

Quantitative oculographic characterisation of internuclear ophthalmoparesis in multiple sclerosis: the versional dysconjugacy index Z score

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Background: There is a poor correlation between multiple sclerosis disease activity, as measured by magnetic resonance imaging, and clinical disability.

Objective: To establish oculographic criteria for the diagnosis and severity of internuclear ophthalmoparesis (INO), so that future studies can link the severity of ocular dysconjugacy with neuro-radiological abnormalities within the dorsomedial brain stem tegmentum.

Methods: The study involved 58 patients with multiple sclerosis and chronic INO and 40 normal subjects. Two dimensional infrared oculography was used to derive the versional dysconjugacy index (VDI)—the ratio of abducting to adducting eye movements for peak velocity and acceleration. Diagnostic criteria for the diagnosis and severity of INO were derived using a Z score and histogram analysis, which allowed comparisons of the VDI from multiple sclerosis patients and from a control population.

Results: For a given saccade, the VDI was typically higher for acceleration v velocity, whereas the Z scores for velocity measures were always higher than values derived from comparable acceleration VDI measures; this was related to the greater variability of acceleration measures. Thus velocity was a more reliable measure from which to determine Z scores and thereby the criteria for INO and its level of severity. The mean (SD) value of the VDI velocity derived from 40 control subjects was 0.922 (0.072). The highest VDI for velocity from a normal control subject was 1.09, which was 2.33 SD above the normal control mean VDI. We therefore chose 2 SD beyond this value (that is, a Z score of 4.33) as the minimum criterion for the oculographic confirmation of INO. Of patients thought to have unilateral INO on clinical grounds, 70% (16/23) were found to have bilateral INO on oculographic assessment.

Conclusions: INO can be confirmed and characterised by level of severity using Z score analysis of quantitative oculography. Such assessments may be useful for linking the level of severity of a specific clinical disability with neuroradiological measures of brain tissue pathology in multiple sclerosis.

Internuclear ophthalmoparesis (INO) is one of the most localising brain stem syndromes and results from a lesion in the medial longitudinal fasciculus in the dorsomedial brain stem tegmentum of either the pons or the midbrain.¹ The medial longitudinal fasciculus is thought to represent a neuroanatomically eloquent site for the involvement of inflammatory demyelination in patients with multiple sclerosis, probably because of its periventricular location. INO is the most common saccadic eye movement abnormality in multiple sclerosis, affecting between 17% and 41% of patients.^{2–4} This oculomotor syndrome is characterised by ocular dysconjugacy during horizontal saccades, with slowing of adducting eye movements, with or without ocular limitation, and abduction nystagmus in the other (abducting) eye.

Bird and Leech initially reported an electro-oculographic study of peak angular saccadic velocities in patients with INO.⁵ However, recent investigations have provided compelling evidence to support the value of the versional dysconjugacy index (VDI) in sensitively confirming the cardinal feature of INO, ocular dysconjugacy.^{6,7} The VDI is a ratio of abducting to adducting eye movements for velocity, acceleration, latency, and eye position (amplitude). The use of the VDI eliminates the inter- and intraindividual variability of measurements derived from the assessment of monocular saccadic parameters. Analysis of interocular ratios for these parameters eliminates such saccade to saccade variability that occurs with

monocular measurements, because Herring's law of yoke pair muscle innervation generates similar absolute values for saccadic parameters during eye movements. In this way foveation with preserved stereoscopic vision is achieved.

