21

Predicting Treatment Outcomes in Infantile Nystagmus: eXpanded Nystagmus Acuity Function (NAFX) Analysis of Ocular Motor Data

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21.1 Introduction

To provide treatment for a patient with infantile nystagmus syndrome (INS) (CEMAS Working Group 2001) with the maximal possible therapeutic effectiveness, the nystagmus must be accurately diagnosed and the waveform quality and characteristic changes with gaze and convergence angle must be determined. For instance, one cannot differentiate INS with a latent component from fusion maldevelopment nystagmus syndrome by clinical observation alone (Abel 2006; Wang & Dell'Osso 2009). This is important because the surgical approaches differ for the two types of nystagmus. Similarly, one cannot accurately determine the position of an INS "null" by either observing or measuring a patient's head turn or differentiate whether a head turn is due to an INS null or the Alexander's law damping of fusion maldevelopment nystagmus syndrome as the fixating eye is adducted. Clinical observation cannot determine whether poor visual acuity reflects poor foveation quality, afferent visual deficits, or both. For the effectiveness of a therapy, visual acuity measurement (either in primary position or at the null) is inadequate

The Challenge of Nystagmus. Edited by Chris Harris, Irene Gottlob and John Sanders.

to measure improvements in visual function.(Wang *et al.* 2006a, b; Wang *et al.* 2007b; Wang & Dell'Osso 2008, 2009) Finally, there currently exist no clinical measures from which one could estimate, *pre-therapy*, the expected *post-therapy* improvements in visual function. Using new analysis techniques applied to accurate eye-movement data, all of the above can now be achieved.

21.2 Methods

21.2.1 Recording

Eye-movement data were taken using state-of-the-art recording systems including infrared reflection, magnetic search coil, and high-speed digital video. Calibration was always monocular while the fellow eye was occluded to obtain accurate position information and to document small tropias and phorias hidden by the nystagmus.

21.2.2 Protocol

Written consent was obtained from subjects before the testing. All test procedures were carefully explained to the subject before experiments 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 light-emitting diodes (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. Experiments consisted of one to ten trials, each lasting under a minute with time allowed between trials for the subject to rest. Trials were kept this short to guard against boredom because INS intensity and foveation accuracy are known to decrease with inattention.

21.2.3 Analysis

Analyses used MATLAB with specially developed "OMtools" software available for download at www.omlab.org. The eXpanded Nystagmus Acuity Function (NAFX) is an OMtools function that evaluates the foveation quality of uni- and biplanar nystagmus waveforms and applies a numerical value between 0 and 1, where 1 is equated to the best-corrected visual acuity of individuals in different age groups (see Dell'Osso & Jacobs 2002; Jacobs & Dell'Osso 2010) Simulations were performed in Simulink using a behavioral ocular motor system model.

21.3 Results

21.3.1 NAFX analysis

Early in the study of INS, it became obvious that a method was needed to assess the quality of each waveform with respect to its ability to capture and hold the image of a target onto the fovea; the often used measures of amplitude, frequency, or, their product, intensity, were inadequate and only loosely correlated with visual acuity (Dell'Osso 1973). The first such attempts produced the nystagmus foveation function and the nystagmus acuity function; the latter refinement of the nystagmus foveation function was the precursor to the current NAFX (Sheth *et al.* 1995; Dell'Osso & Jacobs 2002). The NAFX extracts from eye-movement data all points that simultaneously satisfy position and velocity criteria set in for the patient being studied. From those points only (*all other eye-movement data are removed*) a specially designed algorithm further *discards* isolated data points that could not contribute to visual acuity and *combines* closely spaced points that could. From the resulting "foveation-period-data" a function using the statistics of those periods outputs several computed values, among which is the NAFX – a number between 0 and 1.0 that is the final measure of foveation quality and is linearly correlated to best-corrected visual acuity in the absence of afferent visual deficits. The NAFX allowed, for the first time, a method of inter- and intra-subject evaluations of INS waveforms that could be related to visual acuity. It provided the first *direct* outcome measure (see section 21.4.3 in the Discussion) of INS therapy that reflected visual function rather than cosmesis (e.g., amplitude).

