

Article abstract—We studied a patient with a cerebellar degeneration and hyperactive vestibulo-ocular reflex (VOR). He complained of oscillopsia and blurred vision with head movement. A twofold increase in VOR gain (peak eye velocity/peak head velocity) at high frequencies was associated with a VOR time constant of 6 seconds (low normal). Visual cancellation (“suppression”) of the VOR and smooth pursuit were also abnormal. We hypothesized that his high VOR gain was due to dysfunction of olivocerebellar projections. Physostigmine reduced his VOR gain, consistent with the hypothesis that these projections are cholinergic.

NEUROLOGY 1987;37:53-57

Hyperactive vestibulo-ocular reflex in cerebellar degeneration: Pathogenesis and treatment

Stephen E. Thurston, MD; R. John Leigh, MD; Larry A. Abel, PhD; and Louis F. Dell’Osso, PhD

The vestibulo-ocular reflex (VOR) serves to maintain clear vision by holding images steady on the retina during perturbations of the head. Normally, a head rotation in one direction produces an oppositely directed, compensatory rotation of the eyes in the orbit; thus, eye position in space (gaze) remains constant. The adequacy of the VOR is commonly measured as a ratio: peak eye velocity/peak head velocity (gain). Disease of the vestibular system may cause a *decrease* in VOR gain, resulting in excessive retinal image motion with consequent blurred vision and oscillopsia during head movements. We describe a patient with blurred vision and oscillopsia due to a marked *increase* in the gain of the VOR.

Case report. A 50-year-old man complained of a progressive, 6-year history of oscillopsia and poor vision during head movements. He also reported difficulty reading when lying on his side. For at least 17 years, he had experienced a slowly progressive gait disturbance. He noted particular difficulty walking in the dark and making quick turns. A coarctation of the aorta was repaired at 6 years of age. For the past 15 years, he drank alcohol heavily. He took no medications and did not wear glasses. Family history was negative for gait or visual disturbance.

On examination, uncorrected visual acuity was 20/20-3 OD and 20/25-2 OS, correcting to 20/20 OU with -0.25 D of cylinder for distance and an add of $+1.50$ D of sphere for near. With small-amplitude head shaking at approximately 1 Hz, his visual acuity decreased to 20/200. Pupils were normal. He showed a moderate esophoria and a slight left hyperphoria. Versions were full. In primary position, gaze was steady with the head still. Gaze-evoked nystagmus was present on looking laterally 20° . With the head extended or tilted to the right or left, nystagmus developed, with quick phases beating away from gravity (ageotropic nystagmus). Saccades were hypermetric and pursuit was impaired. The most notable finding was a hyperactive VOR in both horizontal and vertical planes.

This was evident clinically by backup saccades in the same direction as head rotation and during ophthalmoscopic evaluation of the VOR.¹ Gait was wide-based and unsteady. Dysmetria was mild in the upper extremities but severe in the lower extremities. Muscle tone and reflexes were increased in the lower extremities, and extensor plantar responses were present bilaterally. Sensation was normal. Romberg’s sign was present. CT of the head demonstrated marked cerebellar atrophy, greatest medially, with only mild cerebral atrophy. Metrizamide CT myelography was normal up to the cranio-cervical junction. MRI confirmed the CT findings and did not demonstrate abnormalities in the pons or medulla (figure 1).

Methods. Eye and head movements were recorded using the magnetic search coil method. Eye movements were also recorded using infrared oculography and DC coupled electro-oculography (EOG) during chair rotations, as well as on videotape. Saccades were made in response to step displacements of a small target light. Smooth-pursuit targets (laser spot) moved at constant velocities of 11 and 23 deg/sec and sinusoidally at frequencies of 0.1, 0.25, 0.5, and 1.0 Hz with peak-to-peak amplitudes of 10 and 20° , covering a range of peak velocities from 6 to 63 deg/sec. Combined active eye-head tracking was also recorded (magnetic search coil) during sinusoidal target motion at the same frequencies and amplitudes as for smooth pursuit. Optokinetic responses were elicited with a full-field visual surround stepped to a constant velocity of 30 deg/sec; the duration of optokinetic after-nystagmus was measured after the testing room was suddenly switched to complete darkness. The horizontal VOR was measured during en bloc (passive) sinusoidal chair rotation at 0.01 Hz with peak velocities of 50 deg/sec and at 0.25, 0.5, and 1.0 Hz with peak-to-peak amplitudes of 10 and 20° (peak velocities of 15.7 to 126 deg/sec); in addition, 60-deg/sec

