Cerebellar skew deviation and the torsional vestibuloocular reflex

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Abstract—*Background:* Skew deviation is typically caused by brainstem damage, and has not been identified with focal cerebellar lesions. This vertical strabismus has been attributed to asymmetric disruption of vestibuloocular reflex (VOR) projections from otolithic receptors of the utricle to ocular motoneurons, but asymmetry of the utriculo-ocular counter-roll reflex has not been detected. *Methods:* Lesions localized to the cerebellum were identified by MRI in five patients with vertical strabismus. Their skew deviation was measured by prism cover tests in all patients and by search coils in three patients. The angular VOR was tested in patients and 10 controls during sinusoidal ± 10 degree torsional, vertical, and horizontal head-on-body rotations at 0.5, 1, and 2 Hz. Static torsional VOR gain was measured by the change in torsional eye position divided by change in head position during maintained head tilt. *Results:* Static torsional VOR gains were asymmetric in each patient. Three patterns of asymmetry were identified: 1) decreased static gain in one eye in both directions; 2) decreased gains in both eyes in one direction; and 3) asymmetric gain in one direction in one eye alone. Dynamic torsional VOR gains were symmetrically reduced in both directions in both eyes in all patients. *Conclusions:* Focal cerebellar lesions can cause skew deviation. The static torsional vestibuloocular reflex (VOR) is linked to cerebellar control of vertical vergence. Asymmetry between the eyes or in direction of the static torsional VOR provides evidence that monocular or binocular imbalance of the utriculo-ocular reflex leads to cerebellar skew deviation.

NEUROLOGY 2005;65:412–419

Skew deviation is a vertical strabismus caused by supranuclear lesions. It has been attributed to asymmetric disruption of vestibular projections from otolithic receptors of the utricle to the oculomotor and trochlear nuclei,[1,2] but asymmetry of the utriculo-ocular reflex has not actually been quantified or detected. Skew deviation is typically caused by damage to the brainstem tegmentum.[1,3-6] Few reports[1,3,4,7,8] have attributed skew deviation to cerebellar damage after surgery[3] or cerebellar diseases based on clinical findings.[1,4] However, imaging or neuropathologic evidence is lacking.

The static torsional VOR is evoked from the utricles, whereas the dynamic angular VOR during head roll is evoked from the semicircular canals.[9-12] Here we present a quantitative study of dynamic angular and static vestibuloocular reflex (VOR) changes in patients with skew deviation caused by discrete cerebellar lesions, as documented by MRI. VOR changes during static head roll indicate roles of the cerebellum in static torsional VOR and the pathogenesis of skew deviation.

Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the August 9 issue to find the title link for this article.

Methods. Focal cerebellar lesions were identified in five of our patients with skew deviation. Patient 1 is a 60-year-old man who presented with vertical diplopia for 6 months. The diplopia was intermittent and present only in certain gaze. He denied ptosis, bulbar or limb weakness. On examination, vision was 20/25 in the right eye (OD) and 20/20 in the left eye (OS). Pupils, visual field, color vision, and fundus examinations were normal. There was no ptosis. Ductions of each eye were full in all directions. Prism cover test revealed a comitant right hypertropia. Neurologic and cerebellar examinations were normal. Investigations for thyroid eye disease and myasthenia gravis were negative. MR imaging revealed a 1.7 cm mass in the anterior aspect of the left cerebellar hemisphere with mixed signal intensity on T1- and T2-weighted images, surrounded by a dark rim on T2, consistent with a cavernous angioma (figure 1A). His condition remained the same and he continued to use the prescribed prism glasses at last visit, 4 years after initial presentation.

Patient 2 is a 60-year-old woman who had left cerebellar hemorrhage from an arteriovenous malformation with subarachnoid bleeding. She underwent a resection of multiple aneurysms in the left posterior inferior cerebellar artery. She presented to us 6 months postoperatively, complaining of diplopia, intermittent dizziness, and imbalance. Her visual acuity, pupils, visual field, color vision, and fundus examinations were normal. Duction was full in all directions. Prism cover test revealed an incomitant left hypertropia. Frequent square-wave jerks were present. She exhibited an upbeat nystagmus and prominent gaze-evoked nystagmus in all directions of gaze. Saccades were hypermetric. Dysdiadochokinesis and dysmetria were observed in her left upper extremity. She could not walk unaided. MR (T2-weighted) imaging revealed increased signal intensity, consistent with hemorrhagic infarct in the vermis (figure 1B).

Patient 3 is a 32-year-old woman who was referred for assessment of nystagmus. She had a cystic cerebellar pilocytic astrocy-

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Supported by the New Investigator Award (MSH 55058) (A.W.) and grants MT 5404, ME 5509 (J.A.S.), MOP 57853 (A.W. and J.A.S.), and MOP 67104 (A.W.) from the Canadian Institutes of Health Research (CIHR), and the University Health Network Ophthalmology (A.W.) and Neurology (J.A.S.) Practice Plans.

