Infant Botulism in Israel: Knowledge Enables Prompt Diagnosis

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Infantile botulism is a rare and potentially life-treatening disease. Most cases have been reported from California. In Israel, only one case has been reported so far. We present the second, and discuss the characteristics, diagnostic pitfalls and new treatment of this overlooked disease.

Patient Description

A 4 month old previously healthy infant was admitted to another institution after 4 days of decreased appetite, constipation and lethargy, intermixed with episodes of irritability. The patient was afebrile. Within hours he became obtunded and had frequent apneas, requiring endotracheal intubation and mechanical ventilation. Initial metabolic and sepsis workups were normal. He was treated with antibiotics (ceftriaxone and doxycycline) and acyclovir, and was transferred to our Pediatric Intensive Care Unit.

Pregnancy, delivery and development were normal. The child had been breast-fed until 2 weeks prior to admission when formula was begun. The patient tasted some honey on one occasion, 2 months prior to his admission.

On admission to the PICU he was hemodynamically stable, with mild hypertension (heart rate 157/minute, blood pressure 105/50 mmHg). He was severely hypotonic with minimal spontaneous movements and weak reflexes. He opened his eyes weakly and ptosis was prominent. Pupils were equal and responded to light, but corneal reflexes were not elicited, and only minimal eye movements were observed. Gag, cough and sucking reflexes were all absent. Within 12 hours the patient developed flaccid paralysis, loss of deep tendon reflexes, and complete ophthalmoplegia with fixed midsize pupils. His fontanel was full. The rest of the physical examination was unremarkable. Electrolytes, glucose and renal function tests were all within the normal range. Liver enzymes and bilirubin were normal. Creatine phosphokinase was 62 U/L.

Thyroid-stimulating hormone and free thyroxine were normal. pH was 7.44 with mild metabolic acidosis (HCO_3 22) that resolved spontaneously within 3 hours. Lactate levels were within the normal range. Complete blood count showed mild anemia with hemoglobin 10.3 g/dl, platelets 448,000/mm^3. White blood cell count was 9,070/mm^3 with 32% neutrophils, 62% lymphocytes, 5% monocytes and 1% eosinophils. C-reactive protein was 1.9 mg/dl. Cerebrospinal fluid showed mildly elevated protein of 57.5 mg/dl, normal glucose 50 mg/dl and no white cells. Urine screen for toxic agents was negative. Imaging studies including ultrasound and computerized tomography of the brain were both normal. Cardiac echo, abdominal ultrasound and CT and thoracic CT were also normal. Metabolic workup including urine organic acids and plasma amino acids were normal. Herpes virus polymerase chain reaction in the CSF was negative. Serology for *Mycoplasma* and West Nile virus were both negative. Blood, CSF and urine cultures were all negative. Both acyclovir and antibiotics were discontinued within 48 hours.

Electroencephalogram upon admission demonstrated a slow encephalopathic background with no sleep characteristics. There were some changes in the background in response to external stimuli. Twenty-four hours later the EEG normalized. An electromyogram study performed upon admission did not demonstrate a neuromuscular transmission defect. Four days later the study demonstrated reduced amplitude in motor and sensory nerves of the limbs with normal conduction velocity and distal latencies, compatible with an axonal neuropathy. Ten days into the hospital course, a single fiber EMG showed a pathologic jitter indicating a neuromuscular junction disease.

Due to the infants' constipation, a stool sample for culture and botulinum toxin was only sent 4 days after admission. Five days later a mouse neutralization test indicated botilinum-A toxin in the stool. At that point the infant showed signs of recovery with improved muscle tone and some spontaneous breathing. We therefore chose not to use the available equine antiserum. Over the next 4 days the patient continued to improve, regaining muscle strength and corneal, cough and gag reflexes. He was successfully extubated on day 17 of his hospital course and was discharged home a week later. Three months later there are no neurologic deficits or sequelae. Cultures from the honey and the formula he received prior to admission were both negative for *C. botulinum*.

Comment

Botulism is a type of poisoning. Infants can contract it from eating raw honey or other agricultural products. The disease results from the ingestion of spores of *Clostridium botulinum*, which germinate, multiply and produce botulinum toxin within the infant's large intestine. The neurotoxin binds irreversibly to the synaptic membrane of cholinergic nerves and subsequently prevents the release of acetylcholine. Paralysis and death may follow. Recovery occurs when sufficient new and toxin-free nerve

PICU = Pediatric Intensive Care Unit

CSF = cerebrospinal fluid

terminal proteins are available at the neuromuscular junction.