INO is not always evident on clinical examination. In its most subtle form, the range of adduction is normal, whereas only the velocity is reduced. This latter form of INO can be overlooked on examination and may only be evident on formal oculographic recording.^{2,7,8} In a large cohort of patients with multiple sclerosis, INO was identified by eye movement recordings, while the diagnosis was made in only half of these on routine clinical examination.³ Neurological examination for INO can be improved by the use of an OKN tape, which allows more effective observation of saccadic dysconjugacy during the fast phase of nystagmus.⁹

Despite new developments in the oculographic assessment of saccadic eye movements in multiple sclerosis, currently there are no established diagnostic criteria for documenting the presence or level of severity of INO. Objective confirmation of this syndrome would reveal evidence of inflammatory demyelination in a neuroanatomically eloquent site and allow quantitative characterisation of the severity of INO. Correlating the severity of INO with neuroradiological measures of brain tissue pathology in multiple sclerosis would represent a novel strategy through which to link a specific clinical disability with its corresponding imaging abnormality.

We report the results of our investigation into the quantitative oculographic characterisation of INO in multiple sclerosis patients. We used Z score statistical methodology and a frequency histogram distribution analysis in evaluating the VDI in 58 patients with definite multiple sclerosis and oculo-graphically confirmed chronic INO (present for at least six months).

METHODS

Patient characteristics

We studied 58 patients with clinically definite multiple sclerosis who had evidence of chronic unilateral or bilateral INO that had been clinically evident for at least six months and was confirmed by quantitative infrared oculography. The same treating physician (EMF) assessed the presence or absence of INO. Normative data were derived from our analysis of 40 control subjects. The study protocol was approved by the University of Texas Southwestern Medical School's investigative review board.

Eye movement recording techniques

Eye movements were recorded using two dimensional infrared oculography (EyeLink, SMI, Berlin, Germany). Our objective was to confirm adduction slowing consistent with INO and to reveal evidence of occult INO in the other eye in those patients who appeared clinically to have unilateral INO. The binocular recordings were performed at a sampling rate of 250 Hz with a resolution of 0.01°. A separate camera was used to track each eye, while a third camera was used to track four infrared markers mounted on a visual stimulus display which provided corrections for head movement. Patients were seated 100 cm away from a light emitting diode (LED) board, fitted with a lightweight headband-mounted eye tracking system, and their heads were stabilised with a chin rest. As patients were tested in dark conditions, they were dark adapted for 10 minutes before the recording sessions.

A calibration was performed using red LEDs 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 ocular limitation that precluded good calibration were excluded from the study. Horizontal and vertical eye movements were recorded from each eye separately under conditions of binocular viewing. The patient was instructed to make centrifugal saccades to LEDs that were illuminated in a pseudorandom sequence. The LEDs were located straight ahead, -30°, -20°, +20°, and +30° along the horizontal axis. Every other saccade was to a central LED in the straight ahead position. The patients performed approximately 20 saccades to each eccentric LED location. Saccades accompanied by blinks, and saccades that either proceeded the stimulus or had a latency of less than 100 ms were excluded from evaluation.

Eye movement data were analysed off-line using an in-house program written in Matlab®. The interactive program smoothed eye position data with a 100 Hz bandwidth filter and was then used to determine centrifugal saccade peak velocity, peak acceleration, latency, and amplitude. Velocity and acceleration were calculated from eye position by a least squares derivative algorithm.

The versional dysconjugacy index

Assessment of saccade pair ratios (abducting eye/adducting eye), referred to as the versional dysconjugacy index (VDI), appears to be the most useful index for analysing peak acceleration and velocity differences between normal control subjects and those with INO.^{6,7}

Z score analysis of VDI

The Z score represents a standardised number that indicates the proximity of a test result to the mean value derived from a

