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Botulinum toxin treatment in patients with focal dystonia and hemifacial spasm. A multicenter study of the Italian Movement Disorder Group

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In six Centers belonging to the Italian Movement Disorder Study Group, the efficacy of botulinum toxin treatment was evaluated in an open collaborative study in 251 patients with focal dystonia and hemifacial spasm. The percentage of functional improvement ranged from 66% to 81% in patients with blepharospasm, from 40% to 51% in patients with spasmodic torticollis and from 73% to 81% in those with hemifacial spasm. Good results were also obtained in patients with oromandibular dystonia, laryngeal dystonia and writer's cramp. Side effects were mild and transient. Local botulinum toxin injection is the first choice symptomatic treatment in focal dystonia and hemifacial spasm.

Key Words: Botulinum toxin — dystonia — hemifacial spasm.

Introduction

The term dystonia encompasses many disorders in which muscle contractions causing sustained or repetitive involuntary movements force the body into awkward postures. Although some dystonic patients have demonstrable basal ganglia damage, the majority have no apparent central nervous system lesions [9, 14]. According to the clinical distribution of the muscle affected, dystonias are classified as focal dystonia, segmental dystonia, generalized dystonia or hemidystonia [9]. The most frequent focal forms are blepharospasm and cervical dystonia [14].

Hemifacial spasm presents clinically with involuntary unilateral contractions of the facial muscles. The spasms may be a sequela of a facial palsy, but more often no facial nerve lesions can be demonstrated.

Various therapies, surgical [3, 17, 20] and pharmacological [1, 11, 12], have been used to relieve focal dystonia and hemifacial spasm. In pharmacotherapy anticholinergic drugs, benzodiazepines and baclofen have all been tried. Yet, few pa-

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TABLE I. *Number of patients treated with botulinum toxin in each center.*

	Blepharospasm	Torticollis	Other Dystonias	Hemifacial Spasm	Total
Center 1	41	20	13	57	131
Center 2	17	9	0	0	26
Center 3	13	0	0	6	19
Center 4	10	6	0	12	28
Center 5	11	0	0	8	19
Center 6	13	15	0	0	28
Total	105	50	13	83	251

tients obtain satisfactory relief and treatment is often complicated by severe systemic side effects. In 1973 Scott et al. [22] proposed botulinum toxin injections as a specific treatment for strabismus. Subsequently this procedure was used in patients with focal dystonia and hemifacial spasm [2, 4, 7, 10, 13, 15, 19, 23, 24]. Botulinum toxin is a polypeptide released by Clostridium botulinum. Of the eight recognized immunologically-distinct toxins elaborated by different strains of Clostridium botulinum, type A toxin is the most potent poison known to man. Its ingestion causes botulism. When injected, the toxin binds avidly to presynaptic neuromuscular terminals, where it blocks acetylcholine release and thus produces a functional denervation of the muscle, resulting in muscle paralysis [16].

For several years now, six centers belonging to the Movements Disorder Study Group of the Italian Society of Neurology (Roma, Bari, Ferrara, Genova, Messina and Milano) have been treating patients with focal dystonia and hemifacial spasm with local injection of botulinum toxin type A. This study was designed to evaluate the clinical efficacy of botulinum therapy in patients with these two disorders; to compare the therapeutic results obtained in the six centers; and to provide guidelines for botulinum toxin treatment. The study started in 1985 in Rome and the other centers joined the study later.

Patients and methods

251 patients (mean age 57.4 yrs; range 32 to 81) (105 with blepharospasm, 50 with spasmodic torticollis, 4 with oromandibular dystonia, 4 with laryngeal dystonia, 5 with writer's cramp and 63 with hemifacial spasm) were studied in 6 Italian centers (Center 1: Roma; Center 2: Bari; Center 3: Ferrara; Center 4: Genova; Center 5: Messina; and Center 6: Milano) (Table I). The majority of patients had been treated before with various drugs (including anticholinergics, benzodiazepines, and baclofen) without significant benefit. All patients gave their informed consent to the study.

