Botulinum Toxin Injection in the Management of Lateral Rectus Paresis

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Abstract: Seventeen patients with lateral rectus paresis (3 bilateral) were treated by injection of botulinum toxin to the antagonist medial rectus to eliminate its unopposed action or to eliminate its contracture. This allowed maintenance of single binocular vision in most patients while waiting for the palsy to heal, especially important in two children. It allowed avoidance of surgery in some cases, and a reduction or elimination of medial rectus surgery when later intervention was needed for persistent paralysis. The release of medial rectus shortening and stiffness (contracture) after just a few days of denervation was unexpected. This implies an internal muscular mechanism of contracture, perhaps sarcomere overlap, different from the fibrotic changes found in muscles after inflammation or trauma. These results also provide a rationale for experimental denervation treatment of contracture in limb muscle disorders. [Key words: botulinum A toxin, lateral rectus paresis, medial rectus contracture.] Ophthalmology 92:676–683, 1985

The injection of botulinum toxin into extraocular muscles is a new technique for the treatment of strabismus. Since the early reports of the use of this method,[1–3] over 200 patients with strabismus have been treated with botulinum A toxin.

In this paper we review our experience with botulinum A toxin injection of the medial rectus in patients with lateral rectus paresis. The goals of the study were to determine: (1) if medial rectus contracture could be relieved or prevented by this treatment; (2) if treatment could reestablish binocular vision in patients with complete or partially recovered pareses; and (3) if surgical treatment could be aided by preoperative injection.

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MATERIALS AND METHODS

Seventeen patients (10 males, 7 females) with lateral rectus paresis were treated between January 1978 and November 1983. Fourteen patients had unilateral paresis and three had bilateral paresis. Etiologies of the palsies in these cases were head trauma (10 cases), intracranial neoplasm (2 cases), diabetes, neurosurgical procedure, and meningitis (1 case each), and 2 had no determined cause.

The average age of the patients was 39.4 years (range, 2–74 years). The mean follow-up from last injection until either the latest visit or until eye muscle surgery was performed was 213 days (range, 44–680 days).

Injections of purified botulinum A toxin were done under electromyographic control. The method was described in detail in previous reports.[1–3] The minimal effective dose of toxin for strabismus in a human adult is 0.75 units (U). The U is equal to one mouse LD/50 dose of our preparation, about 0.4 ng.[1] For the adult patients, only injections of this dose or greater were included in the analyses. Dosages for children under 10 years of age were determined as a percentage of the full adult dose with this percentage varying according to the weight of the child.

Table 1. Gradings of Clinical Parameters

Lateral Rectus Function, force generation test

	Bilateral Cases	Unilateral Cases
P = Poor	<10 grams	<10% cf. normal contralateral LR
F = Fair	10–40 grams	10–50% cf. normal contralateral LR
G = Good	>40 grams	>50% cf. normal contralateral LR

Contracture, passive forced duction test

0 = Normal: globe can be freely rotated into full abduction
1+ = Can rotate globe over 50% of full abduction
2+ = Can rotate globe from midline up to 50% of full abduction
3+ = Cannot rotate globe to midline

Ductions, active

0 = Normal: can voluntarily rotate eye fully into field of gaze
−1 = Can rotate eye from midline to 75% of full rotation
−2 = Can rotate eye from midline to 50% of full rotation
−3 = Can rotate eye from midline to 25% of full rotation
−4 = Can rotate eye to midline but not into given field
−5 = Cannot rotate eye from opposite field to midline

LR = lateral rectus.

Ocular deviations were determined by cover test and prism and alternating cover test with fixation at 6 m. Lateral rectus function was classified as poor (P), fair (F), or good (G) according to force generation testing[4,5] (Table 1). Contraction of the medial rectus was determined by the amount of limitation of abduction of the eye on passive forced duction testing[4–6] and was graded from 0 (normal) to 3+ (maximal) (Table 1). Ocular ductions were graded from −5 (maximal limitation) to 0 (full rotation into field of action) (Table 1).

