocular muscle paralysis, and a history of several weeks of progressive weakness. Five patients with SMA (33.3%) had abnormal breathing patterns characterized in the medical records as paradoxical breathing or abdominal ("belly") breathing.

New clinical diagnoses mimicking infant botulism during this reporting period were distributed among the categories of miscellaneous disorders, metabolic disorders, and other infectious diseases. Alternate diagnoses established during this reporting period for the first time included the following: acute disseminated encephalomyelitis, Chiari malformation, congenital hypothyroidism, hypovitaminosis A secondary to cystic fibrosis, leukodystrophy, human metapneumovirus, and parechovirus infection. The 3 patients diagnosed with Guillain-Barré syndrome or a variant of Guillain-Barré syndrome ranged in age at onset from 153 days to 357 days; 2 of these patients had antecedent viral illnesses. The 3 patients with parechovirus encephalitis were ex-33 week premature triplets who presented at 31 days old with apneic and bradycardic episodes, low tone, and constipation. Nucleic acid testing of the cerebrospinal fluid of one of the triplets was positive for parechovirus; cerebrospinal fluid testing was not done for the other 2 triplets. The novel clinical mimic disorders identified in the study population are denoted by italics in **Table I**.

The new category of undetermined etiology encompassed the 12 patients for whom no diagnosis was established despite

Table I. Clinical mimics of infant botulism that resulted in treatment with BIG-IV

Clinical mimic diagnoses (1992-June 2005)*		Clinical mimic diagnoses (July 2005-2015)†	
Category	**n (%)**	**Category**	**n (%)**
Probable infant botulism	**9 (28)**	**Probable infant botulism‡**	**20 (26)**
SMA type 1	**5 (16)**	**SMA type 1**	**15 (20)**
Miscellaneous§	**7 (22)**	**Miscellaneous§**	**12 (16)**
Central demyelinating disease		*Abnormalities in gray/white matter and corpus callosum by magnetic resonance imaging*	
Cerebral atrophy secondary to in utero drug exposure		*Acute disseminated encephalomyelitis*	
Cerebral infarctions		*Acute transverse myelitis (n = 2)*	
Diaphragmatic paralysis		*Chiari malformation*	
Miller-Fisher variant of Guillain-Barré syndrome		*Cystic fibrosis and hypovitaminosis A*	
Neuroblastoma stage III (presumptive Lambert-Eaton syndrome)		*Hemophilia A, cervical epidural hemorrhage*	
Spinal epidural hematoma		*Hypothyroidism*	
		Nemaline rod myopathy	
		Miller-Fisher or pharyngeal-cervical-brachial variant of Guillain-Barré syndrome (n = 3)	
Metabolic disorders	**8 (25)**	**Metabolic disorders**	**9 (12)**
Glutaric aciduria type I		*Carnitine deficiency*	
Leigh syndrome		*Congenital disorder of glycosylation*	
Maple syrup urine disease		*Leukodystrophy*	
Mitochondrial disorders (n = 4)		*Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency*	
Succinic semialdehyde dehydrogenase deficiency		*Urea cycle defect*	
		Mitochondrial disorders (n = 4)	
Infectious diseases	**3 (9)**	**Infectious diseases**	**8 (11)**
Enterovirus encephalitis		*Human metapneumovirus pneumonia/bronchiolitis*	
Probable viremia		*Parainfluenza and macrocephaly*	
Respiratory syncytial virus bronchiolitis		*Parechovirus encephalitis (n = 3, triplets)*	
		Roseola	
		Likely resolved sepsis	
		Polio-like enterovirus	
Undetermined¶	—	**Undetermined¶**	**12 (16)**
		Discharge diagnosis of infant botulism, but illness not consistent (n = 8)	
		Dystonia	
		Global developmental delay, unknown etiology	
		Polyradiculopathy, unknown etiology	
		Reflux with weakness, unknown etiology	
Total	**32 (100)**	**Total**	**76 (100)**

*Francisco AMO, Arnon SS. Clinical mimics of infant botulism. Pediatrics. 2007;119:826-8.
†New diagnoses in this population are grouped and denoted by italics (n = 22).
‡Four patients in this category had dual diagnoses of probable infant botulism and 1 other diagnosis (eg, asymptomatic Chiari/syrinx, cystitis, respiratory syncytial virus, and rotavirus).
§Includes neurologic and other genetic conditions.
¶The category Undetermined was not included in the 2007 report referenced above.

extensive evaluation. All 12 patients whose diagnoses were categorized as undetermined had appropriate laboratory testing for infant botulism, with a range of 1-3 stool or enema specimens tested per patient. Six of these patients had few or no cranial nerve findings at presentation. Four patients were 7 months or older at symptom onset. Three patients presented with a history of fever.