Patients with blepharospasm and hemifacial spasm were clinically evaluated on the rating scale of Marsden and Schachter [18], a clinical grading scale that assigns patients a score ranging from 0 to 8 according to their disability. Patients with torticollis were evaluated with the Tsui scale [24] (scores ranging from 0 to 23). Patients with oromandibular dystonia, laryngeal dystonia or hand dystonia were evaluated by the Global Rating Scale proposed by Fahn and Marsden [18].

Patients were evaluated three times: before treatment, 3 to 4 weeks after treatment and again 3 to 5 months later, always by the same physician, a neurologist experienced in movement disorders. Physicians in all the centers assessed the following parameters for each patient: 1) the mean disability score; 2) mean post-treatment score (i.e. the mean of the scores after each injection); 3) best post-treatment score (this value was obtained taking into account the best responses among the different injections performed); 4) onset latency of benefit as reported by the patients (in days); and 5) mean duration of benefit (in weeks). The effect of repeated treatment sessions (every four to six months) on the duration of benefit was studied in 99 patients. These patients received four or more botulinum toxin injections during the study period.

In the six centers, doses, injection techniques and sites of botulinum toxin administration were individualized for each patient. Two commercially available preparations of botulinum toxin type A were used: Oculinum (Allergan, US) and Dysport (Porton Down, UK). The two products differ in potency: one nanogram of Dysport contains 40 mouse units, whereas one nanogram of Oculinum contains 2.5 mouse units [15]. The contents of a vial of Oculinum (100 IU) were diluted in 2 or 4 ml of sterile saline; the contents of a vial of Dysport (2000 IU) were diluted in 10 ml of saline solution. According to the type of dystonia being treated, botulinum was injected into the following muscles: orbicularis oculi muscles (blepharospasm and hemifacial spasm); masseter muscles (oromandibular dystonia); sternocleidomastoid, trapezius or splenius capitis muscles (torticollis);

