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Original Article

Wall-Eyed Internuclear Ophthalmoplegia: History and Hypothesis

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ABSTRACT: *Background:* Most patients with internuclear ophthalmoplegia (INO) are orthotropic, although a subset is exotropic. When INO is bilateral, this is termed wall-eyed bilateral internuclear ophthalmoplegia (WEBINO). In 1979, Sharpe described his "first case" of wall-eyed monocular internuclear ophthalmoplegia (WEMINO) as "a unique clinical syndrome" characterized by unilateral INO and ipsilateral exotropia. *Methods:* WEMINO was clinically identified in seven patients, with oculographic correlation in six and neuropathological confirmation in one. Oculographic features of exotropic INO patients were compared with those of six orthotropic INO patients using magnetic search coil and infrared oculography. *Results:* All clinically defined WEMINO patients showed slowed, hypometric ipsilateral saccades by oculography. Six patients had ipsilateral exotropia, and three had ipsilateral hypertropia. Ipsilateral abducting saccades had faster peak velocities for smaller saccades, more so for orthotropic patients. Exotropic patients had normal sinusoidal mean vestibulo-ocular reflex (VOR) gains and phases; orthotropic patients had subnormal mean VOR gains and phase leads. *Conclusion:* WEMINO is a clinical ocular motor syndrome characterized by unilateral slow, hypometric adducting saccades with exotropia and hypertropia of the ipsilateral eye. We propose that it results from discrete unilateral damage to burst-tonic fibers in the medial longitudinal fasciculus (MLF) with sparing of the adjacent extrafascicular pathways. Paradoxically, orthotropic INO results from more extensive damage to ascending pathways lateral, ventral and caudal to the MLF. Direct injury to the medial rectus subnucleus is not required. This manuscript was in preparation at the time of Dr Sharpe's death in 2013 and is an acknowledgement of his forward-thinking, as his hypotheses have stood the test of time.

RÉSUMÉ : L'ophtalmoplégie internucléaire caractérisée par une exotropie : histoire et hypothèse *Contexte :* La plupart des patients souffrant d'ophtalmoplégie internucléaire (OIN) sont orthotropes, bien qu'un certain nombre d'entre eux soit exotrope. Lorsque ce type particulier d'OIN est bilatérale, on parle alors d'OIN bilatérale exotrope (ou « *wall-eyed* »). En 1979, le Dr Sharpe a décrit son « premier cas » d'OIN monoculaire exotrope comme « un syndrome clinique unique » caractérisé par une OIN unilatérale ainsi qu'une exotropie ipsilatérale. *Méthodes :* L'OIN monoculaire exotrope a été identifiée cliniquement chez sept patients, avec une corrélation oculographique chez six d'entre eux et une confirmation neuro-pathologique chez un. Les caractéristiques oculographiques des patients atteints d'une OIN exotrope ont été ainsi comparées à celles de six patients atteints d'une OIN orthotrope à l'aide d'une bobine magnétique et d'un appareil d'électro-oculographie à infrarouge. *Résultats :* Tous les patients atteints d'OIN monoculaire exotrope identifiés sur le plan clinique présentaient des saccades ipsilatérales ralenties et hypométriques lors d'un examen électro-oculographique. Six patients présentaient par ailleurs une exotropie ipsilatérale et trois une hypertropie ipsilatérale. Les saccades ipsilatérales en abduction présentaient des vitesses maximales plus rapides pour les petites saccades, surtout chez les patients dont l'OIN était orthotrope. De leur côté, les patients dont l'OIN était exotrope présentaient des gains et des phases moyennes subnormales du réflexe vestibulo-oculaire (RVO) ; les patients dont l'OIN était orthotrope donnaient à voir des gains moyens subnormaux du RVO et des avancées de phase (*phase leads*). *Conclusion :* L'OIN monoculaire exotrope est un syndrome clinique de la motricité oculaire caractérisé par des saccades unilatérales lentes, hypométriques et adductrices avec exotropie et hypertropie de l'œil ipsilatéral. Nous proposons que ce syndrome résulte d'une lésion unilatérale discrète des fibres toniques en rafale dans le faisceau longitudinal médial (FLM), les voies extra-fasciculaires adjacentes étant épargnées. Paradoxalement, l'OIN orthotrope résulte d'une atteinte plus importante des voies ascendantes latérales, ventrales et caudales du FLM. Une lésion directe du sous-noyau droit médian n'est donc pas nécessaire. Ce manuscrit était en préparation au moment du décès du Dr Sharpe en 2013 et constitue une reconnaissance de sa pensée visionnaire, ses hypothèses ayant résisté à l'épreuve du temps.

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Highlights

- Most INO patients are orthotropic. Exotropic INO consists of slow hypometric adducting saccades, exotropia and, when unilateral, ipsilateral hypertropia.
- Exotropic INO is due to damage of burst-tonic fibers in the MLF; orthotropic INO requires more extensive damage to extrafascicular pathways.
- Exotropic INO does not require damage to the medial rectus subnucleus.

Introduction

Dr James A. Sharpe (1941–2013) was one of the foremost neurologists and neuro-ophthalmologists in Canada.[1,2] This manuscript was in preparation at the time of his death, and 10 years after his passing, it has been completed in his honor. Internuclear ophthalmoplegia (INO) consists of limitation or slowing of adducting saccades or both due to a lesion of the ipsilateral medial longitudinal fasciculus (MLF), usually in association with jerk nystagmus of the abducting eye.[3–6] The eyes typically remain aligned (orthotropic), maintaining binocular fusion during forward gaze. If unilateral, the patient may note vertical diplopia from disruption of otolith pathways traveling in the MLF; this causes skew deviation in 50% of patients with unilateral INO due to hypertropia of the eye ipsilateral to the adduction paresis.[7]

