Horizontal Rectus Tenotomy in Patients with Congenital Nystagmus

Results in 10 Adults

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Objective: We wished to determine the effectiveness of horizontal rectus tenotomy in changing the nystagmus of patients with congenital nystagmus and, secondarily, how their visual function changed.

Design: This was a prospective, noncomparative, interventional case series.

Participants: Ten adult patients with varied associated sensory defects and oculographic subtypes of congenital nystagmus (including asymmetric periodic or aperiodic alternating nystagmus) and no nystagmus treatment options.

Methods: By using standard surgical techniques, simple tenotomy of all four horizontal recti with reattachment at the original insertion was accomplished. Search-coil eye movement recordings and clinical examinations were performed before and 1, 6, 24, and 52 weeks after surgery.

Main Outcome Measures: The primary outcome measure was the expanded nystagmus acuity function, obtained in "masked" fashion directly from ocular motility recordings. Secondary outcomes included breadth of null zones, preoperative and postoperative masked measures of visual acuity (Early Treatment Diabetic Retinopathy Study [ETDRS] chart), and the National Eye Institute Visual Function Questionnaire (NEI-VFQ-25).

Results: At 1 year after tenotomy and under binocular conditions, 9 of 10 patients had persistent, significant postoperative increases in the expanded nystagmus acuity function of their fixing (preferred) eye; 1 remained high, and 1 was not tested under the same conditions. Average foveation times increased in all 9 fixing (preferred) eyes. Binocular visual acuity measured with the ETDRS chart increased in 5 patients and was unaffected in five, whereas the NEI-VFQ-25 showed an improvement in vision-specific mental health in 9 patients. There were no adverse events. Tenotomy also radically changed the periodicity of one patient's asymmetric periodic or aperiodic alternating nystagmus.

Conclusions: In 9 of 10 adult patients with clinical and oculographic variations in their congenital nystagmus, tenotomy resulted in significant improvements in a nystagmus measure and subjective visual functions. *Ophthalmology 2003;110:2097–2105 © 2003 by the American Academy of Ophthalmology.*

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Congenital nystagmus (CN) is an ocular–motor disorder of unknown etiology that presents at birth or early infancy and is clinically characterized by involuntary oscillations of the eyes. Estimations of the incidence of CN vary enormously from 1 in 350 to 1 in 20,000, although the generally quoted figure is an incidence of 1 in 6550, or 0.015%.[1] Other clinical characteristics with variable association include increased intensity with fixation that is decreased with sleep or inattention, variable intensity in different positions of gaze (null positions), changing direction in different positions of gaze (neutral positions), decreased intensity with convergence (damping), anomalous head posturing, strabismus, and the increased incidence of significant refractive errors. CN can also occur in association with congenital or acquired defects in the visual sensory system (e.g., albinism, achromatopsia, congenital cataracts, and optic nerve or foveal hypoplasia).[2]

Patients with CN usually also have significantly diminished visual acuity. The visual acuity may be inversely

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related to the intensity of the nystagmus in those patients whose ocular motor system can take advantage of reduced intensity to improve the CN waveform and in whom no other sensory defect is present (e.g., foveal or optic nerve hypoplasia) and contributes to further visual loss in patients in whom sensory defects are present.[3] Some patients with CN exhibit adaptive mechanisms to improve their CN waveforms and, thereby, their vision. They can adopt an anomalous head position to shift the null position (area of minimal oscillation and better vision) to straight ahead, stimulate convergence, and, sometimes, adapt by a purposive esotropia, albeit at the expense of binocularity.[4]

One of the most common features of the CN waveforms is segments of the slow phase, wherein the eyes remain at or close to the point of desired fixation, with little or no movement.[5] These foveation periods have been shown to enhance visual acuity. The accuracy and duration of foveation have been directly linked to visual acuity.[6,7] If these periods can be lengthened or increased by the patient (adaptation) or by therapeutic interventions, the patient's visual acuity will be increased.

There is no cure for CN or many of the visual sensory system deficits that are associated with CN. One goal of any treatment directed specifically at CN should be to reduce the intensity of the nystagmus, thereby increasing the potential for more gaze angles during which foveation could take place, increasing foveation periods in the null position, or decreasing slow-phase velocities during foveation periods. All these changes would act to increase the patient's visual acuity or other visual functions. This applies to patients both with and without associated sensory-system defects. These benefits are observed in patients who have undergone the Anderson–Kestenbaum (AK) surgical procedure, although the procedure's primary purpose is to decrease torticollis in patients whose nystagmus intensity is least in gaze angles away from the primary position. It was originally designed to straighten these patients' face turn or head turn, which they were performing to maximize their visual acuity.[8–10]

The discovery of the beneficial secondary effects of the AK[11] effects led to the hypothesis that the same broadening and damping could be achieved by performing a variation of the AK procedure without the resection or recession[12]—that is, simply tenotomizing the four horizontal recti and reattaching them at their original insertions. For 12 years from the initial clinical and electrophysiologic observations of the beneficial secondary effects, an animal model was sought on which the hypothetical procedure could be tried. In 1991, such a model appeared in achiasmatic members of a family of Belgian Sheepdogs.[13,14] Studies of the eye movements of the affected dogs in this family revealed horizontal (and sometimes vertical) CN plus a congenital see-saw nystagmus. It was shown in this animal model that tenotomy alone duplicated the damping effects first documented in human patients after they underwent the full AK procedure.[15]

Study Design and Methods

This study was approved by the National Eye Institute (NEI), Institutional Review Board and Data Safety Monitoring Committee (protocol no. 99-EI-0152). After undergoing an initial screening examination, satisfying inclusion/exclusion criteria, and signing informed consent, the subjects underwent a full initial-protocol ophthalmic examination, baseline oculographic evaluation followed by tenotomy surgery, and follow-up ophthalmic and oculographic examinations. Data collection included historic information, sex, ethnicity, age at diagnosis of CN, prior ophthalmic treatments (spectacles, prisms, or orthoptics), prior medical treatments (acupuncture, biofeedback, medicines, and so on), other ocular conditions and treatments, significant medical illnesses, history of other surgical procedures, and allergies to medicines or environmental agents.

