

# Effectiveness of Botulinum Toxin Administered to Abolish Acquired Nystagmus

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We injected botulinum toxin into the horizontal rectus muscles of the right eyes of 2 patients who had acquired pendular nystagmus with horizontal, vertical, and torsional components. This treatment successfully abolished the horizontal component of the nystagmus in the injected eye in both patients for approximately 2 months. Both patients showed a small but measurable improvement of vision in the injected eye that may have been limited by coexistent disease of the visual pathways. The vertical and torsional components of the nystagmus persisted in both patients. In 1 patient, the horizontal component of nystagmus in the noninjected eye increased; we ascribe this finding to plastic-adaptive changes in response to paresis caused by the botulinum toxin. Such plastic-adaptive changes and direct side effects of the injections—such as diplopia and ptosis—may limit the effectiveness of botulinum toxin in the treatment of acquired nystagmus. Neither patient elected to repeat the botulinum treatment.

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Patients with acquired nystagmus due to neurological disorders, such as multiple sclerosis, often complain of impaired vision and the illusion of movement of their environment (oscillopsia) [1]. These symptoms interfere with reading and watching television, and the oscillopsia may be distressing to the patient. The visual consequences of acquired nystagmus are due to excessive drift of images of stationary objects on the retina; if such retinal image drift can be reduced, then oscillopsia is usually abolished and vision is improved [2].

A number of measures have been tried to suppress acquired types of nystagmus, including prisms and other optical devices [1, 2], as well as a variety of medications [1, 3]. Although these treatments may work in individual patients, none has been uniformly effective. Recently, botulinum A toxin, injected either into the extraocular muscles [4] or into the retrobulbar space [5], has been reported to suppress nystagmus and to improve vision in a few patients; however, no measurements of eye movements were made in these studies. Botulinum toxin is now generally available to ophthalmic and neurological practitioners for treatment of a variety of disorders [6, 7] and is being used for treatment of nystagmus. Thus, there is a need for a quantitative study of the effects of botulinum toxin in the treatment of acquired nystagmus.

We report herein the results of serial measurements from 2 patients with acquired pendular nystagmus prior to, and for 3 months after, injection of botulinum. Our strategy was to select the extraocular muscles best suited for selective injection with botulinum on the basis of measurements of the nystagmus in three planes (horizontal, vertical, torsional). We then compared the changes of the nystagmus amplitude in all three planes with those of the noninjected eye.

## Patients and Methods

Patient 1 was a 27-year-old woman who had been diagnosed as having multiple sclerosis 6 years previously. Her presenting complaint was oscillopsia due to pendular nystagmus. Since diagnosis, the nystagmus had gradually become worse so that she had difficulty reading from her computer screen at work. She had tried a variety of medications for her oscillopsia, without improvement. Other symptoms included episodes of sensory disturbance in her legs and progressive instability while standing or walking. Magnetic resonance imaging showed changes consistent with a diagnosis of multiple sclerosis.

On examination, her corrected visual acuity at distance was 20/40<sup>+2</sup> in the right eye (OD) and 20/70 in the left eye (OS). She was myopic and required  $-0.50$  diopters OD and  $-0.37$  diopters OS for correction. Corrected near visual acuity was J1 + OD and J1 OS, measured at a viewing distance

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of 10 inches and holding the test card in down-gaze. With an optical stabilization device that consisted of a positive spectacle lens worn in combination with a negative contact lens [2], her distance acuity was 20/25<sup>-1</sup> OD and 20/50<sup>-2</sup> OS. She had tried to use this device on a day-to-day basis, but was unable to tolerate the contact lenses. Her visual fields were full, and she correctly identified all Ishihara color plates with both eyes. Her pupillary reactions to light were symmetrical, but there was some pallor of both optic nerve heads. She had pendular nystagmus with an elliptical trajectory (Fig 1) that was of small amplitude but high frequency (approximately 4.3 Hz). It had horizontal, vertical, and torsional components and was more prominent in her left eye. The nystagmus was decreased mildly in down-gaze but not affected by convergence. She was able to draw the trajectory of her oscillopsia as she viewed a light-emitting diode in a dark room (see Fig 1); in both eyes, oscillopsia was elliptical, but in the right eye, the horizontal component was larger.

Patient 2 was a 35-year-old woman with a mild congenital disorder of hearing and speech who was diagnosed as having multiple sclerosis 4 years prior to our studies. Her initial symptoms were clumsiness and weakness. She had impaired vision due to optic nerve demyelination in both eyes that was worse in the left eye. Onset of oscillopsia was gradual; it became prominent approximately 1 year prior to her being studied. Besides her visual symptoms, her main disabilities were limb and truncal ataxia and a spastic paraparesis, for which she took dantrium (25 mg twice daily) throughout the study.

On examination, visual acuity at distance was correctable to 10/40<sup>+2</sup> OD and 10/100 OS. She was myopic and required -4.75 diopter corrections, bilaterally. Her best near visual acuity was J2 OD and J10 OS, measured at a viewing distance of 7 inches, without correction. With an optical stabilization device [2], her distance acuity improved to 20/40<sup>+2</sup> OD and 20/50 OS. Her visual fields showed mild constriction of peripheral isopters, more so in the left than in the right eye. Using the American Optical color plates, she could identify the 6 highest contrast plates with her right eye, but only 2 of these 6 with her left eye. Both optic nerve heads showed pallor, more so on the left. A relative afferent pupillary defect to light stimulation was present in the left eye. Her pendular nystagmus was principally horizontal and was of larger amplitude in the left eye (Fig 2). Its frequency varied between 5.0 and 5.9 Hz. The amplitude of the nystagmus increased in far left gaze and decreased in far right gaze but was not appreciably influenced by convergence. In addition, she had a mild right internuclear ophthalmoparesis. Exodeviation of 20 diopters and right hyperdeviation of 3 diopters were present at near when she was tested by the Maddox wing method. When she drew the trajectory of her oscillopsia (see Fig 2), it was horizontal in both eyes but was smaller and more intermittent in the right eye.

