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The Role of Botulinum Toxin in the Management of Sixth Nerve Palsy

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Summary

Fifty-five patients with sixth nerve palsy have been treated with Botulinum toxin injection to the antagonist medial rectus, either in isolation or in combination with rectus muscle surgery. Forty of these patients (72 per cent) obtained significant benefit from injection at some stage in their management. Botulinum toxin has a major role in conjunction with transposition muscle surgery for the treatment of complete unrecovered sixth nerve palsy. In less severe paresis, a functional cure may be obtained in a significant number of cases with the use of Botulinum toxin alone, 37 per cent in this series. No serious complications were observed. In view of the safety of this procedure it is reasonable to consider an injection of Botulinum toxin in any adult patient with a persisting sixth nerve palsy.

Since the introduction of Botulinum toxin into clinical use in the 1980s, sixth nerve palsy has been used repeatedly as a model for a proposed action of the toxin[1,2,3,4] and also has been one of the prime indications for Botulinum toxin injection as a treatment of strabismus.[1,2,3,5,6,7,8,9] The proposed mechanism of action invokes relative lengthening and atrophy of the injected muscle and contacture or shortening of the antagonist, providing longterm realignment of the eye.[2,3,7] A change in the number of sarcomeres has been demonstrated experimentally in the soleus muscle of the cat.[10] A decrease in number was seen if the denervated muscle was immobilised in a shortened position and an increase if immobilised in a lengthened position. This change in length of both agonist and antagonist may explain the permanent alteration in ocular position yet allow the observed preservation of full muscle function.[11] This same mechanism may be used to explain the persistence of an esotropia following sixth nerve palsy despite the recovery of lateral rectus function.

The precise indications for Botulinum toxin use in the management of sixth nerve palsy, as well as the appropriate timing for injection are not yet completely clear. Some proposed indications for injection of the ipsilateral medial rectus include;

(1) in the acute phase of sixth nerve palsy to prevent 'contracture' occurring in this muscle as a result of lateral rectus weakness. This should allow return of normal motility if the lateral rectus recovers function.

(2) in chronic sixth nerve palsy to release established contracture and possibly restore permanent alignment if there is adequate lateral rectus function remaining.

(3) as a diagnostic procedure to establish the degree of paralysis of the lateral rectus which helps in the selection of appropriate surgical management.

(4) in patients unable or unwilling to undergo surgery under general anaesthesia, Botulinum toxin may be of use in maintaining alignment for cosmetic or functional reasons, recognising

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that repeated injections may be required and that the effect is not permanent.
(5) as an adjunct to ocular muscle surgery, particularly transposition surgery in cases of complete unrecovered sixth nerve palsy. Botulinum toxin may be used to release contracture of the medial rectus and avoid recessing this muscle at the time of surgery on two other rectus muscles. This has advantages in preserving anterior segment circulation and in the maintenance of the maximum range of horizontal movement of the eye.

In this review we look at all our patients who have had Botulinum toxin injections at some stage in the management of sixth nerve palsy in an attempt better to define the indications, appropriate timing and the anticipated results of such treatment.

Materials and methods

Fifty-five patients with lateral rectus paresis, 35 unilateral and 20 bilateral, have been treated with Botulinum toxin at Moorfields Eye Hospital between 1983 and the time of this review. Botulinum toxin was used at some stage in the management but in only the minority was it the sole form of treatment. The average age was 37 years (range 5–79). There were 34 females and 21 males. The aetiology of the palsies is shown in Table I, 50 per cent being due to trauma. Assessment of the patients included prism cover test at six metres with the head as straight as possible and the extent of extraocular movement, specifically abduction of the palsied eye. This was graded as shown in Table II. Assessment of binocular function, Hess charts and the field of binocular single vision were recorded where possible. All patients had Botulinum neurotoxin A injected into the medial rectus of the affected eye or in the case of bilateral palsies, the most severely involved eye. In a few instances both medial recti were injected on the same occasion. These were performed under EMG control as previously described.[3] A total of 101 injections were given. The subsequent management was dependent on the primary indication for toxin injection and falls into two groups (see Fig. 1).

