Antibody-Induced Failure of Botulinum Toxin A Therapy in Cosmetic Indications

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BACKGROUND Botulinum toxin (BT) is a safe and effective treatment for cosmetic indications. Formation of BT antibodies can occur but has previously been reported in cosmetic indications in two cases only.

OBJECTIVE To report another four patients with this phenomenon.

OBSERVATIONS Two patients received abobotulinumtoxinA; one received the current formulation of onabotulinumtoxinA and one both abobotulinumtoxinA and onabotulinumtoxinA. Complete secondary therapy failure (CSTF) occurred after 3-, 5-, 10-, and 13-injection series; cumulative treatment times of 18, 16, 25, and 65 months; and cumulative doses of 240 MU onabotulinumtoxinA, 245 MU abobotulinumtoxinA, 1,180 MU abobotulinumtoxinA, and 120 MU onabotulinumtoxinA/270 MU abobotulinumtoxinA, respectively. Average interinjection intervals were 87, 273, 150, and 119 days, and average single doses were 80 MU onabotulinumtoxinA, 68 MU abobotulinumtoxinA, 82 MU abobotulinumtoxinA, and 30 MU abobotulinumtoxinA/30 MU onabotulinumtoxinA. Risk factors for CSTF included booster injections (2 patients) and increased immune system reagibility (1 patient). BT antibody titers were 2.7, 7.0, and more than 10.0 mU/mL on the mouse diaphragm assay.

CONCLUSIONS CSTF can occur after cosmetic BT injections in patients with high immune system reagibility and in patients receiving booster injections, but also in unremarkable patients with typical treatment parameters. Its incidence is unknown. Recommended treatment parameters may reduce the risk of CSTF, but may not eliminate it.

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Botulinum toxin (BT) has been used with remarkable success to treat various disorders caused by hyperactivity of muscles or of exocrine glands.[1] Its use to treat pain disorders is currently being explored. BT type A (BT-A) and BT type B (BT-B) are used for therapeutic purposes. BT-A is commercially available as onabotulinumtoxinA (Botox/Vistabel, Allergan, Irvine, CA), abobotulinumtoxinA (Dysport/Reloxin, Ipsen, Slough, UK), and incobotulinumtoxinA (Xeomin/Bocouture, Merz Pharmaceuticals, Frankfurt, Germany), and BT-B as rimabotulinumtoxinB (NeuroBloc/Myobloc, Solstice Neurosciences Inc, Malvern, PA). Antibodies against botulinum neurotoxin are formed in some patients receiving BT therapy. Those BT antibodies can block BT's therapeutic action so that partial secondary therapy failure (PSTF) or complete secondary therapy failure (CSTF) is induced.[2] So far, PSTF and CSTF have mainly been described in patients receiving BT therapy for dystonia, spasticity, and cerebral palsy. One case report describes CSTF when BT therapy is used for cosmetic subcutaneous purposes[3] and another one for cosmetic intramuscular purposes.[4] We describe CSTF in four patients receiving BT for cosmetic indications and explore risk factors for CSTF, such as treatment parameters and patient predispositions.

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Cases

Case 1

A 53-year-old woman presented with hyperkinetic skin lines in the glabellar, forehead, and bilateral periocular regions. She had never received BT therapy before. Her treatment details are shown in Tables 1 and 2. She was treated with Dysport (50 MU/mL 0.9% sodium chloride). PSTF occurred after six injection series, a treatment time of 16 months, and a cumulative dose of 860 MU of Dysport and CSTF after 10 injection series, a treatment time of 25 months, and a cumulative dose of 1180 MU of Dysport. Until CSTF occurred, the interinjection interval was 87 $\pm$ 64 days (minimum 14 days, maximum 172 days), the single dose 82 $\pm$ 46 MU Dysport (minimum 19 MU, maximum 128 MU). At the time of CSTF, the mouse diaphragm assay[5] revealed a titer of 7.0 mU/mL.

Case 2

A 46-year-old woman presented with hyperkinetic skin lines in the glabellar, forehead, and bilateral periocular regions. She also complained of biaxillary hyperhidrosis. She had never undergone BT therapy before. A treatment summary is given in Tables 1 and 2. For injection series 1 to 3 and 5 to 6, the patient received the current formulation of Botox (Botox-CF, 50 MU/mL 0.9% sodium chloride); for injection series 4 and 7 to 9 she received NeuroBloc/Myobloc in its original dilution. PSTF occurred after two injection series, a treatment time of 11 months, and a cumulative dose of 160 MU Botox-CF and CSTF after three injection series, a treatment time of 18 months, and a cumulative dose of 240 MU Botox-CF. Until CSTF occurred, the interinjection interval was 273 $\pm$ 86 days (minimum 212 days, maximum 334 days), the single dose 80 MU Botox-CF. At the time of CSTF, the mouse diaphragm assay revealed a BT-A-antibody titer of 2.7 mU/mL. Subsequent injections using NeuroBloc/Myobloc produced normal therapeutic results.