21.3.2 Target acquisition time

Patients with INS complain that they are "slow to see." Indeed our ocular motor system model predicted target acquisition times far in excess of saccadic reaction times. That is, despite near normal saccadic reaction times, new targets were not foveated for intervals of time ranging from one to three times the period of each INS cycle. The ocular motor system model also predicted that the target acquisition times would vary depending on the time within an INS cycle that a target changed position (see Figure 21.1, top) (Wang & Dell'Osso 2007) That is, the closer the time of target change to intrinsic saccades of a particular INS waveform, the longer the target acquisition time. Data from patients with INS confirmed that prediction for those waveforms as well as jerk waveforms (see Figure 21.1, bottom). Note that for the patient with asymmetric, (a)periodic alternating nystagmus (APAN), the variation of target acquisition time was unaffected by the amplitude of the waveform. Furthermore, the four-muscle tenotomy and reattachment procedure (T&R) reduced target acquisition times (Wang & Dell'Osso 2008).

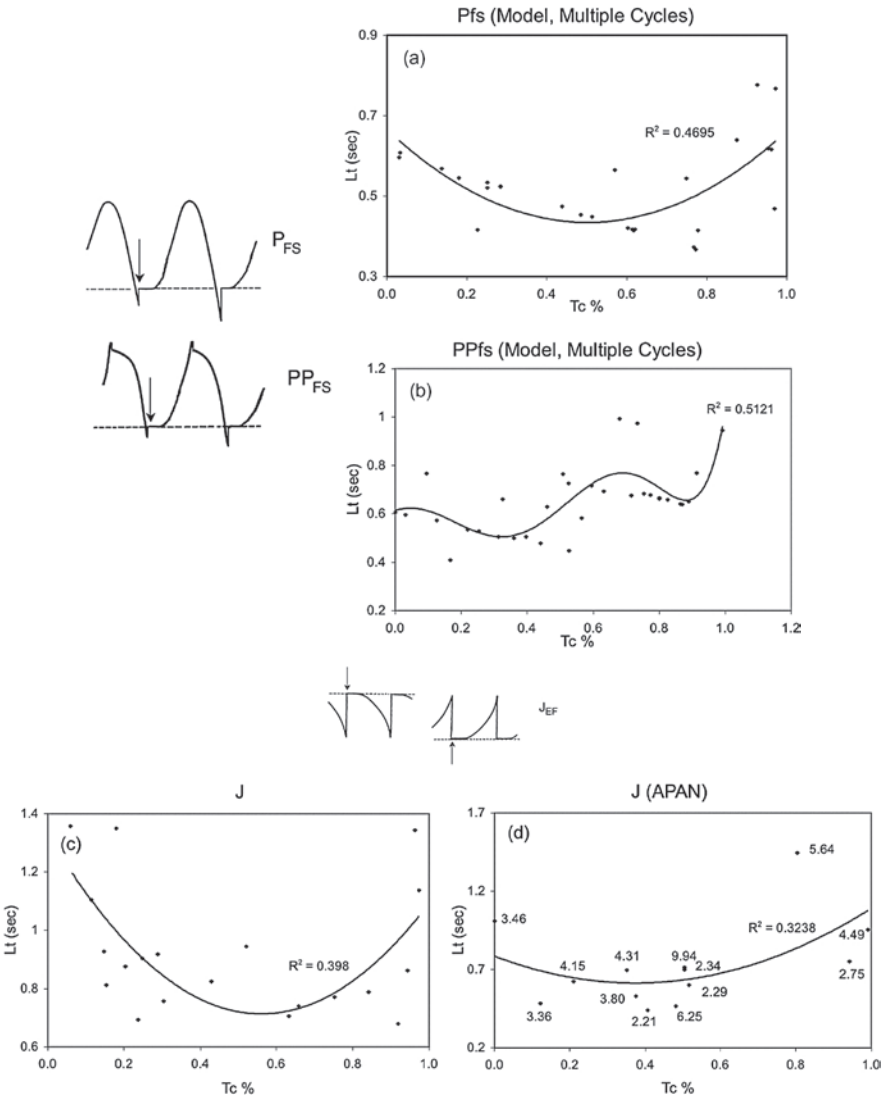

Figure 21.1 (Top) Model predictions of the variation of target acquisition time (Lt) with target timing within the Pfs and PPfs INS waveforms (0–1.0 representing 0–100% of the INS cycle). (Bottom) Patient data showing the variation of target acquisition time with target timing within the J INS waveform for two patients, one with APAN (the numbers next to each data point are the peak-to-peak amplitudes of the waveforms). Lt, target acquisition time; Pfs, pendular with foveating saccades; PPfs, pseudopendular with foveating saccades; J, jerk; APAN, asymmetric, (a)periodic alternating nystagmus.

21.3.3 INS therapies

Ocular motor data-driven studies of INS have produced several successful therapies. They include base-out prisms (Dell'Osso *et al.* 1972), soft contact lenses, (Abadi 1979; Dell'Osso *et al.* 1988; Taibbi *et al.* 2008), and the T&R procedure. (Dell'Osso 1998; Dell'Osso *et al.* 1999; Hertle *et al.