Wall-eyed bilateral internuclear ophthalmoplegia (WEBINO), a term attributed to Martin Lubow by Hoyt and Daroff[3] in 1971, is a variant of bilateral INO characterized by exotropia in the primary position, resulting in horizontal diplopia. The exotropia was originally thought to be due to the involvement of the medial rectus subnuclei.[3] However, in 1924, Spiller[5] reported a patient with WEBINO and preserved convergence in whom neuropathological

examination showed infarction of both MLFs in the midbrain, sparing the oculomotor nuclei. In 1979, Dr Sharpe examined a 51-year-old man presenting with acute horizontal diplopia (Patient 1), who had left INO and primary position left exotropia, presumed to be due to a brainstem stroke. In his notes, Sharpe coined the term wall-eyed monocular internuclear ophthalmoplegia (WEMINO) to describe this patient's findings. However, a review of the literature revealed descriptions of three previous cases with clinical features consistent with WEMINO. In 1950, Cogan *et al.*[8] reported one case of WEMINO, and in 1956, Fine and MacGlashan[9] reported two further cases. None of these had oculographic confirmation of the INO. Since we described four cases of WEMINO in 1994,[10] six other cases have been published with radiological localization of the causative lesions in the pontine tegmentum[11–15] or at the ponto-mesencephalic junction.[16]

We describe the oculographic features of six patients with the clinical manifestations of WEMINO, along with neuropathological correlation in a seventh case. Six orthotropic patients with INO were also assessed quantitatively for comparison with the exotropic INO patients. A proposed hypothesis for exotropic INO syndromes initiated by Dr Sharpe and revised in accordance with more recent literature is presented.

Patients and methods

We examined seven patients with WEMINO consisting of unilateral INO and primary position exotropia (mean age 46; SD 16) and six orthotropic patients with unilateral or bilateral INO (mean age 51; SD 16) (Table 1). Patients were initially distinguished as WEMINO based on clinical assessment by one or both of the authors. Four of the seven WEMINO patients and two of the six orthotropic patients suffered brainstem infarcts.

Table 1. Demographics

	Patient	Side of INO	Side of exotropia	Age	Sex	Diagnosis	Neuroimaging	Additional ocular motor features
Exotropic INO	1	Left	Left	51	Male	Brainstem stroke	CT negative	Left hypertropia
	2	Right	Right	65	Female	Right pontine stroke	CT right pontine tegmentum (Figure 1A)	Right hypertropia; gaze-evoked upbeat nystagmus
	3	Right	Right	30	Female	Presumed demyelinating disease	MRI right pontine tegmentum demyelination (Figure 1B)	
	4	Right	Right	41	Male	Multiple sclerosis		Right/left/up gaze-evoked nystagmus
	5	Right	Right	70	Male	Right midbrain stroke	MRI right caudal midbrain infarct	
	6	Right	Left	40	Female	Right pontine stroke	MRI left pontine tegmentum infarct	
	7	Right	Right	28	Male	Trauma pons and midbrain	CT left medial temporal occipital infarct	Right hypertropia
Orthotropic INO	1	Left > right		46	Female	Multiple sclerosis		
	2	Right		71	Male	Brainstem stroke	CT negative	Left VIth nerve palsy; Right hypertropia
	3	Right > left		45	Male	Multiple sclerosis		
	4	Symmetrical		38	Female	Multiple sclerosis		
	5	Symmetrical		36	Female	Multiple sclerosis		
	6	Symmetrical		72	Male	Brainstem stroke		
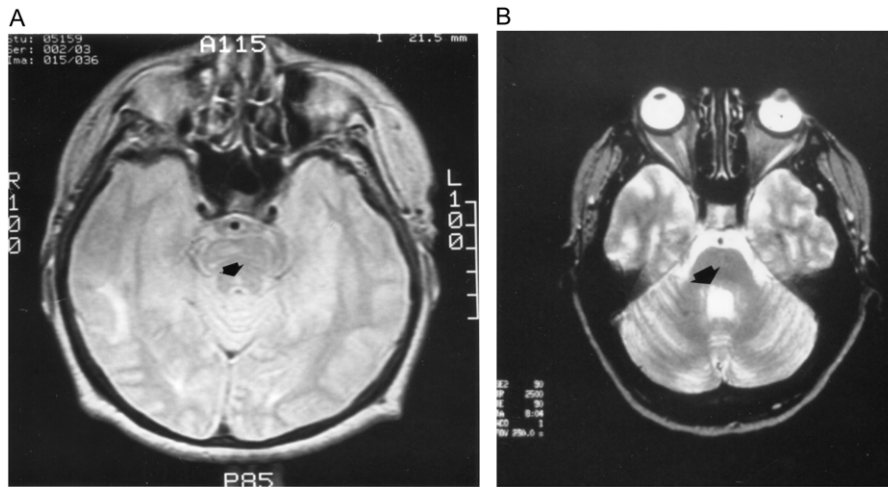
Figure 1. Neuroimaging of exotropic INO patients. (A) MRI scan of Patient 2 shows small hyperintensity in the right pontine tegmentum. (B) MRI of Patient 3 shows T2 hyperintensity in right pontine tegmentum.

Figure 1A is an MRI of the right pontine tegmentum stroke suffered by Patient 2 (arrow). Demyelinating disease occurred in two of the WEMINO patients and four of the orthotropic patients. The MRI scan of the right pontine demyelinating lesion from Patient 3 is shown in Figure 1B (arrow). Five of six orthotropic patients had bilateral INO. Of the WEMINO patients, three had ipsilateral hypertropia. Only one WEMINO patient had exotropia contralateral to the INO. Of the six surviving exotropic INO patients, three had complete resolution of the INO and exotropia (Patients 1, 3 and 6), with one patient showing partial resolution of both INO and exotropia (Patient 5). Of the orthotropic patients, only Patient 2 showed resolution of the INO. Student's *t*-test was used to compare differences between exotropic and orthotropic saccade and vestibulo-ocular reflex (VOR) metrics. For all statistical analyses, a two-sided value of $p \leq 0.05$ was considered significant. Statistical analysis was performed with IBM SPSS, version 28.

Oculographic studies

Binocular eye and head movement recordings were undertaken using a magnetic search coil technique (CNC Engineering, Seattle WA) in five of seven WEMINO patients and all six orthotropic patients with INO.[17] Patient 1 was recorded using infrared oculography.[18] Informed consent was obtained from all patients and control subjects. The study protocol was approved by the University Health Network and University of Manitoba Ethics Committees and conformed to the Declaration of Helsinki. Five of six WEMINO patients and all orthotropic INO patients were recorded within one week of presentation. The exotropic eye was patched during the recording so that the non-paretic eye viewed the target, while movements of both eyes were recorded simultaneously. Orthotropic INO patients were not patched. Patients sat in a vestibular chair with the head secured by occipital and brow supports. Horizontal saccades were made to a laser dot target that subtended 0.25 deg and made predictable steps of 10 or 20 degrees and unpredictable steps of 5, 10, 20 and 40 degrees to the right or left of midposition at 3-sec intervals. Horizontal VOR was assessed during sinusoidal *en bloc* head and body rotation at 0.5 Hz (± 10 degrees to either side of midposition) in darkness, without a fixation target.

