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Longitudinal Studies and Eye-Movement-Based Treatments of Infantile Nystagmus Syndrome: Estimated and Measured Therapeutic Improvements in Three Complex Cases

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ABSTRACT

Introduction and Purpose: To demonstrate the utility of using eye-movement data to reveal the diagnostic characteristics of infantile nystagmus syndrome (INS), determine treatment, and both estimate and document therapeutic improvements in three patients with well-developed foveation periods, fairly broad, lateral gaze "nulls," head turns, strabismus, and complex, multiplanar nystagmus.
Patients and Methods: Infrared reflection, magnetic search coil, and high-speed digital video systems were used to record the eye movements of INS patients, pre- and post-Kestenbaum null-point correction surgery (horizontal or vertical). Data were analyzed and estimations made, using the eXpanded Nystagmus Acuity Function (NAFX) that is part of the OMtools toolbox for MATLAB.
Results: In all three subjects (S1–S3), both peak NAFX and longest foveation domain (LFD) improved from their pre-Kestenbaum values. S1: 0.700–0.745 (6.4%) and 25–34° (36%), respectively. S2: 0.445–0.633 (42.4%) and >40° to >50° (10%), respectively. S3: 0.250–0.300 (20%) and 13° to ≫18° (see text), respectively.
Conclusions: S1: Even at the high ends of the pre-therapy NAFX and LFD spectra, INS foveation (and therefore, visual-function) improvements may be adequate to justify nystagmus surgery and provide clinical improvements beneficial to the patient. S2: INS foveation improvements in the vertical plane are equal to those originally estimated using the horizontal data in prior patients. S3: Two apparent NAFX peaks can be converted into a very broad peak by surgery based on the preferred lower peak.

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Introduction

In many patients, clinical observations alone cannot reliably differentiate infantile nystagmus syndrome (INS) from fusion maldevelopment nystagmus syndrome (FMNS).[1] This is important since they require different surgical considerations (e.g., INS null points vs. Alexander's law damping in FMNS). Also, clinical observations cannot: (1) use head turns to accurately and repeatedly determine the angle of the INS "null" or the required amount of surgical correction; (2) differentiate good from poor foveation (necessary to determine efficacy of surgical intervention); (3) estimate therapeutic improvements (peak and gaze-angle visual acuities); or (4) document other specific visual function improvements actually resulting from therapy. Eye-movement data analysis provides an objective basis for accurate diagnosis of INS. In conjunction with analysis using the eXpanded Nystagmus Acuity Function (NAFX),[2] these data also allow reliable predictions and measures of the above therapeutic improvements; these are of immense help in the physician's and, ultimately, the patient's decision regarding surgery or other therapies. Finally, the NAFX analysis of eye-movement data provides documentation of both the actual beneficial and the detrimental effects of putative INS therapy.[3] One of the main objectives of this paper is to illustrate the use of eye-movement data and their analyses for each of these factors in INS treatment of complex,

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multiplanar cases; they could *not* be accurately evaluated from clinical observations alone.

Patients and methods

Patients

The first patient (S1) was a male who was initially seen elsewhere at the age of 2 years with the clinical diagnosis of possible FMNS. His confrontation-field, anterior-segment, dilated-fundus including optic-nerve exams were normal. There was no family history of nystagmus; his mother had amblyopia and strabismus. The patient's father noted his "shaky eyes" shortly after birth; that was confirmed at the age of 3 by the referring physician who waited to see if he would "outgrow" it. The patient sat close to the TV and held reading material close. An MRI (to rule out lesions and acquired nystagmus) was normal. The diagnosis was amblyopia OD, nystagmus (probably congenital), and exotropia. Table 1 summarizes the clinical data. When examined in our lab, we found his stereo acuity to be 20" of arc, probably due to the good controlled intermittent nature of his exotropia. The patient complained of "things shaking sometimes." Based on our eye-movement analysis (see Results), the following options remained: (1) continue with BO prisms with −1.00 S OU added to his refraction to damp the INS; (2) perform a Kestenbaum procedure to shift and broaden the INS high-acuity range; (3) correct the strabismus plus a tenotomy and reattachment (T&R) of the unoperated muscles to damp the INS; or (4) perform a bimedial recession procedure to damp the INS despite the intermittent strabismus. Despite the positive results using the BO prisms, the latter approach was deemed to be too risky. We decided upon the 4-muscle Kestenbaum procedure and it was performed using equal 6 mm recessions (LLR and RMR) and resections (LMR and RLR) of the extraocular muscles. Had the strabismus been static, adjustments would have been made to achieve both INS damping and strabismus correction.

The second patient (S2) was a female who was first noted elsewhere to have INS at the age of 6 weeks (presumably present since birth); she had a cousin who reportedly also had a history of nystagmus from birth. S2 had strabismus and underwent a strabismus procedure elsewhere at age 20. At 29 years old, she was seen elsewhere with the complaint that her nystagmus had progressively "worsened" since her strabismus surgery. She complained of: "blurring" at distance and at near and that "things now seem to occasionally move around;" occasional horizontal double vision, primarily at near; and denied ataxia or any other specific neurologic deficits nor has she had any relapsing and remitting episodes suggestive of neurologic conditions. Aside from a history of headaches, no other relevant symptoms or family history were uncovered. Transiently she appeared to have a rotary, almost see-saw-like component superimposed on the horizontal nystagmus. Intense attempts to view objects worsened the nystagmus while attempts at convergence made it slightly better. Her fundus exam was unremarkable; Table 2 summarizes the clinical data. An MRI, blood tests, and a TORCH titer were performed. The MRI showed a mild Chiari I type malformation with no hydrocephalus nor syrinx and no associated cerebellar or brainstem problems; metabolic and vascular workups were negative. The patient was referred to our laboratory for eye-movement recordings to determine whether she had only INS or both INS plus an acquired nystagmus and to investigate the possibility of nystagmus surgery to decrease her nystagmus amplitude. Our eye-movement recordings revealed a complex, multiplanar nystagmus combining INS and see-saw nystagmus (SSN). We presumed the SSN was acquired and was superimposed on the INS. We recommended a vertical Kestenbaum procedure to move the up-gaze "null"

Table 1. Clinical data for subject 1.