RESULTS

Thirty-two injections were given with a mean of 1.4 injections per muscle. No muscle received more than three injections.

The affected eyes were classified into three groups. Group I (12 eyes) were eyes whose lateral rectus muscles had poor or fair function and in which there was medial rectus contracture (tightness at least 1+). In Group II (4 eyes) the lateral rectus muscles had poor function and no medial rectus tightness was present at the time of the initial injection. In Group III (5 eyes) the function of the lateral rectus had recovered to the fair or good level with mild (1+) or with no medial rectus contracture.

Case 5 had bilateral total paralysis, and there was some recovery of function of the right lateral rectus. Thus, the left eye (function poor; medial rectus contracted) was included in Group I and the right eye (fair function; no medial rectus contracture) was included in Group III. Case 10, with bilateral total lateral rectus paresis, had injection to both medial rectus muscles (included in Group I) prior to bilateral transposition muscle surgery. Postoperatively, because of residual left esotropia, he had injection to his left medial rectus to prevent recurrence of contracture (this injection was included in Group II).

GROUP I

The data for these eyes are listed in Table 2. The medial rectus contractures were successfully released in 11 of the 12 affected eyes (all except the right eye of case 10).

Case 4. A 52-year-old woman suffered a head injury in a motor vehicle accident. She developed a total sixth nerve palsy of the left eye which did not improve over the following 12 months (Fig 1, *top*). She had 50 diopters of left esotropia with −5 rotation to abduction. Forced ductions of the left eye were 2+ limited on abduction and force generation was 0 in the lateral rectus. An injection of 2.5 U of botulinum A toxin was given to the left medial rectus muscle. Seven days later the left eye was in primary position and the patient was orthophoric (Fig 1, *center*). Abduction and adduction were both −4. Five weeks later, surgery was performed on the left eye. On the day of admission, the patient was still orthophoric, adduction of the left eye was −3, and abduction was −4. Forced ductions at surgery show no medial rectus contracture. The superior and inferior rectus muscles were transposed laterally to the left lateral rectus. One month later, the patient had 35 diopters of left exotropia and had −5 to adduction and −3 to abduction of the left eye. Six months postoperatively, the patient was orthophoric in primary position and had single binocular vision 10° to either side of the primary position (Fig 1, *bottom*).

Figure 2 demonstrates the length-tension curve of the contracted medial rectus before and after injection for case 4.

Six patients with lateral rectus palsy and medial rectus contracture regained single binocular vision in primary position sometime during the treatment with toxin (cases 1, 4, 5, 6, 7, and 8). In five patients (cases 1, 3, 4, 5, and 9) injections prior to muscle transposition surgery eliminated the contractures although in one (case 5), restriction was recurring by the time of surgery. Ipsilateral medial rectus recession was not done in these eyes. After at least four months postoperative follow-up, three of these patients had single binocular vision in primary position and two had single binocular vision using a small amount of prism.

Case 10 had bilateral 5.0 mm recessions of the medial rectus muscles along with transposition surgery in both eyes. The right eye was aligned to primary position; the left eye required a subsequent operation.

Case 8 had undergone five previous surgical procedures on the left eye, including recess-resect procedures and one transposition procedure, and had residual left esotropia with contracture of the medial rectus. He had repeated injections to both medial rectus muscles, and at the last visit was orthotropic in the primary position.

In cases 7 and 8, both unilateral palsies, the contralateral medial rectus muscles were injected in addition to the medial rectus muscles of the affected eyes. This was done to weaken the yoke muscles of the involved lateral rectus muscles to attempt to prevent recurrence of contracture of the involved medial rectus muscles.

