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# MRI characteristics of the MLF in MS patients with chronic internuclear ophthalmoparesis

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**Article abstract**—*Objective:* The authors imaged the medial longitudinal fasciculus (MLF) in 58 patients with MS and chronic internuclear ophthalmoparesis (INO) to determine which MRI technique best shows the characteristic lesion associated with this ocular motor syndrome. *Methods:* Using quantitative infrared oculography, the authors determined the ratios of abduction to adduction for velocity and acceleration, to confirm the presence of INO and to determine the severity of MLF dysfunction in 58 patients with MS and INO. Conventional MRI techniques, including proton density imaging (PDI), T2-weighted imaging, and fluid-attenuated inversion recovery (FLAIR) imaging, were used to ascertain which technique best shows MLF lesions within the brainstem tegmentum. T1-weighted imaging was performed to determine the frequency of brainstem tegmentum hypointensities. *Results:* All patients studied had evidence of an MLF lesion hyperintensity on PDI, whereas T2-weighted imaging and FLAIR imaging showed these lesions in 88% and 48% of patients, respectively. With PDI, dorsomedial tegmentum lesions were seen in the pons in 93% of patients and in the midbrain of 66% of patients. Lesions were observed at both locations in 59% of patients. One patient had an MLF lesion with a corresponding T1 hypointensity. *Conclusions:* PDI best shows the MLF lesion in patients with MS and INO.

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The use of MR techniques has substantially improved our ability to confirm the diagnosis of MS, monitor therapeutic responses to drug treatments, and to monitor the progression of the disease process.<sup>1-7</sup> In general, there appears to be a weak correlation between the neuroanatomic burden of disease, as measured by brain MRI, and clinical disability.<sup>8-12</sup> There appears to be a more convincing correlation between white matter imaging abnormalities associated with isolated neurologic syndromes, such as optic neuritis and internuclear ophthalmoparesis (INO).<sup>13-16</sup> INO is one of the most localizing brainstem syndromes in patients with MS and has been observed in 17% to 41% of patients.<sup>17-19</sup> INO is characterized by adduction slowing, with or without eye movement limitation, and abduction nystagmus in the fellow eye during horizontal saccades. This characteristic abnormality is related to a lesion in the medial longitudinal fasciculus (MLF) in the pontine or midbrain tegmentum, which is most com-

monly caused by MS.<sup>20</sup> The high frequency of this syndrome in patients with MS may relate to the localization of the ocular motor apparatus in the region of the brainstem periventricular zone, an area that is highly predisposed to inflammatory demyelination.

Internuclear ophthalmoparesis is best confirmed with the use of eye movement recordings and the calculation of the ratio of saccade pairs (abducting eye to adducting eye) for velocity and acceleration, the versional disconjugacy index (VDI).<sup>21-23</sup> Many patients with INO have been shown to have MRI abnormalities on T2-weighted images, corresponding to the MLF in the pontine and midbrain tegmentum.<sup>13,24-26</sup> MRI may be helpful in confirming a lesion in the MLF, but not all patients with INO have been reported to have characteristic lesions.<sup>13,24,25,27,28</sup> To date, there has been no detailed analysis confirming the superiority of specific MR techniques in showing the greatest lesion conspicuity in the MLF. We report

**See also pages 751 and 887**

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the results of our investigation into the MRI characteristics of the MLF lesion in 58 patients with definite MS and oculo-graphically confirmed chronic INO.

**Methods.** *Patient characteristics.* We studied 58 patients with clinically definite MS who had evidence of chronic INO (n = 109) that were clinically evident for at least 6 months and confirmed by quantitative infrared oculo-graphy. The study protocol was approved by the University of Texas Southwestern Medical School's investigative review board.

*Eye movement recording techniques.* Our objective was to confirm adduction slowing consistent with INO and to show evidence of occult INO in the other eye, in those patients that clinically appeared to have unilateral INO. Furthermore, we sought to determine whether the severity of the INO would correlate with the presence of the MLF lesion on different conventional MRI techniques.