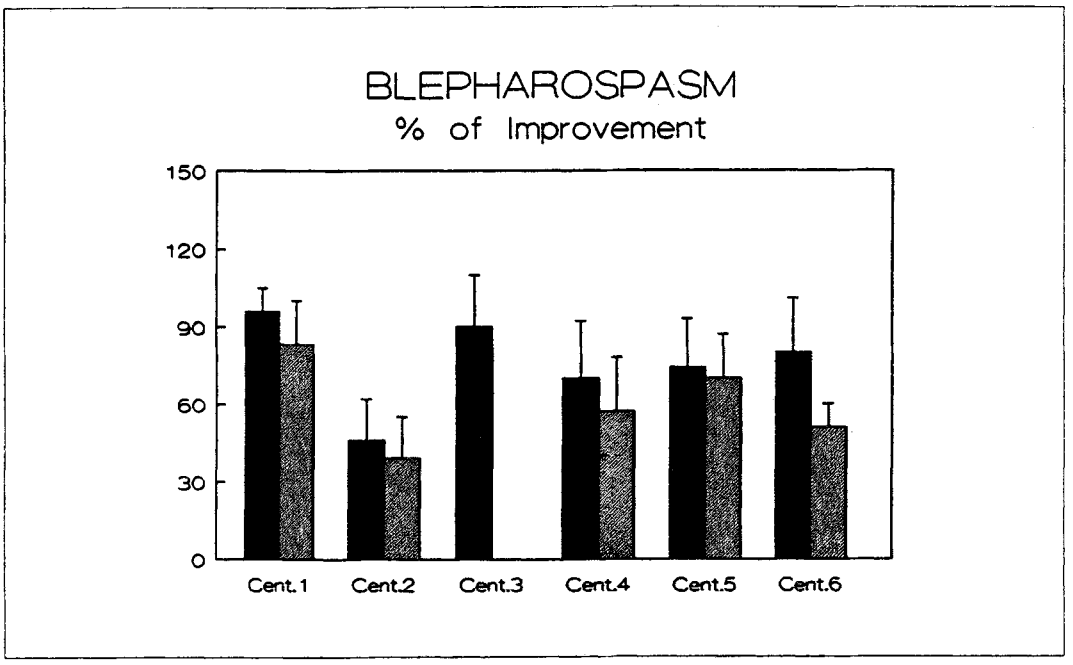

Fig. 1. *Percentages of improvement after botulinum toxin injections in patients with blepharospasm treated in the six centers. Black bars represent the maximum percentages of improvement, and hatched bars the mean percentages of improvement. For patients studied in center 3 the maximum percentage only is reported.*

vocalis cordae muscles (laryngeal dystonia); and forearm flexor or extensor muscles, or both (hand cramp).

The statistical significance of the data was evaluated by paired t-test and analysis of variance (ANOVA). A P value of less than 0.005 was considered to indicate significance. All results are reported as means ± SD.

Results

Analysis of variance showed a difference between the clinical scores obtained before and after botulinum toxin treatment in the patients from the six centers. For this reason, data from each center are presented separately. Because the largest number of patients was studied in Center 1, the results concerning pre- and post-treatment clinical scores, degree and duration of clinical improvement are given in detail for this center and then compared with results sets from the other five centers.

1) Blepharospasm

Before treatment, the 41 patients studied in Center 1 had a mean baseline disability score of 7.0±1.1.

After botulinum toxin the mean score was 1.2±1.3 (83% of improvement) and the best score obtained was 0.3±0.6 (96% of improvement). The mean onset of benefit was 4±2 days and the mean duration of clinical benefit was 10.7±4.3 weeks. The 64 patients treated in the other centers also obtained relief of the spasms; the percentages of "mean" and "maximum" improvement were respectively 39% and 46% (Center 2), 90% (Center 3; "maximum" value only reported), 57% and 70% (Center 4), 70% and 74% (Center 5), 51% and 80% (Center 6). Figure 1 shows the percentages of improvement and Table II shows the mean duration of clinical improvement.

The difference between scores obtained before and after botulinum toxin injection was significant ($p<0.001$).

The effect of repeated treatment sessions on the duration of the clinical benefit was studied in 62 out of 105 patients. Only in 15 (24%) did repeated injections lead to a longer duration of clinical improvement.

Side effects, never lasting longer than 2 to 3 weeks, occurred in 48 patients (45%) (Table III). 40 patients had ptosis (not functionally disabling), 6 had diplopia, 4 had weakness of lower facial muscles, 3 had local complications (hematomas, erythema) and one patient complained of generalized asthenia. Some patients presented more than one complication.

TABLE II. *Mean (±SD) duration (in weeks) of clinical improvement after treatment with botulinum toxin in patients with focal dystonia and hemifacial spasm.*

	Blepharospasm	Torticollis	Hemifacial Spasm
Center 1	10.7±4.3	7.0±2.0	11.0±5.2
Center 2	10.5±4.7	—	—
Center 3	9.3±1.3	—	9.1±1.3
Center 4	9.8±3.0	5.7±3.8	9.6±1.7
Center 5	13.3±4.4	—	10.5±1.3