Age	Refraction OD/OS	Visual acuity OD/OS/OU	Notes	Treatment	EMR
2	+1.50 + 3.00 × 110 +1.00 + 2.50 × 75	0.10/0.20/0.25	FMNS? 20D Int XT LE preferred		
4		0.4/0.5/0.5+	Convergence damping		
5		0.33/0.33/0.33	Null in LG	7D BO prisms[a]	
6–8		0.2 to 0.33+/0.2 to 0.33−/0.25+ to 0.33	20–40° right head turn		
10		0.29−/0.33/0.5LG; 0.25RG; 0.8Nr	Sent for EMR	6 mm LLRc & RMRc +6 mm LMRx & RLRx	Pre-op, 1 week, & 2 & 4 months Post-op
4 months Post-op		0.2/0.2/0.29 & 1.0Nr	Ortho, 6/9 dots titmus		
17		0.4−2/0.5/0.5 + 2 & J1	Ortho, + fly, 3/3 animals, small R head turn		

Visual acuity in the patient's preferred head posture.

FMNS? = thought to be Fusion maldevelopment nystagmus syndrome; EMR = eye movement recordings; Int XT = intermittent exotropia; LG = left gaze; BO = base out; RG = right gaze; Nr = near; LL = left lateral; RM = right medial; LM = left medial; RL = right lateral; Rc = recessions; Rx = resections; Ortho = orthotropic

[a]−1.00S OU not added to refraction

Table 2. Clinical data for subject 2.

Age	Refraction OD/OS	Visual acuity OD/OS/OU	Notes	Treatment	EMR
6 weeks			INS & Strabismus		
20			XT	4 mm LLRc & 4 mm LMRx	
29		0.33–1/0.29–2	4D XT LG 12D XT PP 8D XT RG "Null" UG SSN	Sent for EMR	
30				5 mm RSRc & LSRc +5 mm RIRx & LIRx	Pre-Op
42		0.33 to 0.5 OU		Sent for EMR	
43					Post-Op

Visual acuity in the patient's preferred head posture.
INS = infantile nystagmus syndrome; EMR = eye movement recordings; XT = exotropia; LG = left gaze; PP = primary position; RG = right gaze; LL = left lateral; LM = left medial; Rc = recessions; Rx = resections; LG = left gaze; PP = primary position; UG = up gaze; SSN = see-saw nystagmus; RS = right superior; LS = left superior; RI = right inferior; LI = left inferior.

down to primary position. That 4-muscle procedure was performed elsewhere and post-operative recordings were not obtained at that time. At 42 years old, the patient was seen elsewhere for complaints of loss of hand strength and pain; tests for MS remained negative. Relevant to her nystagmus, she felt that her acuity and nystagmus had slowly worsened and was again problematic. At 43 years old, we again recorded her eye movements; this was our first opportunity to record her eye movements after the surgery—13-year post-vertical Kestenbaum procedure.

The third patient (S3) was a female whose horizontal nystagmus was first observed "at birth;" later the elliptical nature of the nystagmus was noted. At age 14, she was diagnosed elsewhere with INS with a "rotary" component. She preferred an ~18° head turn to the right—eyes left; Table 3 summarizes the clinical data. She had strabismus and no stereo acuity (>1,600"). Her fundus exam was normal. She was referred to our laboratory for eye-movement recordings to determine the type and amount of nystagmus surgery required to straighten her head turn. Her clinical diagnosis was pendular, rotary INS (elliptical) plus SSN. We found a "null" at 18° left gaze and suggested an MRI of the optic chiasm to explore the possibility of achiasma and recommended a Kestenbaum procedure. If the vertical component was problematic after the horizontal surgery, T&R of the vertical rectus (and possibly the oblique) muscles could be considered after allowing for re-establishment of the blood supply. At 15 years old, we recorded her eye movements, 1-year post-Kestenbaum procedure and at 21 years old, we recorded her eye movements, 1-year post-superior rectus recessions.

Methods

Recording

A high-speed digital video system was used for the eye-movement recording. The system (EyeLink II, SR Research, Mississauga, ON, Canada) had a linear range of ±30° horizontally and ±20° vertically. System sampling frequency was 500 Hz, and gaze position accuracy error was 0.5–1° on average. The data from this system were digitized at 500 Hz with 16-bit resolution. The signal from each eye was calibrated with the other eye behind cover to obtain accurate position information; the foveation periods were used for calibration. For this method and infrared reflection (see below), eye positions and velocities (obtained by analog differentiation of the position channels) were displayed on a strip chart recording system (Beckman Type R612 Dynograph).

Some horizontal eye-movement recordings for S1 were made using infrared reflection (Applied Scientific Laboratories, Waltham, MA, USA). In the horizontal plane, the system was linear to ±20° and monotonic to ± 5–30° with a sensitivity of 0.25°. The IR signal from each eye was calibrated with the other

Table 3. Clinical data for subject 3.

Age	Refraction OD/OS	Visual acuity OD/OS/OU	Notes	Treatment	EMR
14	+1.50 + 0.75 × 100/+1.75 + 1.25 × 64	0.25/0.2	Strabismus; INS with "rotary" component; ~18° right head turn	Sent for EMR	
			P/rotary (elliptical) INS + SSN; 18° null in LG	5.5mm RMRc & LLRc + 5.5 mm RLRx & LMRx	Pre-Op
15					Post-Op
18	+1.50 + 1.25 × 108/+1.00 + 1.75 × 63	0.25/0.2	Slight right head turn		
19		0.25 OU	UG with chin down		
20		0.29 OU	Slight right head turn	5 mm RSRc & LSRc	
21					Post-Op

Visual Acuity in the patient's preferred head posture.
SSN = see-saw nystagmus; LG = left gaze; Rc = recessions; Rx = resections; RM = right medial; LL = left lateral; RL = right lateral; LM = left medial; RS = right superior; LS = left superior; UG = up gaze; SSN = see-saw nystagmus.

eye behind cover to obtain accurate position information and to document small tropias and phorias hidden by the nystagmus. The total system bandwidth (position and velocity) was 0–100 Hz. The data were digitized at 400 Hz with 12-bit resolution.

