

Latent and Congenital Nystagmus in Down Syndrome

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Objectives: Although nystagmus has been reported in Down syndrome (DS), it has been poorly characterized, because most investigators have relied on clinical observations rather than on eye movement recordings. This study was conducted to investigate nystagmus in DS, using quantitative measurements of eye movements. **Methods:** Ocular motility and visual functions were examined in 26 unselected adults with DS and compared with those in an age-matched group of 35 subjects with other causes of mental retardation. The eye movements of those with clinically evident nystagmus were recorded with the infrared technique. We also recorded the eye movements of a child with DS and nystagmus. **Results:** Nystagmus was identified in six (23%) adults with DS and in none in the control group. All six patients showed latent/manifest latent nystagmus (LMLN), prominent with the covering of one eye, and esodeviations of 10 to 30 prism diopters. Eye movement recordings confirmed LMLN with its exponentially decaying waveform. Frequencies ranged from 2 to 5 Hz and amplitudes from 5° to 20°. While attempting to fixate straight ahead in the absence of visual cues, three subjects exhibited shifts in the mean eye position. In contrast with the findings in adults, the only child with DS examined had both congenital nystagmus and LMLN waveforms. **Conclusions:** The predominant type of nystagmus in the study subjects with DS is LMLN. The high prevalence of LMLN may reflect abnormal integration of visuospatial information that is typical of DS. The concurrent presence of congenital nystagmus in a child but only LMLN in the adults with DS raises the possibility of age-related waveform changes or could reflect sample variation.

Key words: Congenital nystagmus—Down syndrome—Latent nystagmus.

The cause of nystagmus in subjects with Down syndrome (DS) is unclear. Several investigators have found increased occurrence of nystagmus in DS, ranging from 5% to 30% (1-4). However, the true prevalence of nystagmus in DS is unknown because of the selection bias in many reports in which patients are recruited from oph-

thalmology clinics (2,5). Moreover, the type of nystagmus in DS has been insufficiently characterized, because most investigators have relied on clinical observations rather than quantitative oculography; when the latter was used, latent nystagmus (LN) was identified in some patients (5). In this article, we use the more encompassing term, latent/manifest latent nystagmus (LMLN) for this type of nystagmus and either LN or MLN to describe the nystagmus under monocular (one eye covered) or binocular (both eyes open) viewing. Although LMLN is also congenital and is present at birth, it is different mechanically, in waveforms, and clinically from congenital nystagmus (CN).

Pathogenetic mechanisms of some forms of nystagmus with onset in childhood are still poorly understood. One form for which several mechanisms have been proposed is LN. LN may result from an imbalance in the optokinetic system, possibly secondary to early visual deprivation (6,7). Mustari et al. recently presented (at the International Symposium for Therapy of Ocular Motility and Related Visual Disturbances) (8) their study of the role of the pretectal nucleus of the optic tract in LN in monkey. A related theory implicates defective cortical motion processing caused by nondevelopment of binocular vision (9). Ishikawa suggested that abnormal extraocular proprioception may predispose to LN (10). Dell'Osso et al. (11-13) postulated that LN is caused by a faulty internal representation of egocentric coordinates. The aforementioned mechanisms are not necessarily mutually exclusive; all involve various levels of visuospatial processing.

Recent data from clinical (14-18) and animal (19) studies suggest sensory abnormalities in trisomy 21 on different levels of the sensory system, both peripheral and central. These results led us to hypothesize that abnormal visuospatial processing may be responsible for nystagmus in DS, and that LN is the common form of nystagmus in DS. To test this hypothesis, we proposed to investigate the nature of nystagmus in subjects with DS, using eye movement recordings. Preliminary results have been published as an abstract (20).

METHODS

Subjects and Procedures

We examined ocular motility and visual functions in 26 unselected adults with DS (age range, 31-51 years)

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and compared them with motility and function in an age-matched and IQ-matched group of 35 subjects with other causes of mental retardation. All subjects were recruited through local community training centers; specifically, they had not been referred to us for neuro-ophthalmologic evaluation. Clinical examination included corrected visual acuity at far and near, far fusion (Worth four-dot test), near stereopsis (Titmus test), color vision (Ishihara plates), pupils, slit lamp and fundoscopic examinations in mydriasis, ocular motility, and alignment. Alignment was quantified at distance and near with prism bars during simultaneous alternate cover testing.

