Effects of Extraocular Muscle Tenotomy on Congenital Nystagmus in Macaque Monkeys

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Introduction: Extraocular muscle tenotomy has been reported to damp congenital nystagmus in an achiasmatic sheepdog. We performed extraocular muscle tenotomy to evaluate its effects on congenital nystagmus in primates. ***Methods:*** Magnetic search coil eye movement recordings were used to document the presence of horizontal congenital nystagmus in 2 adult macaque monkeys that also had naturally occurring infantile strabismus. Extraocular muscle tenotomy was performed by operating on all 4 horizontal recti, surgically detaching the muscles from the globe and suturing them back to their original insertions without resection or recession. Eye movement recordings were repeated 4 months after the procedure, comparing the waveform, amplitude, retinal slip velocity, and intensity (frequency $\times$ amplitude) of the nystagmus before and after tenotomy. Visual acuity was also measured before and after surgery in 1 animal. ***Results:*** Preoperatively, a disconjugate, pendular nystagmus was evident in 1 monkey, and the other had a conjugate pendular-jerk nystagmus damped by convergence. After tenotomy, nystagmus mean amplitude decreased 18% to 52% in 1 monkey but increased 14% in the other (*t* test, $P < .002$). Retinal slip velocity and nystagmus intensity increased in both monkeys. After tenotomy, mean velocity increased 22% to 218%, while mean intensity increased 40% to 208% (*t* test, $P < .002$). Visual acuity measured after tenotomy decreased an average of 20% ($\sim$ 2.0 cycles per degree) in each eye. Tenotomy had no noteworthy effects on eye alignment or other aspects of visual behavior other than the congenital nystagmus. ***Conclusion:*** Nystagmus velocity and intensity increased after extraocular muscle tenotomy in 2 monkeys. Further studies are required to establish the clinical value of this procedure as a treatment for various subtypes of congenital nystagmus in humans. (J AAPOS 2002;6:100-7)

Extraocular muscle tenotomy has been reported to damp congenital nystagmus in an achiasmatic Belgian sheepdog.[1] In the procedure, all 4 horizontal rectus muscles are tenotomized and reattached to their original insertions, without resection or recession. We performed extraocular muscle tenotomy in 2 macaque monkeys to assess its effects on congenital nystagmus in primates.

ANIMALS

Two macaque monkeys, a *Macaca nemistrina* (animal HD) and a *Macaca mulatta* (animal PY), were documented by R. G. Boothe at the Yerkes Primate Center in Atlanta, Ga, to have nystagmus and natural strabismus at 3 to 6 weeks of age.[2] At adulthood, the monkeys were shipped to Washington University in St Louis, where they were trained to fixate small tracking targets by using a positive-feedback reward (a squirt of juice). The experimental protocol was approved by the Washington University Animal Studies Committee.

Preoperative monocular visual acuity measured with spatial sweep visually evoked potentials (VEPs) (without correction for refractive error) documented equal, mildly subnormal vision in both eyes of both monkeys (Table).[3,4] Normal monkeys in our laboratory typically achieve spatial sweep VEP acuities greater than 15.0 cycles per degree (cpd).[5] Cycloplegic refraction revealed anisometropia in both animals. Monocular VEPs obtained with a flash stimulus and an array of electrodes across the occiput showed no signs of albinism or achiasma.[6-8] Funduscopic examinations revealed no evidence of optic neuropathy, foveal hypoplasia, or stigmata of ocular albinism. Automated single-cover tests with liquid crystal shutter goggles documented a moderate-angle esotropia in monkey HD and a moderate-angle exotropia in monkey PY (Table).[9] Both monkeys preferred to fixate with their right eyes (they resembled humans with strabismus and nystagmus who often display a fixation preference or a dominant eye but lack acuity decrements sufficient to label them amblyopic in the nonpreferred eye). In addition to the strabismus and

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TABLE. Clinical features of 2 macaque monkeys with congenital nystagmus

Animal label	HD	PY
Species	*M. nemistrina*	*M. mulatta*
Age/sex	10 y/male	5 y/male
Preoperative sweep VEP acuity	9.06 cpd RE	10.98 cpd RE
	9.52 cpd LE	9.39 cpd LE
Postoperative sweep VEP acuity	Not tested	9.13 cpd RE
	Not tested	7.32 cpd LE
Refractive error	+1.50 + 1.50 × 120 LE	+1.00 + 1.00 × 135 RE
	+3.00 + 1.00 × 105 LE	−1.25 + 0.75 × 45 LE
Eye alignment	LET 12.9°	LXT 10.8°
	LHT 1.6°	LHT 0.2°
Age of onset of nystagmus	3-6 weeks	3-6 weeks
Nystagmus waveform	Pendular horizontal and vertical	Pendular-jerk horizontal
Latent nystagmus	Yes	Yes
Pursuit/OKN asymmetry	Yes	Yes
Motion VEP asymmetry	Yes	Yes