Some horizontal eye-movement recordings for S2 were made using a magnetic search coil method with 6-foot field coils (CNC Engineering, Seattle, WA, USA). The coil system bandwidth was 0–150 Hz, linear range of greater than ±20° and sensitivity of 0.1° in all three planes. The subject's head remained within the 30 cm cube of the magnetic field where the translation artifact was less than 0.03°/cm. Horizontal and vertical rotations of the coils of up to 20° produced less than 0.5° of crosstalk in the torsional channel. Data were filtered (bandwidth 0–90 Hz) and digitized at 200 Hz with 16-bit resolution using a PCI-MIO-16XE50 DAQ board (National Instruments, Austin, TX, USA). Scleral-coil (Skalar, Delft, the Netherlands) gains were calibrated using a protractor device capable of rotations in each plane. Coil data were adjusted for bias during analysis; the mean foveation position of each eye was set to 0° to align it to the target position during fixation in primary (central, see below) position. This is routinely done for most other types of eye-movement recording methods and although it does not guarantee that the 0° eye position coincides with a target image on the center of the fovea, it does place 0° at the subject's chosen point of fixation; except for rare cases of extrafoveal fixation or certain types of foveal aplasia, it is reasonable to equate 0° with the foveal center, especially when the subject has good vision.

For all recording methods, monocular primary-position bias and calibration adjustments allowed accurate eye-position information and documentation of small tropias and phorias hidden by the nystagmus. It also ensured that we were always analyzing the fixating eye, especially when the subject switched fixation from one eye to the other. All recordings were performed without any refraction. We have not observed that the saccadic or smooth-pursuit gains of a bright laser spot are affected by a subject's refraction.

Protocol

Written consent was obtained from the subjects before the testing. All test procedures were carefully explained to the subjects before the experiment began, and were reinforced with verbal commands during the trials. Subjects were seated in a chair with headrest and either a bite board or a chin stabilizer, far enough from an arc of red LEDs to prevent convergence effects (>5 feet). At this distance, the LED subtended less than 0.1° of visual angle. The room light could be adjusted from dim down to blackout to minimize extraneous visual stimuli. An experiment consisted of from 1 to 10 trials, each lasting under a minute with time allowed between trials for the subjects to rest. Trials were kept this short to guard against boredom because CN intensity is known to decrease with inattention.

Analysis

All the analyses were conducted using the MATLAB environment (The MathWorks, Natick, MA, USA) and OMtools software (available from http://www.omlab.org). Only eye position was sampled directly; velocity data for analysis were obtained from the sampled position data by a central-point differentiator with $n = 3$ (i.e., using third points pre- and post-center). Position data were low-pass filtered with a fourth-order Butterworth filter with the cutoff frequency of 50 Hz to reduce the noise while minimally affecting the saccades. Data were filtered forward and backward to eliminate phase distortion. Analysis was always done on the fixating eye. Segments with inattention or blinking were not used for this analysis.

The NAFX (part of OMtools) was used to measure T&R-induced foveation changes in the nystagmus at primary position and various gaze angles.[2,4,5] It is an objective and repeatable measure of INS waveform foveation quality that is directly proportional to potential Snellen decimal visual acuity in patients with no additional visual sensory deficits and the post-therapy changes of which are directly proportional to visual acuity changes in all INS patients, irrespective of the presence of afferent visual sensory deficits.[6–8] (As shown in the figures of Chapter 7, the NAFX program provided potential visual acuities as a comparison.) Details of the NAFX's theory and application may be found elsewhere.[2] In this study, each plotted NAFX point represents an average of several fixations, each consisting of 3–10 cycles (1–3 s) of steady foveation immediately following target acquisition.[9] All analyses adhered to the long-established and refined procedures used in our laboratory.

Results

Subject 1: Horizontal INS with high, lateral NAFX peak and broad LFD

Diagnosis and waveform characteristics

Eye-movement data revealed that S1 had typical INS waveforms; thus, the original clinical diagnosis of FMNS was changed to INS. His waveforms were jerk (J), jerk with extended foveation (Jef), pseudocycloid (PC), pseudojerk (PJ), and alternating direction jerk while viewing targets from −10° (left) to +5° (right). The ~3 Hz INS damped and foveation improved with both left gaze and convergence. There was a rare amplitude dissociation in left gaze where the left eye damped almost completely while the right eye had either Jef or PC. Figure 1 documents this dissociation both in time (Figure 1(a)) and as a phase plane (eye position vs. velocity) (Figure 1(b)) that shows a greater amount of left-eye data within the foveation window (i.e., the position and velocity criteria for good foveation) than right-eye data. However, due to the good foveation characteristics of the PC waveforms of the right eye, the NAFX value of the right eye (0.594) was approximately equal to that of the left (0.596) during that interval of an approximately threefold amplitude dissociation.

NAFX and LFD analysis

Figure 2 compares the plots obtained from NAFX values measured pre- and post-Kestenbaum procedure at horizontal gaze angles within the ±30° range tested. Prior to the

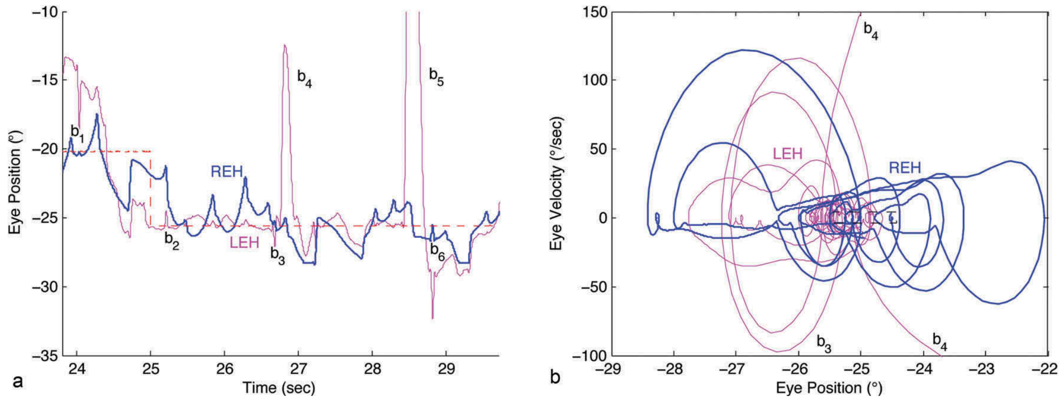


Figure 1. Time (a) and phase-plane (b) plots of the INS waveforms of S1 showing rare amplitude dissociation. The phase plane is from data between the second and fifth blinks. The dashed line indicates target position in (a) and the (±0.5° by ±4°/s) foveation window in (b) and $b_{\#}$-large- and small-numbered blinks. In this and Figures 3 and 5: REH: right eye horizontal; LEH: left eye horizontal; REV: right eye vertical; LEV: left eye vertical; RET: right eye torsional; LET: left eye torsional; right-eye data are shown with heavier lines; dash-dot circles and lines indicate the ±0.5° foveal extent. In all eye-movement figures, rightward, upward, and clockwise directions are positive (all eye-movement directions are defined from the subject's point of view).

