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Botulinum toxin type B: A double-blind, placebo-controlled, safety and efficacy study in cervical dystonia

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Article abstract—We enrolled and treated 122 patients with idiopathic cervical dystonia in a double-blind, placebo-controlled safety and efficacy study of botulinum toxin type B (BotB). Both A-responsive and A-resistant patients were enrolled. Patients received intramuscular injections of either BotB (2,500 U, 5,000 U, or 10,000 U) or placebo. The primary outcome measure of efficacy was the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)-Total score at 4 weeks following study drug administration. Secondary measures of efficacy were TWSTRS-Severity, -Disability, and -Pain subscale scores, and Analog Pain Assessment, Investigator Global Assessment, Patient Global Assessment, and Sickness Impact Profile scores. Duration of effect was estimated with an intent-to-treat analysis of responders. Safety measures included clinical parameters, laboratory tests, and adverse events. The primary and most of the secondary analyses indicated a statistically significant treatment effect and a dose response. BotB is safe, well tolerated, and efficacious in the treatment of cervical dystonia at the doses tested.

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Cervical dystonia (CD) is a focal dystonia characterized by involuntary, patterned contractions of cervical and/or shoulder muscles, resulting in abnormal head postures that are sometimes associated with repetitive, rhythmic, jerky movements. Tremor and musculoskeletal pain frequently accompany the abnormal movements and postures.[1,2] While seldom a life-threatening disease, CD can dramatically affect the ability of the patient to lead a normal life,[3] causing considerable suffering and disability.[4] Oral pharmacologic treatments including anticholinergics, muscle relaxants, and anticonvulsants are generally inadequate, and the efficacy of surgical treatment remains uncertain.[5]

The intramuscular injection of botulinum toxin into affected muscles is an accepted therapy for the symptoms of CD.[1] The results of controlled and open-label clinical trials using botulinum toxin type A for the treatment of CD substantiate its use in clinical practice.[6-11] The injection of type A toxin into muscle results in a temporary chemical denervation. After repeated use, however, some patients develop resistance to the drug, possibly related to the development of blocking antibodies.[12-15] Theoretically the development of immunoresistance to type A toxin might be delayed or reduced by modifying the treatment sequence or dosing regime,[12] or by using other serotypes of botulinum toxin.

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Botulinum toxin type B (BotB) is an antigenically distinct botulinum serotype[16] synthesized by *Clostridium botulinum*.[17] This toxin blocks the release of acetylcholine at the neuromuscular junction by a different mechanism than type A toxin.[18] Antibodies to type A and B toxin do not cross-react.[19,20] This multicenter, placebo-controlled trial provides dose-finding information and an assessment of primary (Toronto Western Spasmodic Torticollis Rating Scale [TWSTRS]-Total) and secondary (e.g., TWSTRS subscale scores, Patient Analog Pain Assessment, Patient and Investigator Global Assessments, Sickness Impact Profile (SIP), and intent-to-treat analysis of responders) outcome measures.

Methods. *Patients.* Patients were at least 18 years of age and had idiopathic CD of 1 to 10 years duration. All had at least two of the following muscles involved: levator scapulae, scalenus medius and anterior, semispinalis capitis, splenius capitis, sternocleidomastoid, and trapezius. Patients had to have a baseline TWSTRS-Total score ≥20, a baseline-Severity subscale score ≥10, a baseline-Disability subscale score ≥3, and a baseline-Pain subscale score ≥1. Patients had to weigh at least 46 kg and have clinically acceptable baseline neurologic and laboratoryevaluations. Patients were excluded if they were a primary nonresponder to type A toxin injection, received any botulinum toxin within the previous 4 months, had not returned to their intertreatment baseline clinical dystonia status, used drugs sporadically that could interfere with the evaluation of the safety and efficacy outcome measures (e.g., narcotics, muscle relaxants, or benzodiazepines), or used aminoglycosides or any investigational drug or device within 30 days of entry into the study or while participating in the study. Patients were also excluded if they were pregnant or nursing; had pure retrocollis or antercollis; cervical contractures that limited passive range of motion; current acute or chronic medical conditions or known drug hypersensitivities that would preclude the administration of botulinum toxin; a myotomy or denervation surgery involving the neck or shoulder region; a history of a clinically significant, persistent neurologic or neuromuscular disorder; or had cardiovascular, renal, hepatic, gastrointestinal, dermatologic, major psychiatric, or hematologic illnesses.