Cpd, cycles per degree; *RE,* right eye; *LE,* left eye; *ET,* esotropia; *XT,* exotropia; *HT,* hypertropia.

congenital nystagmus, the monkeys displayed, under conditions of monocular viewing, mild latent nystagmus, nasotemporal asymmetry of horizontal smooth pursuit, and asymmetric horizontal motion VEPs that typify infantile strabismus.[10]

METHODS

Scleral Coil and Head Restraint Surgery

After initial training, the monkeys were implanted with subconjunctival magnetic search coils in both eyes (a modification of the technique of Judge et al[11]), and a custom-built polycarbonate head restraint device was attached to the skull.[5] The surgical procedure was performed under aseptic conditions with general (ketamine IM and isoflurane by endotracheal tube) and topical anesthesia (proparacaine drops). A 360° conjunctival peritomy was completed, and the coil was attached to the sclera 3 mm anterior to the extraocular muscle insertions with Vetbond biological adhesive (3M Company, St Paul, Minn). The coil wires were looped laterally into a pocket created in the temporal quadrant of Tenon's capsule, and the conjunctiva was reposited to its natural position at the limbus. The scalp was opened along a sagittal incision with a Bovie cutter, and the skull was cleaned. The polycarbonate head restraint was attached with 4 slotted bolts drilled into the skull. The coil wires were tunneled from the lateral orbit beneath the scalp to connectors at the top of the head restraint. The wires, bolts, connectors, and base of the restraint were encased in dental acrylic poured and shaped over the skull. An antibiotic-corticosteroid ointment was applied to the conjunctivae and the edges of the scalp wound. The animal was awakened and returned to its home cage. Postoperative analgesia was administered for 72 hours (buprenorphine IM every 8 hours). The coil wires were used to measure passive current only. Generally, neither the coils nor the head restraint caused chronic irritation or discomfort to the animals.

Eye Movement Recording and Analysis

Within a few days after the coil surgery, the animal was returned to the primate chair for initial eye movement recording. Standard magnetic search coil techniques were used to record eye position.[12,13] The monkey sat in the middle of 3 × 3-ft field coils. A small target (a spot subtending ~.05°) was produced by a laser and moved by reflecting it off a pair of servo-controlled mirror galvanometers. The target was projected onto the back of a translucent screen 50 cm in front of the animal. The room had dim background illumination, and the intensity of the laser spot was 3.0 log units above our threshold for detecting a 100-ms flash.[14] Eye position was calibrated by using a calibration coil and by having the animal perform a lever-response task in which he had to detect 50% dimming of the target within 300 ms while the target remained stationary at known horizontal and vertical positions (previous experiments in normal primates confirmed that foveal fixation was necessary for accurate performance of this task).[5] The calibration sequence was repeated separately for each eye under conditions of monocular viewing. After the initial session, calibration was rapid and remained stable from day to day. The lever was removed, and accurate fixation was encouraged thereafter by rewarding the animal for keeping eye position within a certain window.

Eye movements were recorded several days before the tenotomy procedure and at weekly intervals thereafter over 4 months. The animals viewed binocularly during these sessions and were required to fixate the laser spot at primary position (straight ahead) or at eccentricities of ±10° horizontally and vertically. The target was presented in repeated trials, and, to receive a juice reward, the animal had to maintain eye position of the right or left eye within a 2° fixation window surrounding the target for a randomized interval of 2 to 5 seconds. The small target size, variability of target location, small fixation window, and random duration of required fixation ensured the monkey's high level of visual attention.

The onset, offset, direction (up, down, left, right), and speed (for pursuit trials, 0°-90°/second) of the target were controlled by a computer running Spike2 data acquisition/analysis software with a CED 1401 digital-analog signal processor (Cambridge Electronic Design, United Kingdom). Voltages proportional to horizontal and vertical eye position were digitized at 500 Hz. The eye position signals were passed through a finite impulse response filter (DC to 90 Hz) and differentiated, to obtain eye velocity signals. Angular resolution of the system was about .05°.

The waveforms of nystagmus before and after tenotomy were analyzed off line with a modified version of Spike2. Epochs chosen for analysis were those in which the monkey was rewarded for accurate fixation, ie, keeping the position of either eye during pendular nystagmus to within ±2° of target position or, in the case of jerk nystagmus, returning eye position to within this window with each fast phase. Mean amplitude, frequency, retinal slip velocity, and intensity[15] (amplitude × frequency) were calculated from at least 50 cycles of nystagmus per eye preoperatively and postoperatively. Means were compared with the *t* test, with significance defined as the 1% confidence level.

