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REVIEW

Eye-Movement-Based Assessment of Visual Function in Patients with Infantile Nystagmus Syndrome

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ABSTRACT

Purpose. Infantile Nystagmus Syndrome (INS) is an ocular motor system dysfunction characterized by the rhythmic to-and-fro oscillations of the eyes. Traditionally, the assessment of INS visual function solely focused on null- or primary-position visual acuity. Our purpose is to use the past four decades of INS research to introduce a more complete assessment of visual function in patients with INS.

Methods. All eye-movement data were obtained using high-speed digital video, infrared reflection, or scleral search coil systems.

Results. We have introduced four important aspects of a more complete INS visual function assessment: the eXpanded Nystagmus Acuity Function and visual acuity measurements in primary position; broadness of the eXpanded Nystagmus Acuity Function peak and high-acuity field; target acquisition time; and gaze-maintenance capability.

Conclusions. Visual function in patients with INS is multifactorial and the simple assessment of primary position visual acuity is both inadequate and may not be the most important characteristic in overall visual function. A more complete visual function assessment should also include primary and lateral gaze eye-movement and visual acuity examinations, target acquisition time and gaze holding.

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Key Words: nystagmus, visual function, visual acuity, high-acuity field, target acquisition, gaze maintenance

Infantile Nystagmus Syndrome (INS)[1] is an ocular motor system dysfunction characterized by the rhythmic to-and-fro oscillations of the eyes, affecting about one in 3000 newborns.[2,3] It may be inherited or spontaneous and either associated with a sensory deficit or not. INS is usually noted within the first few months of birth or at birth (especially in inherited cases) but can rarely develop later in life. Those INS patients with poor vision usually have associated sensory deficits responsible for the greater part of their vision loss. However, the nystagmus eye movements do affect visual function to a varying extent, especially when viewing lateral-gaze targets and fast-moving targets.

Approximately fifty percent of INS patients also have impaired stereovision, an indication of strabismus, which is sometimes hidden by the nystagmus eye movements[4]; strabismus can easily be detected by accurate eye-movement recordings. Patients with INS generally donot perceive oscillopsia, however, under certain circumstances, oscillopsia can be elicited. The physical attributes of the stimulus, the experimental condition, and the role of individual attention may influence the perception of oscillopsia.[5,6]

Because INS usually develops from infancy, the sensory visual and ocular motor systems both suffer from a low quality, unstable input because of the constantly moving retina. Successful treatment of nystagmus in infants and children will significantly improve that input, thereby benefiting both systems in their developmental stages. The main goal of any nystagmus treatment should be to increase the foveation quality,[7,8] e.g., lengthening foveation time, increasing foveation-period accuracy, and reducing foveation-period velocity. Reducing nystagmus intensity is a secondary, cosmetic goal. Successful treatment is not limited to increased null- or primary-position visual acuity; nor should that be the sole focus of the treatment evaluation. In this review of the past 40 years ofINS research conducted in our Laboratory, we conclude that accurate eye-movement recordings should be used for diagnosis and both planning and evaluating nystagmus treatments. Be-

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cause we have always recorded eye movements, we were in a unique position to observe that clinical evaluations alone are often inaccurate, inconsistent, and too insensitive to document therapeutic changes; this conclusion is shared by other researchers.[9] This article will review multiple aspects of visual function that may be affected by nystagmus treatments and form a more complete evaluation paradigm for children and adults with INS.

Primary-Position Measured and Potential Visual Acuity

Many INS patients have a "null" point, which indicates higher visual acuity at a certain gaze angle.[7] The null point is established during the developmental period of the visual system and usually does not change its nature over the years, i.e., a static gaze-angle null stays in the same position; a time varying null retains its (a)periodicity. The position of the null point may or may not be in primary gaze. Surgery or prisms can correct a lateral null to primary position, alleviating the need for a head turn. Evaluation of treatment efficacy usually compares the null- or primary-position acuity pre- and posttreatment. In the case of a corrected lateral null, the primary-position acuity would be vastly improved. Clinically, visual acuity is usually measured with a distance line-letter chart.