Table 2. Data from

						Pre-injection Data				Follow-up: 7–21					Follow-up: 30-	
Case No.	Age (years)	Medial Rectus Injected (R/L)	Injection No.	Time from Onset of Palsy (mo.)	Dose (Units)	Deviation (Prism Diopter)	Lateral Rectus Function	Abduction	Medial Rectus Contracture	Lateral Rectus Function	Abduction	Medial Rectus Function	Adduction	Medial Rectus Contracture	Lateral Rectus Function	Abduction
1	24	R	1	13	2.0	50 ET	P	−5	2+		−4		−4			−4
2	26	R	1	33	5.0	50 ET	P	−5	2+		−4		−4		P	−4
3	53	R	1	5	6.25	45 ET	P	−5	1+	P	−4	P	−4	0	P	−4
4	52	L	1	12	2.5	50 ET	P	−5	2+		−4		−4	0	P	−4
5	40	L	1	6	2.5	85 ET	P	−5	3+						P	−5
			2	8	7.5	40 ET	P	−5	2+		−4		−4		P	−4
6	22	L	1	9	5.0	45 ET	P	−4	1+		−4		−4			−4
7	73	R	1	36	2.5	18 ET	F	−2	2+		−1		−4	0		−2
		L	1	39	2.5	12 ET	G	0	0		0		−4	0		0
8	26	L	1	204	0.75	30 ET	P	−4	2+		−4		−4	0		
			2	207	0.75	20 ET	P	−4	0		−4		−2			
			3	208	4.0	17 ET	P	−4	0							−4
		R	1	207	0.75	22 ET	G	0	0	G	0		−1			
			2	208	4.0	17 ET	G	0	0							0
9	59	L	1	3	0.75	60 ET	P	−5	2+						P	−4
			2	5	0.75	60 ET	P	−4	0	F	−3	F	−4	0	F	−2
		R	1	4	0.75	50 ET	P	−5	2+	P	−4	G	−2			
			2	7	0.75	50 ET	P	−5	2+						P	−4
10	18	R	1	3	5.0	110 ET	P	−5	2+		−4		−2		P	−4
			2		6.25	50 ET	P	−4	1+						P	−4
		L	1	3	5.0	110 ET	P	−5	2+		−4		−4	0		−4

R = right; L = left; ET = esotropia; E = esophoria; X = exophoria; O = orthophoria; OS = left eye; OD = right eye; P = poor; F = fair; G = good.

Cases in Group I

After Injection (days)															
50			75–100					Over 150							
Medial Rectus Function	Adduction	Medial Rectus Contracture	Lateral Rectus Function	Abduction	Medial Rectus Function	Adduction	Medial Rectus Contracture	Lateral Rectus Function	Abduction	Medial Rectus Function	Adduction	Medial Rectus Contracture	Final Deviation (Prism Dioper)	Follow-up (days)	Comments
	−2	0		−4		0	0						5 ET	91	2 × 306 days after muscle transpositon OD
	0	0											30 ET	51	Orthophoric in 20° L gaze
F	0	0											20 ET	48	8 ET 143 days after transposition surgery
	−3	0											0	44	Orthophoric 185 days after transposition O.S.
	0	2+											40 ET	34	14 ET 680 days
	−3	0	P	−5		0	1+						30 ET	97	after transposition surgery OS—fuses with 14 Base-out prism. Right medial injected; See Group II
	−2		P	−4		0			−4		0		8 E	485	No abnormal head position
	−2			−1		−1		F	−2		0	0	18 ET	603	Normal left medial
	−2			0		0			0		0		18 ET	505	rectus injected to prevent contracture OD
			P	−4		−2							20 ET	109	Had 5 previous
	−2												17 ET	15	muscle operations OS.
								P	−4		−2	0	0	259	
	−3			0		−1							17 ET	15	Adduction was
								G	0		0		0	259	−2 OS. prior to 1st injection. Normal right medial rectus injected to prevent return of contracture OS.
	−2	0											60 ET	30	6 × 100 days
	−2	0	G	−1	G	−1	0		−1		−1	0	50 ET	285	after muscle
			P	−5	G	0	1+						50 ET	81	transposition
	0		P	−4		0	0						50 ET	90	surgery OD
	−2	1+											50 ET	30	Residual 20 ET
	−3		P	−5		0	2+						80 ET	98	after bilateral
	−4	0	P	−4		0	1+	P	−5		0	2+	80 ET	150	transposition plus med. rectus recessions. Required reoperation OS