Extraocular Muscle Tenotomy

Six months after implanting the eye coils, tenotomy of the medial and lateral rectus muscle was performed on each eye under deep general endotracheal anesthesia with standard aseptic surgical techniques.[16,17] The eyes were prepped with povidone-iodine and draped in a sterile fashion. The eyelids were retracted with a wire pediatric speculum. The tendons of the medial and lateral rectus muscles were identified through the conjunctivae. Small, limbal conjunctival peritomies were created extending from the 2-to-4–o'clock and 8-to-10–o'clock positions. Limited dissection was carried out with blunt Wescott scissors to free intermuscular membranes and Tenon's capsule from the tendon insertion. Care was taken to avoid damaging the previously implanted scleral coils situated anterior to the tendon insertions. A Steven's tenotomy hook was introduced to isolate the tendon followed by a Green strabismus hook. A double-armed 6-0 Vicryl suture attached to an S-29 needle (Ethicon Inc, Sommerville, NJ) was placed 1.0 mm posterior to the insertion of the tendon in the tendon fibers. One mm of tendon margin was incorporated in locking bites. The tendon was disinserted completely by cutting it flush from the sclera with Manson-Aebli scissors (Storz Instrument Co, Saint Louis, Mo). The tendon was reattached, without recession or resection of the muscle, at the original insertion by crossed-swords intrascleral passage of the needles and suture. The conjunctivae were closed at the limbus with 6-0 Vicryl sutures. Cortisporin ointment was applied topically to the eyes. No surgical complications occurred postoperatively in either monkey.

RESULTS

Monkey HD exhibited only pendular nystagmus, but monkey PY had both pendular and jerk nystagmus. In the following Results, we describe the effects of tenotomy on pendular nystagmus in both monkeys and on the jerk nystagmus in monkey PY.

Effect of Tenotomy on Pendular Nystagmus

Figure 1 shows representative, horizontal eye velocity and position recordings of the right and left eyes of monkey HD before tenotomy and 4 months after the surgery. Both eyes displayed a slightly asymmetric pendular waveform (Figure 1, *bottom left tracings*) that was disconjugate and approximately 180° out of phase in both eyes; ie, when the right eye was moving rightward (*upward* in the figure), the left eye was moving leftward. Four months after tenotomy (Figure 1, *bottom right tracings*), the amplitude of the nystagmus remained an average of 48% in the right eye and 82% in the left eye of the respective preoperative amplitudes (*t* test, $P < .01$).

The preoperative amplitude of the nystagmus in monkey HD (smaller than 1°) was substantially less than the dimensions of the monkey fovea centralis[18,19] (approximately 5°), and therefore the animal did not have difficulty keeping the target on the fovea before or after surgery (ie, sustaining "foveation time"[16]). In addition to potential displacement of an image off the fovea, another major mechanism for degradation of vision in nystagmus is unwanted retinal image motion during attempted steady fixation.[20] To quantify retinal image motion, we measured eye (retinal slip) velocity and the intensity of eye oscillation before and after tenotomy.

The eye velocity tracings of Figure 1 and the bar graphs of Figure 2 (*top left*) show that in monkey HD the retinal slip velocity of the nystagmus increased postoperatively by factors of 1.2 in the right eye and 3.2 in the left eye ($P <$ .0002 for both eyes). The intensity (frequency × amplitude) of the nystagmus showed similar increases after tenotomy (bar graphs of Figure 2, *bottom left*). The right eye nystagmus intensity remained 1.4 times greater ($P <$ .002) and the left eye intensity 3 times greater ($P < .000$) than the intensities measured before tenotomy. The bar graphs of Figure 2 (*left*) also reveal an interesting and unexpected effect of tenotomy: the increases in retinal slip velocity and nystagmus intensity measured after tenotomy were substantially larger in the eye that preoperatively had the higher baseline velocity and intensity, ie, the nonpreferred left eye.

The percentage increases after tenotomy in monkey HD (pooling the measurements from both eyes) were as follows: the mean frequency of the nystagmus increased 231% to 250% after tenotomy, the mean retinal slip velocity increased 22% to 218%, and the mean nystagmus intensity increased 40% to 208%. Each increase was significant at the .002 or higher level of confidence.