Both patients gave informed consent for the eye movement measurements and botulinum injections, and the protocol was approved by our Institutional Review Board.

#### *Eye Movement Measurements*

Horizontal, vertical, and torsional rotations of both eyes and the head were recorded using the magnetic search coil tech-

nique [2, 3, 8]. With their heads restrained, the patients faced a projection screen located at a viewing distance of 1.3 meters. First, they attempted steady fixation of a small spot located at the center of an Amsler grid that was rear-projected onto the screen. During separate 15-second trials, they viewed the target binocularly and then monocularly with each eye. During subsequent trials, nystagmus was measured while the patients maintained different gaze angles around the edge of the Amsler grid, which subtended  $\pm 10$  degrees, and at targets located at 30-degrees' eccentricity. In addition, we measured horizontal and vertical saccades made between fixed target locations and horizontal and vertical smooth pursuit as they followed a small target moving sinusoidally through  $\pm 15$  degrees at 0.3 Hz. Stability of gaze was also measured while the patients made active horizontal or vertical head rotations in darkness. Data were filtered (bandwidth, 0-90 Hz) prior to digitization at 200 Hz. Analysis was performed using interactive programs written in the ASYST language [9]. Epochs of 5 to 10 seconds of the oscillations (during attempted fixation) that were free of saccades and blinks were analyzed, and, based on 20 estimates, the mean amplitude of nystagmus in each plane was calculated for each fixating eye. Saccadic pulse gain, smooth-pursuit response gain, and compensatory eye movement gain during head rotations were also determined [1].