From the Ocular Motor Neurophysiology Laboratory and the Neurology Service of the Cleveland Veterans Administration Medical Center; the Department of Neurology, University Hospitals of Cleveland; and Case Western Reserve University, Cleveland, OH.

Supported in part by the Veterans Administration, the Evenor Armington Fund, and NASA contract 9-17439.

Received February 14, 1986. Accepted for publication April 24, 1986.

Address correspondence and reprint requests to Dr. Leigh, Department of Neurology, University Hospitals of Cleveland, Case Western Reserve University, 2074 Abington Road, Cleveland, OH 44106.

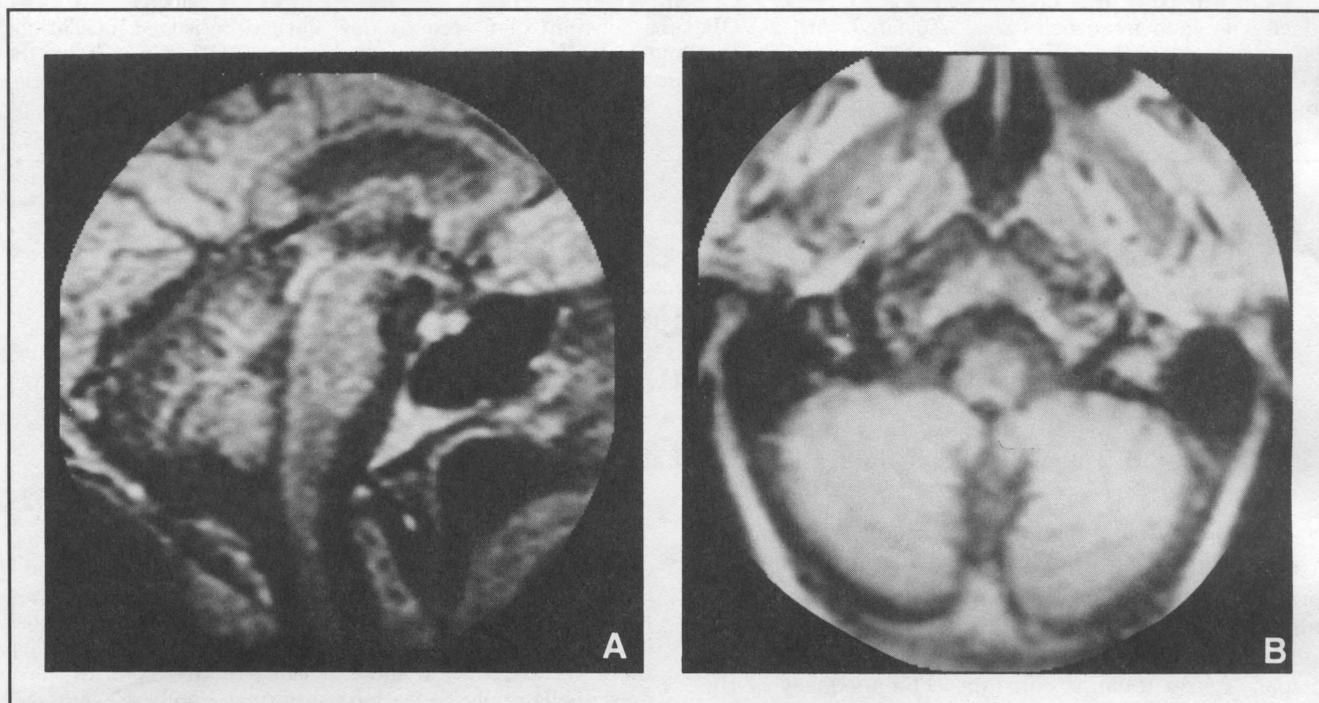


Figure 1. MRI demonstrating cerebellar atrophy. No abnormalities are seen in the pons or the inferior olives. (A) Midsagittal section through the brainstem and cerebellum (TE 40 msec, TR 1,000 msec). (B) Transverse section through the upper medulla and cerebellum (TE 40 msec, TR 900 msec).