For the purpose of this study, CD patients were defined as being "A-resistant" if they met the following clinical criteria: The patient (1) responded in a clinically meaningful way to a previous type A treatment session; (2) failed to respond to the last two successive, adequate treatment sessions with type A toxin (adequate was defined as adequate dose, muscle selection, and toxin administration as judged by the investigator); and (3) received a higher dose of type A toxin during the last dosing session (higher dose relative to the dose at which a clinically meaningful response had previously occurred). Neutralizing type A antibody testing was not performed for this protocol.

Study design and treatments. This was a randomized, multicenter, double-blind, placebo-controlled, four-arm, parallel-group outpatient study examining the effects of a single dosing session with either placebo or BotB (2,500, 5,000 or 10,000 U). The study drug was injected into two to four muscles either with or without EMG guidance at the investigator's discretion. At a screening visit, conducted within 2 weeks of study randomization and enrollment, an Institutional Review Board approved informed consent was obtained and the following were completed: medical history, physical and neurologic examinations, ECG, laboratory tests, pregnancy test (females only), and serum sample for BotB antibody determination and baseline outcome measures. At the initial treatment visit (day 1) patients were evaluated for inclusion, and baseline outcome measures were obtained. Following randomization, the study drug was administered. Patients were contacted by phone at week 1 and then returned to the clinic for evaluation at weeks 2, 4, 8, 12, and 16. At week 4 those patients who had ≥20% improvement in their TWSTRS-Total score as compared with baseline were considered "responders" and continued in the study. After week 4 the percent improvement retained (PIR; the ratio of the improvement from baseline at weeks 8 or 12 to the improvement from baseline to week 4) was computed. To continue patients had to have a PIR ≥50%. Patients were terminated at any other scheduled visit (week 8 or 12) if the PIR was <50% or at week 16 (end of study).

Outcome measures. The TWSTRS-Total score (range, 0 to 87) was the primary outcome measure. It is composed of three subscales: -Severity (range, 0 to 35), -Disability (range, 0 to 32), and -Pain (range, 0 to 20).[21,22] The TWSTRS-Total score was collected at each visit and was used to assess the duration of clinical benefit. Patient Analog Pain Assessments were made by asking patients to evaluate their pain by using a 100-mm analog scale of "worst ever pain" (0 mm) at one end and "no pain" (100 mm) on the other. Patient Analog Pain Assessments were collected at each visit during the study. Patients and investigators were asked to independently make a global assessment of how satisfied they were with the effects of treatment by using a 100-mm analog scale with "much worse" (0 mm) at one end and "much better" (100 mm) on the other. Vertical marks were measured at their intercept with the scale to the nearest millimeter, and values from 0 to 100 were recorded. Patient and Investigator Global Assessments were completed independently and collected at each visit (except baseline) during the study. Patients were also asked to complete a SIP[23] at baseline and week 4. TWSTRS-Videotape documentation was obtained at baseline and week 4.

Statistical analysis. The primary analysis included all patients who entered the study, received the study drug, and had at least one visit during which efficacy data were obtained. The level of significance for main effects was set at alpha = 0.05, and the level of significance for interaction effects was set at alpha = 0.10. The analysis consisted of a single, primary efficacy analysis and multiple supporting analyses. In addition to the overall test, a dose-response analysis and pairwise comparisons of placebo with each of the active treatment groups were performed in SAS by using PROC GLM (version 6, SAS Institute Inc., Cary, NC).[24] TWSTRS scores, Analog Pain Assessments, and SIP scores were all tested by using ANCOVA with the baseline score included as the covariate. Patient and Investigator Global Assessments were tested by using ANOVA.

