3

FUSION MALDEVELOPMENT NYSTAGMUS SYNDROME

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Galileo may have been the only man of his day who believed the Earth revolved around the Sun, but he was right!

—S. F. Singer and D. T. Avery, Unstoppable Global Warming—Every 1500 Years

~~Fusion maldevelopment~~ nystagmus syndrome (FMNS, also known as latent/manifest latent nystagmus, LMLN) exhibits the following: a jerk nystagmus with either a linear or decreasing-velocity exponential slow phase identical to that of gaze-paretic nystagmus; strabismus; alternating hyperphoria/dissociated vertical deviation; and pendular torsional nystagmus in primary position.[1] The constantly present, conjugate, horizontal, jerk nystagmus increases in intensity by monocular occlusion, blurring, or reducing image brightness. A jerk nystagmus with a linear slow phase may be present when both eyes are closed. Rarely, the nystagmus is only evoked by the "pure" or "true" latent condition (LN) and occurs only with uniocular viewing (i.e., the other eye being occluded). That is, there is no nystagmus when both eyes are viewing, but when one eye is occluded, jerk nystagmus develops in both eyes, with the fast phases toward the uncovered eye. The term "manifest latent nystagmus" was first defined by Kestenbaum as being present with both eyes open but only one being used for fixation.[2,3] Using eye-movement recordings, mild FMN with both eyes viewing can

usually be detected in those patients who may appear to have "pure" latent nystagmus clinically. True/pure FMN "latent nystagmus vera" is uncommon. The intensity of FMN decreases when visual attention declines and increases during attempted fixation.[4,5] FMN may clinically resemble other types of nystagmus (e.g., INS with a latent component) and require eye-movement recordings to differentiate it. Indeed, it can even present as spasmus nutans (see Chapter 4).[6]

Patients with FMNS always have strabismus and, to suppress diplopia, vision from the tropic eye is suppressed ("occluded") in the cortex.[7] The FMN present with both eyes open, but only one fixating, is the same nystagmus as the rare FMN that only appears with occlusion of one eye. Thus, the term FMN refers to this *single type* of nystagmus that is present in most FMNS patients with both eyes open while one is fixating but, in some patients, may only be present when one eye is occluded.

3.1 CHARACTERISTICS OF FUSION MALDEVELOPMENT NYSTAGMUS SYNDROME

3.1.1 Waveforms, Models, and Mechanisms

The slow phase of FMN is either linear or a slight decreasing-velocity exponential (initiating the nystagmus) or a prominent decreasing-velocity exponential (following saccadic pulses) and the fast phase is always in the direction of the eye that is fixating, the straight eye. That is, the slow-phase rotation of the fixing eye is always in adduction and the fast-phase is in abduction; fixation with the right eye generates a right-beating nystagmus of both eyes, while fixation with the left eye produces a left-beating nystagmus of both eyes. Figure 3.1 illustrates the waveforms usually seen for binocular and monocular viewing. During binocular viewing, the slow phases are usually linear followed by corrective fast phases but upon occlusion, the nystagmus converts to a saccadic pulse train where the saccades defoveate the target and the decelerating slow phases return the fixating eye to the target.

It has long been known that, just as in normal saccades, the fast phases of FMN may contain dynamic overshoots[3]; the dynamic overshoots' characteristics in both FMNS and INS are normal.[8] Figure 3.2 shows FMN in two patients, one without dynamic overshoots (left panel) and one with dynamic overshoots (right panel). Dynamic overshoots are integral parts of the saccadic fast phases and not the beginnings of the slow phases. The uncommon occurrence of square-wave jerks (SWJ, see Chapter 5, Section 5.3.1) mimics their occurrence in normal observers, and their presence during binocular viewing

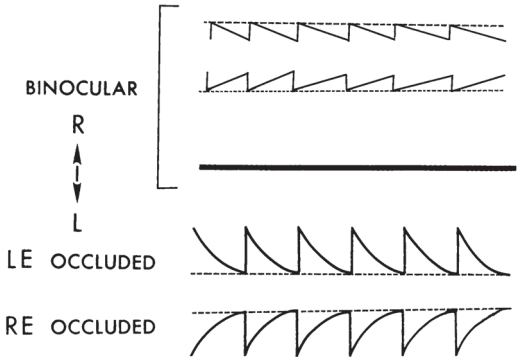

FIGURE 3.1 Illustrations of fusion maldevelopment nystagmus syndrome during binocular viewing (but monocular fixation) and during monocular viewing. Nystagmus with linear slow phases (top) may convert to defoveating saccadic pulses with decelerating slow phases (bottom). Dashed lines indicate target position. LE, left eye; RE, right eye.

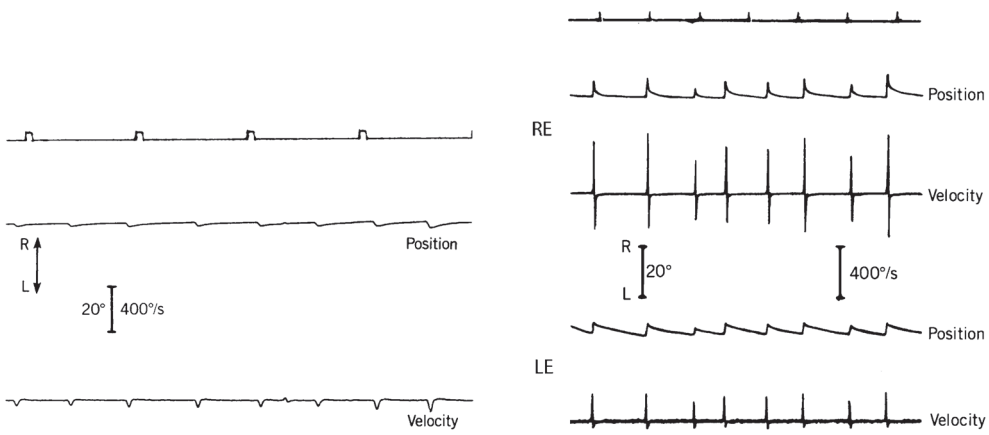

FIGURE 3.2 Fixating left eye of a patient with fusion maldevelopment nystagmus syndrome (left panel) and both eyes of another patient with fusion maldevelopment nystagmus syndrome during right-eye fixation. Note the prominent dynamic overshoots in the saccadic pulses of the fixating right eye and their sharp attenuation in the deviated left eye. Time markers indicate 1-sec intervals; LE, left eye; RE, right eye.

in FMNS is unpredictable and variable. Thus, the presence of either dynamic overshoots or SWJ does *not* represent a mechanistically different "type" of FMN[8]; it is merely the *same* FMN, including these common, normal saccadic dynamics or intrusions. This also applies to the occurrence of other types of nystagmus in addition to FMN (e.g., an undefined "torsional" nystagmus or the high-frequency pendular nystagmus thought to arise from the NOT, resulting in a dual-jerk waveform). In an individual patient, both FMNS and INS may coexist with another type of nystagmus or saccadic intrusion/oscillation. The clearest way to delineate a group of patients with two mechanistically independent eye-movement characteristics is to describe the two conditions (e.g., FMN with dynamic overshoots, FMN plus SWJ, or FMN plus "torsional" nystagmus). Attempts to define FMNS as consisting of multiple "types" based on the presence or absence of these normal occurrences is both confusing and not mechanistically justified. For simplicity, the basic FMNS waveforms shown in Figure 3.1 do not contain either dynamic overshoots in their fast phases or the confounding addition of other types of nystagmus.