velocity steps were applied. During VOR testing in complete darkness, the patient was instructed to imagine a stationary target light on the wall in front of him. The effect of fixating a visible stationary target upon the VOR was also studied for each of the stimulus conditions. Visual cancellation of the VOR was measured while patient was fixating a target moving with the head. VOR gain calculations incorporated a correction for the different axes of rotation of the eye and head.² The active VOR was also measured as the subject voluntarily oscillated his head in yaw in darkness at approximately 0.5 and 1.0 Hz with peak-to-peak amplitudes of approximately 10° (figure 2). The cervicocolar reflex (COR) was measured by holding the head stationary in space while rotating the body sinusoidally in darkness at 0.5 Hz with peak-to-peak amplitudes of 32° (peak velocities of 50 deg/sec); the patient was instructed first to imagine a stationary target on the wall and second to imagine a target moving with his body. Caloric nystagmus was elicited with 22 and 50 °C air stimuli to either tympanic membrane, and visual suppression of caloric nystagmus was measured during fixation of a small target light.

Results. Saccades were hypermetric, but saccadic peak-velocity/amplitude relationships were normal. Smooth-pursuit gain (peak eye velocity/peak target velocity) was 0.7 (range, 0.6 to 0.8) for 0.1-Hz sine waves with peak-to-peak amplitudes of 20°, but fell to 0.15 (0.08 to 0.18) with 1.0-Hz stimuli with 20° peak-to-peak amplitudes. Combined active eye-head tracking gain (peak gaze velocity/peak target velocity) varied from -0.2 to -0.96 for 1.0 Hz sinusoidal target motion with

peak-to-peak amplitudes of 20°; gaze movement was in the direction opposite to target movement. Optokinetic slow phase gain (peak slow phase eye velocity/target velocity) was 0.5. The duration of optokinetic after-nystagmus was 3 to 5 seconds. VOR gain during en bloc sinusoidal rotation (figure 3) was symmetric and increased from 0.8 (range, 0.7 to 0.9) at 0.01 Hz (peak velocities of 50 deg/sec) to 1.9 (range, 1.6 to 2.4) at 1.0 Hz (peak velocities of 63 deg/sec). With velocity steps, the VOR gain was 3.0 (range, 2.5 to 3.5), and the time constant was 6 seconds. VOR gain measured during en bloc sinusoidal rotation while fixating a visible stationary target was 1.7 (range, 1.2 to 2.0) at 1.0 Hz and 20° peak-to-peak amplitudes (peak velocities of 63 deg/sec). The gain of the VOR during visual cancellation (normally near 0) increased from 0.6 (range, 0.5 to 0.8) at 0.2 Hz and peak-to-peak amplitude of 20° to 1.2 (range, 1.1 to 1.4) at 0.8 Hz and the same amplitudes. Active VOR gain was 2.1 (range, 1.6 to 2.5) at 1.0 Hz and 20° peak-to-peak amplitudes. The maximum gain (peak eye velocity/peak chair velocity) of the COR while imagining a stationary target was 0.3; the direction of eye movement was opposite to the direction of trunk movement (figure 3). When the patient imagined a target moving with the chair, the COR gain increased to 0.7 (range, 0.4 to 1.0). The average slow phase velocity of caloric nystagmus was 24 deg/sec. Visual suppression of caloric nystagmus was absent.