For inclusion in the study, the patient must have had a clinical and oculographic diagnosis of CN, had binocular best-corrected visual acuity of 20/400 to 20/50, been able to understand and sign informed consent, undergo a complete ophthalmic evaluation, undergo standard eye movement recording, undergo extraocular muscle surgery, and have been available for 1 year of follow-up.

Exclusion criteria for patients included prior extraocular muscle surgery; other treatment options available for their nystagmus (specifically those CN patients with an eccentric null position or convergence damping of their nystagmus); other indications for extraocular muscle surgery (e.g., a significant head posture or strabismus requiring surgical correction); a null position $>10°$ from the primary position horizontally, 5° vertically, or 5° torsionally; systemic medication known to affect ocular oscillations; concurrent medical conditions or known risks that would increase their chance of an adverse event due to general anesthesia (greater than an American Society of Anesthesiologists class I); and a family history of malignant hyperthermia.

The NEI Data and Safety Monitoring Committee (DSMC) was responsible for reviewing the study design and, as appropriate, recommending design changes. In addition, the Data and Safety Monitoring Committee assessed study data, particularly for adverse or beneficial effects of experimental treatment. The Data and Safety Monitoring Committee convened before the initiation of the trial to review the protocol, reviewed accumulated data on a regular basis, and met ad hoc to address any significant problem related to patient safety brought to its attention by any study patient or investigator.

Ophthalmic examinations were performed 3 times within a 3-month period before tenotomy and at 1, 6, 24, and 52 weeks after tenotomy and included Early Treatment Diabetic Retinopathy Study visual acuity by certified, masked technicians; pupillary examination; ocular motility examination; nystagmus pattern in all fields of gaze, as well as response to convergence, cover, and the presence and amount of any head posturing at distance and 33 cm; stereo testing with the Wirt stereo test; slit-lamp biomicroscopy of the lids and anterior segments; cycloplegic refraction; and dilated examination of the retina and optic nerves with indirect ophthalmoscopy.

Eye movement recordings were performed by two investigators (EJF and DY) not involved with the clinical examination or surgery 3 times within a 3-month period before tenotomy and at 1, 6, 24, and 52 weeks after tenotomy. Eye-movement data were collected by using the magnetic induction and scleral search-coil technique in all patients. Calibration was accomplished by using targets placed horizontally at 0° and $\pm$15°, 20°, 25°, and 30°. Eye-position signals were digitized on-line at 1000 Hz and stored on a computer for later analysis.

Surgery was performed by one investigator (RWH) on all patients under general anesthesia. With use of standard strabismus surgical techniques, all 4 horizontal rectus muscles were identified and isolated, and a suture was placed through the tendon. The tendon was cut off of the surface of the globe and immediately reattached at the original insertion site. The wounds were closed in

standard fashion, and antibiotic/steroid ointment was then placed in the eyes. Standard postoperative care consisted of daily application of antibiotic/steroid drops 4 times daily for 7 days and follow-up examinations at 1 day, 1 week, 6 weeks, 6 months, and 1 year.

Eye-movement data were analyzed in a masked fashion by one investigator (LFD) not involved with the clinical examination, eye-movement recording, or surgery. Data from each recording session (identified only by a random number) before and after tenotomy were analyzed in random order after being resampled at 200 Hz. The primary outcome measure was the eXpanded Nystagmus Acuity Function, (NAFX).[16] The Nystagmus Acuity Function (NAF) and, later the NAFX, originated from the Nystagmus Foveation Function.[7,17,18] The NAF was developed to provide an objective measure of the quality of a nystagmus waveform, to predict best-corrected visual acuity in CN patients under benign conditions, and to assess the effects of treatments on the CN oscillation. The NAF is a function that predicts the best-corrected visual acuity possible in subjects with nystagmus on the basis of objective measurements from eye movement recordings of their waveform characteristics during fixation of a small, light-emitting diode. It combines the foveation time per cycle and the standard deviations of both eye position and velocity during target foveation into a function that is linearly proportional to best-possible visual acuity.

The NAFX incorporates the time intervals of foveation periods and their position and velocity standard deviations (SD) into a measure of the quality of a CN waveform (i.e., how likely it was to allow good acuity). It assesses the upper limits of the acuities of individuals with poor foveation capabilities. Neither the NAFX nor the NAF, which it includes, depends on the methodology of data collection (e.g., infrared, video, or magnetic search coil), the type of nystagmus (CN, latent/manifest latent nystagmus, and so on), or the particular nystagmus waveform.

In this study, NAFX values (the primary outcome measure) calculated for fixation intervals from each recording session were averaged, and it is those average NAFX values that appear in the figures. For patients with CN plus asymmetric (a)periodic alternating nystagmus (APAN), the NAFX values used were for fixation during the best portions of the APAN cycle in each direction. In addition, peak-to-peak CN amplitudes and foveation-period durations were calculated as secondary outcome measures.

The NEI Visual Function Questionnaire (VFQ-25) is a survey that measures the dimensions of self-reported vision-targeted health status that are most important for persons who have chronic eye diseases.[19,20] Because of this goal, the survey measures the influence of visual disability and visual symptoms on generic health domains, such as emotional well-being and social functioning, in addition to task-oriented domains related to daily visual functioning. The VFQ-25 consists of a base set of 25 vision-targeted questions representing 11 vision-related constructs, plus an additional single-item general health rating question. The VFQ-25 contains the single general health rating question that has been shown to be a robust predictor of future health and mortality in population-based studies.[19,20] All items are scored so that a high score represents better functioning. Each item is then converted to a 0- to 100-point scale so that the lowest and highest possible scores are set at 0 and 100 points, respectively. The overall score is the mean of all responses to all 12 domains and represents a global estimate of a patient's visual function. The composite score is best used in situations in which an overall measure of vision-targeted health-related quality of life is desired—for example, in studies in which it is not clear what the specific effect of ocular disease or a new treatment might be, such as this tenotomy study.

Table 1. Clinical Characteristics

Patient No.	Age (yrs)/ Sex	Clinical Notes
1	39/M	Albinism, CN, ET, OS preference
2	30/M	Albinism, CN, ET, OS preference
3	39/M	Idiopathic CN, Ortho, no preference
4	49/M	Albinism, CN/APAN, ET, OS preference
5	39/M	Idiopathic CN/APAN, Ortho, no preference
6	28/F	Albinism, CN, ET, OS preference
7	39/M	Idiopathic CN/APAN, XT, OS preference
8	20/M	Achiasma, CN/SSN, ET, HT, OS preference
9	55/F	Idiopathic CN/APAN, Ortho, OD preference
10	34/F	Albinism, CN/APAN, ET, OD preference

APAN = asymmetric (a)periodic alternating nystagmus; CN = congenital nystagmus; ET = esotropia; F = female; HT = hypertropia; M = male; OD = right eye; Ortho = orthotropia; OS = left eye; SSN = see-saw nystagmus; XT = exotropia.