Disclosure: The authors report no conflicts of interest.

Received November 11, 2004. Accepted in final form April 12, 2005.

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toma, which was first resected at age 4. Since then, she underwent two shunting procedures for obstructive hydrocephalus. At age 18, she had a re-resection of the astrocytoma and a revision of the ventriculoperitoneal shunt. On examination, her visual acuity, pupils, visual field, color vision, and fundi were normal. Ductions were full in all directions. Prism cover test revealed a comitant left hypertropia. Smooth pursuit was saccadic. Saccades exhibited overshoot dysmetria. There was a right beating nystagmus on right gaze. Her left limbs were ataxic. Her tandem gait was unsteady. MRI revealed a 4-cm residual cystic astrocytoma and surrounding area of encephalomalacia in the vermis and adjacent left cerebellar hemisphere. The brainstem was normal (figure 1C).

Patient 4 is a 73-year-old man who presented with intermittent vertical diplopia for 3 months. On examination, visual acuity was 20/40 OD and 20/30 OS. Pupils, visual field, color vision, and fundus examinations were normal. Ductions were full in all directions. Prism cover test revealed a comitant right hypertropia. He had a transient torsional nystagmus that beat clockwise from the patient's reference (that is, upper pole of the eye beating toward his right shoulder). The remainder of the neurologic examination was normal. Investigations for thyroid eye disease and myasthenia gravis were negative. MRI revealed a small infarct in the superior aspect of the right cerebellar hemisphere (figure E-1A on the *Neurology* Web site at www.neurology.org). His condition remained stable and he continued to use his prism glasses at his last visit, 3 years after initial presentation.

Patient 5 is a 34-year-old woman who had intermittent vertical diplopia, worse on right lateral gaze, for 1 year. She had no other symptoms. Her visual acuity, pupils, visual field, color vision, and fundi were normal. Ductions were full in all directions. Prism cover test revealed an incomitant left hypertropia, which was present only on right gaze. The results of the neurologic examination were otherwise normal. Investigations for thyroid eye disease and myasthenia gravis were negative. The diplopia resolved spontaneously after 6 months.

Twenty months after her initial presentation, she presented with a recurrence of vertical diplopia, episodic headaches, vomiting, and positional vertigo. Prism cover test revealed an incomitant left hypertropia, which was present on right gaze. CT scan revealed a large lesion within the right cerebellar hemisphere. It extended downward to the vermis at the level of the foramen magnum, and upward toward the tentorium. She underwent a posterior fossa exploration with resection of the tumor (figure E-1B). Pathologic examination revealed a hemangioblastoma. Her skew deviation resolved after tumor removal, and she remained symptom free with no tumor recurrence 18 years after the resection.

Methods. Three patients agreed to participate in eye movement recordings.

Experimental protocol. With one eye occluded, subjects viewed a red laser spot of 0.25 deg in diameter, rear-projected onto a uniformly gray vertical flat screen 1 m away from the nasion. Subjects made active sinusoidal ± 10 deg head on body rotations about an earth-vertical axis to elicit the horizontal VOR, and about an earth-horizontal axis to elicit the vertical VOR, at approximately 0.5 and 2 Hz. The torsional VOR was elicited by head rotation in roll about the line of sight at approximately 0.5, 1, and 2 Hz. Head movements were paced by a periodic tone. The maintenance of desired amplitude and frequency of head movements was encouraged by placement of the examiner's hands on each parietal area of the subject's skull. The procedure was performed in light to elicit visually enhanced VOR (VVOR), and repeated with the other eye fixating and the fellow eye occluded. The VOR was then recorded in complete darkness while subjects were instructed to fixate on an imaginary earth-fixed target.

To measure the static torsional VOR, patients fixated on the center target with one eye occluded as we measured their ocular responses to static, passive head rolls of about 30 deg toward each shoulder, as measured with a search coil. The procedure was then repeated with the other eye fixating and the fellow eye occluded, and also in total darkness.

Recordings of eye movement and calibration. Positions of each eye were simultaneously measured by a three-dimensional magnetic search coil technique. The field system consists of a 6 ft (183 cm) diameter coil field arranged in a cube (CNC Engineering, Seattle, WA), with two orthogonal magnetic fields. In each eye, the patient wore a dual-lead scleral coil annulus designed to detect horizontal, vertical, and torsional gaze positions (Skalar Instrumentation, Delft, Netherlands). Head position was recorded by another coil taped to the subject's forehead. Each subject's head was centered in the field coils. Horizontal, vertical, and torsional movements were calibrated by attaching the scleral coil to a rotating protractor before each experiment. The coil was first calibrated for ± 30 deg torsionally in the straight ahead position. The protractor was then rotated 30 deg right, and the signal was measured again as the mounted coil was rotated ± 30 deg torsionally. The same procedure was performed with the protractor rotated 30 deg up. Phase detectors employing amplitude modulation as described by Robinson[13] provided signals of torsional gaze position within the linear range. There was minimal crosstalk; horizontal and vertical movements produced deflections in the torsional channel of less than 4% of the amplitude of the horizontal and vertical movement. The difference in torsional deflections between straight ahead and 30 deg right (or up) positions was less than 4%. Torsional precision was about ± 0.2 deg.

