Infantile Nystagmus and Abnormalities of Conjugate Eye Movements in Down Syndrome

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Purpose. Subjects with Down syndrome (DS) have an anatomical defect within the cerebellum that may impact downstream oculomotor areas. This study characterized gaze holding and gains for smooth pursuit, saccades, and optokinetic nystagmus (OKN) in DS children with infantile nystagmus (IN).

Methods. Clinical data of 18 DS children with IN were reviewed retrospectively. Subjects with constant strabismus were excluded to remove any contribution of latent nystagmus. Gaze-holding, horizontal and vertical saccades to target steps, horizontal smooth pursuit of drifting targets, OKN in response to vertically or horizontally-oriented square wave gratings drifted at 15°/s, 30°/s, and 45°/s were recorded using binocular video-oculography. Seven subjects had additional optical coherence tomography imaging.

Results. Infantile nystagmus was associated with one or more gaze-holding instabilities (GHI) in each subject. The majority of subjects had a combination of conjugate horizontal jerk with constant or exponential slow-phase velocity, asymmetric or symmetric, and either monocular or binocular pendular nystagmus. Six of seven subjects had mild (Grade 0–1) persistence of retinal layers overlying the fovea, similar to that reported in DS children without nystagmus. All subjects had abnormal gains across one or more stimulus conditions (horizontal smooth pursuit, saccades, or OKN). Saccade velocities followed the main sequence.

Conclusions. Down syndrome subjects with IN show a wide range of GHI and abnormalities of conjugate eye movements. We propose that these ocular motor abnormalities result from functional abnormalities of the cerebellum and/or downstream oculomotor circuits, perhaps due to extensive miswiring.

Keywords: nystagmus, Down syndrome, cerebellum

Infantile nystagmus (IN) has a reported prevalence in Down syndrome (DS) ranging from 9% to 30% based on clinical detection of a rapid, monocular or binocular, oscillation of small amplitude, conjugate pendular or jerk nystagmus, or latent nystagmus.[1–3] The only two studies that included eye movement recordings reported fusion maldevelopment nystagmus (FMN) in five of six DS subjects with congenital esotropia[4] or waveforms consistent with IN in 14 of 16 DS subjects.[5] Costa[6] reported low horizontal optokinetic nystagmus (OKN) gains in 32% of DS subjects in the only assessment of eye movements elicited by a controlled visual stimulus. Evidence of an underlying visual sensory defect in DS children with IN is limited to a 0.2 to 0.3 log unit reduction in visual acuity compared to age-matched controls and a 0.2 deficit in mean contrast sensitivity for drifting grating.[7,8] Taken together, this constellation of ocular findings in hypotonic DS subjects with delayed motor skills implicates abnormalities of ocular and somatic motor systems.

The most consistent brain anatomic finding in humans[9,10] and in the mouse model of DS[11,12] is a small cerebellum. Histologic studies of the Ts65Dn mouse model of DS show reductions in density of the molecular layer, internal granule layer (IGL) and Purkinje cell layer.[12,13] During prenatal development and up to 14 months postnatally, the human cerebellum undergoes refinements of the neural circuitry forming functional modules with discrete connections between the Purkinje cells and downstream deep cerebellar nuclei.[14,15] Each modular region of the cerebellum is, in turn, connected to downstream brainstem regions responsible for the generation and precision of saccades, smooth pursuits, and OKN. Therefore, measurement of conjugate eye movement behavior can implicate specific neuronal ensembles within the cerebellum and downstream brainstem regions in the creation of gaze-holding instabilities (GHI), based on established relationships between discrete lesions to these structures and abnormalities in conjugate eye movement.[16] The primary objectives of this study were 2-fold: (1) to characterize the spectrum of GHIs in DS, and (2) to quantify and compare the conjugate eye movements of subjects with DS and nystagmus with those of normal control subjects. The underlying hypothesis was that the GHI and abnormalities of conjugate eye movements in DS are consistent with impairments in specific regions of the cerebellum and/or corresponding downstream oculomotor circuits.