Results

Table 1 contains the age, sex, and associated eye disease of the 10 enrolled patients. The average age of the patients at the time of surgery was 36.4 years (median, 37.5 years; range, 19–55 years). Seven patients were white, one was Hispanic, and 2 were black. Seven were men. Five patients had albinism, one patient had achiasma, 4 patients had APAN, one patient (with achiasma) also had see-saw nystagmus, and 7 patients had associated childhood strabismus and no indication for surgical treatment of their strabismus. There were no adverse events secondary to surgery or the examination techniques.

Primary Outcome Measure

For each patient, the NAFX values calculated during fixation in primary position were averaged in each session and plotted for both preoperative sessions and each postoperative recording session. Figure 1 is a representative output of the NAFX program for fixation intervals taken from both the pretenotomy and posttenotomy data for subject 2. The waveforms in the posttenotomy data had lower amplitudes (7.4°–4.8° peak to peak, −35.1%), more (5–11 in this 4-second period, +120%) and longer (24–37 msec, +54.2%) foveation periods, and lower position (SD, 1.34°) and velocity (SD, 2.97°/second) variation of the foveation periods. Tenotomy resulted in a 52.4% increase in the NAFX (from 0.332 to 0.506), despite the higher frequency of CN, and a cosmetic improvement (lower-amplitude CN).

Figure 2 is a representative output of the NAFX program for fixation intervals taken from both the pretenotomy and posttenotomy data for subject 3 (measured at 20° left gaze). Unlike the previously described case, the waveforms in the posttenotomy data had similar amplitudes and a similar number and length of foveation periods but had much lower position (SD, 0.28°) and velocity (SD, 2.91°/seconds) variation of the foveation periods. Tenotomy resulted in a 30.5% increase in the NAFX (from 0.338 to 0.441), despite the clinically indistinguishable CN.

Figure 3 shows the average NAFX values during the course of this study for the 5 patients with CN (top) and the five with CN and APAN (bottom). We fitted the data for each subject with logarithmic curves and also plotted and curve-fitted the average NAFX for all patients (heavy dashed curve). All patients except subjects 6 and 7 (dashed curves) showed an

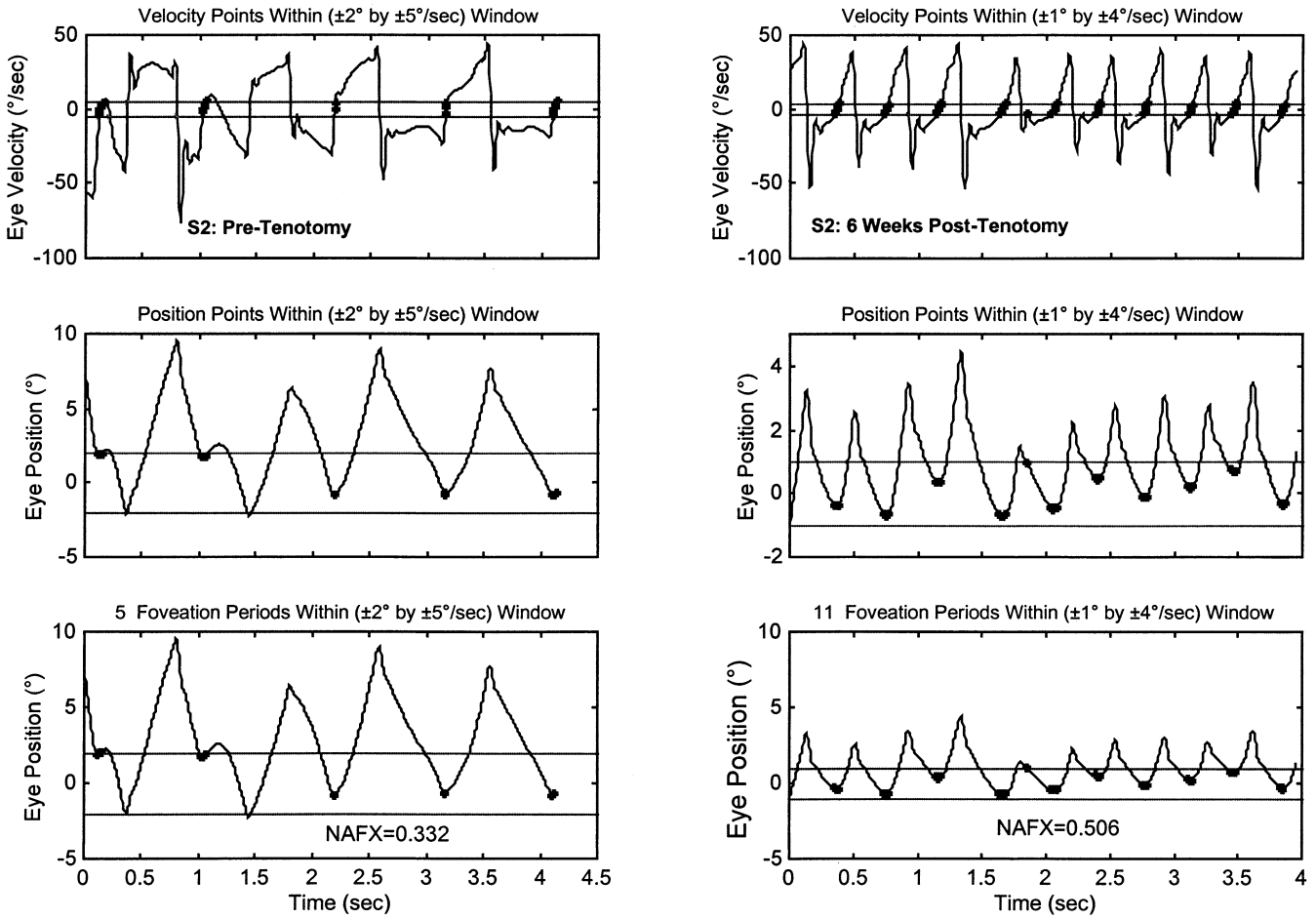

Figure 1. Expanded Nystagmus Acuity Function (NAFX) outputs for preoperative and postoperative data from patient 2 (S2). As a result of the tenotomy, the congenital nystagmus (CN) amplitude decreased, the number and length of foveation periods increased, and the position and velocity variations decreased. The net result was an increased NAFX.