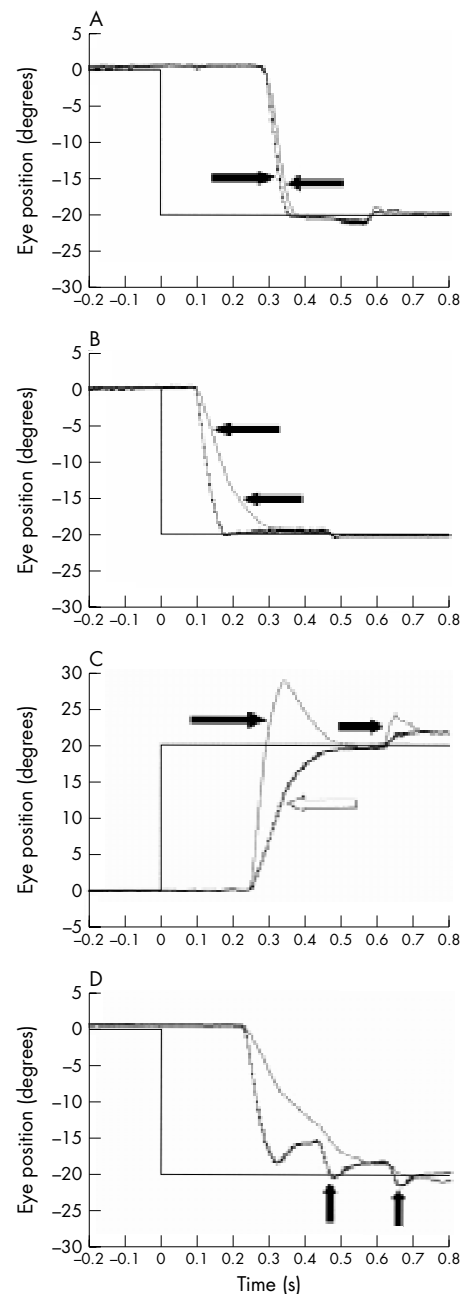


Figure 1 (A) An infrared oculogram showing mild dysconjugacy with adduction slowing (arrows) during a 20° leftward saccade consistent with a right internuclear ophthalmoparesis. (B) There is more severe adduction slowing (arrows) during a 20° leftward saccade. (C) Severe adduction slowing is seen in the left eye (open arrow) during a 20° rightward saccade. The right, abducting eye overshoots the target (large arrow) and then returns to the target position. A second, smaller overshoot is observed as the adducting eye approximates the target (small arrow). (D) Adduction slowing is observed in the right eye during a 20° leftward saccade. Abduction nystagmus is seen in the left eye which diminished as the right eye approximated the target (arrows).

standard or reference population, and is expressed in units of standard deviation. The standard population is typically one in which the quantity of interest has a Gaussian distribution, which has a bell shaped probability density function. Standard deviations and means are contingent upon what is being measured, whereas the Z score is a relative measure. Deriving the Z score from raw scores allows different measures to be compared or combined. Further, the Z score can be used to

monitor changes in a measure over time or in response to therapeutic agents. Standard methodology for assessing case-control data with respect to the sensitivity and specificity of diagnostic tests often involves the use of receiver operator characteristic curves. However, with respect to INO there is no established gold standard for confirming the diagnosis. Our aim therefore was to find a way of differentiating multiple sclerosis patients with significant adduction slowing consistent with INO from a control or reference population.

The Z scores for individual multiple sclerosis patients with INO were determined for velocity and acceleration by subtracting the mean values of the VDI derived from the normal control subjects from the VDI values derived from each INO patient, and then dividing by the SD for the normal control (NC) mean for VDI. Velocity and acceleration were assessed separately:

$$Z_{\text{INO}} = [\text{VDI}_{\text{INO}} - \text{mean}(\text{VDI}_{\text{NC}})] / [\text{SD}(\text{VDI}_{\text{NC}})]$$

RESULTS

Infrared oculography

Of our 58 multiple sclerosis patients studied, 23 (40%) were thought to have unilateral INO on clinical examination. However, 51 (88%) had oculographic evidence of bilateral INO and only seven (12%) were truly unilateral (109 INOs in all). As such, 70% of those thought to have unilateral INO on clinical examination were actually bilateral by objective assessment. Infrared oculograms showed the classic features of INO including adduction slowing and abduction nystagmus (fig 1). In each recording session, around 80 saccades were analysed (about 20 in each direction).