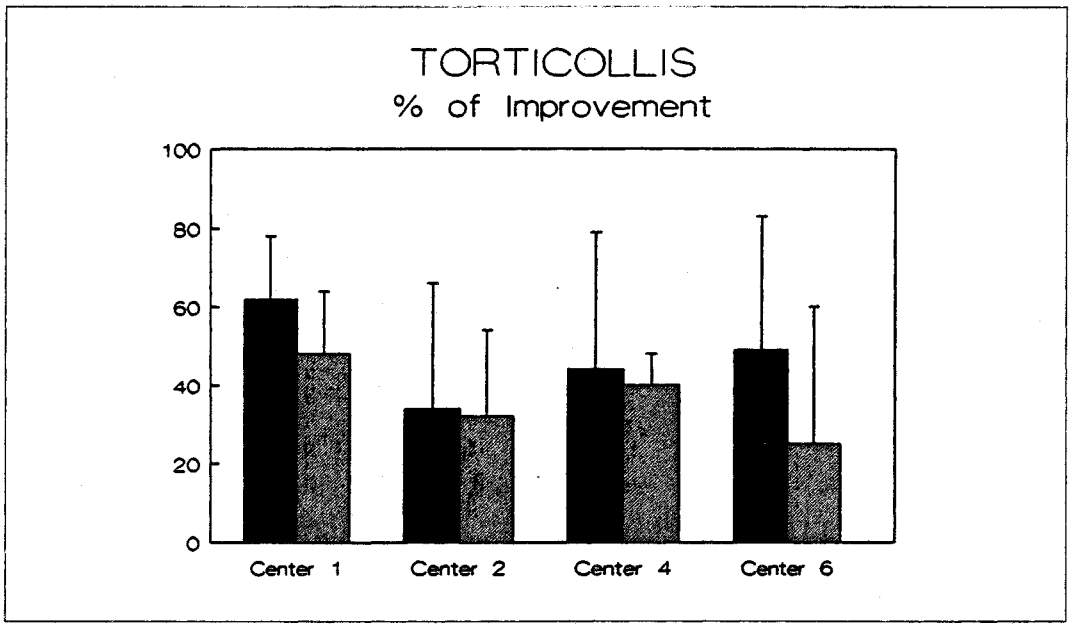

Fig. 2. *Percentage of improvement after botulinum toxin injections in patients with spasmodic torticollis. Black bars represent the maximum percentages of improvement and hatched bars the mean percentages of improvement.*

2) Spasmodic torticollis

In the 20 patients studied in center 1 the mean baseline disability score before treatment was 11.4±3.2. After botulinum toxin treatment, the mean score was 5.7±2.1 (50% of improvement) and the best score obtained was 4.2±1.8 (63% of improvement). The mean onset of benefit was 7.1±2.7 days and the mean duration of benefit was 7±2 weeks (see Table II). The difference between pre- and post-treatment scores was significant ($p<0.001$). Torticollis also improved in patients studied in the other centers; the "mean" and the "maximum" percentages of improvement were respectively 32% and 34% (Center 2), 40% and 44% (Center 4), 25% and 49% (Center 6) (Fig. 2). Table II presents the mean duration of clinical improvement. In all the centers, most patients reported a reduction in the intensity and severity of pain after treatment.

12 patients had transient side effects: 9 had dysphagia, 1 had dysphonia, 1 generalized weakness and 1 presented a mild brachial plexopathy (Table III). All these complications resolved spontaneously within a month.

3) Other focal dystonias

Center 1 also treated patients with other less common focal dystonias. In the 4 patients with *oromandibular dystonia* botulinum toxin injection led to an improvement of 65±21%, with a mean duration of 6±1.7 weeks, without side effects. The 4 patients with *laryngeal dystonia* who were treated, all showed an improvement (70 to 90%) in their voice. No complications were reported. All 5 patients with *writer's cramp* had a moderate improvement of their writing (Fig. 3). Two of them exhibited a mild, transient weakness in the injected muscles, which regained normal strength within three weeks.