* 2003, 2004). INS therapies are patient specific, being determined by the eye-movement characteristics of the patient's INS waveforms. They are not interchangeable and no single procedure should ever be used for, or claimed to produce, the best therapy for all patients. That being said, the treatment of INS does not depend on, and should not be influenced by, the presence, absence, or severity of any associated afferent visual deficits (i.e., based on the ocular motor analysis of their INS, the same surgery is indicated for a patient with albinism as for one without). The reason for this is that it is the percentage NAFX and VA improvements that determine the resulting life improvements rather than the absolute visual acuity. The NAFX allows the physician to estimate the percentage improvement and, with the patient, make a more informed decision about therapeutic efficacy. Those patients with sensory deficits and poor NAFX values can receive substantial percentage increases that will improve their lives in many measurable ways (e.g., becoming self-sufficient, holding a job, etc.); the same percentage increases for those with higher initial acuities, while also beneficial and worth achieving, might have a lesser effect on life style (a lower 'cost–benefit'). An example of this is in patients whose acuity is just below that required for a driver's license; for them, even a modest improvement is life-changing.

Figure 21.2 shows how either convergence or soft contact lenses raises and broadens the curve of NAFX versus gaze angle. The three plots at the top demonstrate that INS amplitude is not a good indicator of foveation accuracy (and, therefore, visual acuity). At both −20 and 25°, the NAFX values are similar despite the large difference in INS amplitudes. At 0°, the NAFX is the highest while the INS amplitude is intermediate between the other two. Ocular motor data from this and other patients with binocular INS whose nystagmus damps with convergence demonstrate that this group of patients would benefit most from either the bimedial rectus recession procedure or base-out prisms. In the former, the two medial horizontal rectus muscles are recessed to produce an artificial divergence that must be overcome by the patient converging to binocularly fixate distant targets; in the latter the patient must also converge because of the prisms (−1.00S is added to prepresbyopic patients' prescriptions to negate the accommodation accompanying convergence). In both cases, the patient's peak NAFX values (i.e., at the "null") increase and the plot of NAFX versus gaze angle has a broader peak. The latter finding is, in many ways, a more important improvement in visual function than the improvement in the peak value. It is measured by the longest foveation domain (LFD),

