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ABSTRACT

Since 1992, Human Botulism Immune Globulin has been provided by the California Department of Health Services to infants with probable infant botulism, the intestinal toxemia form of human botulism. Human Botulism Immune Globulin became available in California in 1992–1997 within a randomized, controlled, double-blinded, pivotal clinical trial and subsequently became available nationwide in 1998–2003 in an open-label study until its licensure in October 2003 as BabyBIG. Thereafter, Human Botulism Immune Globulin remained available nationwide as an approved orphan-drug product. To achieve prompt neutralization of circulating botulinum toxin, the decision to treat with Human Botulism Immune Globulin has been based on clinical criteria that include a consistent history and physical findings of bulbar palsies, hypotonia, and weakness. After licensure, the charts of patients who did not have laboratory-confirmed infant botulism were reviewed to identify their actual diagnoses. The ~5% of 681 patients treated with Human Botulism Immune Globulin who did not have infant botulism fell into 5 categories: spinal muscular atrophy, metabolic disorders, other infectious diseases, miscellaneous, and probable infant botulism lacking laboratory confirmation.

Infant botulism is the infectious intestinal toxemia form of human botulism that results when ingested spores of *Clostridium botulinum* (or, rarely, neurotoxigenic *Clostridium butyricum* or *Clostridium baratii*) colonize the large intestine and then produce botulinum toxin in its lumen.[1,2] Botulinum toxin blocks the release of acetylcholine at the neuromuscular junction and other peripheral cholinergic synapses, which results in constipation, lethargy, poor feeding, generalized weakness, decreased head control, hypotonia, diminished deep-tendon reflexes, hypoventilation, and cranial nerve palsies. Symmetrical bulbar nerve palsies (eg, ptosis, sluggish pupillary response to light, ophthalmoplegia, poor suck, decreased gag reflex, difficulty swallowing, expressionless face) are cardinal features of infant botulism that help distinguish it from other causes of subacute- to acute-onset generalized weakness.

After an ~15-year development period that included 2 clinical trials,[3] the US Food and Drug Administration licensed Botulism Immune Globulin Intravenous (Human) (BIG-IV) as BabyBIG to the California Department of Health Services (CDHS) in October 2003. Because BIG-IV is the only specific treatment for infant botulism, it became the standard of care for infants who presented with the clinical picture of infant botulism. Treatment with BIG-IV should be given as early as possible in the illness to neutralize botulinum toxemia and thereby shorten hospital stay maximally.[3,4]

Approximately 5% of the 681 patients since 1992 who were treated with BIG-IV (or placebo during the randomized, controlled clinical trial[3]) were found not to have infant botulism, and in most of these cases an alternative diagnosis was established. The tabulation of those conditions that so closely mimicked infant botulism that the attending physicians and the consulting

Key Words: botulinum toxin, *Clostridium botulinum*, Botulism Immune Globulin Intravenous (Human), BabyBIG, BIG-IV, spinal muscular atrophy, SMA, metabolic disorders, mitochondrial disorders

Abbreviations: BIG-IV, Botulism Immune Globulin Intravenous (Human); CDHS, California Department of Health Services; RCT, randomized, controlled trial; OLS, open-label study; SMA, spinal muscular atrophy; CSF, cerebrospinal fluid; RSV, respiratory syncytial virus; EMG, electromyography

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The California Department of Health Services distributes Botulism Immune Globulin Intravenous (Human) as a public service orphan drug that may be obtained by telephoning 510-231-7600 at any time (or visit the Web site: www.infantbotulism.org).

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physicians at the Infant Botulism Treatment and Prevention Program concurred that the patient should be treated with BIG-IV may serve as a bedside aid in the correct diagnosis of suspected infant botulism cases.

METHODS

Assessment of eligibility for treatment with BIG-IV differed between the 1992–1997 California randomized, controlled trial (RCT), the 1998–2003 nationwide open-label study (OLS), and the subsequent nationwide licensed distribution of BIG-IV. In the RCT, after notification of a possible case of infant botulism, 1 of 2 physician-investigators from CDHS traveled to the bedside to evaluate the patient together with the attending physician; the decision to treat was made jointly, with informed consent obtained from the parents. In the OLS and after licensure, 1 of the CDHS physician-investigators was contacted by telephone by the attending physician, who communicated the medical history, clinical findings, and standard laboratory testing results. If the CHDS physician-investigator concluded that the clinical findings made infant botulism the likely diagnosis, he arranged for shipment of BIG-IV to the hospital, where the attending physician obtained informed consent and administered BIG-IV to the patient. In both the RCT and the OLS and after licensure, definitive laboratory testing of stool or enema for the presence of *C botulinum* toxin and organisms was expected to be performed after treatment with BIG-IV, with due recognition that testing might take several days to be completed.