A therapeutic trial of baclofen 40 mg/d produced mild worsening of visual symptoms. Diazepam 45 mg/d produced no clinical improvement or significant change in VOR gain (2.3; range, 2.0 to 2.8) measured with 60-deg/sec-velocity steps. Physostigmine salicylate, 1 mg

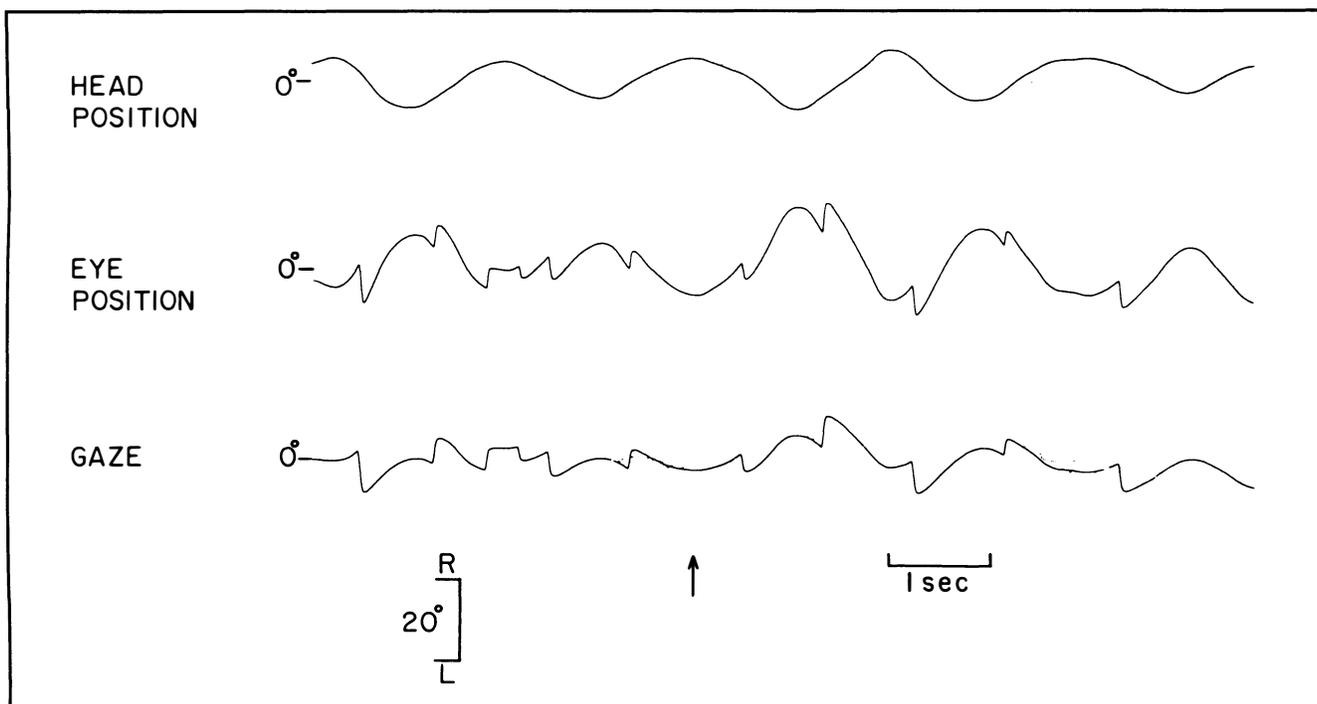


Figure 2. Scleral search coil recording of the VOR during active head shaking at approximately 0.5 Hz in light (before arrow) and darkness (after arrow), demonstrating instability of gaze during head movement. Simultaneous tracings are of head position in space, eye position in the orbit, and gaze (eye position in space). R = right; L = left.