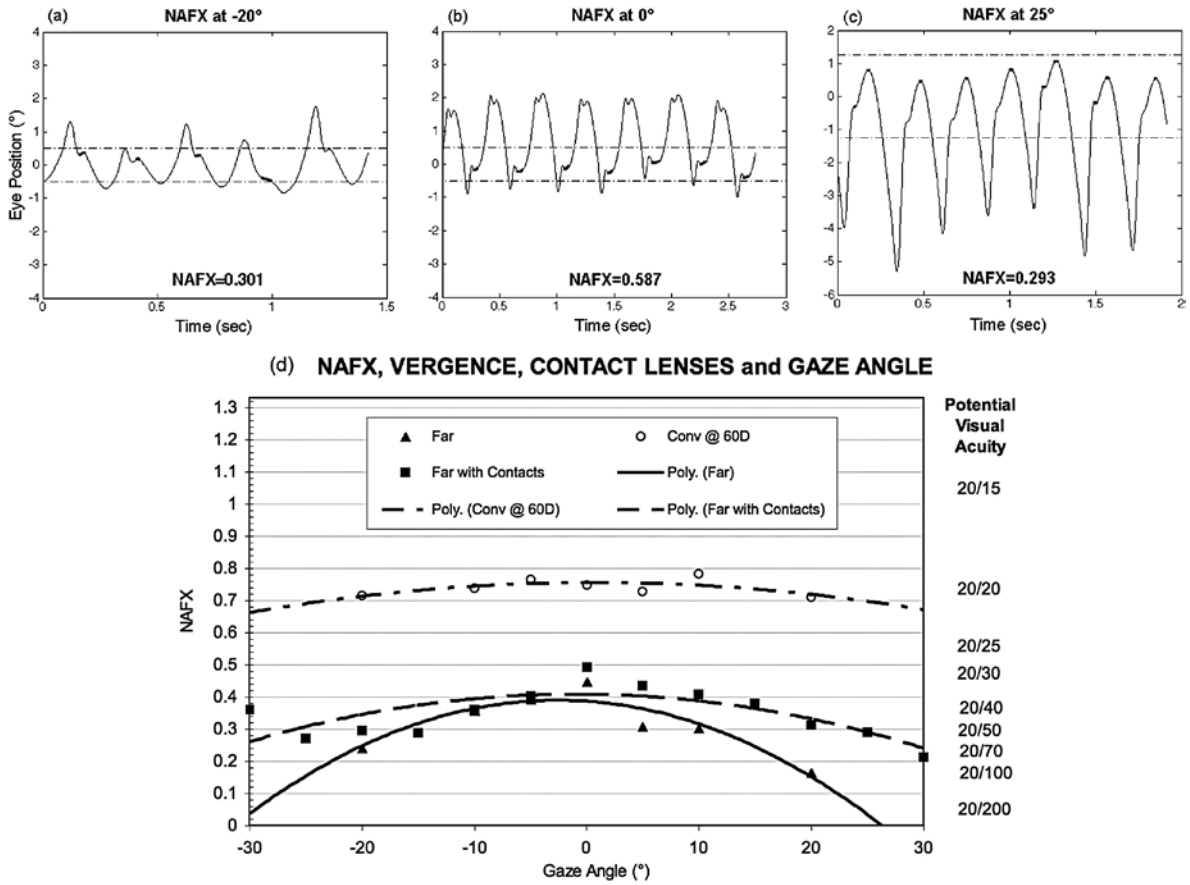

Figure 21.2 Plots of NAFX versus gaze angle for a distant target (with and without contact lenses) and a target at 60 diopter convergence and sample intervals of eye-movement data during fixation of targets at –20, 0, and 25°.

which is the range of gaze angles within which the NAFX (and, therefore, visual acuity) is within 10% of its peak value (Wang *et al.* 2006a).

In patients with INS who exhibit an NAFX peak at a particular non-primary-position gaze angle, the four-muscle Kestenbaum procedure, consisting of two recessions and two resections, is used to move the eyes oppositely to the NAFX-peak position; this effectively repositions the latter to primary position. For smaller lateral NAFX-peak positions, the two-muscle Anderson procedure plus T&R of the remaining two muscles in the plane of the INS will accomplish the same therapeutic improvements. There are no data demonstrating that the improvements in visual function for any two-muscle nystagmus surgery (excluding the bimedial recession procedure discussed above) equal those for four-muscle procedures; therefore, an Anderson procedure alone is not recommended in INS if maximal therapeutic effectiveness is desired. The notion of "saving" two muscles by not operating on them is a false economy and has no place in nystagmus surgery; this is unlike pure strabismus surgery, where even single muscles are sometimes operated on.