The primary efficacy analysis compared the TWSTRS-Total scores at week 4 among the treatment groups using ANCOVA with the week 4 score as the dependent variable

and the independent variables being center, treatment group, and baseline TWSTRS score. Secondary efficacy analyses included ANCOVA of the TWSTRS-Severity, -Disability, and -Pain subscale scores; analyses of the proportion of patients in each treatment group who achieved clinical benefit (≥20% improvement in TWSTRS-Total score from baseline to week 4);[25] analyses of the analog assessments (Patient Analog Pain, and Patient and Investigator Global Assessments) and SIP scores. For the assessment of duration of effect, a post hoc intent-to-treat analysis was performed on the proportion of responders in each dose group at each visit by using Fisher's exact test. This intent-to-treat analysis assigned a "nonresponder" status to all patients for whom data were not present (i.e., a patient who terminated at week 4 was considered a nonresponder at all subsequent visits, a patient who missed a week 8 visit but was a responder at weeks 4, 12, and 16 was considered a nonresponder at week 8).

Evaluation of safety and tolerability. Spontaneously reported and investigator-elicited (e.g., open-ended question) adverse events were collected at each visit during the study. Hematology, blood chemistry, and urinalysis data were collected at screening, week 4, and the termination visit. Electrocardiographic data were collected at screening and week 4. BP, pulse, temperature, and respiratory rate were collected at each study visit. To identify BotB antibody-related immunoreactivity in treated patients, an ELISA was performed on blood samples taken before treatment and at week 4 (proprietary assay, Athena Neurosciences, Inc., South San Francisco, CA).

Test material formulation and dose selection. The study drug was provided by Athena Neurosciences, Inc. in 5-mL vials containing either 2,500 or 5,000 U of BotB in 1-mL sterile solution. The same sterile solution (without toxin) was used as the placebo. Each patient was randomized and then received the combined contents of two vials of the study drug during a single dosing session. At the discretion of the investigator, the 2 mL of the combined study drug could be further diluted by adding 0.9% sterile normal saline without preservative up to a maximal final volume of 5 mL. Doses selected for this study were based on previous BotB studies that demonstrated safety and tolerability up to 12,000 U per dosing session and potential clinical effect at ≥2,400 U per session.[26-29]

Results. *Patient population and disposition.* One hundred twenty-two patients age 19 to 81 years entered the study. Eighty-two patients (67%) were female and 40 patients (33%) were male. Age, gender, and duration of disease (years of disease) were distributed similarly across the groups. All patients in the placebo and 2,500-U groups were Caucasian. In the 5,000-U group, 30 patients (97%) were Caucasian and one patient (3%) was Hispanic. In the 10,000-U group, 27 patients (90%) were Caucasian, one patient (3%) was Hispanic, and two patients (7%) were African-American. All patients completed the study per the protocol.

Efficacy results. TWSTRS-Total scale. TWSTRS-Total scores improved from baseline to week 4 for all treatment groups, and improvement increased as dose increased. At week 4, improvement was 3.3 points for the placebo group, 11.6 points for the 2,500-U group, 12.5 points for the 5,000-U group, and 16.4 points for the 10,000-U group. Table 1 presents the p-values for the analyses of the improvement in TWSTRS-Total, -Severity, -Disability, and -Pain scores from baseline to week 4. The overall difference among treatment groups ($p = 0.0001$) and the analysis of dose response ($p = 0.0001$) were highly statistically significant. All three comparisons of placebo versus each active group were highly significant as well (see table 1).