Eye movements were recorded using two-dimensional infrared video oculo-graphy (EyeLink; SMI, Berlin, Germany). The binocular recordings were performed at a sampling rate of 250 Hz with a resolution of 0.01°. A third camera tracks four infrared markers mounted to a visual stimulus and provides corrections for head movement. Patients were seated 100 cm away from a light-emitting diode (LED) board and fitted with a lightweight headband-mounted eye tracking system. Their heads were stabilized with a chin-rest. Because patients were tested in dark conditions, they were dark adapted for 10 minutes before recording sessions.

A calibration was performed using red LED located at straight ahead, +20° and -20° vertically, and +30° and -30° horizontally. All patients were able to perceive the red LED targets. Each eye was calibrated separately. Patients with INO and evidence of ocular limitation that precluded good calibration were excluded from the study. After calibration, the patient was then instructed to make centrifugal saccades to LED that were illuminated in a pseudorandom sequence. The LED were located straight ahead, -30°, -20°, +20°, and +30° along the horizontal axis. Every other saccade was to a central, straight-ahead position. The patients performed approximately 20 saccades to each eccentric LED location. Horizontal and vertical eye movements were recorded from each eye separately under conditions of binocular viewing. Saccades accompanied by blinks and saccades that proceeded the stimulus or had latency of less than 100 milliseconds were excluded from evaluation. Eye movement data were analyzed offline using an in-house program written in Matlab. The interactive program smoothed eye position data with a 100-Hz bandwidth filter and then was used to determine centrifugal saccade peak velocity, peak acceleration, latency, and amplitude.

*The VDI.* Analysis of saccade pair (abducting eye to adducting eye) ratios (VDI) appears to be the most useful parameter in the analysis of peak acceleration and velocity differences between control subjects and patients with INO.<sup>21,23</sup> This type of analysis minimizes technique-dependent intraindividual and interindividual variations observed with monocular absolute saccade parameter values. The normal ranges for these values were derived from 40 control subjects.

**Table MRI acquisition sequences**

Sequence	Repetition time	Echo time	Field of view	No. of excitations
T1	650	14	20 × 20; 256 × 224	2
T2	4,000	125	20 × 20; 256 × 512 or 220 × 256	2
PDI	4,000	21	12 × 12; 256 × 512 or 140 × 256	2
FLAIR (TI = 2,000)	9,500	105	20 × 20; 160 × 256	1

PDI = proton density imaging; FLAIR = fluid-attenuated inversion recovery; TI = inversion time.

*Z-score analysis of VDI.* The Z-scores for individual patients with MS and INO were determined for velocity and acceleration by subtracting the mean values of the VDI derived from control subjects from the VDI values derived from each patient with INO and then dividing by the SD from the normal control mean for VDI.

$$\text{VDI Z-score} = (\text{mean VDI}_{\text{INO}} - \text{mean VDI}_{\text{NC}}) / (\text{SD NL mean})$$

The VDI Z-score indicates the number of standard deviations away from the mean of our normal control population. Velocity and acceleration were assessed separately. VDI for acceleration was always higher (more sensitive) than that for velocity but with a higher degree of variability on repeated measures analysis (higher coefficient of variation). As such, the Z-scores for velocity measures were higher than those derived for acceleration measures. The velocity Z-score is preferred in that, compared with acceleration Z-scores, it provides a more reliable measure by which to discriminate abnormal VDI values derived from patients with INO compared with those derived from control subjects. To satisfy oculo-graphic criteria for INO diagnosis, we used a VDI for velocity of greater than or equal to 1.234, which represents approximately two standard deviations away from the highest VDI value obtained from a control subject (highest normal control VDI, 1.09) and approximately four standard deviations away from the mean value of the VDI derived from the control group (velocity  $\text{VDI}_{\text{NC}}$ ,  $0.922 \pm 0.072$ ).