Table I *Aetiology of sixth nerve paresis*

Aetiology	*Number of patients*	*Group A*	*Group B*
Trauma	28	6	22
Microvascular	5	4	1
Tumour	5	2	3
Infectious	6	6	0
Multiple sclerosis	1	1	0
Intracranial vascular abnormality	4	4	0
Sarcoidosis	1	1	0
Unknown	5	3	2
Total	55	27	28

Table II *Extra ocular muscle function*

Normal duction	0
Minimal restriction	−1
Moderate restriction	−2
Marked restriction	−3
No movement past midline	−4

Group A

A group of 27 patients had injections as an isolated treatment modality. Four of these have been reported previously.[10] They were all reassessed within two weeks of the injection to determine the effect and to decide on subsequent management. In 12 patients it was necessary to give more than one injection before the usefulness of the Botulinum toxin could be determined. Five of these patients had had surgery for their sixth nerve palsy prior to this treatment. These patients fall into one of three categories according to the outcome.
(1) Functional cure: this is defined as a residual phoria, or a tropia corrected with <5 diopters of horizontal prism and satisfactory relief of diplopia.
(2) Unfit for general anaesthetic: these patients were considered unfit for a general anaesthetic and Botulinum toxin was used to maintain alignment, recognising that this was a temporary correction and numerous injections would be required.
(3) Botulinum toxin unhelpful in further management: this category includes those patients whose subsequent management involved surgery not in conjunction with Botulinum injections or those where long term occlusion of one eye was appropriate.

Group B

Twenty eight patients received Botulinum

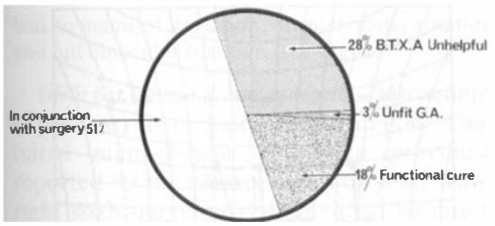

Fig. 1. *Use of Botulinum toxin in patients with sixth nerve palsy.*

toxin injections to the medial rectus as an adjunct to surgery. This was lateral transposition of the vertical recti for complete unrecovered sixth nerve palsy in 20 cases, a Jensen procedure in three, a medial rectus Faden in one and a retransposition in four. Twenty-two of these patients have been reported in detail.[21] The patients had surgery performed within two weeks of injection to gain maximal advantage of the toxin paralysis and subsequent management was dependent on the outcome of this surgery. In eleven cases the patients had injections several months prior to surgery, primarily as a diagnostic test to confirm the clinical impression of complete unrecovered palsy. They then received a second injection just prior to surgery. Fourteen patients had had previous surgery and 14 had not. The final outcome of treatment after any subsequent surgery had been performed was assessed as satisfactory or poor in terms of ocular alignment in the primary position of gaze and the field of diplopia free vision.

Results

Group A

Functional Cure (see Table III). According to our criteria ten patients (37 per cent) obtained a functional cure with the use of Botulinum toxin. Eight patients received a single injection, one received three and one received five. Only one patient had previously had surgery performed—a recess/resect procedure on the affected eye. The duration of the palsy ranged from 1.5 months to seven years. Only one of these ten cases was secondary to trauma. This was the only bilateral case and required three injections.

Case Report: Patient 7

A five year old child developed a right sixth nerve palsy two weeks following otitis media, meningitis and a right mastoidectomy. When first seen she had a sixty prism dioptre esotropia and no abduction of the right eye beyond the midline −4. Fusion was demonstrable on the synoptophore examination (see Fig. 2a). After four weeks there was an increasing esotropia and signs of contracture were evident (see Fig. 2b). An injection of Botulinum toxin was administered to the right medial rectus under Ketamine anaesthesia six weeks after the onset of the palsy. She became exotropic and developed a right hypertropia. On examination eight months later she

