Correspondence

Consent issues in the management of cerebrovascular diseases

To the Editor: In the special article on consent issues in the management of cerebrovascular diseases,1 the authors put the cart before the horse by emphasizing the tradeoff between immediate risk and long-term benefit. They note that for carotid endarterectomy, accurate local data on morbidity and mortality for the surgical and medical options are essential components of the adequate-information component of informed consent. They neglect evidence that this information is usually not available2 and is difficult to empirically ascertain,3 and do not mention that there is evidence suggesting little or no benefit in many locales.4,5 The following discussion concentrates on endarterectomy for high-grade symptomatic stenosis.

The benefit demonstrated in NASCET6 is based (among other caveats) on a 2.1% major complication (major stroke or death) rate with benefits diminishing until they disappear at a rate of 10%.8 In clinical practice, many surgeons are performing endarterectomies with unacceptable complication rates. From 1992 to 1995, the perioperative mortality rate among Medicare patients alone (1.4% to 2.5%)3 is close to or exceeds the major complication rate in NASCET. These rates combine asymptomatic and symptomatic cases. If, as found in clinical trials, the perioperative mortality rate in the symptomatic case is greater than in the asymptomatic case,6 the previously cited rates mask an even greater mortality rate in the symptomatic case.

The difficulty in determining individual complication rates is illustrated in the following example. Consider three surgeons with complication rates of 0.1 (no benefit), 0.06 (diminished benefits), and 0.021 (full benefit). Using a Bernoulli model,7 the average number of operations before the first major complication would be 9, 15, and 46, respectively.9 In New York state during 1995, 48% of surgeons performed 5 or fewer operations and 73% performed 15 or fewer.4 These figures combine asymptomatic and symptomatic cases. Failures occurring more than a year after nine successful operations will tend to be ignored.

The conclusion that there is no benefit with a complication rate of 10% is likely based on the assumption that locally performed uncomplicated operations result in the same risk reduction in stroke as that obtained by the carefully chosen NASCET surgeons. However, the complication rate may be a surrogate marker for surgical proficiency; i.e., a higher complication rate may correlate with less (or no) risk reduction for successful operations. In this case, even assuming the local risk of stroke in a medically treated group is the same as that found in NASCET, the lack of benefit would occur at a complication rate of less than 10%.9 This discrepancy may be explained by the underlying risk of stroke. The two major trials of endarterectomy for symptomatic stenoses9,10 had similar eligibility criteria but the risk of ipsilateral stroke in the medically treated groups averaged 5.6%/year in ECST9 and 13%/year in NASCET,6 a 7.2% difference (p < 0.003). The difference has been attributed to different methods of measuring angiographic stenosis.10 Differences will be exaggerated in practice, where surgeons may operate on the basis of different imaging methods such as ultrasound or MRA.9 Local indications for endarterectomy may differ from the eligibility criteria for the trials in other ways. In New York state, between 1990 and 1995, 12.2% of endarterectomies were performed on patients with potential sources of cardioembolism.1 Thus, determining the local benefit of endarterectomy would require a repeat trial under local conditions, with a sufficient number of patients. This is a practical impossibility in view of the prevalence of low-volume hospitals.3,4 Few people would choose to fly knowing that their plane had been tested only under ideal weather conditions.

Martin M. Pincus, MD, PhD, Brooklyn, NY

Reply from the Authors: I thank Dr. Pincus for his informative letter. He convincingly shows that it may be difficult or impossible in practice for neurologists to know confidently the “accurate local data on morbidity and mortality” that we stipulated was a condi-
This lack of correlation between brain MRI disease assessments and MSF has now been shown using a variety of fatigue measures, including the 9-item and 29-item Fatigue Severity Scale, the Checklist Individual Strength Questionnaire, the Daily Fatigue Score, and Fatigue Frequency measurements. A variety of brain MRI measures have been used in these studies, including noncontrast lesion load assessment by number of lesions and ordinal and semiquantitative scoring systems. Our study and recent data of Mainiero et al. show a lack of association between number and volume of gadolinium-enhancing lesions measured in cross-sectional and longitudinal studies. Finally, brain atrophy measured by qualitative and quantitative measures does not explain MSF. Taken together, these similar conclusions reached by different groups using different methodologies strengthen the hypothesis that neither focal white matter lesions nor atrophy in the brain are sufficient to explain fatigue.

The question is what other aspects of the MS disease process contribute to the pervasive fatigue experienced by so many patients. Other avenues of investigation toward the study of MSF include the effects of MS on cerebral gray matter and the consideration of peripheral mechanisms, both of which would be missed by conventional MRI. A growing body of evidence indicates that MS is a global brain disease that has important effects on both cortical and subcortical gray matter and that this gray matter involvement is common. Recent neuroimaging and pathologic studies have emphasized this effect of MS on gray matter. PET studies show that MS patients have widespread brain hypometabolism including cortical and subcortical gray matter. This hypometabolism worsens over time. Hypointense lesions on T2-weighted images seen in the brain and thalamus, and occasionally in the cerebral cortex, suggesting T2 shortening due to pathologic gray matter iron deposition in MS. Direct plaquelike involvement of gray matter by the MS disease process has been shown in autopsy studies. Roelcke et al. showed that hypometabolism in the frontal cortex and basal ganglia is associated with MSF and hypothesized that this may represent an effect of diaschisis due to white matter lesions. However, the inability to associate MSF with MRI white matter lesions suggests that direct involvement of cortical and subcortical gray matter rather than diaschisis should be further explored as a cause of MSF. Direct mechanisms of gray matter involvement contributing to fatigue could include demyelination, inflammation, neuronal injury, or iron deposition. In addition, as suggested by Dr. Kaires, dysfunction of cell membranes in the central or peripheral nervous system is another factor that might influence MSF.