*MRI analysis.* Image acquisition was performed with a 1.5-T MRI scanner (GE, Milwaukee, WI) that generated 3-mm thick axial slices with a 0.3-mm gap. Specific imaging sequences were used to provide T1, T2, proton density imaging (PDI), and fluid-attenuated inversion recovery (FLAIR) weighting (table).

*Image analysis.* The brainstem tegmentum was evaluated across the caudal-rostral extent of the MLF using 3-mm thick axial slices with a 0.3-mm gap. Lesions in the dorsomedial brainstem tegmentum (pontine or midbrain) were characterized by a hyperintensity on T2-weighted imaging, PDI, or FLAIR imaging sequences or by a hypointensity on T1-weighted scans. Care was taken not to confuse the normal-appearing pseudohyperintensity of the dorsomedial brainstem tegmentum with true lesion conspicuity.<sup>13,27</sup>

**Results.** *Infrared oculo-graphy.* Of our 58 patients with MS, 51 (88%) had oculo-graphic evidence of bilateral INO,

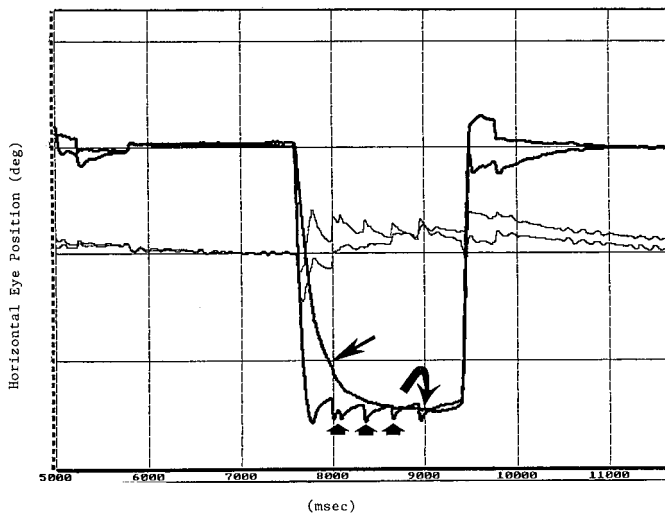


Figure 1. An infrared oculogram illustrates a 30° leftward saccade. Classic features of internuclear ophthalmoparesis are shown, including slowing of the adducting eye (large straight arrow) and abduction nystagmus (small arrows). Ultimately, the slow adducting eye achieves the target (curved arrow).

and 7 (12%) were unilateral (109 total). Infrared oculograms showed the classic features of INO, including adduction slowing and abduction nystagmus in the fellow eye (figure 1). A number of the cases of INO identified oculographically were not evident on clinical examination, even when observing the saccadic phase of optokinetic nystagmus. In fact, a number of patients who were suspected of having unilateral INO were found to have significant bilateral adduction slowing on infrared oculography. The least severe INO group had VDI values from 1.24 to 1.50, which corresponded to Z-scores of 4.4 to 8 for velocity and 2.9 to 5.7 for acceleration. In the most severe group, characterized by a VDI range of 4.5 to 5.0, the Z-scores were 49.7 to 56.6 for velocity and 37.6 to 42.9 for acceleration. These observations show the striking ability to discriminate between patients with INO and control subjects, including those with the most subtle component of adduction slowing.

**MRI analysis of the MLF in INO.** Of the 58 patients with MS and INO, all were found to have evidence of an

abnormality in the region of the MLF on PDI. Fifty-one (88%) had MLF lesions on T2-weighted imaging, and only 28 (48%) were evident on FLAIR imaging. Although two different fields of view were assessed for PDI and T2-weighted images (table), we did not find any differences between them in our ability to show a definite MLF lesion, although lesion conspicuity was superior for the 512 matrix than for the 256 matrix.