Table III *Functional cure*

Case No.	*Age onset*	*Lat*	*Aetiology*	*Duration months*	*Previous surgery*	*No. inj.*	*Init dev.*	*Abd*
1*	19	R	Guillain Barre	7	Nil	1	60	−1
2*	45	B	RTA	8	Nil	3	50	−2
3	68	L	C/C fistula	24	Nil	1	45	−3
4	51	R	Meningitis	36	Nil	1	45	−2
5	16	L	Cerebellar abcess	36	Nil	5	60	−1
6	22	L	Viral	2	Nil	1	35	−4
7	5	R	Meningitis	1.5	Nil	1	60	−4
8	53	R	Meningioma	15	Nil	1	35	−3
9	32	R	Multiple sclerosis	84	R MR+ LR−	1	14	−2
10	39	R	Unknown	5	Nil	1	65	−4

* Previously reported.[10]
Lat Laterality.
No. inj. Number of injections.
Init. dev. Initial deviation measured in prism dioptres of esotropia.
Abd Abduction.

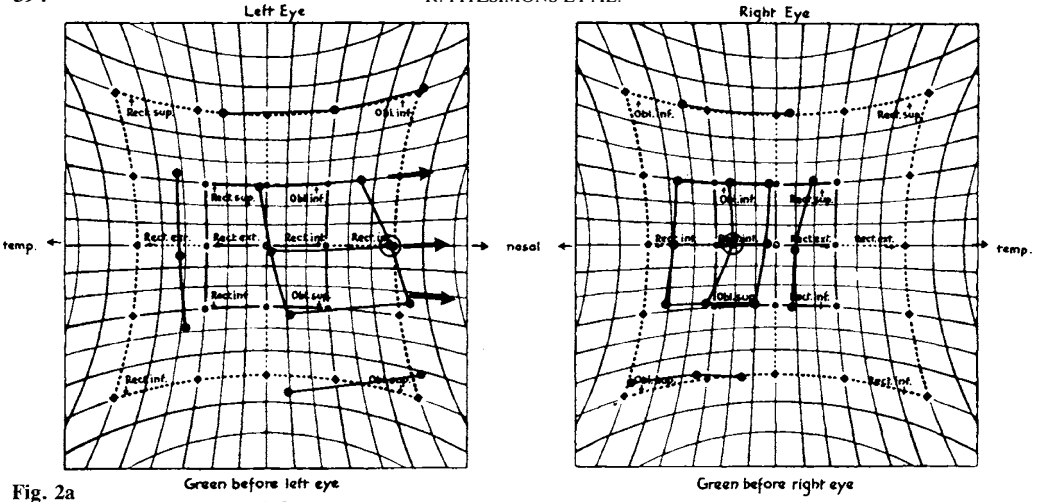

Fig. 2a

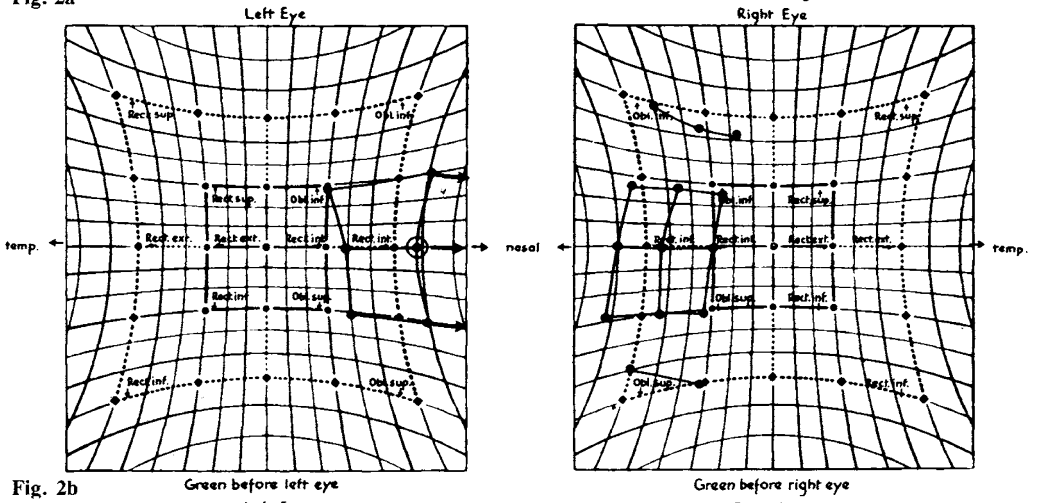

Fig. 2b

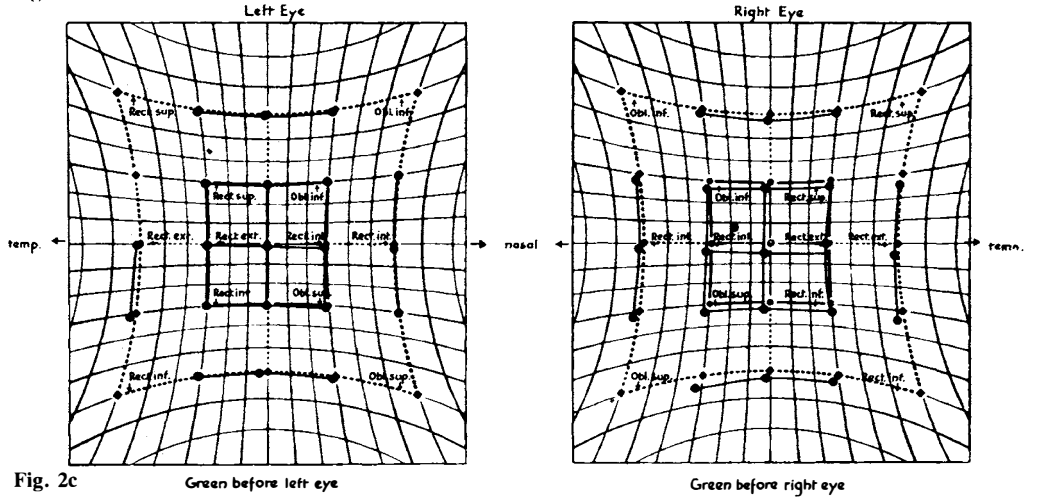

Fig. 2c

Fig. 2. *Patient 7: Serial Hess charts showing 2a initial esodeviation, 2b increasing deviation and contracture of right medial rectus, 2c final status after Botulinum toxin injection to right medial rectus.*

had no manifest deviation, normal ocular rotations and full binocular function (see Fig. 2c).

Unfit for General Anaesthesia. Two patients (7 per cent) are included in this category. Their initial management has been previously reported.[10] One is a woman of 67 years with a right sixth nerve palsy thought to be due to hypertension. She suffered from severe bronchiectasis and general anaesthesia was considered unwise. Over a period of three years she received seven injections of Botulinum toxin (see Fig. 3). The second was a girl of 19 yearswho had an intracranial arterio-venous malformation. Over three years she required thirteen injections of toxin to maintain satisfactory alignment. Surgery was eventually performed under local anaesthesia.

Botulinum Toxin Unhelpful in Further Management (see Table IV). Fifteen patients (56 per cent) obtained no lasting benefit from injection and were subsequently managed by surgery in ten cases or occlusion of one eye in five. Seven patients had a single injection, six had two injections, one had three and one had four injections. The duration of the palsies ranged from four months to forty years. Five cases were bilateral and four had had previous surgery.

Group B (see Tables V and VI)
This group of patients represents the most common indication for Botulinum injection for sixth nerve palsy in this series. Trauma accounted for 80 per cent of these palsies and over 50 per cent were bilateral. Thirteen patients required further surgery after our combined procedure, twelve had no further surgery and in three the outcome is uncertain and further surgery may be required. The final outcome according to our criteria was satisfactory in 17, poor in six and as yet uncertain in five.