To measure the offset of coil signal, during the gimbal calibration, the coil was rotated through 360 deg to measure its maximum and minimum readings. If there were no offset, these two readings should be equal and opposite. If they were not, the mean of the two readings was the offset, which was then subtracted from all coil recordings.

After insertion of the scleral coils, horizontal and vertical eye movements were calibrated by saccades from the straight ahead reference position to steps of a laser target. Consistency of calibrated positions before and after coils insertion provided evidence that the gimbal calibrations were valid. As torsional eye position depended on the same magnetic field as vertical eye position, the accuracy of vertical calibration before and after coils insertion provided further evidence that the torsional calibration was also accurate. Any coil slippage was assessed by requiring subjects to repeatedly refixate at the straight ahead reference position after each eye movement. Consistency of calibrated torsional coil signals after each eye movement provided evidence that the coil did not slip on the eye. Eye position data were filtered with a bandwidth of 0 to 90 Hz and roll-off frequency of -3 dB, and digitized at 200 Hz. They were recorded on disc for off-line analysis. Analog data were also displayed in real time by a rectilinear thermal array recorder (Model TA 2000, Gould Inc., OH).

Data analysis. In one dimension, the input (head velocity) and output (eye velocity) of the VOR are regarded as scalar quantities (i.e., real number), and the reflex is characterized by its gain, which is the ratio of eye velocity to head velocity. In most natural head rotation, however, the input and output of the VOR are not scalars but three-component vectors (the angular velocity vectors of the head and eye), having not only magnitudes but also directions. Thus, a more complete characterization of the VOR requires a description, not only of the relative sizes of eye and head velocities, but also of their relative directions; that is, the axes about which the eye and the head rotate.

The VOR, however, can be treated as one dimensional if head rotation occurs around only one axis. For example, during pure horizontal head rotation (that is, around the earth-vertical axis), the vertical and torsional components of the three-component rotation vector become zero. In this situation, the velocity of rotation can be derived by differentiation of position data. In this study, whereas horizontal, vertical, and torsional head positions were measured simultaneously, gaze position data were measured in one dimension. That is, horizontal gaze positions were recorded during horizontal head motion, vertical gaze positions during vertical head motion, and torsional gaze positions during head roll. Pure head rotation around one axis was approximated by analyzing only data where the other two axes showed less than 1 deg variation from baseline.

Eye position was derived by subtracting head position from gaze position signals. Fast phases of vestibular nystagmus were identified by a computer program using velocity and acceleration criteria.[14] Results of fast-phase identification were edited on a video monitor, allowing the operator to verify cursor placement for fast-phase removal. Eye positions between 80 msec before and after the identified fast-phases were removed and the gaps were replaced with quadratic fits. Their average slopes were used to calculate the contribution of the ongoing slow phase during the fast phase. The offset due to the fast phase was then removed and