The direct results of peripheral nystagmus therapy [e.g., prisms, contact lenses, or extraocular muscle (EOM) surgery] are improved INS waveforms. Measured visual acuity is only an indirect and idiosyncratic measure of INS waveform characteristics.[10–12] The improvement of measured acuity is dependent on a number of factors in addition to improvement of nystagmus; these factors include afferent visual deficits, patient age, associated strabismus, amblyopia, uncorrected refractive errors, and associated central nervous system disease. The quality of INS foveation periods is the single most important characteristic that directly affects visual function (not nystagmus amplitude nor frequency). It is also the characteristic that is directly affected by therapies that alter EOM function. Therefore, an objective measure of the direct, eye-movement effects of nystagmus therapies related to target foveation quality was needed to assess INS and evaluate the results of therapy.

The Nystagmus Acuity Function (NAF) was developed to fill that void. It measures nystagmus foveation quality at various gaze angles. It is an objective measure of waveform foveation, and a predictor of potential visual acuity for INS patients with no afferent deficits (see the next paragraph for INS with afferent deficits). The NAF measures directly the treatment-induced waveform changes, specifically, the patient's ability to maintain fixation within a "foveation window" of $\pm 0.5°$ (position) and $\pm 4.0°/s$ (velocity).[13] It combines the following factors of nystagmus-waveform characteristics during target foveation: foveation time per cycle, the standard deviations of eye position, and the standard deviations of eye velocity.[7,14,15] The NAF is defined by the following equation:

$$\mathrm{NAF} = (1 - \sigma_{pv})[1 - \varepsilon^{-t_f/\tau}]$$

where the pooled estimator $\sigma_{pv} = \sqrt{(SD_p^2 + SD'^2_v)/2}$, $SD'_v = 0.125(SD_v)$, t_f is the foveation-period duration, and $\tau = 33.3$ ms.[15–17]

The NAF is a function that is predicated on the assumption of an intact visual system and is linearly proportional to potential Snellen (decimal) visual acuity; Fig. 1 shows this age-dependant linear relationship. The individual lines reflect the different maximum acuities of normal subjects for each age range.[18,19] A subsequent version of the NAF, the eXpanded Nystagmus Acuity Function (NAFX),[15,20] extended the position window to $\pm 6.0°$ and the velocity window to $\pm 10.0°/s$ for patients incapable of controlling fixation well enough for good foveation (this is a common scenario in INS patients with afferent visual deficits). The NAFX is defined by the following equation:

$$\mathrm{NAFX} = (1 - \sigma_{pv})[1 - \varepsilon^{-t_f/\tau}]$$

where the pooled estimator $\sigma_{pv} = \sqrt{(SD_p^2 + SD'^2_v)/2}$, $SD'_v = (p/v)(SD_v)$, t_f is the foveation-period duration, τ is calculated from the average τ surface.[15]

The NAF and the NAFX (both unitless numbers between 0 and 1.0, 1.0 being the best) have been successfully used to evaluate the foveation quality of both INS and Fusion Maldevelopment Nystagmus Syndrome (FMNS, formerly called latent/manifest latent nystagmus) patients.[10,12,13,21,22] Fig. 2 shows an example of the NAFX calculation performed by the interactive user interface created in our lab (software available at http://www.omlab.org/OMLAB_page/software/software.html). The calculation starts with choosing a steady, blink-free fixation section at the gaze angle of interest. Then, proper position and velocity windows for this section are set within the user interface. Detailed instructions are available online.[20] The upper panel of Fig. 2 is the velocity trace of the chosen fixation section, the bold part of the waveform corresponding to the foveation periods detected by the velocity criteria of the NAFX algorithm. The middle panel of Fig. 2 is the position trace of the chosen fixation section; the bold part of the waveform corresponding to the foveation periods detected by the position criteria of the NAFX algorithm. The lower panel of Fig. 2 is the final output of the NAFX, with the bold part of the waveform satisfying both the position and velocity criteria; i.e., they are foveation periods and are the only data used to calculate the NAFX. Thus, the amplitude of the INS waveform is not correlated with visual acuity. It is suggested that multiple measurements be performed and averaged at each gaze angle.

A more recent use of the NAFX is to estimate the upper limits of visual acuity improvement that could be achieved with the reduction of nystagmus.[12] For example, some INS patients already have a high primary-position NAFX with a corresponding potential acuity close to 20/20; however, their measured acuity might only be 20/100 because of a deficit in the afferent visual system that limits visual acuity improvement. Having obtained the primary-position NAFX information of such a patient before hand, it is unlikely that treatment of the patient's nystagmus could raise the already-high NAFX values any higher, or increase the measured peak visual acuity. Therefore, such patients should not expect increased acuity as a result of any treatment. There are, however, other aspects of visual function that can be improved (and, therefore, should be evaluated); they will be covered in the next sections. In addition, the reduction or elimination of torticollis provides its own functional benefits.