Analogue signals of the target, gaze (eye-in-space) and head position were digitized online at 200 Hz and analyzed by interactive computer programs as previously described.[17] Eye velocity signals were obtained by digitally differentiating eye position signals. Saccades were identified as previously described.[17,18] Peak velocities and amplitudes of individual saccades were used to calculate the asymptotic peak velocity from a best-fit exponential curve ($PV = V [1 - \exp(-A/C)]$), where PV is peak velocity, V is the asymptotic velocity, A is saccade amplitude and C is a constant). Saccadic gain was defined as the ratio of the initial saccade amplitude to the target amplitude.

As Patient 1 was recorded with infrared oculography, INO was defined as hypometria of adducting saccades with gains less than 0.66 or slow adducting saccades with asymptotic peak velocities less than 305 deg/s.[18] For the remaining 11 patients recorded with scleral search coil, INO was defined as hypometria of adducting saccades with gains less than 0.89 or slow adducting saccades with asymptotic peak velocities below 361 deg/s. Normative data for scleral search coil recordings were obtained from nine control subjects (mean age 34 years; SD 7).

Pathological examination

A 28-year-old patient with WEMINO was examined pathologically (Patient 7). He had been admitted in a coma after an assault, with CT showing bifrontal cerebral contusions, subarachnoid and intraparenchymal hemorrhages and occipital skull fracture. His recovery was complicated by elevated intracranial pressure, generalized seizures and hydrocephalus requiring a ventriculo-peritoneal shunt. He regained consciousness, and 10 weeks after admission, he complained of horizontal diplopia. Examination revealed normal visual acuity, pupils and fundi. He had right homonymous superior quadrantanopsia. In the primary position, he fixated with the left eye and showed right exotropia and right hypertropia in the primary position with complete right INO.

Four months after admission, he died of aspiration pneumonia. Necropsy revealed contusions of both frontal and temporal lobes and hemorrhagic infarction of the inferomedial left temporal and occipital lobes. Histological examination of the upper midbrain showed focal infarcts, lateral to the right MLF; the right oculomotor nerve nucleus was not involved (Figure 2A). In the lower midbrain, infarction was located adjacent to the right MLF and involved the brachium conjunctivum (Figure 2B,C). Sections through upper-mid-pons showed infarction of the right MLF (Figure 2D). There was no involvement of pontine tegmentum left
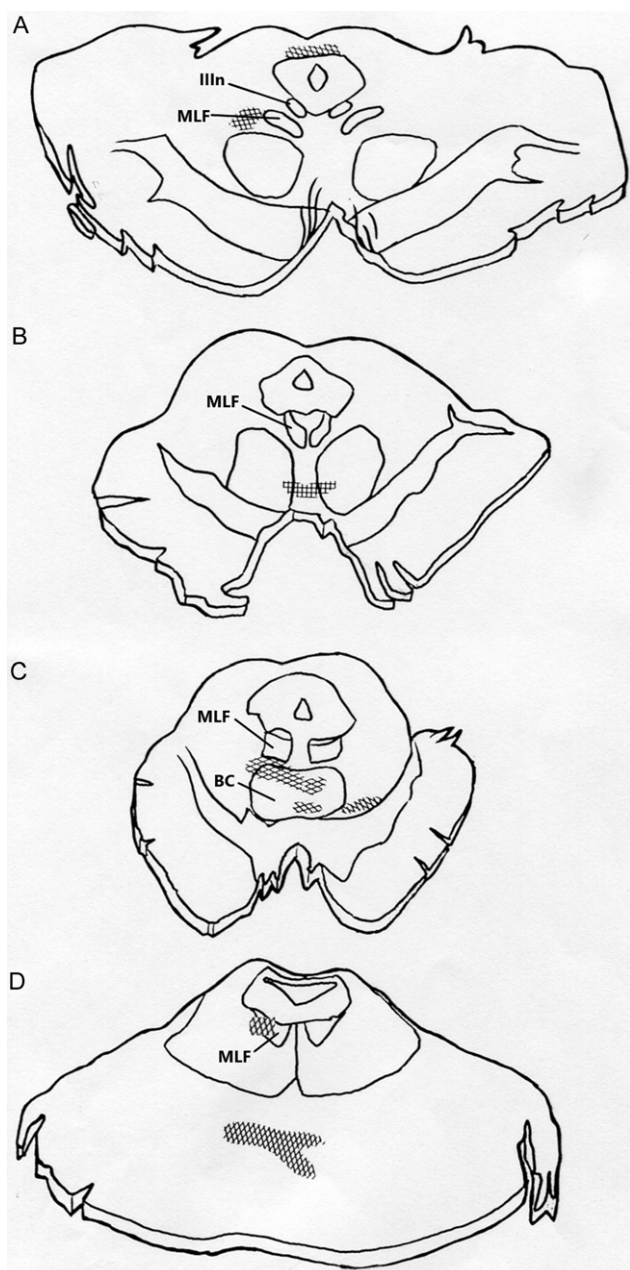
Figure 2. Histological examination of Patient 7's brainstem; hatched areas show regions of infarction. (A) Upper midbrain shows focal infarcts lateral to the right MLF and dorsal to the periaqueductal gray matter with no involvement of either oculomotor nerve nuclei. (B and C) Lower midbrain cuts show infarction adjacent to the right MLF and involving brachium conjunctivum (BC). (D) Upper to mid-pons shows infarction of the right MLF and basis pontis.

of midline. Oculography could not be performed prior to this patient's death.

Results

Saccade metrics

On clinical examination, all seven patients with WEMINO were exotropic, with unilaterally hypometric and slow adducting saccades and abducting nystagmus of the fellow eye. None showed abnormalities of ductions in the fellow eye clinically.

Quantitatively, all exotropic patients showed slow, hypometric adducting saccades ipsilateral to the INO when compared with velocities and gains of normal horizontal saccades (Table 2).