It has recently been proposed that the effectiveness of the T&R procedure might be improved by an augmented suture technique that consists of adding one or two extra sutures to the tendon (Dell'Osso *et al*. 2009). It was further proposed that if successful, an augmented tendon suture procedure (sans tenotomy) might suffice.

Several drugs have been shown to have beneficial effects on INS (Tomsak *et al.* 2005; Sarvananthan *et al.* 2006; Shery *et al.* 2006) and gene therapy has successfully been applied in both canines and humans with Leber's congenital amaurosis (Jacobs *et al.* 2003; Bennicelli *et al.* 2008; Maguire *et al.* 2008). The identification of genetic abnormalities in some patients with INS has yet to result in a viable therapy (Kerrison *et al.* 2001; Thomas *et al.* 2008). A recent observation made in our laboratory was that INS waveforms showed improved NAFX as a result of the subject taking acetazolamide; that observation raises the possibility that some with INS may have a channelopathy and perhaps drugs similar to acetazolamide might prove therapeutically effective.

21.3.4 NAFX-based estimation of visual function improvements

Despite the fact that the NAFX was developed to measure and predict the potential best-corrected visual acuity for specific nystagmus waveforms under the presumption that only INS was limiting acuity (i.e., there were no associated afferent visual deficits), its use has been extended to estimate pre-therapeutically the actual, measured visual acuity and NAFX-peak broadening improvements that may be expected from the T&R procedure (Wang *et al.* 2006a, 2007b). This is not only possible for patients with no afferent visual deficits but also for those with such deficits. Figure 21.3 shows how the pre- versus post-T&R NAFX curve (either the percentage