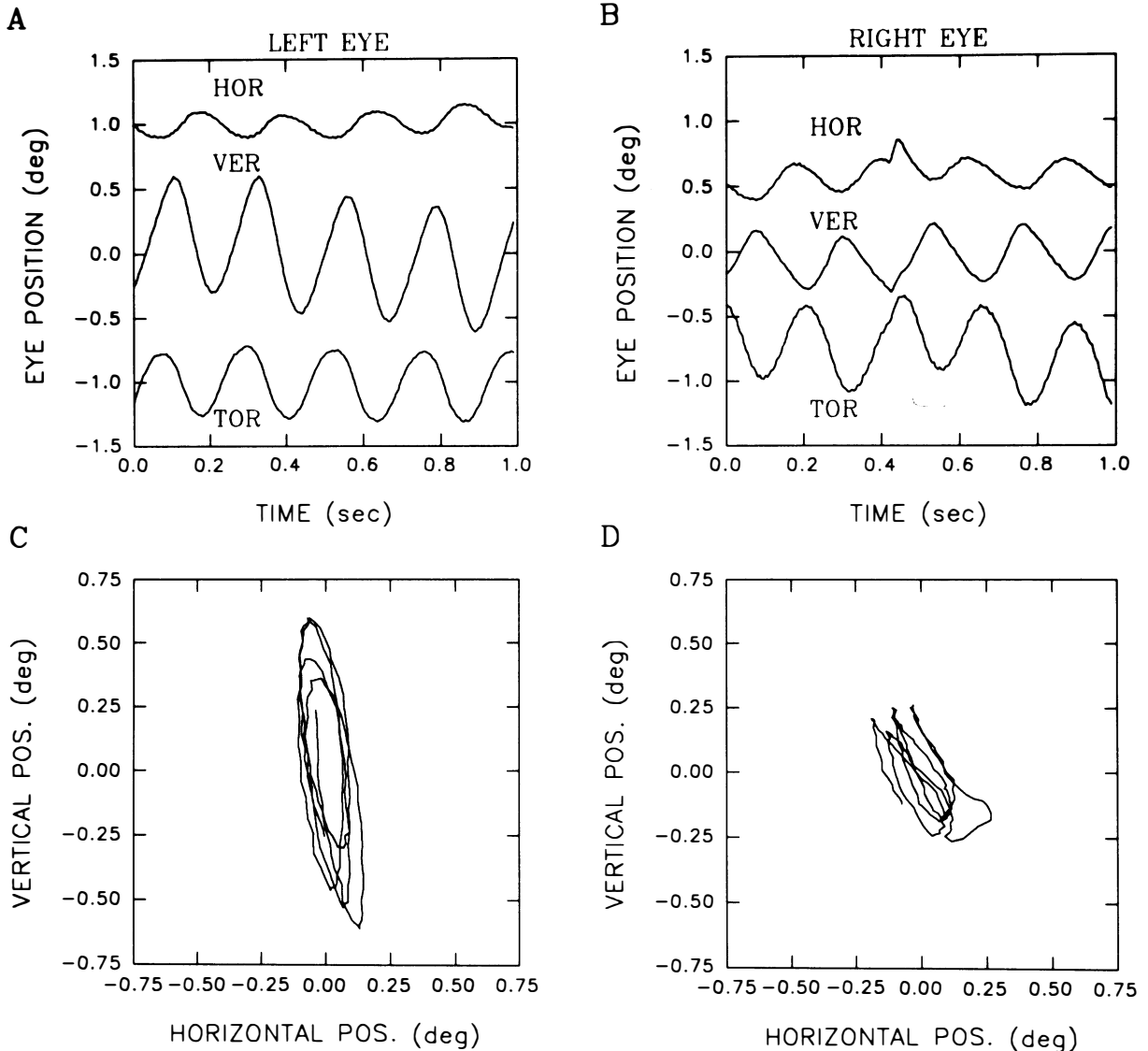
#### *Injection Procedure*

We selected the eye with better visual acuity; for both patients this was the right eye. In Patient 1, the predominant component of her elliptical oscillopsia was in the horizontal plane. In Patient 2, oscillopsia was almost entirely horizontal. Accordingly, we injected botulinum A toxin (3 U in 0.1 mL/muscle) into the lateral and medial rectus muscles of the right eye of both patients under electromyographic control [6, 10]. Prior to injection, a topical anesthetic was applied. In Patient 1, the injections were made in two stages: first, into the right lateral rectus muscle, and, 2 weeks later, into the right medial rectus muscle. In Patient 2, both right medial and lateral rectus muscles were injected during one session.

## **Results**

### *Patient 1*

One week after injection of the right lateral rectus muscle and prior to injection of the right medial rectus muscle, 28 diopters of esotropia developed. We recorded her eye movements again at this time, and found that the amplitude of her nystagmus was little changed, even in the right field of gaze. From the time of her first injection she chose to view either binocularly or, during visually demanding tasks, she patched her left eye. One week after the second injection, she reported that the horizontal component of oscillopsia in her right eye was abolished, but that a vertical component persisted and was more annoying than the original elliptical trajectory. Visual acuity at distance had improved in her right eye to 20/25<sup>-3</sup>, and near acuity, measured in the same way as prior to injection, was unchanged. Eye movement recordings confirmed that the horizontal component of her nystagmus was essen-



O.S.

O.D.