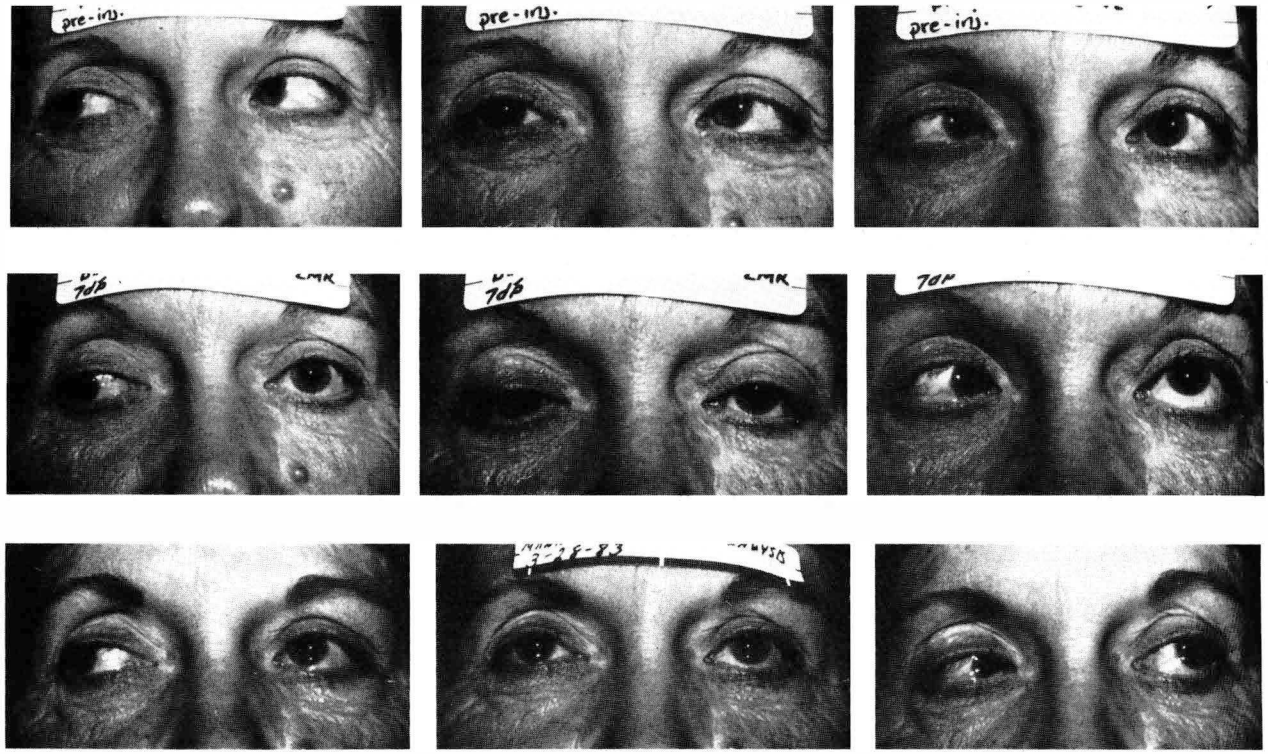

Fig 1. Case 4. Total left sixth nerve palsy with medial rectus contracture. *Top,* prior to injection of left medial rectus: 50 diopters of left esotropia and −5 to abduction in left eye. *Center,* seven days after injection: orthophoria in primary position; abduction and adduction, both −4, in left eye. *Bottom,* six months after muscle transposition surgery to left eye: orthophoria in primary position and single binocular vision 10° to either side of primary position.

GROUP II

Data for these eyes are recorded in Table 3. All eyes were injected within eight weeks of the onset of a complete lateral rectus palsy and prior to the onset of medial rectus contracture.