Saccadic VDI coefficient of variation

The coefficient of variation (CV) is a measure of variability for repeated measures and is defined by the standard deviation divided by the mean. For normal control subjects, the CV of the VDI derived from individual recording sessions was 0.03 for velocity, and ranged between 0.07 and 0.09 for acceleration. For multiple sclerosis patients with INO (MS-INO), the CV ranged from 0.06 to 0.08 for velocity and 0.13 to 0.22 for acceleration. These data suggest that in both normal subjects and those with MS-INO there is less saccade to saccade variability for velocity measures than for acceleration measures.

Relation of VDI and Z score

Using the Shapiro-Wilkes goodness of fit test, the null hypothesis that normal control VDI scores had a Gaussian distribution was not rejected. The horizontal saccadic VDI for acceleration was typically higher (more sensitive) than that for velocity, but with a higher degree of variability on repeated measures analysis (higher CV). As such, the Z scores for velocity measures were higher than those derived from comparable acceleration VDI measures. Thus the VDI velocity Z score is preferred in that, compared with VDI acceleration Z scores, it provides a more reliable measure for discriminating abnormal VDI values derived from INO patients from those derived from normal subjects.

The mean (SD) value of the VDI velocity obtained from 40 normal control subjects was 0.922 (0.072). Previous studies have shown that the VDI is slightly less than unity when using electro-oculography, whereas it is slightly greater than unity for the scleral search coil technique.^{6,7} We believe that our mean value for VDI derived from control subjects is related to the infrared video-oculography technique.

The highest VDI for velocity derived from a normal control subject was 1.09, which is 2.33 SD away from the normal control mean VDI. We therefore chose 2 SDs beyond this value (that is, a Z score of 4.33) as the minimum criterion for confirming the presence of an INO. This Z score corresponded to a VDI value of 1.23.

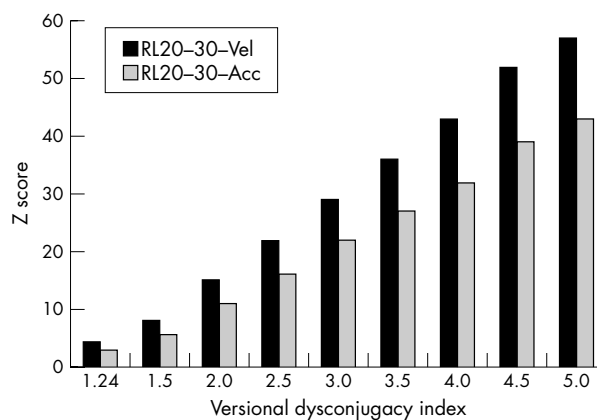


Figure 2 Z scores (ordinate) and the corresponding values for the versional dysconjugacy index (VDI) (abscissa) derived from multiple sclerosis patients with internuclear ophthalmoparesis (INO). Comparisons are made between velocity and acceleration. The standard deviation for repeated measures was consistently lower for velocity than for acceleration, resulting in markedly higher Z scores for VDI-velocity. At a given VDI, the velocity measures differentiate INO patients more effectively from a reference population of control subjects than the acceleration measures.

The severity of INO was plotted as the VDI (abscissa) and associated with corresponding Z scores (ordinate) (fig 2). The least severe INO group had VDI values from 1.24 to 1.50, which corresponded to Z scores of 4.4 to 8.0 for velocity and 2.9 to 5.7 for acceleration. In the most severe group, characterised 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 individuals with INO and normal controls, including those with the most subtle component of adduction slowing.

