VIDEO

Accuracy of clinical detection of INO in MS

Corroboration with quantitative infrared oculography

T.C. Frohman, BA; E.M. Frohman, MD, PhD; P. O'Suilleabhain, MD; A. Salter, BS; R.B. Dewey, Jr., MD; N. Hogan, MD, PhD; S. Galetta, MD; A.G. Lee, MD; D. Straumann, MD; J. Noseworthy, MD; D. Zee, MD; J. Corbett, MD; J. Corboy, MD; V.M. Rivera, MD; and P.D. Kramer, MD

Abstract—The authors compared the accuracy of clinical detection (by 279 physician observers) of internuclear ophthalmoparesis (INO) with that of quantitative infrared oculography. For the patients with mild adduction slowing, INO was not identified by 71%. Intermediate dysconjugacy was not detected by 25% of the evaluators. In the most severe cases, INO was not identified by only 6%. Oculographic techniques significantly enhance the precision of INO detection compared to the clinical exam.

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Recent objective criteria for internuclear ophthalmoparesis (INO) utilizing quantitative infrared oculography have been proposed, suggesting that the bedside neurologic exam may not be sufficiently sensitive to detect many subtle cases.[1-3] There has been no formal analysis of the ability of clinicians to accurately detect slowing of adduction during clinical testing of horizontal saccades.[2] Here we present the findings from our investigation on the ability of clinicians to detect INO (characterized by slowing of adduction) in patients with multiple sclerosis (MS) who have varying levels of adduction slowing, as defined by infrared oculography. We further analyzed the accuracy of detecting INO with respect to level and type of neurologic training.

Methods. *Patient characteristics.* We performed infrared oculography and prepared a videotape of the horizontal saccadic eye movements in 18 individuals. These individuals consisted of MS patients with INO (nine bilateral and three unilateral), MS patients without INO,[3] and normal subjects.[3] The study protocol was approved by the University of Texas Southwestern Medical School's investigative review board.

Eye movement recording techniques to confirm or exclude INO. Eye movements were recorded using two-dimensional infrared oculography (EyeLink; SMI, Berlin, Germany), as previously described.[1-3] Our objective was to confirm slowing and/or limitation of adduction consistent with INO.

Patients were instructed to make centrifugal saccades to light-emitting diodes (LED) that were illuminated in a pseudo-random sequence. The LED were located straight ahead and at −20 and +20° along the horizontal axis. The patients performed approximately 20 saccades to each eccentric LED location. Eye movement data were analyzed off-line using an in-house program written in Matlab (MathWorks, Newton, MA).

Analysis of INO detection rates. The versional dysconjugacy index, that is, the ratio of abduction to adduction eye movements for peak velocity (VDI_{vel}), was used to define the diagnostic criteria. The presence or absence of INO was confirmed when the VDI_{vel} Z score was >2.5. For the current study, a VDI_{vel} of 1.11 (2.6 SD away from our mean VDI_{vel} derived from 40 control subjects)[2] was selected as the minimum threshold to establish the presence of INO. Based on the VDI_{vel} *Z* scores, the 36 eyes were analyzed for INO. We partitioned the VDI_{vel} *Z* scores into four different divisions of dysconjugacy: normal ≤2.5; mild ≥2.5 to 10; intermediate >10 to 20; severe >20 to 60 (figure 1).

We also assessed whether the detection rates were different if eye movements were characterized by amplitude measurements. As a measure of positional dysconjugacy, we used the first-pass amplitude (FPA), which is defined as the position of the adducting eye when the abducting eye has achieved the peripheral fixation target.[3] The mean FPA derived from our normal subjects was 1.01 ± 0.04. Corresponding *Z* scores were calculated for MS patients with INO.

Clinical detection of INO. Immediately after infrared oculographic recording as described above, patients and normal subjects were videotaped while exhibiting leftward and rightward 20° horizontal saccades with a digital 60-Hz mounted camera recorder.

The completed videotape containing 18 subjects was distributed to collaborating centers and presented during an organized session. At the beginning of the videotape, participants (n = 279) were given specific instructions on the identification of INO, prin-

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From the Departments of Neurology (Drs. Frohman, O'Suilleabhain, Dewey, and Hogan, T.C. Frohman and A. Salter) and Ophthalmology (Drs. Frohman and Hogan), University of Texas Southwestern Medical Center at Dallas, and Department of Neurology and the Mexican study group (Dr. Rivera), Baylor College of Medicine, Houston; Department of Neurology (Dr. Galetta), University of Pennsylvania, Philadelphia; Departments of Ophthalmology, Neurology, and Neurosurgery (Dr. Lee), University of Iowa, Ames; Department of Neurology (Dr. Noseworthy), Mayo Clinic, Rochester, MN; Department of Neurology (Dr. Zee), Johns Hopkins Hospital, Baltimore, MD; Department of Neurology (Dr. Corbett), University of Mississippi, Jackson; Department of Neurology (Dr. Corboy), University of Colorado, Boulder; New Jersey Neuroscience Institute (Dr. Kramer), Seton Hall University, South Orange, NJ; and Department of Neurology (Dr. Straumann), Zurich University Hospital, Switzerland.