Combined with pretherapy measured acuity, the NAFX can also be used to predict the measured acuity improvement postfour-muscle tenotomy in patients with visual deficits.[12] The ability to inform patients how much their nystagmus may improve is unique in the history

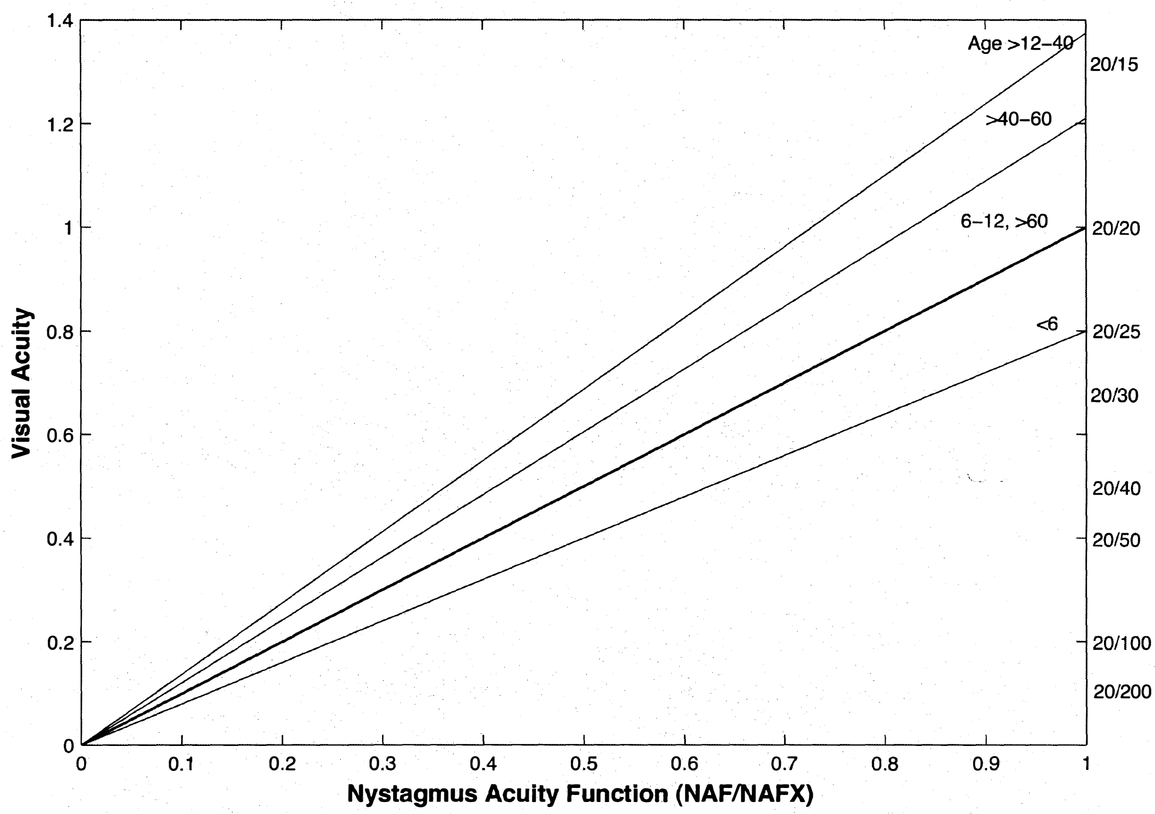

FIGURE 1.
The age-dependent linear relationship between potential visual acuity and NAF/NAFX. The five lines correspond to the following age groups: <6, 6 to 12, 12 to 40, 40 to 60, >60, as noted on the Figure. The lines for the age groups of 6 to 12 and >60 overlap each other. Snellen acuities are noted on the right side of the figure. For any calculated NAFX value, the corresponding potential visual acuity can be read from the patient-appropriate age line.

of nystagmus surgery and could not be achieved without the advent of the NAFX measure of waveform foveation quality.

In other cases, although the foveation quality is improved (shown by an increased average NAFX) and patients and parents do report behavioral changes, the measured acuity is not.[12] To understand this apparent contradiction, it is important to note that clinical examination differs from daily life experience in that patients may feel stressed by the former. Because IN is known to be affected by psychological factors,[23–25] it could have been exacerbated from its baseline level during the clinical examination. Therefore, it is possible for patients to show no improvement in measured acuity despite increases in NAFX values and in real-world (unstressed) acuity. The complex relationship between nystagmus, afferent visual deficits, and measured visual acuity makes it challenging to obtain an adequate evaluation of INS therapies.

