A Case of Infant Botulism due to Neurotoxicogenic *Clostridium butyricum* Type E Associated with *Clostridium difficile* Colitis

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**Abstract** Reported here is the sixth case of intestinal toxemia botulism caused by *Clostridium butyricum* type E in Italy since 1984. In this case, the patient was concomitantly affected with colitis due to *Clostridium difficile* toxin. A review of previously reported cases revealed that some of these patients may also have had intestinal toxemia botulism associated with *Clostridium difficile* colitis, based on the reported symptoms. Given that this association has been shown to exist not only in Italy but also in the USA, it is recommended that individuals with intestinal botulism and symptoms of colitis undergo testing for *Clostridium difficile* and its toxins in fecal samples.

**Introduction**

Botulism as intestinal toxemia is a distinct clinical entity first described in 1976, that occurs almost exclusively in the first months of life (infant botulism) and very rarely in young people or adults (infant-like botulism) [1]. Since 1984, 17 cases of infant botulism and three infant-like cases have been reported in Italy. Surprisingly, five of them (3 infant and 2 infant-like) were caused by type E botulism neurotoxin produced by an organism identified as *Clostridium butyricum* [2, 3, 4]. Of these five patients, four presented acute gastroenteric symptomatology, and in two of these cases the severity of the symptoms led to surgery for suspected acute appendicitis [2, 3].

Similarly, the patient described here was concomitantly affected with botulism due to *Clostridium butyricum* type E and colitis; however, this is the first patient in Italy for whom the association of pathologies has been confirmed by the isolation of *Clostridium butyricum* spores and *Clostridium difficile* toxin in stool samples.

**Case Report**

In May 2001, a 27-week-old male infant presented to the Emergency Room of the Pediatric Department of the University of Padova with a 4-day history of constipation, poor sucking, decreased oral intake and decreased activity. His medical history was unremarkable; he had been breast-fed, had started solid food 1 month before admission and had never been given honey nor corn syrup. He lived with his family in a small town in northeastern Italy, and their house had recently been renovated.

On admission the child was afebrile and clinical examination revealed weak cry and suck, irritability, dry oral mucous membranes and lack of tears. The neurological examination showed an alert, somewhat interactive infant with mild hypotonia, even though he was able to sit and control his head, mild bilateral ptosis, flaccid facial expression and only slightly decreased deep tendon reflexes. A few hours after admission, the child presented fever (39.5°C), progressive deterioration of his reactivity and diarrhea.

Laboratory assessments showed a leukocyte count of 5340/mm³ (with 33% neutrophils, 53% lymphocytes, 8% monocytes, 1% eosinophils and 5% basophils), and C-reactive protein 120 mg/l; electrolytes, blood urea nitrogen, creatinine, glucose, lactate and ammonia concentrations were in the normal range. Urinalysis results showed no abnormal findings, except for 75 leukocytes/field. Cerebrospinal fluid (CSF) examination was unremarkable. Cultures of blood, urine, stool and CSF were performed. Electroencephalogram, renal and abdominal ultrasound and renal di-mercapto-succinic-acid scan did not show any pathological findings.

The initial diagnosis was severe infection (suspected sepsis) with dehydration, and the child was placed on intravenous fluids and cefotaxime for 7 days. In order to detect the etiology of enteritis, a fecal sample was submitted for detection of non-spore-forming bacteria, viruses, and *Clostridium difficile* toxin. In order to clarify the neurological symptoms, fecal samples were also collected and sent to the National Reference Center for Botulism for examination.

After 48 h an initial improvement was noted. Fever and diarrhea subsided and the child started to suck and become more interactive; he still presented mild hypotonia with dry mouth and lack of tears, but urine output was normal and there were no signs of dehydration. Subsequently, culture results were obtained: blood, CSF and stool cultures were negative for non-spore-forming bacteria and viruses, and urine culture was positive for...
Escherichia coli. Toxin of Clostridium difficile and spores of a neurotoxicogenic Clostridium sp. producing botulinum neurotoxin type E were detected in stool samples. The neurotoxicogenic strain was phenotypically and genotypically identified as Clostridium butyricum using previously described methods [5, 6, 7].