There was no significant difference in mean gains or asymptotic peak velocities of ipsilateral adducting saccades between exotropic and orthotropic INO patients (Table 2). Both exotropic and orthotropic patients had normal peak velocities for ipsilateral adducting saccades less than 5 degrees. Saccade velocities decreased in a similar fashion for both groups of INO patients for larger ipsilateral adducting saccades, compared with control subjects (Figure 3).

For contralesional saccades, quantitative measurements of INO in clinically defined WEMINO patients showed that one patient (Patient 5) had slow, hypometric adducting saccades and two patients (Patients 4 and 6) had slow normometric adducting saccades, all consistent with bilateral INO (WEBINO). In addition to slow contralesional adducting saccades, Patient 6 also had slow, hypometric ipsilateral abducting saccades, slow contralesional abducting saccades and exotropia in the contralateral eye, more in keeping with paralytic pontine exotropia. Otherwise, ipsilateral abducting saccades were of normal asymptotic peak velocity and gain for the orthotropic group and for the remaining five exotropic patients (Table 2).

Ipsilateral abducting saccades had significantly prolonged durations in INO patients, both exotropic (171 ms, SD 10 ms, $p < 0.0001$) and orthotropic (190 ms, SD 34 ms, $p = 0.0193$) compared with control subjects (125 ms, SD 4 ms). Although INO patients would typically make ipsilateral abducting saccades of normal gain and peak velocity, they would intermittently make a series of 3–5 small, hypometric saccades in order to achieve the target (Figure 4). These smaller abducting saccades had greater than normal peak velocities (Figure 5). For orthotropic patients, 97% of 10-degree ipsilateral abducting saccades had velocities greater than two standard deviations above the mean for control subjects (193 deg/sec), compared with 48% of saccades for exotropic patients. These saccades all met the oculographic definition of saccades based on velocity and duration criteria[17] and may represent "fractionation" of larger abducting saccades, as described by Feldon *et al.*[19]

Horizontal vestibulo-ocular reflex (VOR)

Exotropic INO patients had normal mean VOR gains during sinusoidal head rotation at 0.5 Hz for both adduction and abduction, as measured in the eye ipsilateral to the INO (Table 3). Orthotropic INO patients had subnormal mean VOR gains for both abduction and adduction. Orthotropic patients had greater phase leads than exotropic patients, but there were no statistically significant differences between groups.

Discussion

Dr Sharpe coined the term WEMINO in 1979 when he examined Patient 1. He defined it as a "genuine prenuclear disorder" consisting of unilateral INO and exotropia.[10] In WEMINO, the exotropic eye is ipsilateral to the side of the MLF damage, and there is no gaze palsy, unlike paralytic pontine exotropia, which consists of unilateral pontine gaze palsy and INO. Paralytic pontine exotropia is a common element of the one-and-a-half syndrome due to damage to the paramedian pontine reticular formation

Table 2. Horizontal saccade gains and velocities

	Ipsilateral				Contralateral			
	Adducting		Abducting		Adducting		Abducting	
	Mean gain	Asymptotic peak velocity (deg/s)	Mean gain	Asymptotic peak velocity (deg/s)	Mean gain	Asymptotic peak velocity (deg/s)	Mean gain	Asymptotic velocity (deg/s)
Patient 1*	0.58	160	1.13	510	0.75	340	1.00	470
Patient 2	0.69	260	0.94	430	0.89	445	0.91	550
Patient 3	0.88	310	0.9	405	0.89	400	0.87	390
Patient 4	0.69	190	0.84	410	1.02	340	0.95	360
Patient 5	0.28	110	0.79	210	0.64	290	0.84	305
Patient 6	0.58	130	0.63	160	0.91	200	1.01	240
Exotropic INO	0.62 ± 0.20	193	0.87 ± 0.17	354	0.85 ± 0.13	336	0.93 ± 0.07	386
Orthotropic INO ($n = 6$)	0.65 ± 0.14	173	1.05 ± 0.22	364	0.77 ± 0.07	204	0.94 ± 0.11	360
Control subjects ($n = 9$)	0.95 ± 0.03	427 ± 33	0.92 ± 0.05	420 ± 31	0.95 ± 0.03	427 ± 33	0.92 ± 0.05	420 ± 31

*Patient recorded with infrared oculography. Normal mean gain 0.86 ± 0.10; normal asymptotic peak velocity 495 ± 95 deg/sec.[18]
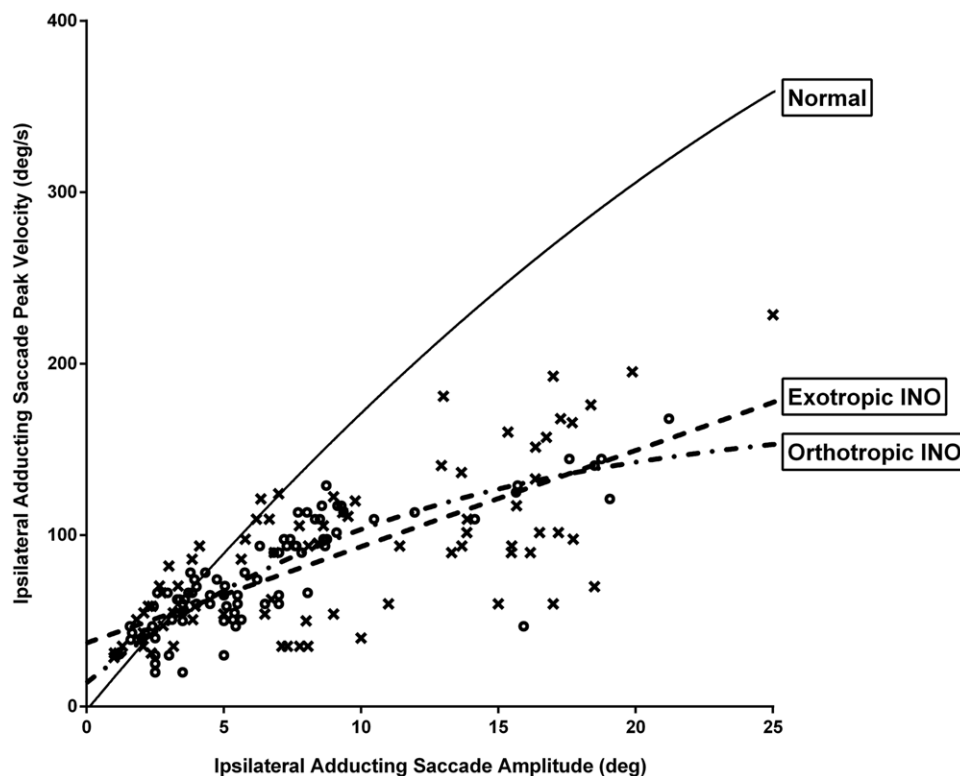
Figure 3. Graphic representation of saccade peak velocity versus saccade amplitude for ipsilateral adducting saccades for internuclear ophthalmoplegia (INO) patients versus control subjects (solid line). Both exotropic and orthotropic INO patients had normal peak velocities for ipsilateral adducting saccades less than 5 degrees and reduced peak velocities for larger ipsilateral adducting saccades compared with control subjects. x are exotropic patients; o are orthotropic patients.