We collected medical charts of all suspected infant botulism cases treated with BIG-IV (or placebo) since use of it began in 1992[3] for which the diagnosis of infant botulism was not laboratory confirmed. We defined the actual diagnoses of these cases as "clinical mimics" of infant botulism and reviewed the medical charts to identify them.

RESULTS

Between February 24, 1992, and June 30, 2005, a total of 681 infants were treated with BIG-IV or placebo. Thirty-two patients (4.7%) were identified who did not have laboratory-confirmed infant botulism. These 32 patients could be divided into 5 diagnostic categories: spinal muscular atrophy (SMA) type I ($n = 5$); metabolic disorders ($n = 8$); infectious diseases ($n = 3$); miscellaneous ($n = 7$); and probable infant botulism ($n = 9$) (Table 1).

The 5 patients with SMA type I ranged in age from 1½ to 3 months. Four (80%) of the 5 patients with SMA were treated with BIG-IV during the RCT, and 7 (88%) of the 8 patients with metabolic disorders were treated with BIG-IV during the OLS or licensed-distribution periods. Four of the patients with metabolic disorders had MRI of the brain. The patient with glutaric aciduria type I and 2 patients with unknown types of mitochondrial disorders had the similar MRI finding of bilateral basal ganglia infarcts. The patient with Leigh's syndrome had abnormal computed tomography of the head results that showed decreased attenuation in the basal ganglia consistent with infarcts. The patient with maple syrup urine disease had normal cranial MRI results.

TABLE 1 **Clinical Mimics of Infant Botulism That Resulted in Treatment With BIG-IV**

Diagnosis	*N* (%)
Probable infant botulism[a]	9 (28)
Metabolic disorders	8 (25)
Glutaric aciduria type I	
Maple syrup urine disease	
Leigh's syndrome	
Succinic semialdehyde dehydrogenase deficiency	
Mitochondrial disorder ($n = 4$)	
Miscellaneous	7 (22)
Miller Fisher variant of Guillain-Barré syndrome	
Neuroblastoma stage III (presumptive Lambert-Eaton syndrome)	
Cerebral atrophy secondary to in utero drug exposure	
Cerebral infarctions	
Spinal epidural hematoma[b]	
Diaphragmatic paralysis[b]	
Central demyelinating disease[b]	
SMA type I	5 (16)
Infectious diseases	3 (9)
Enterovirus encephalitis	
RSV bronchiolitis	
Probable viremia	
Total	32 (100)

[a] Laboratory diagnosis was not established because of difficulty in obtaining or correctly submitting stool or enema specimens.
[b] The condition was considered idiopathic.

Three patients had an infectious etiology identified. One patient with enterovirus encephalitis had normal cerebrospinal fluid (CSF) at the time of referral; the actual diagnosis was later established by a positive CSF enterovirus polymerase chain reaction test. A second patient who was eventually diagnosed as having respiratory syncytial virus (RSV) bronchiolitis did not have symptoms typical of RSV present at admission. A third patient was thought to have a nonspecific viral syndrome because neurologic status returned to normal within 5 days of admission and laboratory study results were normal.

Seven patients had a variety of final diagnoses. The patient with the Miller Fisher variant of Guillain-Barré syndrome was 365 days old at onset and initially had normal CSF. However, subsequent examination of CSF found a significantly elevated protein concentration (100 mg/dL), and electromyography (EMG) identified a demyelinating neuropathy. At referral, the patient with stage III neuroblastoma had normal laboratory study results and a pulmonary infiltrate. Respiratory distress

and the infiltrate persisted despite antibiotic therapy. A computed tomography scan found a large mass that extended from the right hilum to the thoracic outlet, which biopsy identified as neuroblastoma. However, antibody associated with either Lambert-Eaton or other paraneoplastic neuromuscular syndromes was not detected in the patient's serum.

Nine patients had a final diagnosis of "probable infant botulism" because the laboratory studies needed to establish the diagnosis were either not requested or not performed. EMG of 5 of these patients identified a presynaptic transmission defect at the neuromuscular junction consistent with infant botulism.