Fifty-four (93%) patients had lesions in the pontine MLF region (figure 2). Even in circumstances in which T2-weighted and FLAIR imaging techniques were equivocal in showing the MLF lesion, PDI provided clear confirmation of lesion conspicuity (figure 3). With PDI, 38 (66%) had lesions in the midbrain ventral to the cerebral aqueduct (figure 4), and 34 (59%) had lesions at both locations. Evidence of T1 hypointensity (short repetition time [TR] and short echo time [TE]) in the region of the MLF was observed in only one (2%) patient. The lesional abnormality was large and extended into the right lateral pons spanning portions of the tegmentum and basis pontis. In all other cases, tegmentum hypointensity could not be identified.

There was no correlation between the severity of the VDI of INO with the presence or absence of an MLF lesion on any imaging technique. Subjectively, larger lesions did not appear to predict a more severe VDI. Furthermore, those patients with unilateral INO did not appear to have MLF lesions restricted to the involved side, but instead had lesions that crossed the midline of the brainstem tegmentum. This is not surprising because of the recognized heterogeneity and poor specificity of lesions identified by conventional MRI techniques (T2, PDI, and FLAIR).

Only two (29%) of the seven patients with unilateral INO had evidence of an MLF lesion on FLAIR imaging, compared with 51% of patients with bilateral INO. This observation suggests that dorsomedial brainstem tegmentum lesions large enough to cross the midline and involve both MLF, are more likely to produce sufficient conspicuity to be identified on FLAIR imaging compared with those that are restricted to one side. In contrast, all the unilateral cases were found to have identifiable lesions by PDI.

**Discussion.** Our neurophysiologic observations with infrared video oculography, using the VDI, show the ability to discriminate between patients

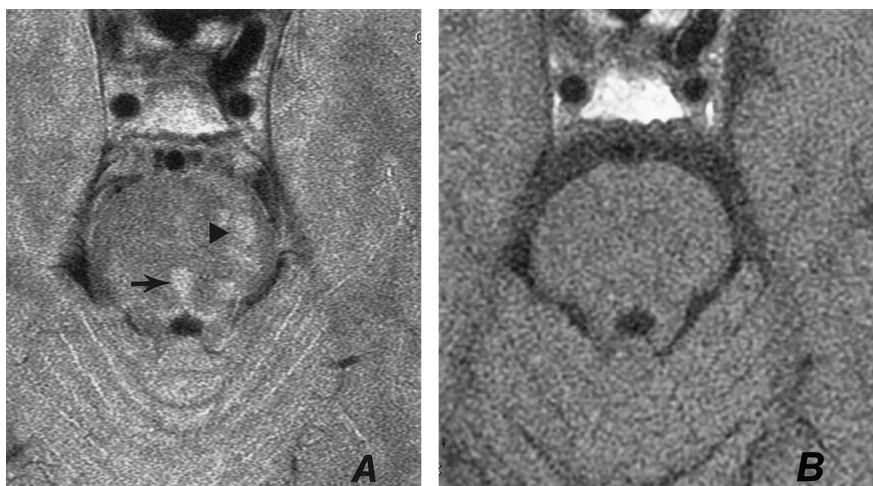
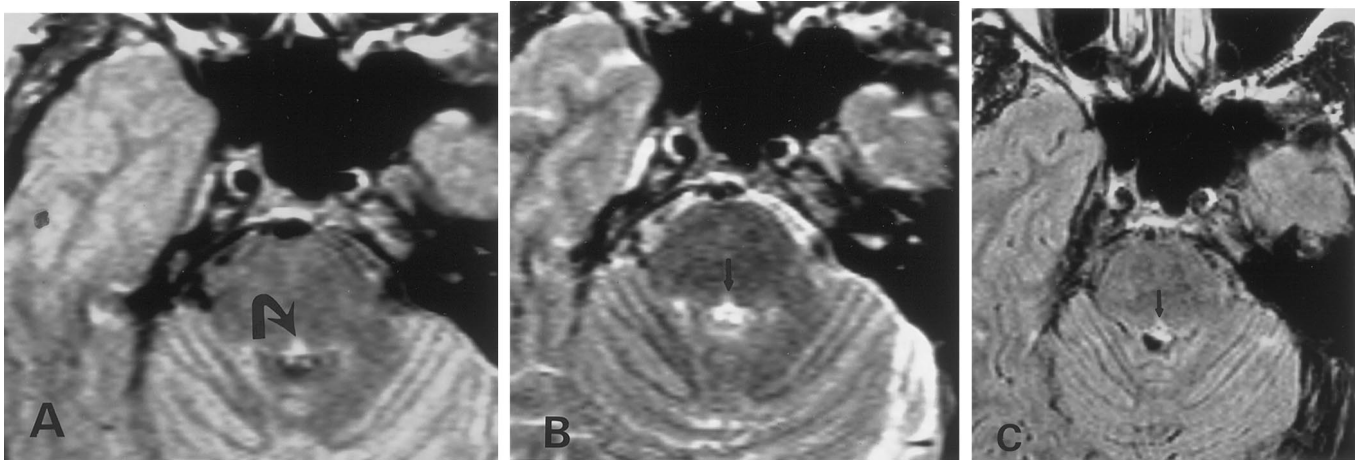