Table 1 *Summary of* p *values for the analyses of improvement in TWSTRS-total and TWSTRS subscale scores at week 4*

	TWSTRS*			
Analysis	Total	Severity	Disability	Pain
Placebo vs. 2,500 U	**0.0016**	0.0511	**0.0165**	**0.0019**
Placebo vs. 5,000 U	**0.0005**	**0.0021**	**0.0122**	**0.0013**
Placebo vs. 10,000 U	**0.0001**	**0.0007**	**0.0001**	**0.0001**
Dose response	**0.0001**	**0.0009**	**0.0004**	**0.0004**

* Boldface p values indicate $p < 0.05$.

TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale.

TWSTRS-Severity subscale scores. TWSTRS-Severity subscale scores improved from baseline to week 4 for all treatment groups, and improvement increased as dose increased. At week 4, mean improvement was 1.6 points for the placebo group, 3.5 points for the 2,500-U group, 4.5 points for the 5,000-U group, and 4.7 points for the 10,000-U group. In the ANCOVA on the week 4 data the overall difference among treatment groups ($p = 0.0030$) and the dose response ($p = 0.0009$) were highly significant. The comparisons of placebo with the two highest active groups were also highly significant (see table 1), but the placebo versus 2,500-U comparison did not reach significance ($p = 0.0511$).

TWSTRS-Disability subscale scores. TWSTRS-Disability subscale scores improved from baseline to week 4 for all treatment groups, and improvement tended to increase as dose increased. At week 4 mean improvement was 0.7 points for the placebo group, 3.8 points for the 2,500-U group, 3.6 points for the 5,000-U group, and 5.4 points for the 10,000-U group. In the ANCOVA on the week 4 data the overall difference among treatment groups ($p = 0.0018$) and the dose response ($p = 0.0004$) were highly significant. All three comparisons of placebo with each active group were also significant (see table 1).

TWSTRS-Pain subscale scores. TWSTRS-Pain subscale scores improved from baseline to week 4 for all treatment groups, and improvement tended to increase as dose increased. At week 4 mean improvement was 1.0 points for the placebo group, 4.4 points for the 2,500-U group, 4.3 points for the 5,000-U group, and 6.4 points for the 10,000-U group. In the ANCOVA on the week 4 data the overall difference among treatment groups ($p = 0.0004$) and the dose response ($p = 0.0004$) were significant. All three comparisons of placebo with each active group were also significant (see table 1).

Responders analyses. The percentage of patients in each treatment group who responded at week 4 increased as the dose increased (table 2; 27%, 58%, 61%, and 77% for placebo, 2,500, 5,000, and 10,000 U respectively). The percentage of patients who responded to treatment at week 4 was greater in the 10,000-U group than in any other group

Table 2 *Number and percent of responders* by dose group by week using TWSTRS-Total scores*

Variable	Placebo (N = 30)		BotB 2,500 U (N = 31)		BotB 5,000 U (N = 31)		BotB 10,000 U (N = 30)	
Responders 4 weeks after injection	8	27%	18	58%	19	61%	23	77%
Responders 8 weeks after injection	5	17%	11	35%	13	42%	16	53%
Responders 12 weeks after injection	3	10%	5	16%	9	29%	9	30%
Responders 16 weeks after injection	2	7%	1	3%	6	19%	5	17%

* A patient is considered a responder if he or she experienced improvement from baseline to week 4 of at least 20% on the TWSTRS-Total score. Patients were considered responders at visits after week 4 if Percent Improvement Retained was ≥50%.

TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale; BotB = botulinum toxin type B.

for the TWSTRS-Total, -Disability, and -Pain scores (table 3). There was a significant dose response for each of the four TWSTRS scores (see table 3, $p < 0.001$, $p = 0.035$; $p = 0.002$, and $p = 0.001$ for TWSTRS-Total, -Severity, -Disability, and -Pain respectively). Significant differences also occurred between placebo and at least one of the active treatment groups for each of the four TWSTRS scores (see table 3). Table 4 presents the distribution of responses among clinically defined A-resistant patients and among those patients who only failed to respond to their last type A dosing session. The percentages of responders demonstrate a similar response for this subset of CD patients as shown in the responders analysis for all enrolled patients.