VISUAL ACUITY

20/70

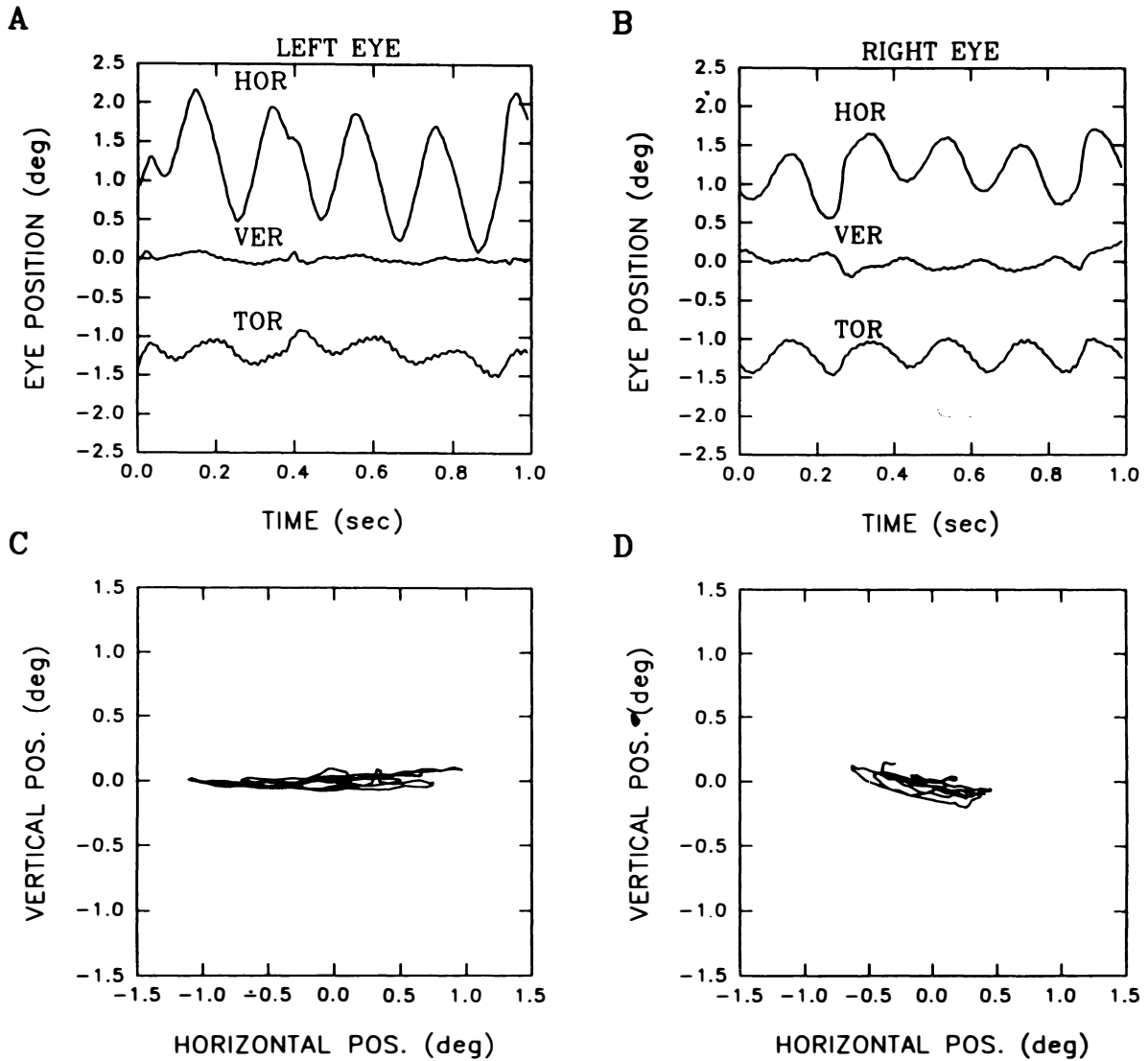
20/40<sup>+2</sup>

OSCILLOPSIA



Fig 1. Characteristics of the nystagmus of Patient 1 prior to injection of the right eye with botulinum toxin. In (A) and (B), time plots of nystagmus of the right and left eyes are shown, respectively. Note that each record was made when that eye was viewing the central target. The horizontal (HOR) and torsional (TOR) records have been offset from the vertical (VER) record for convenience of display. Upward deflections correspond to

rightward, upward, or clockwise eye rotations, with respect to the patient. In (C) and (D), the scan path of each eye in the horizontal and vertical planes corresponding to the time plot above is shown. The scan path of the left eye has a larger vertical component than that of the right eye. Note how the scan paths correspond to the direction of oscillopsia reported subjectively by the patient. (O.S. = left eye; O.D. = right eye.)



	O.S.	O.D.
<b>FAR ACUITY</b>	10/100	10/40 <sup>+2</sup>
<b>NEAR ACUITY*</b>	J 10	J 2
<b>OSCILLOPSIA</b>	—	—

Fig 2. Characteristics of the nystagmus of Patient 2 prior to injection of the right eye with botulinum toxin. The conventions are similar to those used for Figure 1. The scan path shows that the predominant component is horizontal in both eyes. The patient reported horizontal oscillopsia, which was intermittent in the right eye.