Subjects with clinically evident nystagmus and their guardians were approached regarding eye movement recording. After the subjects provided informed consent, their eye movements were recorded using the infrared technique. We also recorded the eye movements of a 3-year-old child with DS, who was referred to us because of abnormal eye movements.

Eye Movement Recording

Measurements of horizontal eye movements were made using the infrared reflection method. In the horizontal plane, the system is linear to $\pm 20^\circ$ and monotonic (single-valued) to $\pm 25^\circ$ to 30° with a sensitivity of 0.25° . The infrared signal from each eye was calibrated with the other eye covered to obtain accurate position information and document small tropia and phoria, possibly masked by the nystagmus. The child's records were uncalibrated. Eye velocities were obtained by analog differentiation of the position channels. The strip-chart recording system was rectilinear (Beckman Type R612 Dynograph, Fullerton, CA); total system bandwidth (position and velocity) was 0 to 100 Hz. Data were digitized with 12-bit resolution using a data translation board (model DT2801). The movements of both eyes were sampled at 200 Hz and stored in a computer for later analysis.

Experimental Protocol

During infrared recording, the subject was seated at the center of a 5-ft radius arc containing an array of light-emitting diodes (LEDs) subtending 0.1° . The head was stabilized in primary position using a chin cup, and the subject was instructed to move only the eyes while viewing each target as it was turned on. All recordings were carried out in a dimly illuminated room, with subjects viewing either monocularly or binocularly. The subjects did not wear their habitual correction during the experiment, because accurate fixation of LED targets does not require refractive correction. Fixation was examined by asking the subjects to view a stationary LED at 0° , alternating right eye, left eye, and binocular viewing. Saccades and effects of gaze angles were examined by asking the subjects to track horizontally stepping LEDs, at 5° , 10° , 15° , and 20° in each direction, with both eyes viewing. Smooth pursuit was examined with the subjects tracking a sinusoidal target moving at about 0.2 Hz in the horizontal plane with both eyes viewing. To evaluate the effects of near viewing, the subjects were asked to shift gaze between the far and near (15 cm) targets at 0° , both stepping and smoothly moving, while viewing with both eyes. The effects of darkness were evaluated by having the subjects fixate a stationary LED at 0° with both eyes viewing; after the lights and the LED were extinguished, the subjects were instructed to continue looking straight ahead. During the whole session, the subjects were continually encouraged to remain alert and to attend to the required task.

RESULTS

Alignment abnormalities were common in the DS group in general, with esotropia found in 16 subjects (62%), exotropia in 4 (15%), and orthotropia in the remaining 6 (23%). In contrast, most of the control subjects with other causes of mental retardation had orthotropia (70%), with exotropia in 8 (24%) and esotro-

TABLE 1. Clinical characteristics of the six adults and one child with LMLN

N/sex/age	VA far near	Far fusion	Near stereopsis	Alignment	Nystagmus	Other
1/f/39	20/200 OU J7 OU	Suppressed OD	"Fly-positive"	Eso (?15PD)	MLN RE > LE	High myopia
2/f/30	20/50 OU	Present (?)	400 sec of arc	Eso (?10PD)	LN	Moderate myopia
3/m/51	20/50 OU J1-2 OU	—	—	Eso (30PD)	MLN	Congenital cataracts
4/f/31	20/200 OD 20/100 OS J8 OU	Suppressed OD	—	Eso (30PD)	LN	High myopia
5/m/35	20/60 OD 20/40 OS	Present	—	Eso (mild at far, 20 PD at near)	LN Jerk left LE > RE	Hyperopia
6/f/35	20/60 OU J1 + OU	Suppressed OS	100 sec of arc	Eso (?15 PD)	MLN LE > RE	Mild ON dysplasia
7/m/3	NA	Suppressed OD	NA	Eso (25 PD)	CN?	Aphakia

Subjects 1–5 preferred to fixate with their left eye.

VA, visual acuity; PD, prism diopters; ON, optic nerve; Eso, esodeviation; OD/RE, right eye; OS/LE, left eye; OU, both eyes; NA, not available; LMLN, ; N, number; F, female; M, male; MLN, .

