

Clinical Features of Antibody-Induced Complete Secondary Failure of Botulinum Toxin Therapy

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Key Words

Botulinum toxin therapy · Antibodies, botulinum toxin · Therapy failure · Clinical features

Abstract

In some patients treated with botulinum toxin type A (BT), secondary therapy failure occurs. It can either be partial (PSTF) or complete (CSTF). One of the main causes for CSTF is the formation of antibodies against BT. We wanted to study the clinical features of BT antibody-induced CSTF to improve its detection. For this, 27 patients with various dystonic syndromes and antibody-failure were studied. In 22 patients CSTF was preceded by a total of 63 injection series with PSTF. The number of injection series with preceding PSTF was 2.52 ± 2.37 with a range from 0 to 8. When PSTF occurred, the maximal efficacy of BT therapy was reduced on 55 occasions and the efficacy duration on 48 occasions. CSTF occurred after treatment times of 61–1,507 days with grouping around 324.9 ± 148.9 days and $1,155.7 \pm 436.8$ days and patients with short interinjection intervals significantly overrepresented in the first group (Mann-Whitney U test, $p = 0.009$). Sex and age at initiation of BT therapy, single BT dose, and number of booster injection series were not

different in both groups. Immunological complications could not be detected in any of the patients. Clinical features of antibody failure described in this study show that the shorter the interinjection intervals, the earlier antibody failure occurs. They make it highly unlikely for patients with long-standing BT therapy to develop antibody failure, and they might be useful to identify antibody failure before elaborate BT antibody testing is initiated.

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Introduction

Botulinum toxin type A (BT) has been used since 1984 to treat dystonia [1] and various other muscle hyperactivity syndromes [2]. Generally, the results of BT therapy are so impressive that it is considered the treatment of choice for most of its indications. In some patients, however, therapy failure occurs. This therapy failure can either be primary, i.e., BT therapy never worked sufficiently, or it can be secondary, i.e., BT therapy worked sufficiently when it was initiated, but then lost its efficacy during the further course of the treatment. Secondary therapy failure can either be partial (PSTF) or complete (CSTF) [3]. For-

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mation of antibodies against BT is one of the causes of CSTF [4–8]. We wanted to describe the clinical features of BT antibody-induced CSTF (antibody failure) to improve its diagnosis.

Patients and Methods

Patients

Altogether 27 patients who had received BT therapy for various dystonic syndromes in the Dyskinesia Outpatient Clinic, Georg August University, Göttingen, Germany, or in the Botulinum Toxin Outpatient Clinic, National Hospital for Neurology and Neurosurgery, London, UK, during the last 13 years were included in this study. Fourteen patients suffered from cervical, 6 from segmental, 5 from generalized, and 2 from axial dystonia. All of them showed antibody failure defined as follows: (1) satisfactory improvement of cervical dystonia on at least one initial injection series; (2) three consecutive injection series failed to produce any effect, neither improvement nor side effects, as confirmed by the patient and by neurological examination monitoring target muscle weakness and atrophy and dystonia severity; (3) the BT-induced reduction of the electromyographic activity of the sternocleidomastoid muscle was at least two standard deviations less than the values determined in a group of controls receiving the same amount of BT [9, 10], and (4) causes other than BT antibody formation [3] were excluded. In 20 patients direct BT antibody testing could be performed by mouse protection bioassay [11], by mouse diaphragm bioassay [12], or by both methods. All patients tested showed evidence of BT antibody formation on at least one of the BT antibody tests. PSTF was defined as a response to BT therapy which was reduced by at least 30% in its maximal efficacy or its duration as compared with the average initial response of the particular patient. Eighteen of the patients studied were female, 9 were male. Their age at initiation of BT therapy was 44.4 ± 13.4 years. None of the patients had allergies nor had received immunomodulatory drugs. BT therapy was performed either with Botox® (Allergan, Irvine, Calif., USA) or with Dysport® (Ipsen Pharmaceuticals, Maidenhead, UK) or with both consecutively. For dose comparison 1 equivalent mouse unit (EMU) was defined as being equal to 1 Botox mouse unit and 3 Dysport mouse units [13, 14].

Statistics

For statistical analysis, the Mann-Whitney U test and Fisher's exact test were used, as indicated. Unless otherwise stated, group values are given as mean \pm SD.

Results

Characteristics of BT Therapy

From initiation of BT therapy until the first occurrence of CSTF, the treatment time was 694.2 ± 519.3 days, the number of injection series 8.5 ± 5.8 , the number of injection series with an interval of less than 21 days ('booster injection series') 1.2 ± 1.2 , the interval between injection

series 80.1 ± 34.1 days, the single BT dose $471.8.1 \pm 268.5$ EMU and the cumulative BT dose $3,935.0 \pm 3,011.8$ EMU.

Partial Secondary Therapy Failure

PSTF preceding CSTF occurred in 22 of the 27 patients studied on a total of 63 occasions. It did not occur in 5 patients. The number of injection series with PSTF preceding first occurrence of CSTF was 2.52 ± 2.37 with a range from 0 to 8. When PSTF occurred, the maximal efficacy of BT therapy was reduced on 55 occasions and efficacy duration on 48.