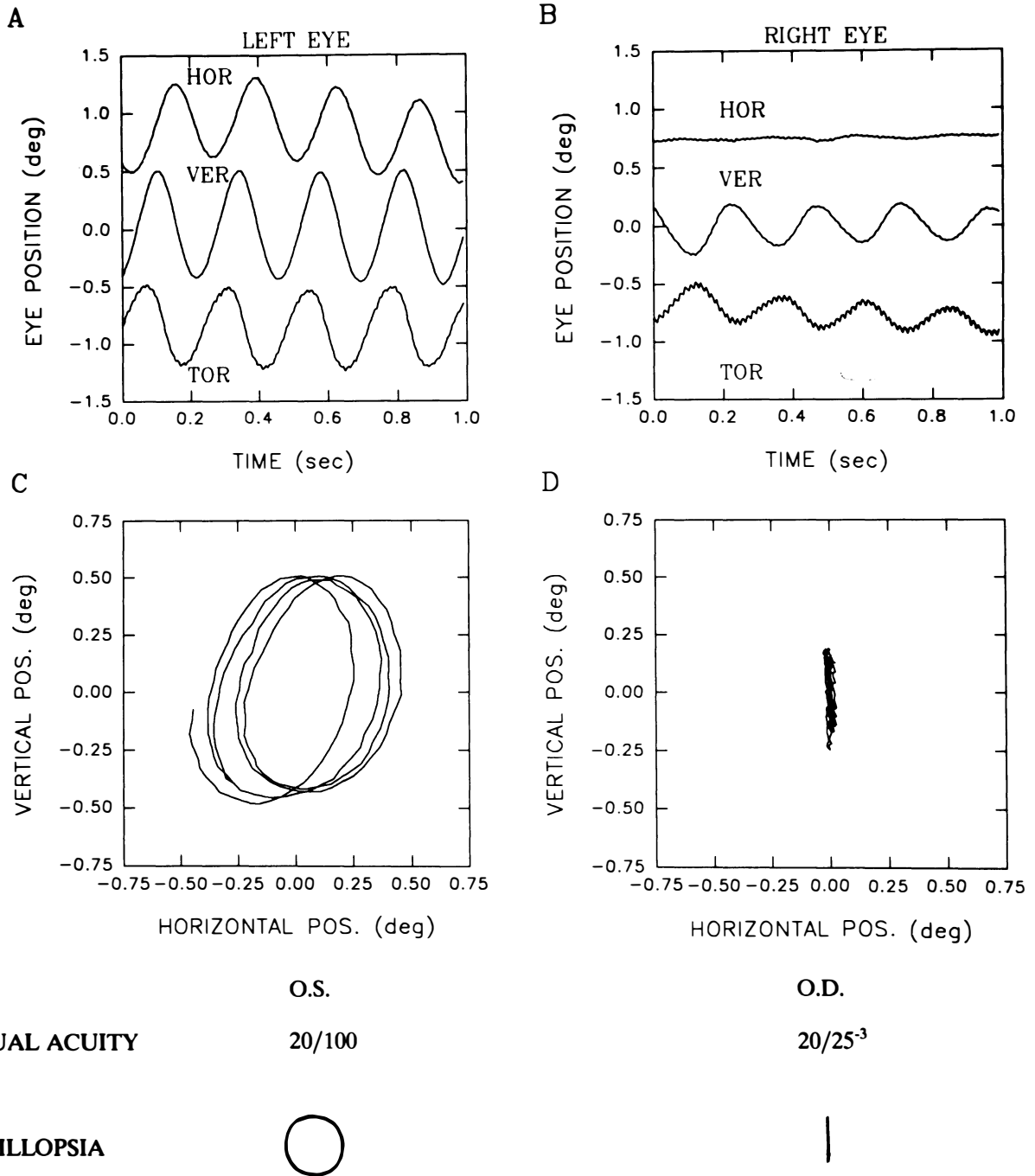


Fig 3. (A–D) Characteristics of the nystagmus of Patient 1 one week after injection of the right medial rectus muscle and 2 weeks after injection of the right lateral rectus muscle. The conventions are similar to those used for Figure 1. Note that the horizontal component of nystagmus in the right eye has been nearly abolished and that visual acuity has increased in this eye. The amplitude of the horizontal component of nystagmus in the left, noninjected eye has increased, however, and visual acuity in this eye has decreased.

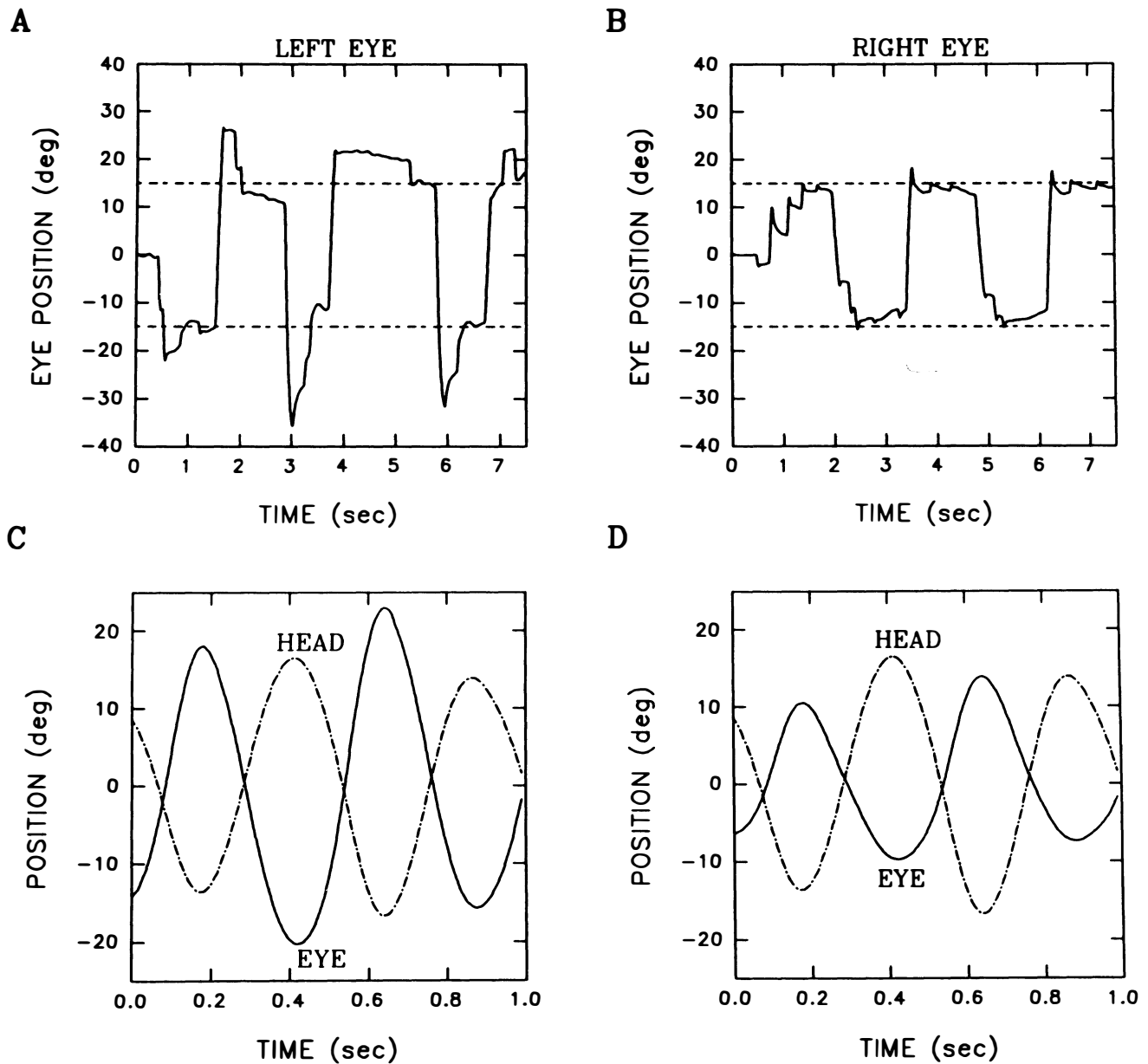
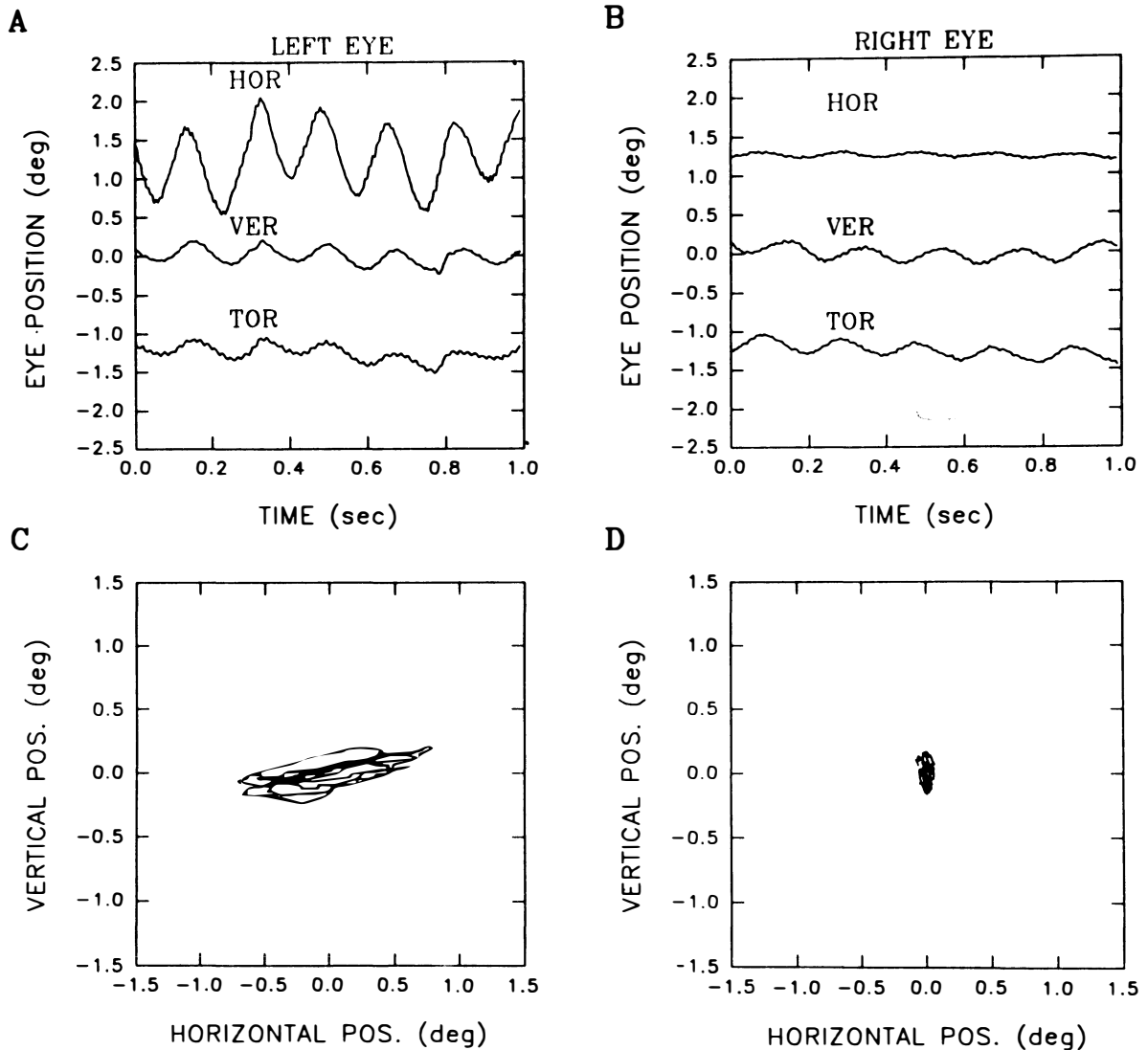