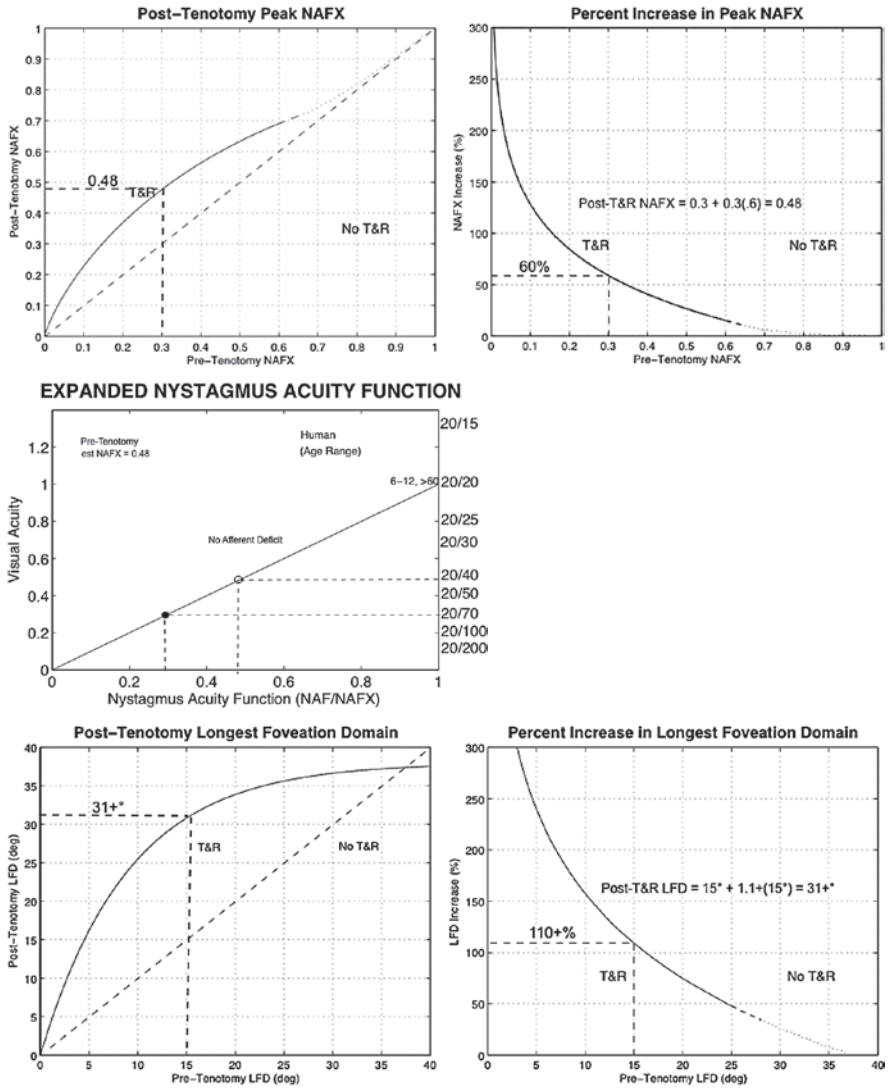

Figure 21.3 (Top) Plots of post-T&R versus pre-T&R NAFX values (left) and percentage increase (right) showing how to calculate the estimated improvements from an initial value of 0.3. (Middle) NAFX versus visual acuity line for an INS patient 6–12 or >60 years old showing how to estimate the post-T&R improvement in visual acuity. (Bottom) Plots of post-T&R versus pre-T&R LFD values (left) and percentage increase (right) showing how to calculate the estimated improvements from an initial value of 15°.

change or the absolute curve derived from it) can be used to estimate the expected improvement in an 8-year-old patient with INS with a pre-T&R value of 0.3 at 0°, a measured visual acuity of 20/70, and an LFD of 15°. The plots shown are derived from those Wang *et al*. (2006a), taking into account the fixed NAFX endpoints of 0 and 1. Using either of the top plots, the estimated 60% NAFX improvement to 0.48 is determined from the pre-therapy NAFX of 0.3 and, from the middle plot, the estimated improvement in measured visual acuity is determined from the estimated post-therapy NAFX of 0.48. The bottom plots show how the NAFX-peak broadening, measured by the LFD, is estimated from either the percentage change or the absolute curve derived from it. What if this patient also had an afferent visual deficit, e.g., ocular albinism with foveal hypoplasia), and his pre-therapy visual acuity was 20/200 instead of 20/70? A similar procedure can be used that separates the decrement in acuity due to the afferent visual deficit from that due to the INS. The same initial step is followed as in Figure 21.3, top, but a new NAFX line with the same slope is drawn through the point where the initial NAFX and pre-T&R visual acuity intersect (dashed line in Figure 21.4). That line is now used to estimate the post-T&R acuity improvement. Estimation of the LFD in this patient with an afferent visual deficit is the same as shown in Figure 21.3, bottom. These NAFX and LFD improvement curves are the same across the spectrum of patients with INS, independent of age or associated sensory deficits.

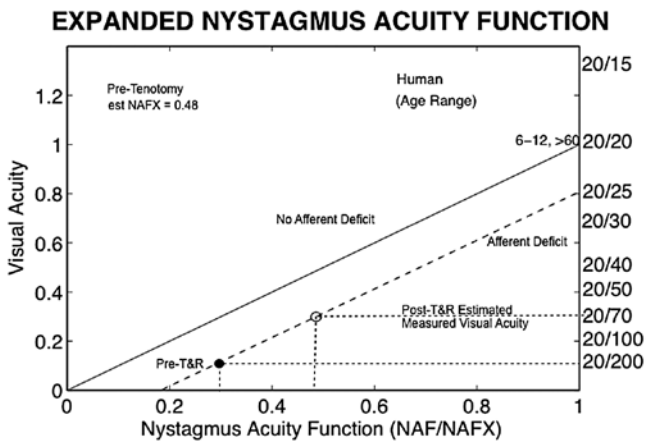

Figure 21.4 NAFX versus visual acuity lines for an INS patient 6–12 or >60 years old with an afferent visual deficit (visual acuity = 20/200) showing how to estimate the post-T&R improvement in visual acuity.