Table 1. Ophthalmological Findings

Subject No.	Age, y	Age Corrected logMAR OD	Age Corrected logMAR OS	Refraction OD	Refraction OS	Alignment at Distance
1	0.4	−0.20	0.12	−7.50 +2.00 × 90	−7.50 +2.00 × 90	Ortho
2	0.4	0.43	0.43	+4.00	+4.00	Ortho
3	0.4	−0.18	−0.18	+3.00	+3.00	Ortho
4	0.8	0.24	0.41	+2.00 +2.50 × 90	+2.00 +2.50 × 90	Ortho
5	0.8	0.39	0.71	+1.50 +1.50	+1.50 +1.50	Ortho
6	1.0	0.48	0.32	pl +1.50 × 60	pl +1.50 × 120	Ortho
7	1.0	0.50	0.32	−1.50	−1.50	Ortho
8	1.1	0.50	0.50	+2.50 +1.50 × 75	+2.50 +1.50 × 105	Ortho
9	1.5	0.44	0.61	+1.00 +2.00 × 85	+1.00 +2.25 × 95	0-10 ET
10	1.5	0.63	0.63	pl +1.00 × 90	pl +1.00 × 90	Ortho
11	6.8	1.04	0.88	+3.00 +1.00 × 65	+3.50 +1.00 × 125	Ortho
12	7.5	0.61	0.61	+5.50 +0.50 × 40	+5.50 +0.50 × 135	Ortho
13	7.8	0.54	0.54	+1.50	+1.50	Ortho
14	9.5	0.67	0.77	−1.50 +3.50 × 80	−1.25 +4.00 × 80	Ortho
15	10.7	0.67	0.67	+ 0.50 +4.00 × 90	+ 0.50 +4.00 × 90	Ortho
16	12.6	0.98 OU		−15.00	−15.00	Ortho
17	14.9	0.77	0.77	+4.00	+4.00	Ortho
18	0.9	0.21	0.21	−4.50 +1.00 × 90	−4.50 +1.00 × 90	Ortho

OD, right eye; OS, left eye; OU, both eyes; pL, plano; Ortho, orthotropic.

Methods

This retrospective chart review study was approved and monitored by the Institutional Review Board of Seattle Children's Hospital. The medical records of 18 DS children with IN were identified. The research adhered to the tenets of the Declaration of Helsinki. All subjects had trisomy 21 confirmed by karyotyping.

All subjects had comprehensive eye examinations with emphasis on assessment of visual acuity, binocular eye alignment, and gaze holding in primary gaze and at eccentricities of 15° up, down, right, and left. Binocular deviations were quantified using the prism cover test or the Krimsky test depending upon subject cooperation. Clinical examination included assessment of pupillary responses, slit-lamp examination, and dilated fundus examination. Details of visual acuity measurement and conversion to age-corrected logMAR acuity already are described.[17]

Spectral domain optical coherence tomography (SD-OCT) combined with a scanning laser ophthalmoscope (Spectralis OCT-SLO; Heidelberg Engineering, Heidelberg, Germany) was available in seven subjects, including six with eye movement recording and one subject with monocular pendular nystagmus in whom eye movements were not recorded but could be visualized on the SLO. Data were acquired at 40,000 A-scans/s in high resolution mode. Pupil sizes were larger than 3 mm. If nystagmus amplitude was low, the instrument performed averaging by active eye tracking to compensate for eye-motion artifacts. Several single line scans were performed targeting the fovea. All single line scans were inspected to determine which SD-OCT image contained the foveal center as defined by the deepest point of the foveal pit with the associated increased lengthening of the outer segments. The central foveal thickness (CFT) was defined as the distance from the outer limit of the RPE-Bruch's membrane to the vitreoretinal interface of the foveal pit. Our measurement of CFT is very similar to that by Yanni et al.[18] in children and Tick et al.[19] in adults also using the Spectralis instrument.

A total of 17 DS subjects with IN and 12 controls (mean age, 9.5 years) had quantitative recording of gaze holding during binocular viewing using identical protocols. Eye movements were recorded with one of two binocular video-oculography systems (2D VOG/VO425; SMI/Interacoustics, Berlin, Germany/Copenhagen, Denmark). Temporal resolution for VOG was 60 or 100 Hz depending on the system used. The spatial resolution for VOG is 0.1°, with a calibrated accuracy of 0.5° in children. Subjects sat independently or in a parent's lap, with the head manually restrained. They viewed a back-projected visual stimulus on a screen subtending approximately 60° at a fixation distance of 60 to 80 cm. Gaze holding was measured in primary gaze in the dark and while fixating a 0.1° target at eccentricities of 15° up, down, right, and left. Depending on cooperation, gaze-holding was recorded continuously for a minimum of 30 seconds and maximum of 4 minutes. To elicit saccades, the target was pseudo-randomly stepped between 5° and 25° horizontally or vertically. Pursuit was elicited by moving a point target sinusoidally ±10° along the horizontal meridian at peak velocities of 10°/s, 20°/s, and 30°/s. To elicit OKN square wave gratings with a spatial frequency of 0.1 cycle/deg and 80% contrast horizontally or vertically on a screen at constant velocities of 15°/s, 30°/s, and 45°/s. Calculation of gain for saccades, smooth pursuit, and OKN has been described previously.[20] For smooth pursuit, we use the term "apparent pursuit" to refer to the combination of slow and fast phase eye movements elicited by the stimulus but combined with the underlying IN. Exclusion from data analysis was (1) cycles where apparent pursuit gain was >1.4, (2) desaccaded data were ≤40% of the cycle, and (3) phase was greater than ±45°. The gains for all conditions represent the average of both eyes when adequate binocular recordings were obtained. If there was a breakdown of binocular eye alignment, then only the fixating eye was scored.

