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Dysfunction of pontine omnipause neurons causes impaired fixation: macrosaccadic oscillations with a unilateral pontine lesion

L. Averbuch-Heller
A. A. Kori
K. G. Rottach
L. F. Dell'Osso
B. F. Remler
R. J. Leigh

Department of Neurology, University Hospitals and Veterans Affairs Medical Center, Case Western Reserve University, Cleveland, OH, USA

Abstract Macrosaccadic oscillations of eyes (MSO) are regarded as a form of saccadic dysmetria secondary to cerebellar dysfunction. They are usually conjugate, horizontal, and symmetric in both directions of gaze. Using magnetic search coils, we studied a patient with MSO that developed five years following head injury and involved synchronously horizontal, vertical, and torsional planes. The MSO were characterized by directional preponderance and were associated with ipsilateral pontine lesion. We propose a disturbance of fixation mechanisms due to unilateral disinhibition of saccadic burst neurons in three planes. This could arise from either primary or secondary dysfunction of omnipause neurons, due to impaired input from the contralateral superior colliculus. The delayed onset is suggestive of denervation supersensitivity as the underlying pathophysiology.

Key words Saccadic intrusions; omnipause neurons; superior colliculus; denervation supersensitivity

Correspondence to: Dr. R. John Leigh, Department of Neurology, University Hospitals of Cleveland, 2074 Abington Road, Cleveland, OH 44106, USA Tel: (216)-421-3224; Fax: (216)-421-3040

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Introduction Normally, we hold our eyes quite steadily during fixation. Inappropriate saccades that disrupt steady fixation are termed saccadic intrusions. One example of saccadic intrusions is macrosaccadic oscillations (MSO). MSO are to-and-fro oscillations of the eyes, consisting usually of large horizontal saccades that occur in bursts, building up and then decreasing in amplitude, with intersaccadic intervals of about 200 msec.[1,2] Described originally in cerebellar patients, MSO are thought to reflect saccadic dysmetria, when patient's saccades are so hypermetric that they overshoot the target continuously in both directions.[3]

Using magnetic search coil technique, we studied a patient with delayed onset, post-traumatic, large-amplitude MSO in the horizontal, vertical, and torsional planes, associated with a unilateral pontine lesion. These oscillations provide insight into the neural fixation mechanisms.

Case report A 34-year-old man presented with the complaint of jumping of his visual world – oscillopsia – for ten months. Five years previously, he suffered severe head trauma involving a coup injury in the left frontal region and a contrecoup injury in the right upper brainstem region as shown by CT scan; no cerebellar lesion was evident. He sustained left hemiplegia and horizontal double vision. Eleven months after the injury, he was seen by an ophthalmologist who did not document any abnormal eye movements except for poor convergence. On current examination, his general neurological status was unchanged. Right hand coordination was preserved; he was able to operate a computer 'mouse' accurately with his right hand. Visual acuity, color perception, visual fields, pupils, fundus, and slit-lamp examination were all normal. When he attempted to view a target in the center of his field of vision, large saccades continuously intruded on steady fixation. These were mainly horizontal, but occasionally diagonal, and appeared in clusters. They were suppressed when the patient turned his eyes to the extremes of horizontal gaze. There was a full range of extraocular movements, with concomitant esodeviation of about 8 prism diopters. No convergence could be elicited. MRI demonstrated hyperintense signals on T2-weighted images in the left posterior frontal region and the right pons, which were non-enhancing (Fig. 1). The pontine lesion extended down to the level of the abducens nucleus and in-