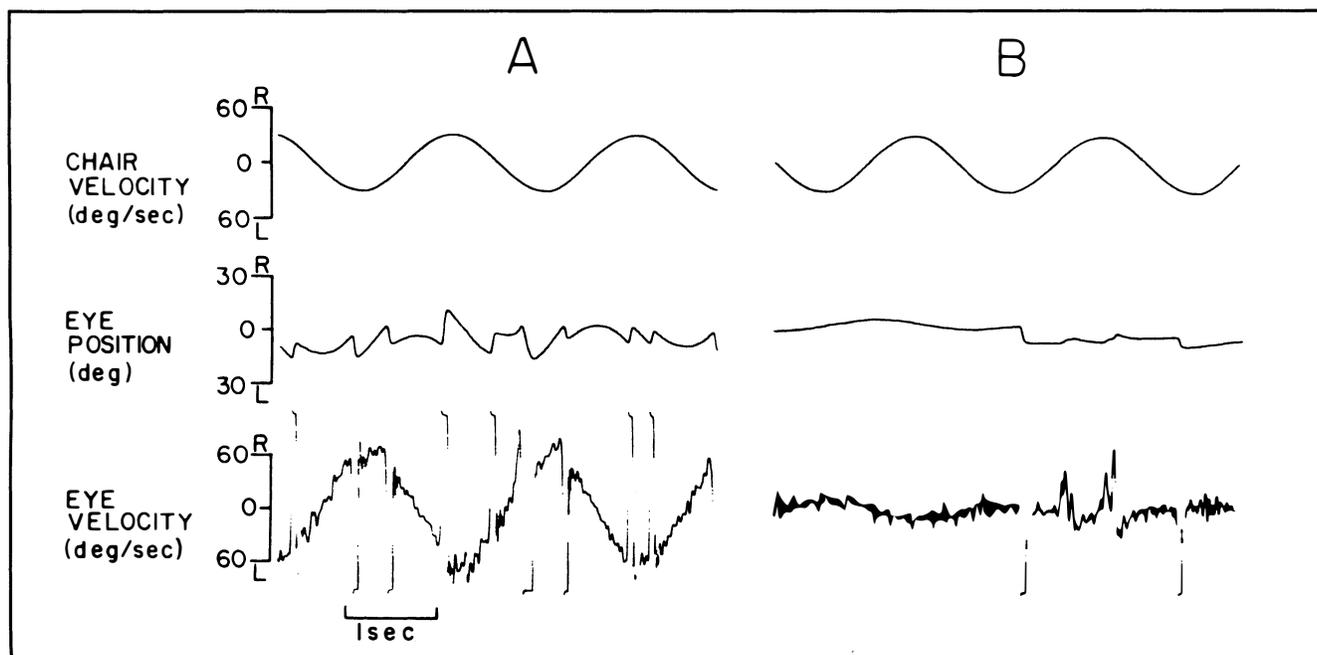


Figure 3. EOG recording of the VOR (A) and COR (B). In A, simultaneous recordings during en bloc rotation are of chair (head and trunk) velocity in space and eye position and velocity in the orbit. Eye velocity exceeds chair (head) velocity. In B, tracings are of chair (trunk) velocity in space with the head fixed and eye position and velocity in the orbit. R = right; L = left.

given IV, produced subjective improvement of vision and gait. Visual acuity during head shaking increased from 20/200 to 20/100. Forty minutes after physostigmine, the VOR gain, measured in response to 60-deg/sec-velocity step rotations in the dark, decreased to 1.5

(range, 1.3 to 1.7) from the preinjection value of 3.0 (range, 2.5 to 3.5). Gain measured during en bloc sinusoidal stimuli at 0.5 Hz and peak-to-peak amplitudes of 20° decreased to 1.3 (range, 1.2 to 1.4) from the preinjection value of 1.7 (range, 1.5 to 2.0). Gain of the VOR