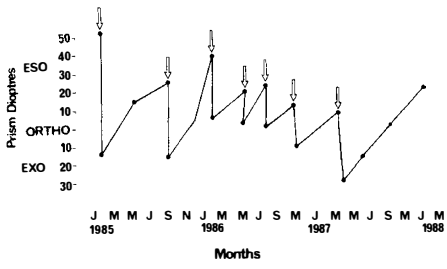

Fig. 3. *Patient 11: Treatment of sixth nerve palsy by repeated injection of Botulinum toxin into the right medial rectus in a patient considered unfit for surgery. ↓ indicates an injection.*

Case history: Patient 30
A 19-year old man suffered injuries when a fork-lift truck fell on him. He suffered a left sixth nerve palsy and a skull fracture. Sixteen months after the accident he had a total left lateral rectus palsy and was unable to achieve binocular single vision even with a face turn. The esotropia measured 25 prism dioptres. He could fuse and had evidence of binocular function on synoptophore examination (see Fig. 4a). His left medial rectus was injected with Botulinum toxin and one week later he had a Jensen procedure performed on the left eye, without a medial rectus recession. On the first post operative day he had a 45 prism dioptre exotropia and no horizontal movement of the left eye. Vertical movement was full. Twelve months later he had no abnormal head posture, cover testing in the primary position revealed a small esophoria and he had some limitation of left abduction. He had a large field of single binocular vision with some residual diplopia on left gaze (see Fig. 4b).

Discussion

That Botulinum toxin injection has a place in the management of sixth nerve palsy is certain. Although accepting that this reported series represents a highly selected population, we were able to obtain significant benefit for 40 of the 55 patients (72 per cent) at some stage in their management. It is useful to look at each of the proposed indications in turn.

The treatment of sixth nerve palsy in the acute phase, although conceptually attractive, has not yet been studied on a controlled prospective basis and that it offers any significant advantage to the patient in the long term is uncertain. We have treated only four patients within a six month period following the onset of their palsy (case no. 6, 7, 10, 14). Three resulted in functional cure and one required surgery. The major problem with assessing such injections is that there are a large number of patients who suffer a 'medical' sixth nerve palsy e.g. diabetic, microvascular, postviral, and whose natural history is one of complete recovery. This also applies to many palsies seen in childhood.[12] An injection in this group,

Table IV *Botulinum unhelpful in further management*

Case no.	*Age onset*	*Lat*	*Aetiology*	*Duration months*	*Previous surgery*	*No. inj.*	*Init dev.*	*Abd.*
13	48	L	Aneurysm	36	nil	3	90	−4
14	45	R	RTA	4	nil	1	70	−4
15	21	B	RTA	14	nil	2	25	−2
16	10	L	Unknown	25 yrs	L MR−LR+ R MR−Faden	1	25	−3
17	25	R	Sarcoidosis	48	nil	2	4	−2
18	18	B	Trauma	40 yrs	nil	2	70	−1
19	25	R	Neuro-fibromatosis	10 yrs	nil	2	40	?
20	54	R	Varicella	10 yrs	nil	2	>45	−3
21	74	B	Polycythemia	50	nil	1	>45	−4
22	58	L	Vascular	24	nil	1	50	−2
23	52	B	RTA	24	R Jensen R MR−	2	90	−4
24	50	B	Cerebellar infarct	15	nil	4	46	−2
25	19	R	Trauma	36	R MR− R transposition R SO tuck L MR−Faden LR+	1	2	?
26	28	R	Hypertension	7 yrs	R LR+ R MR−LR+ L LR+ R Jensen	1	25	−2
27	55	L	Unknown	5 yrs	nil	1	25	−3

Lat Laterality
No. Inj Number of injections
Init Dev Initial deviation in prism dioptres of esotropia
Abd Abduction

although undoubtedly paralysing the medial rectus, will do nothing to alter the natural history. There is also a group of patients with 'surgical' palsies such as those caused by trauma, neurosurgery, and tumours where the natural history is one of loss of function and no recovery. Botulinum toxin in this case will not achieve a functional cure but may be of benefit in minimising contracture and achieving a good result when combined with surgery. There may be a small group between these two where the intervention with Botulinum toxin prevents contracture and sufficient lateral rectus function returns such that relatively normal motility is preserved in a patient who would otherwise have been left with a persistant esotropia. In children, as reported by Magoon and Scott,[13] an injection may be of use to enable binocular single vision to be preserved and obviate the risks in this age group of suppression and amblyopia. A review of available literature looking for all the identifiable cases of sixth nerve palsy treated with Botulinum injection within six months of onset reveals 33 patients.[5,7,8,13,14,15,16] Twenty three (70 per cent) obtained a good outcome with good horizontal rotations and no or minimal esodeviation on cover test. Six required surgery and in four there was a significant residual deviation and further management is not reported. If the period of 'acute' palsy is defined as within two months of onset, fourteen patients are included, eleven (78 per cent) obtaining normal binocular function. The aetiology of the palsies is not specifically stated in 31 of the 33 patients. No attempt is made to compare these results with a control group of similar age, duration and aetiology of palsy to see if the outcome is indeed any better than the natural history. Rush and Younge reported a spontaneous recovery rate of 49.6 per cent in cases of sixth nerve palsy, including patients of all aetiologies. Those patients whose palsies were due to a vascular cause had a recovery rate of 71 per cent.[17]