Case 11. A 59-year-old man had diabetes mellitus for eight years as well as coronary artery disease for several years. He suffered an acute onset of right sixth nerve palsy and 14 days later was referred for treatment. He had 25 diopters of right esotropia and could not abduct the right eye beyond midline. Forced duction testing showed no restriction of the right eye to abduction. The EMG showed no muscle action potential in the lateral rectus and the force generation was 0. Twenty-one days after the injection of 2.5 U of botulinum A toxin into the right medical rectus he had 10 diopters of right exotropia, and both abduction and adduction were −3. By four months after injection, the adduction was −1 and abduction was normal. One year later, rotations of the right eye were normal and he was orthophoric in primary position.

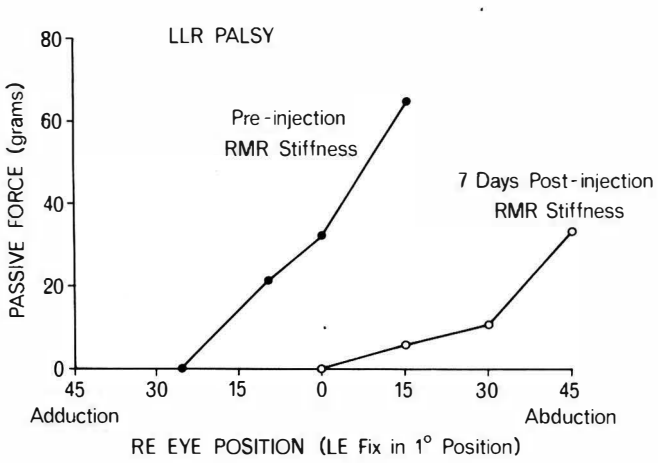

Fig 2. Length–tension curves for contractured left medial rectus before and after injection (case 4). Note the reduction in stiffness and shift of areas of maximum restriction after the botulinum treatment.

Both cases 12 and 13 were young children who developed head turns soon after the onset of the palsy. Case 13 was developing an amblyopia in the paretic eye at the time of injection. In three patients (cases 11, 12, 13) the lateral rectus paresis fully recovered and there was orthophoria in the primary position with no medial rectus contracture.

GROUP III

Data for these five eyes are listed in Table 4. Lateral rectus function in each eye was either fair or good. The pareses were stable and all had been followed at least six months since their onset.

Case 14. A 43-year-old man had a nasopharyngeal carcinoma diagnosed in 1976 and a right sixth nerve paresis was diagnosed at that time. Radiotherapy and chemotherapy controlled the growth of the neoplasm over the next 36 months but the palsy only partially recovered. He was referred for treatment of a

residual lateral rectus paresis. He had 16 diopters of right esotropia. Abduction of right eye was −1. Adduction was normal. Force generation was 40 g in the right lateral rectus and 80 g in the left lateral rectus. Forced ductions were free in the right eye. A dose of 0.75 U was injected into the right medial rectus. Twenty-seven days later, he had 12 diopters of right esotropia. The abduction of the right eye was still −1 and adduction was normal, but the force generation in the right lateral rectus had improved to 70 grams. A second injection of 0.75 U was given. Four months later he was orthophoric in all positions of gaze and rotations were full in the right eye.

Three eyes (cases 5, 14, 15), regained full abduction after injection. The abduction in case 17 did not improve beyond −1 but the patient was orthophoric in the primary position. In case 16 the esotropia recurred and the patient required recess-resect surgery to the affected eye.

SIDE EFFECTS

Side effects from 32 injections are listed in Table 5. All cases of induced ptosis resolved completely within two months. The induced overcorrections ranged from 15 to 22 diopters of exotropia. All cases of overcorrection became orthotropic within three months except for case 11 who became orthotropic seven months after the injection.

The case of induced hypertropia resolved within two months. The cases of hemorrhage and abnormal sensation resolved within two months.