Our knowledge of the epidemiology of infant botulism is incomplete because the current data include only those patients who required hospitalization and reached medical care on time. Outpatients and cases of sudden death remain underdiagnosed. Infant botulism has now been reported from all continents except Africa. The majority of cases (90%) has been reported from the United States, although *Clostridium botulinum* spores are ubiquitous in the soil of all continents. This is most probably an indicaton of better physician awareness and availability of diagnostic tools rather than a truly higher incidence [1]. In Israel, there has been only one report of infant botulism to date [2]. The role of formula versus breast-feeding as predisposing factors for contracting the illness remains unclear. However, there is a clear association between being breast-fed and being hospitalized for infant botulism, but whether breast-feeding predisposes infants or slows the clinical process enough to allow those patients to be hospitalized rather than die at home is still unresolved. It should be emphasized though, that the mean age of formula-fed patients hospitalized for infant botulism was significantly younger as compared to breast-fed infants. Also, patients who developed fulminant onset of disease and stopped breathing at home were all formula-fed infants [1]

There may be a link between botulism and sudden infant death syndrome, and this connection has been raised in the past. Recently, Bohnel and colleagues [3] tested 57 cases of SIDS in Germany for the presence of botulinum neurotoxin and/or bacterial forms of *Clostridium botulinum* with subsequent neutralization tests using the international standard mouse bioassay. Free toxin was found in nine and bacterial forms were detected in six samples. According to the international literature, these 15 cases are to be interpreted as infant botulism..This study shows a remarkably high incidence (26.3%) of infant botulism among SIDS victims [3].

As our case demonstrates, even when a classic clinical picture exists, the diagnosis of infant botulism may be difficult, and the final confirmation of botulinum toxin in the stool may be delayed due to constipation. Electrophysiologic studies are a quick and reliable tool to confirm the diagnosis. There are three typical electrophysiologic abnormalities in infant botulism: a) low amplitude compound muscle action potentials to supramaximal nerve stimulation, b) tetanic or post-tetanic facilitation of CMAPs in response to 20–50 Hz stimulation, and c) prolonged post-tetanic facilitation of the CMAPs. Yet, evaluating this phenomenon involves the performance of single nerve stimulation at regular intervals. There are a few pitfalls in electrodiagnosis. The major one remains the inadequate performance of the studies. Sheth et al. [4] reported on two infants with confirmed botulism in whom characteristic electrophysiologic features were absent, and they mention some of the technical difficulties that may lead to a false EMG result. They recommend tetanic stimulation for at least 10 seconds at 50 Hz to mimic the effects of exercise prior to tetanic stimulation. In our case, we were able to demonstrate a neuromuscular transmission defect only in the third test, after multiple previous efforts to perform an adequate single fiber EMG failed. Thus, the EMG, which usually enables early diagnosis, might be confusing.

Treatment for infantile botulism remains supportive. Close observation in a PICU should be the rule for every case of progressive weakness, since involvement of the respiratory muscle and/or loss of airway protecting reflexes may require respiratory support. Feeding should be continued enterally with a nasogastric or nasojejunal tube, and constipation should be avoided. Antibiotics should be reserved for proven bacterial infection, since bacterial death and lysis may lead to a neurotoxin surge and worsening paralysis. When appropriate, the use of nalidixic acid or trimethoprim-sulfamethoxazole antibiotics is preferred because *C. botulinum* is known to be resistant to both drugs.

Human-derived botulinum antitoxin is now available in the U.S. from the California Department of Health Services. Its efficacy and safety were recently demonstrated in a randomized double-blind, placebo-controlled study. It reduced mean hospital stay per case from 5.5 weeks to 2.5 weeks [1]. Treatment should be started as early as possible. Recent data have shown that after 10 days of illness, initiation of the antitoxin does not shorten hospital stay significantly (personal communication, S.S. Arnon, 2002). Currently, the California Department of Health Services does not supply the antitoxin outside the U.S. (personal communication, S.S. Arnon, 2002). Thus, the only specific treatment available in Israel is the equine-based antiserum, which carries a high incidence of hypersensitivity reactions [5]. Full and complete recovery is expected after regeneration of the poisoned non-myelinated nerve endings.

In summary, our case confirms once again the existence of infantile botulism in Israel. The diagnostic tools are readily available and physician awareness is a key point for referring stool samples to confirm the diagnosis. Public awareness of the role of raw honey is crucial for prevention. Physicians who perform EMG studies in a suspected case should be aware of the potential pitfalls. Since an excellent specific antitoxin is only available in the U.S., we urge the Ministry of Health to make an effort to make the drug available in Israel for future cases.

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SIDS = sudden infant death syndrome

CMAPs = compound muscle action potentials