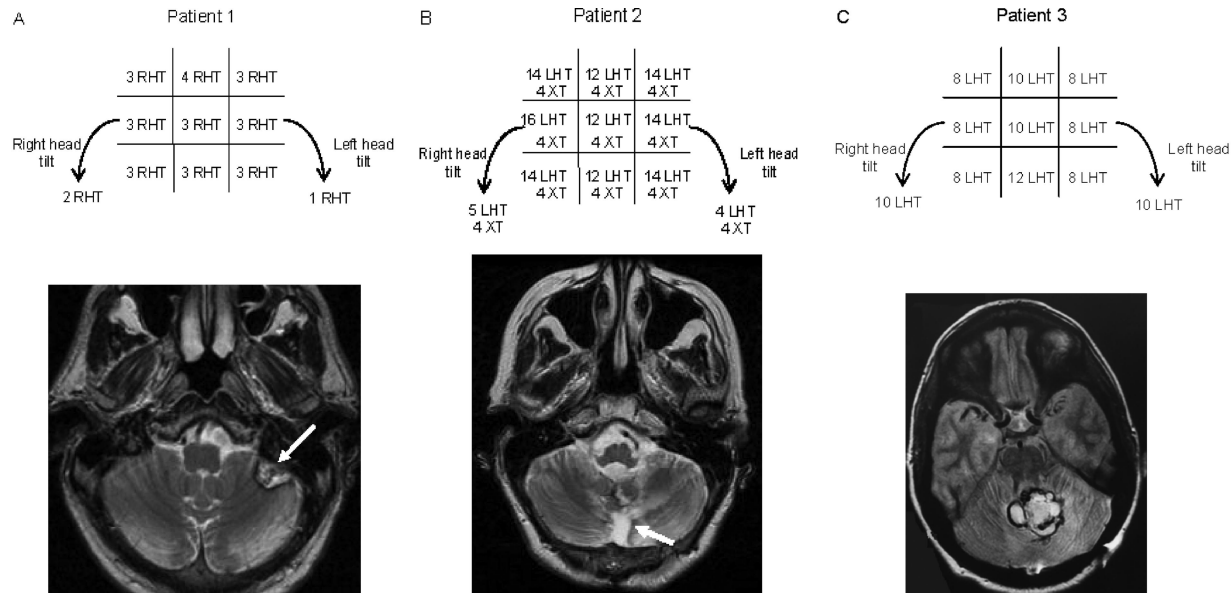

Figure 1. Ocular deviations and MRI of study patients. Vertical and horizontal deviations (in prism diopters) were measured by the prism and cover test in nine cardinal diagnostic positions of gaze and during static lateral head tilt (RHT = right hypertropia; LHT = left hypertropia; XT = exotropia). Patient 1. T2-weighted image showing a cavernous hemangioma in the left cerebellar hemisphere. Patient 2. T2-weighted image showing hemorrhagic infarct in the vermis. Patient 3. T1-weighted image with gadolinium enhancement showing a residual cystic astrocytoma and surrounding area of encephalomalacia in the vermis and adjacent left cerebellar hemisphere.

the ongoing slow phase was interpolated to yield a cumulative trace of eye position.

Using position data, each cycle of rotation was identified by marking adjacent peaks with opposite direction, and the frequency was computed. Using a least square sinusoidal fit,[15] eye and head positions were fitted with one cycle, and the phase and amplitude were computed. The ratio of the amplitude of the eye and the amplitude of the head was the gain, and the difference between the phase of the eye and the phase of the head was the phase shift.

To calculate the gain in each direction, eye and head position data from each half cycle was used and reflected to form a full cycle. Each cycle was then fitted using a least square sinusoidal fit,[15] and the gain was computed for each direction. In addition, we plotted head velocity against eye velocity, and performed a linear regression for each direction. The slopes of the fitted lines were the gains, and the results were comparable to those computed by the least square sinusoidal fit technique.

Subjects wore spectacles glasses, if habitually worn, during VOR testing. To account for the prismatic effect or rotational magnification induced by spectacle adaptation,[16,17] horizontal and vertical VOR gains were adjusted by using the formula

$$M_{pred} = 40 / (40 - D) \qquad (1)$$

where D is the lens power in diopters and M_{pred} is the predicted magnification.[16,17] The lens power, D, was measured by us. For example, a hyperope who habitually wears a +10 D spherical lenses has an M_{pred} = 40/40-10 = 1.3. This means that while wearing +10 D, a VOR gain of 1.3, instead of 1.0, is required to prevent the visual scene from moving on the retina during head rotations.

For the measurement of static torsional VOR, head and gaze position signals were sampled for 6 seconds in each of 20 trials of 30 deg lateral tilt. The position of the eye in the head was derived from the difference between head and gaze position signals. Head and eye positions were computed off-line over each 6-second period after the eye had come to a torsional resting position (defined as having angular velocity #1 deg/second). Responses containing blinks or rapid drifts were not analyzed. Change of torsional eye position was plotted as a function of static change of head position after roll, and a linear regression was performed. Static torsional VOR gain, defined as change in torsional eye position divided by change in head position in static roll, was calculated from the slope of the regression line.

Ten normal subjects served as controls (5 women; mean age 49 ± 12 years; median age 55 years; age range 19 to 69 years). Statistical analyses of VOR gains and phase were performed using Z tests. Values were defined as significant when $p < 0.05$.

The research protocol was approved by the University Health-Network Ethics Committee and followed the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients and control subjects.

Results. *Dynamic torsional VOR gain and phase.* Representative head and eye movement tracings during torsional head rotation at about 0.5 Hz in darkness are shown in figure 2. Dynamic torsional VOR and VVOR gains for normal controls and three patients are displayed as box plots in figure E-2 (available on the *Neurology* Web site at www.neurology.org). In each subject, there were no significant differences in gains between each eye (i.e., right vs left eye), between directions of head roll (i.e., clockwise vs counterclockwise), and between viewing with either eye (i.e., right vs left eye viewing). Gain values were, therefore, reported as pooled data. In all three subjects, gains were reduced in dark with no improvement in light. In Patient 1, torsional VOR gains in dark were reduced for head roll at 0.5 Hz ($p < 0.05$), and at 1 Hz ($p < 0.08$). Torsional VVOR gains in light were reduced at 1 Hz and 2 Hz ($p < 0.05$), and at 0.5 Hz ($p < 0.08$). In Patient 2, torsional gains were reduced ($p < 0.05$) at all frequencies tested, in dark and in light. In Patient 3, torsional VOR and VVOR gains were reduced at $p < 0.05$ level for all frequencies tested, except for gain in dark at 1 Hz, which was reduced at $p < 0.08$ level. In light and in dark, the mean phase differences between the eye and head positions approximated 180°, designated as zero phase shift.