It should be noted that no systemic side effects occurred in any patient at any time during the study.

DISCUSSION

If a lateral rectus muscle remains totally paralyzed for more than three or four weeks, and if the patient does not force the eye towards abduction by patching or prisms, then increasing esotropia is seen as the medial rectus shortens. A limitation of passive abduction of the eye can be demonstrated; there can be an associated reduction in elasticity (increase in stiffness).[4–8] This combination of shortening and increased stiffness constitutes the clinical condition of contracture.

The most striking finding in this study was the release of such medial rectus contractures by the botulinum toxin injections. This was seen in 11 of 12 eyes (Group I).

The releases of the medial rectus contractures in these cases were consistently associated with the finding of complete (−4) limitation of adduction in the first three weeks after injection. The dose required varied from 0.25 U to 6.5 U. In some cases, a second or third injection at the initial or at a higher dose level was required to establish this situation. Thus, the amount of induced medial rectus paralysis two or three weeks after injection tells if a given injection is sufficient or if a higher dose will be required to release the contracture. With the release of the contracture, the patient frequently obtains binocular vision over a small area of gaze.

Table 3. Data for Cases in Group II

Case No.	Age (years)	Medial Rectus Injected (R/L)	Time from Surgery (s) or Onset of Palsy (p) (weeks)	Dose (Units)	Reinjection Data		Follow-up after Injection (days)								Final Deviation (Prism Diopter)	Follow-up (days)	Comments
					Deviation (Prism Diopter)*	Abduction	71–21		30–50		75–125		Over 150				
							Abduction	Adduction	Abduction	Adduction	Abduction	Adduction	Abduction	Adduction			
10	18	L	8 (s)	10.0	20 ET	−4	−4	−4			−4	−1			12 ET	153	3 E 45 days after 2nd surgery (recess-resect OS)
11	59	R	2 (p)	2.5	25 ET	−4	−3	−3	−2	−3	0	−1	0	0	0	508	
12	4	R	8 (p)	1.25	30 ET	−4	−2	−1			0	0			0	118	Right face turn prior to injection
13	2	R	5 (p)	1.0	30 ET	−4	−2	−2	−1	0	0	0			0	76	Initially had right face turn; amblyopia developed in OD before injection

R = right; L = left; ET = esotropia; E = esophoria; O = orthophoria; OS = left eye; OD = right eye.

Table 4. Data for

Case No.	Age (years)	Medial Rectus Injected (R/L)	Injection No.	Time from Onset of Palsy (mo.)	Dose (Units)	Reinjection Data			7–21			30–50	
						Deviation (Prism Diopters)	Lateral Rectus Function	Abduction	Lateral Rectus Function	Abduction	Adduction	Lateral Rectus Function	Abduction
5	40	R	1	6	1.25	85 ET	F	−3		−2	−2		
14	43	R	1	36	7.75	16 ET	F	−1				G	−1
			2	37	7.75	12 ET	G	−1		0	−1		
15	55	L	1	22	2.5	14 ET	G	−1					0
16	48	L	1	28	3.75	30 ET	G	−2					
17	67	R	1	12	2.5	12 ET	G	−1		−1	−4	G	−1

R = right; L = left; ET = esotropia; O = orthophoria; OS = left eye; F = fair; G = good.

If total lateral rectus palsy persists, the eye will regain its esotropic position and the medial rectus will again shorten once the effect of the drug has worn off (case 5, right eye; case 10, left eye). This usually occurs within three months. Even with repeated injections, the contracture may recur in such cases. Thus, botulinum toxin injection does not in itself lead to a cure of a chronic, total lateral rectus palsy.

