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Case Report

A Previously Healthy Infant with Decreased Feeding, Progressive Weakness, Unresponsiveness and Respiratory Failure: Is it the Brain to Blame?

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ABSTRACT

A 3 and a half month old otherwise healthy girl born in the USA presented with insufficient nursing noticed by her mother at the sixth day of their vacation in Russia. She was fed with breast milk and supplemental formula only. In the following three days, oral intake and urinary output decreased gradually, and she was observed to have a low pitched cry and constipation. There was no fever. She was taken to a local hospital in Russia, where the physical examination revealed hypotonia, tachycardia, tachypnea and desaturation. Laboratory investigations including complete blood cell count, biochemistry, venous blood gas and peripheral blood smear analysis were normal. In the following hours, she developed muscle weakness in all extremities with unresponsiveness to painful stimuli. Horizontal nystagmus was noted and her pupils were bilaterally dilated with no light reflex. Acute meningoencephalitis was suspected with possible seizure activity and she was treated with corticosteroids, antibiotics, barbiturate and valproic acid.

Keywords: Pediatrics; Infantile botulism; Acute flaccid paralysis; Antitoxin; Pediatric intensive care; Neurotoxins; Pediatric GIT

INTRODUCTION

Girl was subsequently intubated due to respiratory failure and transferred to our pediatric intensive care unit in Turkey by air ambulance upon request of her family.

On arrival to our unit the patient was intubated and was under sedation with pentobarbital. She was on P-SIMV mode of ventilatory support (PEEP: 5, PIP: 18, Frequency: 30, FiO_2: 25%). Her vital signs were as follows: body temperature 36.9°C, heart rate 122 beats/min, oxygen saturation 96%, blood pressure 101/72 mmHg (50-90 percentile), and her respiratory rate was 36/min. On physical examination her weight was 5950 g (50-75 percentile), length was 63 cm (75-90 percentile) and head circumference was 40 cm (50-75 percentile). Glasgow coma score was 3. The anterior fontanel was open and flat. The pupils were equal and dilated (6 mm) with no light reflex, yet horizontal nystagmus was noted intermittently. Her muscle strength was 0/5 in four extremities and she had no deep tendon reflexes and gag reflex. Pulmonary and cardiac examinations were normal. The abdomen was soft to palpation, bowel sounds were hypoactive in four quadrants of the abdomen. The capillary filling time was <2 seconds, and peripheral pulses were palpable in four extremities. No skin findings were noted.

Laboratory examination, which included a complete blood count, peripheral blood smear, serum electrolytes, renal and hepatic function tests, ammonia, sedimentation, C-reactive protein, procalcitonin tests, cerebrospinal spinal fluid and urinalysis did not reveal any pathology. Diffusion-weighted magnetic resonance imaging (DWI-MRI) showed no pathology. DWI-MRI is the preferred screening in our institution for investigation of (non-traumatic) decreased consciousness due to its short duration. With the negative initial laboratory and radiologic results and the history of acute progressive weakness advancing to respiratory failure, decreased feeding and constipation, and the clinical cardiopulmonary stability on ventilator support, her low GCS was attributed to acute flaccid paralysis with ptosis, giving a false impression of coma. This thought process raised the diagnosis of