Analog assessments. At week 4 the mean pain ratings increased (improved) substantially for all three active treatment groups (baseline to week 4 as follows: 45.8 to 67.5 in the 2,500-U group, 49.7 to 70.2 in the 5,000-U group, and 46.2 to 75.1 in the 10,000-U group). For the placebo group the change was much less (baseline to week 4 was 52.0 to 52.5). In the ANCOVA on the week 4 data for the pain rating, the overall difference among treatment groups ($p = 0.0049$) and the dose response ($p = 0.0017$) were significant. For the comparisons of placebo versus all three active groups, significant differences were also noted ($p = 0.0149$ for placebo versus 2,500 U, $p = 0.0084$ for placebo versus 5,000 U, and $p = 0.0007$ for placebo versus 10,000 U). Patient and Investigator Global Assessment ratings of treatment effects generally increased as dose increased. The overall difference among treatment groups for both global assessment measures was statistically significant ($p = 0.0001$).

Assessing duration of effect. The length of time that patients continued in the study reflected the time that they responded to the study drug. The mean time in the study increased as the dose increased, from 45.1 days for the placebo group to 61.1 days for the 2,500-U group, 66.9 days for the 5,000-U group, and 75.1 days for the 10,000-U group. The range (minimal and maximal number of days that patients remained in the study) was similar for each of the treatment groups: 27 to 120 days for the placebo group, 27 to 117 days for the 2,500-U group, 26 to 120 days for the 5,000-U group, and 27 to 120 days for the 10,000-U group. Table 5 presents a summary of the analyses of the proportion of responders in each dose group by each visit using the TWSTRS-Total score. A significant dose response and a significant difference between placebo versus 10,000 U through week 12 were noted. This analysis is consistent with the mean time in the study described earlier in this paragraph.

Table 3 *Number and percentage of responders by dose group by TWSTRS-Total and subscale scores at week 4*

Variable	Dose response	Placebo (N = 30) N (%)	BotB 2,500 U (N = 31) N (%)	BotB 5,000 U (N = 31) N (%)	BotB 10,000 U (N = 30) N (%)
TWSTRS-Total		8 (27%)	18 (58%)	19 (61%)	23 (77%)
p value*	**<0.001**		**0.021**	**0.010**	**<0.001**
TWSTRS-Severity		7 (23%)	14 (45%)	19 (61%)	15 (50%)
p value*	**0.035**		0.085	**0.004**	**0.022**
TWSTRS-Disability		6 (20%)	17 (55%)	14 (45%)	20 (67%)
p value*	**0.002**		**0.009**	**0.040**	**<0.001**
TWSTRS-Pain		12 (40%)	19 (61%)	20 (65%)	25 (83%)
p value*	**0.001**		0.118	0.071	**0.001**

* *p* Values for dose response are determined across all treatment groups, while *p* values for within-group determinations are a pairwise comparison of active versus placebo. Boldface *p* values indicate $p < 0.05$.

TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale; BotB = botulinum toxin type B.

Table 4 *A-resistant patient responses by dose group at week 4*

Dose level (U)	Clinical A-resistant criteria met*			No response for last treatment session only†			Totals		
	Responder‡	Nonresponder§	Subtotal	Responder‡	Nonresponder§	Subtotal	Responder‡	Nonresponder§	Overall % responders
Placebo	2	6	8	0	1	1	2	7	22
2,500	3	3	6	1	1	2	4	4	50
5,000	3	1	4	2	0	2	5	1	83
10,000	6	2	8	3	0	3	9	2	82
Total	14	12	26	6	2	8	20	14	—

* Patients who met clinical criteria of being A-resistant patients as outlined in the text.
† Patients who did not meet clinical criteria of being A-resistant but gave a history of no response to their last adequate dosing session with type A toxin.
‡ Responder to treatment as defined in text.
§ Nonresponder to treatment as defined in text.