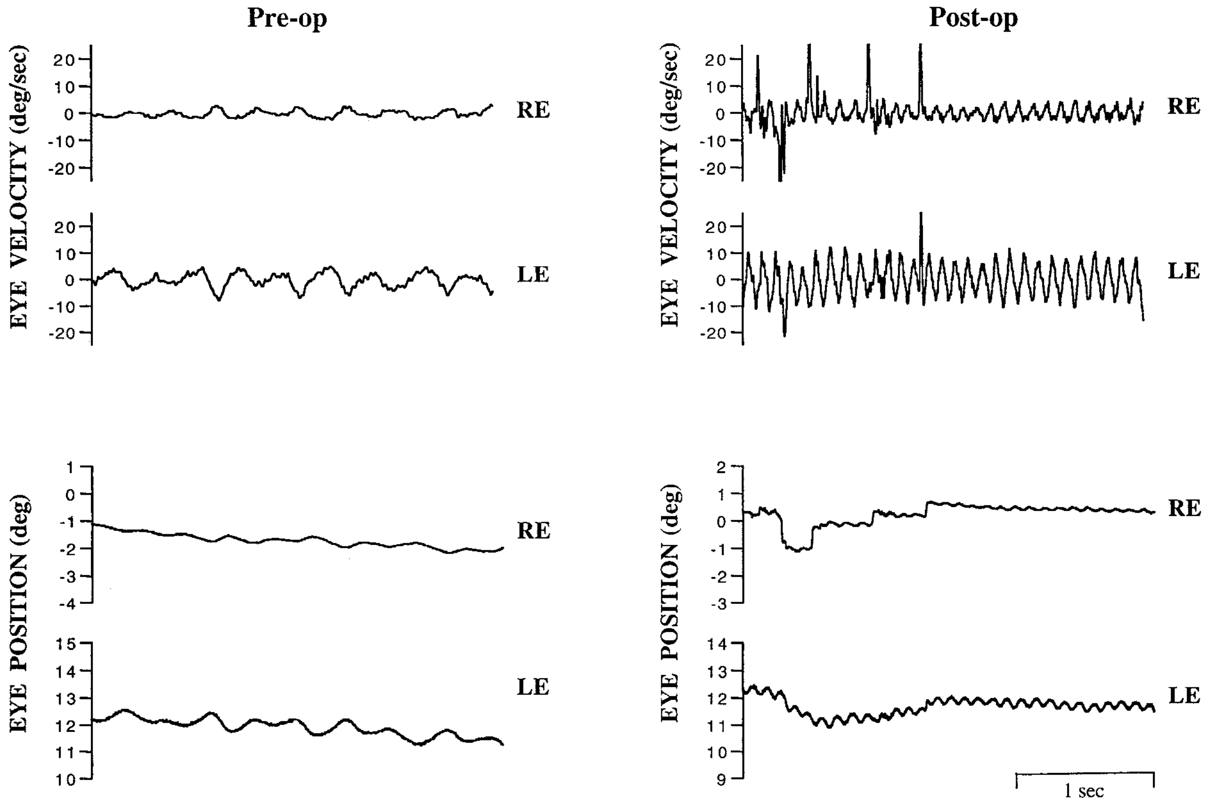

FIG 1. Eye position and velocity recordings of right and left eye of monkey HD before and 4 months after tenotomy. Both eyes displayed slightly asymmetric pendular waveform that was disconjugate and approximately 180° out of phase; ie, when right eye moved rightward, left eye moved leftward. Four months after tenotomy (*right set of tracings*), amplitude of nystagmus (~0.5°-0.75°) decreased, but nystagmus velocity and intensity increased. Animal viewed spot at 0° binocularly and preferred to fixate with right eye (left-eye esotropia). Positive values along ordinate indicate rightward positions and velocities. *RE*, right eye; *LE*, left eye.

The pendular nystagmus of monkey PY before and 4 months after tenotomy surgery is shown in Figure 3. In contrast to the disconjugate nystagmus of monkey HD, the nystagmus in monkey PY was conjugate. Tenotomy did not produce a noteworthy reduction in the amplitude of the pendular nystagmus (−3% in both eyes), which measured less than 0.5° before and after tenotomy (nonsignificant, P = .0601). As shown in the bar graphs of Figure 2 (*top right*), retinal slip velocity in monkey PY decreased an average of 22% after tenotomy in the right eye and 20% in the left eye (nonsignificant, P = .200 and P = .190, respectively). Nystagmus intensity in monkey PY (Figure 2, *bottom right*) increased after tenotomy by small increments, 8% in the right eye and 8% in the left eye (also nonsignificant, P = .460 and .370).

Effects of Tenotomy on Jerk Nystagmus

The eye velocity and position tracings of Figure 4 show the horizontal, conjugate jerk nystagmus of monkey PY. The jerk nystagmus was evident whenever the animal was not required to attentively fixate the laser target. To damp the jerk nystagmus, the animal converged its eyes 2° to 4°, and, by using this strategy, was able to maintain fixation near the laser spot and receive the reward. A comparison of Figures 4 and 3 reveals that the convergence damping strategy effectively blocked large-amplitude jerks (~ 4°-8° in Fig 4), but the pendular component of the nystagmus and small-amplitude conjugate jerks persisted (~ 0.5° in Figure 3).