3.1.1.1 TYPES (FUSION MALDEVELOPMENT NYSTAGMUS SYNDROME PLUS NUCLEUS OF THE OPTIC TRACT)

Just as in INS, FMNS may also coexist with NOT nystagmus. That is, superimposed on the jerk FMN (with either linear or decelerating slow phases) will be a low-amplitude, high-frequency pendular nystagmus. When the additional pendular oscillation of NOT nystagmus is present, the resulting waveform would be the same as shown in Figure 2.3 for linear INS slow phases (DJR_L) or consist of the pendular oscillation superimposed on the decelerating slow phases illustrated in Figure 3.1.[9] Figure 3.3 shows eye-movement data from patients with FMNS + NOT nystagmus (specifically, dual-jerk FMN) and demonstrates the independence of the two types of nystagmus; either one may be damped without affecting the other.

3.1.1.2 THE FIXATING EYE

The slow phases of FMN are either linear or decelerating, and the fast phases are always in the direction of the fixating eye.[3] The nystagmus of patients with strabismus, alternating

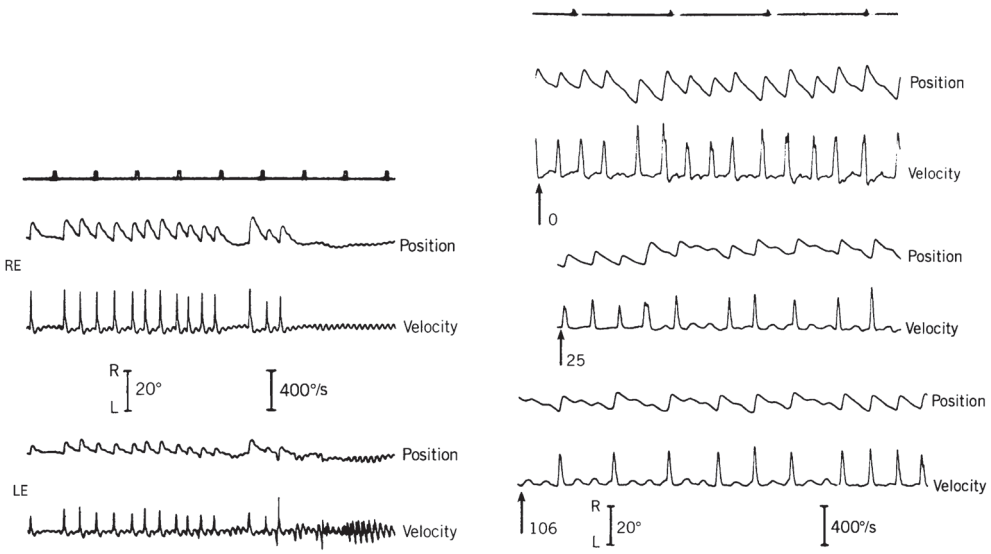

FIGURE 3.3 Eye movements (position and velocity) of patients with fusion maldevelopment nystagmus syndrome (FMNS) plus nucleus of the optic tract (NOT) nystagmus illustrating the independent variations of either component of the dual-jerk FMN waveforms. Shown are damped FMN but consistent NOT nystagmus (left panel) and time-variable NOT but consistent FMN nystagmus (right panel). Numbered arrows in right panel indicate the time in seconds from a continuous record. Time markers indicate 1-sec intervals; LE, left eye; RE, right eye.

fixation, and FMNS with both eyes open has fast phases that are always in the direction of the fixating eye. Such patients may be easily misdiagnosed as having INS, because the nystagmus is present with both eyes open. Recordings are required to document the decelerating or linear slow-phase waveforms characteristic of FMNS from the accelerating slow phases predominant in the INS.

Although "conjugate," FMN exhibits some morphological differences between the fixating and deviated eye, the latter being less precise (so-called rubber-band conjugacy); this is evident in Figure 3.2 (right panel), where the deviated left eye mimics but does not duplicate the motion of the fixating right eye. It is also consistent with the hypothesis that the two eyes are driven independently and not by a single composite signal.[10] Figure 3.4 shows the effects on FMN of reversing the occlusion of one eye in either an esotropic or exotropic patient. In addition to a reversal of the FMN, a position shift to take up fixation is accomplished by enhanced fast phases and diminished slow phases. Depending on the directions involved, fast phases are sometimes also diminished.

In addition to occlusion, intent or darkness also may alter FMN. In Figure 3.5 a patient was able to change his FMN by merely attempting to fixate with either one or both eyes (left panel), and another patient's FMN changed when placed in darkness (right panel). In both panels, both eyes were open at all times (i.e., manifest FMN). When the patient in the left panel switched intent from looking with the left eye to looking with both eyes, the manifest FMN damped considerably and the left eye became slightly esotropic while the right eye took up fixation with no manifest FMN. In the right panel, the patient's jerk right manifest FMN immediately switched to jerk left in darkness, suggesting a predisposition for left-eye fixation (i.e., left-eye dominant).

The curious observation of a darkness-induced shift in the "fixating" eye shown in Figure 3.5 was clarified by our study of a patient with FMNS who had a prosthesis in his congenitally blind right eye.[11] Not surprisingly, he exhibited

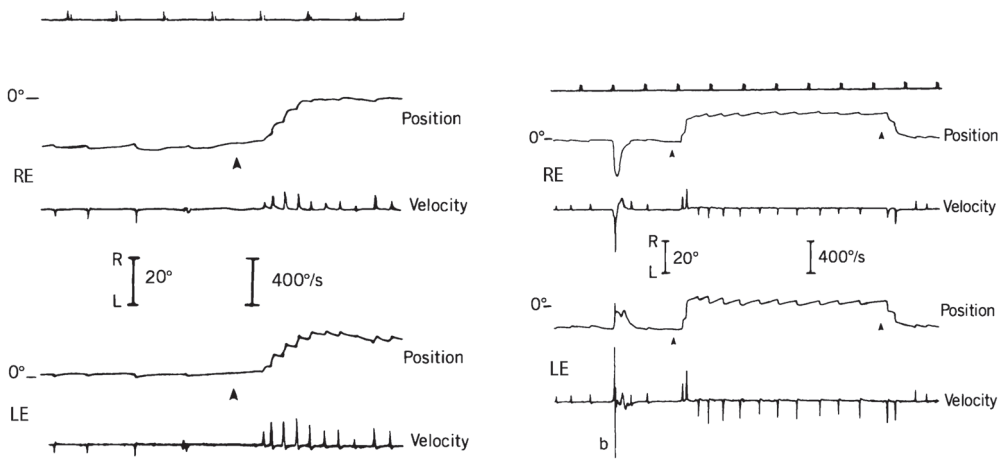

FIGURE 3.4 Eye movements (position and velocity) of patients with fusion maldevelopment nystagmus syndrome and either esotropia (left panel) or exotropia (right panel) upon reversing cover to the fixating eye. Both a direction reversal of the fusion maldevelopment nystagmus and a position shift of both eyes take place to allow fixation by the previously occluded and deviated eye. Arrowheads indicate reversal of cover from the right to left eye (left panel) and from the left to right and back to left eye (right panel). Time markers indicate 1-sec intervals; b, blink; LE, left eye; RE, right eye.

jerk-left FMN during normal fixation but, immediately after the lights were turned off, his "manifest" FMN switched to jerk right while his only intact left eye became esotropic; jerk-left FMN returned when the lights were turned back on (see Fig. 3.6, left panel). As we had observed with many FMNS patients with sight in both eyes, Figure 3.6 (right panel) shows that he also was able to willfully choose his "fixating" eye (including the prosthetic eye) in the dark and by doing so, change the direction of his FMN. We concluded that eye dominance was cortically predetermined and not altered by visual abnormalities.