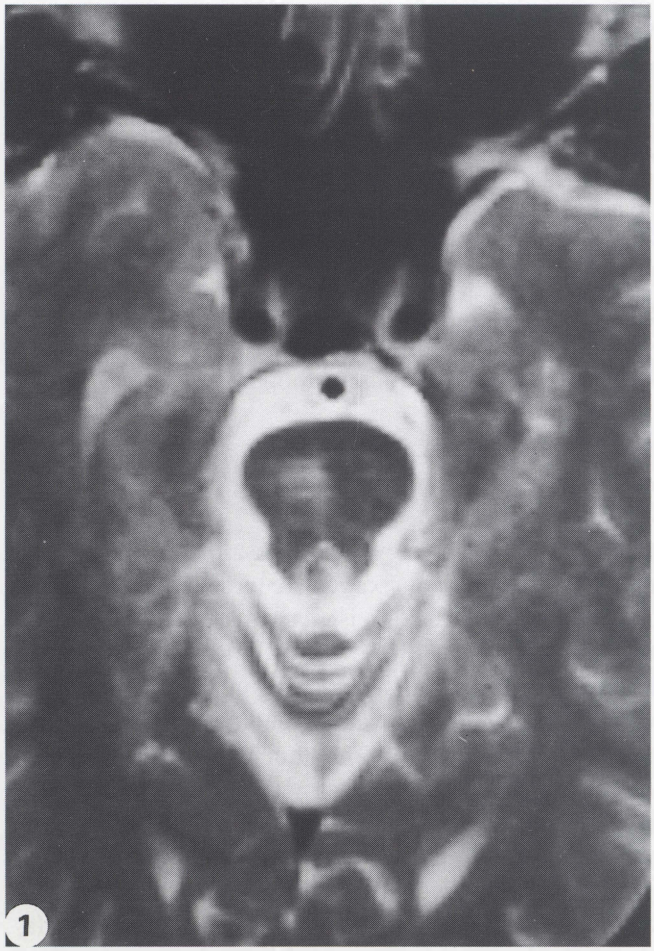

Fig. 1. MRI. Axial T2-weighted image shows a hyperintense signal in the right pons. The lesion is to the right of midline, involving the tegmentum and basis pontis.

volved both the tegmentum and basis pontis. No abnormalities of the cerebellum were evident.

Methods

EYE MOVEMENT MEASUREMENTS Horizontal, vertical, and torsional rotations of both eyes and of the head were recorded using the magnetic search coil technique.[4] With head stationary, the patient attempted steady fixation, with each eye in turn, of visual targets located near primary position and at eccentricities of ± 20 deg horizontally and ± 15 deg vertically at viewing distances of 1.2 m (far target) or 18 cm (near target). The effects of viewing a near target binocularly (attempted convergence) were also measured. Horizontal and vertical saccades were made between the fixed target locations, and horizontal and vertical smooth pursuit was measured as the patient followed a small target moving through ± 15 deg sinusoidally at 0.3 Hz. Visually enhanced vestibulo-ocular reflex (VVOR) was measured while the patient made active horizontal or vertical head rotations, viewing first the far and then the near target. Data were filtered (bandwidth 0-90 Hz) prior to digitization at 200 Hz. Analysis was performed using interactive programs written in the ASYST language.[5] The gain of the smooth pursuit response and the gain of compensatory eye movements during head rotations (VVOR) were determined as previously described.[4]

Results Fixation was frequently disrupted by large-amplitude, predominantly horizontal saccadic intrusions. Each saccade took the eye away from central fixation and was followed by an oppositely directed saccade within 200 msec (Fig. 2). The oscillations were conjugate and of similar amplitude in both eyes, with synchronous horizontal, vertical, and torsional components. In the horizontal and torsional planes, the first saccade was always directed to the patient's right and clockwise; in the vertical plane, it could be

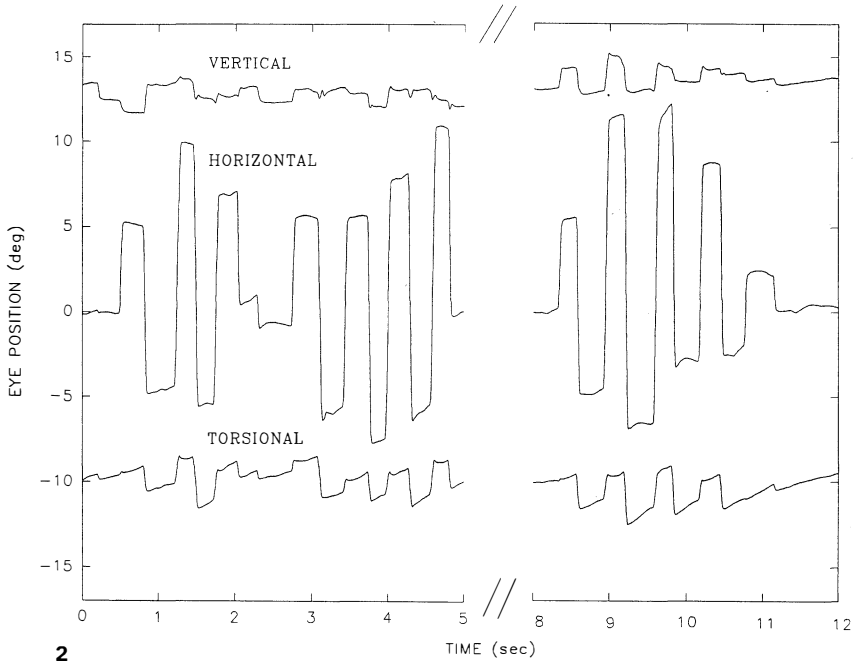

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Fig. 2. Two segments of the right eye recording during attempted fixation of a distant target. Fixation is interrupted by bursts of saccadic intrusions, which are time-locked in the horizontal, vertical, and torsional planes. Note that the first saccade is always to the right or clockwise, but has no consistent direction vertically. The return saccade usually overshoots the central fixation point. Torsional and vertical tracings have been offset for convenience of display. Upward deflections correspond to rightward, upward, or clockwise eye rotations, with respect to the patient.