21.4 Discussion

21.4.1 INS therapies

Therapies for INS have been, and are being, developed that attempt to reduce the detrimental effects at either an afferent visual site, centrally, or peripherally (Dell'Osso 2005). That is, by treating afferent visual deficits so that the ocular motor system might recalibrate itself and reduce the oscillation (e.g., gene therapy for Leber's congenital amaurosis), by using pharmacological agents that act centrally to damp the INS oscillation itself, or by optically, proprioceptively, or surgically altering the proprioceptive tension-control loop in the extraocular muscles to reduce the eye oscillation itself (Dell'Osso *et al.* 1999; Hertle *et al.* 2003; Wang *et al.* 2006b, 2007a).

Currently, there is great interest in developing drugs that might control INS. The goal of drug therapy is to administer a systemic agent that will reduce the oscillation with few or no side effects (a difficult task) and no long-term effects (usually unknown for new drugs). Given the pediatric nature of the INS population, the latter is very important. New drugs have no track record of long-term safety and therefore, pose a danger to this population. It must be kept in mind that drug therapy would be required for the life of the patient, not only raising the specter of an unknown, long-term side effect but also imposing a lifetime economic cost to the patient. Contrast that to the essentially risk-free, one-time nature of outpatient surgery on the extraocular muscles, and a strong case can be made that the latter is the most conservative medical treatment for INS.

21.4.2 NAFX-based estimation of visual function improvements

The ability to estimate improvements in peak visual acuity and the range of gaze angles within which high acuity will be possible is useful in two ways: (1) to determine *a priori* the extent to which a therapy will produce visual function benefits and, therefore, whether the therapy is appropriate; and (2) to provide the patient with more realistic expectations about how the therapy might affect their visual function. Neither of these had been possible before the advent of ocular motor data analysis using the NAFX.

As the example in this Chapter illustrates, it is important to note that, when calculated as a percentage increase in acuity, the prognosis for visual improvement is the *same* for patients with INS alone and those whose INS is accompanied by afferent visual deficits such as ocular albinism – it is based on their pre-surgical NAFX and LFD values. Because the same visual function improvements may have greater impact in the quality of life of patients with the poorest vision, all patients with INS should be afforded the *same* treatment options.

From the NAFX and LFD improvement curves in Figure 21.3 one can also determine if any therapy is indicated. Pre-therapy NAFX values greater than 0.6 or LFD values greater than 25° are likely to preclude any significant improvements in these static measures; the dynamic measure of target acquisition time may or may not improve in those conditions. However, if *either* of the static values is in the lower range, therapy should provide measurable improvement in that visual function.

21.4.3 NAFX-based outcome measures of visual function improvements

The primary outcome measure of strabismus surgery is alignment of the eyes, a direct ocular motor measure of an ocular motor procedure (EOM strabismus surgery). Similarly, the primary outcome measure of nystagmus surgery, also an ocular motor procedure, must be a direct ocular motor measure, the NAFX and its variation with gaze angle. This is a direct measure of foveation quality and its improvement and has the added advantage of being linearly correlated with visual acuity across a range of gaze angles. Any study of INS therapies that uses either a single visual acuity measure or several acuity measures at different gaze angles as a primary outcome measure is scientifically flawed and prone to false-negative outcomes. It is the prerogative and scientific imperative of the principal investigator to ensure the scientific integrity of their study. Neither the funding agency nor its representative committee should attempt to inject "politically correct" or "medically desirable" substitutions for the best available primary outcome measure. The NAFX separates the motor and sensory components of measured acuity and allows both measurement and *a priori* estimation of the direct improvements in the former; visual acuity does neither and is subject to too many confounding influences. The secondary outcome measure of INS therapy should be target acquisition time, also a direct motor measure. Although visual acuities at different gaze angles should be measured in such a study, they are at best tertiary measures and the medical aim of improving visual acuity must not supersede the scientific requirement to assess accurately the direct effects of INS surgery on the foveation quality of the patient's waveforms.

Acknowledgments

This work was supported in part by the Office of Research and Development, Medical Research Service, Department of Veterans Affairs.

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