Acceleration VDI exceeds velocity VDI

We analysed the relation between velocity and acceleration with respect to the VDI. In the majority of INO patients whom we analysed, the VDI for acceleration exceeded the VDI for velocity (for 20° and 30° saccades to the left or right). The mean ratio of the VDI acceleration to VDI velocity derived from normal subjects was slightly greater than unity, with values almost identical to those observed by Flipse *et al* (table 1).⁷ However, INO patients consistently had mean ratios that were substantially greater than unity (table 1). The ratios were always about the same, irrespective of the direction or size of the saccade. These observations corroborate the findings of Flipse, who identified a sharper distinction between normal subjects and multiple sclerosis patients with INO.⁷ In their investigation, acceleration ratios (VDI) constituted the most sensitive measure (2.9 times the control values), followed by velocity (2.03), duration (0.73), and amplitude (1.19). However, the VDI values were not converted to Z scores, and hence they did not take into account the different variability (SDs away from the normal control mean values) associated with acceleration and velocity assessments. Analysing their individual patient data and calculating the Z scores for similar absolute VDI scores shows that velocity is the most sensitive determinant in differentiating INO patients from a standard or reference population.⁷

When comparing the VDI values for velocity and acceleration derived from INO patients and normal controls, a bimodal distribution was observed, with fine discriminatory capability (fig 3). Cut off values of 1.18 and 1.33 were identified for velocity and acceleration, respectively. Some multiple sclerosis subjects have at least one eye in the lower mode (those with unilateral INO), whereas no normal individuals have VDIs in the higher mode. This provides a basis for using VDI—with the

Table 1 Relation between acceleration and velocity versional dysconjugacy indices in controls and patients with internuclear ophthalmoparesis

Subjects	L20°VDI-A/VDI-V	L30°VDI-A/VDI-V	R20°VDI-A/VDI-V	R30°VDI-A/VDI-V
Normal	1.04 (0.07)	1.07 (0.06)	1.03 (0.06)	1.04 (0.06)
MS-INO	1.56 (0.27)	1.59 (0.27)	1.42 (0.32)	1.42 (0.36)

Values are mean (SD).

A, acceleration; L, left; MS-INO, multiple sclerosis patients with internuclear ophthalmoparesis; R, right; V, velocity; VDI, versional dysconjugacy index.

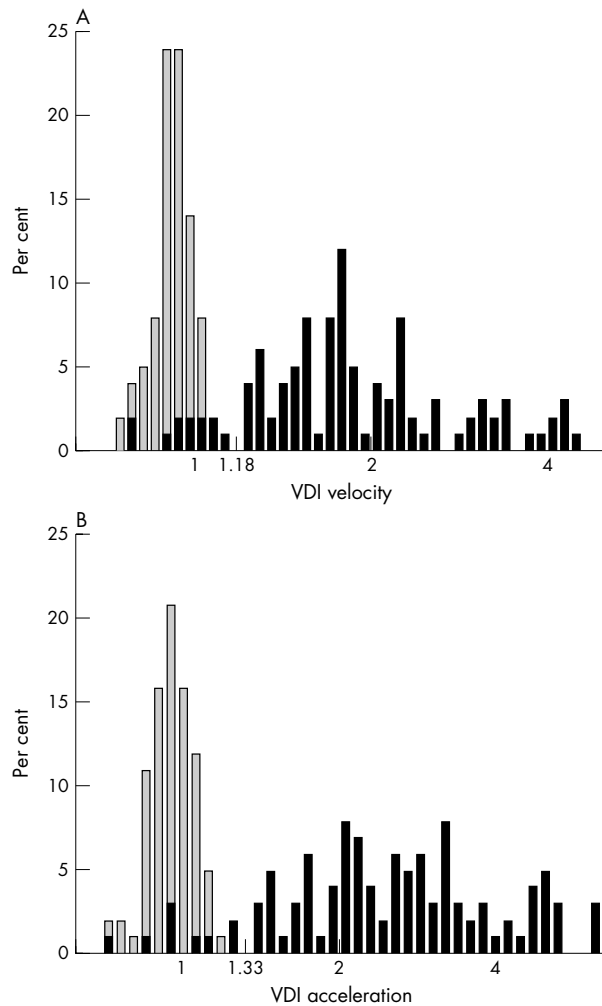


Figure 3 Histograms showing the distribution of the versional dysconjugacy index (VDI) values for velocity (panel A) and acceleration (panel B), derived from leftward and rightward saccades. Normal controls are shown in light shading and multiple sclerosis (MS) patients in black. The x axis is logarithmic. The few MS patients who fall into the lower mode are those without evidence of internuclear ophthalmoparesis (INO) in a particular direction (that is, multiple sclerosis patients with unilateral INO).

cut off values specified—as a discriminator for confirming INO, which is complementary to the Z score assessment.