Fig 4. Horizontal eye movements of Patient 1 two weeks after the second injection of botulinum into the right horizontal rectus muscle. Upward deflections correspond to rightward movements. In (A) and (B), saccades made to targets located  $\pm 15$  degrees from the midline (broken lines) are shown. When the patient viewed with her right eye (B), saccades were generally hypometric, with dynamic overshoots. Following saccades to the eccentric target, the eye drifted back, requiring a corrective saccade. When she viewed with her left eye (A), there was pronounced saccadic hypermetria. In (C) and (D), compensatory eye movements during active horizontal head rotations in darkness are shown. The same time segment of head position (HEAD) is shown in both. It is evident that the compensatory movements (EYE) of the left eye (C) exceeded those of the right eye (D) by more than 50%.





	O.S.	O.D.
<b>FAR ACUITY</b>	10/100	10/40 <sup>+3</sup>
<b>NEAR ACUITY</b>	J 7	J 1+
<b>OSCILLOPSIA</b>		

Fig 5. Characteristics of the nystagmus of Patient 2 one week after injection of the right medial and lateral rectus muscles. The conventions are similar to those used for Figure 1. Note that the horizontal component of nystagmus in the right eye has been nearly abolished and that visual acuity for near objects has improved. The intermittent oscillopsia in the right eye has disappeared. The amplitude of the horizontal component of nystagmus in the left eye has also decreased slightly, but the vertical component has increased; oscillopsia in the left eye, however, was unchanged.