Three of the 20 patients categorized as probable infant botulism, but lacking laboratory confirmation, had positive tests for the BoNT type B gene by use of a research polymerase chain reaction assay; however, the standard direct toxin assay and culture for *C botulinum* were negative. Two probable infant patients with botulism had inadequate laboratory testing, as the fecal specimens for diagnostic testing were not collected until 1-2 months after symptom onset, by which time fecal excretion of *C botulinum* toxin and organisms may have ceased. One patient had rotavirus-positive diarrhea at the time of collection of the diagnostic specimen, which, the testing laboratory commented, may have interfered with testing for botulism; no subsequent diagnostic specimen was submitted.

Thirty-three (43.4%) patients with clinical mimic diagnoses had electromyography and nerve conduction studies (EMG/NCS) performed. Eight patients ultimately diagnosed with SMA had EMG/NCS. In 5 of these patients with SMA, EMG/NCS findings were reported as "consistent with" or supportive of botulism, and in the 3 other patients, the EMG/NCS findings were reported as consistent with SMA. In the undetermined category, 6 patients (50%) had EMG/NCS done as part of their evaluation; 2 patients had facilitation of muscle contraction with repetitive stimulation of involved muscle groups, a finding supportive of the diagnosis of infant botulism.[15,16] Only one-quarter of the 33 patients who had EMG/NCS performed had findings consistent with the diagnoses ultimately established.

Table II compares the earlier and the present populations with clinical mimic diagnoses.[14] The percentage of probable infant botulism diagnoses in the 2 populations remained similar (28% vs 26%). Distribution across the categories of metabolic disorders and miscellaneous diagnoses changed, with lower percentages in the current population compared with the

Table II. Comparison of the 2 patient groups of clinical mimic diagnoses

Diagnostic categories	First clinical mimics group (1992-June 2005)* N	%	Second clinical mimics group (July 2005-2015) n	%	Totals (1992-2015) N	%
Probable infant botulism	9	28	20	26	29	27
SMA type 1	5	16	15	20	20	19
Miscellaneous	7	22	12	16	19	18
Metabolic disorders	8	25	9	12	17	16
Infectious diseases	3	9	8	11	11	10
Undetermined	0	0	12	16	12	11
Total	32	100	76	100	108	100
Time interval	13.4 y		10.5 y		23.9 y	
Percent of hospitals that referred a patient with a clinical mimic diagnosis during the time period	15.4% (26/169)		21.8% (56/257)		24.3% (75/309)	
Number of US states with a treated-negative patient	10		31		33	
Total number of BIG-IV-treated patients during time period†	681		1226		1907	
Percent of BIG-IV-treated patients with clinical mimic diagnoses	4.7%		6.2%		5.7%	

*Francisco AMO, Arnon SS. Clinical mimics of infant botulism. Pediatrics. 2007;119:826-8.
†Number of BIG-IV-treated patients in the first clinical mimics group included 64 placebo-treated patients in the randomized, controlled pivotal clinical trial.[13] Number of BIG-IV-treated patients in the second clinical mimics group includes 54 international patients. All international BIG-IV-treated patients had laboratory-confirmed infant botulism.

previously reported group. Approximately one-fifth of hospitals using BIG-IV during each reporting periods treated patients whose final diagnoses were clinical mimics of infant botulism. These hospitals were located in 31 US states in the current reporting period and in 10 US states in the earlier reporting period. To date all BIG-IV-treated patients with clinical mimics diagnoses have been US residents.

Discussion

Clinical awareness of the rare disease infant botulism and of diagnoses that mimic its presentation is essential to correct recognition and prompt treatment both of infant botulism and alternative diagnoses. In the 23 years 1992-2015, approximately 6% of BIG-IV-treated patients did not have laboratory-confirmed infant botulism (**Table II**).[14] This report has identified new clinical mimics diagnoses, but the diagnostic categories remained the same as in our earlier report.[14] In cases with insidious-onset symptoms, few or absent cranial nerve palsies, asymmetric neuromuscular weakness, or ascending paralysis, clinicians should pursue alternative diagnoses to infant botulism.

