REGULAR CORRESPONDENCE

Internuclear Ophthalmoplegia

We read with interest the article by Dr Keane on internuclear ophthalmoplegia (INO). There is an area of doubt concerning the exact focus of neurologic damage in the enrolled INO cases about which we would like to learn more from the author.

Medial rectus limitation or slowing, dissociated nystagmus and preserved convergence are deemed as the essential components of INO due to medial longitudinal fasciculus damage.[1] However, the adduction palsies seen in INO are not unique and can be mimicked by adduction defect due to infranuclear ophthalmoplegia.[2] The only clinical checkpoint that can distinguish these 2 is the recognition of an impaired vertical vestibulo-ocular reflex.[2] Perhaps Dr Keane can enlighten us further with respect to this query.

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In reply

I appreciate the interest of Dr Liu and his colleagues and hope that I can reassure them that the diagnosis of INO does not require demonstration of an impaired vertical vestibulo-ocular reflex. The major features of INO[1] (limited or slowed medial rectus action and abduction overshoot and nystagmus) compose one of the most recognizable patterns in neurologic diagnosis, now regularly confirmed by demonstration on magnetic resonance imaging of a lesion in the medial longitudinal fasciculus.[2] The principal difficulty in diagnosing INO lies in failure to appreciate mild, or even moderate, slowing of adduction saccades in the presence of a full range of motion.[3]

The minor signs of INO[1] (skew deviation, vertical nystagmus, impaired convergence, impaired vertical pursuit, and an abnormal vertical vestibulo-ocular reflex) are inconsistently present and depend on the completeness of injury to the medial longitudinal fasciculus and whether one or both sides are involved. An impaired vertical vestibulo-ocular reflex may be difficult to confirm on clinical examination: particularly in elderly individuals, vertical neck and eye movements have a narrower range than their horizontal counterparts. In addition, bilateral simultaneous caloric testing is difficult to synchronize and the intensity of stimulation must be reduced in the awake patient.

Infranuclear pseudo-INO, which can mimic perfectly the major signs[4] and may even simulate the minor signs[5] of INO, is seen occasionally in myasthenia; rarely in the Fisher and ophthalmoplegic Guillain-Barré syndromes; and exceptionally with other causes of medial rectus weakness, including the pseudo-myasthenic, pseudo-INO of neurotoxic snake envenomation.[6] If neurological diagnosis were limited to this 1 sign, pseudo-INO would be difficult to distinguish. In practice, it is rarely a diagnostic problem except for those unaware of this mimicry. Myasthenic pseudo-INO is almost always accompanied by telltale ptosis and usually can be reversed by Tensilon administration. In addition, many patients with pseudo-INO already have a well-established diagnosis as was the case in 18 of my 27 myasthenic patients with this sign. Of the remaining 9 patients, 7 had limb or bulbar weakness and all had ptosis.

For the rare patient with pseudo-INO as the sole apparent presenting sign of myasthenia, there are a number of neuro-ophthalmologic maneuvers to elicit masked weakness, including evoking lid or saccadic fatigue, eliciting the lid twitch and lid peek signs, and demonstrating the rapid eye movements of myasthenia. Continued observation often will reveal the diagnosis: within a day or 2, pseudo-INO of the Fisher/Guillain-Barré syndrome usually progresses to generalized ophthalmoplegia and the myasthenic patient may reveal diurnal fatigue or a major change in the pattern of eye movements. Although the protean signs of myasthenia will always pose an occasional challenge, the overriding diagnostic error in myasthenia lies with failure to consider the diagnosis.

When taken in clinical context, the major signs reliably diagnose INO.

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Additional Information: Since my letter was submitted, the article "Internuclear Ophthalmoplegia: Causes and Long-Term Follow-up in 65 Patients," by Bolanos et al (*Acta Neurol Scand.* 2004;110:161-165), has come to my attention.

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Delusions and Hallucinations in Alzheimer Disease

I enjoyed reading the article by Dr Scarmeas and colleagues[1] detailing the results of their carefully planned cohort study. This study examined the association between the presence of hallucinations and delusions and the development of clinically important outcomes (eg, decline on a cognitive outcome, decline on a functional outcome, institutionalization, and death). In modeling the effects of hallucinations and delusions on these outcomes, the investigators adjusted for the use of neuroleptic drugs (ie, antipsychotics) and cholinesterase inhibitors. The authors provided data on the relationship between neuroleptic drug use and the clinical outcomes, and a recent meta-analysis shed further light on the potential risks of neuroleptic drug treatment in dementia.[2] I wonder if Dr Scarmeas and colleagues can provide further insights into the influence of cholinesterase inhibitors on their measured outcomes.

There has been ongoing debate about the value of cholinesterase inhibitor treatment. Although some studies have identified little meaningful benefit on clinically important outcomes with these drugs,[3] other research has found cholinesterase inhibitor use is associated with delayed nursing home placement and slower progression of cognitive decline.[4] No clear consensus has yet appeared. What impact did exposure to cholinesterase inhibitors have on the 4 outcomes measured in this study?

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In reply

We thank Dr Gill for the positive comments about our study. Because the Predictors study started more than 14 years ago, when cholinesterase medications were not available, only 41% of the patients used in our analyses were ever prescribed these medications. In models such as those used in our report, we detected no significant association between use of cholinesterase inhibitors and any of the 4 outcomes (but there was a trend toward a protective effect for mortality).

One has to keep in mind that examination of the effect of medications is vulnerable to a variety of potential biases. Most important, this is an observational cohort and the medications were administered in a nonrandomized fashion. In our study, patients who received cholinesterase inhibitors were members of the more recent Predictors 2 cohort; were more likely to be men; and had fewer medical comorbidities, better cognitive performance, and better functional status at baseline. Statistical control cannot truly eliminate inherent differences deriving from lack of randomization. Also, despite the advantages of using a time-dependent approach of a dichotomously coded medication administration every 6 months, we cannot completely take into account the potential effect of different types of cholinesterase inhibitors and doses, alterations in prescriptions occurring in intervals shorter than 6 months, etc.

The potential impact of cholinesterase inhibitors on long-term disease outcomes is a very important issue, particularly because the clinical efficacy of these medications is not impressive and their cost quite considerable. We are currently in the process of examining these associations in our cohort in a more detailed way, which will be the topic of another manuscript.

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Interferon Beta-1a Treatment and African Americans

In the article "Response to Interferon Beta-1a Treatment in African American Multiple Sclerosis Patients," the authors[1] suggest that African Americans (AAs) are less responsive to interferon beta-1a than white Americans (WAs), paralleling an earlier publication[2] that showed a more rapid progression of multiple sclerosis in AA patients. Their conclusions have implications for further study, but their data raise several questions.

The EVIDENCE[3] trial showed a better response for thrice weekly than for once weekly treatment with interferon beta-1a. Because only 36% of their AAs were treated thrice weekly compared with 51% of the WAs, might one expect the AA group to have a reduced response because of this difference?

Is the greater increase in mean number of exacerbations and mean number of new lesions in AAs evidence of a reduced response? In this small AA group, a very few outliers could skew the mean. If increases from week 24 to week 48 were due to more rapid progression in a few AAs, one cannot label the whole group as reduced responders. Evaluation of the range and standard