Figure 2. (A) A lesion in the dorsomedial pons (arrow) is illustrated on proton density imaging (256 × 512 matrix) that extends into the ventral tegmentum. Other areas of hyperintensity are also evident (arrowhead). (B) A T1-weighted scan from the corresponding level fails to show any hypointensity or black holes.



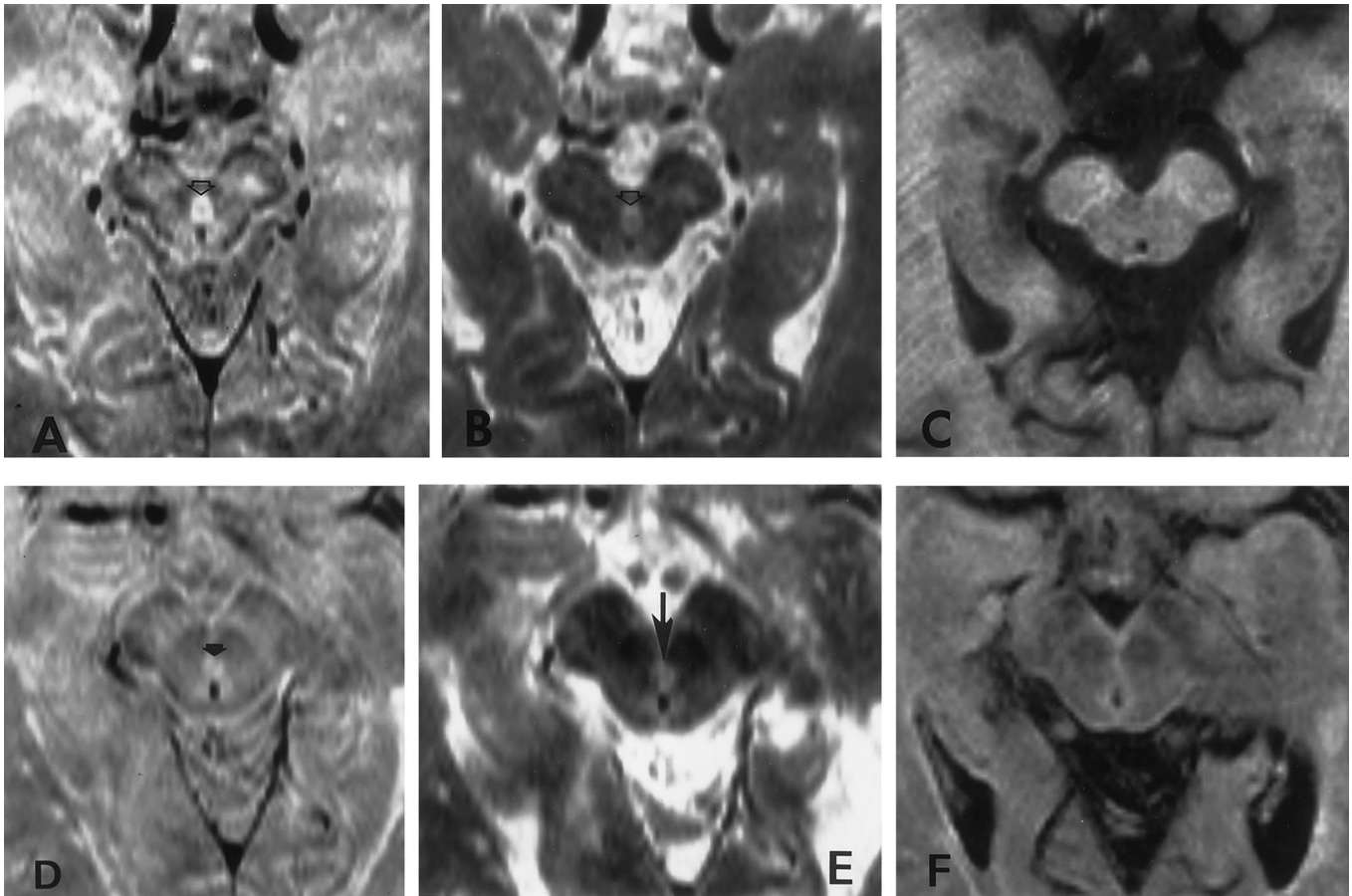
*Figure 3. In this sequence of images, an inconspicuous abnormality extending from the subependymal zone of the pontine tegmentum (curved arrow) is confirmed on proton density imaging (140 × 256 matrix) (A), but not with T2-weighted imaging (220 × 256 matrix) (B) or fluid-attenuated inversion recovery (C) imaging techniques. Although there is the suggestion of hyperintensity (arrows) on T2-weighted and fluid-attenuated inversion recovery imaging, this finding could easily be confused with the normal pseudohyperintensity that is commonly observed in this region of the brainstem.*

with INO and healthy control subjects, including those with the most subtle component of adduction slowing. In fact, many of the mildest cases of INO evaluated with oculography were occult on clinical grounds. The identification of INO in patients with MS may be important in that it may confirm evidence of a second site of inflammatory demyelination, confirming dissemination of lesions in the CNS. For example, evidence of subclinical slowing of adduction in patients with monosymptomatic optic neuritis significantly increases the likelihood of developing clinically definite MS. In one study, 22 patients were examined and 9 were shown to have evidence of adduction slowing by oculography. Seven (78%) of the nine patients developed definite MS within 2.2 years.<sup>29</sup>

In a study that examined nine patients with definite MS and INO, four were shown to have MLF region lesions on T2 spin-echo imaging with a 0.5-T magnet and slice thickness of 5 to 9 mm.<sup>25</sup> The lower magnetic field strength and larger image slice thickness may have accounted for the lower detection rate of lesions compared with that in our study. In contrast, the ability of PDI (at 1.5 T with 3-mm cuts) to confirm the presence of an MLF lesion in each of our 58 patients with oculographically confirmed INO suggests that careful imaging analysis can show a lesion in an eloquent neuroanatomic pathway in most patients. Syndromes related to lesions in the posterior fossa and spinal cord are responsible for a significant component of MS-related disability. Our results show that all the patients with confirmed INO have evidence of high signal intensity abnormalities in the brainstem tegmentum in the region of the MLF, which is best identified with PDI. The reduced capability of FLAIR and T1-weighted MR techniques to identify such lesions, as compared with PDI, strongly suggests that imaging batteries for MS should include PDI sequences.