To obtain eye-movement recordings for consistent comparison of NAFX values, we suggest that a stress-free visual target (e.g., LED or laser spot) should be used, because distinguishing letters and shapes adds another level of stress, especially for patients of a younger age. In addition, the recording condition should be kept consistent pre- and posttreatment for valid evaluation.[26]

Breadth of the High-Acuity Field

The null breadth (better measured by the NAFX "peak") of INS individuals determines the high-acuity field they can utilize. We define the high-acuity field as the range of gaze angles where the acuity is >90% of the best acuity (at the NAFX peak).[12] Improved lateral-gaze vision (a broader NAFX peak) could greatly reduce the need for head movements to align the best-acuity point to the target of interest. A broader peak would be especially helpful to children with INS whose developing visual system could still benefit from a better input within a wider range of visual angles. Therefore, visual acuity at a number of gaze angles should be assessed when evaluating treatment effectiveness.[27] Examinations focused solely on the null- or primary-position NAFX and visual acuity document only one aspect of the posttreatment changes and are not only inadequate but also may not measure the patient's more important improvements in visual function.

Observed increases in the breadth of the null gave birth to the four-muscle tenotomy and reattachment (T&R) procedure.[8,28,29] A gaze-angle-dependent nystagmus intensity analysis of the postsurgical effects of Kestenbaum procedure[30,31] documented that the nystagmus nulls were not only moved but also broadened; the former was due to repositioning of the extraocular muscles and the latter was attributed to the T&R of these muscles. It was then hypothesized that a pure four-muscle T&R procedure would damp the nystagmus in the corresponding plane, resulting in a broader NAFX peak.[29,32] This procedure greatly benefits those patients with a primary-position sharp peak, for whom the Kestenbaum procedure was contraindicated.[10,12,33]

NAFX vs. gaze-angle curves document foveation improvements over the broad range of gaze angles tested in the experimental paradigm.[12,22] Comparison of the pre- and postsurgical NAFX vs.