Relation of VDI ratios and target eccentricity (20°/30°)

Analysis of saccades in a normal population shows a consistent relation between peak velocity, acceleration, and the size of the eye movement (amplitude). The larger the saccade, the greater the peak velocity and acceleration. For normal subjects, the values of these saccadic variables fall within a relatively limited range, referred to as the main sequence.^{10, 11} In examining our data, it was apparent that the use of the VDI

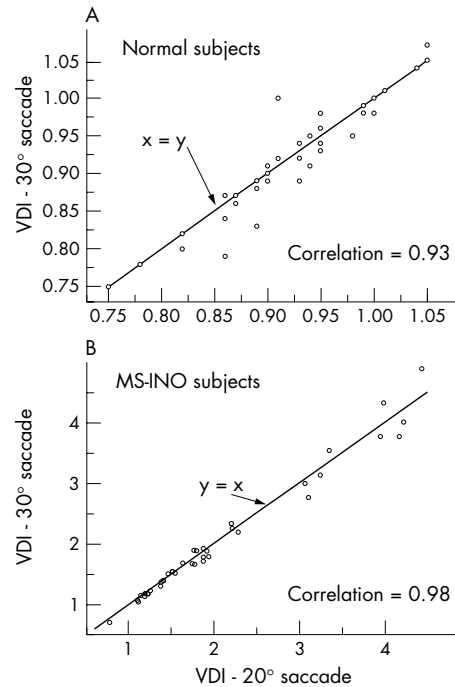


Figure 4 (A) The versional dysconjugacy index (VDI) ratio for normal subjects does not appreciably vary with saccade size. A plot of point pairs for left hand side velocity outcomes typifies the strong relation between 20° and 30° horizontal saccades. (B) The VDI ratio for multiple sclerosis patients with internuclear ophthalmoparesis (MS-INO) does not vary significantly with saccade size. The relation shown in panel A for normal patients is sustained for MS-INO patients over a considerably wider range of observations.

greatly diminishes main sequence effects, as VDI values were independent of the size of the saccade. We found that the VDI, while greater for acceleration versus velocity, was independent of the size of the saccade (that is, 20° v 30°).

Using the Wilcoxon signed rank test we conducted several tests of hypotheses regarding the equality of VDI statistical distributions. By not rejecting the null hypotheses (minimum observed significance = 0.1), we were able to conclude that for velocity and acceleration, the 20° and 30° same side horizontal excursions yielded comparable VDI results. This allowed us to establish a single normal subject standard of comparison using the combined velocity VDI statistics. Figure 4A typifies the strong relation of VDI ratios for 20° and 30° leftward saccades. The results were similar for rightward saccades (data not shown).

For the MS-INO patients, we also found that same side velocity VDI ratios were effectively independent of target eccentricity. This was also true for acceleration VDI ratios. Figure 4B is an example of the closeness of the relation in MS-INO patients. Given the large disparity between the normal and MS-INO subjects, we saw no need to formally establish equivalence bounds regarding 20° and 30° VDI observations.

As another means of quantifying the closeness of target eccentricity outcomes, we evaluated the ratio of VDI-20°/VDI-30° for leftward and rightward saccades. In all circumstances, the ratio (mean (SD)) ranged between 1.00 (0.06) and 1.02 (0.04). Given this finding, future investigations that assess INO with the VDI methodology can substantially reduce the number of saccades and the time required for data acquisition, as only a single sized saccade is necessary for each horizontal target direction.