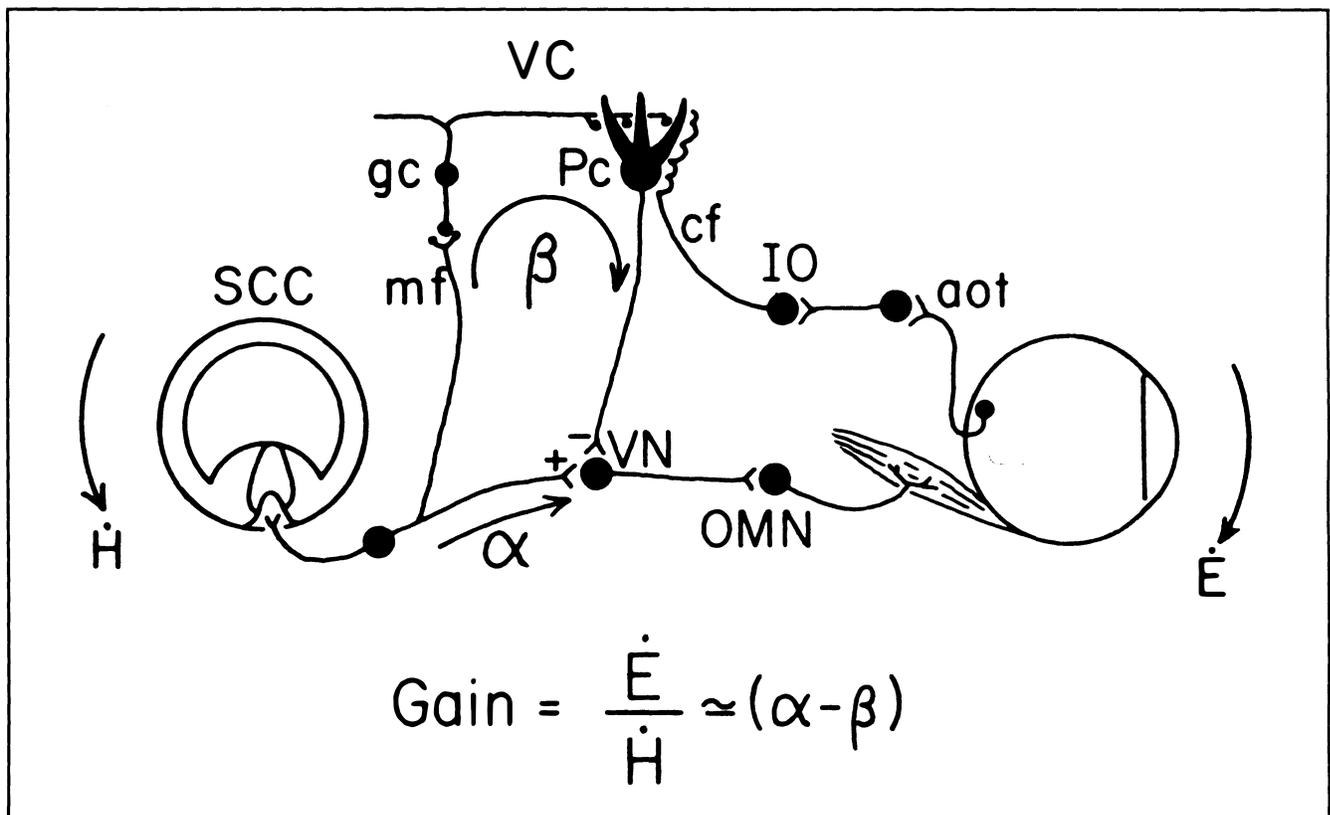


Figure 4. Pathways theoretically involved in visual modification of the VOR (from Robinson¹⁹). The gain of the direct VOR pathway (SCC-VN-OMN) is paralleled by a side loop (mf-gc-Pc) through the vestibulocerebellum. The gain of the side loop can be modified by retinal error information arriving via cf; we postulate that this pathway is cholinergic and is affected by physostigmine. SCC = semicircular canal; VN = vestibular nucleus; OMN = ocular motor nucleus; VC = vestibulocerebellum; mf = mossy fiber; gc = granule cell; Pc = Purkinje's cell; aot = accessory optic tract; IO = inferior olive; cf = climbing fiber; α = direct VOR pathway; β = side loop; \dot{H} = head velocity; \dot{E} = eye velocity.

while fixating a target moving with the head (visual cancellation) measured at 0.45 Hz and peak-to-peak amplitudes of 20° remained abnormally high at 1.0 (range, 0.9 to 1.1).

Discussion. In our patient, a twofold increase in the gain of the VOR caused blurred vision and oscillopsia during head movement due to eye movement in excess of that required to stabilize gaze. This contrasts with blurred vision and oscillopsia due to peripheral vestibular dysfunction, in which compensatory eye movements are inadequate to stabilize gaze.