immediate increase in the NAFX and retention of that increase after 1 year; subject 7 began with a high NAFX (0.755). The average NAFX values increased from 0.334 to 0.404 (a potential increase of 1 Snellen line) for the CN group and from 0.450 to 0.689 (a potential increase of 2.5 Snellen lines) for the APAN group. In Figure 4, we plotted the percentage increase in the NAFX values during the course of the study for the 2 groups. These data, along with the average NAFX increase for all patients (heavy dashed curve), were fitted with logarithmic curves. After 1 year, the average increase was approximately 28% (individual ranges were −14.2% to 80.2%) for the CN group and approximately 58% (individual ranges were 1.4%–108.1%) for the APAN group.

Secondary Outcome Measures

Visual Acuity. Table 2 shows visual acuity and Early Treatment Diabetic Retinopathy Study total letter change measured before and at 52 weeks after tenotomy. Five of 10 patients had a ≥5-letter increase, corresponding to at least a 1-line improvement in best-corrected acuity.

National Eye Institute Visual Function Questionnaire. Table 3 shows results of the NEI-VFQ-25 at 52 weeks after tenotomy. Nine of the 10 adult patients showed an increase in overall VFQ-25 score. Patient 8 was the lone exception, with a baseline score of 78 and a 1-year score of 68.

CN Amplitude. Three patients had significant damping (>25%) after 1 year, one had slight damping (2.5%), and the amplitude for subject 3 increased a few tenths of a degree (<7%) (see Discussion). The average damping was approximately 16%.

Primary and Secondary Outcome Measures

Table 4 shows the relationship between the NAFX-predicted visual acuities and the measured acuities before and 52 weeks after tenotomy. For the 7 subjects with predicted increases in their potential best-corrected visual acuities, five showed measured increases of one or more Snellen lines (including two [subjects 1 and 2] with albinism), and 2 (subjects 4 and 10, both with albinism) showed no changes. The 2 subjects whose NAFX changes (<10%) predicted no change in potential acuities showed no measured changes (one, subject 7, had a predicted preoperative acuity of 20/20, and the other, subject 8, had achiasma). Finally, the only subject (subject 6, also with albinism) whose NAFX values predicted slightly lower acuity after tenotomy showed no measured change.

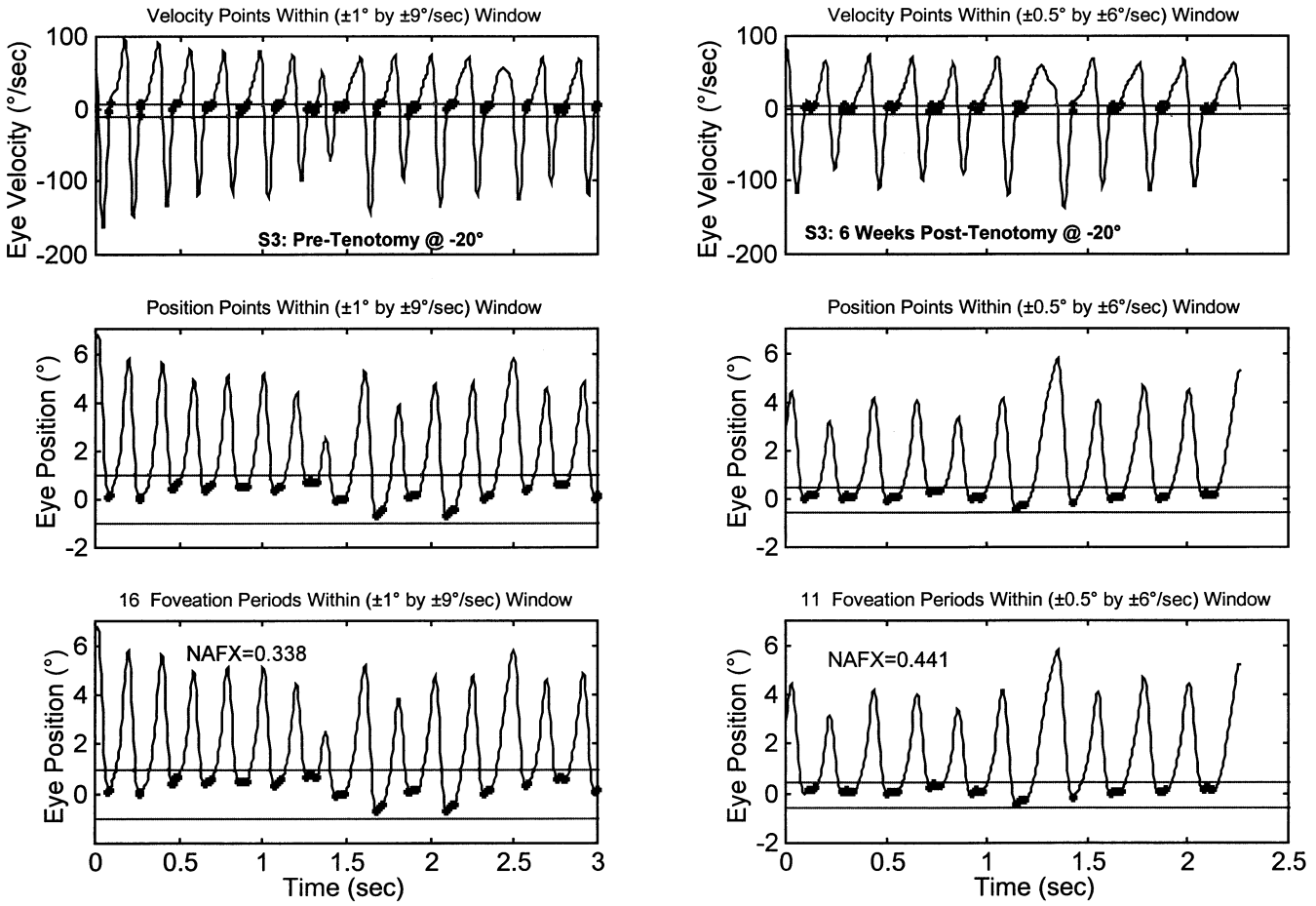

Figure 2. Expanded Nystagmus Acuity Function (NAFX) outputs for preoperative and postoperative data from patient 3 (S3). As a result of the tenotomy, the congenital nystagmus amplitude decreased, the length of foveation periods increased, and the position and velocity variations decreased. The net result was an increased NAFX.