(PPRF) or abducens nucleus and MLF on the same side and producing exotropia of the eye opposite to the side of the unilateral brainstem lesion.[20] This would explain the findings in Patient 6, whose exotropia was contralateral to the INO.

Despite having the characteristic appearance of WEMINO clinically, three of the six patients who underwent oculography showed varying degrees of abnormal adduction of the contralesional eye, thus having WEBINO. Two measures of versional dysconjugacy indices[21,22] were also calculated for these patients; only one patient (Patient 4) was classified as having bilateral INO by these indices.

Anatomy

Four patients had radiological or neuropathological evidence of isolated damage to the MLF in the pontine tegmentum (Patients 2, 3,
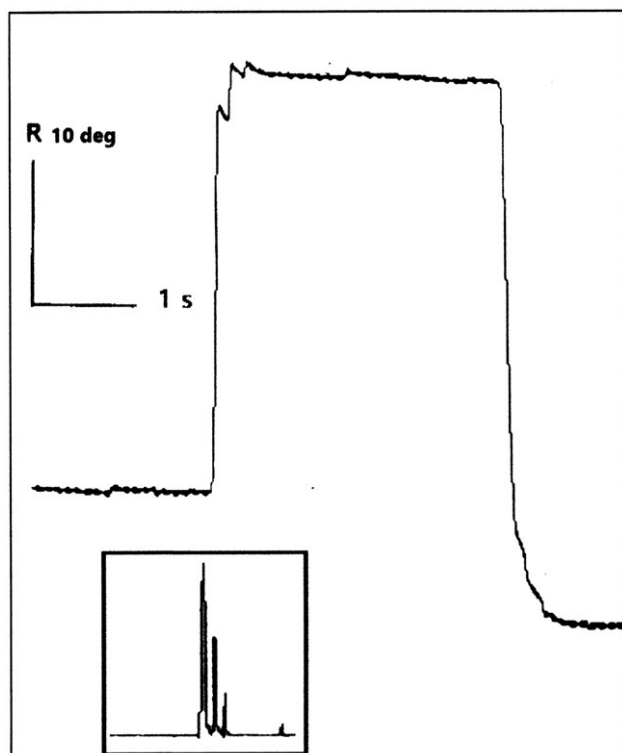
Figure 4. Ocular motor scleral search coil gaze position recording of the right eye of Patient 2 with right internuclear ophthalmoplegia. Rightward saccades are ipsilateral abducting saccades showing a series of four small, hypometric saccades for a 20-degree center-crossing target. Insert shows velocity tracing for the same saccade indicating multiple saccades used to acquire target.

6 and 7). We cannot be certain that the right medial rectus subnucleus was undamaged in Patient 5, but the failure of right eye adduction in this patient was accompanied by abducting nystagmus in the fellow eye, in keeping with INO, not MR palsy.[23] Although oculomotor motor neurons have been found among the fascicles of the MLF, about 1 mm lateral to the oculomotor nucleus,[24] no other patient had involvement likely to include the third nuclear complex.

Of special historical relevance is the first pathological correlation of exotropia and INO that specified damage to the MLF. In 1924, Spiller[5] described a patient with bilateral INO, "marked divergent strabismus" and preserved convergence, resulting from infarction of both MLFs at the level of the trochlear nuclei, sparing the oculomotor nuclei. Gonyea[25] described a WEBINO case with absent convergence, due to infarction of both MLFs in the pons, again sparing the oculomotor nuclei. McGettrick and Eustace[26] attributed the WEBINO syndrome to lesions affecting the PPRF and MLF but provided no radiological or neuropathological support for their speculation. Further cases of WEBINO have been reported with radiological confirmation of damage to the pons or midbrain (see ref 27, 28 for review). Damage to the medial rectus subnucleus of the oculomotor complex is clearly not required to produce exotropia. While we do not know whether our patients had preexisting heterotropias, in those whose INO resolved, their exotropia also resolved, suggesting a common mechanism.