Complete Secondary Therapy Failure

Latencies between initiation of BT therapy and first occurrence of CSTF ranged from 61 to 2,341 days. Figure 1 gives an overview over the distribution of this latency. The majority of latencies fell between 0 and 1,599 days. Only one latency occurred after 2,341 days. Between 0 and 1,599 days, the latencies were grouped around 324.9 ± 148.9 days (short-latency group) and $1,155.7 \pm 436.8$ days (long-latency group). When patient characteristics, such as sex and age at initiation of BT therapy, and BT therapy parameters, such as number of booster injections, interinjection interval, and single BT dose, were compared between the short- and the long-latency groups (table 1), no statistically significant differences could be detected with the exception of the interinjection interval which was significantly overrepresented in the short-latency group (Mann-Whitney U test, $p = 0.009$).

Additional Observations

Immunological complications, such as fatigue or hot-cold dysesthesias, lid edema, skin rash, joint pain, muscle pain, or diffuse 'flu like symptoms' could not be detected in any of the patients.

Discussion

Antibody failure often persists for several years [15], thus effectively terminating BT therapy and depriving patients from one of their most promising therapy options. Detection of BT antibodies can either be tried by direct BT antibody tests, such as the mouse protection bioassay [11], the mouse diaphragm bioassay [12], or a radioimmunoprecipitation assay [16], or by indirect tests monitoring the electromyographic activity of a target muscle before and after BT application [17]. Since BT antibody testing is complex, time-consuming, not readily

Fig. 1. Histogram of latencies between initiation of botulinum toxin therapy and first occurrence of complete secondary therapy failure. The majority of latencies fell between 0 and 1,599 days. Only one latency occurred between 2,300 and 2,399 days. Between 0 and 1,599 days, the latencies were grouped around 324.9 ± 148.9 days (short-latency group) and $1,155.7 \pm 436.8$ days (long-latency group).

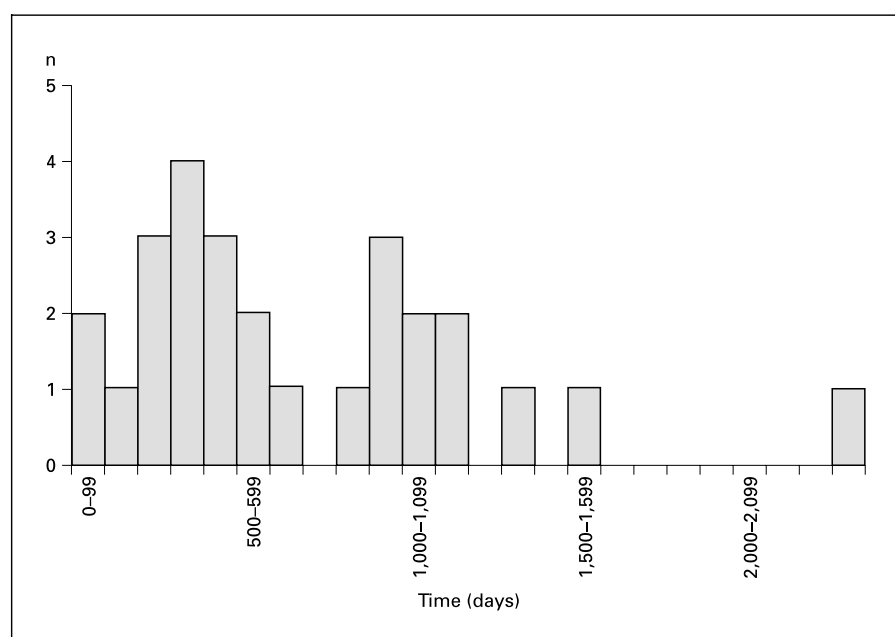


Table 1. Patient characteristics and botulinum toxin therapy parameters in patients with short and long latencies between initiation of botulinum toxin therapy and complete secondary therapy failure

Parameter	Short-latency group	Long-latency group	p
Sex, females/males	8/7	10/2	0.217 ^a
Age at initiation of BT therapy, years	46.5 ± 13.0	41.8 ± 13.9	0.373 ^b
Number of booster injection series, n	1.4 ± 1.2	1.0 ± 1.0	0.456 ^b
Interval between injection series, days	67.3 ± 29.1	96.6 ± 33.9	0.009 ^b
Single BT dose, EMU	512.1 ± 282.2	421.5 ± 253.2	0.256 ^b

Booster injection series = injection series with interinjection intervals of less than 21 days; EMU = equivalent mouse unit.

^a Fisher's exact test; ^b Mann-Whitney U test.

available, and may eventually produce contradictory results, preceding analysis of the clinical situation should be useful.

Antibody failure shows relatively uniform clinical features. It occurs typically either around 350 days or around 1,200 days after initiation of BT therapy. Antibody failure occurring more than 1,507 days after initiation of BT therapy is exceedingly rare, making it highly unlikely for patients receiving BT therapy for more than 4 years to develop antibody failure. Since development of late antibody failure has been a major concern amongst patients receiving long-term BT therapy, this result might alleviate those concerns. Patients with antibody failure occurring

around 350 days after initiation of BT therapy had significantly shorter interinjection intervals than those with antibody failure occurring after around 1,200 days. Short interinjection intervals are per se an identified risk factor for BT antibody formation [4, 18]. The shorter interinjection intervals are the earlier the BT antibody formation occurs. Usually, CSTF is preceded by injection series with PSTF. Few patients, however, may switch abruptly from a normal clinical response to CSTF. When PSTF occurs, it is equally often characterized by reduced maximum efficacy and efficacy duration. Immunological complications, especially diffuse 'flu like symptoms', could not be detected in any of our patients.

The clinical features of antibody failure described in this study show that the shorter the interinjection intervals, the earlier antibody failure occurs. They make it highly unlikely for patients with long-standing BT therapy to develop antibody failure, and they might be useful to identify antibody failure before elaborate BT antibody testing is initiated.

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