The infant was kept on the cefotaxime regimen and rapidly gained strength. At the time of discharge (7 days after admission) his cry had returned to normal and he was feeding normally. Follow-up examinations, performed weekly for 2 months, yielded normal results. Neurotoxicogenic spores were detected in follow-up stool samples until 1.5 months following the onset of symptoms. Two months after admission, serum was tested for the presence of circulating antitoxin against botulinum toxin type E, with negative results.

Discussion

The association between intestinal toxemia botulism and gastrointestinal symptomatology has been observed previously in cases of botulism caused by neurotoxicogenic strains of Clostridium butyricum in Italy. However, the case presented here is the first in which the presence of Clostridium difficile toxin and Clostridium butyricum type E spores has been demonstrated in the feces of a patient with both gastroenteric and botulism symptoms.

Recently, Schecter et al. [8] demonstrated an association between infant botulism caused by Clostridium botulinum and Clostridium difficile-associated diarrhea in patients in the USA. In their report, the authors described six cases of infants suffering from concomitant infant botulism and diarrhea; in five of these cases, Clostridium difficile toxin and spores were detected in fecal samples, while in the sixth case Clostridium difficile-associated diarrhea could only be suspected, since a test for Clostridium difficile was not available. The authors hypothesized that colonic stasis caused by Clostridium botulinum toxin might be the primary factor favoring the proliferation of Clostridium difficile, which often asymptomatically colonizes healthy neonates and infants.

Botulinum neurotoxin produced by neurotoxicogenic Clostridium butyricum could act in the same way, thus favoring the multiplication of Clostridium difficile. Although, among the Italian cases Clostridium difficile was only sought in our patient, we hypothesize that the same mechanism might also have occurred in the previous cases characterized by very similar clinical pictures. Interestingly, all of these patients had been treated with wide-spectrum antibiotics, and three of them showed a worsened neurological symptomatology associated with botulism. In the present case, the infant was treated with a broad-spectrum antibiotic, because the suspected diagnosis at admission was severe infection. This therapy was continued for 7 days in order to treat a concomitant urinary tract infection due to Escherichia coli, an association of infections that has been described previously [9] and is probably due to urinary retention as a consequence of bladder hypertonia.

In our experience, antibiotic therapy is applied rather frequently in cases of infant botulism, either as empiric therapy before the definitive diagnosis has been reached or to treat secondary infections, which is consistent with data reported elsewhere in the literature [10, 11]. However, the use of antibiotic therapy for managing uncomplicated infant botulism should be avoided, since it can cause lysis of intraluminal clostridia with a consequent increase in the amount of toxin available for absorption. Also, some antibiotics, particularly aminoglycosides, might exacerbate the neurological symptoms due to the effect these agents have on neuromuscular transmission [1, 12]. Antibiotics are only indicated to treat complications, and in such cases, sulfamethoxazole-trimethoprim and nalidixic acid should be preferred because Clostridium botulinum is resistant to them.

Considering the increasing incidence of Clostridium butyricum as a new agent of botulism in Italy, we decided to test the sensitivity of our patient's isolate to 16 antimicrobial agents [13]. In comparison with Clostridium botulinum, Clostridium butyricum was equally susceptible to sulfamethoxazole-trimethoprim and more susceptible to nalidixic acid.

In conclusion, whenever diarrhea is observed in children with intestinal toxemia botulism, stool samples should be examined repeatedly for Clostridium difficile and its toxin. If antibiotic therapy is necessary, it should be considered that the species of neurotoxicogenic clostridia involved may be other than Clostridium botulinum, thereby possibly displaying a different antibiotic susceptibility pattern.

References