After the tenotomy surgery (Figure 4, *right*), the average amplitude of the jerk nystagmus increased by a factor of 1.14 in both eyes (P = .000). The bar graphs of Figure 5 show the effect of tenotomy on the retinal slip velocity and the intensity of the jerk nystagmus. After tenotomy, retinal slip velocity increased 40% ($P < .002$) in the right eye and 46% ($P < .002$) in the left eye; nystagmus intensity increased 88% (P = .000) in the right eye and 92% (P = .000) in the left eye.

Visual and Other Ocular Motor Behaviors

Testing before and after surgery showed that tenotomy had no noteworthy effect on other ocular motor behaviors in either monkey, including fixation preference, eye alignment, mild latent nystagmus, or pursuit asymmetry. Although both animals had subnormal vision before tenotomy (typical of congenital nystagmus in humans[20]), this appeared to present no major behavioral impediment. After tenotomy, visual acuity (measured by spatial sweep

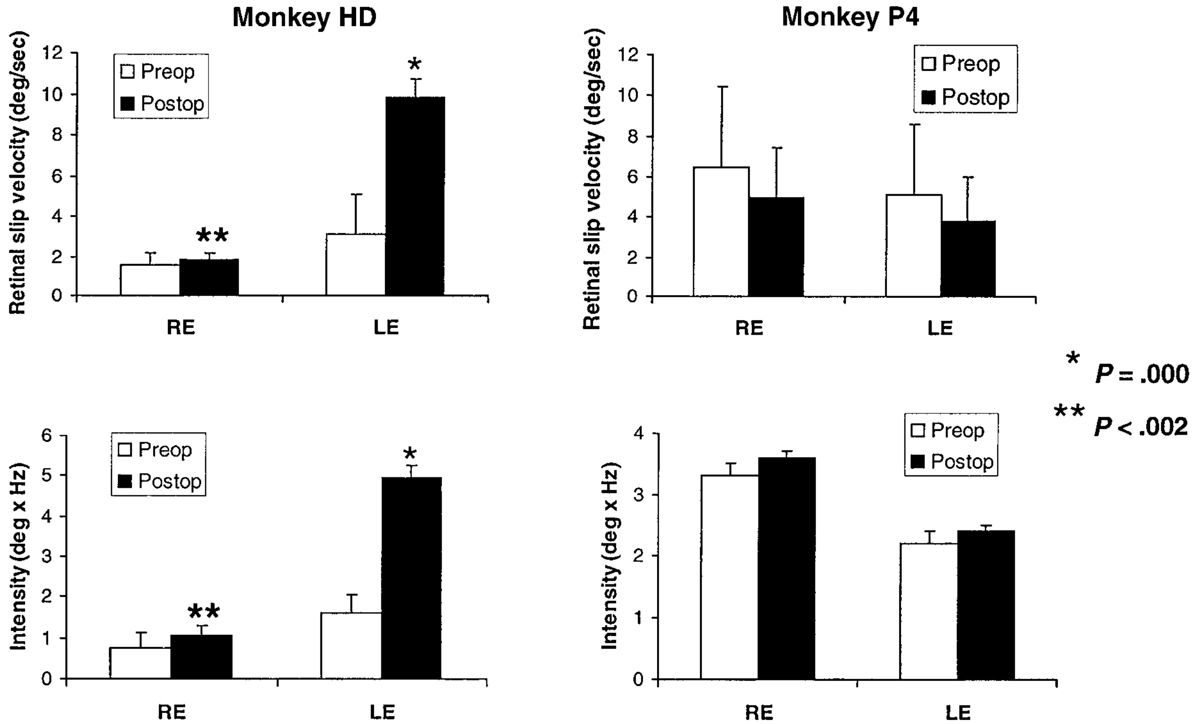

FIG 2. Mean (± SD) retinal slip velocity and mean pendular nystagmus intensity in monkeys HD and PY before and after tenotomy. In monkey HD (*left*), both nystagmus velocity and intensity increased after surgery, especially in left eye. Changes in pendular nystagmus velocity and intensity were not statistically significant in monkey PY (*right*).

VEP) declined 17% (−1.85 cpd) in the right eye and 22% (−2.07 cpd) in the left eye of animal PY (Table). When fixating the VEP stimulus screen, animal PY exhibited both pendular and large-amplitude jerk nystagmus. Animal HD was killed for neuroanatomic studies without measuring postoperative acuity. Before and after the tenotomies, the animals reached for and manipulated small biscuits, fruit pieces, and toys almost as dexterously as other normal and strabismic macaque monkeys.