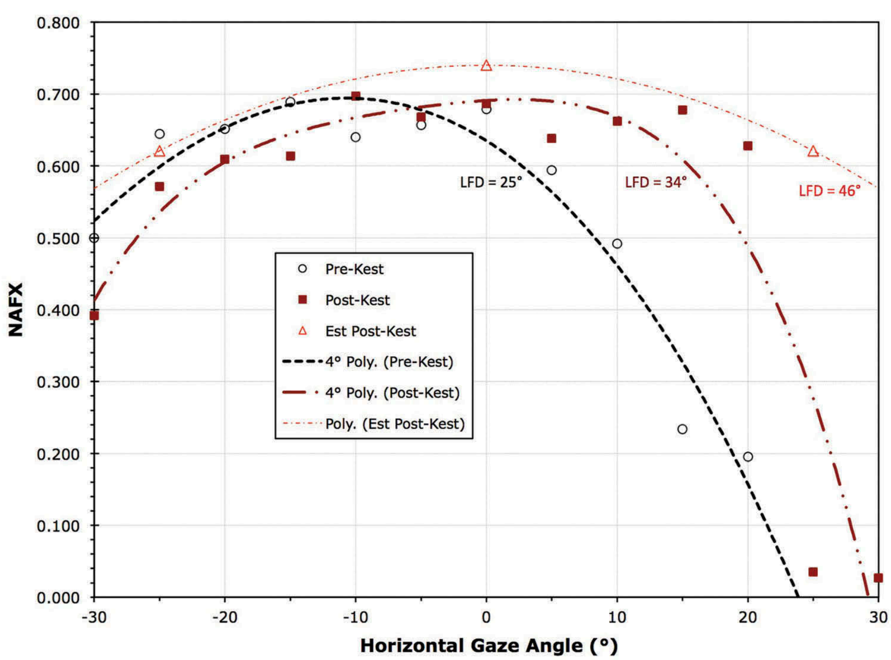


Figure 2. Plots of the NAFX vs. horizontal gaze angle for horizontal eye-movement data from S1 before and after the Kestenbaum procedure plus the estimated post-Kestenbaum plot for comparison. LFD values are shown for each curve. Trend lines were fourth-order polynomial fits to the data—see text for explanation. Rightward gaze angles are positive.

surgery, the NAFX peak was 0.700 at 10–15° in left gaze; the LFD was 25°. Based on those numbers, the estimated post-Kestenbaum NAFX peak was calculated to be 0.740 (a 6% improvement) at 0° and the LFD, 46° (an 83% improvement), as shown by the estimated curve. From the analysis of many patients, we have found that accurate fitting of the NAFX vs. gaze angle data was usually accomplished using a simple second-order polynomial. For example, a second-order fit of the pre-Kestenbaum data shown in Figure 2 had an r^2 value of 0.93338. However, the fit of the post-Kestenbaum data was not as good; the r^2 value was 0.78455. This did not accurately reflect the actual broadening indicated by the high-NAFX data points around primary position. To obtain a more accurate fit, we used fourth-order polynomial fits of both the pre- and post-Kestenbaum data. As expected, the already good fit to the pre-Kestenbaum data improved only slightly ($r^2 = 0.93514$) and the 25° LFD was unchanged. However, the r^2 value of the post-Kestenbaum data fit improved to 0.85386, and, although, this lowered the peak-NAFX value slightly (0.695), the LFD was 34° (a 36% improvement). Thus, the procedure resulted in a broader range of high-acuity waveforms centered near primary position.

Subject 2: Biplanar, diagonal INS + SSN with up gaze NAFX peak and very broad LFD

Diagnosis and waveform characteristics

Pre-operative eye-movement data revealed that S2 had the following typical INS waveforms: pendular (P), pendular with foveating saccades (Pfs), Jef, PC, and PJ. Vertically, there were a 4-Hz SSN component in phase with the horizontal INS (resulting in a diagonal INS, right eye moving downward and left eye upward as both moved rightward and vice versa); and a 5–10° peak-to-peak, 0.83 Hz SSN. Torsionally, there were also two components: a small, conjugate, asymmetric, pendular, 4 Hz waveform and a 10–15° peak-to-peak, conjugate, asymmetric, pendular, 0.83 Hz waveform. The clockwise component corresponded to the rising left and dropping right eye, typical of SSN (see Figure 3(a,b), which document these directional relationships and the complex scan paths during each SSN

