Clinical Neurophysiology 120 (2009) 1135–1138

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Electrodiagnosis of botulism and clinico-electrophysiological correlation

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ARTICLE INFO

Article history:
Accepted 20 January 2009
Available online 1 May 2009

Keywords:
Electrodiagnosis
Botulism

ABSTRACT

Objective: An electrophysiological study can help to confirm the diagnosis of botulism. This study was aimed at validating a simple and reliable electrodiagnostic test and at correlating the findings with clinical severity.
Methods: Pre- and post-exercise single supramaximal stimulations (SSSs) were performed in 63 patients with botulism. The sensitivity and specificity of amplitude of compound muscle action potential (CMAP) and percentage increment (PI) of SSS were determined. These two parameters were then correlated with respiratory failure. The relationship between the amplitude of CMAP and PI was also studied.
Results: SSS with a PI of 25% showed a sensitivity of 95.2% and a specificity of 100% in association with botulism. The area under the receiver operating characteristic (ROC) curve of CMAP and PI was associated with the respiratory failure by 0.7 and 0.6, respectively. An inverse relationship between the amplitude of CMAP and PI was also demonstrated.
Conclusions: SSS is sensitive and specific in the diagnosis of botulism. There was some correlation of the findings with clinical severity. The inverse relationship between the amplitude of CMAP and PI reflects the pathophysiology of this disorder.
Significance: This study has validated SSS as being a simple and reliable electrodiagnostic test for botulism.

1. Introduction

Botulism is a rare presynaptic neuromuscular junction (NMJ) disorder caused by the potent toxins of an anaerobic, spore-forming, Gram-positive bacteria *Clostridium botulinum*. The botulinum toxin consists of a heavy and a light chain that are taken up by endocytosis into the presynaptic nerve ending at the NMJ. Once inside the neuron, the light chain is cleaved free from the heavy chain by the reduction of a single disulphide bond and acts as a zinc-dependent protease which can attack one or more of the three SNARE (soluble *N*-ethylmaleimide-sensitive factor attachment protein receptors) proteins. The SNARE protein complex is the key process that enables the vesicles in the nerve terminals, which contain acetylcholine, to fuse with the neural cell wall and be released into the synaptic cleft (Simpson, 2004; Horowitz, 2005). Therefore, the release of acetylcholine is prevented and muscles cannot contract resulting in flaccid paralysis.

Botulism can present diagnostic difficulties, especially if it occurs as a sporadic case. However, in the setting of an outbreak in which several persons are affected, the disease can be diagnosed more readily. In food-borne botulism, which is caused by the ingestion of food contaminated with botulinum toxin, the initial phase of the disease is usually presented with gastrointestinal (GI) symptoms. Difficulty in swallowing is the most common and early neurological symptom, followed by ptosis, ophthalmoparesis or ophthalmoplegia and proximal muscle weakness. The disease can progress rapidly in severe cases, with involvement of respiratory muscles resulting in respiratory failure. An electrophysiological study usually shows characteristic changes that may be diagnostic. Other investigations include bioassay and polymerase chain reaction test for the toxin and culture for *C. botulinum* of the serum, gastric secretion and stool of the patients and the suspected food. However, the results of these tests may not be available for several days (Cherington, 2004; Sobel, 2005). The initial management is often determined solely on the basis of clinical diagnosis. Meanwhile, an electrophysiological study, if available, can be helpful in confirming the diagnosis or in excluding other diseases with similar clinical presentations, for example, Guillain–Barré syndrome or its Miller-Fisher variant and myasthenia gravis.

In March 2006, there was a large outbreak of food-borne botulism affecting a group of people who had had lunch at a religious rite in Nan, a northern province of Thailand. Home-canned bamboo shoots were implicated as the sources of the toxin. The purpose of

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1388-2457/$36.00
doi:10.1016/j.clinph.2009.01.019

this study was to demonstrate the pattern of post-exercise facilitation (PEF) by performing pre- and post-exercise single supramaximal stimulation (SSS) with a view to validate a rapid, simple and reliable diagnostic test that is sensitive and specific for botulism and to correlate the findings with clinical severity.

2. Methods

2.1. Patients

A total of 63 inpatients were included in this study. The date and time of ingestion of the implicated food and occurrence of GI and neurological symptoms were noted. Electrophysiological studies and other investigations were performed.

2.2. Electrophysiological study

An electrophysiological study was performed by using a Dantec Keypoint electromyograph (EMG) machine in all patients on days 7–8 of the neurological symptoms. In view of the fact that many patients were very sick, invasive and painful tests were avoided.