Static torsional VOR. Gain values during static torsional VOR are shown in figure 3. Comparisons are made

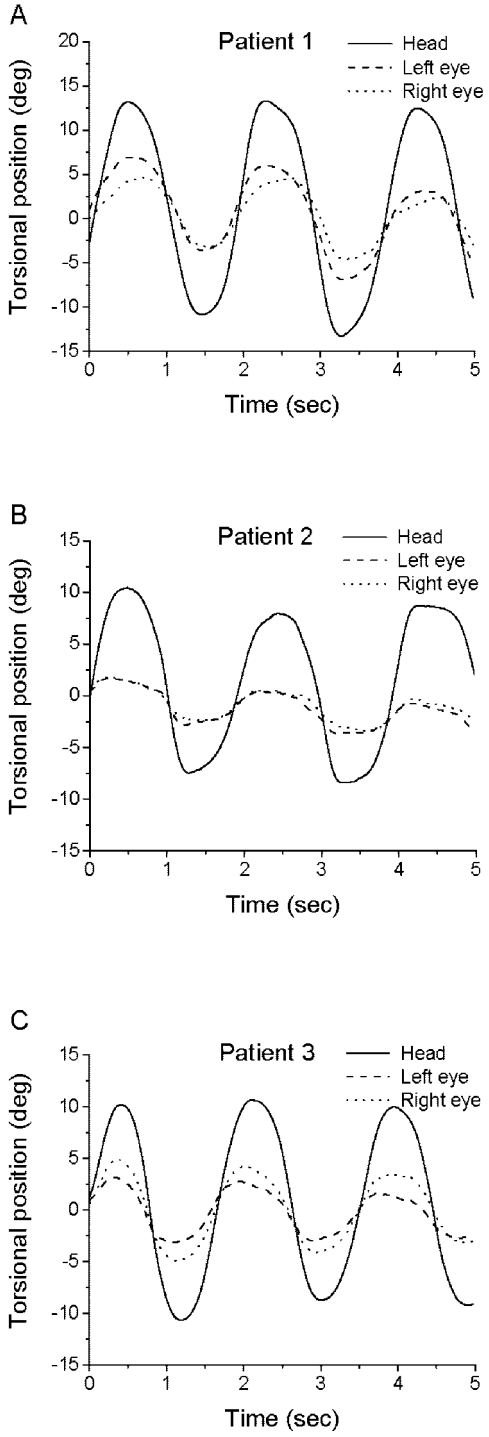

Figure 2. Dynamic torsional vestibuloocular reflex, with saccades (quick phases) removed, of patients 1, 2, and 3 during torsional head rotation about the line of sight at about 0.5 Hz in darkness.

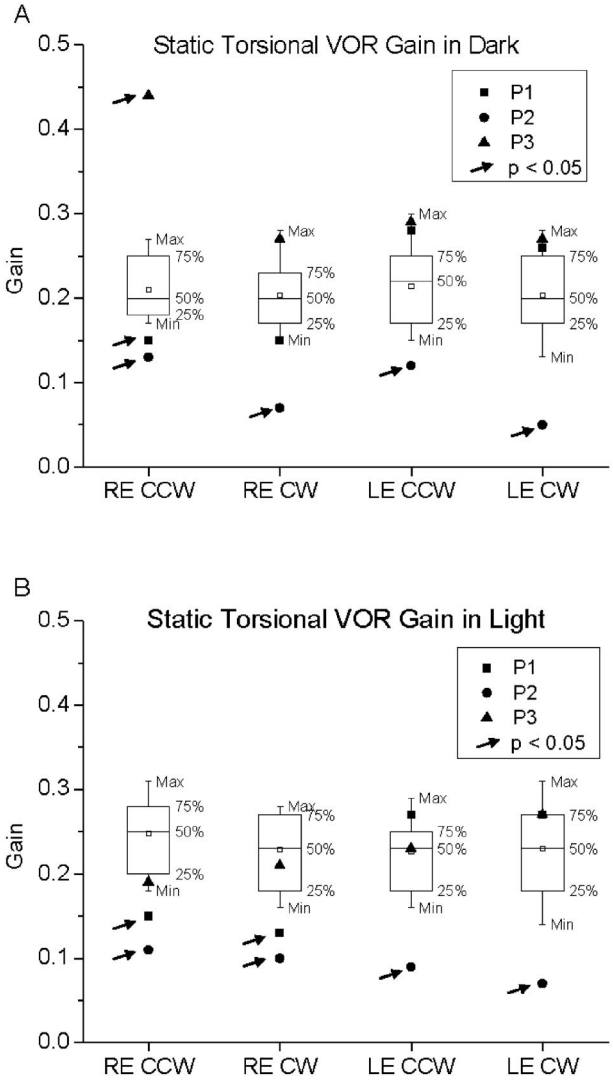

Figure 3. Box plots showing static torsional vestibuloocular gains in dark and in light in each patient during static head roll to either side. The data are displayed to show the maximum, minimum, mean, median, 25th, and 75th percentiles. RE = right eye; LE = left eye; CW = clockwise eye movement; CCW = counterclockwise eye movement (from subjects' point of view).