Congenital nystagmus in humans typically increases in intensity when they are attentive or aroused and diminishes or disappears during periods of eye closure and sleep.[20] Similar behaviors were observed in the 2 monkeys; the highest intensity nystagmus was apparent during rewarded trials that required attentive fixation, and the nystagmus disappeared when the animals were left in the dark for extended periods, resulting in eye closure and drowsiness.

Video recordings of fixation behavior before and after tenotomy revealed no abnormal head postures (to place the eyes in a "null position") or head oscillations[20] when the animals were performing the fixation task with the head unrestrained (the monkeys kept their heads remarkably stationary during these sessions because they used their lips to suck constantly on the rigid copper juice delivery tube at the midline of the head and affixed to the primate chair). In a recording session before tenotomy, a search coil was also attached to the unrestrained head to precisely record head movements during the fixation task. These recordings further verified absence of torticollis and head oscillation.

DISCUSSION

Our results show that complete tenotomy of all 4 horizontal rectus muscles, followed by reattachment of the muscles to their original insertions, caused substantial increases in the frequency, velocity, and intensity of congenital nystagmus in 2 macaque monkeys. Nystagmus amplitude decreased 18% to 52% in 1 animal after tenotomy but increased 14% in the other. Nystagmus velocity increased 22% to 218% after surgery, and nystagmus intensity increased 40% to 208%. These experiments were performed to determine if surgical tenotomy might be valuable as a treatment for congenital nystagmus in humans.[21] Macaque monkeys have a visual and ocular motor system highly similar to that of humans and appear to be an ideal animal model for studying clinical ocular motor abnormalities, including congenital nystagmus.[22,23] Extrapolating these results to human patients leads to the conclusion that tenotomy may produce mixed results as a treatment for congenital nystagmus.

The 2 chief mechanisms by which congenital nystagmus degrades vision are displacement of the image off the fovea of the retina (reduced "foveation time") and blurring of the image because of unwanted visual motion (retinal slip).[20] Foveation time was not an issue in monkey HD because the pendular nystagmus before and after tenotomy had an amplitude less than the dimensions of the macaque