Exotropia and saccade metrics

According to Dr Sharpe, one of the enigmas regarding INO is the typical orthotropia during forward gaze. Surgical lesions of both MLFs in monkey pons[29,30] produce exotropia with preserved convergence, while chemical damage to one MLF produces exophoria of the ipsilateral eye that increases with the degree of dysfunction.[31] Horizontal burst-tonic fibers travel within the
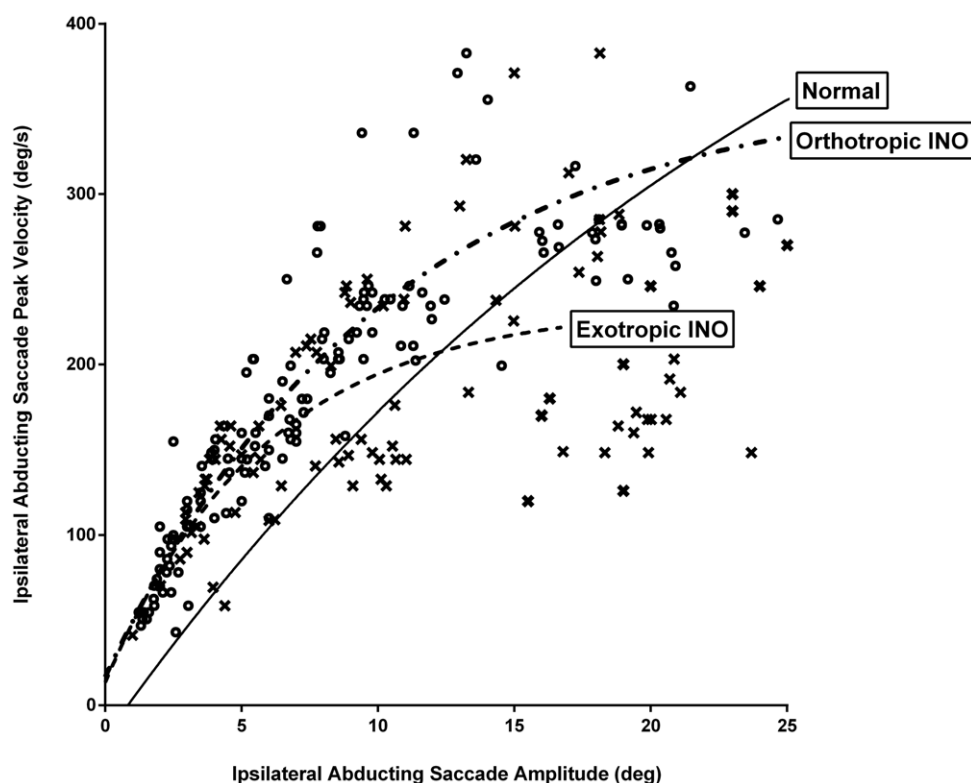
Figure 5. Graphic representation of saccade peak velocity versus saccade amplitude for ipsilateral abducting saccades for internuclear ophthalmoplegia (INO) patients versus control subjects (solid line). For orthotropic patients, 97% of 10-degree ipsilateral abducting saccades had velocities greater than two standard deviations above the mean for control subjects (193 deg/sec), compared with 48% of ipsilateral abducting saccades for exotropic patients. x are exotropic patients; o are orthotropic patients.

Table 3. Horizontal vestibulo-ocular reflex (VOR) gains and phases

	Sinusoidal VOR 0.5 Hz		
	Adducting gain	**Abducting gain**	**Phase**
Exotropic INO	0.73 ± 0.05	0.74 ± 0.08	−0.5 ± 1.0
Orthotropic INO	0.64 ± 0.14	0.66 ± 0.15	−2.6 ± 2.3
Normal	0.88 ± 0.10	0.90 ± 0.11	4.5 ± 3.1

medial portion of the MLF, arising from the contralateral abducens nucleus and projecting to the ipsilateral medial rectus subnucleus.[32] These fibers discharge with bursts before and during saccades in the on-direction and fire tonically at rates linearly related to eccentric horizontal eye position during fixation.[32,33] Burst-tonic MLF fiber activation occurs over a large range, beginning as far as 65 degrees in the off direction,[33] which could account for exotropia with isolated MLF lesions.

In our study, all INO patients had ipsilateral abducting saccades with increased peak velocities for saccades of under 10 degrees amplitude. In monkeys, discrete chemical lesions of the MLF cause hypometric abducting saccades with increased peak velocities.[31] Feldon *et al.*[19] showed normometric, slightly slowed ipsilateral abducting saccades with prolonged durations, similar to our patients. These saccades were "fractionated," and their small components had higher than normal velocities. This phenomenon was attributed to deficient ipsilateral medial rectus inhibition.[19] Normally, the ipsilateral medial rectus is switched off during contralateral saccades, but intermittent braking exerted on abducting saccades by unopposed inhibitory signals produces saccades with prolonged duration, normal amplitude and velocity and faster small subcomponents, similar to those seen in our INO patients.[19] Inhibitory signals to medial rectus motor neurons project from the ipsilateral pontine reticular formation,[34,35] likely coursing ventral to the MLF in the pontine tegmentum,[36,37] but inhibitory signals to the medial rectus subnucleus have not been recorded in the MLF of monkeys.[32] Thomke *et al.*[38] proposed "abduction paresis of prenuclear origin" resulting from damage to an uncrossed pathway ascending adjacent to the MLF that carries inhibitory fibers to the medial rectus subnucleus. Their patients were typically orthophoric or esotropic and had slowing of large abducting saccades (>20–40 degrees); smaller saccade amplitudes were not tested.[38] Localization of the lesions in their patient cohort was undertaken with electrophysiological studies and was not verified by neuroimaging. The abduction paresis was attributed to impaired inhibition of the tonic activity of the medial rectus muscle during lateral gaze. On the basis of these studies, if tonic inhibition of the ipsilateral medial rectus motor neurons is lost, orthophoria or esotropia results, and small ipsilateral abducting saccades have longer durations and higher than normal velocities. While almost all small ipsilateral abducting saccades in our orthotropic group had increased peak velocities, fewer ipsilateral abducting saccades had increased peak velocities in the exotropic group, suggesting greater maintenance of tonic ipsilateral medial rectus inhibition.

Pola and Robinson[39] postulated that the eyes usually remain horizontally aligned in INO because a lesion of one MLF causes decreased excitation of the ipsilateral medial rectus and decreased inhibition of the contralateral medial rectus, deviating the eyes conjugately toward the side of the MLF lesion. The brain adjusts for this deviation with an equal and opposite conjugate command, keeping the eyes orthotropic. However, there has been no anatomical confirmation of a crossed inhibitory pathway to the contralateral medial rectus subnucleus.

Vestibular function

Exotropic INO patients had normal mean VOR gains during sinusoidal *en bloc* head rotation for both adduction and abduction, as measured in the eye ipsilateral to the INO, compared with orthotropic INO patients who showed subnormal mean VOR gains for both abduction and adduction. Aw *et al.*[40] measured vestibular function in orthotropic INO patients with head impulse testing. Their testing showed reduced horizontal VOR gains for adducting compared with abducting eye movements. Using slower impulse vestibular stimulation, we had previously shown similar, but symmetrical reductions in INO patients.[41] VOR latency was not prolonged, and we concluded that the direct VOR pathway in the MLF was intact enough to initiate a response, without delay, albeit at much lower gain. Steady-state sinusoidal VOR gains were normal, suggesting integrity of vestibular pathways carrying integrated position signals outside of the MLF, such as the Ascending Tract of Dieters (ATD). The ATD is an uncrossed excitatory ocular motor pathway arising from the ventral part of the lateral vestibular nucleus, passing through the ipsilateral abducens nucleus without synapsing and coursing lateral to the MLF, to excite ipsilateral medial rectus motor neurons, inferior rectus motor neurons and the Edinger–Westphal complex.[42–44] Axons of the ATD excite the medial rectus during ipsilateral angular and linear head movement.[42,45] In our cohort of orthotropic patients, VOR gains were subnormal and showed phase leads, suggesting damage to indirect, extrafascicular VOR pathways carrying integrated vestibular eye position signals.[41]

Conclusion

WEMINO is an uncommon clinical variant of INO described by Dr J. A. Sharpe initially in 1979. It is best defined as a clinical ocular motor syndrome characterized by unilateral slow or hypometric adducting saccades or both, with exotropia and hypertropia of the ipsilateral eye.