between each eye (i.e., right vs left eye), and between the direction of eye movement (i.e., clockwise [CW] vs counterclockwise [CCW], with respect to the subject). In normal subjects, there were no significant differences between each eye, and between directions of eye movement. In Patient 1, who had a right hypertropia as a result of a left-sided cerebellar lesion, gains were reduced in the right eye, but normal in the left eye. In the right eye, gain in CCW direction was reduced when tested in dark, whereas in light, gains in both CCW and CW direction were reduced ($p < 0.05$). In contrast, in Patient 2, who had a left hypertropia as a result of a lesion in the vermis, gains were reduced in both eyes ($p < 0.05$). The reduction in gains in CW direction was more than that in CCW direction in both eyes in dark (i.e., conjugate asymmetric reduction). In Patient 3, who had a left hypertropia and predominantly left-sided involvement of the cerebellum, gains were increased in the right eye during CCW movement only in dark ($p < 0.05$).

Horizontal VOR gain and phase. Figure E-3 shows the gain values for horizontal VOR and VVOR. In each subject, there were no significant differences in gains between each eye (i.e., right vs left eye), between directions of head rotation (i.e., rightward vs leftward), and between viewing with either eye (i.e., right vs left eye viewing). Gain values were, therefore, reported as pooled data. Gains were decreased in one patient (Patient 2), but they were variable

in two patients (Patients 1 and 3). Patient 1 had reduced gains during horizontal head rotation at 0.5 Hz in dark only ($p < 0.05$). Patient 2 had reduced gains for both frequencies, in dark and in light ($p < 0.05$). Patient 3 had a normal gain at 0.5 Hz in dark, but an increased gain at 2 Hz in dark ($p < 0.05$). Gains were normal when tested in light in Patient 3. In all three patients, neither eye showed any significant phase shift from zero in light or in dark.

Vertical VOR gain and phase. The distributions of vertical VOR and VVOR gains are shown in figure E-4. In each subject, there were no significant differences in gains between each eye (i.e., right vs left eye), between directions of head rotation (i.e., upward vs downward), and between viewing with either eye (i.e., right vs left eye viewing). Gain values were, therefore, reported as pooled data. Gains were normal in one patient (Patient 1), decreased in a second patient (Patient 2), and variable in a third patient (Patient 3). Patient 1 had normal gains, whereas Patient 2 had reduced gains for both frequencies tested, in dark and in light ($p < 0.05$). Patient 3 had a normal gain at 0.5 Hz in dark, but an increased gain at 2 Hz in dark ($p < 0.05$). Gains were normal when tested in light in Patient 3. There was no significant phase shift from zero, in light or in dark, in any patient.

Discussion. Although over a quarter century has passed since imbalance of the utriculo-ocular reflex was first proposed to be responsible for skew deviation[1] and the ocular tilt reaction,[2] no study had identified imbalance of this static ocular counter-roll reflex. In normal humans, static lateral head tilt causes sustained conjugate low amplitude counter-roll of the eyes and a small vertical misalignment.[18-20] Clockwise head rotation (from the subject's reference, i.e., toward the right shoulder) is accompanied by counter-rolling, combined with slight upward movement of the right eye and downward movement of the left eye in the orbits.[20] This reflexive vertical divergence of the optical axes is partly compensatory to downward translation of the right eye and upward translation of the left eye relative to the earth-horizontal plane due to the head roll.[20] The reflexive vertical divergence is also partly compensatory to the vertical divergence that is induced by convergence of the eyes during head roll.[21,22] The ocular tilt reaction is a pathologic synkinetic triad of skew deviation, ocular torsion, and head tilt. It is attributed to brainstem or acute peripheral vestibular lesions that disrupt otolith inputs.[2,23,24] Sustained off-vertical axis rotation of the body at a constant speed induces continuous translational head acceleration against gravity, such that the dynamic otolithic-ocular reflex persists, but the angular VOR, which is generated by the semicircular canals, fades away. Patients with skew deviation from brainstem lesions have asymmetric responses to off-vertical axis rotation, indicating that asymmetric dynamic otolith signal of the translational VOR is associated with skew deviation.[25] However, it remains unclear whether disruption of the dynamic otolithic-ocular pathway in the brainstem simply reflects an associated finding, but not the cause of skew. Since the static torsional VOR is elicited by gravitational otolith receptors in the utricles, the asymmetric static torsional VOR gains recorded in our patients provide direct evidence that skew deviation is caused by a static imbalance of otolith input.