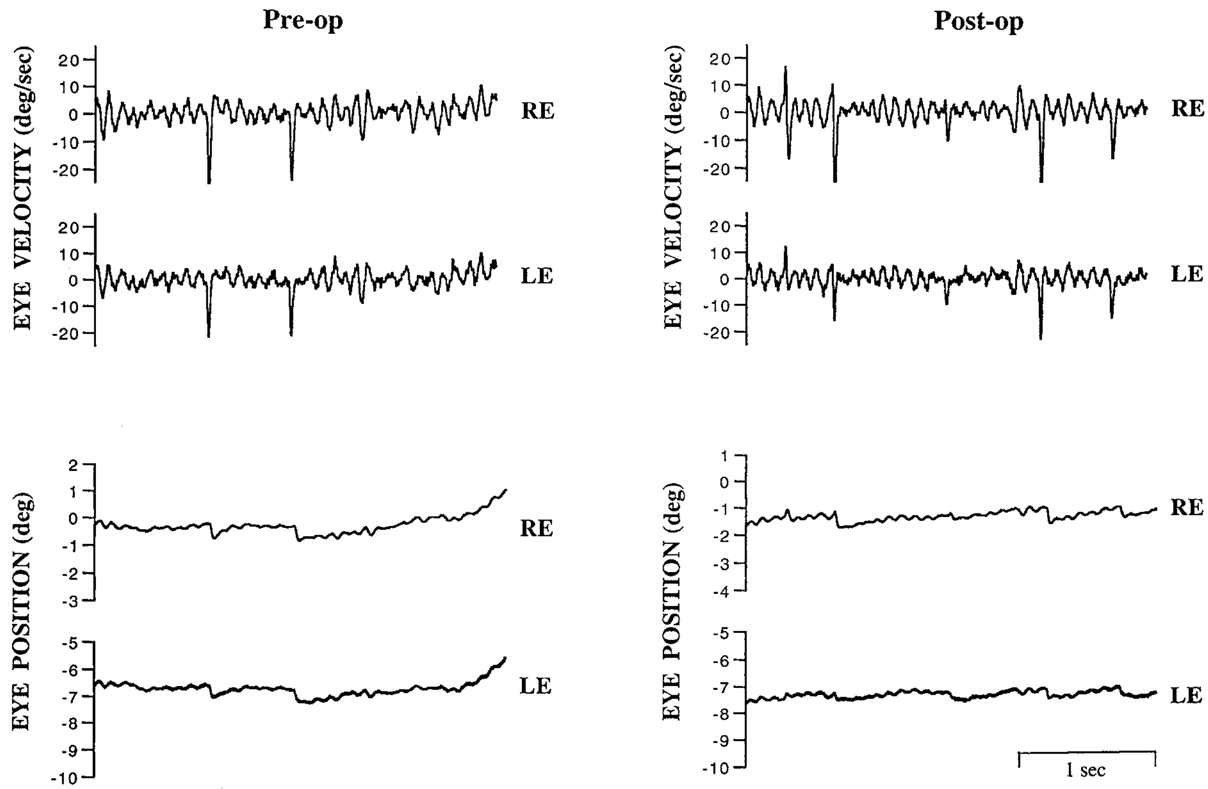

FIG 3. Eye position and velocity recordings of pendular nystagmus in monkey PY before and 4 months after tenotomy. Nystagmus was conjugate with pendular amplitude averaging ~0.4°. Note relatively convergent position of both eyes (~3° convergence from baseline exotropia of ~11°) and small-amplitude superimposed jerks of ~0.75°. When animal relaxed convergence, large-amplitude jerk nystagmus was evident (Figure 4). No substantial change in pendular nystagmus was evident after tenotomy. Animal viewed spot at 0° binocularly and preferred to fixate with right eye. Conventions same as for Figure 1.

fovea.[18,19] In monkey PY, which had large-amplitude jerk nystagmus, we measured acuity after tenotomy. The retinal slip velocity and nystagmus intensity increased 40% to 92%, and the animal's acuity declined. Acuity in congenital nystagmus is correlated strongly with low retinal slip velocities,[24,25] and visual acuity in normal humans is known to be degraded if horizontal motion of a target exceeds 2.5° per second or if obliquely directed motion exceeds 1.0° per second.[26]

Surgical treatments for congenital nystagmus in humans include resection and recession of rectus muscle pairs in each eye (the Anderson-Kestenbaum procedure[27,28]) or recession of all horizontal rectus muscles (large-recession procedure[24,29,30]). Both surgical therapies have been shown to reduce retinal slip velocities and improve subjective visual acuity.[15,24] Neither has been reported to increase velocities or degrade acuity. The mechanism for improvement in the case of the Anderson-Kestenbaum procedure is a shift in the null (ie, low frequency and velocity) gaze position of the nystagmus brought about surgically by passive changes in muscle tension within the orbits (nonlinear changes in ocular motor plant dynamics[15]). These orbital changes may also allow a reduction in fixation effort and anxiety that can intensify congenital nystagmus.[15,20] The putative mechanism for the reduction in large-recession surgery is the creation of a relative null position by lowering muscle tension in all horizontal muscles.[24,29,30] Tenotomy alone, without alterating muscle reattachment position, should have little if any effect on passive muscle tension.

Dell'Osso et al[16] reported reduction of congenital nystagmus amplitude and intensity using tenotomy in an achiasmatic Belgian sheepdog. The animal displayed conjugate and disconjugate horizontal and vertical pendular-jerk nystagmus and disconjugate vertical pendular (seesaw) nystagmus. Tenotomy of all 4 horizontal rectus muscles in the sheepdog reduced the horizontal nystagmus amplitude by 74% to 76%. The frequency of the pendular component of the horizontal nystagmus did not change. The frequency of the jerk component decreased by 46%. Retinal slip velocities were not reported preoperatively and postoperatively. Dell'Osso et al[16] suggested that the probable explanation for the beneficial effects of tenotomy in the sheepdog was an "interruption of the afferent proprioceptive loop, producing a damped peripheral ocular motor response to the [efferent] nystagmus signal."

One monkey we studied (animal HD) and the Belgian sheepdog studied by Dell'Osso et al[16] had atypical features when compared with children and adults who have classi-