DISCUSSION

SMA type I and metabolic disorders are the 2 most common diagnoses that mimic infant botulism. Patients with SMA type I have a longer history of generalized weakness than do patients with infant botulism, in whom the weakness is subacute to acute in onset. Also, patients with infant botulism typically have ophthalmoplegia and decreased anal sphincter tone, whereas SMA type I typically spares the extraocular muscles and sphincters.[5] Metabolic disorders are best diagnosed by the appropriate laboratory studies.

Although cranial nerve palsies occur in both infant botulism and in the Miller Fisher variant of Guillain-Barré syndrome, these diagnoses may be distinguished by CSF analysis, nerve conduction studies, and EMG. The age of the patient may also aid in differentiation, in that 95% of laboratory-confirmed cases of infant botulism occur in patients who are <6 months old, whereas Guillain-Barré syndrome typically occurs in older children. In infant botulism, EMG may reveal a characteristic but not diagnostic pattern of brief-duration, small-amplitude, overly abundant motor-unit action potentials termed BSAPs[6] (shown as Figure 1 in ref 7). However, absence of BSAPs does not exclude the diagnosis of infant botulism.[1,2] Paraneoplastic syndromes with neuromuscular junction involvement may also mimic infant botulism. The diagnosis of infant botulism could not be established for 9 (28%) patients because of the failure to obtain or correctly submit a stool or enema specimen for testing.

A careful history and neurologic examination remain the best bases for distinguishing infant botulism from its clinical mimics. The presence of multiple cranial nerve palsies is an essential part of identifying infant botulism, and in this context, a feeble cry, poor suck, weak gag, difficulty swallowing (drooling), and expressionless face should be viewed to be bulbar in origin. Ptosis may not be evident unless the patient is held in a sitting position (often requiring head support because of neck weakness), while disconjugate gaze and fatigability of the pupillary light reflex may require sustained examination (see Table 153–2 in ref 1). Fatigability with repetitive muscle activity (eg, feeding, breathing, pupillary constriction) is the clinical hallmark of botulism.

The conditions listed in Table 1 constitute a working list of alternative diagnoses for use with patients who present with signs and symptoms suggestive of infant botulism but then lack laboratory confirmation of diagnosis after adequate collection and submission of stool or enema specimens. Consideration of these "clinical mimic" conditions at admission of the hypotonic infant with bulbar palsies may result in earlier correct diagnosis and in appropriately targeted use of BIG-IV.

CONCLUSION

Treatment with BIG-IV should be initiated promptly (and not delayed for laboratory confirmation of diagnosis) because prompt treatment ends further progression of the illness. BIG-IV immediately neutralizes all circulating botulinum toxin and remains present in neutralizing amounts in the circulation for ~6 months, thereby allowing regeneration of nerve endings to proceed. Early treatment with BIG-IV within 0 to 3 days of admission shortens hospital stay by ~1 week more than does later treatment at 4 to 7 days and also significantly reduces the associated costs of hospitalization.[3]

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REFERENCES

1. Arnon SS. Infant botulism. In: Feigen RD, Cherry JD, Demmler GJ, Kaplan SL, eds. *Textbook of Pediatric Infectious Diseases*. 5th ed. Philadelphia, PA: Saunders; 2004:1758–1766
2. Long SS. *Clostridium botulinum* (botulism). In: Long SS, Pickering LK, Prober CG, eds. *Principles and Practice of Pediatric Infectious Diseases*. 2nd ed. New York, NY: Churchill Livingston; 2002: 984–991
3. Arnon SS, Schechter R, Maslanka SE, Jewell NP, Hatheway CL. Human Botulism Immune Globulin for the treatment of infant botulism. *N Engl J Med.* 2006;354:462–471
4. Fox CK, Keet CA, Strober JB. Recent advances in infant botulism. *Pediatr Neurol.* 2005;32:149–154
5. Talbot K, Davies KE. Spinal muscular atrophy. *Semin Neurol.* 2001;21:189–197
6. Engle WK. Brief, small, abundant motor-unit action potentials: a further critique of electromyographic interpretation. *Neurology.* 1975;25:173–176
7. Johnson RO, Clay SA, Arnon SS. Diagnosis and management of infant botulism. *Am J Dis Child.* 1979;133:586–593

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