SMA type 1 continues to be the most common individual diagnosis among the clinical mimic diagnoses, occurring in a combined 19% of patients (**Table II**). SMA typically spares the extraocular muscles and sphincters, whereas patients with infant botulism have involvement of both. Infants with SMA type 1 often have a history of progressive weakness spanning weeks to months preceding hospitalization or a history of decreased fetal movement, or both, in contrast to the majority of infant botulism patients whose perceived onset of weakness preceding hospitalization typically ranges from hours to days. In patients for whom the likely diagnosis is either SMA or infant botulism, prompt and in-parallel laboratory evaluation for both conditions is prudent. Although SMA remains the leading genetic cause of infant mortality in the US, the US Food and Drug Administration recently licensed nusinersen, the first treatment approved for this illness.[17,18] Nusinersen is a survival motor neuron-2-directed antisense oligonucleotide used for treatment of infants and older patients with the disease.[17,18]

Approximately one-quarter of the clinical mimic diagnoses were classified as probable infant botulism because their clinical presentation, recovery pattern, and time to full recovery were consistent with those of laboratory-confirmed infant patients with botulism treated with BIG-IV. These considerations led to the conclusion at discharge that the patient likely had infant botulism despite negative laboratory testing. However, almost all patients categorized as having probable infant botulism had appropriate laboratory testing performed (ie, a satisfactory enema or stool specimen was collected and submitted in a timely manner for testing by a qualified diagnostic public health laboratory). For many patients, 2 or more stool or enema samples were tested. Two patients in the probable infant botulism diagnostic category were discharged to home before a diagnostic specimen had been collected, and an additional patient did not have infant botulism diagnostic testing done. In contrast, in our earlier report all 9 patients with a probable infant botulism diagnosis were assigned to this category as a result of failure to obtain or appropriately submit a diagnostic stool or enema specimen.[14] Prompt collection of a stool or enema sample and timely submission to a qualified botulism testing laboratory remain paramount in diagnosing infant botulism.

Laboratory testing for infant botulism is done at state public health laboratories or at the federal Centers for Disease Control and Prevention. Because testing may take up to several days to complete, and earlier administration of botulinum antitoxin maximally shortens hospital stay,[13] BIG-IV should be administered promptly to all patients suspected of having infant botulism without delaying treatment for confirmatory laboratory testing. BIG-IV treatment does not obviate submitting

a fecal or enema specimen for botulism testing, and treatment with BIG-IV does not interfere with the fecal botulinum assay.

Electromyography studies in botulism may demonstrate characteristic patterns of brief-duration, small amplitude, abundant motor-unit action potentials (BSAPs) or an incremental response with rapid repetitive nerve stimulation.[15,19] Nerve conduction studies typically are normal in botulism. EMG/NCS may be helpful in evaluating patients with suspected infant botulism; however, as described in the literature and in this report, false positives can occur.[16,20] In addition, the absence of suggestive findings on EMG/NCS does not preclude the diagnosis of infant botulism. EMG/NCS results should be interpreted in the context of other clinical and diagnostic findings in evaluating patients with suspected infant botulism and should not be considered to be a definitive diagnostic tool. It may be noteworthy that only one-quarter of the 33 patients with clinical mimic diagnoses who had EMG/NCS performed had findings consistent with the diagnoses eventually established.

Possible limitations of our study include reliance on discharge summaries, with outreach to attending physicians where indicated to ascertain the actual final diagnoses, and the unavailability of postdischarge information that would establish a clinical mimics diagnosis. Other possible limitations were incomplete laboratory testing and delayed or limited evaluations for alternative illnesses.

Prompt administration of BIG-IV to patients with infant botulism maximally shortens hospital stay and associated hospital costs.[13] To ensure prudent use of this public service orphan drug, patients suspected of having a diagnosis that is a clinical mimic of infant botulism should have a comprehensive neurologic examination with meticulous evaluation of cranial nerves as early in their illness as possible. For those patients who have clinical findings that are not consistent with infant botulism, parallel evaluation for alternate diagnoses should be promptly started. Clinicians may consider the categories of clinical mimics of infant botulism in this report to be a useful list of differential diagnoses for infant botulism and its closely clinically similar illnesses. BIG-IV is available nationally and internationally to treat patients with suspected infant botulism. Physicians seeking expert medical consultation and BIG-IV for patients with suspected infant botulism may immediately contact the CDPH Infant Botulism Treatment and Prevention Program, 24/7/365 at telephone +1-510-231-7600. ■

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