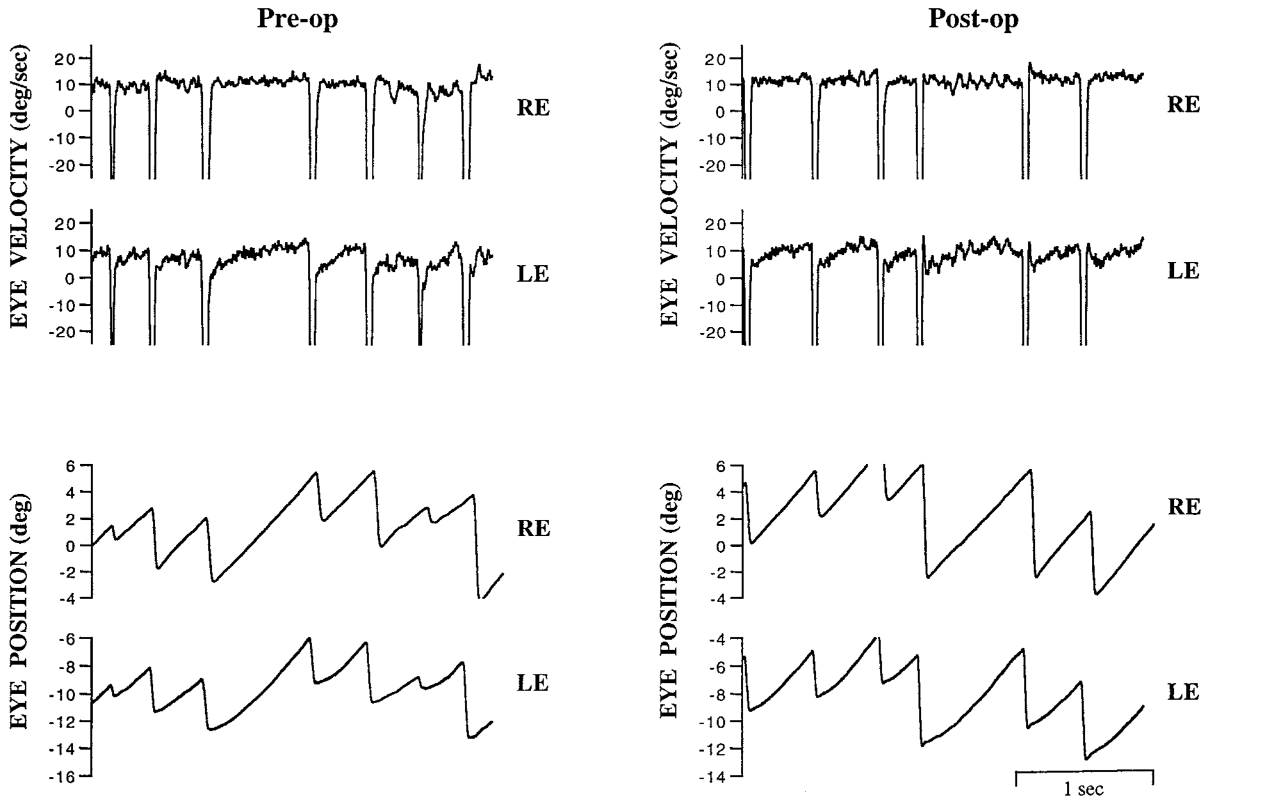

FIG 4. Eye position and velocity recordings of jerk nystagmus in monkey PY before and four months after tenotomy. Nystagmus was conjugate with slow phase amplitude averaging 4°-8°. Amplitude, velocity, and intensity of jerk nystagmus increased in each eye after surgery. Note in eye-velocity tracings presence of small-amplitude pendular nystagmus, evident during each jerk nystagmus slow phase (Figure 3). Animal viewed spot at 0° binocularly and preferred to fixate with right eye. Conventions same as for Figure 1.

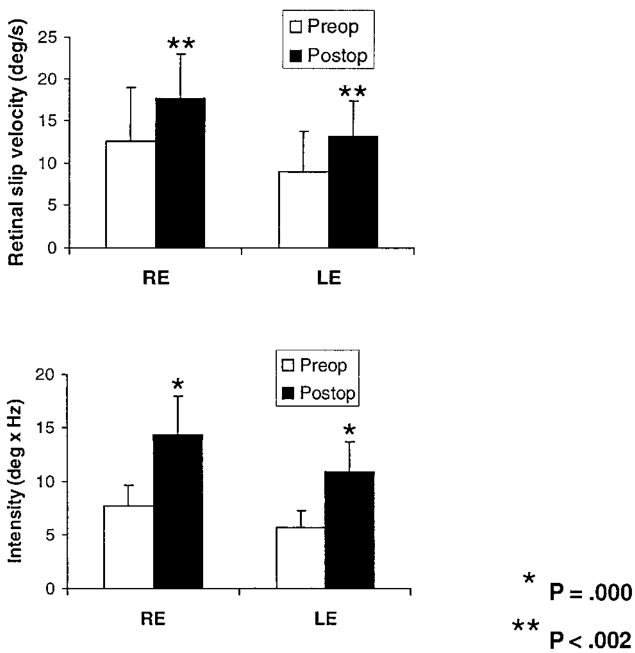

FIG 5. Mean (± SD) retinal slip velocity and mean jerk nystagmus intensity in monkey PY before and after tenotomy. Velocity and intensity of jerk nystagmus increased proportionately in each eye after surgery.

cal congenital nystagmus.[20,31] The most noteworthy atypical features in our monkey were disconjugate waveforms with vertical and horizontal components. However, animal PY displayed features typical of classical congenital nystagmus, including conjugate horizontal pendular-jerk waveforms and nystagmus damping with convergence.[20] The next step in exploring better clinical treatments for nystagmus will be to investigate the effects of tenotomy in other monkeys and in consenting adult human patients.

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