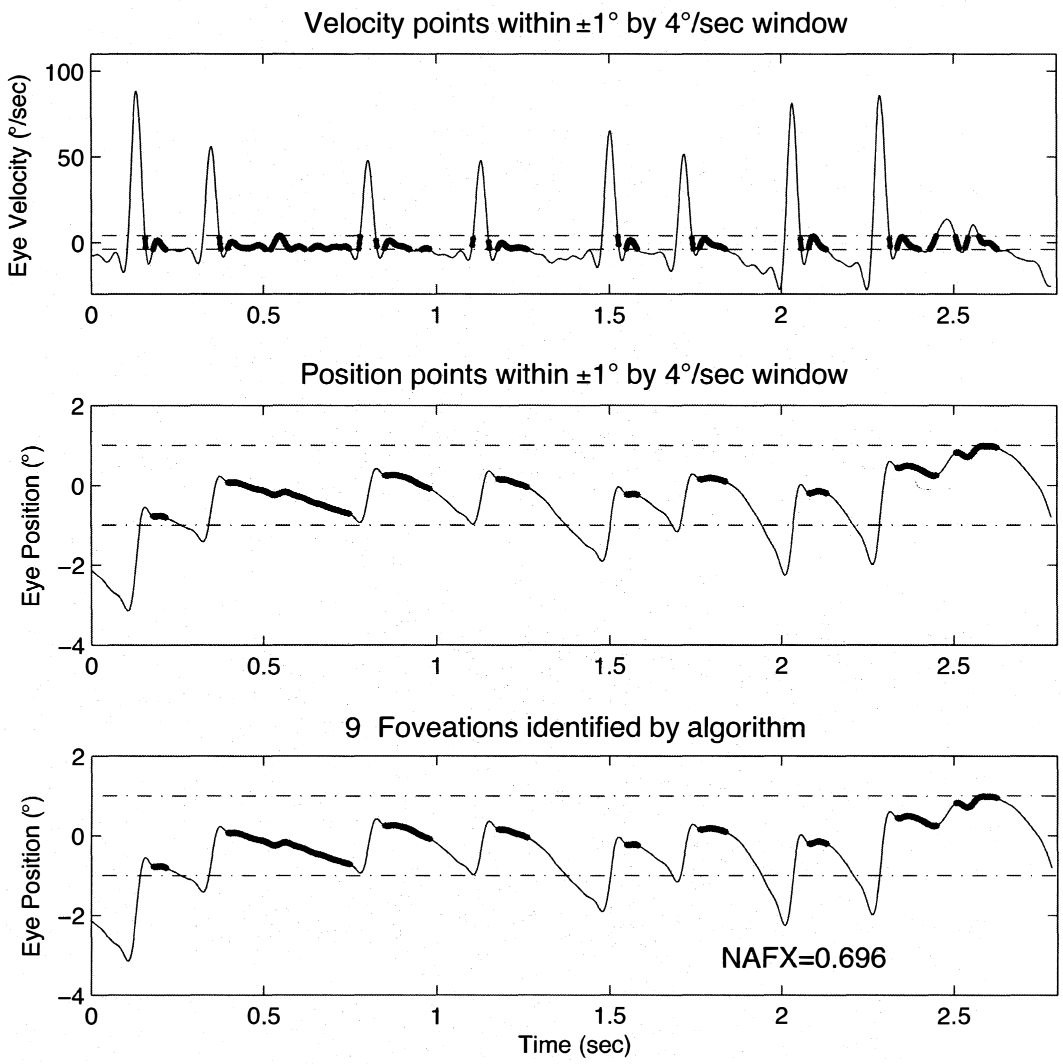

FIGURE 2.

NAFX-program outputs for a fixation section. Velocity traces (upper row) and position traces (middle and lower row) are shown. In each subplot, the NAFX algorithm-determined foveation periods satisfying the foveation-window criteria are shown thickened. The NAFX value for this section is 0.696.

gaze-angle curves determines if the nystagmus treatment increased potential acuity across a wider range of gaze angles. In a number of previous studies, we have successfully utilized the NAFX vs. gaze-angle curves to provide a way of measuring the "broadening" effect of T&R.[12,22] Fig. 3 is a demonstration of one such patient, with a postsurgical elevated and broadened high visual function field. Clinically, we agree that visual acuity should be measured at different lateral gaze angles before and after nystagmus treatments to better characterize their effectiveness.[27]

Indeed, with a broader NAFX peak, INS individuals have a wider high-visual-function field in which they can perform tasks with sufficient accuracy. This results in better performance in accuracy/speed critical events, which leads to the dynamic measurement that we will introduce in the next section.

Target Acquisition Time

To mimic the real-world scenario of acquiring and tracking moving targets, another realistic assessment of postsurgical changes is to measure the eye-movement responses to dynamic, jumping/moving visual targets. This aspect is critically important for visual function during locomotion and sports. Researchers have studied multiple properties of INS target foveation and acquisition,[34–38] and recently, a dynamic measurement of INS target acquisition time was established.[39] That time is measured from the target initiation to the beginning of the first foveation period on the target (i.e., the first foveation period in the patient's foveation window that is followed by subsequent foveation periods within that window). It has been demonstrated that INS target acquisition time has an intricate relationship with the timing of target onset vis-à-vis its occurrence within the INS cycle, i.e., when target onset is near to the intrinsic foveating/braking saccades, a longer target acquisition time results.[39–41]

The target-acquisition-time measurement is also an important aspect of evaluating treatment effects. An earlier study by Sprunger et al.,[42] measured the recognition time of a fixed optotype target at an INS patient's threshold visual acuity postfour-muscle recession surgery. Recently, we published a study demonstrating the postT&R, target-acquisition-time improvement of INS patients.[40] The five patients in that study, aged from 9 to 45, all had a decrease in target acquisition time ranging from 200 to 500 ms. Fig. 4 contains plots of