Therefore, just as fixation attempt is responsible for the genesis of IN (presumably by modulating

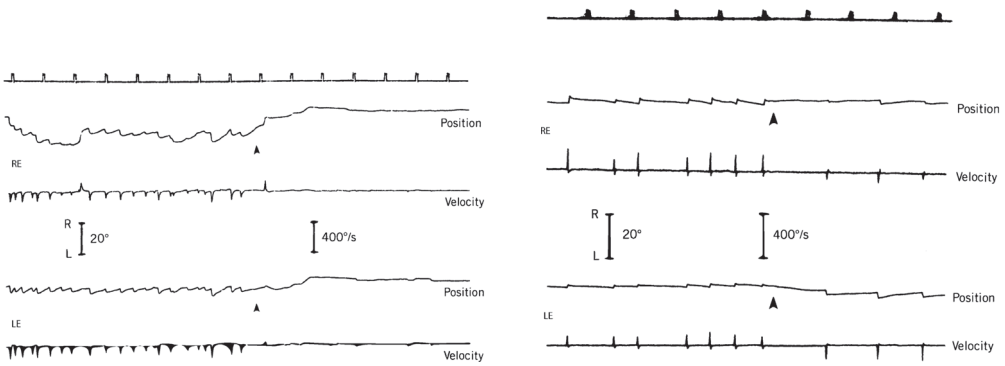

FIGURE 3.5 Eye movements (position and velocity) of patients with fusion maldevelopment nystagmus syndrome illustrating the effects of "looking" with one eye (left panel) or of darkness (right panel). Before the arrowhead in the left panel, the patient was "looking" with the left eye and after it, with both eyes. In the right panel, the patient was in the light and, at the arrowhead, was placed in the dark. Note the spontaneous reversal of direction in the manifest fusion maldevelopment nystagmus. Time markers indicate 1-sec intervals; LE, left eye; RE, right eye.

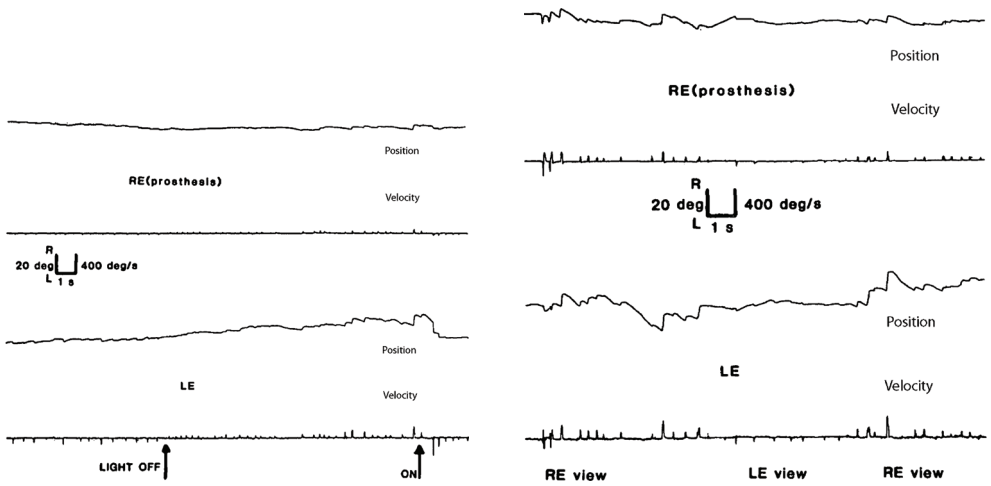

FIGURE 3.6 Eye movements (position and velocity) of a patient with fusion maldevelopment nystagmus syndrome and a right-eye prosthesis showing the effects of darkness (left panel) and willful changes in "viewing" eye in darkness (right panel). LE, left eye; RE, right eye.

the internal feedback loop that controls the damping of smooth pursuit), monocular/binocular fixation attempt is able to modulate the tonic imbalance (slow-phase velocity) driving FMN.

3.1.1.3 TARGET FOVEATION AND DUAL-MODE FAST PHASES

Because the good acuity of INS patients is related to the long, postsaccadic foveation periods of many waveforms, it was difficult to explain the equally good acuity of FMNS patients, given the absence of such periods. However, accurate studies of FMN foveation in a patient with 20/15 acuity revealed a dual strategy.[12] During the low-amplitude, linear-slow-phase FMNS waveform, the saccadic fast phases foveate the target, and the low-velocity slow phases take the eye away from the target with little effect on acuity. During the higher amplitude, decelerating slow-phase FMNS waveform, the saccadic fast phases *defoveate* the target, allowing foveation during the low-velocity, tail ends of the slow phases (see Fig. 3.7); this ensures the best acuity possible and was the first recorded demonstration of the saccadic system acting deliberately to defoveate the target. As the phase plane in Figure 3.7 (right panel) shows, most of the data (i.e., time) is during the slow phases and within the foveation window. There is very little time spent during the high-velocity leftward fast phases or their rightward dynamic overshoots, which can be seen just above the slow-phase data points that appear as the large black area within the foveation window. In Figure 3.8, the effects of placing and removing cover over each eye are shown. Initially, both eyes were on target (within the foveal radius) and there was minimal FMN. Cover resulted in FMN with both foveating or defoveating fast phases and esotropia; cover removal damped the now manifest FMN.

Defoveating saccades result from generating a pulse, but not a step, of innervation to drive the fast phases of the FMNS nystagmus. Therefore, the common neural integrator controlling eye position must be kept from integrating these defoveating pulses by an internal signal representing the correct/desired eye position vis-à-vis the target. These hypotheses were combined in a physiologically realistic, behavioral OMS model (see Chapter 2) capable of simulating responses of an individual with FMNS.[13–15] The model simulated FMN based on the tonic imbalance hypothesized to be its cause. In Figure 3.9, OMS model simulations of the effects on FMN of both alternate fixation (during binocular viewing) and alternate cover are shown. During alternate fixation, the foveating fast-phase waveform of FMN is likely to remain, whereas during alternate cover, defoveating fast phases are more likely.