SSS was performed in all the patients. Using a bipolar surface electrode, single supramaximal stimulus (pulse duration 0.1 ms) was delivered to the ulnar nerve with a recording surface electrode on the abductor digiti minimi (ADM). After the compound muscle action potential (CMAP) was obtained at rest, the patient was asked to fully abduct the little finger against resistance for 10 s. This was followed by another SSS. The amplitude of pre- and post-exercise CMAP and the difference between the two were noted. A similar study was performed in 60 patients with other neuromuscular disorders serving as controls. The sensitivity and specificity of SSS in association with botulism and clinical severity were determined from the amplitude of resting CMAP and degree of change of post-exercise CMAP (expressed as percentage change or increment). Furthermore, the amplitude of resting CMAP was correlated with the percentage change of post-exercise CMAP with a view to demonstrate the relationship of these two parameters which may reflect the pathophysiology of this disease.

2.3. Other laboratory investigations

The leftover canned bamboo shoots were sent for toxin identification and culture. The toxin identification was done by Digoxenin-label IgGs ELISA (CDC-Atlanta, GA, USA) and it suggested *C. botulinum* type A. *C. botulinum* was grown by anaerobic culture. Further identification by the multiplex polymerase chain reaction confirmed *C. botulinum* type A.

2.4. Statistical analysis

The means with standard deviations (SDs) and the frequencies with percentages were used to describe patient characteristics in the cohort of this outbreak. The Mann–Whitney test was used to compare the medians of the resting CMAP amplitude and the post-exercise percentage change of controls with those of patients with botulism, and to compare the results of patients with respiratory failure to those without respiratory failure.

The sensitivity and specificity of SSS in association with botulism and respiratory failure were determined by using a receiver operating characteristic (ROC) curve analysis to assess the resting CMAP amplitude and percentage increment. The areas under the curve (AUCs) of the resting CMAP and the percentage increment associated with botulism and respiratory failure were estimated.

The relationship between the resting CMAP amplitude and the percentage increment of post-exercise CMAP amplitude was assessed by regression analysis.

All analyses were performed by using STATA version 9.2. A p value of less than 0.05 was considered significant.

3. Results

3.1. Clinical features

A total of 63 patients, that is, 19 men (30.2%) and 44 women (69.8%) with an age range of 14–73 years (mean ± SD = 45.5 ± 10.9), were included in this study. Most of the cases first presented with GI symptoms within several hours to a few days after the ingestion of food with a median time to onset of 25 h (range = 10–168). These were followed by neurological symptoms and signs with a median time to onset of 48 h (range = 24–168). The most striking and early neurological symptom and sign was difficulty in swallowing. Other neurological signs included ptosis, ophthalmoparesis or ophthalmoplegia, proximal muscle weakness and respiratory failure (Table 1). Twenty-four patients developed respiratory failure requiring mechanical ventilation. In severe cases, the respiratory muscles were always affected; however, the power of limb muscles varied considerably from being normal or slightly weak proximally to being almost completely paralysed. The deep tendon reflexes (DTRs) were normal in most of the patients (92%), depressed in four patients and were absent in one, who was almost completely paralysed. The hyporeflexia was more pronounced in the lower limbs. In previous reports, the DTRs were either not mentioned or generally said to be either hypoactive (Shapiro et al., 1998) or preserved (Cherington, 2004).

The control subjects were 60 patients with myasthenia gravis, Guillain–Barré syndrome, other polyneuropathy, amyotrophic lateral sclerosis and myopathy. There were 24 men (40%) and 36 women (60%) with an age range of 17–89 years (mean ± SD = 49.2 ± 18).

3.2. Electrophysiological findings: SSS

3.2.1. Resting CMAP and percentage change in patients with botulism and controls

On SSS, most patients had small amplitudes of the resting CMAP of ADM ranging from 0.3 to 7.5 mV with a median of 3 mV. All the patients showed an incremental response on stimulating after

Table 1
Clinical characteristics of the patients.

Characteristics	Total	*N* (%)
Sex		
Male	63	19 (30.2)
Female		44 (69.8)
Age; mean (SD)	63	45.5 (10.9)
Onset of GI symptoms, hours; median (range)	63	25 (10–168)
Onset of neurological symptoms, hours; median (range)	63	48 (24–168)
Gastrointestinal symptoms		
Nausea	57	29 (50.9)
Vomiting	57	35 (61.4)
Abdominal pain	57	28 (49.1)
Diarrhea	57	22 (38.6)
Neurological signs		
Dysphagia	63	59 (93.6)
Ptosis	61	54 (88.5)
Ophthalmoparesis or ophthalmoplegia	62	38 (61.3)
Dilated and fixed or sluggishly reactive pupils	55	9 (16.4)
Weakness of neck flexor	62	51 (82.3)
Weakness of the extremities	63	41 (65.1)
Deep tendon reflexes	63	
Normal		58 (92.0)
Depressed		4 (6.4)
Absent		1 (1.6)
Pain sensation: normal	63	63 (100)
Respiratory failure	63	24 (38.1)

SD, standard deviation; GI, gastrointestinal.