Common to both orthotropic and exotropic INO patients is a lesion in the MLF that damages burst-tonic fibers carrying velocity and position commands to medial rectus motor neurons, causing ipsilateral paresis of adduction. There is a clear overlap with WEBINO, which can be explained by extension of damage to include the contralateral MLF. Damage to direct VOR pathways transmitted through the MLF may reduce initial VOR gains in all INO patients; however, steady-state VOR gains are normal in exotropic patients and subnormal in orthotropic patients, with greater phase leads suggesting damage to indirect VOR pathways outside the MLF in orthotropic patients. Finally, the loss of tonic inhibition of ipsilateral medial rectus motor neurons results in orthotropia, longer duration ipsilateral abducting saccades and

small, possibly "fractionated" ipsilateral abducting saccades with increased peak velocities. While small, fast ipsilateral abducting saccades occurred in both orthotropic and exotropic cohorts, fewer ipsilateral abducting saccades had increased peak velocities in the exotropic group, suggesting greater maintenance of tonic ipsilateral medial rectus inhibition. Inhibitory signals to the medial rectus do not travel in the MLF but likely ascend ventral to the MLF in the pontine tegmentum. Therefore, orthotropia requires paramedian damage to extend beyond the MLF, ventrally and laterally, involving integrated vestibular position signals in the ATD and inhibitory connections to the ipsilateral medial rectus subnucleus. Exotropic INO patients (both WEMINO and WEBINO) may have more discrete damage to the MLF with limited involvement of extrafascicular pathways. In neither case is damage to medial rectus motor neurons required.

References

1. Ranalli PJ, Morrow A. James A. Sharpe, MD, FRCP(C) (1941-2013). *J Neuro-Ophthalmol.* 2014;34:e6–e7. DOI: 10.1097/WNO.0000000000000139.

2. Barton JJS, Hershenfeld SA, Johnston JL, et al. James Sharpe's contributions to neurology and neuro-ophthalmology: a posthumous Tribute 10 Years on. *Can J Neurol Sci.* 2023;51:1–5. DOI: 10.1017/cjn.2023.15.

3. Hoyt WF, Daroff RB. Supranuclear disorders of ocular control systems in man. In: Bach-y-Rita P, Collins CC, ed. *The Control of Eye Movements.* Academic Press; 1971: 175–235.

4. Cogan DG. Internuclear ophthalmoplegia, typical and atypical. *Arch Ophthalmol.* 1970;84:583–9.

5. Spiller WG. Ophthalmoplegia internuclearis anterior: a case with necropsy. *Brain.* 1924;47:345–57.

6. Leigh RJ, Zee DS. *The Neurology of Eye Movements, 5 edn, Contemporary Neurology Series.* Oxford Academic; 2015: 864. https://doi.org/10.1093/med/9780199969289.001.0001

7. Zwergal A, Cnyrim C, Arbusow V, et al. Unilateral INO is associated with ocular tilt reaction in pontomesencephalic lesions: INO plus. *Neurology.* 2008;71:590–3.

8. Cogan DG, Kubik CS, Smith WL. Unilateral internuclear ophthalmoplegia: report of eight clinical cases with one postmortem study. *AMA Arch Ophthalmol.* 1950;44:783–96. DOI: 10.1001/archopht.1950.00910020796002.

9. Fine M, MacGlashan CB. Unilateral internuclear ophthalmoplegia of vascular origin. *AMA Arch Ophthalmol.* 1956;56:327–37. DOI: 10.1001/archopht.1956.00930040335002.

10. Johnston JL, Sharpe JA. The WEMINO syndrome - wall-eyed monocular internuclear ophthalmoplegia: An oculographic and neuropathologic characterization. *Neurology.* 1994;44(Suppl 2):A310.

11. Ikeda Y, Okamoto K. Lesion responsible for WEMINO syndrome confirmed by magnetic resonance imaging. *J Neurol Neurosurg Psychiatry.* 2002;73:202–9.

12. Jeon SB, Chung SJ, Ahn H, Lee J-H, Jung JM, Lee MC. Wall-eyed monocular internuclear ophthalmoplegia (WEMINO) with contraversive ocular tilt reaction. *J Clin Neurol.* 2005;1:101–3.

13. Tsuda H, Kamata K, Tanaka K, Kishida S. WEMINO syndrome with skew deviation and facial palsy. *Intern Med.* 2011;50:2435–6. DOI: 10.2169/internalmedicine.50.6226.

14. Ceballos-Lizarragaa R, Palomino-Díazb C, Romero-Figueroac JA. Wall-eyed monocular internuclear ophthalmoplegia (WEMINO) and Millard-Gubler syndromes in a patient with isolated pontine infarction: topographic, oculomotor, and radiological analysis of two very uncommon conditions. *Case Rep Neurol.* 2019;11:230–7. DOI: 10.1159/000501794.

15. Chandran SR, Balakrishnan RK, Umakanthan K, Govindarajan K. Neurocysticercosis presenting as isolated wall-eyed monocular internuclear ophthalmoplegia with contraversive ocular tilt reaction. *J Neurosci Rural Pract.* 2012;3:84–8.

16. Shaikh AG, Ghasia FF, Rasouli G, DeGeorgia M, Sundararajan S. Acute onset of upbeat nystagmus, exotropia, and internuclear ophthalmoplegia—A tell-tale of ponto-mesencephalic infarct. *J Neurol Sci.* 2013;332:56–8. DOI: 10.1016/j.jns.2013.06.012.

17. Johnston JL, Miller JD, Nath A. Ocular motor dysfunction in HIV 1 infected subjects: a quantitative oculographic analysis. *Neurology.* 1996;46:451–7.