Case 3

A 51-year-old woman presented with hyperkinetic skin lines in the glabellar and bilateral periocular regions. She had never received BT therapy before. Her treatment details are shown in Tables 1 and 2. For injection series 1 to 9, she was treated with Dysport (50 MU/mL 0.9% sodium chloride) and for injection series 10 to 13 with Botox-CF (50 MU/mL 0.9% sodium chloride). PSTF occurred after 12 injection series, a treatment time of 60 months, and a cumulative dose of 90 MU Botox-CF and 270 MU Dysport and CSTF after 13 injection series, a treatment time of 65 months, and a cumulative dose of 10 MU Botox-CF and 270 MU Dysport. Until CSTF occurred, the interinjection interval was 150 days and the single dose 30 MU Dyport and 30 MU Botox. At the time of PSTF, the BT-A antibody titer was 1.0 mU/mL; at the time of CSTF, it was in excess of 10 mU/mL. After CSTF had occurred, BT therapy was stopped, and annual mouse diaphragm assays demonstrated constant BT-A antibody titers in excess of 10 mU/mL for the next 4 years.

Case 4

A 45-year-old woman presented with hyperkinetic skin lines in the glabellar and forehead regions. She had never received BT treatment before. Her treatment details are shown in Tables 1 and 2. On injection series 1 to 6 she was treated with Dysport (200 MU/mL 0.9% sodium chloride). PSTF occurred after three injection series, a treatment time of 3 months, and a cumulative dose of 210 MU Dysport and CSTF after five injection series, a treatment time of 16 months, and a cumulative dose of 474 MU Dysport. Until CSTF occurred, the interinjection interval was 119 $\pm$ 86 days (minimum 15 days, maximum 193 days) and the single dose 68 $\pm$ 31 MU Dysport (minimum 30 MU, maximum 105 MU). At the time of CSTF, the mouse diaphragm assay revealed a BT-A antibody titer in excess of 10 mU/mL. Applying Xeomin instead of Dysport did not produce a therapeutic effect either.

Discussion

Various factors increase the risk of antibody formation against BT. These include large BT doses given

TABLE 1. Details of Botulinum Toxin Therapy

Injection Series	*Interinjection Interval (days)*	*Botulinum Toxin Dose (MU)*	*Botulinum Toxin Drug*	*Target Muscles*	*Treatment Result*	*Mouse Diaphragm Assay (mU/mL)*
Case 1						
1		140	Dysport	G/F	Normal	
2	83	180	Dysport	G/F	Normal	
3	128	180	Dysport	G/F/E	Normal	
4	19	10	Dysport	G/F		
5	98	180	Dysport	G/F	Normal	
6	161	170	Dysport	G/F	PSTF	
7	23	70	Dysport	G/F	PSTF	
8	172	100	Dysport	G/F/E	PSTF	
9	14	50	Dysport	G/F	PSTF	
10	42	100	Dysport	G/F	CSTF	7.0
Case 2						
1		80	Botox	G/F	Normal	
2	334	80	Botox	G/F	PSTF	
3	212	80	Botox	G/F	CSTF	
4	123	80	NeuroBloc/ Myobloc	G/F	Normal	
5	120	136	Botox	G/F/E	CSTF	
6	92	40	Botox	A	CSTF	2.7
7	223	2,500	NeuroBloc/ Myobloc	ulA/G	Normal	
8	15	150	NeuroBloc/ Myobloc	G	Normal	
9	14	1,650	NeuroBloc/ Myobloc	ulA/G	Normal	
Case 3						
1		30	Dysport	G/E		
2	150	30	Dysport	G/E	Normal	
3	150	30	Dysport	G/E		
4	150	30	Dysport	G/E	Normal	
5	150	30	Dysport	G/E	Normal	
6	150	30	Dysport	G/E	Normal	
7	150	30	Dysport	G/E	Normal	
8	150	30	Dysport	G/E	Normal	
9	150	30	Dysport	G/E	Normal	
10	150	30	Botox	G/E	Normal	
11	150	30	Botox	G/E	Normal	
12	150	30	Botox	G/E	PSTF	1.0
13	150	30	Botox	G/E	CSTF	>10
Case 4						
1		75	Dysport	G	Normal	
2	15	30	Dysport	F	Normal	
3	193	105	Dysport	G/F	PSTF	
4	80	60	Dysport	F	PSTF	
5	186	75	Dysport	G	CSTF	
6		25	Dysport	G	CSTF	
7	264	33	Xeomin	G/N	CSTF	>10

G, glabella; E, periocular region; F, forehead; A; axilla; N; nose; ulA; unilateral axilla; PSTF, partial secondary therapy failure; CSTF, complete secondary therapy failure.