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Address correspondence and reprint requests to Dr. E.M. Frohman, Department of Neurology, University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Blvd., Dallas, TX 75235; e-mail:elliot.frohman@utsouthwestern.edu

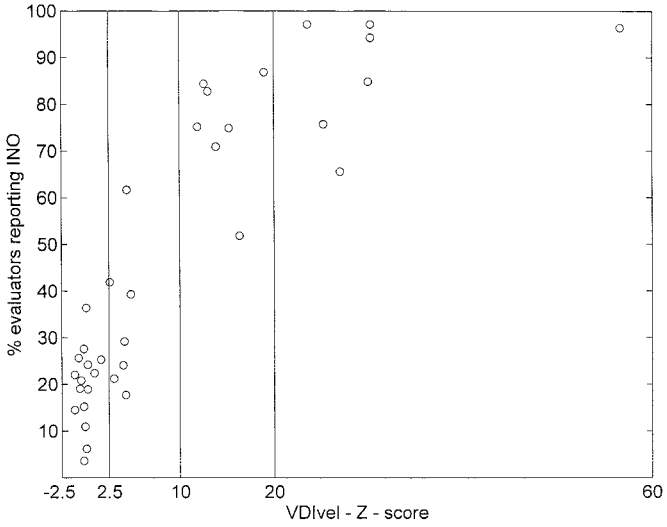

Figure 1. In this figure, we show the relationship between the versional dysconjugacy index (VDI_{vel}) Z score and the internuclear ophthalmoparesis (INO) detection rate. The vertical lines on the graph demarcate the Z-score thresholds partitioning the eyes into level of severity for adduction slowing. Z scores up to 2.5 represent normal conjugacy; >2.5 to 10 mild dysconjugacy; >10 to 20 moderate dysconjugacy; >20 to 60 severe dysconjugacy. Each circle corresponds to the VDI_{vel} Z score derived from an individual patient for a 20° saccade in a particular direction (either left or right).

cipally emphasizing the cardinal feature of adduction slowing during horizontal saccades. Each segment of the videotape lasted for approximately 30 seconds. The participants were then asked to view each examination and indicate on an answer sheet whether they detected a unilateral INO (right or left), bilateral INO, or no evidence of INO. Physician evaluation groups included neurologists in private practice (n = 50), academic neurologists (n = 77), MS specialists (n = 12), neuro-ophthalmologists (n = 23), neurology (n = 85) and ophthalmology (n = 19) residents, and medical students (n = 13). With use of these criteria, 21 eyes met criteria for INO and 15 did not.

Results. *Coefficient of variation of saccadic VDI_{vel}.* For normal control subjects, the coefficient of variation (CV; defined as the SD/mean) of the VDI_{vel} derived from individual recording sessions was 0.03 for velocity, whereas for MS INO patients, the CV was about 0.06. The CV for FPA measurements was similar (data not shown). This very low degree of variability for each sequential saccade suggests that each of the triggered eye movements observed by the evaluators was very similar in terms of the degree of conjugacy or dysconjugacy.

Detection of INO. The four severity divisions of dysconjugacy that we selected differed ($p = 0.001$). Nevertheless, the detection rates of INO between the normal and mildest cases and the intermediate and severe cases did not differ. For normal eyes, INO was reported to be present by 21% of the observers (median; range 4 to 36%; type I error). For the mildest cases of adduction slowing (VDI_{vel} *Z* scores of ≥2.5 to 10), INO was not detected in 71% (median; 39 to 82%). Intermediate dysconjugacy (VDI_{vel} *Z* scores of >10 to 20) was not identified by one-quarter of the participants (median; 13 to 48%). Evaluators performed substantially better when assessing the most severe cases of INO (VDI_{vel} *Z* scores of >20 to 60) as only a median of 6% of participants failed to detect the syndrome (see figure 1). The analysis of detection rates using amplitude measures of dysconjugacy (FPA) did not significantly differ from our analysis of velocity assessments (data not shown). In figure 2, we illustrate three MS patients with mild, moderate, and severe INO. See the supplementary material on the *Neurology* Web site (go to www.neurology.org) for the corresponding video sequences that were evaluated by participants for these three patients.

Detection rates among evaluator groups. The rates at which each of the evaluator groups reported INO did not differ for the normal control, mild INO, and severe INO divisions. Among the intermediate INO division, the groups did differ ($p = 0.015$), with students being less likely to report INO (median 54%) as compared with the ophthalmology residents (79%), neurology residents (72%), neurologists (77%), MS specialists (91%), and neuro-ophthalmologists (91%). INO was detected in normal subjects (type I error) by 20% of neurologists, 18% of neurology residents, 11% of ophthalmology residents, 17% of medical students, 16% of MS specialists, and 9% of neuro-ophthalmologists (all medians).