Skew deviation is typically caused by damage to the brainstem tegmentum.[1,3-6] In patients with skew deviation from unilateral brainstem infarction, rostral pontomesencephalic lesions cause ipsilesional hypertropia, and caudal pontomedullary lesions cause contralesional hypertropia.[6] The hypertropic eye is incyclotorted, and the hypotropic eye excyclotorted.[6]

Damage to the cerebellum has been implicated as a cause of skew deviation. Magendie[7] and later Hertwig[8] produced skew deviation in cats by sectioning the middle cerebellar peduncle, but adjacent tegmental structures may have been damaged. Others[1,3,4] have attributed skew deviation to cerebellar damage from surgery[3] or cerebellar diseases based on clinical findings.[1,4] In those cases,[1,4,26] however, brainstem involvement had not been excluded by either imaging or pathologic correlation. One reported patient had abnormal ocular torsion and tilt of subjective visual horizontal from a cerebellar infarct, but not skew deviation.[27] Patients with cerebellar degeneration or dysgenesis may exhibit vertical phoria or small tropia but they do not typically have diplopia,[26] and brainstem circuits are also involved in spinocerebellar degenerations or developmental malformations. Alternating skew deviation, in which the hypertropic eye occurs on the side of horizontal gaze direction, alternating with the direction of gaze, has been associated with lesions of the cervicomedullary junction or cerebellar pathways,[4,26,28] but skew deviation with focal lesions of the cerebellum alone had not been previously documented.

We provide evidence of skew deviation caused by focal cerebellar lesions, with no imaging or clinical signs of brainstem involvement. We found no correlation between the laterality of the hypertropic eye and the side of unilateral cerebellar lesions. The sites of cerebellar lesions (figure 1 and figure E-1) varied, suggesting that the lesions had effects on otolith-ocular pathway remote from the sites of focal damage.

There are several potential anatomic and physiologic substrates for cerebellar skew deviation. The vestibulocerebellum receives otolith projections both directly from the labyrinth and indirectly via the vestibular nuclei.[29,30] Primary utricular afferents have strong direct projections to the vestibular nuclei, the cerebellar nodulus, and ventral uvula and weaker projections to the anterior vermis, the fastigial nuclei, and the flocculus and ventral paraflocculus.[31] All areas of the cerebellar cortex that receive primary otolith afferent inputs are heavily interconnected with both the vestibular and fastigial nuclei. Purkinje cells in the vestibulocerebellum monosynaptically inhibit neurons in the vestibular nucleus, the site of second order otolithic-ocular neurons.[32] Recent evidence suggests that due to the inherent ambiguity in distinguishing linear (translation) vs gravitational acceleration (head tilt), the cerebellum

plays a critical role in sensorimotor signal transformation in the otolith-ocular pathway by computing an internal estimate of gravity.[33,34] Lesions of the nodulus alone, or of the nodulus and uvula together, impair otolith-ocular reflexes.[35,36] In monkeys, lesions of the nodulus or uvula cause an inability to reorient vertical semicircular canal signals on the basis of gravitoinertial signals from otolithic receptors,[35] and a loss of steady-state nystagmus induced by the otolithic reflex in response to rotation off the earth-vertical axis.[36]

Impaired adaptation of vertical phoria may contribute to vertical misalignment. Phoria adaptation to vertical binocular disparity is frequently impaired in patients with cerebellar dysfunction.[37] Focal cerebellar lesions might give rise to skew deviation by impairing adaptation to vertical phoria, or by interfering with repair of any imbalance of otolith inputs, or by both mechanisms.

In monkeys, cerebellectomy, apparently without involvement of brainstem utriculo-ocular pathways, was reported to cause alternating skew deviation.[38] Our finding that patients with unilateral cerebellar lesions (Patients 1, 4, and 5) or asymmetric cerebellar lesions (Patient 3) had non-alternating skew deviation is consistent with an hypothesis that alternating skew might appear with bilateral symmetric cerebellar lesions, and non-alternating skew deviation might occur with unilateral cerebellar lesions.[39,40]

The dynamic torsional VOR is elicited primarily by the vertical semicircular canals with some contribution from the otolith.[9-12] Ablation of the cerebellar nodulus and ventral uvula reduces dynamic torsional VOR gains and causes phase advances at very low frequencies in monkeys.[41] Visual input, which normally improves the performance of the torsional VOR, is ineffective in increasing the gains in lesioned animals.[41] Dynamic torsional VOR gains were also found to be abnormal in patients with skew deviation caused by brainstem lesions.[19] Responses were conjugate but asymmetric in three reported patients,[19] with abnormal dynamic gains (increased in one, and decreased in two others) during head roll away from the side of the brainstem lesion. In our three patients with cerebellar skew deviation, the torsional VOR was tested using higher frequency than those used in a previous animal study.[41] We found that dynamic torsional VOR gains in patients with cerebellar skew were conjugate, symmetric, and reduced. In addition, there was no improvement in gains during dynamic head roll in light. No phase shift occurred at the frequencies tested. The decrease in dynamic torsional VOR gains in our patients provides evidence that the cerebellum participates in control of the torsional vestibuloocular subsystem.