Results

Table 1 shows the relevant ophthalmologic findings of the 18 subjects with DS evaluated between 0.4 and 14.9 years of age, with a mean age of 4.6 years. Of the 18 subjects, nine were male. All subjects had developmental delay ranging from mild to severe. All but four subjects had visual acuity below age-matched controls (logMAR > 0.3). The four subjects with normal acuity were measured with Teller cards and were less than 1 year of age. After correction for age, visual acuity

Table 2. Summary of Nystagmus Waveforms

Subject No.	Age, y	Jerk*	Constant Velocity†	Horizontal Pendular‡	Horizontal Pendular§	Vertical Pendular‖	Square-wave Jerks
1	0.4	X		B / M			X
2	0.4	X					
3	0.4						X
4	0.8	X		B		X	
5	0.8	X		M			X
6	1.0				X		
7	1.0	X	X	B			
8	1.1	X	X	B		X	
9	1.5	X		B			
10	1.5				X		
11	6.8	X	D				
12	7.5	X	D				
13	7.8	X	X				
14	9.5	X					
15	10.7		D		X		
16	12.6	X	D				
17	14.9		X				
18#	0.9			M			

* Conjugate horizontal jerk with exponential slow phase; >5°, 2 to 4 Hz.
† Conjugate horizontal jerk, constant velocity slow phase. D, under complete darkness.
‡ Amplitude <3°, frequency 5 to 7 Hz. B, binocular; M, monocular.
§ Amplitude 3° to 12°, frequency 2 to 4.5 Hz, asymmetric between eyes.
‖ Amplitude <3°, frequency 5 to 7 Hz.
Clinical assessment, estimated frequency is 5 Hz, amplitude 1°.

averaged 0.49 logMAR. For subjects able to perform recognition acuity, average visual acuity was 0.59 logMAR. Cycloplegic refraction revealed −15.00 to +4.00 diopters of spherical error and astigmatism ranging from 1.00 to 4.00 diopters in 11 subjects. The ocular media (cornea, lens, and vitreous) were optically transparent, and dilated fundus examination was uniformly normal. Subject #12 had a normal electroretinogram. All subjects had a diagnosis of DS confirmed by a geneticist and chromosomal testing. Six of the 18 subjects had a cardiac malformation (atrial septal defect, ventricular septal defect, or double-outlet right ventricle) or gastrointestinal malformation (duodenal atresia). All had a normal birth history except subject #9, who was born at 29 weeks following in utero exposure to drugs. None of the subjects had a hypoxic/ischemic event associated with cerebral damage.

Gaze Holding

Table 2 summarizes the nystagmus waveforms in all DS subjects. Each subject showed 1 to 4 nystagmus waveform types. Multiple nystagmus waveforms were more frequent in subjects below 1.6 years of age. Two subjects (#5, #18) initially showed monocular horizontal, pendular nystagmus, which diminished on follow-up examination. Figure 1 shows a spectrum of GHI from a single subject. The initial segment of gaze holding shows a largely monocular asymmetric pendular nystagmus. Later in the recording, both eyes show the intrusion of square wave jerks. Gaze holding in the dark reveals a constant velocity slow-phase waveform consistent with vestibular nystagmus.

Saccades

Figures 2A and 2B shows the horizontal and vertical saccadic gains versus target step amplitude for individual subjects with DS, respectively. Saccades (#1–15) to horizontal and vertical target steps were elicited in six (0.4–9.5 years) and 10 (0.4–10.7 years) subjects, respectively. The gains were highly variable across ages and across target steps. Saccade latency ranged from 133 to 786 ms with a mean of 285 ms. Relative to controls, gains for individual subjects with DS could be hypermetric, normometric, or hypometric. For horizontal saccades, two subjects showed directional asymmetries, with hypermetric saccades to the left and hypometric saccades to the right. Two subjects were consistently hypometric to the left and right. No subject showed normal saccade gain for horizontal target directions and all amplitudes. For vertical saccades, three subjects were consistently hypometric. One subjects was hypometric for downward target steps and hypermetric for upward target steps. No subject showed normal saccade gain for vertical target directions and all amplitudes. Figure 3 shows that peak velocity of horizontal and vertical saccades overlaps with the main sequence seen in control subjects. The data in Figure 3 also show the expected nonlinear increase in saccade peak velocity with increasing saccade amplitude.[16]

Apparent Pursuit

Apparent pursuit eye movements were superimposed on the slow phase of the underlying nystagmus in all but one subject with intermittent nystagmus and epochs of stable gaze. Figure 4A shows representative eye movements to a target drifting sinusoidally along the horizontal meridian. Blank spaces represent saccades that were removed from the VOG trace. Given our inability to isolate the contribution of each component, we refer to the gain of the sinusoidal fit to the observed slow phase eye velocity relative to the target velocity as apparent pursuit gain. Figure 4B shows apparent gain from the average of both eyes for each subject (11, 12, and 14 subjects at target peak velocities of 10°/s, 20°/s, 30°/s, respectively). Each subject's data point at each velocity represents an average of 8, 11, and 23 cycles. Apparent pursuit gains of DS subjects on average ranged from 0.3 to 0.4 across stimulus velocities and were overall below the mean and 1 SD of the control data.