DISCUSSION

The data we present indicate that INO in patients with multiple sclerosis can be confirmed by oculographic measures according to the proposed diagnostic criteria. Furthermore, this technique is useful for determining the magnitude of the dysconjugacy that characterises INO. We suggest that the oculographic diagnosis of INO should be confirmed by using comparisons of VDI values with respect to control or standard populations. To do this we employed Z score methodology. The Z score is the number of standard deviations that separate a result from the mean value for a parameter derived from a reference population, and it is not dependent upon units of measurement. In the oculographic diagnostic criteria that we propose, a velocity Z score of 4.33 was chosen to represent the minimum threshold for the confirmation of INO. The highest velocity VDI derived from normal controls was 1.09, which represents a Z score of 2.33 with respect to the mean VDI derived from the control population. As such, we have conservatively chosen a Z score of 4.33, a value 2 SD beyond the highest velocity VDI score observed in the control subjects studied in our laboratory (n = 40). The highest VDI for acceleration derived from a normal control subject was 1.28, corresponding to a Z score of 3.33. As such, acceleration criteria for confirming the presence of INO would require a Z score of at least 5.33, which would be equivalent to a VDI of 1.47. The minimum VDI to confirm INO by velocity criteria (with a Z score of 4.33) would be 1.23, a lower level of interocular dysconjugacy. When using a histogram analysis of the frequency distribution of VDIs derived from INO patients and normal subjects, we corroborated the superiority of velocity as a discriminator compared with acceleration.

The receiver operator characteristic curve analysis is a standard method with which to assess the specificity and sensitivity relations of a diagnostic test. However, an acknowledged gold standard must be available before this strategy can be applied. Currently there is no established gold standard for the confirmation of INO. We therefore used the Z score and histogram approaches to confirm the presence of INO. Individual laboratories will need to establish normal control data from which Z score and histogram analyses can be derived, in order to confirm or refute the suspected diagnosis of INO in patients with multiple sclerosis.

Our neurophysiological observations with infrared oculography, using the Z score analysis of the VDI, prove its ability to differentiate between normal individuals and patients with INO, including those with the most subtle component of adduction slowing. In fact, 70% of those patients thought to have unilateral adduction slowing on clinical examination were found to have bilateral INO.

We found no significant differences in VDI with respect to the size of the centrifugal fixation target (20° v 30° saccades). We therefore suggest that oculographic assessment for INO need only use leftward and rightward saccades of a single size. Ultimately this observation suggests that future investigations that assess INO using VDI methodology can reduce the number of saccades and the time required for data acquisition substantially. Furthermore, the CV for repeated measures of the VDI is low, and hence only a limited number of saccades (perhaps 10 in each horizontal direction) is necessary to confirm the presence of the characteristic ocular dysconjugacy in INO.

The identification of INO in multiple sclerosis patients may be important in that it can provide 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 that they will develop clinically definite multiple sclerosis. In one study, 22 patients were evaluated and nine were shown to have evidence of adduction slowing by oculography. Seven of these nine patients developed definite multiple sclerosis within 2.2 years.¹²

We have recently found that all 58 of our multiple sclerosis patients with chronic INO had evidence of a lesion in the dorsomedial tegmentum of either the pons or the midbrain on proton density weighted imaging.¹ While proton density or T2 weighted hyperintensities appear to be histopathologically non-specific, newer magnetic resonance techniques—such as magnetisation transfer and diffusion tensor imaging—are under development and will provide more sophisticated information about lesion pathology in multiple sclerosis. We suggest that objective measures of the clinical severity of chronic INO in patients with multiple sclerosis may be correlated with neuroradiological abnormalities in the region of the medial longitudinal fasciculus. If successful, this model system may represent a novel way of linking clinical disability with radiological measures of lesion pathology. The comprehensive assessment of lesions in the medial longitudinal fasciculus in patients with multiple sclerosis and INO will lead to a greater understanding of the histopathological elements contributing to tissue injury and physical disability in a specific multiple sclerosis related clinical syndrome.

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