TABLE III. *Side effects after botulinum toxin injection in patients with blepharospasm, spasmodic torticollis and hemifacial spasm. Some patients had more than one side effect.*

Side effects	Blepharospasm	Torticollis	Hemifacial spasm
None	57	38	53
Ptosis	40	0	19
Diplopia	6	0	3
Weakness of lower facial muscles	4	0	16
Local complications	3	0	2
generalized asthenia	1	1	0
Dysphagia	0	9	0
Dysphonia	0	1	0
Brachial plexopathy	0	1	0

4) Hemifacial spams

In the 57 patients studied in center 1 the mean disability score before treatment was 6±1.2. After treatment the mean score was 1±1.6 (82% benefit), and the best score obtained was 0.6±1.3 (90% improvement). The mean onset of benefit was 4.8±4.7 days and the mean duration of clinical improvement was 11±5.2 weeks. An improvement in the hemifacial spasm was also seen in patients studied in the other centers (Table II); the "mean" and the "maximum" percentages of improvement were respectively 51% and 72% for Center 3,52% and 52% for Center 6. In Center 4, only the mean "maximum" improvement was calculated (91%). The difference between scores obtained before and after botulinum toxin injection was significant ($p<0.005$).

The effect of repeated treatment on the duration of the benefit was studied in 37 patients. Only 5 of these appeared to derive longer-lasting benefit. Side effects, never persisting for longer than 2 or 3 weeks, occurred in 30 patients (36.1%) (see Table III). 19 had mild ptosis, 16 had weakness of the lower face muscles, three had diplopia and two had local complications (a small hematoma).

Discussion

The results of our study show that local injection of botulinum toxin provides satisfactory relief in patients with focal dystonia and hemifacial spasm. Considering all the patients from the six centers participating in the study, the "mean" and "maximum" improvement was respectively 66% and 81% for blepharospasm, 40% and 51% for torticollis and 73% and 81% for hemifacial spasm. Patients with oromandibular and laryngeal dystonia and with writer's cramp also obtained good improvement. Botulinum toxin thus appears to have been more effective in treating blepharospasm and hemifacial spasm than it was in treating spasmodic torticollis. Some authors suggest that botulinum provides less relief in torticollis be-

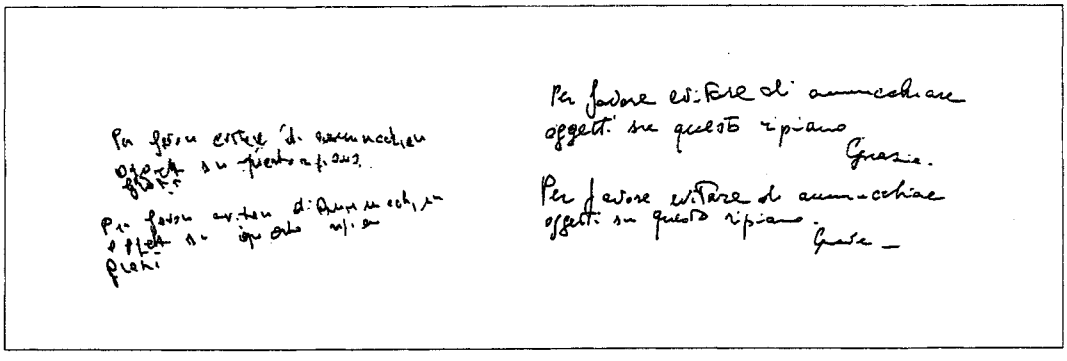

Fig. 3. *Writing in a patient with writer's cramp before (left) and after (right) treatment with botulinum toxin. Note how the writing improved after treatment.*

cause the spasms characteristically affect a larger number of muscles; some muscles contributing to the dystonia may therefore be deeper and more inaccessible. Although the benefit was less marked in patients with torticollis than it was in other forms of focal dystonia, an important finding was the relief of neck and shoulder pain reported by patients with torticollis. The improvement is due, at least in part, to the reduced muscles activity after toxin injections.

The effect of the repeated botulinum treatment on the duration of clinical benefit was studied in 99 patients (62 with blepharospasm and 37 with hemifacial spasm). Only 20% of these patients had longer-lasting improvement. Repeated treatment thus appears to have little effect on the duration of the clinical benefit.