either in the upward or downward direction, though it was always time-locked with the components in the other planes. During attempted fixation of the target at 1.2 m, the amplitude was maximal in horizontal plane (mean 13.6 deg, range 10.4-15.5 deg); it was small and about equal in the vertical and torsional planes (vertical, mean 1.2 deg, range 0.9-1.6 deg and torsional, mean 1.3 deg, range 0.9-1.9 deg). During viewing of the target at 18 cm, the amplitudes were decreased in all planes of oscillation (horizontal, mean 8.8 deg, range 6.4-11.3 deg; vertical, mean 0.9 deg, range 0.3-1.2 deg; torsional, mean 0.8 deg, range 0.4-1.0 deg). The intersaccadic interval was about 200 msec (range 160-240 msec). The return saccade was usually bigger than the first one, and often overshot the fixation point by 2-5 deg. The frequency of the oscillation was about 1.5 Hz, with occasional interruptions for about 2 sec. The oscillation changed little in darkness, with monocular viewing, or during voluntary saccades, smooth pursuit, and vestibular eye movements. Gaze holding was preserved during intersaccadic interval in horizontal plane, maintaining the square-wave appearance of the oscillations. In the torsional plane, intersaccadic clockwise drifts were evident; in vertical plane, there were small downward drifts in the left eye only. For voluntary saccades to visual target, gains (initial saccade amplitude/target amplitude) were 0.90 for rightward saccades and 1.13 for leftward saccades. The peak velocity/amplitude relationship was normal for both voluntary saccades and the saccadic intrusions. The gain of the horizontal VVOR was 1.02. The gain of the horizontal smooth pursuit was 0.89.

Discussion Our patient's visual disability was due to frequent, large saccadic oscillations that intruded on steady fixation. Each involuntary movement away from fixation was followed after about 200 msec by a return saccade, often overshooting the fixation point. These movements correspond to what has been called 'macrosaccadic oscillations' (MSO), although the latter are usually induced by a voluntary gaze shift. MSO are traditionally interpreted as a sign of saccadic dysmetria due to midline cerebellar dysfunction.[2,3] This explanation may not account for several features characterizing the spontaneous MSO in our patient, such as: 1) occurrence of the saccadic intrusions during attempted central fixation; 2) strict laterality concerning horizontal and torsional saccades (the first saccade in the burst being always to the right and clockwise), with no directional preponderance for vertical saccades; and 3) presence of the intrusions in darkness. These findings are consistent with simultaneous disinhibition of the three categories of the burst neurons: those for horizontal, vertical, and torsional saccades. Such disinhibition could be produced by impaired function of omnipause neurons.

Omnipause neurons play the role of a gating mechanism for saccades; they are crucial for suppressing unwanted saccades during fixation and slow eye movements.[6] Located in the caudal pons within raphe interpositus nucleus (RIP) adjacent to the abducens nucleus,[7] omnipause neurons exert a tonic inhibition on horizontal saccadic burst neurons in the pontine paramedian reticular formation (PPRF),[8] and on the vertical saccadic burst neurons in the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF).[9] It has been found that even single omnipause neurons frequently project to all saccadic generators (horizontal, vertical, and torsional).[10] Inputs into omnipause neurons arise in the superior colliculus (SC), frontal eye fields, and mesencephalic reticular formation, with SC being particularly

important for sustaining steady fixation.[11,12] Electrophysiological studies show that most pause cells cease discharging for saccades in all directions.[3] Therefore, omnipause neuron dysfunction should affect all saccadic generators, causing unwanted saccades simultaneously in horizontal, vertical, and torsional planes, similar to the findings in our patient.

The lesion on the MRI in our patient is localized to the right pons, extending down to the level of the abducens nerve fascicles, involving the tegmentum ventral to the MLF. This location is compatible with the right RIP as well as the site of decussation of the crossing bundle of fibers from the left RIP to the right riMLF. Saccadic intrusions have been previously documented in association with pontine lesions. Experimental lesions in the region of nucleus reticularis tegmenti pontis (NRTP) in the monkey produce vertical square-wave jerks.[13] Saccadic intrusions have been also reported with internuclear ophthalmoplegia.[14-16] It could be hypothesized that saccadic intrusions in these cases were actually produced by damaging the adjacent omnipause neuron projections (JA Büttner-Ennever, personal communication).