Despite this fact, botulinum toxin can be a useful adjunct to preoperative management of these cases. While the drug is acting, contracture is no longer demonstrated, and a muscle transposition procedure may be performed without the need for ipsilateral weakening of the medial rectus (cases 1, 3, 4, 5, 9) or with a medial rectus recession of a smaller amount than usual (case 10, right eye). Such transposition procedures generally involve transposition of part or all of the vertical rectus muscles; if no medial rectus recession is required, these can be undertaken with much less fear of anterior segment ischemic problems. In addition, we have found the amplitude of horizontal gaze of the eye postoperatively is better when no medial rectus recession is added to the transposition procedure. The exact timing and amount of surgery following medial rectus injection is not clearly defined by our cases, but it is apparent that surgery should be done within three months after an adequate injection that successfully releases the contracture.

Table 5. Side Effects from Treatment (32 injections)

Complications	Total No.	Case No.
Overcorrection	5	7, 8, 11, 15, 17
Ptosis	5	1, 2, 10 (3 injections)
Hypertropia	1	2
Subconjunctival hemorrhage	1	2
"Pulling sensation"	1	14

Injection of the medial rectus can be done to prevent contracture in total sixth nerve palsy (Group II). This allows the paretic muscle to recover without having to pull against a shortened antagonist. Thus, normal alignment and full recovery of function can be obtained. This was true of three cases in Group II, including two children under 4 years of age. The amblyopia of case 13 resolved after the injection and a subsequent short interval of patching. Prior to the advent of injection to the medial rectus muscles, we have found that in such children the result is usually a small angle esotropia without normal binocular vision.

In cases of lateral rectus paresis with partial recovery (Group III), injection of the medial rectus sometimes allowed further recovery of function of the lateral rectus without the need for muscle surgery. Good alignment and abduction were obtained in three of the five cases, although the clinical measurements indicating moderate paresis remained unchanged for several months prior to the injections.

Muscle shortening and restriction to passive duction is observed in situations other than total lateral rectus palsy. It occurs frequently in endocrine exophthalmos. However, in contrast to the good success in relieving contractures associated with lateral rectus palsy, we have found that injection has little effect on the tightness of these muscles.[9]

It appears, therefore, that there are two mechanisms of "contracture"; one, as seen associated with lateral rectus palsy, which responds to the induced paralysis of botulinum toxin, and a second, as exemplified by endocrine exophthalmos, which does not respond. These two kinds of eye muscle contracture are not differentiated by existing clinical tests such as comitance measurements and forced duction tests.

Botulinum toxin acts presynaptically at nerve terminals to prevent calcium-dependent release of neurotransmitter; a state of denervation results.[10–16] Since no

Cases in Group III

Follow-up After Injection (days)												
	75–100			125–150			Over 200					
Adduction	Lateral Rectus Function	Abduction	Adduction	Lateral Rectus Function	Abduction	Adduction	Lateral Rectus Function	Abduction	Adduction	Final Deviation (Prism Diopters)	Follow-up (days)	Comments
	G	−2	−2		−1	0	G	0	0	14 ET	680	Left lat. rectus had poor function requiring transpostion surgery
0				G	0	0				12 ET 0	29 135	
−2				G	0	0		0	0	0	258	
	G	−2	0							20 ET	85	Had recess-resect surgery OS
−1										0	44	

connective tissue elements are affected, the type of contracture that responds to toxin injection may be an internal change in the muscle that is reversible in a state of denervation. Alterations in number of sarcomeres in muscle fibers has been reported in passively shortened and extended skeletal muscles.[17] A related structural change, such as overlap of sarcomeres, may be the cause of contracture in eye muscles in chronic paralytic strabismus.

In contrast, the contracture of endocrine exophthalmos, which does not respond to injection, is characterized by significant connective tissue changes. Histology of eye muscles in this condition shows abnormality of connective tissue elements within and around the muscles.[18,19] Botulinum-induced denervation does not appear to alter the contracture associated with such fibrotic muscles.

The encouraging preliminary results of botulinum toxin treatment of lateral rectus palsy show the need for basic studies of muscle contracture, and provide a basis for exploration of the treatment in comparative clinical trials of oculomotor palsy, and of peripheral muscle disorders characterized by contracture.

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