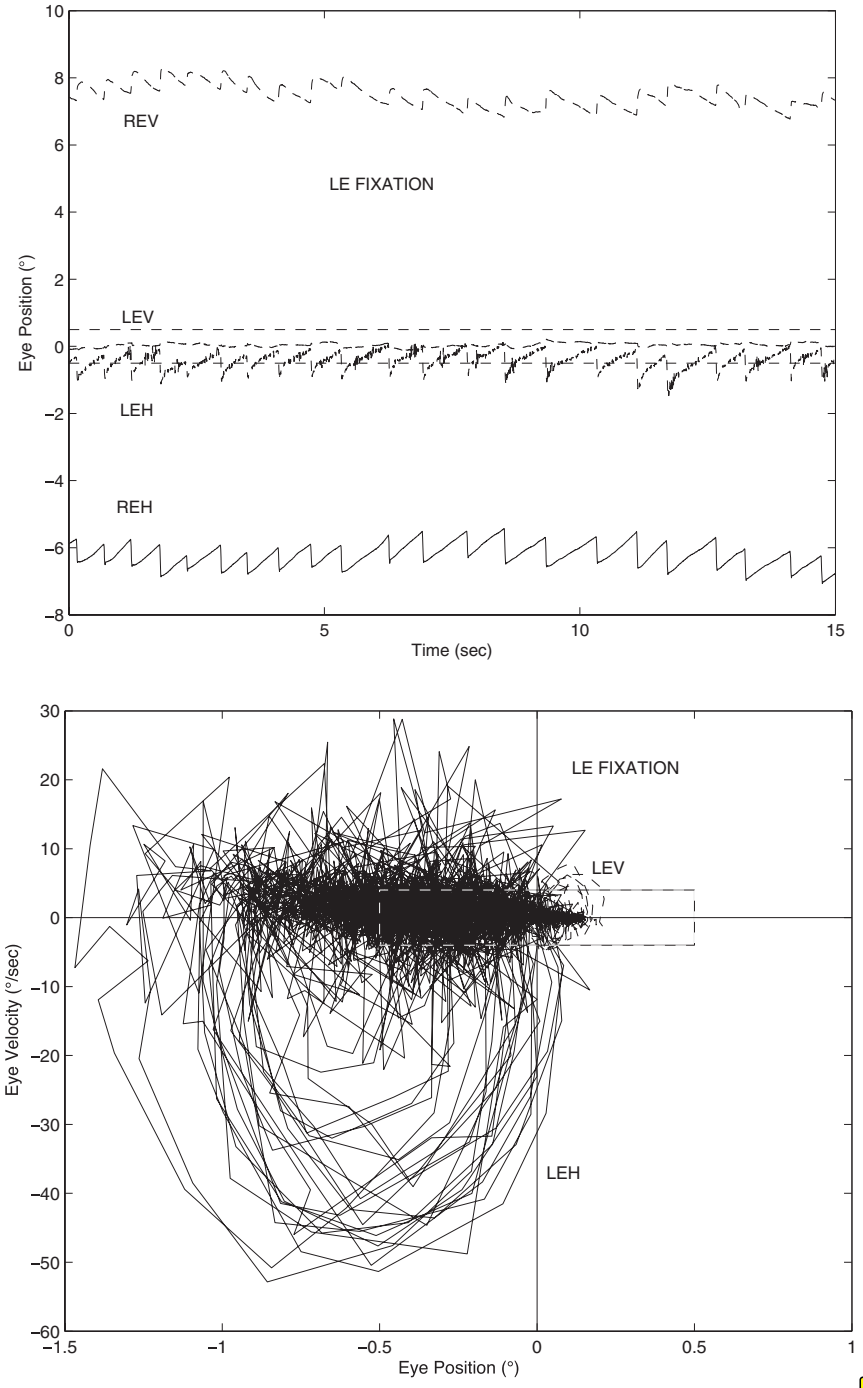

FIGURE 3.7 Horizontal (H) and vertical (V) eye movements of a patient with manifest fusion m[illegible]velopment nystagmus (top panel) and phase plane of the fixating left eye (~~top~~ panel). The fast phases are defoveating with dynamic overshoots allowing foveation during the decelerating slow phases. LE, left eye; RE, right eye; dashed lines, foveal extent (~~bottom~~ panel) and the foveation window (bottom panel)~~; outer dashed lines, radius of the target~~.

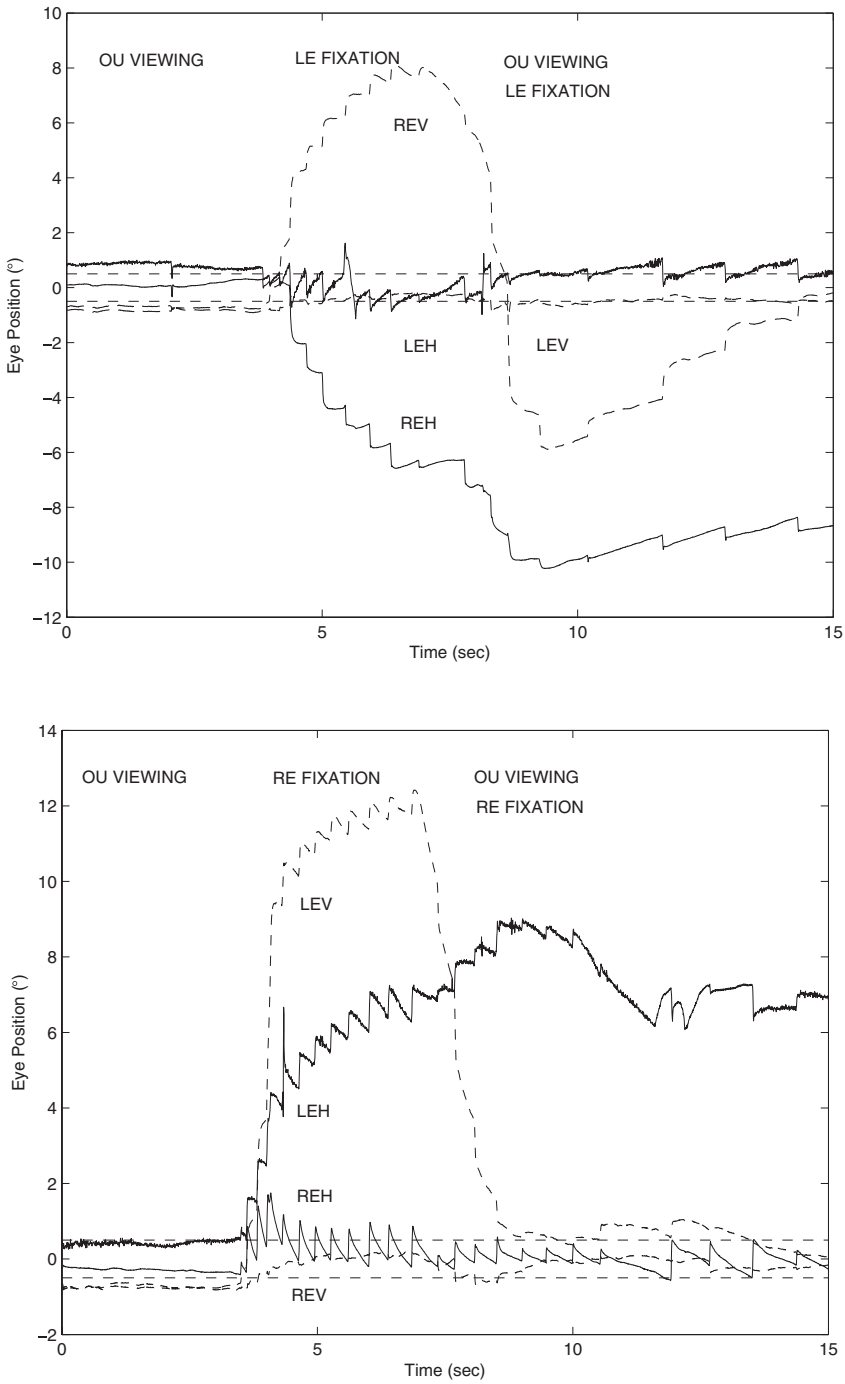

FIGURE 3.8 Horizontal (H) and vertical (V) eye movements of a patient with manifest fusion m velopment nystagmus showing the effects of placing and removing cover over the ~~left~~ (top panel) and ~~right~~ (bottom panel) eyes. LE, left eye; OU, both eyes; RE, right eye; dashed lines, foveal extent ~~(top panel) and the foveation window (bottom panel); outer dashed lines, radius of the target~~.