Discussion

Numerous treatments have been described for CN. These include dietary manipulation, drugs, contact lenses, prisms, biofeedback, intermittent photic stimulation, acupuncture, transcutaneous vibratory or electronic stimulation of the face and neck, injection of botulinum toxin, and a variety of surgical procedures.[8,21–27] Excepting those treatments that directly improve visual acuity (spectacle and contact lens correction of refractive errors), all these treatments have in common a desired effect of reducing the nystagmus intensity directly or indirectly, thus allowing for an increase in visual acuity. In a review of 361 patients undergoing surgical repositioning of the eyes for congenital nystagmus from 21 reports in which vision was measured both before and after surgery, 273 (76%) had improved vision after the surgery.[28] Most of these studies were retrospective reviews and did not use objective eye movement recordings before and after treatment of the nystagmus.

Surgical treatment of nystagmus has a long and well-documented history. Surgery is usually indicated in patients with CN and an anomalous head posture due to an eccentric null gaze position, those with strabismus, or those who have good binocular function and whose nystagmus decreases and vision improves during convergence (convergence damping). Those patients who have good binocular function, do not damp with convergence, exhibit no null position, or have a null gaze in primary position are not normally surgical candidates. In 1953, Kestenbaum[9] recommended surgery on one eye, with surgery on the second eye after a period of stabilization. Anderson,[8] about this time, presented 4 patients in whom he recessed the recti muscles in the direction of the slow phase of the nystagmus. In both sets of patients, the head position and vision improved. Many authors have reported on series of patients for whom surgical repositioning of the extraocular muscles has improved head positioning, nystagmus intensity, and vision.[21,24,29–33] In 1979, Dell'Osso and Flynn[11] examined eye movements with infrared oculography and documented the effect of this type of procedure on patients with CN. They reported the unusual and unpredicted, but beneficial effects of broadening the null zone, improved foveation in the null zone and increasing the range of gaze positions over which foveation improved

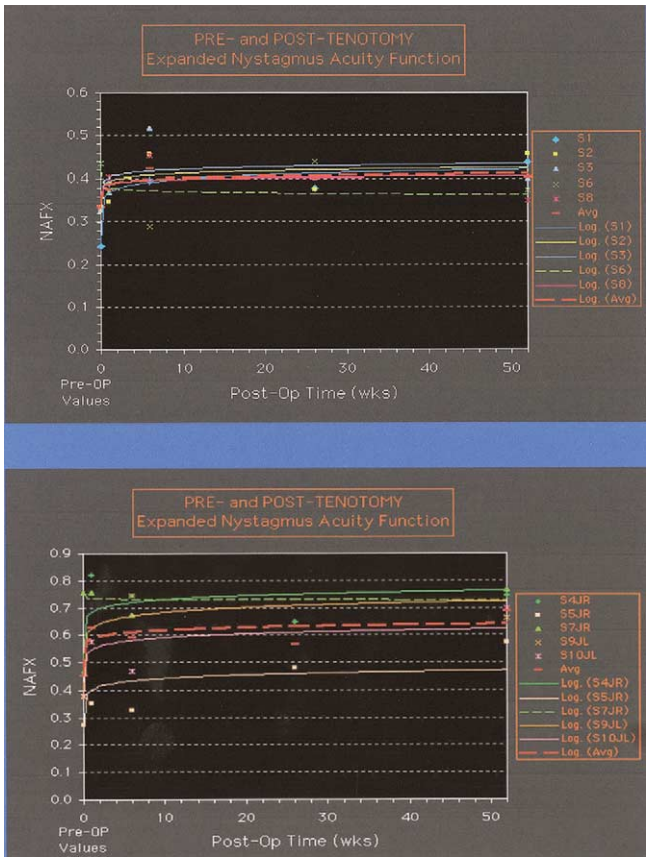

Figure 3. Plots of NAFX data for five patients (subjects 1–3, 6, and 8) with CN (top) and five (subjects 4, 5, 7, 9, and 10) with CN plus APAN (bottom) over the 1-year study. APAN = asymmetric (a)periodic alternating nystagmus; Avg = average of patients in each graph; CN = congenital nystagmus; Log. = logarithmic curve fits of the NAFX vs. postoperative time data; NAFX = eXpanded Nystagmus Activity Function; S1, S2, S6 and S8 = subjects 1, 2, 6, and 8 at 0°; S3 = subject 3 at left 20°; S4JR, S5JR, S7JR = subjects 4, 5, and 7 during jerk right; S9JL and S10JL = subjects 9 and 10 during jerk left.