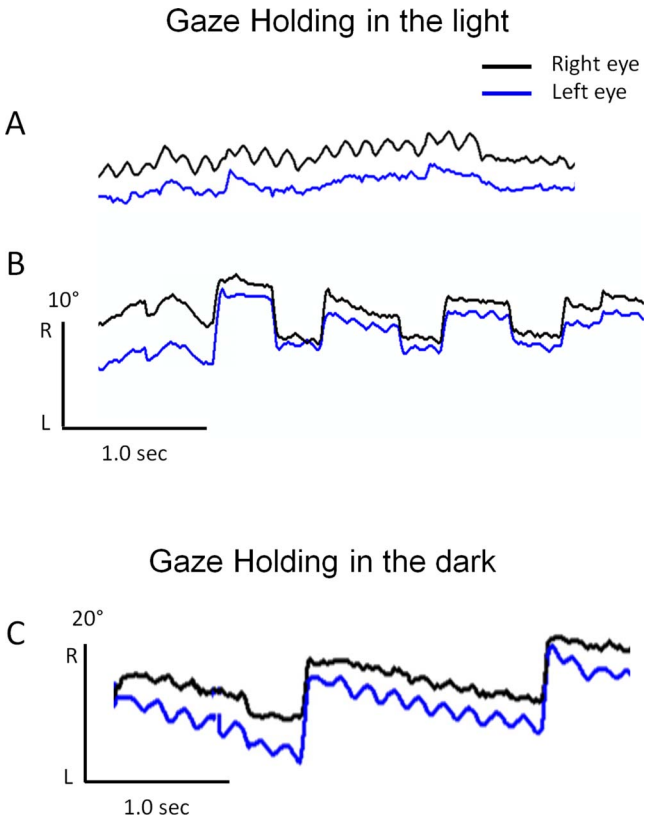

FIGURE 1. Three segments of a video-oculography recording session from subject #5. The *top two segments* (**A**, **B**) were recorded during the first 17 seconds of a 45-second recording. Segment (**C**) was recorded while the subject was in complete darkness. Rightward horizontal eye movements are represented by *upward deflections* and leftward movements are represented by *downward deflections*.

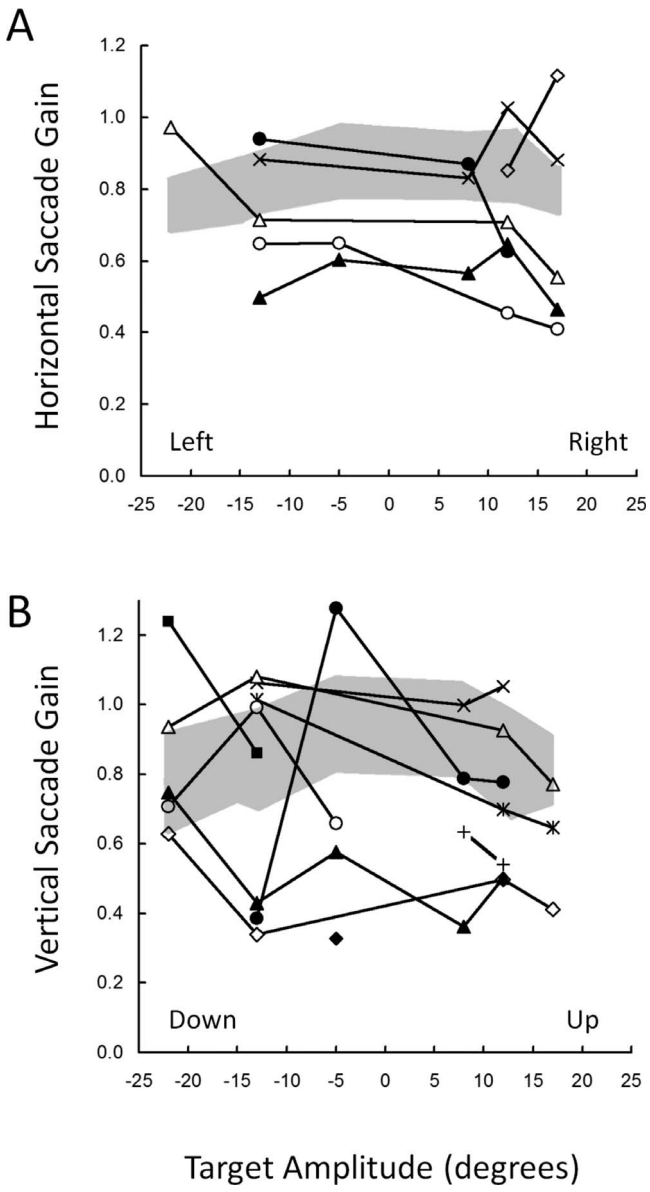

FIGURE 2. Horizontal (**A**) and vertical (**B**) saccadic gains of individual subjects with Down syndrome. The average gain for each subject is represented by different *symbols* connected with *lines*. For horizontal targets, positive and negative values on the *abscissa* represent rightward and leftward displacements in degrees, respectively. For vertical targets, positive and negative values on the *abscissa* represent upward and downward displacements in degrees, respectively. The *shaded areas* are the mean ± 1 SD of controls.