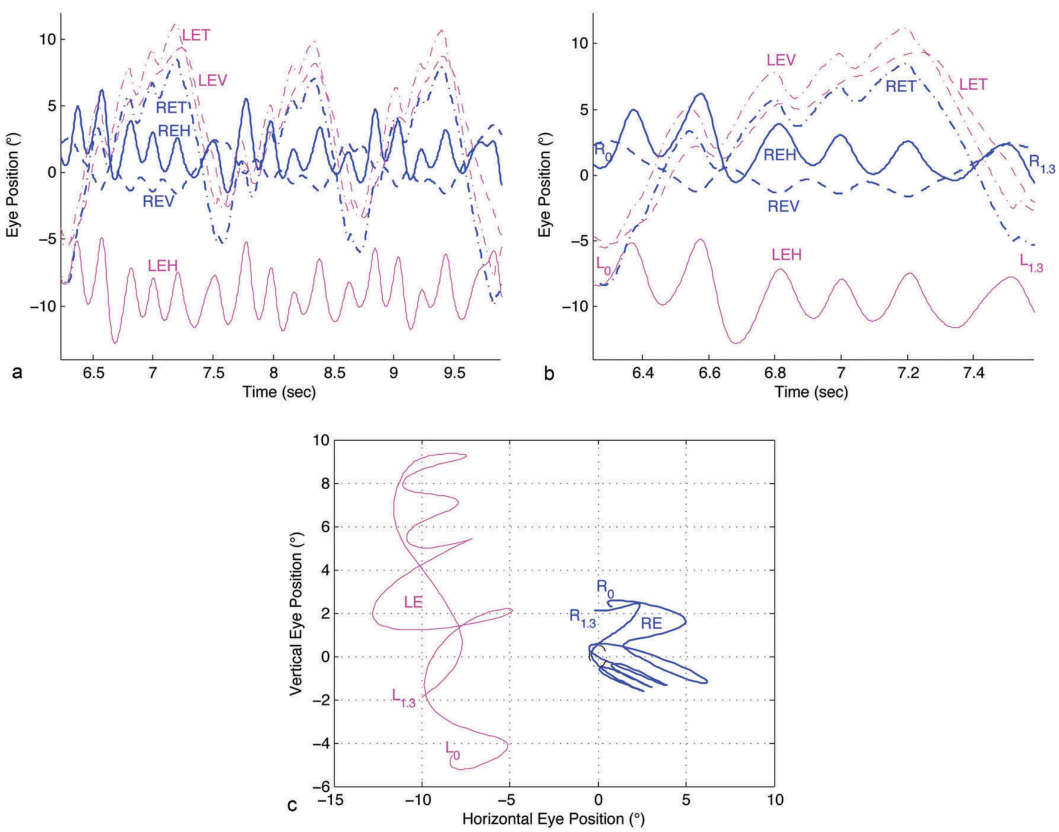


Figure 3. Plots of the INS waveforms of S2 showing: (a) the time relationships of the individual components in the multiplanar nystagmus while fixating a target at 0° with the RE (LE, 10° exotropic); (b) the time components during a single SSN cycle (~1.3 s); and (c) the "coil-like" scan paths of the fixating right and exotropic left eye during that single SSN cycle. Although not shown in (c), the plots in (b) demonstrate that as the RE went down, it also had cw torsion and when it went up, ccw torsion; the reverse was true for the LE. For clarity in (b) and (c), the initial and final time points of each eye are labeled with the subscripts "0" and "1.3", respectively.

cycle). As Figure 3(b,c) illustrates, during the downward peak of the 0.83 Hz SSN, target foveation was achieved by the right eye during the upper left portion of the 4 Hz waveform (i.e., after the upward motion of its 4 Hz SSN). Upon occlusion, the SSN of the fixating eye was less than that of the covered eye and left-eye fixation damped the torsional components of both eyes. Near fixation did not affect the nystagmus, left gaze resulted in higher amplitude INS (with no true "null" in right gaze), and 20° up gaze damped *all* nystagmus components.

NAFX and LFD analysis

Thirteen years post-vertical Kestenbaum procedure, vertical eye-movement data revealed both a reduction in INS amplitude and an improvement in the NAFX in primary position. Figure 4(a) compares the plots obtained from vertical NAFX values measured pre- and post-Kestenbaum procedure at gaze angles within the respective ±20° and ±10° ranges tested. Prior to the surgery, the broad NAFX peak was 0.445 at ~5° in up gaze; the LFD was >40°. Based on those numbers, the estimated post-Kestenbaum NAFX peak was calculated to be 0.594 (a 35% improvement) at 0° and the LFD, 50° (a 10% improvement), as shown by the estimated curve in Figure 4(a). After the surgery, the NAFX peak was 0.633 (a 42.4% improvement) at 0° and the LFD was >50°. Because the limited vertical data range measured did not allow a more accurate curve fit of the data or calculation of the LFD, the central portion of the data was fit with a linear function. Figure 4(b) shows the vertical peak-to-peak amplitude plots measured pre- and post-Kestenbaum procedure at gaze angles within the ranges tested. Prior to the surgery, the average vertical amplitudes varied from a low of 1.56° at 20° (up) to 4.75° at −3° (down). After the surgery, they varied from a low of 1.15° at 5° (up) to 2.69° at −10° (down). The primary-position average vertical amplitude of 4.70° decreased 72.6% to 1.29°.

We also used the two-dimensional NAFX[5] to assess the resulting radial improvements in the primary-position, multiplanar nystagmus. The radial eye-motion NAFX improved 42.4% from a pre-Kestenbaum NAFX of 0.444 in primary position to a post-Kestenbaum value of 0.633; in this case (as Figure 4(a) shows), the radial NAFX calculations mimicked those made from the vertical eye-movement component.