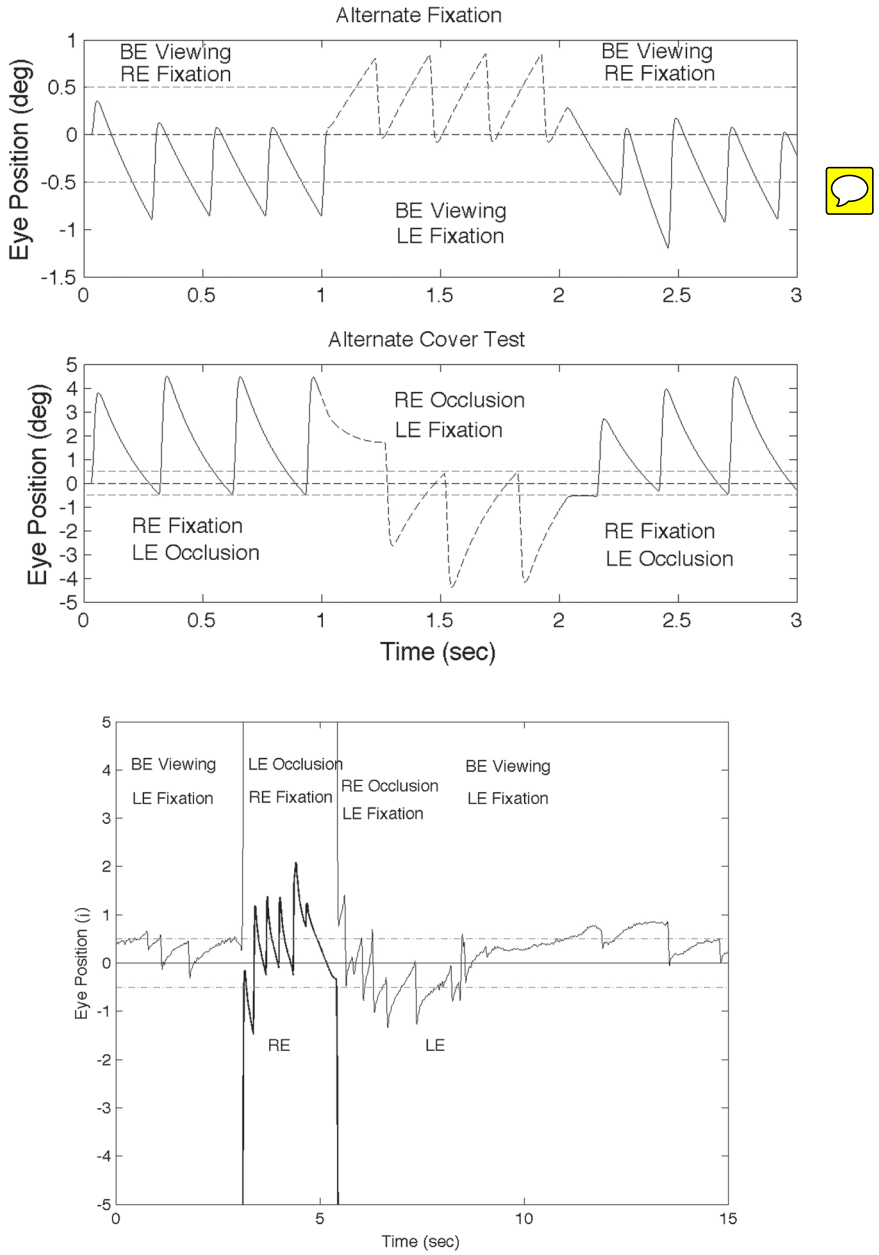

FIGURE 3.9 Behavioral ocular motor system model simulations of alternate fixation and alternate cover on fusion maldevelopment nystagmus (top panel) and of alternate cover in a fusion maldevelopment nystagmus syndrome patient for comparison. LE, left eye; RE, right eye.

3.1.1.4 FOVEATION ACCURACY

FMNS can cause the patient to have much worse monocular than binocular visual acuity. However, as the patient whose data are shown in Figures 3.7 and 3.8 demonstrates, accurate foveation is still possible under both conditions in some patients, thereby preserving their visual acuity. Foveation can be just as accurate in some patients with FMNS as it is in others with INS. The fixation subsystem can either prolong foveation periods just after foveating saccades in INS or at the ends of decelerating, foveating

slow phases that follow saccadic pulses in FMNS. However, it cannot create foveation periods when there is a non-zero velocity slow phase immediately following a foveating slow phase; that is, as the dashed waveforms in Figure 3.10 illustrate, there exist no waveforms where extended foveation periods precede either linear or decelerating slow phases.

3.1.2 Variation with Gaze Angle

The intensity of FMNS is maximal in abduction and minimal in adduction, causing an "adduction" null with the fixing eye and not a true "gaze" (eye in orbit) null position (see Chapter 5, Table 5.3). In Figure 3.11, OMS model simulations of the Alexander's law[16] effects of gaze angle on FMN are shown for both small and large effects during both monocular occlusion and binocular viewing. For the same FMN in primary position, the larger amplitude variation with gaze angle results in a waveform transition at a more central gaze angle in both conditions albeit with a more damped FMN for the manifest case.

Finally, to take full advantage of Alexander's law in order to minimize the amplitudes of their nystagmus, many patients with FMNS alternate their fixing eye such that it is always the adducting eye. Thus, they fixate with the left eye when looking right and vice versa. Figure 3.12 shows OMS model simulations of the effects of this strategy for different gaze angles in both directions for small and large Alexander's law effects.

3.1.3 Head Position

Because of the propensity to place the fixating eye in adduction, viewing targets directly in front of the patient necessitates rotation of the head in the opposite direction (e.g., right eye to the left, in adduction, with head rotated to the right). In addition to causing the anomalous head posture, this may give the mistaken clinical impression of a nystagmus (usually INS) with two "nulls" if the clinician fails to detect the change in the fixating

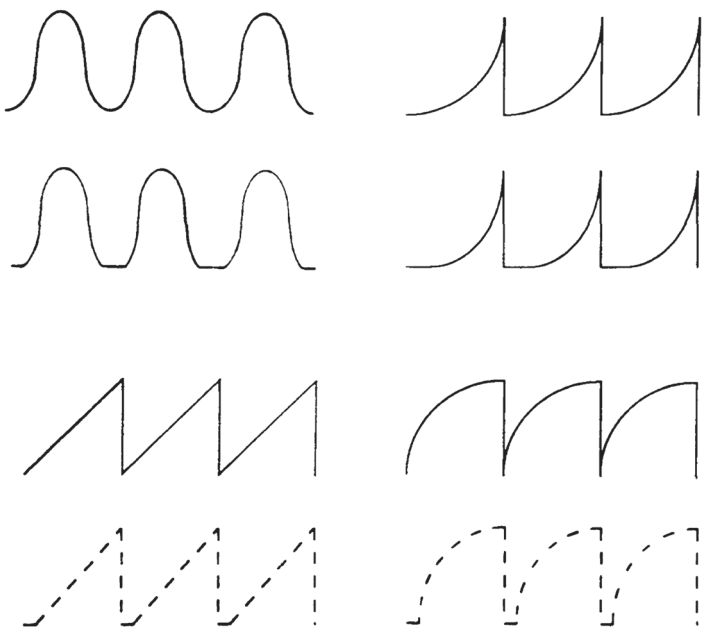

FIGURE 3.10 Illustrations of the four major nystagmus waveforms (clockwise from the top left, pendular, jerk with accelerating slow phases, jerk with linear slow phases, and jerk with decelerating slow phases) coupled with the addition of extended foveation periods in those waveforms where it is possible for the ocular motor system to produce them. Dashed waveforms do not exist.