Optokinetic Nystagmus

Horizontal optokinetic nystagmus (hOKN) was superimposed on the underlying nystagmus. Horizontal optokinetic nystagmus was distinguished from IN by scoring only epochs with serial sequences or isolated epochs of "saw-tooth" nystagmus in the appropriate direction. Epochs without eye movement or with eye movement in the wrong direction were excluded. Average hOKN gains were below controls for one or more stimulus velocities of 15°/s, 30°/s, and 45°/s (Fig. 5A). Average hOKN gains typically decreased with increasing velocity for rightward and leftward drifting gratings relative to age-similar controls. Vertical OKN gains (Fig. 5B) were highly variable and comparable to the gains obtained with hOKN.

Retinal Imaging

Optical coherence tomography imaging was available in subject 11 and subjects 13 to 18; age at the time of OCT imaging ranged from 7.8 to 14.9 years. All subjects with SD-OCT images had a normal optic nerve diameter in the horizontal and vertical directions (1537–2000 μm). Peripheral to the fovea, all retinal layers appeared normal in all eyes. In all subjects, the fovea showed thickening of the outer nuclear layer and lengthening of the photoreceptor outer segment layer. The average CFT in seven subjects (13 eyes) was 264.3 μm (SD 26.0). Central foveal thickness ranged from 212 to 286 μm, which is larger than that reported by Yanni et al.[18] (219.6 μm; SEM 1.7) and by Tick et al.[19] (230 μm; SD 21). One subject (#17) with constant velocity slow-phase nystagmus had a normal-appearing fovea and normal CFT. The remaining subjects showed varying continuation of the ganglion cell layer, inner plexiform layer, or inner nuclear layer over the fovea center with a shallow foveal pit (Fig. 6). All DS subjects in our sample had foveal anatomy score between normal and grade 1 following the grading system described by Thomas et al.[21]

DISCUSSION

We documented a conjugate, horizontal, jerk nystagmus with exponential slow phase (12 patients) or constant velocity slow phase (eight patients), monocular or binocular horizontal or