Far fusion was measured by the Worth-4-dot test, near stereopsis by the Titmus test.

TABLE 2. Nystagmus characteristics of five adults and one child with LMLN

Subject	LN	MLN presence/direction	MLN in darkness ON/OFF	LMLN frequency (Hz)	LMLN amplitude (°)	LMLN amplitude RE vs LE	CN type/frequency (Hz)
1	JL > JR	+/JL > JR	JL/JL	≈2	2-10	RE > LE	—
2	JL ≈ JR	±/JL in left gaze	JR/JR	JR ≤3 JL ≈ 5	1-10	RE ≈ LE	—
3	JL ≈ JR	+/JL	JL/JL	≈3	2-20	RE < LE	—
4	JL > JR	+/JL	NA/±JR	2-3	1-20	RE ≈ LE ^a	—
5	JL only	+/JL	JL/JL	≈3	1-5	RE ≈ LE	—
6	Not available for recording						
7	JL > JR	+/JR?	NA	1-4	NA	NA	Pendular/2-5 Jerk/1.5-3

JR, jerk right; JL, jerk left; NA, not available; ON, central target on; OFF, central target off; RE, right eye; LE, left eye; LMLN, ; LN, ; MLN, ; CN, .

^a For this subject, RE < LE during MLN.

? The JR nystagmus could have been either MLN, CN with a latent component, or a mixture of the two.

pia in only 2 (6%). Ocular motility was clinically normal in 20 of the DS subjects.

We identified nystagmus clinically in six adult subjects with DS and none in the control group. Their clinical characteristics are summarized in Table 1. All showed LMLN, more prominent with one eye covered, and esodeviations from 10 to 30 prism diopters. Far vi-

sual acuity ranged from 20/40 to 20/200, with near vision, J1+ to J8. Stereopsis was absent or diminished (Table 1). Subjects 1 through 5 preferred their left eyes for fixation. Eye examination demonstrated mild optic nerve dysplasia in one and peripheral congenital cataracts in two. The child with DS had nystagmus with pendular and jerk components, prominent during binocu-