Table V *Group B no previous surgery*

Case no.	*Age onset*	*Lat*	*Aetiology*	*Duration months*	*Surgery*	*Further surgery*	*Outcome*
28	23	B	Astrocytoma	19	L transposition	Y	poor
29	46	B	Trauma	16	R transposition	Y	satis
30	19	L	Trauma	16	L Jensen	N	satis
31	18	R	RTA	11	R transposition	Y	satis
32	43	B	RTA	9	R transposition	?	poor
33	62	B	RTA	10	R transposition	N	satis
34	66	B	RTA	11	R transposition	Y	poor
35	79	R	Unknown	5 yrs	R transposition	Y	satis
36	50	B	RTA	16	R Jensen MR− L transposition	Y	?
37	37	B	RTA	8	R transposition	Y	?
38	23	R	Astrocytoma	20	R transposition	N	satis
39	61	B	RTA	30	R transposition	N	satis
40	52	L	Unknown	7	L transposition	?	?
41	37	L	Trauma	20	R transposition	?	?

Lat Laterality

Table VI *Group B previous surgery*

Case no.	*Age onset*	*Lat*	*Aetiology*	*Dur*	*Previous surgery*	*Surgery*	*Further surgery*	*Outcome*
42	48	B	Clivus chordoma	29	R Jensen R MR− L MR−	L transposition	N	satis
43	75	B	RTA	40	R MR−LR+ L MR−LR+	L transposition	N	poor
44	18	R	RTA	19	R trans. R MR−	L MR Faden	Y	?
45	37	R	Trauma	4	R LR explore	R transposition	Y	satis
46	20	B	RTA	18	R MR−LR+ R MR−LR+	R transposition	N	satis
47	23	B	RTA	10 yrs	R MR−LR+ L LR+	R transposition R IR−	N	satis
48	15	L	Trauma	16	L trans L MR−	L retransposition	N	satis
49	30	R	RTA	27	R Jensen R MR− L MR− L MR Faden	R retransposition	Y	satis
50	18	R	RTA	23 yrs	R MR−LR+	R transposition	Y	poor
51	24	B	Trauma	48	L MR− R MR−LR+	L transposition	N	satis
52	24	R	RTA	28	R Jensen R MR−	R retransposition	N	satis
53	64	L	vascular	5 yrs	L MR−LR+ R MR−LR+ R Faden	R Jensen	Y	satis
54	28	B	RTA	17	L Jensen L MR−	R Jensen	Y	satis
55	15	L	Trauma	48	L trans L MR−	L retransposition	N	poor