SIP scores. Patients who received active treatment showed more improvement in SIP scores on average from baseline to week 4 than did patients who received placebo. These results were not statistically significant, however, and the meaning of these results was further obscured by differences among the treatment groups at baseline. The data for SIP did not show the dose-related improvement that was demonstrated for the TWSTRS scores and analog assessments.

Table 5 *Summary of* p *values for the intent-to-treat responders analysis**

Comparison analyzed	Week 4	Week 8	Week 12	Week 16
Placebo vs. 2,500 U	**0.021**	0.119	0.513	0.485
Placebo vs. 5,000 U	**0.010**	**0.033**	0.078	0.167
Placebo vs. 10,000 U	**<0.001**	**0.001**	**0.044**	0.243
Dose response	**<0.001**	**0.003**	**0.035**	0.092

* Boldface p values indicate $p < 0.05$.

Adverse events. Table 6 presents adverse events with an occurrence ≥5% by treatment group. Eighty percent of patients experienced at least one adverse event, most of which were mild or moderate in intensity. The frequency of adverse events tended to increase with increasing doses of BotB. The most frequent adverse events in the 10,000-U group were dry mouth and dysphagia. Dysphagia was reported as mild (duration ranged from 1 minute to the duration of study participation) in five (16%), three (10%), and eight patients (27%) in the 2,500-, 5,000- and 10,000-U dose groups respectively. Two patients experienced a serious adverse event (basal cell carcinoma and hospitalization for elective cardiac catheterization). The etiology of both serious events was preexistent to study entry and neither event was study drug related.

Other safety assessments. There were no clinically significant changes in clinical laboratory evaluations, ELISA assays, ECGs, or vital signs.

Discussion. We present the results of a controlled study of three doses of BotB versus placebo in pa-

Table 6 *Adverse events occurring in ≥5% of patients*

Adverse event	Placebo (N = 30)		2,500 U (N = 31)		5,000 U (N = 31)		10,000 U (N = 30)	
	N	%	N	%	N	%	N	%
Dry mouth	1	3	1	3	3	10	10	33
Dysphagia	0	0	5	16	3	10	8	27
Pain (2° to CD)	4	13	3	10	3	10	7	23
Infection*	0	0	4	13	4	13	5	17
Injection site pain	3	10	5	16	6	19	5	17
Headache	2	7	3	10	2	6	4	13
Flu syndrome*	0	0	2	6	3	10	3	10
Nausea	1	3	3	10	1	3	3	10
Pain (other)	2	7	2	6	3	10	3	10

* Nineteen of 21 adverse events listed as "infection" and "flu syndrome" were flus, influenza, upper respiratory infections, colds, and head colds. The other two "infections" were yeast and strept throat infections. One patient (5,000 U) reported two adverse events (cold and strept throat). None of the 21 reported adverse events were considered study drug related by the investigator.

CD = cervical dystonia.

tients with CD. This study provided BotB dose-finding information and an assessment of primary and secondary outcome measures. Our results indicate that BotB is safe, well tolerated, and efficacious as a single treatment session of 2,500 U, 5,000 U, or 10,000 U. All patients completed the study as outlined in the protocol. Antibodies to BotB were not detected in any of the patients, and no laboratory dose-response trends were evident.

The primary (TWSTRS-Total) and most of the secondary analyses (TWSTRS-Severity, TWSTRS-Pain, TWSTRS-Disability, Analog Pain Assessment, Patient Global Assessment and Investigator Global Assessment) demonstrated a significant treatment effect. The proportion of patients who responded increased with increasing doses. Both A-responsive and A-resistant patients responded similarly. In a post hoc, conservative, intent-to-treat analysis of responders to assess the duration of effect, the data demonstrated that BotB had a statistically significant effect versus placebo through week 12 in the highest dose group.