Comparison of Amplitudes of Nystagmus Components Before and After Botulinum Injection<sup>a</sup>

	Patient 1				Patient 2			
	Left Eye		Right Eye (injected)		Left Eye		Right Eye (injected)	
	Before	After	Before	After	Before	After	Before	After
Horizontal	0.18 (0.02)	0.58 (0.12)	0.20 (0.06)	0.04 (0.02)	1.66 (0.20)	0.96 (0.12)	0.75 (0.08)	0.08 (0.03)
Vertical	0.95 (0.07)	0.79 (0.26)	0.39 (0.05)	0.28 (0.10)	0.10 (0.04)	0.28 (0.05)	0.20 (0.04)	0.21 (0.06)
Torsional	0.59 (0.04)	0.63 (0.07)	0.62 (0.07)	0.28 (0.08)	0.32 (0.04)	0.23 (0.04)	0.39 (0.06)	0.23 (0.03)

<sup>a</sup>Data are mean, peak-to-peak amplitudes (standard deviation in parentheses), in degrees, measured during one session prior to injection and during one session 1 week after injection of both the horizontal rectus muscles. Note that measurements were made when each eye was attempting to fixate a target at primary position.

tially abolished (Fig 3); smaller declines in the vertical and torsional components also occurred. At this time (1 week after the second injection), an exotropia of 9 diopters was present in primary position, but the range of voluntary movement in her right eye was nearly full. Over the next 2 weeks, she became orthophoric, as demonstrated by the alternate cover test. No ptosis was produced, but a subconjunctival hemorrhage followed injection of the lateral rectus muscle.

These findings contrasted with changes produced in her left (noninjected) eye. One week after the second injection, she reported that oscillopsia had increased in the left eye. Visual acuity in her left eye at distance had decreased to 20/100 and at near to J2<sup>-1</sup>. This deterioration was probably due to a three-fold increase in the amplitude of the horizontal component of nystagmus in her left eye (see Fig 3; Table). The amplitude of the vertical component of her left eye decreased slightly, and the torsional component was unchanged.

Prior to injection, horizontal saccades of both eyes showed normal velocities and mild hypometria. Two weeks after the second injection, most horizontal saccades of the right eye were hypometric, but with dynamic overshoots (Fig 4B); average saccadic pulse gain was 0.9. Saccadic velocity was mildly decreased. Following each saccade to an eccentric target, a centripetal drift occurred. In the noninjected eye, saccades were of normal velocity but were consistently hypermetric, with a typical saccadic pulse gain of 1.6 (Fig. 4A). Horizontal smooth-pursuit gain of the right eye, while it was viewing, was 0.46, but of the left, while it was viewing, was 0.84. The gain of compensatory eye movements during horizontal head rotations in darkness was 0.65 for the right eye (Fig 4D) but 1.23 for the left eye (Fig 4C). Differences between saccadic, pursuit, and vestibular movements of the right and left eyes in the vertical plane were less than 20%.

The horizontal component of the patient's nystagmus started to return to the right eye approximately 6 weeks after the second injection, and at 3 months her nystagmus and visual function were almost back to the state prior to injection. As the horizontal component

of the nystagmus returned, the gain of saccadic, pursuit, and vestibular movements of the left eye declined. Overall, Patient 1 reported that the benefits of the botulinum injections were offset by the persistent vertical oscillopsia and worsening of vision in her noninjected eye. She would only consider the possibility of further treatment if the injections could abolish both horizontal and vertical components of her oscillopsia in both eyes.

*Patient 2*

One week after the injections, Patient 2 showed an exotropia of approximately 20 diopters and a right hypertropia of 12 diopters; however, she reported only occasional diplopia. She chose to view binocularly and did not patch her left eye. Her best visual acuity at near had improved in her right eye to J1+, but corrected distance vision was essentially unchanged. The intermittent horizontal oscillopsia in the right eye had disappeared. Eye movement recordings confirmed that with the right eye close to primary position, the horizontal component of her nystagmus was nearly abolished (Fig 5); a small decline in the torsional component also occurred. The range of voluntary movement in her right eye was almost full for abduction but limited to approximately 15 degrees of adduction. When the patient attempted to fully adduct the right eye, the horizontal component of the nystagmus partially returned, but in other gaze angles it was absent. A mild ptosis (approximately 3 mm) was produced in the right eye, but resolved by 2 months.

The left (noninjected) eye showed a 40% decline in the amplitude of its horizontal component after injection of the right eye; the vertical component showed a slight increase and the torsional component was unchanged (see Table). She reported no change in the oscillopsia in the left eye. Her best visual acuity in her left eye had improved slightly at near to J7, but corrected distance vision was unchanged at 10/100 (see Figs 2 and 5).

Prior to injection, horizontal saccades showed changes consistent with a mild right internuclear oph-



thalmoparesis; most saccades were mildly hypometric or normometric. One week after the injections, saccades of the right eye made into the restricted, left field of gaze were very slow (< 50 degrees/sec); other horizontal saccades were mildly slowed and showed mild hypometria (typical saccadic pulse gain: 0.8–1.0), with some dynamic overshoots. Following saccades to eccentric targets, especially in the left field of gaze, a centripetal drift occurred. In the noninjected eye, horizontal saccades showed normal velocity; leftward saccades were consistently hypermetric (typical saccadic pulse gain of 1.5), but rightward saccades were mildly hypometric. Horizontal smooth pursuit was not developed enough for a reliable comparison to be made between the two eyes. However, the gain of compensatory eye movements during horizontal head rotations in darkness was between 0.75 and 1.0 for the right eye (for leftward and rightward eye movements, respectively), but was 1.5 for the left eye. Differences between saccadic and vestibular movements of the right and left eyes in the vertical plane was less than 10%.

The horizontal component of the patient's nystagmus started to return to the right eye approximately 2 months after the second injection and, at the same time, her deviation resolved. By 3 months, her nystagmus and visual function were almost back to the state prior to injection. As the horizontal component of the nystagmus returned, the gain of saccadic and vestibular movements of the left eye declined. Overall, Patient 2 thought that the benefits of the botulinum treatment were marginal, and she preferred to try other possible treatments for her visual symptoms.