In this study, it was common to identify MLF region lesions at multiple brainstem levels. As such, it is generally not feasible to ascertain which area of conspicuity constitutes the causative location for INO in individual patients. One important caveat with respect to INO is that there has not been any published investigation that has assessed neurophysiologic evidence of INO in patients with MLF lesions on MRI. Our patients were selected for imaging analysis on the basis of evidence of INO as confirmed on infrared video oculography. We have not performed a more general screening of our patients with MS to identify those with MLF location lesions who have corresponding evidence of adduction slowing on oculography. Such an analysis would be of great importance in terms of the specificity of the lesion in INO.

Fluid-attenuated inversion recovery imaging has improved the conspicuity of white matter lesions, especially in the supratentorial periventricular zones and at the gray-white junction, whereas it detects fewer lesions in the posterior fossa compared to conventional spin echo (CSE).<sup>30,31</sup> In one study, CSE identified 138 posterior fossa lesions, whereas only 66 abnormalities (48%) could be shown on FLAIR.<sup>30</sup> The FLAIR technique is influenced by CSF and vascular flow artifacts, both of which are prominent in the posterior fossa, potentially accounting for the reduced lesion detection rate in this region when compared with CSE.<sup>32</sup> In the same study, the superiority of FLAIR with respect to identifying gray-white junction lesions was confirmed by showing 542 lesions, compared with only 306 by CSE. The two techniques were comparable with respect to periventricular lesion confirmation, despite the greater conspicuity of FLAIR. In another study, it was shown that CSE detects a larger volume of posterior fossa lesions compared with FLAIR and that posterior fossa and cerebellar lesions correlate strongest with functional



**Figure 4.** A midbrain lesion in the region of the MLF is observed ventral to the cerebral aqueduct (open arrows). The lesion is most conspicuous on proton density imaging ( $140 \times 256$  matrix) (A) compared with T2 ( $220 \times 256$  matrix) (B). T1-weighted imaging failed to show evidence of any hypointensity (C). In another patient, a rostral midbrain lesion is localized to the dorsal tegmentum, ventral to the aqueduct, best seen on proton density imaging (short arrow) (D) compared with T2-weighted (long arrow) (E) or fluid-attenuated inversion recovery (lesion absent) (F) imaging.

status score compared with other sites (periventricular and subcortical).<sup>33</sup>

We provide corroborative evidence on the superiority of PDI compared with FLAIR in confirming the presence of a posterior fossa lesion associated with a distinctive clinical syndrome. Our finding that only 48% of the lesions identified with PDI were observed with FLAIR represents the same detection rate for posterior fossa lesions as previously reported.<sup>30</sup>

MS lesions that are hypointense on T1-weighted (short TR and short TE) sequences (i.e., “black holes”) (correspondingly bright on T2-weighted images) have been associated with histopathologic evidence of more severe tissue disorganization corresponding to demyelination and axonal loss.<sup>34</sup> Furthermore, the degree of T1 hypointensity is significantly correlated with the percentage of residual axons in MS tissue. In one study, T1-isointense MS tissue shows 75% residual axon density, whereas severely hypointense lesions show only 30% residual axons.<sup>34</sup> Nevertheless, these abnormalities are infrequently observed in the posterior fossa. In a study involving 65 patients with MS and chronic lesions, half of 1,274 supratentorial lesions were characterized by severe hypointensity on T1-weighted MRI,

whereas severe hypointensities were not seen in the optic nerve or spinal cord, and in only 1 of 168 chronic brainstem lesions (all others were isointense with brain).<sup>35</sup> These findings suggest that neuroanatomically eloquent lesions produce distinctive physical disability and chronic tissue destruction, without necessarily being associated with corresponding T1 hypointensities.<sup>36-39</sup> Our observations support this contention; only 1 of our 58 patients with chronic INO had evidence of brainstem tegmentum hypointensity.