In this collaborative study, all the centers reported some clinical improvement in the patients treated, although Centers 2, 4 and 5 reported less effective results. The divergence might possibly arise from differences in the severity of the clinical signs and symptoms of the patients treated. A more likely explanation is that the centers used different types and dosages of botulinum toxin. In Italy, two preparations of botulinum toxin type A are available: Oculinum (Allergan) and Dysport (Porton - Down). Oculinum can be used at several dilutions (2, 4 or 8 ml of saline solution for each vial of 100 units), whereas for the Dysport only one dilution is proposed (10 ml of saline solution for each vial of 2000 units). This study documents that good relief of disability is obtained with the following doses: 0.1 to 0.2 ml of diluted Oculinum for each local intramuscular injection in three or four points per eye for blepharospasm and hemifacial spasm (total 15 to 40 units of Oculinum per eye); 2 ml (100 units of Oculinum) per muscle in spasmodic torticollis if two muscles are involved; if more muscles are involved, doses can be increased up to a total of 5 ml for all the muscles (250 units). The masseter muscle needs 0.7 to 1 ml (35 to 50 units). In patients with writer's cramp, the doses must be adjusted according to muscle distribution and size. The doses used in our patients varied from 10 to 50 units of Oculinum toxin per muscle. In patients with laryngeal dystonia, in whom adverse effects correlate strictly with doses, we recommend diluting Oculinum toxin in 4 ml instead of 2 ml of saline solution and injecting 0.1 ml (2.5 units) into each vocal cord.

Many patients had side effects; these never persisted and disappeared spontaneously within one to four weeks. In patients with blepharospasm and hemifacial spasm, the most frequent side effect was ptosis, due to the spread of toxin to the levator palpebrae muscle. Direct spread of toxin may also determine weakness of the lower facial muscles in patients with hemifacial spasm. These patients could be more susceptible to toxic damage because of subclinical facial nerve defects. In our study patients with torticollis complained most frequently of dysphagia. This common complication, occurring particularly when the sternocleidomastoid muscle was injected, became less frequent when botulinum toxin was injected into the upper part of the muscle, an observation suggesting that dysphagia is caused by spread of the toxin to the pharyngeal muscles.

All our study centers reported a higher frequency of side effects when toxin treatment was first introduced. As physicians gained experience with the procedure, complications became less severe and less frequent. A progressive improvement in the results was particularly notable in center 1, where treatment with botulinum toxin began in 1985.

In conclusion, in experienced hands botulinum toxin injection appears to be a safe, effective procedure — accompanied only by minor, transient complications. It deserves to become the first choice symptomatic treatment in the management of focal dystonia and hemifacial spasm.

Sommario

In 6 centri facenti parte del Gruppo Italiano per lo Studio dei Disturbi del Movimento è stata valutata l'efficacia della somministrazione di tossina botulinica A in 251 pazienti affetti da distonia focale e da spasmo del facciale.

Nei pazienti con blefarospasmo, la percentuale media di miglioramento osservata è compresa tra il 66 e l'81%, mentre nei pazienti con torcicollo varia tra il 40% e il 51%. Nei pazienti affetti da spasmo del facciale la percentuale media di miglioramento è compresa tra il 73% e l'81%. Buoni risultati sono stati ottenuti anche nella terapia di distonie focali meno frequenti, come la distonia oromandibolare e laringea e il crampo dello scrivano. Gli effetti collaterali osservati sono risultati generalmente lievi, locali e transitori.

Lo studio conferma quindi l'utilità della tossina botulinica nella terapia sintomatica delle distonie focali e nello spasmo del facciale.