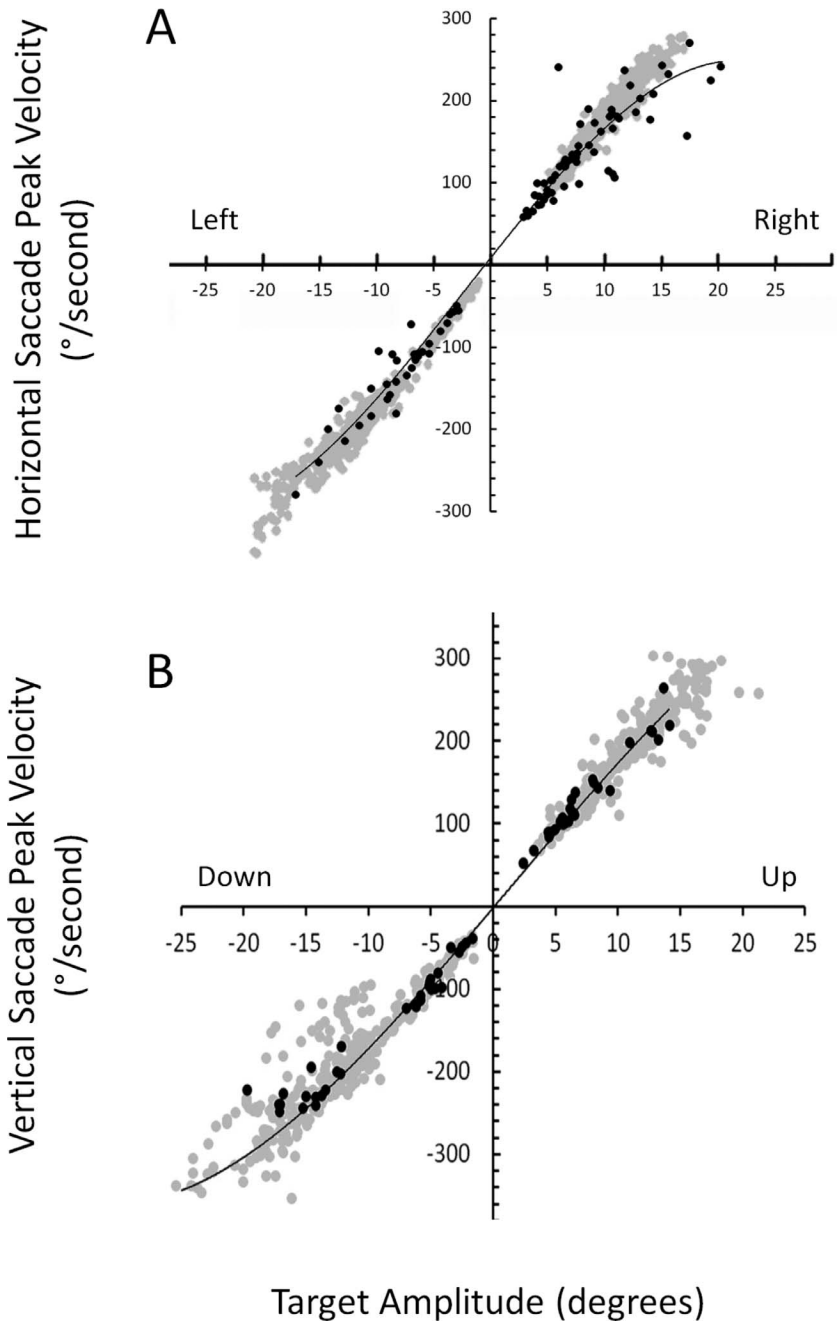

FIGURE 3. Horizontal (**A**) and vertical (**B**) main sequence of individual saccades in subjects with Down syndrome. For horizontal targets, positive and negative values on the *abscissa* represent rightward and leftward displacements in degrees, respectively. For vertical targets, positive and negative values on the *abscissa* represent upward and downward displacements in degrees, respectively. The *grey dots* represent individual saccades from controls.

vertical pendular oscillations (five patients), and square wave jerks (three patients) in 18 DS children. We used the term GHI rather than IN syndrome to emphasize the interleaved, and variable stream of binocular or monocular, horizontal, or vertical nystagmus with pendular or jerk waveforms and saccadic intrusions. Collectively, the heterogeneity of the GHI, and the subtle anatomic abnormality of the macula suggest that macular hypoplasia is unlikely to account for GHI in DS.

The presence of a jerk nystagmus with constant velocity slow-phase is consistent with a functional abnormality of the vestibular end organ or of central vestibulo-cerebellar pathways. A peripheral vestibular abnormality seems unlikely given that Costa et al.[22] reported minimal alterations in the VOR gain and time constant compared to controls during rotary chair testing of DS children. On the other hand, a central vestibular basis for the observed nystagmus would be supported by the observation that DS children show reduced ability to suppress induced VOR with visual fixation.[22] It is well documented that asymmetric cerebellar and/or medullary brainstem lesions can produce constant velocity vestibular nystagmus.[16]

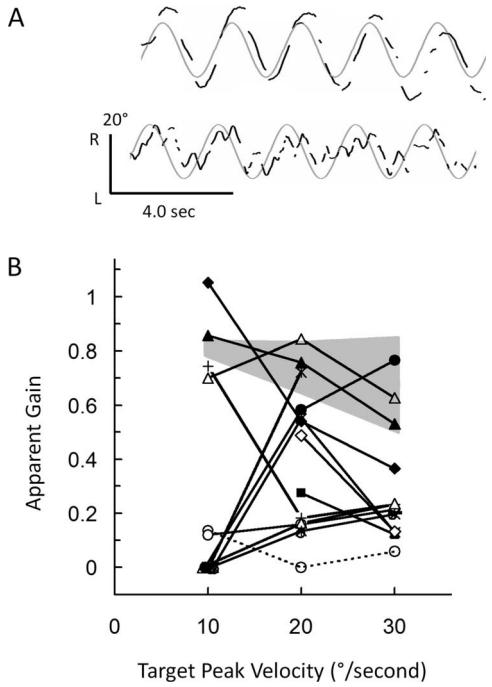

FIGURE 4. (A) Horizontal apparent pursuit in two subjects with Down syndrome (*black lines* after removing saccades) to a target drifting sinusoidally ±10° at velocities of 30°/s (*grey line*). The directional conventions are the same as in Figure 1. Horizontal apparent pursuit gains at velocities of 10°/s, 20°/s, or 30°/s. The average gain for each subject is represented by different *symbols* connected with *lines*. The *shaded area* is the mean ±1 SD of controls.