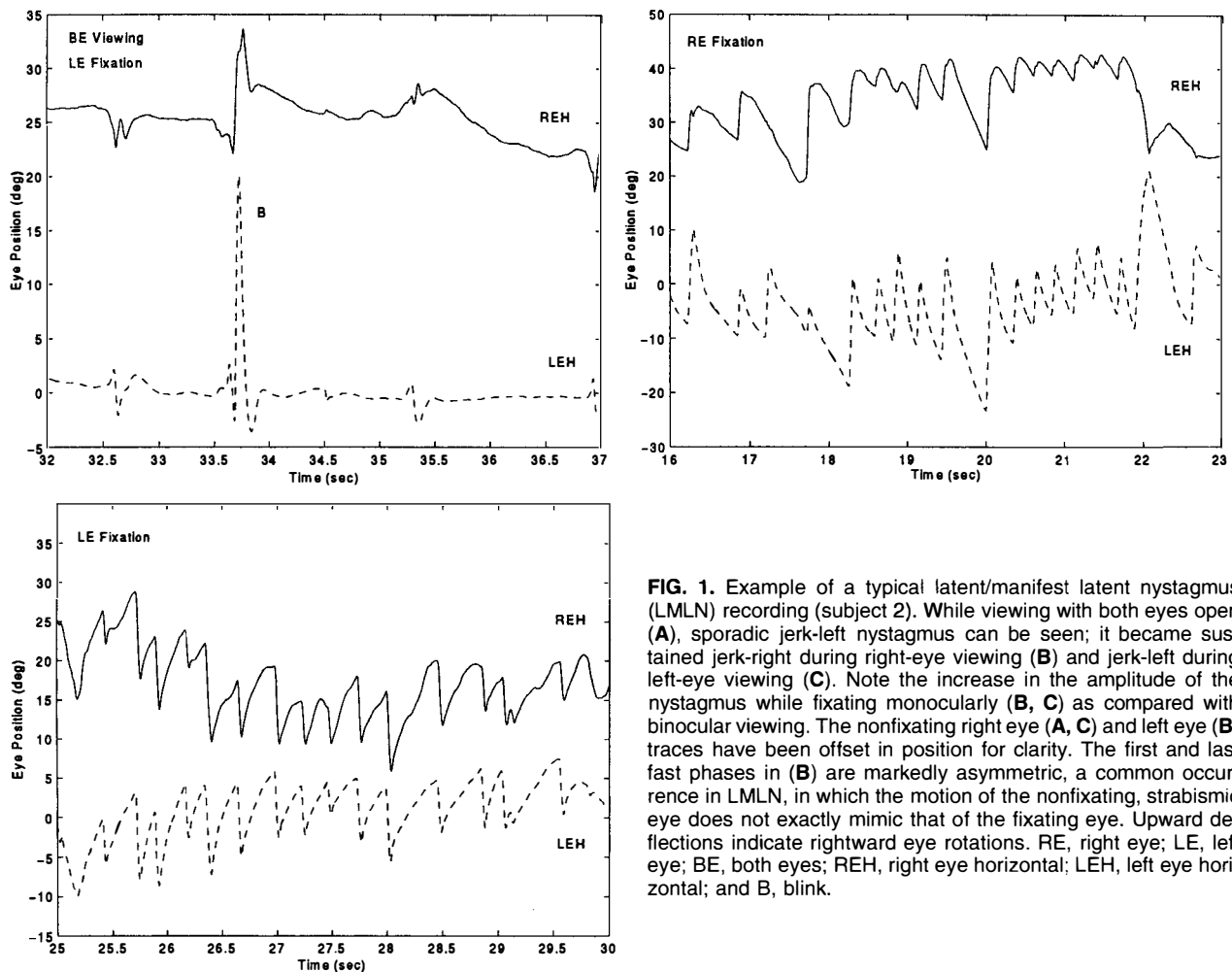


FIG. 1. Example of a typical latent/manifest latent nystagmus (LMLN) recording (subject 2). While viewing with both eyes open (A), sporadic jerk-left nystagmus can be seen; it became sustained jerk-right during right-eye viewing (B) and jerk-left during left-eye viewing (C). Note the increase in the amplitude of the nystagmus while fixating monocularly (B, C) as compared with binocular viewing. The nonfixating right eye (A, C) and left eye (B) traces have been offset in position for clarity. The first and last fast phases in (B) are markedly asymmetric, a common occurrence in LMLN, in which the motion of the nonfixating, strabismic eye does not exactly mimic that of the fixating eye. Upward deflections indicate rightward eye rotations. RE, right eye; LE, left eye; BE, both eyes; REH, right eye horizontal; LEH, left eye horizontal; and B, blink.