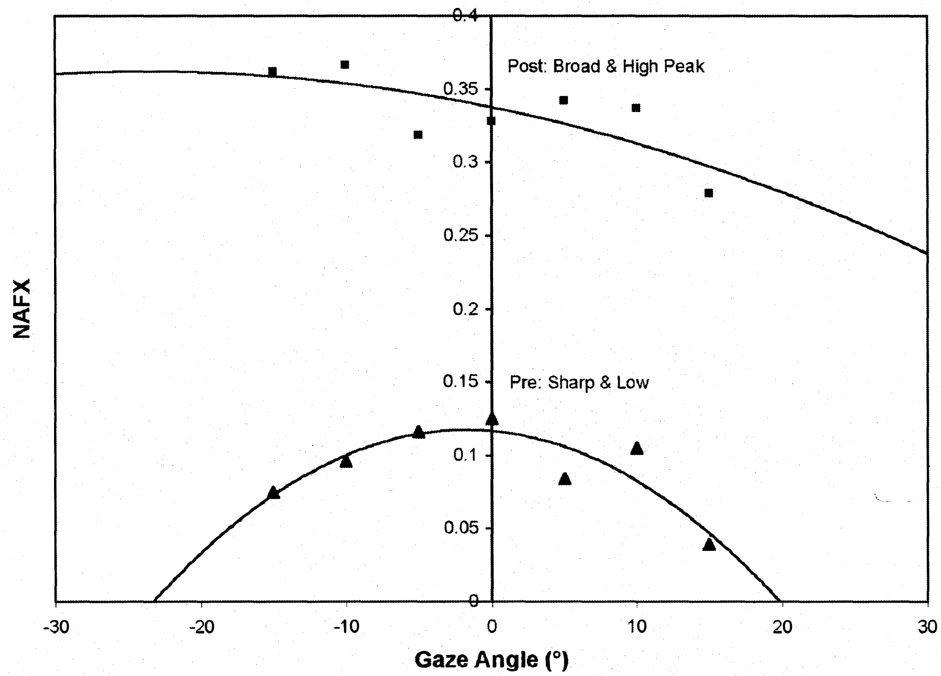

FIGURE 3.

Two NAFX vs. gaze-angle curves showing a marked improvement of static visual function postfour-muscle T&R. The patient had an elevated and broadened NAFX peak region. Triangles denote presurgical NAFX values; squares denote postsurgical NAFX values; rightward gaze angles are positive.

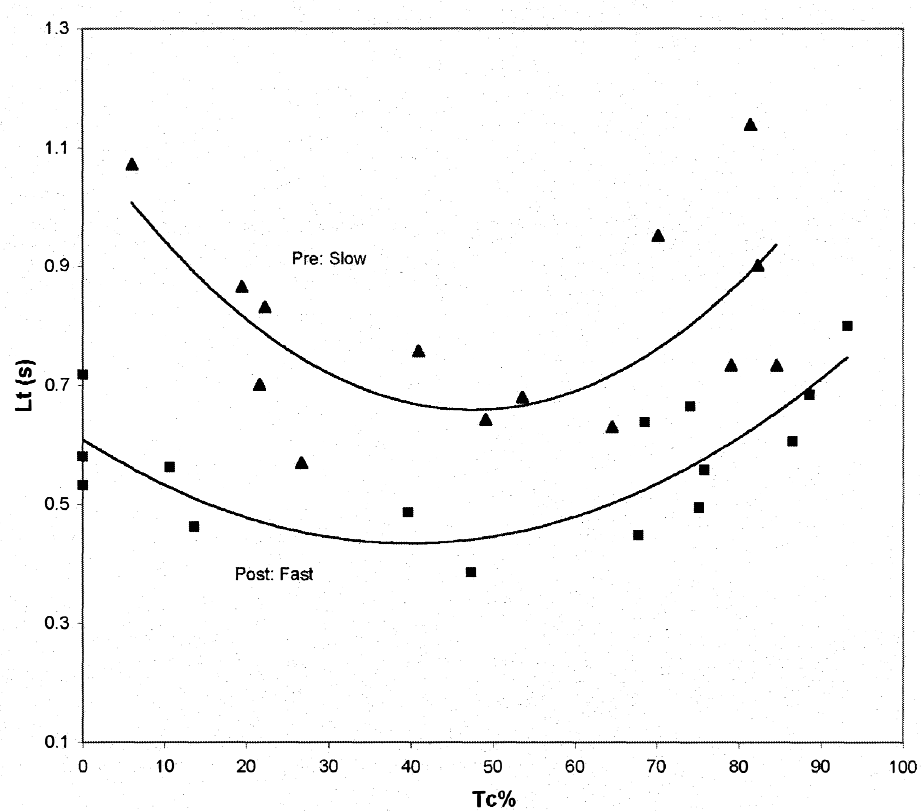

FIGURE 4.

Two target-acquisition-time curves showing a marked improvement of dynamic visual function postfour-muscle T&R. The patient had decreased target-acquisition-time values vs. target timing. Lt: target acquisition time; Tc%: normalized target onset time within the current nystagmus cycle. Triangles denote presurgical Lt values; squares denote postsurgical Lt values; both are in seconds.