The TWSTRS-Total and TWSTRS subscale scores are useful outcome measures of efficacy in this and other studies.[28-32] Comparable results were observed with the Analog Pain Assessment, Patient Global Assessment and Physician Global Assessment. The SIP did not reflect the changes noted by the other primary and secondary outcome measures in this population.

Our study was powered to demonstrate the effect of treatment at week 4; thereafter, patients were terminated from the study who did not meet the TWSTRS-Total continuation criteria. Assessing the duration of effect was not part of the original design or analysis. The study was designed to enroll a majority of patients who were type A responsive and without type A treatment for at least 4 months prior to study drug administration. We could not realistically insist that type A-responsive patients continue in the study for more than 4 weeks if they did not respond. Even if this were required for study entry, the analysis of duration of effect would have been markedly modified by the loss of a substantial number of placebo patients who would have withdrawn from the study to obtain their type A treatment after failing to respond to placebo. Using the conservative intent-to-treat criteria for the proportion of responders at each visit, we have still demonstrated a significant response in both the dose-response analysis and the 10,000-U versus placebo analysis through week 12.

We observed a dose response for common adverse events (dry mouth and dysphagia). Even though dysphagia was only reported as mild in all patients in the high-dose group, future dose selection should balance the increasing efficacy of higher doses of BotB against the increasing frequency of related adverse events as appropriate.

In conclusion, this study has demonstrated that BotB is safe and efficacious in the treatment of CD in a dose-dependent manner and as a primary treatment in both type A-responsive and A-resistant patients. Given these results, consideration should be given to investigating alternate administration of type A and B toxins in the treatment of CD as a potential strategy to delay or minimize the risk of developing resistance to either serotype.

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Posteroventral pallidotomy in a patient with parkinsonism caused by hypoxic encephalopathy

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Article abstract—We report a patient with a hypokinetic-rigid form of parkinsonism caused by hypoxic encephalopathy, in whom parkinsonian symptoms were markedly alleviated by staged bilateral posteroventral pallidotomy.

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Parkinsonism can result from a variety of insults to the brain,[1] including vascular lesions involving the basal ganglia.[2-4] Subregional deafferentation of the basal ganglia output nuclei resulting from pathology of the striatum and its outflow pathways may cause *extranigral* forms of parkinsonism.[5,6] We report a patient with parkinsonism caused by bilateral putamino-pallidal lesions, which occurred as a consequence of hypoxic encephalopathy. The parkinsonian symptoms of the patient, which were poorly responsive to medication, were markedly alleviated by bilateral posteroventral pallidotomy (PVP), a procedure now widely used in the treatment of idiopathic Parkinson's disease (PD).[7-9]

Case report. A 45-year-old, right-handed woman with no history of PD or hypertension underwent surgery for cancer of the left breast under general anesthesia on April 17, 1995. The next day she was found unconscious and cyanotic and suffering from cardiopulmonary arrest in the rest room of the hospital. The exact duration of hypoxia/ischemia was unknown. She recovered after resuscitation and was diagnosed as having pulmonary embolism. After several weeks in the hospital, she began having difficulty opening her mouth and speaking, and developed clumsiness in movements of the extremities. She also noted a slowing of her gait and a loss of coordination in walking, sometimes stumbling and falling. Although she was discharged from the hospital in June 1995, these neurologic symptoms slowly and progressively worsened. Six months after discharge she was unable to speak at all and had difficulty caring for herself.

She was admitted to our hospital on April 10, 1996. She had diminished facial expression and could not speak; she communicated by means of writing or pointing to Japanese letters written on a board. A writing test showed typical features of micrographia. She could open her mouth only with great difficulty and could do so only slightly, but she could chew and swallow food. After she had closed her eyes tightly, she could not open them again unaided. She was slow to respond. Mental status examination, however, demonstrated good memory, concentration, orientation,

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