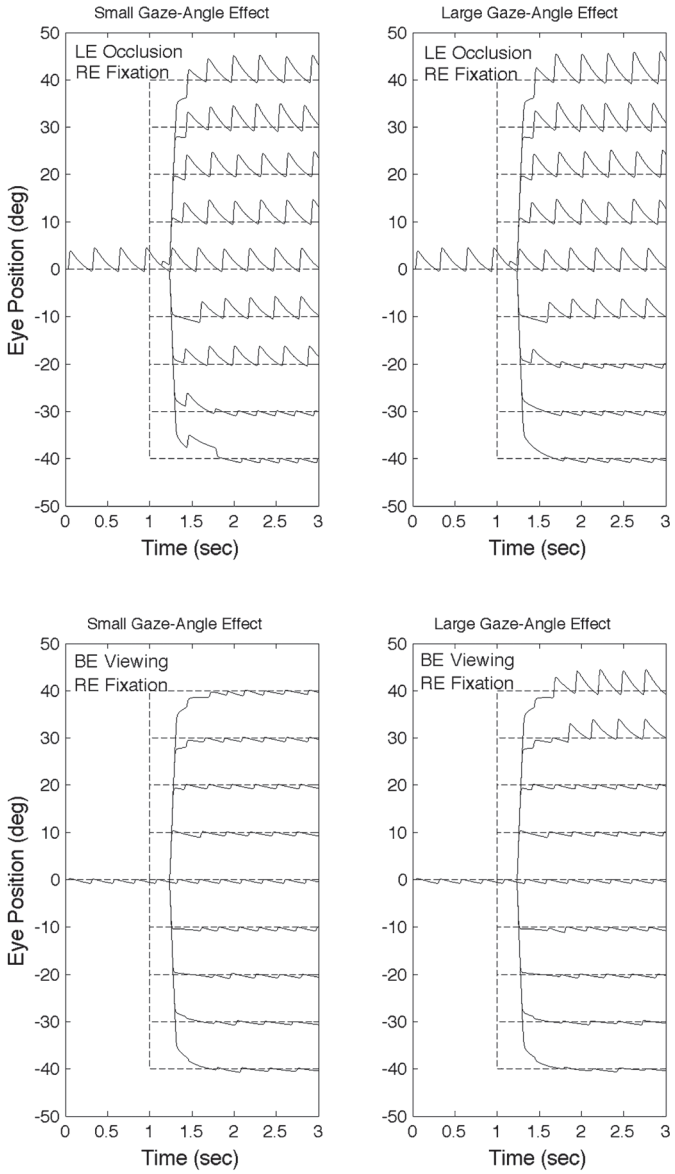

FIGURE 3.11 Behavioral ocular motor system model simulations of gaze angle on fusion maldevelopment nystagmus syndrome amplitude and waveform transition angle (for both small and large Alexander's law effects) during both monocular occlusion (top panels) and binocular viewing (bottom panels). BE, both eyes; LE, left eye; RE, right eye.

eye or realizes that there is no true null (i.e., the nystagmus does not increase as the eye is rotated further in adduction).

Using scleral search coil eye-movement recordings of 10 patients with dissociated vertical deviation and FMNS, Guyton et al. showed that nystagmus (horizontal, vertical, and torsional) practically always appeared initially, when one eye was occluded, and became damped as a dissociated vertical deviation (DVD) developed with head tilting.[17] The damping occurred over 0.3 to 3 seconds and was often only partial, identified as a decreasing slope of the nystagmus slow phases. Occasionally, if the DVD response diminished, the FMN reappeared. As was discussed earlier for FMN, the DVD

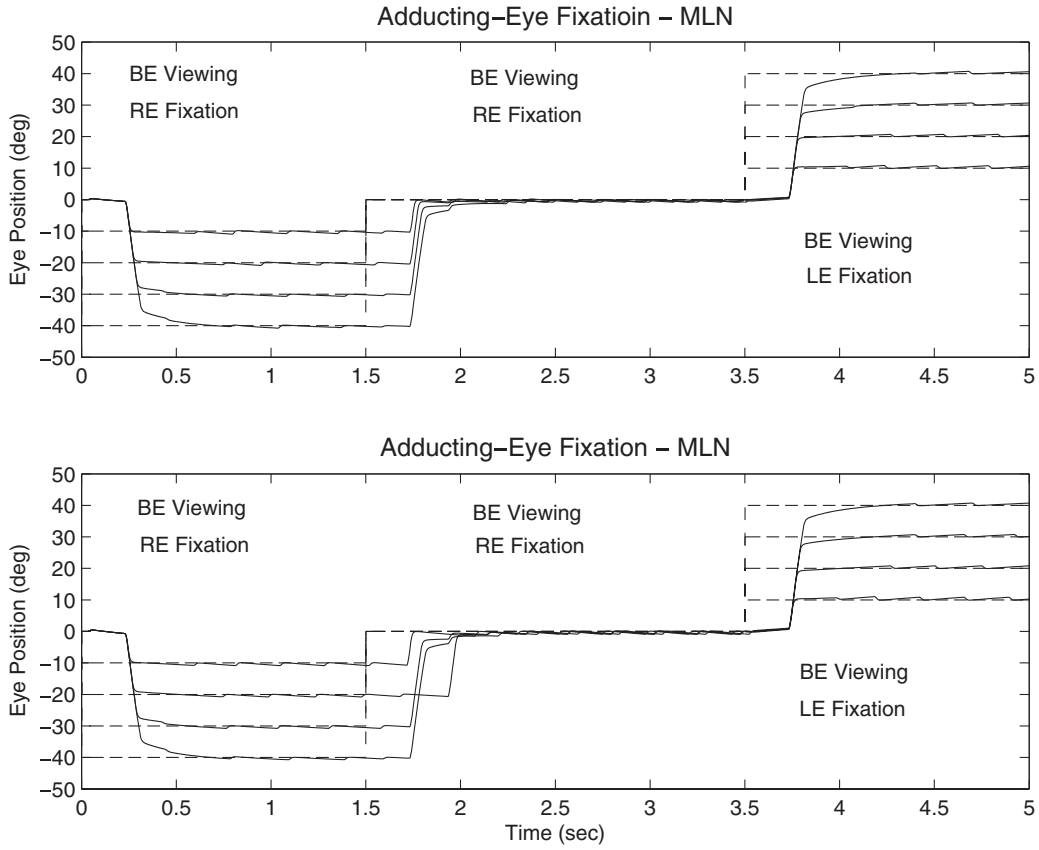

FIGURE 3.12 Behavioral ocular motor system model simulations of adducting eye fixation on fusion maldevelopment nystagmus syndrome for both small (top panels) and large (bottom panel) Alexander's law effects. BE, both eyes; LE, left eye; RE, right eye.

response could be recorded in total darkness in those individuals who could voluntarily imagine switching "fixation" (attention) from one eye to the other. A head tilt also damped the FMN and appeared to decrease the need for DVD. That evidence supports the view that DVD is an acquired (learned), often anticipatory, cyclovergence response, occurring upon taking up unilateral fixation, serving to improve vision by damping or blocking FMN.

3.1.4 Foveation, eXpanded Nystagmus Acuity Function, and Acuity

Despite the lack of extended foveation periods in FMN with linear or slightly decelerating slow phases, the low amplitudes of these slow phases may still allow for good visual acuity. As long as sufficient data points fall within the foveation window of the eXpanded nystagmus acuity function (NAFX; centered at the ends of the fast phases) for each FMN cycle, the NAFX value, and visual acuity, will be high. When the FMN waveform consists of saccadic pulses whose decelerating slow phases foveate the target, the same applies since the NAFX window is now centered on the tail ends of the slow phases. We have documented visual acuities as high as 20/15 in a patient with both waveforms.[12]

3.1.5 Efference Copy, Foveation, and Oscillopsia Suppression

The discussion in Chapter 2, Section 2.1.10 regarding the roles of efference copy and

foveation in the suppression of oscillopsia in INS is equally applicable in FMNS. Patients with FMNS do not normally experience oscillopsia because their efference-copy signal of the FMN motor command is used to negate the nystagmus portion of the retinal signal, leaving the target portion uncontaminated and allowing for the perception of spatial constancy. Thus, in our OMS model of FMNS, that stable reconstructed target signal is produced internally by the same mechanism as in INS and is used to drive the correct ocular motor responses to target position and velocity—analogous to INS and FMNS patients, the model has no oscillopsia when simulating either.