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infantile botulism, with cranial nerve and bulbar involvement. Stool, gastric juice, rectal swab and blood serum samples were sent for toxin analysis. Since there was a high degree of clinical suspicion, antitoxin treatment was started before the results of the toxin analyses were available, using 'Botulism Heptavalent Antitoksin, (A,B,C,D,E,F,G), BAT ®' obtained through the National Poison Advisory Center. Antitoxin was administered within 24 hours of intensive care hospitalization. No allergic reactions were observed. Her electroencephalogram (EEG) showed no epileptogenic potential. Electromyography (EMG) examination EMG which was performed at 11th day of the patient's symptoms 60% pathological increment with 10 Hz repetative stimulation through right nerves ulnaris (recorded through right musculus abductors digiti minimi). Motor nerve conductions could not be recorded except for right tibial nerve which had very low motor action potentials (0,3 mV and conduction velocity 28,6 m/s). Concentric needle EMG was normal these EMG findings were consistent with presynaptic end plate a disruption and motor axonal neuropathy. On the third day of hospitalization, minimal motor movements were observed at the distal parts of her extremities. Enteral nutrition via nasogastric tube was started with formula until breastmilk was available, and increased to full enteral feeds on the fourth day. Physical therapy exercises were also initiated. The patient was extubated on the twelfth day. Upon atelectasis, non-invasive respiratory support was given *via* Bilevel Positive Airway Pressure device and then she was weaned to high flow oxygen nasal cannula. Her activity level and muscle strength increased progressively. After the first week, recoveries of mimic muscles (laughing, crying and sucking) were observed. On the fourteenth day, she was breastfeeding ad lib. The patient was successfully discharged on the 21st day of hospitalization on full feeds and no medications.

FINAL DIAGNOSIS

In light of the history of perfectly well infant before travel, development of constipation and hypotonia with pupillary findings and weak cry, suck and swallow suggestive of bulbar involvement, and negative inflammatory data, normal biochemistry, CSF findings and cranial MRI, the diagnosis of infantile botulism was highly considered and antitoxin was given as soon as it was available before laboratory confirmation of the toxin. On the 18th day of hospitalization, results from stool samples of our patient was positive for *C. botulinum* Toxin A and B.

DISCUSSION

Clostridium botulinum is a gram-positive, anaerobic, spore-forming organism that can produce seven different neurotoxins. Toxin A and Toxin B are responsible for 90% of cases. In infantile botulism, *Clostridium botulinum* is intraintestinally colonized [1]. The toxin produces a flaccid motor paralysis beginning in the bulbar muscle. Paralysis is of descending pattern, although speed and degree of involvement may vary. The disease was first described in 1976 by Picket et al. [2] the release of presynaptic acetylcholine is irreversibly inhibited by neurotoxins produced in the intestine and transmitted to the synaptic space through the bloodstream [3]. Acetylcholine deficiency in the neuromuscular junction is the primary cause of symptoms. Respiratory failure is perhaps the most feared complication of pediatric botulism [4], and mechanical ventilation support is needed in approximately half of the children with infantile botulism who develop respiratory failure. According to the classical knowledge, consumption of honey and canned food is an important factor for the entry of spores, but this history is not present in 85% of cases [5]. Other risk factors include Caucasian race, age, constipation, living and breastfeeding in rural or construction sites. Swallowing microscopic dust particles that carry spores could be hard to rule out from the history. Our patient did not have a history of honey or home canned food exposure before infection, but *Clostridium botulinum* spores in microscopic dust particles could have been swallowed some indeterminate time ago and produced toxin inside the large intestine. Many cases cannot be prevented because the bacterium lives in dust and soil. It can be found inside homes on floors and carpets even after cleaning.

Infantile botulism often begins with constipation, although this sign can be overlooked by caregivers and physicians. Nonetheless first noticed symptoms are difficulty in feeding (i.e. sucking and swallowing), weak cry and diminished facial expression. Infected infants have difficulty in holding the head, hypotonia, lethargy and listlessness. Drooling could be falsely attributed to teething rather than to dysphagia due to bulbar involvement. Respiratory effort may become shallow and rapid, resulting in respiratory failure in severely affected cases. Cranial nerve involvements result in ptosis and absent pupil reflexes. The presentation in some cases are abrupt with paucity of the usual clinical signs with catastrophic results as Sudden Infant Death Syndrome (SIDS) or misleading for other diagnoses [6,7]. Our patient had difficulty in holding her head and developed progressive difficulty in sucking and swallowing. Those symptoms are nonspecific and can be seen in other diseases as well; therefore infantile botulism should be considered in the differential diagnosis [8]. Similar symptoms may be suggestive of sepsis [9]. Sepsis was excluded due to hemodynamic stability, absence of fever and negative inflammation markers. Unlike sepsis, in infantile botulism, no fever is seen and blood counts, cerebrospinal fluid findings and blood cultures are negative. Patients should also be investigated for dehydration, electrolyte abnormalities and congenital metabolic disorders. Neuromuscular causes such as Spinal Muscular Atrophy (SMA), Guillain-Barre syndrome, infantile myasthenia gravis and muscle dystrophies are also important in differential diagnosis [5]. Pupillary or eye involvement in SMA is rare, and the progression to respiratory failure is not as abrupt as in this case. Ascending paralysis, as opposed to descending is typical in Guillain-Barre syndrome. Infantile myasthenia gravis can usually be excluded based on maternal history.