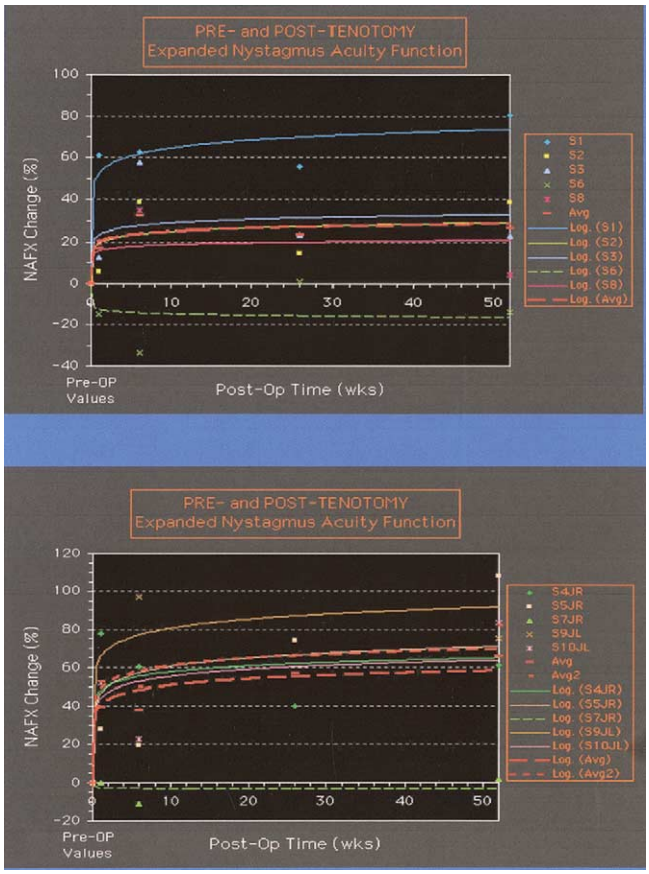

Figure 4. Plots of NAFX percent change for five patients (subjects 1–3, 6, and 8) with CN (top) and five (subjects 4, 5, 7, 9, and 10) with CN plus APAN (bottom) over the 1-year study. APAN = asymmetric (a)periodic alternating nystagmus; Avg(2) = average of patients in each graph; CN = congenital nystagmus; Log. = logarithmic curve fits of the NAFX vs. postoperative time data; NAFX = eXpanded Nystagmus Activity Function; S1, S2, S6 and S8 = subjects 1, 2, 6, and 8 at 0°; S3 = subject 3 at left 20°; S4JR, S5JR, S7JR = subjects 4, 5, and 7 during jerk right; S9JL and S10JL = subjects 9 and 10 during jerk left.

and the nystagmus intensity diminished. There was no ready explanation for these observed effects, which could be related to simply mechanically shifting the positional bias of the eyes.

As Figures 1 and 2 show, four-muscle tenotomy improved the CN waveforms and, therefore, the potential visual acuities of these patients. The improvement was immediate (as we documented in the canine model, 1 day after tenotomy[15]) and was maintained throughout the 1-year study. Because the secondary effects of the AK procedure were shown to persist for 5 years,[34] we conclude that stability has been reached and that the waveforms may be permanently improved.

Coincident with the NAFX improvements were increases in the average foveation periods of those patients with CN and no APAN. Foveation-period duration improvement was expected. However, as has been demonstrated elsewhere,[16,35] CN amplitude is not a good indicator of visual acuity. Here, one of the patients (subject 3) did not show damping of the CN waveform, despite an improved NAFX. The data in Figures 1 and 2 point out the importance of evaluating the quality of the CN waveforms rather than merely the amplitudes or frequencies. As the data in Figure 1 show, subject 2's CN amplitude decreased significantly as a result of the tenotomy, whereas, as Figure 2 shows, subject 3's amplitude was less affected and less clinically obvious. Also, subject 3's CN frequency increased, allowing more foveation periods per second; this was conducive to higher acuity. Thus, despite variable effects on CN intensity, tenotomy allowed both patients to achieve waveform improvements that resulted in large increases in their NAFX and potential visual acuities.

There are differences in the outcome data, as illustrated in Table 4, which compares the primary outcome measure (NAFX) with the measured change in Early Treatment Diabetic Retinopathy Study visual acuity, a secondary outcome measure. The relationship among Snellen visual acuity, nystagmus, and other sensory visual functions is complex. Some of our patients' Snellen acuities did not increase in proportion to their NAFX. We anticipated this possibility

Table 2. Secondary Outcome Measure: Acuity Change

Patient No.	Age (yrs)	VA OU PRE	VA OU POST	ETDRS Letter
1	39	20/160	20/125	+8*
2	30	20/63	20/50	+6*
3	39	20/40	20/25	+6*
4†	49	20/100	20/100	+3
5†	39	20/40	20/32	+7*
6	28	20/80	20/80	−3
7†	39	20/50	20/50	−3
8	20	20/80	20/80	−3
9†	55	20/50	20/40	+6*
10†	34	20/80	20/80	−2

ETDRS = Early Treatment Diabetic Retinopathy Study; OU = both eyes; POST = 52 weeks after tenotomy; PRE = before tenotomy; VA = visual acuity.
*Patients with increased measured visual acuity.
†Congenital nystagmus plus asymmetric (a)periodic alternating nystagmus.

Table 4. Primary and Secondary Outcome Measures*

Patient No.	Age (yrs)	VA OU PRE	NAFX PRE	VA OU POST	NAFX POST
1	39	20/160†	0.243†	20/125†	0.437 (0.425)†
2	30	20/63†	0.330†	20/50†	0.458 (0.430)†
3	39	20/40†	0.327†	20/25†	0.402 (0.440)†
4‡	49	20/100	0.463	20/100	0.744 (0.770)
5‡	39	20/40†	0.275†	20/32†	0.573 (0.480)†
6	28	20/80	0.436§	20/80	0.374 (0.365)§
7‡	39	20/50	0.755	20/50	0.765 (0.730)
8	20	20/80	0.336	20/80	0.350 (0.405)
9‡	55	20/50†	0.379†	20/40†	0.664 (0.730)†
10‡	34	20/80	0.380	20/80	0.697 (0.620)

*Binocular visual acuity (VA OU) and eXpanded Nystagmus Acuity Function (NAFX) values measured before (PRE) and 52 weeks after (POST) tenotomy. Values in parentheses are from fitted curves.
†Patients with increased NAFX and measured visual acuity.
‡Congenital nystagmus plus asymmetric (a)periodic alternating nystagmus.
§The only patient whose NAFX decreased.

in the design of this study; that is why we used ocular motility recordings of the nystagmus as the primary outcome measure. Our hypothesis was that the tenotomy surgery would change the nystagmus. The effect on vision of changing a patient's nystagmus is related to a number of unknown, unpredictable variables, including, but not limited to, patient age, underlying visual sensory system disease, associated strabismus, associated amblyopia, uncorrected refractive errors, and associated central nervous system disease.

Subject 7, whose best preoperative APAN waveform resulted in an NAFX of 0.755, did not show improvement as a result of the tenotomy. This may indicate an upper bound beyond which no waveform improvement should be expected; more data are needed to support this speculation. If that is the case, and we exclude subject 7 from our calculations, the average NAFX improvement for the APAN group increases from approximately 58% to 68%, as is shown by "Avg2" (heavy, short-dashed line) in Figure 4 (bottom). Subject 6 had a decrease in her postoperative NAFX. This may be due to some as yet undefined clinical variables in some patients who have the CN waveform. We did look at this subject specifically to try to answer this question. She had oculocutaneous albinism with a small-angle esotropia and a refractive error of $-4.50 + 5.00 \times 30$ (right eye) and $-6.00 + 5.00 \times 60$ (left eye), which was uncorrected for ocular motor recordings after surgery, but not before surgery. The difference in her vision during these postoperative recording sessions could explain the persistent decrease in her NAFX.