We utilized analysis of variance (general linear model procedure) to ascertain whether we could demonstrate differences in detection rate based upon level of training or particular subspecialty. Neuro-ophthalmologists (correct: 83%) scored better than neurologists (73%), MS specialists (78%), ophthalmology residents (73%), neurology residents (73%), and medical students (69%) ($F[4,274] = 4.8$, $p = 0.0009$). No other contrasts reached significance (post hoc Scheffé test at $p = 0.05$).

Discussion. In this study, we assessed the accuracy of clinical detection of INO by physician evaluators. The utilization of infrared oculography allowed us to validate the presence of this syndrome by specific criteria and to quantitatively characterize the relationship between the severity of the syndrome and the accuracy of clinical detection.

The detection rates were highly accurate across all physician groups when the degree of adduction slowing was severe. Milder cases of INO were frequently not identified by the majority (71%) of evaluators. Even when the degree of adduction slowing was between 10 and 20 SD away from the values derived from normal subjects, one-quarter of the evaluators were still unable to detect this high degree of dysconjugacy. Whereas neuro-ophthalmologists performed significantly better than the other groups, we were unable to demonstrate any other comparisons that differentiated physicians by type or level of training. We found that 21% of observers detected INO in normal subjects (type I error) and that this rate was lowest for neuro-ophthalmologists (9%).

This investigation suggests that INO may be overlooked on clinical examination and that neurophysiologic techniques can provide greater precision in its diagnostic confirmation. Determining the relationship between the severity of this specific clinical syndrome and its corresponding radiologic measures of tissue injury will require the application of objective neurophysiologic methods such as quantitative oculography.

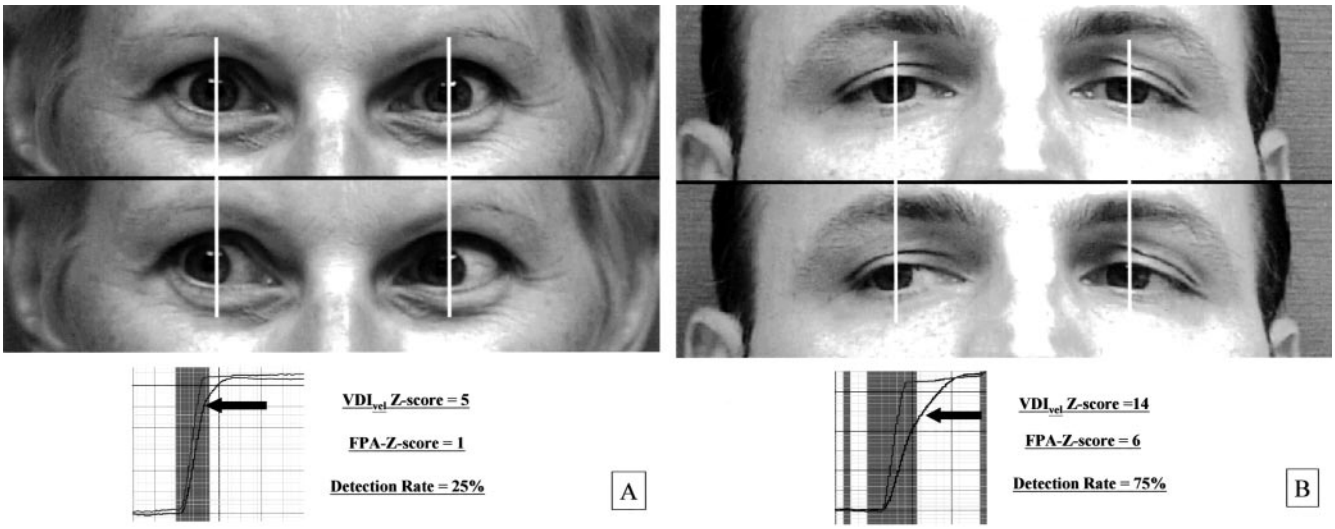

Figure 2. Three patients with multiple sclerosis with confirmed internuclear ophthalmoparesis (INO) that exhibit different levels of dysconjugacy are illustrated. The vertical white bars (initially on the midpupillary line) are used to show the displacement of the eyes from the midline position. The photographs show the position of the adducting eye at the point in time when the abducting eye has first achieved the +20° target (FPA = first-pass amplitude). In patients with INO, the position of the adducing eye lags behind the abducting eye, with less displacement away from the midline position. We show three patients with mild (A), moderate (B), and severe (C) levels of dysconjugacy, during a 20° saccade to the right. Beneath each photograph is a corresponding infrared oculogram showing the divergence of the right and left eye movement tracings (arrows). The quantitative data for the versional dysconjugacy index (VDI_{vel}) and FPA Z scores and the INO detection rates for the evaluator groups are shown.

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