3.2 ETIOLOGY OF FUSION MALDEVELOPMENT NYSTAGMUS SYNDROME

FMNS is "congenital" in the same sense as INS (i.e., a congenital predisposition). However, several cases have been recorded of the manifest form of FMNS ("MLN" occurring with both eyes open), associated with retrolental fibroplasia.[3] Early theories postulated that a unilateral retinal stimulus was the necessary condition for FMNS, but this concept was discounted by observations of FMN in monocular fixation with a blind eye or with an acoustic stimulus in complete darkness. FMNS occurs in patients with strabismus who, although viewing with both eyes open, are fixing monocularly.

Strabismus is a necessary (but not sufficient) condition for FMNS.[7] That is, all individuals with FMNS have strabismus, consisting of either a phoria or tropia under cover and a tropia with both eyes open, if nystagmus is present under these respective conditions. Conversely, FMNS is not significantly associated with early-onset strabismus.[18] Rarely, on occlusion of a preferred eye, during which fixation with an amblyopic eye is forced, both eyes drift in the direction of the covered eye without corrections by fast phases; this is called "latent deviation." Early surgical correction of infantile strabismus may convert the nystagmus of FMNS present with both eyes open (the manifest condition) to nystagmus present only upon occlusion of one eye (the "vera" or "latent" condition),[19] thereby supporting a previous hypothesis.[7]

In children with FMNS and fusion, the development of amblyopia with subsequent diminishing fusion or the recurrence of a frank tropia, thus disrupting binocular vision, will make an FMN become either more intense or manifest, thus the potential for creating visual symptoms due to the nystagmus where none were present before. The magnitude of the resulting manifest FMN is proportional to the degree of the interocular visual disparity. However, successful treatment of amblyopia or strabismus will decrease the intensity, occasionally giving the appearance of complete absence. FMNS has also been reported in children with unilaterally reduced vision and esotropia associated with congenital disorders such as cataract or optic nerve hypoplasia. These children will often maintain a head turn to position the fixating eye in adduction.[11,20,21]

Various theories have been advanced to explain FMNS. These include a primitive vestibular tone imbalance, poor egocentric localization, a subcortical optokinetic system anomaly, a subcortical maldevelopment of retinal slip control, abnormal cortical motion processing, a disorder of proprioception, and a phylogenic persistence of the dominance of the nasal half of the retina.[3,22–31] In Chapter 2 we identified the direct cause of most IN waveforms as a failure of calibration in the damping mechanism of smooth pursuit. The direct cause of FMN is a tonic imbalance that drives the eyes with constant velocity (producing linear slow phases). The source of the imbalance may be the nasotemporal asymmetry present in normal infants that disappears as fusion develops or, as we hypothesized, egocentric direction confusion (see Section 3.2.3).

3.2.1 Familial (Gene Defect)

Just as in INS, there are some families whose members have FMNS. That suggests that, in those families, there is a genetic component that facilitates (*not causes*) the development of FMNS (see discussion of genetics and INS in Chapter 2, Section 2.2.1).

3.2.1.1 DOWN SYNDROME

FMNS is common in Down syndrome, where it may coexist with INS.[32] Of 35 adult patients with Down syndrome, 6 (23%) had FMNS; none had INS. In addition, one child was studied who had some INS waveforms in addition to FMNS. This was far above the reported 15% prevalence of FMNS in the general population. Near stereopsis was preserved in two of the adults and some fusion (the Worth four-dot test) in two others. Five of the six preferred left-eye fixation and three were left handed, a high percentage suggesting an unusual pattern of hemispheric dominance.

3.2.2 Optokinetic Asymmetry

FMNS has been associated with nasotemporal asymmetry of the horizontal optokinetic response and smooth pursuit during monocular viewing. Roelofs first observed horizontal optokinetic asymmetry in patients with FMNS.[33] Kommerell suggested that FMNS could be regarded as the consequence of horizontal optokinetic asymmetry.[23] Hoffman developed a model to explain nasotemporal asymmetry based on combined cortical and subcortical input to the nucleus of the optic tract in the cat.[34] In 1983, Schor proposed that FMNS and nasotemporal optokinetic asymmetry are mediated by the nucleus of the optic tract.[35] Human nasotemporal asymmetry has received considerable attention because it persists throughout life in humans with early-onset infantile strabismus. Nasotemporal asymmetry is seen in rabbits, kittens, monkey infants, and human infants within the first 6 months of life.[35]

However, the hypothesis that the FMNS is caused by nasal-temporal asymmetries in the optokinetic reflex is not supported by evidence that subjects with FMNS are able to use retinal slip information to adapt motion-detection sensitivities[36] and are able to pursue symmetrically.[4] Also, because nasal-temporal asymmetries exist in individuals with strabismus but not FMNS,[36] this cannot be the primary causal factor in the genesis of the nystagmus. Asymmetries in the monocular optokinetic response of monkeys deprived of binocular input early in life may result from, rather than cause, their nystagmus. In normal monkeys, each NOT is driven binocularly; in these monkeys, they are driven by the contralateral eye.[37] Although the resulting imbalance may provide the tonic signal that produces the FMN slow phases (inactivation of the NOT with muscimol abolishes the nystagmus), the cause of the imbalance appears to lie in higher centers. The spontaneous reversal of FMN in the dark has led to the speculation that eye dominance is predetermined.[11,38] Shallo-Hoffmann et al. identified an alternating vertical component to FMNS[39] and Brodsky linked the genesis of FMNS and dissociated vertical divergence (DVD) to the dorsal light reflex present in many animals.[40] In cases of FMNS plus DVD, the nystagmus may have a vertical component.[41]

3.2.3 Egocentric Direction Confusion

Cortical switching that must occur in the calculation of egocentric direction when going from binocular to monocular viewing.[3] Under binocular conditions, egocentric direction, referenced to the "cyclopean eye," is obtained by summing the gaze angle of each eye with the other and dividing by two. However, with monocular viewing, egocentric direction depends *only* on the viewing eye, and the cortical operation of summing and dividing by two must be altered to process unchanged information from the viewing eye. We hypothesized that the shift in egocentric direction toward the non-viewing eye causes the slow drift of the eyes in that direction. Both eyes are then corrected by a saccade in the direction of the viewing eye, which brings the eyes to the target (or, in darkness, to the intended gaze angle). This hypothesis was supported by unilateral strabismus surgery causing central effects on egocentric localization.[42] Thus, FMNS nystagmus may be generated by this inability to properly alter the cortical mathematical operation normally used to define egocentric direction (i.e., this deficit in higher centers may result in a tonic imbalance in the visual-vestibular subsystem, producing the linear slow phases of FMN). Our 1979 hypothesis for the cause of FMNS was also supported by Tychsen et al.,

who studied FMNS in patients and nonhuman primates.[43] They related egocentric direction confusion to unbalanced infantile, monocular interhemispheric MSTd drive, which they found was necessary and sufficient for FMNS. The shift to monocular egocentric localization can also produce this mode whereby the saccadic system generates defoveating saccades that momentarily carry the fixating eye past the target in a temporal direction, followed by a decelerating-velocity nasal drift back toward the target.[12]