Table 3. Secondary Outcome Measure: NEI-VFQ* Change

Patient No.	Age (yrs)	PRE-VFQ	POST-VFQ
1	39	48†	64†
2	30	63†	83†
3	39	83†	85†
4‡	49	77†	79†
5‡	39	79†	95†
6	28	77†	88†
7‡	39	62†	74†
8	20	78	71
9‡	55	78†	82†
10‡	34	81†	93†

*National Eye Institute Visual Function Questionnaire test score before tenotomy (PRE-VFQ) and 52 weeks after tenotomy (POST-VFQ).
†Patients who reported increased visual functioning.
‡Congenital nystagmus plus asymmetric (a)periodic alternating nystagmus.

Tenotomy had a dramatic effect on the periodicity of subject 10's CN. The preoperative data did not show direction reversals during fixation in primary position, even during a 5-minute continuous recording. However, the post-tenotomy data showed classic APAN. It was not until the data were unmasked that this was appreciated and the preoperative data had to be reanalyzed as APAN data. Thus, as Shallo-Hoffmann et al[36] and Shallo-Hoffman and Riordan-Eva[37] have pointed out, APAN with long periods may easily be missed and is more common than the literature suggests. In this case, despite multiple clinical examinations and recording sessions, CN reversal was only seen in preoperative data during far right gaze, and the diagnosis was missed until after the tenotomy surgery exposed the APAN.

The integrity of the afferent visual system may ultimately determine the mature clinical characteristics and waveform quality in any one patient.[38] A sensitive measure of the afferent system is represented in motility recordings by foveation periods. One of the most common features of the CN waveforms is the presence in segments of the slow phase wherein the eyes remain at or close to the point of desired fixation with little or no movement. These foveation periods have been shown to enhance visual acuity. The accuracy and duration of foveation have been directly linked to visual acuity, especially in those CN patients in whom no other sensory system disease can be found.[5,17,39,40]

There is abundant basic science and some clinical evidence supporting a hypothesis that central nervous system

gain/modulation of the oscillation may be due to afferent changes from the extraocular muscles after the procedure.[15] The primary afferent neurons providing sensory innervation of the mammalian extraocular muscles are located in the trigeminal ganglion.[41] Afferent fibers from V1 (the ophthalmic branch of the trigeminal nerve) either directly connect to or influence the brainstem and the cerebellar and cortical areas associated with eye-movement control.[42,43] Recently discovered nerve endings in the extraocular muscles at the tendino-scleral interface (its "enthesis") may shed light on a further mechanism of action of tenotomy surgery.[44]

Given these numerous studies, it is likely that afferent information from the extraocular muscles (either as proprioceptive signals or as other sensory information) serves as a continuous and long-term calibration signal. The underlying pathophysiology of congenital nystagmus has been attributed to and modeled as a high-gain instability in the pursuit system.[35,45,46] The clinical and electrophysiologic consequences of extraocular muscle tenotomy in patients with CN may be due to interruption of the afferent proprioceptive loop, producing a damped peripheral ocular–motor response to the nystagmus signal.

In conclusion, we have demonstrated that in 9 of 10 adult patients (including 5 with albinism and 1 with achiasma) with clinical and oculographic variations in their CN, tenotomy resulted in significant improvements in their nystagmus, along with improvements in subjective visual function. In 8 of the 10 patients, their NAFX increased significantly (20%–90%), allowing greater potential acuity; in 1, it was unchanged (±3%); and in 1 it decreased slightly. In 4 of the 5 patients with constant CN (i.e., no APAN), the CN amplitude decreased; the latter results in a cosmetic improvement in addition to the acuity improvement. It is likely that these effects may be even greater if the procedure is performed on a less mature visual system; this second phase of our study is nearing completion and will be the subject of a future report.