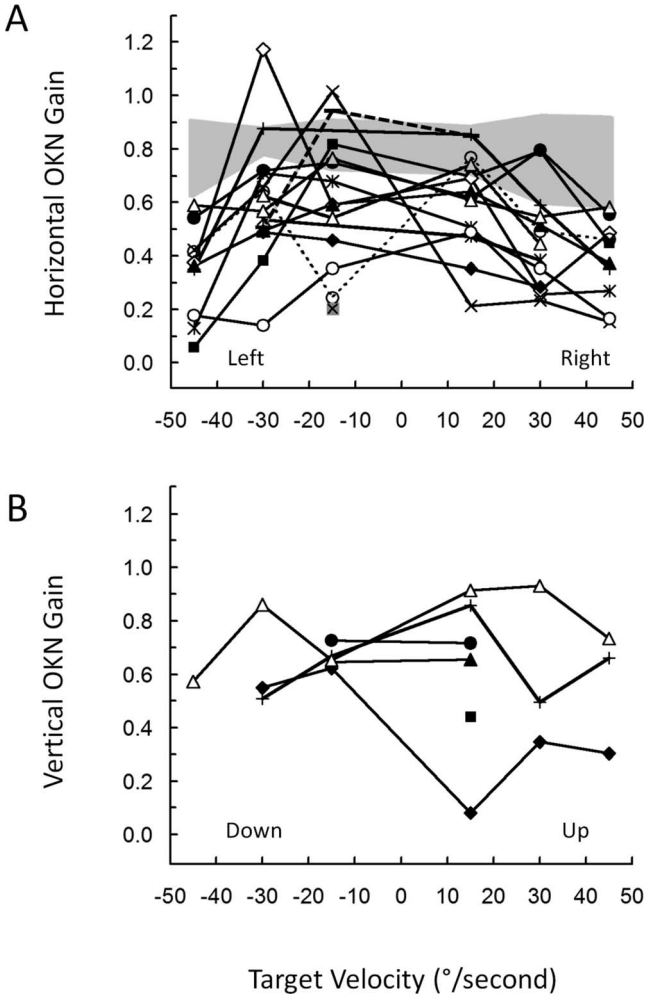

FIGURE 5. (A) Horizontal optokinetic nystagmus gains to a target drifting at velocities of 15°/s, 30°/s, or 45°/s. Positive and negative values on the abscissa represent rightward and leftward motion, respectively. The shaded area is the mean ±1 SD of controls. (B) Vertical optokinetic nystagmus gains to a target drifting at velocities of 15°/s, 30°/s, or 45°/s. Positive and negative values on the *abscissa* represent upward and downward motion, respectively. The average gain for each subject is represented by different *symbols* connected with *lines*. Control data are not available for vertical optokinetic nystagmus.

Conjugate, horizontal, jerk nystagmus with exponentially increasing or decreasing slow phase was the most common nystagmus subtype, observed in 12 of 18 DS subjects. This waveform can be decomposed into a pendular oscillation upon which a saccade is superimposed. Depending on the timing of the saccade relative to the pendular oscillation, the slow phase can be increasing or decreasing exponentially. Chen et al.[23] showed that positive feedback signals in the direction of the slow phase can amplify preexisting small amplitude, pendular oscillations thereby generating nystagmus. Potential origins for the pendular oscillation include premotor neurons in the pursuit, gaze integratorm or optokinetic pathways, or the upstream structures in the cerebellum which modulate the activity of these structures.[24,25]

A subset of DS subjects had pendular nystagmus that was either binocular or monocular. A plausible mechanism for pendular nystagmus could be dysregulation of cerebellar inputs to omnipause and burst neurons in the brainstem. Suppression of omnipause activity during sleep produces slow rolling pendular eye movements. Monocular pendular eye movements could be associated with activation of monocular vestibular pathways known to contribute to vergence,[26–28] or activation of the ipsilateral connection between the lateral vestibular nucleus and the oculomotor nucleus which courses through the ascending tract of Dieiter.[26]

Intermittent presence of square wave jerks (SWJ) in DS subjects is consistent with an underlying abnormality of the cerebellum. Square wave jerks are characterized by back-to-back saccades of 0.5° to 5.0° in opposite directions at a normal intersaccadic interval (approximately 200 ms). The frequent occurrence of SWJ and other saccadic intrusions have been reported in a variety of cerebellar pathologies.[29–31]

In summary, the heterogeneous gaze holding instabilities seen in DS subjects are consistent with a brainstem or cerebellar etiology. The specific mechanism cannot be established on the basis of the GHI alone. If oculomotor or vestibular structures in the cerebellum or vestibular nuclei are involved, then other conjugate eye movements controlled by these structures also would show significant abnormalities in DS subjects with GHI. To evaluate this, we studied three types of conjugate eye movement known to require processing in the cerebellum. We observed that these behaviors were disrupted in parallel with the GHI that we observed.