Subject 3: Biplanar INS with right and left NAFX peaks and small LFDs

Diagnosis and waveform characteristics

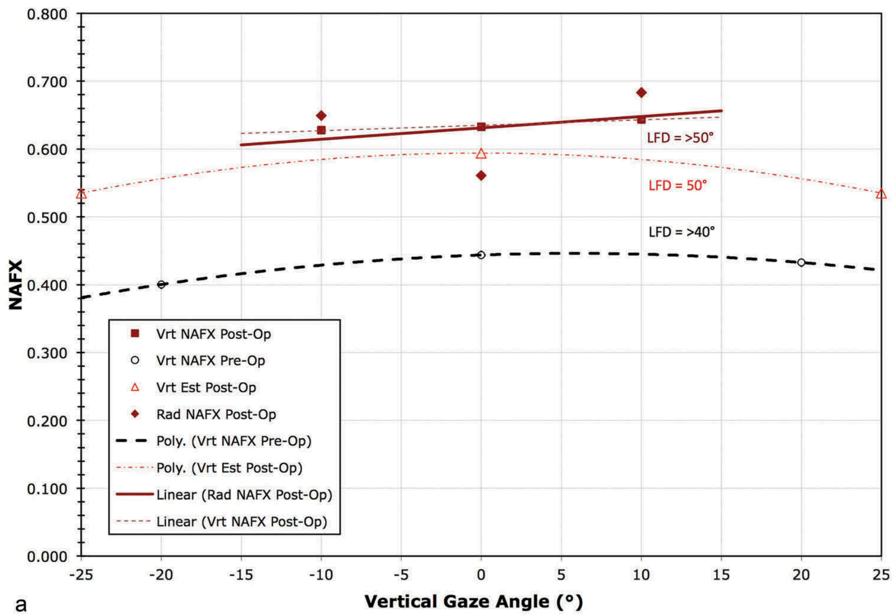
Pre-operative eye-movement data revealed that S3 had the following typical INS waveforms: P, Pfs, J, and Jef. The ~2.5 Hz INS damped and foveation improved somewhat with convergence. In addition, there was a disconjugate, pendular, SSN that superimposed on the INS to produce an elliptical nystagmus that was counter-clockwise in the right eye and clockwise in the left. Data from each eye, taken during fixation of that eye, revealed a latent component resulting in better foveation when each eye was in adduction. The peak-to-peak extents of the horizontal and vertical components of the INS waveforms were approximately 5° and 3°, respectively, for the right eye and 5° and 6° for the left eye. At different horizontal and vertical target positions, the fixating eye was predominantly OS in right gaze. Figure 5(a) shows the elliptical, see-saw scan paths (horizontal vs. vertical motion) of several cycles during fixation of the −20° horizontal target. Target foveation occurred after the upward portion of LE SSN while the deviated RE was at its lower portion.

NAFX and LFD analysis

Figure 5(b) shows the horizontal, vertical, and radial eye position vs. time plots of the INS waveforms of S3 during RE fixation at (0,0)° where both the horizontal and vertical components of the NAFX were similar. NAFX values calculated from each of the two components and from the radial motion showed that the latter did not track either the horizontal or the vertical calculations, so the radial data were used for the NAFX and LFD evaluations. Figure 6 compares the plots obtained from NAFX values measured pre- and post-Kestenbaum procedure at gaze angles within the ±30° range tested. Prior to the surgery, the NAFX peaks were 0.250 at 18° left gaze (preferred) and 0.430 at 18° right gaze; the LFDs were 13° and 11°, respectively. Despite the lower numbers for the peak in left gaze, the patient preferred to use it and we based our estimated predictions on it. The estimated post-Kestenbaum NAFX peak was calculated to be 0.442 (a 76.8% improvement) at 0° and the LFD, 29° (a 123% improvement), as shown by the estimated curve in Figure 6. Note: the estimated curve is based on the usual second-order fit, which was clearly not the case here. After the surgery, the NAFX peak in left gaze improved 25% to 0.300 and extended 20° to 0° before improving further in right gaze past 25°. The later, vertical recession surgery accomplished the removal of the chin-down head position.

Discussion

Eye-movement data provided definitive diagnoses, quantified the nystagmus signal and allowed: (1) estimation of potential therapeutic improvements in both peak acuity and the range of gaze angles with high acuity; (2) objective measurements of these post-therapy improvements; and (3) longitudinal documentation of INS characteristics—we provide data for S1 over 8 years, S2 over 43 years, and



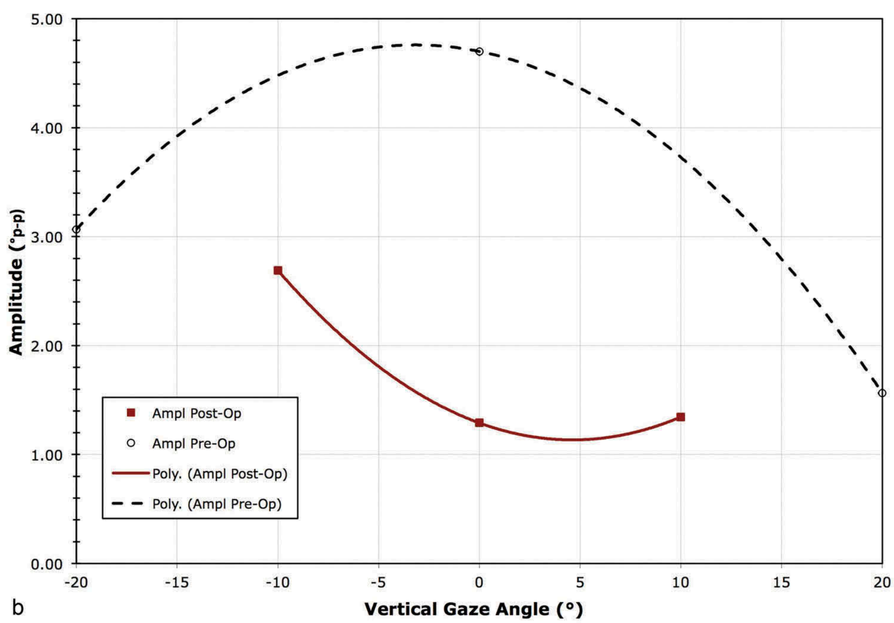


Figure 4. (a) Plots of the NAFX vs. vertical gaze angle for vertical and radial eye-movement data from S2 before and after the vertical Kestenbaum procedure plus the estimated post-Kestenbaum plot for comparison. LFD values are shown for each curve. (b) Plots of INS amplitude vs. gaze angle for S2 before and after the vertical Kestenbaum procedure. All trend lines were second-order polynomial fits to the data except for the linear fits to the vertical and radial post-op data. Upward gaze angles are positive.

S3 over 21 years. Although careful clinical analysis may allow accurate identification and proper treatment of *some* cases of uniplanar (e.g., horizontal) INS,[10] as the time plots, phase plane, and scan paths in this paper illustrate, complex uni- and multiplanar cases require monocularly calibrated eye-movement data to identify the foveating eye, the characteristics of the nystagmus, the conditions under which accurate foveation occurs, and the most effective therapy.

Note: Identification of the "foveating" eye at any point in the record is not synonymous with the "dominant" eye. Patients with INS (and FMNS) often switch the foveating/fixating eye for targets at different gaze angles or even during fixation of a target at a particular gaze angle.