References

1. Norn MS. Congenital idiopathic nystagmus. Incidence and occupational prognosis. Acta Ophthalmol 1964;42:889–96.
2. Abadi RV. Visual performance with contact lenses and congenital idiopathic nystagmus. Br J Physiol Opt 1979;33:32–7.
3. Leigh RJ, Rushton DN, Thurston SE, et al. Oscillopsia, retinal image stabilization and congenital nystagmus. Invest Ophthalmol Vis Sci 1988;29:279–82.
4. Dell'Osso LF, Ellenberger C, Abel LA, Flynn JT. The nystagmus blockage syndrome: congenital nystagmus, manifest latent nystagmus or both? Invest Ophthalmol Vis Sci 1983; 24:1580–87.
5. Dell'Osso LF. Fixation characteristics in hereditary congenital nystagmus. Am J Optom Arch Am Acad Optom 1973;50:85–90.
6. Bedell HE, White JM, Abplanalp PL. Variability of foveations in congenital nystagmus. Clin Vis Sci 1989;4:247–52.
7. Sheth NV, Dell'Osso LF, Leigh RJ, et al. The effects of afferent stimulation on congenital nystagmus foveation periods. Vis Res 1995;35:2371–82.
8. Anderson JR. Causes and treatment of congenital eccentric nystagmus. Br J Ophthalmol 1953;37:267–81.
9. Kestenbaum A. Nouvelle opération du nystagmus. Bull Soc Ophthalmol Fr 1953;6:599–602.
10. Flynn JT, Dell'Osso LF. The effects of congenital nystagmus surgery. Ophthalmology 1970;86:1414–27.
11. Dell'Osso LF, Flynn JT. Congenital nystagmus surgery: a quantitative evaluation of the effects. Arch Ophthalmol 1979; 97:462–9.
12. Dell'Osso LF. Extraocular muscle tenotomy, dissection, and suture: a hypothetical therapy for congenital nystagmus. J Pediatr Ophthalmol Strabismus 1998;35:232–3.
13. Dell'Osso LF, Williams RW. Ocular motor abnormalities in achiasmatic mutant Belgian sheepdogs: unyoked eye movements in a mammal. Vis Res 1995;35:109–16.
14. Dell'Osso LF, Williams RW, Jacobs JB, Erchul DM. The congenital and see-saw nystagmus in the prototypical achiasma of canines: comparison to the human achiasmatic prototype. Vis Res 1998;38:1629–41.
15. Dell'Osso LF, Hertle RW, Williams RW, Jacobs JB. A new surgery for congenital nystagmus: effects of tenotomy on an achiasmatic canine and the role of extraocular proprioception. J AAPOS 1999;3:166–82.
16. Dell'Osso LF, Jacobs JB. An expanded nystagmus acuity function: intra- and intersubject prediction of best-corrected visual acuity. Doc Ophthalmol 2002;104:249–76.
17. Dell'Osso LF, van der Steen J, Steinman RM, Collewijn H. Foveation dynamics in congenital nystagmus. I: Fixation. Doc Ophthalmol 1992;79:1–23.
18. Sheth NV. The Effects of Afferent Stimulation on Congenital Nystagmus [master's thesis]. Cleveland: Case Western Reserve University; 1994.
19. Mangione CM, Lee PP, Pitts J, et al. Psychometric properties of the National Eye Institute Visual Function Questionnaire (NEI-VFQ). NEI-VFQ Field Test Investigators. Arch Ophthalmol 1998;116:1496–504.
20. Mangione CM, Lee PP, Gutierrez P, et al. Development of the 25-item National Eye Institute Visual Function Questionnaire. Arch Ophthalmol 2001;119:1050–8.
21. Calhoun JH, Harley RD. Surgery for abnormal head position in congenital nystagmus. Trans Am Ophthalmol Soc 1973;71: 70–83.
22. Carlow TJ. Medical treatment of nystagmus and ocular motor disorders. Int Ophthalmol Clin 1986;26:251–64.
23. Blekher T, Yamada T, Yee RD, Abel LA. Effects of acupuncture on foveation characteristics in congenital nystagmus. Br J Ophthalmol 1998;82:115–20.
24. Cooper EL, Sandall GS. Surgical treatment of congenital nystagmus. Arch Ophthalmol 1969;81:473–80.
25. Helveston EM, Ellis FD, Plager DA. Large recession of the horizontal recti for treatment of nystagmus. Ophthalmology 1991;98:1302–5.
26. Kirschen DG. Auditory feedback in the control of congenital nystagmus. Am J Optom Physiol Opt 1983;60:364–8.
27. Mallett RF. The treatment of congenital idiopathic nystagmus by intermittent photic stimulation. Ophthalmic Physiol Opt 1983;3:341–56.
28. Hertle RW. Protocol 99-EI-0152: Horizontal Rectus Tenotomy in the Treatment of Congenital Nystagmus. Bethesda, MD: The National Eye Institute, National Institutes of Health; 1999. Available at: http://www.clinicaltrials.gov/ct/show/NCT00001866?order=1. Accessed August 4, 2003.
29. Goto K, Muranushi Y. Treatment of nystagmus present in the change of head positions—use of ATP [in Japanese]. Jibiinkoka 1967;39:879–90.
30. Pratt-Johnson JA. The surgery of congenital nystagmus. Can J Ophthalmol 1971;6:268–72.
31. Pratt-Johnson JA. Results of surgery to modify the null-zone

position in congenital nystagmus. Can J Ophthalmol 1991;26: 219–23.
32. Parks MM. Symposium nystagmus. Congenital nystagmus surgery. Am Orthop J 1973;23:35–9.
33. Nelson LB, Wagner RS, Harley RD. Congenital nystagmus surgery. Int Ophthalmol Clin 1985;25:133–8.
34. Flynn JT, Dell'Osso LF. Surgery of congenital nystagmus. Trans Ophthalmol Soc UK 1981;101:431–3.
35. Dell'Osso LF. Nystagmus basics. Normal models that simulate dysfunction. In: Hung GK, Ciuffreda KJ, eds. Models of the Visual System. New York: Kluwer Academic/Plenum; 2002;711–39.
36. Shallo-Hoffmann J, Faldon M, Tusa RJ. The incidence and waveform characteristics of periodic alternating nystagmus in congenital nystagmus. Invest Ophthalmol Vis Sci 1999;40: 2546–53.
37. Shallo-Hoffmann J, Riordan-Eva P. Recognizing periodic alternating nystagmus. Strabismus 2001;9:203–15.
38. Hertle RW, Zhu X. Oculographic and clinical characterization of thirty-seven children with anomalous head postures, nystagmus, and strabismus: the basis of a clinical algorithm. J AAPOS 2000;4:25–32.
39. Dell'Osso LF, Daroff RB. Congenital nystagmus waveforms and foveation strategy. Doc Ophthalmol 1975;39:155–82.
40. Gresty M, Halmagyi GM, Leech J. The relationship between head and eye movement in congenital nystagmus with head shaking: objective recordings of a single case. Br J Ophthalmol 1978;62:533–5.
41. Buttner-Ennever JA, Cohen B, Horn AK, Reisine H. Pretectal projections to the oculomotor complex of the monkey and their role in eye movements. J Comp Neurol 1996;366:348–59.
42. Eisenman LM, Sieger DD, Blatt GJ. The olivocerebellar projection to the uvula in the mouse. J Comp Neurol 1983;221: 53–9.
43. Kimura M, Takeda T, Maekawa K. Contribution of eye muscle proprioception to velocity-response characteristics of eye movements: involvement of the cerebellar flocculus. Neurosci Res 1991;12:160–8.
44. Hertle RW, Chan C, Galita DA, et al. Neuroanatomy of the extraocular muscle tendon enthesis in macaque, normal human, and patients with congenital nystagmus. J AAPOS 2002; 6:319–27.
45. Dell'Osso LF, Jacobs JB. A robust, normal ocular motor system model with congenital nystagmus (CN) including braking and foveating saccades. In: Sharpe JA, ed. Neuro-ophthalmology at the Beginning of the New Millennium: Proceedings of the International Neuro-ophthalmology Society Meeting, Toronto, Ontario, Canada, September 10–14, 2000. Englewood, NJ: Medimond Medical Publications; 2000:107–11.
46. Jacobs JB. An Ocular Motor System Model That Simulates Congenital Nystagmus, Including Braking and Foveating Saccades [dissertation]. Cleveland: Case Western Reserve University; 2001.