Lat Laterality
Dur Duration of palsy

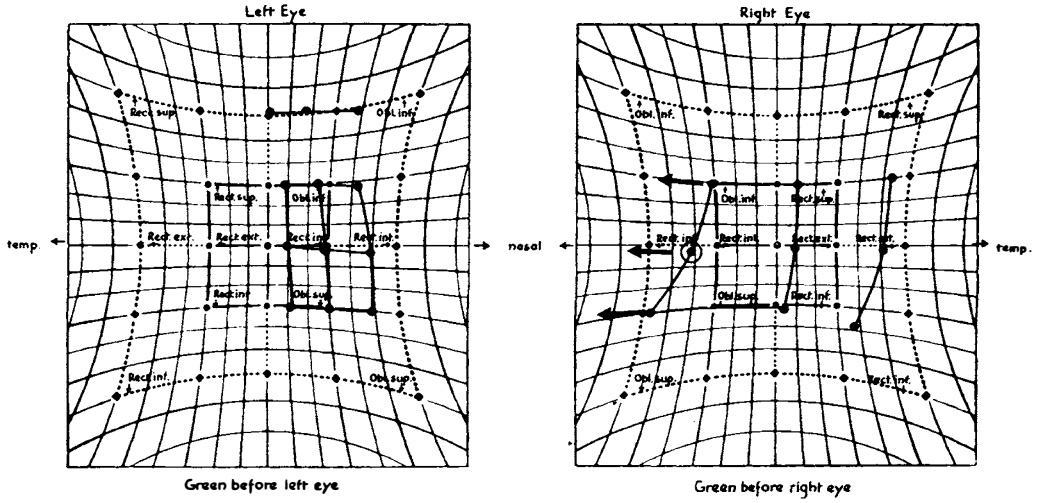

Fig. 4a

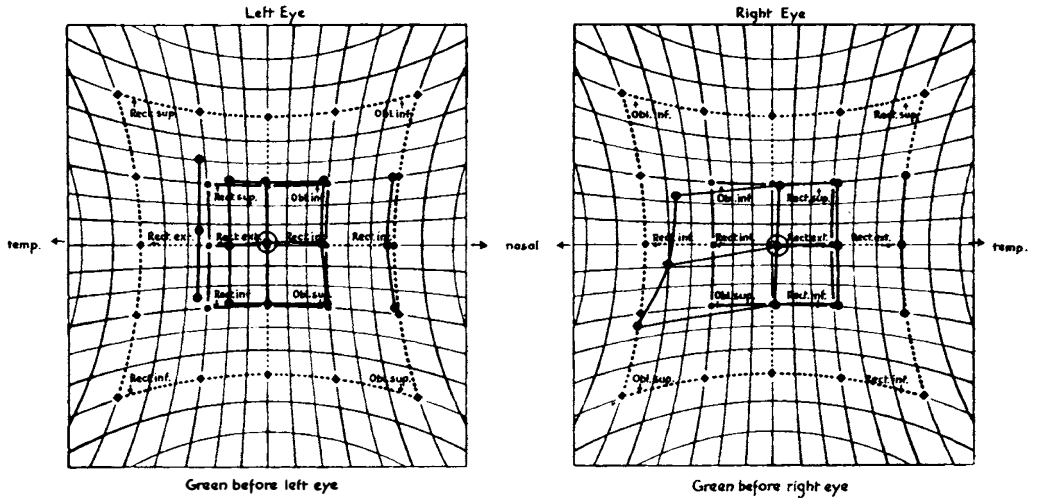

Fig. 4b

Fig. 4. *Patient 30: Hess charts showing 4a initial deviation and 4b final status after combined Botulinum toxin injection and transposition surgery.*

There are a number of disadvantages in treating such patients with toxin early in the course of the disorder. A patient with lateral rectus weakness will usually have an area of single binocular vision which can be utilised by adopting a face turn to the affected side. Paralysis of the medial rectus on this eye brings the eye to a virtually static position close to primary and gives a small field of single vision. Any attempted lateral gaze results in diplopia, reversing on horizontal movement from one side to the other. This situation may well be symptomatically much worse than the original condition. Another potential disadvantage is the masking of developing neuro-ophthalmological signs. Progression of a sixth nerve palsy is often a sign of more sinister aetiology and warrants more intensive investigation than a steadily recovering paresis. Such changes may not be evident following Botulinum injection. It has been shown that established contracture can be relieved by the use of toxin many