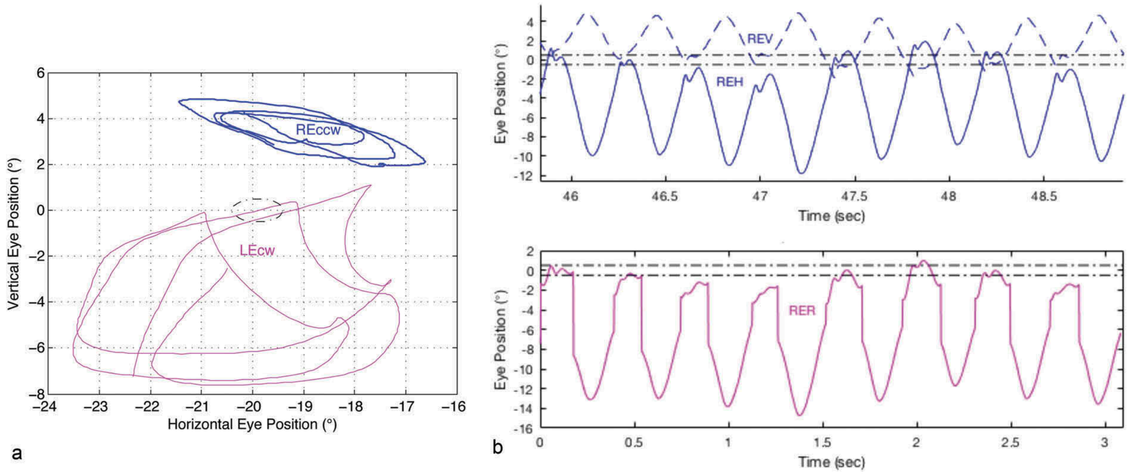


Figure 5. Illustrations of scan paths (a) and eye position vs. time plots (b) of the INS waveforms of S3 during LE fixation at 0°. Shown in (b) are the horizontal and vertical components and the calculated radial component during RE fixation.

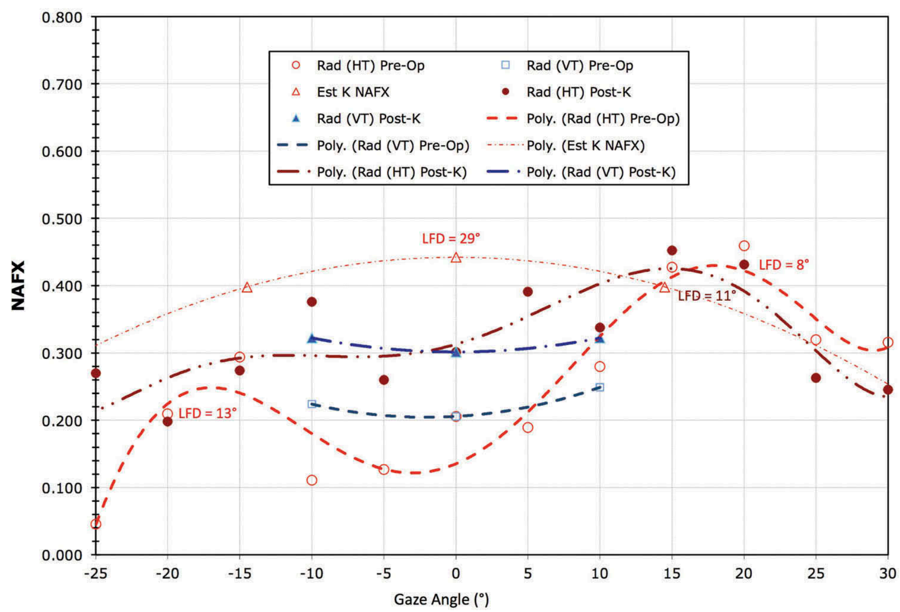


Figure 6. Plots of the NAFX vs. gaze angle for radial eye-movement data from S3 before and after the Kestenbaum procedure plus the estimated post-Kestenbaum plot for comparison. LFD values are shown for each curve. Radial data are shown for both horizontal (HT) and vertical (VT) target positions.

Performing ocular motor analyses on the non-fixating eye is meaningless regarding potential or measured visual acuity and is problematic in determining effective therapy.

Subject 1: Horizontal INS with high, lateral NAFX peak and broad LFD, convergence damping, and strabismus

If the peak NAFX value of 0.700 for S1 had been at or near primary position instead of in left gaze, the small estimated improvement could contraindicate a 4-muscle T&R procedure. The LFD of 25° could also be used as a possible contraindication to a T&R, despite the estimated improvement to 46°. However, due to the lateral placement of the NAFX peak, we were able to assess the improvements obtained from the 4-muscle T&R that is intrinsic to the Kestenbaum procedure despite the relatively high pre-surgery NAFX and LFD values. As a result, we verified that the curves used to estimate post-T&R improvements are equally reliable for high pre-surgery NAFX and LFD values. Thus, patients with high-foveation-quality INS waveforms who wish to maximize their visual function (e.g., for sports or other professional reasons) can opt to have eye-muscle surgery for their INS and their physicians can perform the surgery with confidence that even modest estimated improvements will actually result. An important observation from Figure 1 is that the cosmetic improvement of reduced INS amplitude does *not* necessarily correspond to improved foveation (NAFX) or visual acuity. As Figure 2 shows, despite no improvement in peak NAFX (or acuity), there was a shift of the NAFX peak to primary position and a broadening of the peak (and, therefore the high-acuity range of gaze angles). Thus, this patient alone demonstrates that studies that rely solely on INS amplitude (or intensity) improvement or on peak visual acuity measures are prone to false-negative outcomes. Thus, eye-movement data provided: positive identification of the nystagmus type; several therapeutic approaches not obvious from clinical evaluation alone; objective data upon which to make the best choice; and objective data to document the improvements.