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References

[1] ALEXANDER G.E., MOSES H.: *Carbamazepine for hemifacial spasm.* Neurology 32:286-287, 1982.
[2] BERARDELLI A., CARTA A., STOCCHI F. ET AL.: *Botulinum A toxin injection in patients with blepharospasm, torticollis and hemifacial spasm.* Ital. J. Neurol. Sci. 11:589-593, 1990.
[3] BERTRAND C.M., MOLINA-NEGRO P.: *Selective peripheral nerve denervation in 111 cases of spasmodic torticollis.* Adv. Neurol. 50:637-643, 1988.
[4] BRIN M.F., FAHN S., MOSKOWITZ C. ET AL.: *Localized injection of botulinum toxin for the treatment of focal dystonia and hemifacial spasm.* Mov. Disord. 4:237-254, 1987.
[5] DUTTON J., BACKLEY E.: *Botulinum toxin in the management of blepharospasm.* Arch. Neurol. 43:380-382, 1986.
[6] ELSTON J.S., RUSSELL R.W.R.: *Effects of treatment with botulinum toxin on neurogenic blepharospasm.* Br. Med. J. 290:1857-1958, 1985.
[7] ELSTON J.S.: *Botulinum toxin A in clinical medicine.* J. Physiol. (Paris) 84:285-289, 1990.
[8] FAHN S.: *Treatment of dystonia with high dosage anticholinergic medications.* Neurology 29:605, 1979.
[9] FAHN S., MARSDEN C.D., CALNE D.B.: *Classification and investigation of dystonia.* In: *Marsden C.D. and Fahn S. eds.*, Movement Disorder, London Butterworth 333-358, 1987.
[10] GELB D.J., LOWENSTEIN D.H., AMINOFF M.J.: *Controlled trial of botulinum toxin injections in the treatment of spasmodic torticollis.* Neurology 39:80-84, 1989.
[11] GRANDAS F., ELSTON J., QUINN N., MARSDEN C.D.: *Blepharospasm: a review of 264 patients.* J. Neurol. Neurosurg. Psychiatry 51:616-623, 1988.
[12] HERZBERG L.: *Management of hemifacial spasm with clonazepam.* Neurology 35:1676-1677, 1985.
[13] JANKOVIC J., ORMAN J.: *Botulinum A toxin for cranial cervical dystonia: a double-blind placebo-controlled study.* Neurology 37:616-623, 1987.
[14] JANKOVIC J., FAHN S.: *Dystonic syndromes.* In: Jankovic J., Tolosa E., eds. "Parkinson's disease and movement disorders", Baltimore, MD: Urban and Schwarzenberg, 283-314, 1988.
[15] JANKOVIC J., BRIN M.F.: *Therapeutic uses of botulinum toxin.* N. Eng. J. Med. 324:1186-1194, 1991.
[16] KAO I., DRACHMAN D.B., PRICE B.L.: *Botulinum toxin mechanism of presynaptic blockade.* Science 193:1256-1258, 1976.
[17] MACCABEE J.J.: *Surgical treatment of spasmodic torticollis.* In: Marsden C.D. and Fahn S., Eds. Movement Disorders, London Butterworths Int. Med. Rev. 308-314, 1982.
[18] MARSDEN C.D., SCHACHTER M.: *Assessment of extrapyramidal disorders.* Br. J. Clin. Pharmacol. 11:129-151, 1981.
[19] MAURIELLO J.A.: *Blepharospams, Meige's syndrome and hemifacial spasm: treatment with botulinum toxin.* Neurology 35:1499-1500, 1985.
[20] NIELSEN V.K., JANNETTA P.J.: *Effects of facial nerve decompression.* Neurology 34:891-897, 1984.
[21] QUINN N., HALLETT M.: *Dose standardisation of botulinum toxin.* Lancet, 1:964, 1989.
[22] SCOTT A.B.: *Botulinum toxin injection of eye muscles to correct strabismus.* Trans. Am. Ophthalmol. Soc. 79:734-770, 1981.
[23] SCOTT A.B., KENNEDY R.A., STUBBS H.A.: *Botulinum A toxin injection as a treatment for blepharospasm.* Arch. Ophthalmol. 103:718-719, 1985.
[24] TSUI J.K.C., EISEN A., STOESSL A.J. ET AL.: *Double-blind study of botulinum toxin in spasmodic torticollis.* Lancet 2:245-247, 1986.