The static torsional VOR is elicited by gravitational otolith receptors in the utricles. Among four patients with skew deviation caused by brainstem lesions, static torsional VOR gains were conjugate and symmetric in response to rightward and leftward head roll.[19] A model for static otolith-ocular function predicted differential effects of unilateral peripheral and central vestibular lesions on static torsional VOR gain.[42] Unilateral peripheral vestibular lesion or a complete lesion of the vestibular nuclei was predicted to produce asymmetric but conjugate gains, whereas a unilateral partial (medial) vestibular nuclei lesion or a unilateral MLF lesion would produce dysconjugate and asymmetric gains.[42] Direct stimulation of one utricular nerve in cats produces predominantly incyclotorsion with a small elevation and adduction of the ipsilateral eye, and predominantly excyclotorsion with a small depression and abduction of the contralateral eye.[43]

Static torsional gains were asymmetric in our patients with cerebellar skew deviation. One patient (Patient 1) had dysconjugate but symmetric gains with decreased gains in the right eye only, another (Patient 2) had conjugate but asymmetric gains with decreased gains in both eyes, and a third one (Patient 3) had dysconjugate and asymmetric gains with increased gains in the right eye during CCW movement only. We assessed changes in static torsion using magnetic scleral search coils. Absolute torsional eye position can be estimated roughly by fundus photography,[44] but we relied on changes in torsion to more precisely assess the static torsional VOR. Static torsion that accompanies skew deviation[1,2,24] might affect measurement of torsional gain causing it to appear asymmetric. We did not measure static or dynamic torsional gain starting from different non-erect head positions in control subjects to simulate torsional offset of the eyes with the skew deviation. Static torsional gains are nonlinear for large ranges of head or eye torsion but linear for smaller head tilts (under 40 degrees).[22] However, any static torsional offset did not cause asymmetry of the dynamic torsional gain. Asymmetric static torsional VOR gains in our patients provide evidence that skew deviation is caused by binocular or monocular imbalance of the utriculo-ocular reflex.

In contrast to these effects on the torsional static VOR, the cerebellar lesions of our patients caused only a mild change in the horizontal and vertical angular VOR. Bilateral flocculectomy in monkeys produces no consistent effects on horizontal VOR gains and phase.[45] Ablation of the cerebellar nodulus and ventral uvula in monkeys results in increased time constants and small phase leads of the horizontal VOR at low frequencies, while the vertical VOR remains unaltered.[41] In our study, the responses to horizontal and vertical head rotations were variable. The varied effects of cerebellar lesions on horizontal and vertical angular VOR gains may reflect a regulatory role of the cerebellum, such that any underlying default properties of VOR circuits in the brainstem are exposed by cerebellar lesions.

With the head upright and stationary, visually guided eye movements, such as saccades and smooth pursuit, are confined to Listing's plane with torsion being constrained.[46-48] In contrast, the angular VOR exhibits three rotational degrees of freedom. Tor-

sional eye movements differ considerably from horizontal and vertical movements in their requirements for image stabilization. At frequencies that correspond to most natural head rotations (0.5 to 5 Hz), horizontal and vertical VOR gains are close to −1.0,[49-52] such that the entire retinal image is stabilized during the horizontal and vertical VOR. In contrast, torsional VOR gains are low.[53-57] Low torsional VOR gains may reflect a compromise strategy between optimal retinal image stabilization and the constraint on torsion in compliance with Listing's law.[58] As a result, during head roll, the retinal image is stabilized over a small portion of the retina, the fovea, to achieve the highest visual acuity.[58]

The differences in functional requirements between the horizontal-vertical and torsional systems are likely to be reflected in their brainstem and cerebellar organization. We found distinctly different effects of cerebellar lesion on the VOR during torsional, vertical, and horizontal rotations in our patients: a consistent reduction of dynamic (angular) torsional VOR gains, vs variable changes in horizontal and vertical angular VOR gains. These results support the notion that torsional signals are processed separately from horizontal and vertical signals due to distinct functional requirements for visual-vestibular interactions.

The sites of cerebellar damage in our patients implicate the vermis or the hemisphere in the pathogenesis of skew deviation. Investigation of the torsional VOR in more patients with skew deviation of either brainstem or cerebellar origin should clarify the mechanisms and prevalence of the static VOR asymmetries detected in our patients. The asymmetry of the static torsional VOR (mediated by the utricles) and the symmetry of the dynamic torsional VOR (mediated by the semi-circular canals) identified in these patients provide evidence that imbalance of the utriculo-ocular reflex, rather than imbalance of the canal-ocular reflex, is a mechanism of cerebellar skew deviation.

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