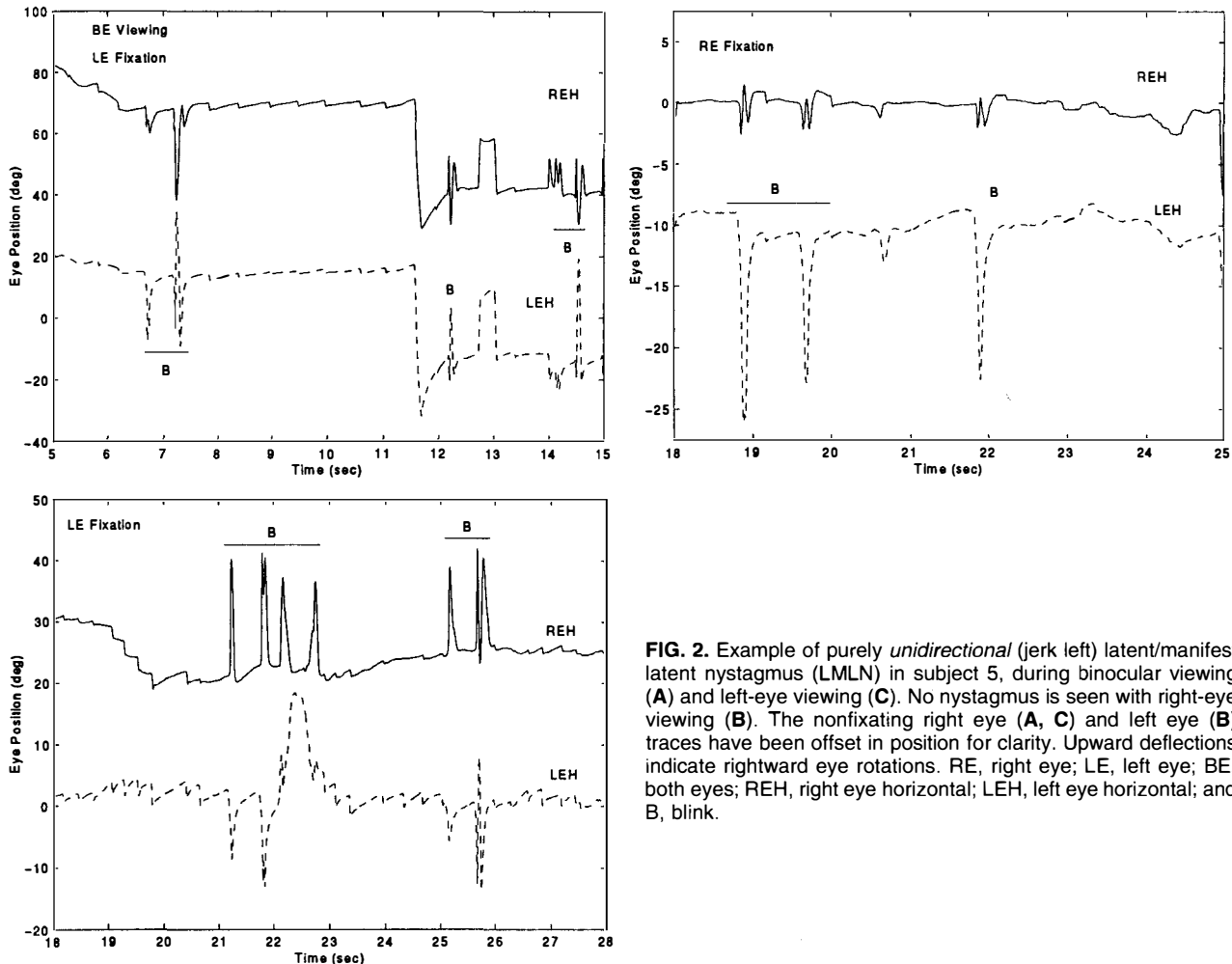


FIG. 2. Example of purely *unidirectional* (jerk left) latent/manifest latent nystagmus (LMLN) in subject 5, during binocular viewing (A) and left-eye viewing (C). No nystagmus is seen with right-eye viewing (B). The nonfixating right eye (A, C) and left eye (B) traces have been offset in position for clarity. Upward deflections indicate rightward eye rotations. RE, right eye; LE, left eye; BE, both eyes; REH, right eye horizontal; LEH, left eye horizontal; and B, blink.

lar viewing, and esotropia of 25 prism diopters. He was aphakic, after successful surgery for bilateral congenital cataracts. He could sustain central fixation and preferred to fixate with his left eye.

Eye movement recording was performed in five adult subjects and the child. It established the presence of LMLN with exponentially decaying waveforms in all the adult subjects with DS. We did not observe CN waveforms in any of our adult subjects. The child (subject 7) exhibited a complex combination of waveforms consisting of CN and LMLN. The CN waveforms were of both jerk and pendular varieties and also had a latent component. At times, the nystagmus was disconjugate, mimicking spasmus nutans. The ocular motor data are summarized in Table 2.

With binocular viewing, MLN was documented by the recordings to a varying degree in the five adult subjects with clinically evident nystagmus who underwent eye movement measurement. Predominant direction of the nystagmus was jerk left in all subjects. Nystagmus increased during monocular viewing and changed direction with alternating fixating eyes in four subjects (Fig. 1). In one subject, the nystagmus was unidirectional (Fig. 2), and was observed mainly while viewing with the left eye.