months after its onset,[15] obviating the need to inject very early in the course of the palsy. The majority of those in Scott's[15] series in whom contracture was relieved had the palsy for more than six months. The longest duration was 204 months. Further evidence of the ability of toxin to relieve established contracture is present in this study. We have six patients in whom a functional cure was obtained with the use of Botulinum toxin injection alone after seven, eight, 24, 36, 36 and 15 months duration of the palsy, an average of 21 months. There are also 28 patients in whom toxin was used specifically to relieve established contracture prior to surgery. We have no direct evidence in these patients that contracture was present initially, but after such a long period it is an almost universal occurrence.[15] Functional cure in six patients in Group A and the attainment of an exodeviation immediately after surgery in patients in group B both strongly imply that contracture has been relieved. In view of the successful results in some patients injected after prolonged periods following the onset, it would seem worthwhile to consider an injection for any patient with an unrecovered sixth nerve palsy. The majority of sixth nerve palsies that will fully recover do so within three months,[18] thus injection any time after this period would be reasonable. In an attempt to identify features in the patients in Group A that would indicate a better prognosis for a functional cure we have compared laterality, traumatic aetiology duration, previous surgery, initial deviation and abduction (see Table VII). It can be seen that those who obtained a functional cure were more often unilateral, non-traumatic, of shorter duration and had less previous surgery. The initial deviation and abduction deficit were similar in the two groups. The duration of the palsy was shorter in the functional cure group and this difference is significant according to the Wilcoxon rank sum test ($p<0.01$). None of the other parameters can be demonstrated to have a statistically significant difference in this study. Exceptions are apparent to each of these features and as shown by case nine who had a palsy for seven years and had previous surgery whilst still gaining a good result. It seems worthwhile to consider an injection in these patients, accepting that, depending on referral bias, perhaps only a third will achieve a functional result.

Table VII *Comparison of patients in Group A*

	Functional cure 10		*Botulinum Toxin unhelpful 15*	
Unilateral	9	(90%)	10	(66%)
Traumatic	1	(10%)	5	(33%)
Duration				
>3 years	1	(10%)	8	(54%)
<3 years	9	(90%)	7	(46%)
<1 year	5	(50%)	1	(6%)
Previous surgery	1	(10%)	4	(26%)
Initial Deviation (average)	46		45	
Abduction (average)	−2.6		−2.7	

The use of Botulinum toxin as a diagnostic procedure has been reported by Ketley.[19] It can be used in patients with sixth nerve palsy both to assess residual lateral rectus function, although this is usually reliably determined by clinical assessment and saccadic velocities, and also to enable assessment of binocular function, particularly following head trauma where disruption of fusional ability is known to occur.[20]

We have illustrated the use of toxin in patients unfit for surgery under general anaesthetic. This situation is directly comparable to other situations in which an ocular deviation is altered by Botulinum toxin and undoubtedly is a small but important indication for its use.

Our experience using Botulinum toxin in combination with vertical transposition muscle surgery is reported elsewhere in detail.[21] It is at least as effective as more conventional management, and offers advantages in adults of using the most effective procedure to produce abduction, minimal risk of anterior segment ischaemia, maximal preservation of horizontal range, more accurate alignment by subsequent use of adjustable sutures and easier reoperation if necessary. Fifty per cent of these patients will require further surgery, probably more than this if there has been no previous surgery performed. In this group of patients whose complete unrecovered sixth nerve palsies present significant management problems, a satisfactory outcome was achieved in the majority using this approach. Compli-

cations have been reported with the use of Botulinum toxin,[3] but all reports of its use confirm the complete absence of systemic side-effects and minimal ocular morbidity. We also observed no systemic effects. We had no potentially serious ocular complications such as ocular perforation or retrobulbar haemorrhage. We observed ptosis in five cases, vertical muscle involvement in four cases and a number of subconjunctival haemorrhages. All were transient, recovered fully and did not appear to affect the outcome. The overall incidence of complications was 10 per cent.

Conclusion

Botulinum toxin injection of the antagonist medial rectus in patients suffering from sixth nerve palsy is a useful adjunct to conventional management. Its role in prevention of contracture in the acute phase is unproven and warrants controlled prospective investigation. A significant number of patients may achieve a functional cure with this treatment alone and thus avoid surgery completely. It is not possible accurately to predict which patients will respond but in view of the consistently reported safety of this procedure, it is probably worthwhile trying a single injection in most cases. The most common indication for use of Botulinum toxin in our series was in combination with transposition surgery for cases of complete unrecovered palsy. In these patients it has significant advantages over conventional management.

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