18. Sharpe JA, Zackon DH. Senescent saccades: effects of aging on their accuracy, latency and velocity. *Acta Oto-Laryngol.* 1987;104:422–8. DOI: 10.3109/00016488709128270.

19. Feldon SE, Hoyt WF, Stark L. Disordered inhibition in internuclear ophthalmoplegia. Analysis of eye movement recordings with computer simulations. *Brain.* 1980;103:113–37.

20. Sharpe JA, Rosenberg MA, Hoyt WF, Daroff RB. Paralytic pontine exotropia. *Neurology.* 1974;24:1076–81.

21. Frohman EM, Frohman TC, O'Suilleabhain P, et al. Quantitative oculographic characterization of internuclear ophthalmoparesis in multiple sclerosis: the versional dysconjugacy index Z score. *J Neurol Neurosurg Psychiatry.* 2002;73:51–5.

22. Nij Bijvank JA, van Rijn LJ, Balk LJ, Tan HS, Uitdehaag BMJ, Petzold A. Diagnosing and quantifying a common deficit in multiple sclerosis: internuclear ophthalmoplegia. *Neurology.* 2019;92:e2299–e2308. DOI: 10.1212/WNL.0000000000007499.

23. Al-Sofiani M, Kwen PE. Isolated medial rectus nuclear palsy as a rare presentation of midbrain infarction. *Am J Case Rep.* 2015;16:715–8. DOI: 10.12659/AJCR.893875.

24. Buttner-Ennever JA, Akert K. Medial rectus subgroups of the oculomotor nucleus and their abducens lnternuclear input in the monkey. *J Comp Neurol.* 1981;197:17–27.

25. Gonyea EF. Bilateral internuclear ophthalmoplegia. Association with occlusive cerebrovascular disease. *Arch Neurol.* 1974;31:168–73.

26. McGettrick P, Eustace P. The w.e.b.i.n.o syndrome. *Neuro-Ophthalmol.* 1985;5:109–15.

27. Uzawa A, Takeda Y, Kuwabara S. Wall-eyed bilateral internuclear ophthalmoplegia by ischemic stroke case report and literature review. *Neurologist.* 2020;25:82–4. DOI: 10.1097/NRL.0000000000000271.

28. Chen C-M, Sung-Hsiung Lin S-H. Wall-eyed bilateral internuclear ophthalmoplegia from lesions at different levels in the brainstem. *J Neuro-Ophthalmol.* 2007;27:9–15.

29. Evinger LC, Fuchs AF, Baker R. Bilateral lesions of the medial longitudinal fasciculus in monkeys: effects on the horizontal and vertical components of voluntary and vestibular induced eye movements. *Exp Brain Res.* 1977;28:1–20.

30. de Jong JMBV, Cohen B, Matsuo V, Uemura T. Midsagittal pontomedullary brain stem section: effects on ocular adduction and nystagmus. *Exp Neurology.* 1980;68:420–42.

31. Gamlin PDR, Gnadt JW, Mays LE. Lidocaine-induced unilateral internuclear ophthalmoplegia: effects on convergence and conjugate eye movements. *J. Neurophysiol.* 1989;62:82–95.

32. Pola J, Robinson DA. Oculomotor signals in the medial longitudinal fasciculus of the monkey. *J Neurophysiol.* 1978;41:245–59.

33. King WM, Lisberger SG, Fuchs AF. Responses of fibers in the medial longitudinal fasciculus (MLF) of alert monkeys during horizontal and vertical conjugate eye movements evoked by vestibular or visual stimuli. *J Neurophysiol.* 1976;39:1135–49.

34. Highstein SM, Cohen B, Matsinami K. Monosynaptic projections from the pontine reticular formation to the IIIrd nucleus in the cat. *Brain Res.* 1974;15:340–4.

35. Grantyn A, Grantyn R, Gaunitz U, Robine KP. Sources of direct excitatory and inhibitory inputs from the medial rhombencephalic tegmentum to

lateral and medial rectus motoneurons in the cat. *Exp Brain Res.* 1980;39:49–61.

36. Buttner-Ennever JA, Miles TA, Henn V. The role of the pontine reticular formation in oculomotor function. *Exp Brain Res.* 1975;23 (Suppl 23):31.

37. Buttner-Ennever JA, Henn V. An autoradiographic study of the pathways from the pontine reticular formation involved in horizontal eye movements. *Brain Res.* 1976;208:155–64.

38. Thomke F, Hopf HC, Kramer F. Internuclear ophthalmoplegia of abduction: clinical and electrophysiological data on the existence of an abduction paresis of prenuclear origin. *J Neurol Neurosurg Psychiatry.* 1992;55:105–11.

39. Pola J, Robinson DA. An explanation of eye movements seen in internuclear ophthalmoplegia. *Arch Neurol.* 1976;33:447–52.

40. Aw ST, Chen L, Todd MJ, Barnett MH, Halmagyi GM. Vestibulo-ocular reflex deficits with medial longitudinal fasciculus lesions. *J Neurol.* 2017;264:2119–29. DOI: 10.1007/s00415-017-8607-8.

41. Sharpe JA, Johnston JL. The vestibulo-ocular reflex. Clinical, anatomical and physiological correlates. In: Sharpe JA, Barber HO, ed. *The Vestibulo-Ocular Reflex and Vertigo.* Raven Press; 1992: 15–39.

42. Reisine H, Strassman A, Highstein SM. Eye position and head velocity signals are conveyed to medial rectus motoneurons in the alert cat by the ascending tract of Deiters. *Brain Res.* 1981;211:153–7.

43. McCrea RA, Strassman A, May E, Highstein SM. Anatomical and physiological characteristics of vestibular neurons mediating the horizontal vestibulo-ocular reflex of the squirrel monkey. *J Comp Neurol.* 1987;264:547–70.

44. Zwergal A, Strupp M, Brandt T, Buttner-Ennever JA. Parallel ascending vestibular pathways. *Ann N York Acad Sci.* 2009;1164:51–9. DOI: 10.1111/j.1749-6632.2009.04461.x.

45. Chen-Huang C, McCrea RA. Viewing distance related sensory processing in the ascending tract of Deiters vestibulo-ocular reflex pathway. *J Vest Res.* 1998;8:175–84.