LMLN changed little at different gaze angles. In the adults, frequencies ranged from 2 to 5 Hz and amplitudes from 1° to 20°. When dissociated (as it was in two subjects), higher amplitude LMLN did not correlate with worse vision in that eye. Saccades were normal, but eye movements during smooth pursuit were asymmetric, reflecting the prevailing direction of the nystagmus slow phases rather than a directional asymmetry in the smooth-pursuit subsystem (21). In darkness, all subjects exhibited strong drifts in the direction of the slow phases (extended slow phase). In subjects 1, 3, and 5, attempts to fixate straight ahead without visual cues resulted in rightward shifts in the mean eye position around which nystagmus occurred (Fig. 3).

In the child (Table 2, subject 7), LMLN frequencies ranged from 1 to 4 Hz; lack of cooperation because of his age precluded accurate amplitude calibration. His CN had frequencies of 2 to 5 Hz (pendular) and 1.5 to 3 Hz (jerk and jerk with extended foveation). Examples of the child's nystagmus are shown in Figure 4.

DISCUSSION

We found that 23% of unselected adult subjects with DS had nystagmus. In all these cases, the nystagmus was

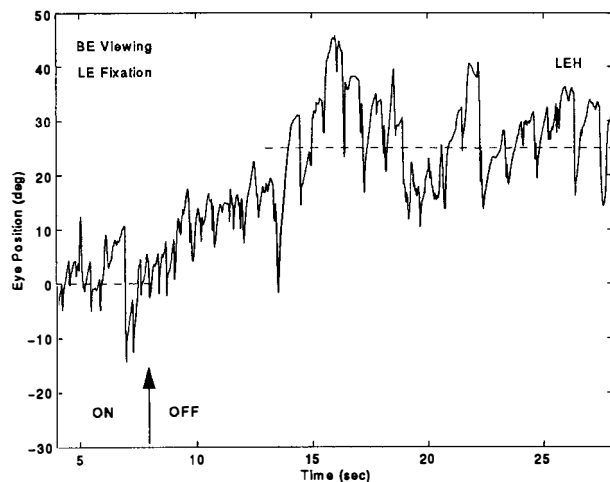


FIG. 3. Example of attempted fixation in darkness (subject 3), while looking binocularly straight ahead. The central target was extinguished (OFF) after the initial presentation. All subjects exhibited drifts in the direction of the slow phases (extended slow phase). Attempts to fixate straight ahead in the absence of visual cues were accompanied by rightward shifts in the mean eye position (dashed line) around which nystagmus occurred, implying deviation of the subjective zero. Upward deflections indicate rightward eye rotations. RE, right eye; LE, left eye; BE, both eyes; REH, right eye horizontal; LEH, left eye horizontal; and B, blink.

LMLN. Such a high occurrence of LMLN is far above the expected prevalence of LMLN in the general population. It also greatly exceeds the reported percentage of LMLN among other types of infantile nystagmus: LMLN has been generally estimated to comprise only 15%, with the majority being CN (80%), and mixtures of the two (5%) (22). Even in those with strabismus associated with infantile nystagmus, LMLN is responsible for only 35% of nystagmus types (22). The presence of both CN and LMLN waveforms in the aphakic child in our series is also surprising, given the low incidence of such mixtures; only CN would be expected to be associated with the sensory deficit.

Traditionally, latent nystagmus has been associated with nondevelopment of binocular vision (9). Yet, near stereopsis was at least to some extent preserved in two of our adults with DS and LMLN (Table 1) who showed esotropia during far viewing but esophoria while viewing a near target. Another two DS subjects, who were esotropic at near but only esophoric at far, could fuse on the Worth four-dot test, suggesting the existence of some binocular vision. Thus, the presence of rudimentary stereopsis did not prevent development of LMLN, possibly indicating that impaired binocular vision may not be directly implicated in the pathogenesis of LMLN.

Interestingly, five of six adults with DS preferred to fixate with their left eyes. Such preponderance of left ocular dominance raises a question of an altered hemispheric dominance in DS. That the subjects chose their left eyes for fixation, although such preference corresponded to the more prominent LN (subjects 1, 4, 5, and

7) is remarkable. This finding implies that eye dominance is determined by factors other than visual circumstances, including blindness, as previously described by Dell'Osso et al. (13) Although eye dominance and hand dominance are not directly related, three of our adult subjects were left-handed, suggesting an unusual pattern of hemispheric dominance in DS.