Subject 2: Biplanar, diagonal INS + SSN with up gaze NAFX peak and very broad LFD

Despite the large pre-vertical Kestenbaum differences between the peak INS amplitude and those at ±20°, the NAFX values were essentially the same (see Figure 4(a,b). Post-vertical Kestenbaum procedure, all vertical amplitudes were reduced but there remained a twofold difference in the vertical INS amplitudes of S2 between +10° (up) and −10° (down); down gaze was greater than up gaze yet the NAFX values were approximately equal (see Figure 4(b)). These vertical amplitude differences with little or no resulting NAFX differences further illustrate that INS amplitude (or, its product with frequency, i.e., “intensity”) is *not* a good measure of either foveation quality or visual acuity; this was previously shown for horizontal INS data[11] and also demonstrated during the period of amplitude dissociation of S1, when the NAFX values of the two eyes were approximately equal. The small-signal gain reduction produced by a therapeutic procedure results in a prolonged foveation time but the following acceleration away from the target may remain unchecked by a foveating saccade for a longer time post-therapy than it was pre-therapy. Thus, there is better acuity (due to the longer foveation time) despite the overall nystagmus waveform being larger than pre-therapy. Another possibility is that the post-therapy waveform differs from the pre-therapy waveform, with a longer foveation time in a larger, post-therapy waveform than was present in a smaller, albeit different, pre-therapy waveform. Therefore, *the use of INS amplitude or intensity as an outcome measure in clinical trials is problematic if the goal of therapy is improvement in visual function rather then cosmetic*. But, if there was no visual function advantage to up gaze (equal NAFX values), why did S2 prefer up gaze? INS patients do not select preferred gaze positions for cosmetic reasons since they are unaware of their INS waveform amplitudes. We can only speculate from the limited data collected at those points that there was better alignment in up gaze than in down gaze.

Normally, analysis of the major component of multiplanar INS will provide accurate data from which to estimate or document therapeutic improvements in target foveation. However, in cases where one component does not far exceed the other, target foveation quality can more accurately be determined using the two-dimensional NAFX on the radial motion data of the fixating eye. The horizontal component of S2’s INS was larger than the vertical, especially during the time interval when target foveation took place (see Figure 3). In this case, the two-dimensional radial NAFX values improved by 42.4% (as did the vertical NAFX values), reflecting the improvement from the vertical Kestenbaum procedure. It should be noted that because of the 0.83 Hz SSN that was superimposed on the 4 Hz INS waveform, good foveation occurred only during the ~0.4-s time intervals when the right eye was near the downward peak of the 0.83 Hz SSN cycle; those short intervals were separated by ~1.2 s during which the right eye was moving upward and back downward to its nadir (see Figure 3) and would adversely affect visual function in many real-life situations (e.g., sports, driving, etc.).

The vertical Kestenbaum procedure was apparently successful since it remained so 13 years later, confirming our longitudinal data from other patients showing that the objectively measured results of INS surgery are *permanent* and the “null” does not revert to/toward its pre-Kestenbaum position, as had been suggested in the absence of objective eye-movement data. Also, pre-vertical-surgery estimations of NAFX improvements, based on curves from horizontal NAFX data, were accurate; thus, *foveation improvements due to eye-muscle surgery are independent of the plane of the INS*. Thus, eye-movement data provided positive identification of the nystagmus SSN-delayed foveation periods; a therapeutic approach for a vertical "null;" objective data to predict therapeutic outcomes; and objective data to document the improvements.

Subject 3: Biplanar (elliptical) INS + SSN with 0.250 NAFX peak and 13° LFD, chin-down head position, and strabismus

The data from S3 identified a latent component that is usually clinically misreported as INS with "two" nulls (to date, an impossible manifestation in INS) because of the shift in the NAFX peak with the shift in fixating eye as it went into adduction. In fact, the control-system instability in INS has only one null under a fixed set of conditions. An INS null may shift with changes in the fixating eye, with pursuit or VOR motion, or with time (Asymmetric, (a)Periodic Alternating Nystagmus). With both eyes open, S3 chose to fixate with the adducting eye, giving rise to the twin peaks in the resulting NAFX plot of the fixating eye vs. gaze angle. Note: In the hundreds of cases we have studied with eye-movement data, this is the first exhibiting two NAFX peaks and where the lower peak (in left gaze) determined the preferred (right) head turn. The eye-movement data provided the foundation for the Kestenbaum procedure that was performed.

Unlike the slower SSN of S2, the SSN in S3 was synchronized with the 2.5 Hz INS waveform. Thus, as Figure 5(a) illustrates for left-eye fixation, target foveation was achieved during the upper portion of *each* cycle of the biplanar 2.5 Hz waveform. As the right-eye foveation data of Figure 5(b) show, the major horizontal component's contribution to poor foveation (~±2°) far exceeded the vertical component's (~±0.5°); thus, overall foveation improvement would require improvement of the horizontal component.

As the height and breadth of the post-Kestenbaum curve in Figure 6 show, there was improvement across all gaze angles from −25° to 15°, especially in the central 30°. This allowed better acuity without the need for head turns and alignments in this most-used area. Thus, eye-movement data: identified a latent component not obvious from clinical evaluation alone; documented a lesser peak NAFX; provided objective data to predict therapeutic outcomes; and provided objective data to document the improvements.

Taken together, these three cases demonstrate the use of eye-movement data to accurately diagnose INS, determine therapy, and to both predict and provide objective measures of, the short- and long-term results of that therapy. The clear and unambiguous documentation of the relationship between complex, multiplanar INS waveforms and target foveation provided by eye-movement data from each case allowed important, specific observations to be made and conclusions to be drawn that were not possible from clinical observations alone.

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Dedications

This paper is dedicated to the memory of Martin Steinbach (31 October 1941–24 June 2017), whom I first met in 1967 when I gave a lecture on nystagmus waveforms and control-system modeling to an MIT graduate class of Professor Larry Young; Marty was a student in that class. Over the ensuing 50 years, we maintained a friendship punctuated by getting together at ARVO and other eye-movement meetings, including the 2007 festschrift held in my honor in Cleveland. In addition to his sharp mind and our common scientific interests, Marty was a kind and good friend; I and all who were fortunate enough to know him will miss him.

-L. F. Dell'Osso

I am honored to be part of this paper dedicated to the memory of Dr Steinbach. I got to know him during my PhD studies with Dr Dell'Osso, and had many exchanges with him at the ARVO conferences held in Fort Lauderdale. Back in 2008, Dr Steinbach generously helped me with my green card application. He was very understanding when I reached out to him to ask for his help, wrote for me whatever I needed, and kindly got back to me very quickly despite his busy schedule. Thanks to his help, my application went through smoothly. I am so sorry to hear about his passing. He will be missed by many good friends and colleagues whom he has generously helped over the years.

-Z. I. Wang

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