Apparent pursuit gains were variably reduced across DS subjects. Immaturities of motion processing are unlikely to account for the low SP gains given that 1- to 5-month-old infants show sensitivities to temporal flicker, direction of

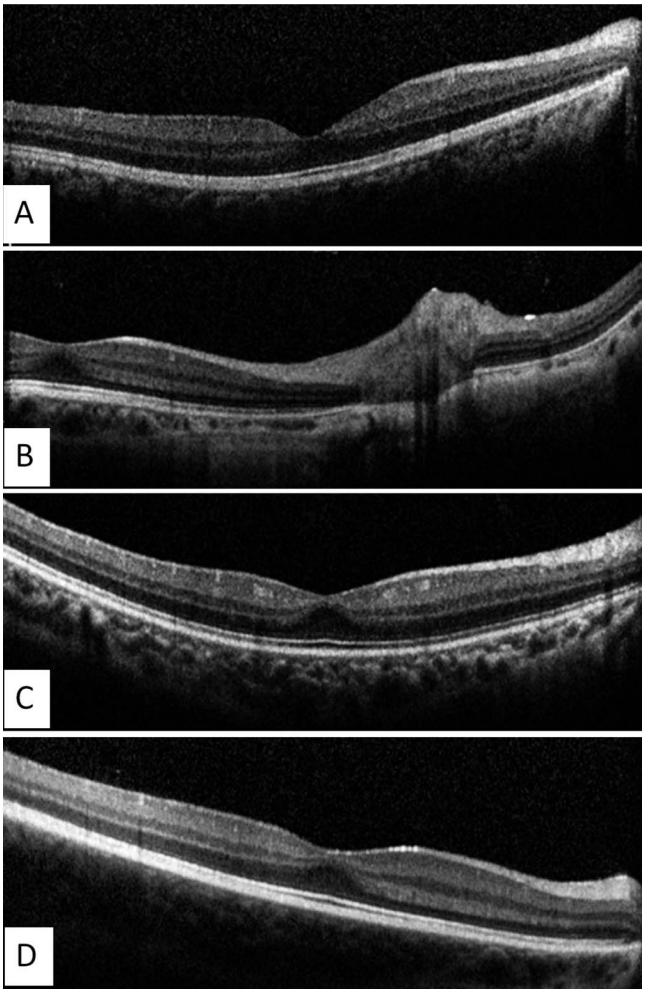

FIGURE 6. Optical coherence tomography (OCT) line scan of the right fovea in four subjects with Down syndrome. (**A**) subject #17 shows a normal fovea. (**B–D**), three subjects showing a thick central foveal thickness with continuation of retinal layering overlying the fovea.

motion, and motion coherence.[32–36] and Virji-Babul et al.[37] reported minimal motion discrimination deficits. Phillips et al[38] demonstrated that infants between 1 and 4 months of age demonstrated normal tracking gains of 0.8 ± 0.2 at target velocities of 8°/s. We propose that dysregulation of circuits between the ventral paraflocculus (VPF), CFN, and downstream motor neurons underlie the low apparent pursuit gains. Attentional deficits associated with DS may contribute to the reduced SP gains as the frontal (FEF) and parietal areas (MT) of the brain are modulated by attention and motion.[39]

We found that subjects with DS generated appropriately directed saccades but the gains were variably reduced. The observation that the saccades of children with DS follow the main sequence indicates that the burst neurons and oculomotor neurons are functioning normally, and, therefore, implicates neurons upstream in the saccade pathway.[40,41] Errors in final eye position are presumably detected in the intermediate layer of the superior colliculus, which in turn projects to the beta nucleus of the medial accessory olive.[42,43] Error signals then are transmitted by way of climbing fibers inputs to the Purkinje cells within the OMV where signals that determine saccade amplitude are adjusted until the position error is minimized.[44–47] We propose that a functional defect in this cerebellar feedback loop could underlie the saccadic abnormalities observed in DS children.

Gains for hOKN under binocular viewing were uniformly low. Although immature in normal infants, binocular OKN reaches gains near 1.0 for stimulus velocities up to 34°/s by 6 months of age.[48,49] Given that the mean age of our subjects was 4.8 years the subnormal gains at higher velocities are not attributable to age-related immaturities. Costa et al.[50] reported similar reductions of hOKN gains in 32 DS subjects. In addition, we document that the reduction in hOKN gains parallels the reduction in SP gains. Optokinetic nystagmus is a reflexive conjugate eye movement that stabilizes gaze in response to full field retinal slip induced by relative motion of the visual world. The parallel response of SP and hOKN to motion stimuli is consistent with the notion that horizontal OKN and SP share neural pathways in the cerebellum and brainstem.[51,52]

The GHI and abnormalities of conjugate eye movements in DS can be indirectly linked to overexpression of 33 genes in a minimal critical region of chromosome 21 that encompasses the Down Syndrome Cell Adherence Molecule (DSCAM). The DSCAM has an important regulatory role in the migration, differentiation, and axonal guidance of neurons throughout the CNS including the cerebellum.[53,54] The Ts65Dn mouse model is associated with reduced number of dendritic spines and neurite outgrowth responsible for information processing throughout the CNS.[55] Specifically DSCAM has been shown to eliminate inappropriately placed neurons through cell death and to restrict connections of exploring dendrites.[56] Abnormal expression of DSCAM across multiple brain regions, may account for the dysregulated neural connectivity between the Purkinje cells, deep cerebellar nuclei and downstream oculomotor circuits which underlie GHI and abnormalities of conjugate eye movements observed in DS.

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