Studies in subhuman primates have shown that FMNS arises after incomplete development of visual input from occipitotemporal cortex to subcortical vestibular pathways. In monkeys with FMNS, there is a loss of binocularity in the NOT, the subcortical structure that feeds into the vestibular system, with most cells driven by the contralateral eye.[35] The areas that normally provide binocular input to the NOT are the middle temporal (MT) visual area and the medial superior temporal (MST) visual area in occipitotemporal cortex.[44,45] When strabismus was surgically induced in infant monkeys during the first 2 weeks of life, these monkeys also developed FMN and visual area MT/MST loses binocularity. If either eye is covered during infancy, visual area MT/MST and NOT develop normal binocularity, but the striate cortex still shows loss of binocularity and these monkeys do not develop FMN. This finding suggests that the initial cause of FMNS is loss of binocularity in visual area MT/MST from the misaligned eyes in early infancy. Neuroanatomical experiments have supported the Schor hypothesis that the NOT may be the site of FMN generation. FMNS occurs in nonhuman primates following artificial induction of esotropia within the first 2 weeks of life.[44,45] Experiments have shown that a loss of binocular connections within striate cortex (area V1) in the first months of life may be the necessary and sufficient cause of FMNS.[43,46,47]

The severity of FMNS increases systematically with longer durations of binocular decorrelation and greater losses of V1 connections. Decorrelation durations that exceed the equivalent of 2–3 months in human development result in an FMNS prevalence of 100% in the nonhuman primate model.[43,46,47] No manipulation of brainstem motor pathways was required in this model. The binocular maldevelopment originating in area V1 is passed on to downstream extrastriate regions of cerebral cortex that drive conjugate gaze, notably MST. Conjugate gaze is stable when MST neurons of the right and left cerebral hemispheres have balanced binocular activity. Fusion maldevelopment in infancy causes unbalanced monocular activity.[43,46,47] If input from one eye dominates and the other is suppressed, MST in one hemisphere becomes more active. Acting through downstream projections to the ipsilateral nucleus of the optic tract, the eyes are driven conjugately to that side. The unbalanced MST drive is evident as the nasalward gaze-holding bias of latent FMN when viewing with either eye.

In summary, most patients have nystagmus from either the INS or the FMNS; some have both; and three unambiguous patient groups have been identified: INS, FMNS, and INS + FMNS.[9,48,49] The three groups exhibit different clinical signs and relations to strabismus; most series of INS patients show that many have strabismus, but all FMNS are strabismic.[50–53] Thus, INS and FMNS are specific, easily differentiated syndromes and do not, as has been suggested,[29] represent a unitary disorder with a broad spectrum of expression. Because no acquired, time-independent, primary-position jerk nystagmus reverses direction with alternate eye cover, a simple reverse-cover test can be a powerful clinical tool.

Clinical Pearl: To distinguish between benign (non–neurologically threatening), infantile, primary-position, jerk nystagmus and that which is neurologically threatening, first verify that there is no periodic alternation in direction and then perform bilateral, sequential, cover-uncover testing. If the cover test causes a reversal in the nystagmus direction consistent with FMNS, the nystagmus is benign (FMNS or INS with a latent component). If not, attempt to rule out INS (by history, clinical signs [see Table 2.1], and waveforms).

Clinical Pearl: If the results of an alternate-cover test indicate a benign, infantile,

primary-position, jerk nystagmus (i.e., it causes a reversal in the nystagmus direction consistent with FMNS or INS with a latent component), perform the test again but in far adduction of the fixating eye (e.g., far left gaze when the left eye is occluded). If the nystagmus again reverses (i.e., becomes jerk left in left gaze with left eye occluded), it is INS with a latent component. Repeat the test in adduction of the other eye fixating. If the nystagmus remains in the direction of the fixating eye, it may be either FMNS or INS with a large latent component.

3.3 TREATMENTS OF FUSION MALDEVELOPMENT NYSTAGMUS SYNDROME

When considering therapy for FMNS, it is important to understand the different components that contribute to the nystagmus and how (and at what site) each proposed therapy works. Similar to INS, there are both sensory and motor components. The absence of fusion is the sensory component that contributes to the tonic motor imbalance that drives FMN. The effect of gaze angle (Alexander's law) is the motor component modulating the FMN. Finally, the proprioceptively controlled small-signal gain of the extraocular muscles (a motor component) also can modulate the FMN. Therefore, different therapies and adaptations by the patient can act in distinct mechanistic ways to damp the FMN and, in some cases, restore fusion.

The primary treatment of FMNS is a combination of medical, optical, and surgical therapy to create, restore, or improve binocular function. Since the intensity of the FMN is related to the degree of binocular function, improving fusion will damp the FMN and improve visual function. The addition of nystagmus surgery, in the form of tenotomy and reattachment (T&R) of any horizontal rectus muscles not operated on to realign the eyes, should also further damp the FMN.

3.3.1 Fixation Preference

Patients with FMNS may be visually guided by one eye; this is due, in large part, to afferent asymmetry associated with ametropia, amblyopia, or structural disease of the eye and brain. Many of these patients will prefer the fixing eye in adduction, thus adopting a head/face turn toward the fixing eye regardless of the primary position deviation. When forced to fixate with the nonpreferred eye, the intensity of the FMNS will increase, visual functions will decrease, and a new (opposite) head/face position will be evident. Some patients spontaneously switch fixating eyes while looking at a single target.

3.3.2 Alexander's Law

Taking advantage of Alexander's law is also a consideration when determining treatment options. It would be disadvantageous to move the fixating eye medially as it would require additional abduction innervation to fixate targets in either primary position or further in abduction. In esotropia, the fixating eye (or, both eyes) is moved into abduction so that the adduction innervation required to maintain fixation damps the FMN by taking advantage of Alexander's law (motor component of FMN). It is also possible to achieve fusion to damp FMN (sensory-motor component of FMN). However, in exotropia, if one moves the fixating eye medially to achieve the straightening effect on the exotropic eye for primary position targets, that may exacerbate the motor component of FMN unless the patient achieves fusion. In the latter case, the sensory-motor effect of fusion in decreasing the FMN could be greater than the abduction innervation in increasing the FMN. In those exotropic FMNS patients for whom fusion is impossible, recessions of all four horizontal recti with a large differential (more on the lateral than the medial recti) has proven successful in treating both the exotropia and the motor component of the nystagmus.

3.3.3 Eye-Muscle Surgery

It is also possible to surgically enhance the acuity of some patients with FMNS at the same time as correcting the strabismus and head posture. These operations are considered broadly as treatment of "strabismus and nystagmus with or

without an anomalous head posture" (see operation algorithm, Chapter 7, Appendix C, and Appendix D, Figs. D.2 and D.4). In summary, to address both the FMN, head posture (if not alternating), and strabismus in the same procedure, the two horizontal rectus muscles on the eye responsible for the head posture are recessed and resected to straighten the head while the two horizontal recti on the nonfixing eye are recessed and resected to correct the resulting strabismus. The advantage of operating on all four horizontal recti is that, in addition to treating the strabismus and head posture, there is the potential of fusion and further damping of the FMN produced by the T&R effect on the proprioceptive control of the small-signal gain of the extraocular muscles. Another advantage of the T&R additions to the strabismus procedure is that, in addition to damping the FMN, those muscles receiving a T&R are left intact and may be used for future strabismus adjustments that might become necessary.

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