### Discussion

These quantitative measurements indicate that injection of botulinum toxin into selected extraocular muscles may temporarily abolish nystagmus while largely preserving control of voluntary movements. In both patients, abolition of the horizontal component of nystagmus resulted in disappearance of horizontal oscillopsia and modest improvement in vision. The extent of visual improvement was limited, however, especially in Patient 2, by coexistent disease of the visual pathways. Furthermore, some variability of measurements of visual acuity is encountered in patients with demyelination of the optic pathways. Importantly, neither patient wanted to repeat the injection of their horizontal rectus muscles.

One drawback of botulinum treatment of nystagmus not previously noted is that movements in the noninjected eye may become worse. In Patient 1, the nystagmus itself increased in the noninjected eye, causing a decline in the vision of that eye. How could this exacerbation of nystagmus be explained? Possible clues were (1) saccadic, smooth-pursuit, and vestibular

movements of the noninjected eye all showed increases in gain; (2) these gain changes were restricted to the horizontal plane; (3) the patient viewed either binocularly or with the injected eye; and (4) our measurements were made when the eye in question was fixating or when the patient was in darkness, therefore excluding "open-loop" and "secondary deviation" mechanisms.

On the basis of these lines of evidence, we postulate that plastic-adaptive changes of saccadic, smooth-pursuit, and vestibular eye movements, similar to those reported with clinical or experimental palsy of extraocular muscles, had occurred [11–13]. It also seemed possible that the increase of the horizontal component of nystagmus in the noninjected eye of Patient 1 was due, in some way, to these plastic-adaptive changes. Patient 2, however, showed no increase of the horizontal component of nystagmus in her noninjected eye, even though she showed increased gain of saccadic and vestibular movements. Therefore, more studies are required to determine the relationship between acquired pendular nystagmus—an oscillation caused by a variety of processes [1]—and the plastic-adaptive mechanisms that respond to ocular motor paresis. Whatever this relationship, plastic-adaptive changes induced by extraocular paresis need to be taken into account when planning botulinum treatment of acquired nystagmus; one possible strategy might be injection of selected muscles of both eyes.

The movements of the injected eye (see Fig 4B) exhibited the same combination of hypometria with dynamic overshoots and gaze-holding failure seen in eyes affected by myasthenia gravis [14–16] or the Lambert-Eaton myasthenic syndrome [17]. The movements of the noninjected eye (Fig 4A) exhibited hypermetria similar to that encountered in these neuromuscular diseases after administration of edrophonium chloride, which reveals an adaptive increase in central gain to compensate for the extraocular paresis. Thus, although the muscle weakness due to botulinum toxin, myasthenia, and Lambert-Eaton syndrome are due to different mechanisms at the neuromuscular junction, the plastic, central gain changes and resulting eye movements are similar. This constellation of metric and trajectory disorders, especially the presence of dynamic overshoots, is not found in nerve palsies despite the fact that the resulting hypometria also results in an increase in central gain. This discrepancy might be due to differential effects of disorders of the neuromuscular junction on gamma and alpha motoneuron systems [14–18]. Although the role of extraocular proprioception has been in doubt, recent studies suggest that it does contribute to the control of eye movements [19].

In this study, we selected muscles corresponding to one plane of eye rotation for injection so we could compare the effects produced in this plane (horizontal)

with those in the other two (vertical and torsional). Although we abolished the horizontal component of oscillopsia in the injected eye of both patients, Patient 1 found the residual vertical oscillopsia more annoying than the original elliptical oscillopsia. Selective injection of vertically acting muscles with botulinum is possible; however, either this or retrobulbar injection may produce ptosis [4, 5]. Retrobulbar injection of relatively large amounts of botulinum toxin (typically 25 U) depends on diffusion of the solution into all extraocular muscles, a process that is less controlled than injection of individual muscles. We arbitrarily chose the dose of 3 U/muscle based on results of botulinum treatment of strabismus [6, 10]; smaller doses might have a similar effect, but we have not yet had the opportunity to establish a dose-response relationship in patients with nystagmus. It appears from experimental studies [20] that the medial rectus muscle may be more susceptible to the effects of botulinum toxin than the lateral rectus muscle; this was the case in our patients, both of whom developed exotropia.

How does botulinum compare with drug and optical treatments for acquired nystagmus? Drug therapies are truly effective in only a minority of patients [1, 3]. An optical device, consisting of a high-positive spectacle lens worn with a high-negative contact lens does abolish nystagmus and improve vision in most patients [2, 21], but in both of our patients, it proved impracticable because of discomfort (Patient 1) or ataxia that prevented insertion of the contact lens (Patient 2). In comparison to these methods, botulinum toxin may prove superior in selected patients with acquired nystagmus, especially those in whom only minor disease of the visual pathways coexists. Furthermore, if the injection does produce unwanted side effects (such as diplopia), they are likely to be temporary, which is not the case for surgical procedures [22]. The limitations of botulinum treatment include diplopia, ptosis, and the potential for inducement of plastic-adaptive changes of the noninjected eye, as well as the need for repeated injections. These factors need to be weighed against the variable visual improvement that can be achieved by abolishing nystagmus.

In conclusion, the role of botulinum toxin in the treatment of acquired nystagmus has yet to be established by further studies using reliable measurements of eye movements and visual function.

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