Although there is currently no established explanation for this discrepancy, brainstem and spinal cord white matter is structured in bundles of longitudinal parallel pathways. In contrast, the supratentorial white matter involves a more complicated arrangement of many crossing pathways that lead to a more reticular configuration. Damage to the brainstem and spinal cord white matter bundles may be followed by apposition of unaffected surrounding tissue bundles that eliminate the potential for tissue cavitory change, and therefore the development of black holes. Apposition of fascicular bundles after tissue injury may culminate in a shrinkage effect, ultimately leading to tissue loss and atrophy. This

process may explain the observed atrophy that can be seen in the spinal cord, optic nerve, and brainstem (in conjunction with fourth ventricular enlargement).<sup>40</sup> In contrast, supratentorial white matter lesions potentially disrupt pathways with disparate trajectories where postinjury tissue apposition is less likely to occur, thereby resulting in the development of black holes.

Unfortunately, the presence of white matter abnormalities on conventional imaging techniques cannot be correlated to specific histopathologic changes that might be useful to predict clinical and neurophysiologic severity. Lesions that are primarily demyelinating, with sparing of axon cylinders, might be more responsive to physiologic enhancers and therapies that promote myelin repair. Alternately, when substantial axonal disorganization has occurred, one would predict less capability for such therapeutic responses. With our ability to sensitively characterize the neurophysiologic severity of INO, we now hope to correlate these findings to changes on more sophisticated MR measures, including magnetization transfer and diffusion tensor imaging.

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CME

## Individual semicircular canal function in superior and inferior vestibular neuritis

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**Article abstract**—*Objective:* To examine the concept of selective superior and inferior vestibular nerve involvement in vestibular neuritis by studying the distribution of semicircular canal (SCC) involvement in such patients. *Background:* Vestibular neuritis was traditionally thought to involve the superior and inferior vestibular nerves. Recent work suggests that in some patients, only the superior nerve is involved. So far there are no reported cases of selective involvement of the inferior vestibular nerve. *Methods:* The authors measured the vestibuloocular reflex from individual SCC at natural head accelerations using the head impulse test. The authors studied 33 patients with acute unilateral peripheral vestibulopathy, including 29 with classic vestibular neuritis and 4 with simultaneous ipsilateral hearing loss, 18 healthy subjects and 15 surgical unilateral vestibular deafferented patients. *Results:* In patients with preserved hearing, eight had deficits in all three SCC, suggesting involvement of the superior and inferior vestibular nerves. Twenty-one had a lateral SCC deficit or a combined lateral and anterior SCC deficit consistent with selective involvement of the superior vestibular nerve. Two patients with ipsilateral hearing loss had normal caloric responses and an isolated posterior SCC deficit on impulsive testing. The authors propose that these two patients had a selective loss of inferior vestibular nerve function. *Conclusion:* Vestibular neuritis can affect the superior and inferior vestibular nerves together or can selectively affect the superior vestibular nerve.

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Sudden total unilateral loss of vestibular function attributable to disease or injury results in a stereotyped clinical syndrome consisting of vertigo, nystagmus, postural imbalance, nausea, and vomiting.<sup>1</sup> The nystagmus is predominantly horizontal with a torsional component and beats away from the side of the lesion. These symptoms and signs invariably resolve almost completely by a process of central com-

pensation, even when peripheral vestibular function does not recover.

Sudden spontaneous unilateral loss of vestibular function, acute unilateral peripheral vestibulopathy, with preserved hearing and no other symptoms or signs of brainstem dysfunction, is generally attributed to viral infection and is called vestibular neuritis (VN).<sup>1,2</sup> It has been suggested that reactivation of herpes simplex type 1 virus<sup>3</sup> could cause VN in a manner resembling facial palsy (Bell’s palsy) and sudden unilateral hearing loss. At least in the early phases of VN, lateral semicircular canal (SCC) func-

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