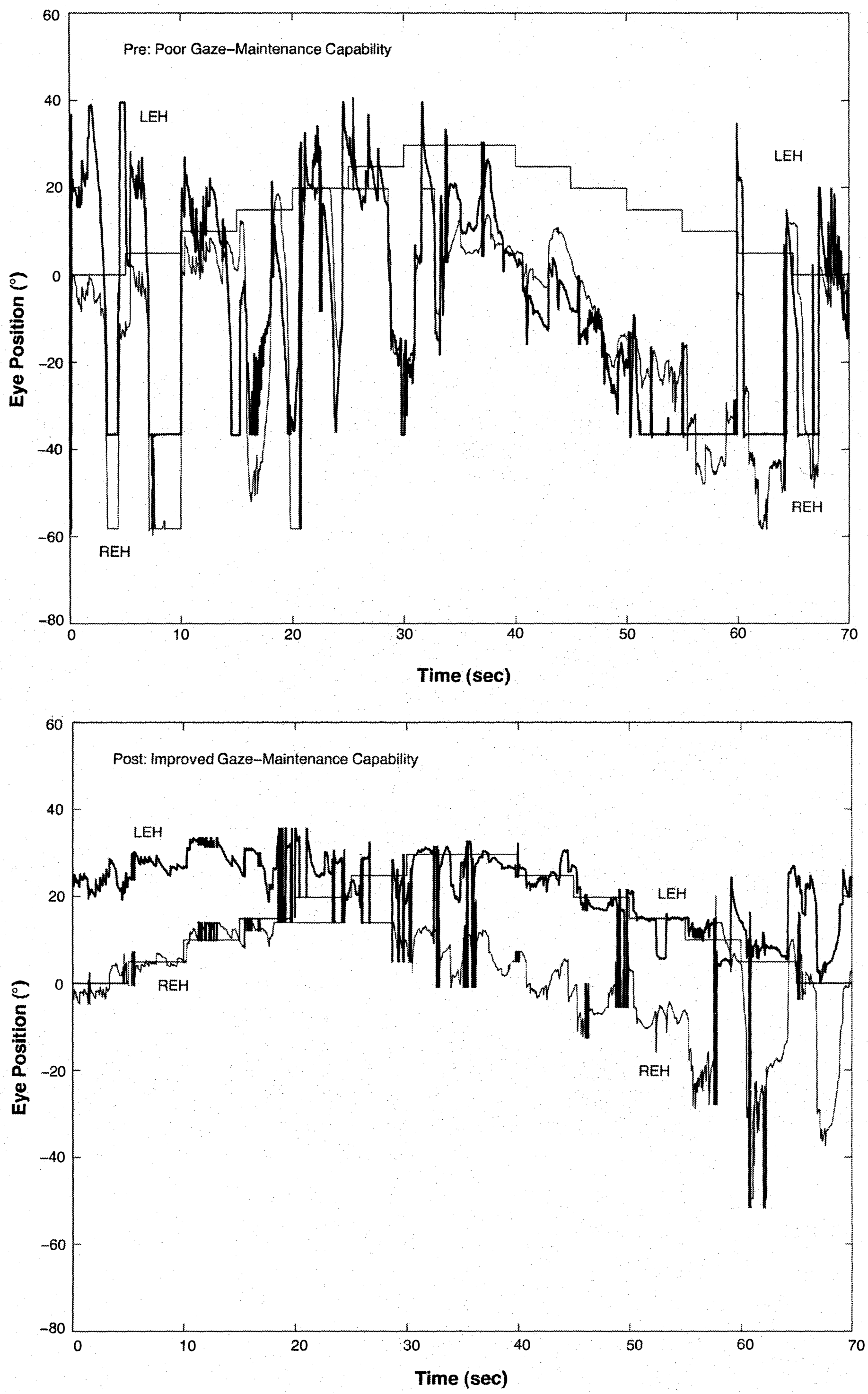

FIGURE 5.