The presence of strabismus in LMLN is considered obligatory (23). Indeed, all study patients with DS had esodeviations. However, the cause of the strabismus in LMLN is unclear. Recently, extraocular proprioception has been shown to be important in the normal development of ocular alignment (24), supporting Ishikawa's hypothesis that LN may be secondary to abnormal extraocular proprioception (10). Although no data are presently available on extraocular proprioception in DS, a plethora of evidence attests to an abnormal sensory system, on the levels of sensory nerves (18), primary sensory cortex (16), and visuospatial integration (15). Children with DS have lower conduction velocities and lower action potentials in their sensory nerves (18). Short-latency somatosensory evoked potentials in DS show prolonged interpeak latencies and abnormally large amplitudes of cortical potentials N20 and P25 in the parietal area (16). In addition to these macropotentials, potentials related to reafferent sensory information are absent (17). Processing of proprioceptive information in DS is impaired, as reflected by kinesthetic aftereffects disrupting the spatial frame of reference (14) and poor location memory (15). Further evidence for associative cortex dysfunction in DS comes from animal models. Mice with segmental trisomy 16 (Ts65Dn mice), which serve as a model for DS, exhibit severe deficits in the integration of visual and spatial information (19).

These data suggest that impaired processing of sensory signals in DS may lead to abnormal formation of visuospatial maps, thus resulting in a defective internal representation of egocentric coordinates. Such abnormal internal representation of egocentric coordinates may be responsible for ocular misalignment and LMLN (both conditions being common in DS), as proposed by Dell'Osso et al. (11–13). Conversely, strabismus itself (25,26) and strabismus surgery (27,28) have been shown to affect egocentric localization. Therefore, esotropia in DS can either be caused by abnormal egocentric localization or can be directly responsible for it. Further studies are necessary to separate these two possible and interrelated mechanisms.

Evidence in support of the faulty internal representation of spatial coordinates in our adult DS subjects comes from their behavior in darkness. While attempting to fixate straight ahead in the absence of visual cues, these subjects showed rightward shifts of the mean eye position around which the LMLN oscillation occurred. These shifts could not have resulted from switching the fixating eye, because they were not accompanied by a reversal of the LMLN direction (Table 2). Such shifts in the mean eye position were observed in addition to the drifts in the