During the course of the disease, complications such as inappropriate ADH syndrome (16%), apnea (12%), urinary tract infection (UTI) (11%), pneumonia (7%), sepsis (5%), seizures (5%), atelectasis (55%), tracheitis (20%), tracheal granuloma (16%), inability to tolerate extubation (7%) and stridor (5%) after extubation can be seen [10]. In our patient, inappropriate ADH syndrome was observed on the seventh day, UTI on the ninth day, atelectasis after extubation on the fifteenth day, and anisocoria in the pupils on the sixteenth day. Anisocoria in our patient could be due to asymmetrical recovery from the disease which actually progresses symmetrically from cranial to caudal direction.

Important factors in the prognosis of infantile botulism are duration of ICU stay and mechanical ventilation support and delayed oral feeding. Early administration of antitoxin therapy and supportive care prevent complications and reduce hospital stay and mortality [11]. The prognosis is very good in early diagnosed cases treated by supportive care and antitoxin treatment. Mortality rate was reported as <2% [12]. In the United States, human derived botulism antitoxin (BabyBIG) developed for infant botulism is in

use, but due to its high cost, its use is limited in other countries [9]. Although horse derived *botulinum* antitoxin has been available in the USA since 1940 [13], its use is limited due to the risk of hypersensitivity to horse antigens and its very short half-life (5-7 days) [14,15]. There are not enough controlled studies on horse-induced botulism antitoxin and this limits its use [15]. In our case 'heptavalent Botulism antitoxin (A, B, C, D, E, F, G), BAT ®, which was a horse antitoxin, was administered and no allergic reactions were observed. The vial of antitoxin contained 18 ml of antitoxin in a 50 ml vial. Each vial consisted of 4500 IU Type A, 3300 IU Type B, 3000 IU Type C, 600 IU Type D, 5100 IU Type E, 3000 IU Type F and 600 IU Type G. Our patient was given 1.8 mL antitoxin as a 10-hour infusion which was 10% of the recommended dose for this antitoxin. The total amount of antitoxin administered was 450 IU Type A, 330 IU Type B, 300 IU Type C, 60 IU Type D, 510 IU Type E, 300 IU Type F and 60 IU Type G. In a case series of infantile botulism reported by Cuetos et al. in Argentina, 7500 IU Type A and 5500 IU Type B horse derived antitoxin was given and clinical improvement was observed without any allergic reaction [16].

CONCLUSION

The most important point in the diagnosis of infantile botulism is the clinical suspicion of the disease. Infantile botulism should be considered in children with sudden onset of weakness in sucking, hypotonia, constipation and flaccid paralysis. It may be difficult to determine the alertness of the patients due to ptosis and neuromuscular paralysis. Nystagmus may be due to ocular muscle involvement. Botulism should be considered in the differential diagnosis of an “unconscious” patient in addition to seizure, encephalitis, coma and metabolic disease. Toxin studies are important in the definitive diagnosis, but the results can take up to two weeks to be completed. Because botulism antitoxin significantly reduces morbidity, rapid administration of antitoxin even in the absence of definitive diagnosis may reduce complications and improve prognosis.

AUTHOR CONTRIBUTIONS

CS: Contributed to conception, drafted the manuscript. OO: Contributed to conception, drafted the manuscript. FE, GT, EKK: Contributed to conception. FIG: Contributed to conception, critically revised the manuscript for important and intellectual content and gave final approval. MNO: Contributed to conception, critically revised the manuscript for important and intellectual content and gave final approval.

DECLARATION OF CONFLICTING INTEREST

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