RIP is a midline structure, and its projections are usually considered bilateral.[6,7] However, there is some evidence that the influence exerted by omnipause neurons upon burst neurons may be lateralized. It was shown that omnipause efferent projections to riMLF, and its afferents from SC, appear to be mainly contralateral.[11,12,17] Saccade generation is based on push-pull interaction between the 'fixation' cells and the 'saccade' cells within SC.[18] Balance of the activity in favor of the latter will result in a saccade. Unilateral injections of bicuculline into SC in monkeys produced 'irrepressible saccades to the side contralateral to the injection' during attempted fixation, reminiscent of the findings in our patient.[19,20] The effect was probably exerted via the contralateral projections from SC to omnipause and saccadic burst neurons. This further substantiates the possibility of the lateralized control over the fixation mechanisms.

Horizontal burst neurons in the right PPRF produce rightward saccades; burst neurons in the right riMLF produce clockwise torsional saccades.[21] However, in the vertical plane excitation of the right riMLF can produce both upward and downward saccades, as the riMLF on each side contains burst neurons for both up- and downgaze.[22,23] Thus, unilateral disinhibition of all three types of the burst neurons on the right would result in irrepressible intrusion of saccades, which would be rightward and clockwise in the horizontal and torsional planes, respectively, but might be either upward or downward in the vertical plane. This was the case with our patient. Torsional components of the oscillation cannot be explained by Listing's law, being essentially unchanged with constant horizontal and varying vertical components, and therefore, are centrally produced.[24] Hence, we postulate unilateral disinhibition of all burst neurons as responsible for the initiation of each 'cluster' of MSO in our patient.

Abnormality of omnipause neuron control over saccadic burst neurons has been previously suggested for saccadic oscillations that lack intersaccadic intervals, *i.e.* 'back-to-back' saccadic intrusions of saccadic flutter or opsoclonus.[3] On the other hand, saccadic intrusions such as those of our patient or smaller square-wave jerks were ascribed to different mechanisms. Square-wave oscillations, such as occur in progressive supranuclear palsy, large-amplitude MSO, and saccadic back-to-back oscillations might repre-

sent a continuum of fixation abnormalities with common underlying pathophysiology. In support of this, Tychsen and colleagues[16] have reported a patient with stereotypic cycles consisting of tinnitus and square-wave jerks evolving into opsoclonus, associated with clinical evidence of pontine dysfunction. As for the typical absence of the vertical components in MSO,[1,2] in the majority of the cases reported, only horizontal eye movements were recorded, so that the vertical and torsional components of the oscillation might have been overlooked. Whenever the vertical eye movements were measured, a vertical component of MSO was found.[25,26]

Cerebellar dysmetria probably does contribute to the pattern of the oscillation in our patient, with successive saccades constantly overshooting the fixation site. This latter point is also strengthened by the hypermetric saccades to the left (gain 1.13). Yet, saccadic dysmetria by itself cannot account for the occurrence of the initial intrusions while fixating a central target, and would be unlikely to produce the stereotyped, direction-specific nature of the oscillations. This is supported by the fact that neither patients with cerebellectomy[27] nor monkeys with experimentally produced cerebellar lesions exhibit MSO.[28,29] Moreover, it has been shown that the cerebellum is less concerned with initiation of a saccade, but more with optimizing its metrics.[30] Therefore, saccadic dysmetria alone does not provide a sufficient explanation for MSO occurring during fixation.

Finally, the delay in the development of MSO after the head trauma in our patient resembles the delayed onset of pendular nystagmus in oculopalatal myoclonus or see-saw nystagmus with meso-diencephalic lesions.[31,32] In oculopalatal myoclonus, the rhythmic movements appear after the development of the olivary hypertrophy.[33] Such time delay has been attributed to denervation supersensitivity.[34] A similar mechanism might be responsible for the late-onset MSO in our patient. Delayed development of denervation supersensitivity could account for the absence of saccadic intrusions immediately after experimentally lesioning RIP.[35] Similarly, neuronal dysfunction on a physiological level would explain the normal anatomical appearance of the omnipause neurons in some patients with opsoclonus, in whom immunological abnormalities have been implicated.[36,37] Usually the time between the initial insult and the subsequent appearance of the oscillation due to denervation hypersensitivity is months rather than 4-5 years. It is possible, however, that MSO developed earlier, but the patient became aware of it only recently, with the functional deterioration of his vision. Oscillopsia is not a characteristic feature of saccadic intrusions, due to visual suppression that occurs normally during a saccade.[38] Oscillopsia in our patient might result from the inability to sustain steady fixation, with return saccades taking his eyes across the target. This might become more of a problem with progressively increasing amplitude of MSO, eventually resulting in oscillopsia.

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