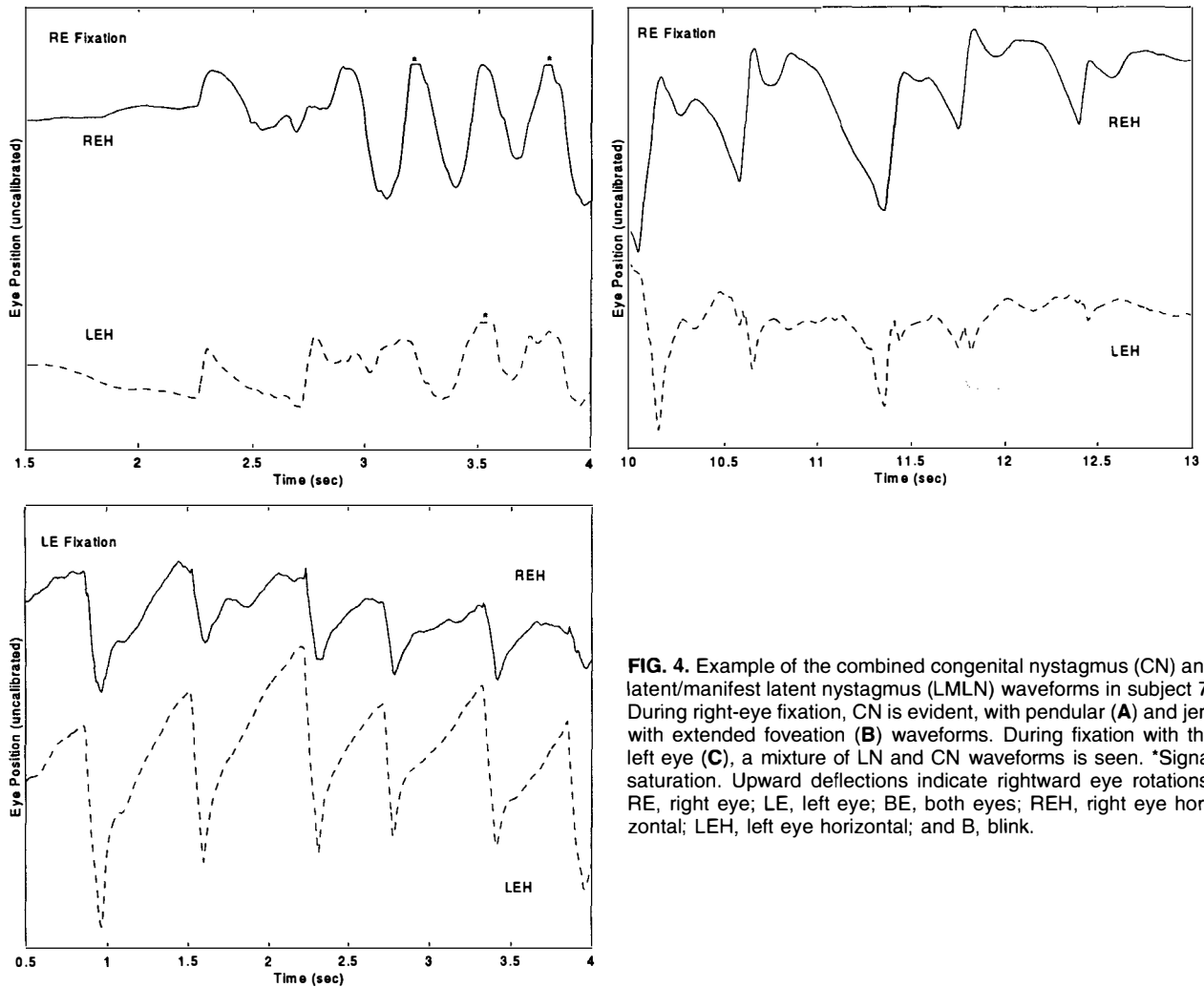


FIG. 4. Example of the combined congenital nystagmus (CN) and latent/manifest latent nystagmus (LMLN) waveforms in subject 7. During right-eye fixation, CN is evident, with pendular (**A**) and jerk with extended foveation (**B**) waveforms. During fixation with the left eye (**C**), a mixture of LN and CN waveforms is seen. *Signal saturation. Upward deflections indicate rightward eye rotations. RE, right eye; LE, left eye; BE, both eyes; REH, right eye horizontal; LEH, left eye horizontal; and B, blink.

direction of the slow phase (rightward), possibly implying a rightward deviation of the "subjective zero." This differs from normal fixation behavior in darkness, in which the subjective zero corresponds to the actual zero target, in spite of eye-movement drifts around it (29). In our opinion the shifts of the mean eye position in darkness reflect abnormally represented egocentric coordinates.

In contrast to the invariable LMLN appearance of nystagmus in our adult DS group, in the one child with DS whom we examined, the nystagmus had both CN and LMLN waveforms. In the only previous quantitative study, Lawson et al. (5) studied nystagmus in five children with DS with a mean age of 10 years. Using electro-oculography, they identified two forms of nystagmus: LN and that which they termed "sensory-defect nystagmus" with accelerating slow phases—that is, CN. The absence of CN waveforms in our group of adults with DS, although present in children with DS, requires consideration. One possibility, albeit unlikely, is age-related diminution of CN. Such a damping or elimination of CN, along with an accentuation of LMLN, could be facilitated by degenerative changes that affect

the posterior associative cortex of subjects with DS because of the early-onset Alzheimer's disease that is ubiquitous in DS (30). Alternatively, these differences between the age groups may merely represent a sample variation.

In conclusion, frequent occurrence (23%) of LMLN in adults with DS may reflect abnormal processing of visuospatial information, consistent with recent findings in patients and animal models of trisomy 21; misalignment of the eyes and impaired binocularity also ensue. This supports the role of dysfunctional visuospatial integration in the pathogenesis of LMLN. The presence of the combination of CN and LMLN waveforms in a child with DS, but only LMLN in adults, raises the intriguing possibility of Alzheimer's disease-related changes in the waveforms.

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