TABLE 2. Details of Botulinum Toxin Therapy

Parameter	*Case 1 (Dysport)*	*Case 2 (Botox)*	*Case 3*	*Case 4 (Dysport)*
Injection series until PSTF, *n**	6	2	12	3
Treatment time until PSTF, months*	16	11	60	7
Cumulative botulinum toxin dose until PSTF, MU*	860	160	90 (Botox) 270 (Dysport)	210
Injection series until CSTF, *n**	10	3	13	5
Treatment time until CSTF, months*	25	18	65	16
Cumulative botulinum toxin dose until CSTF, MU*	1, 180	240	120 (Botox) 270 (Dysport)	245
Interinjection interval, days, mean ± SD (range)	87 ± 64 (14–172)	273 ± 86 (212–334)	150 (150–150)	119 ± 86 (15–193)
Single dose, MU, mean ± SD (range)	82 ± 46 (19–128)	80 (80–80)	30 (30–30) (Dysport) 30 (30–30) (Botox)	68 ± 31 (30–105)

*Inclusive of time of injection series with partial secondary therapy failure (PSTF) or complete secondary therapy failure (CSTF).SD, standard deviation.

at each injection series (large single doses), short intervals between injection series (short interinjection intervals), and injection series with intervals of less than 3 weeks (booster injections).[6] Recently, the immunological quality of the BT drugs used was also recognized as a risk factor.[7] Additionally, it has been suggested that the reagibility of the individual patient's immune system (the ability of an antigen to stimulate an immune response) influences BT antibody formation.[6] Below we explore these risk factors.

BT Drugs

Out of the four patients with BT antibody formation identified, two received Dysport (case 1, case 2), one Botox-CF (case 2), and one Dysport and Botox-CF (case 3). So far, only two patients with CSTF after cosmetic use of BT have been reported.[3,4] We are reporting the second patient who received exclusively Botox-CF, in which CSTF was thought to be highly unlikely.[8] The occurrence of CSTF after Botox-CF confirms previous suspicions that Botox-CF may not be free of CSTF risks.[9,10] For the first time, we are reporting two patients who developed CSTF after cosmetic use of Dysport. The use of the BT-B drug NeuroBloc/Myobloc in patients with CSTF due to BT-A antibody formation (case 2) is a valid option to overcome resistance and was previously described.[11] Using Xeomin in this situation was not successful (case 4) because of the well-known structural and immunological similarities between the different BT-A drugs. Lack of reports on CSTF after cosmetic use of NeuroBloc/Myobloc despite its well-known high antigenicity[12] may well be related to its low market share. With this low number of cases, immunological differences between different BT drugs cannot be detected.

Reagibility of the Individual Immune System

CSTF occurred after three injection series and a treatment time of 18 months (case 2), 5 injection series and a treatment time of 16 months (case 4), 10 injection series and a treatment time of 25 months (case 1), and 13 injection series and a treatment time of 65 months (case 3). Whereas CSTF after two injection series seems rare and might indicate a special predisposition of the receiving patient,[13] CSTF after 5, 10, and 13 injection series falls within the usual time window.[14] CSTF occurrence after 5 years of treatment is unusual, but possible.[14] Variable numbers of PSTF ranging from one (cases 2, case 3) to two (case 4) to four (case 1) preceded all CSTF.[14]

Single BT Dose

Single BT doses applied in our patients were all low compared with BT doses previously reported in CSTF.[6]

Interinjection Intervals

Average interinjection intervals applied in our patients were 87 days (case 1), 119 days (case 4), 150 days (case 3), and 273 days (case 2). None of the regular interinjection intervals applied in our patients was shorter than the 12-week interinjection intervals generally recommended to avoid CSTF. Minimal interinjection intervals were 14 days (case 1) and 15 days (case 4), thus constituting "booster injections" currently not recommended.

Analysis of the Individual Cases

Analyzing all risk factors in the different patients reported, case 2 is remarkable with respect to CSTF occurrence after two BT applications only. This case, therefore, may present a patient with a special predisposition for CSTF. Cases 1 and 4 are remarkable for the application of booster injections, supporting the current recommendation not to apply booster injections in BT therapy. Case 3 is unremarkable.

Additional Observations

In CSTF, the mouse diaphragm assay revealed BT antibody titers of 2.7 mU/mL (case 2) and more than 10 mU/mL (cases 1, 3, and 4). In PSTF, the BT antibody titer was 1 mU/mL, confirming previous relationships between BT response and BT antibody titers.[5] The therapeutic efficiency of BT-B confirmed the therapeutic relevance of the intermediate BT antibody titer in case 2.[11] Whereas BT antibody titers usually decrease within a few years, long-term persistence can be seen, as in case 3.[15]

CSTF can occur after cosmetic injections. Its incidence is unknown. Irregular follow-ups, change of injectors, fluctuating motivations, and difficulties in quantification of the therapeutic effect may complicate detection of CSTF in cosmetic applications. The incidence of CSTF in cosmetic applications may, therefore, be higher than currently thought. Although CSTF is more likely to occur in patients with a predisposition to CSTF, in patients receiving booster injections, and in patients receiving large BT doses at short interinjection intervals. It may also occur in unremarkable patients with unremarkable treatment details. CSTF can occur after application of Botox-CF, which was originally thought to make CSTF highly unlikely.

Although adherence to recommended treatment parameters is advisable to reduce the risk of CSTF, the risk will not be entirely eliminated. Development of new BT drugs with less antigenicity may also help to prevent CSTF.

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