Pre- and postfour-muscle T&R eye-position data of an 8-year-old girl fixating on a rightward stepped target (0° to +30° and back to 0°), showing a marked improvement of gaze-maintenance capability posttenotomy. Blinks have been partially removed for clarity of viewing. LEH, left eye horizontal (thick tracing); REH, right eye horizontal (thin tracing). The stepped visual target is shown with a solid thin line; rightward gaze angles are positive.

target acquisition times vs. point in the INS cycle at which the target jumped to a new position. The acquisition times to arrive at step targets of various sizes were recorded before and after the tenotomy procedure and fitted with second-order polynomial curves, which were then compared. The posttenotomy curve was lower than the pretenotomy curve, indicating faster target acquisition. Similar improvement was observed in the other four patients in that study. Lowering target acquisition times for both static and moving targets directly improves visual function in areas such as recognition times and, more strikingly, in sports. We hypothesized that the general improvement of visual input across all gaze angles, i.e., a broader NAFX peak, was responsible for the overall "speeding up" of the INS ocular motor system. If that hypothesis holds true, one would expect to find that the more broadening improvement, the more target acquisition improvement. A future study, examining a larger population of patients, would be needed to quantify this correlation.

Gaze-Maintenance Capability

Gaze maintenance is the ability to hold fixation on a target of interest. To the best of our knowledge, there is no systematic methodology to measure the gaze-maintenance capability in INS individuals and how that capability is altered by effective nystagmus treatments. Recently, we examined an 8-year-old child with both INS and FMNS for postfour-muscle T&R evaluations. We did not find any change in her primary-position NAFX. Her presurgical NAFX averaged 0.670 (corresponding to a potential acuity of 20/30); this high value precluded substantial NAFX improvement.[12] However, she exhibited striking differences in the gaze-maintenance capability in the pre- and postsurgical examinations. Fig. 5 shows a comparison of her responses to a series of rightward and leftward step targets. The presurgical task performance was poor; she was struggling to arrive on the target and maintain her gaze. The postsurgical performance, however, showed maintained foveation of all the stepped targets. The postsurgical record also documented alternation of the fixating eye: in the first part of the recording, she fixated with the right eye but switched to the left eye in the later part. Although still exhibiting some fluctuation, she was on target most of the time. It is important to note that there was only a 6-month gap between the two examinations and, therefore, it was not an attention-level change that caused the gaze-maintenance improvement. Poor gaze stability is common in children with INS but it was only the initially high NAFX that, by precluding an NAFX improvement, made this a novel finding. Moreover, the patient's mother noted a significant improvement in her daily life behaviors, e.g., she now sits much farther away from the TV than before the T&R procedure. This is not an isolated anecdotal observation; it is representative of the immediate behavioral improvements noted in many other cases as well as those documented in the first canine subject to receive the four-muscle T&R procedure.[28]

Establishing an objective measurement of INS gaze-maintenance capability in children is challenging because their eye-movement recordings usually contain inattention, blinks, and head movements that can be easily misinterpreted by anyone without experience in INS-waveform evaluations, or by an automated algorithm. One possible methodology is to use the NAFX to distinguish those foveation periods within, and outside of, the patient's foveation window, and calculate the percentage of "on target" foveation time during a visual task.

DISCUSSION

We have introduced four important aspects of a more complete INS visual function assessment paradigm: (1) NAFX and visual acuity measurements in null or primary position; (2) breadth of the NAFX peak and high-acuity field; (3) speed of target acquisition and (4) gaze-maintenance capability. To obtain the data for the above assessments, the eye-movement recording paradigm should include visual tasks in both primary position and lateral gaze, each target position lasting long enough (>5 s) for target acquisition to occur. A few repetitions of each task are recommended to ensure that enough data points can be collected for averaging or curve fitting.

Recording children with INS is inevitably more challenging than recording adults. In addition to the difficulty of paying attention to targets and following instructions, INS children might feel stressed to look at targets in a constrained (head fixed) condition and refuse to cooperate. In our lab, we perform uncalibrated, qualitative recording for infants that establishes a definitive diagnosis of the type of nystagmus present. Children aged from 2 to 5 are usually difficult to record; their eye-movement recordings, although clinically valuable, may not be of the highest quality for publication purposes. From a cooperative child, we are able to diagnose the type of nystagmus and estimate the null points. The decision to have surgery is then made by the parents and surgeon, with the understanding that an early surgery can bring more benefits to the development of the visual system, and that possible surgery at a later point in life will be easier to plan. After the age of 5, it is usually possible to obtain high-quality, accurately calibrated ocular motor recordings.[26]

Because of the necessity of eye-movement data for accurate diagnosis, estimation of possible therapeutic improvements, determination of the most effective therapy, and documentation of therapeutic improvements, eye-movement recordings should become an integral part of nystagmus evaluation and treatment.

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