The gain increase was greatest for high-frequency head rotation and least (or normal) for low-frequency rotations and caloric stimulation. Such frequency dependence of VOR gain has been described in patients with deficient peripheral vestibular function.³

The increase in VOR gain was associated with a modest increase in COR gain. The normal COR is highly variable (Fuller JH, personal communication), with eye movement reported as ipsilateral⁴⁻⁷ or contralateral⁸⁻¹⁰ to trunk movement, and gains reported from 0.02 to 0.1 for stimulus frequencies comparable with our own. The COR contributes relatively little to the stabilization of gaze in normal humans. Following vestibular dysfunction, however, the gain of the COR

may increase adaptively in the ipsilateral direction to provide up to 25% compensation.¹¹ An increase in COR gain has also been attributed to decreased cerebellar inhibition of the COR and suggested as the cause for "cervical nystagmus" in a patient with a cerebellar tumor.¹² In our patient, the COR gain was increased in the opposite direction to that reported in labyrinthine-defective patients with decreased VOR gains,¹¹ but in the appropriate direction to compensate for a hyperactive VOR. This observation also implies a retained ability to modify the COR, in spite of an inability, presumably central, to modify the VOR. Another consequence of the increased VOR gain was that smooth pursuit with the head stationary was of higher gain than combined eye-head tracking.

Vestibulo-ocular reflex gain may increase slightly in man due to cerebellar system disease,¹³⁻¹⁸ although estimates have seldom been made at higher frequencies of head rotation. Reported gains approach 1.0 in the dark (normal, 0.6 to 0.9). In the light, the highest gain reported for the human horizontal VOR is 1.2¹⁵ (normal, 0.9 to 1.0). Vestibulocerebellectomy in the cat¹⁹ and flocculectomy in the monkey²⁰ both increase VOR gain to 1.17. VOR gains as high as those observed in our patient, however, have been reported only in animal studies.^{21,22} Demer and Robinson²¹ infused lidocaine

into the decussation of climbing fibers from the inferior olivary nuclei to the flocculi and produced a prompt, large, reversible increase in VOR gain. To explain their results, they utilized Ito's model (figure 4), which proposed that the gain of the VOR is modified by retinal image slip information carried by climbing fibers^{19,21,23}; removal of the climbing fiber input resulted in a rise of the VOR gain to a default value of around 2.0.

Although neuroradiologic studies did not reveal structural abnormalities of the inferior olives in our patient, we suspected that olivocerebellar pathways were involved. Animal studies^{21,22} suggest that such lesions in man would cause an increased VOR gain and persistence of symptoms due to the inability to adaptively modify the VOR gain using retinal error information.

The dorsal cap, a major source of inferior olivary efferents to the vestibulocerebellum, is histochemically strongly positive for acetylcholinesterase.²⁴ This suggests that these projections (figure 4) could be cholinergic, even though acetylcholinesterase is not a highly specific marker for cholinergic neurons. We therefore gave physostigmine, a cholinesterase inhibitor, to attempt to reduce the VOR gain. This produced a significant drop in VOR gain and improvement of visual acuity during head shaking. Such a response is consistent with a cholinergic hypothesis. This pharmacologic effect seems to have been specific, since neither diazepam nor baclofen produced a significant change in VOR gain or visual symptoms, respectively. Baclofen inhibits the release of glutamate,²⁵ a putative neurotransmitter of the granule cell²³ (figure 4), and shortens the VOR time constant without affecting the gain.²⁶

Physostigmine has been reported to benefit the ataxia in cerebellar degeneration.²⁷ Tijssen et al²⁸ reported that physostigmine improved visual suppression of caloric nystagmus in hereditary ataxia. This effect was apparently due to improved fixation suppression. We found that the VOR gain decreased, and we did not find a significant change in visual suppression of rotational nystagmus.

Further studies are required to (1) measure the VOR gain in cerebellar degeneration at the frequencies of natural head rotations (0.5 to 5.0 Hz) and (2) study the effects of physostigmine on VOR gain. Measurement of the VOR may be a valuable way to quantitatively evaluate physostigmine.

Addendum. The patient described in this report is currently taking physostigmine, 1 mg, po, bid (FDA/IND protocol number 27,992). On this dosage he reports less oscillopsia and clearer vision during everyday life.

Acknowledgments

The authors thank Mr. Alfred O. DiScenna and Ms. Kathy Haddon for technical help, Dr. Stephen Wiener for MRI, and Ms. Holly Stevens for editorial assistance.

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