Rohit Bakshi, MD, Buffalo, NY

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References

Ibuprofen treatment versus gradual introduction of interferon β-1b in patients with MS

To the Editor: We read with interest the article by Rice et al. on ibuprofen treatment and gradual introduction of interferon (IFN) β-1b in patients with MS to minimize flu-like symptoms. They conclude that gradual dose introduction and use of nonsteroidal anti-inflammatory drugs could improve long-term tolerability. We agree. In fact, at least in Europe, this is the usual way to start therapy: begin with a half dose and then use paracetamol or ibuprofen for the management of flu-like symptoms appearing early on. Such recommendations notwithstanding, flu-like symptoms limit dosage in a number of patients. Recently, Neurology published our article describing how low-dose oral steroid use is helpful in reducing flu-like symptoms at onset of IFNβ-1b therapy in patients with MS. In it, we studied 71 patients who started IFNβ-1b therapy. Patients were randomized to receive prednisolone plus paracetamol or paracetamol only and were monitored for side effects. Systemic side effects were minimal in the steroid group compared with the nonsteroid group during the first 15 days of treatment (p = 0.005). There were no side effects attributable to steroids. Rice et al. describe that ibuprofen alone or in combination with doses escalated on the increased frequency of injection site reactions. Steroid use when starting therapy has been our policy for the last 3 years. Thus far, there are 148 patients with MS on IFNβ-1b with no drop-outs due to systemic effects.

Rice et al. suggest that fever during IFN therapy is directly mediated by the binding of IFN to thermosensitive neurons in the hypothalamus and secondarily by the release of prostaglandins, which then induce fever. We recently showed a strong relation between peripheral blood mononuclear cells' (PBMC) release of interleukin (IL)-6 and fever at the onset of IFN therapy. Likewise, we observed that treatment with low-dose steroids decreases the production of IL-6 in patients without fever. We believe that the mechanism of action of IFN in the development of fever is mediated by the release of IL-6 by PBMC.

We agree that minimization of IFN side effects is essential to the long-term use of the drug. Therefore, besides the recommendations as to gradual dose introduction and use of nonsteroidal anti-inflammatory drugs, the use of steroids could be helpful in reducing flu-like symptoms and improve long-term tolerability of IFNβ-1b.

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References

Parkinson’s disease in twins

To the Editor: Some years ago I was asked by an asymptomatic cotwin of a patient with PD whether an [18F]dopa PET scan could predict whether he would develop the illness. Vieregge et al.’s article is the second recent study examining the progression of asymptomatic twins identified as having abnormal, and putatively presymptomatic, scans. The editor and authors should be congratulated for publishing what is essentially a negative study; not one of such asymptomatic cotwins with an abnormal scan has developed PD in 6 years. An important explanation is omitted from the discussion. [18F]dopa PET is a technique that has limited reproducibility, numerous potential technical errors, and in the identi-
lication of preclinical disease, is likely to produce false positives and false negatives. Without reproducibility data, the authors and readership cannot be confident of the reliability of identification of abnormal subjects. This study indicates that the technique has determined to have erroneously identified preclinical subjects. The recent similar follow-up study from this country does not give any greater confidence in the technique. In that study, 10 of 18 asymptomatic monozygotic (MZ) cotwins and 3 of 16 asymptomatic dizygotic (DZ) cotwins had abnormal PET scans; thus far, only 4 of the MZ cotwins have developed clinical PD. Three of these four had tremor and one had minimal limb bradykinesia at the time of the first scan. The implication is that the technique used in both these studies cannot identify asymptomatic cotwins of patients (and, by extrapolation, preclinical individuals in the general population) who are likely to develop typical PD with any useful level of sensitivity or specificity.

P.K. Morrish, MD, Brighton, UK

Reply from the Authors: We thank Dr. Morrish for the interest in our paper. However, we do not agree with the opinion that it represents a "negative" study. Rather, our results together with other recent data should lead to a re-evaluation of some of the current hypotheses about the genetic etiology of PD. Most importantly, our longitudinal results concur with those of the cross-sectional twin study of Piccini et al.1 and while our paper was in press. Both studies show that a genetic component cannot be demonstrated in the etiology of the motor syndrome of Lewy body parkinsonism according to clinical criteria when discordant MZ and DZ twin pairs are compared when gathered from an overall "sporadic" PD population. Our study also shows that five out of seven (not seven, as stated by Dr. Morrish) motor-asymptomatic cotwins (3 MZ; 2 DZ) had abnormal striatal influx constants of 18-fluorodopa during an initial study of PET6 but did not develop PD motor signs after 6 years of clinical observation.

Dr. Morrish questions whether the 18-fluorodopa PET technology is sufficiently reproducible to identify a "preclinical" subject with PD. As long as we regard the disorder of the abovementioned twin samples as similar to that of the overall sporadic PD population, we will not be surprised to observe considerable variations in factors such as age at onset, disease course, clinical typing, associated features (e.g., depression, dementia, vegetative system), treatment response, and disease duration between and within MZ or DZ twin pairs. This also applies to the length of the preclinical period. It is not surprising that different mathematical extrapolations of the 18-fluorodopa metabolism provided a duration of 10 to 20 years or of 40 to 50 years for the preclinical period in sporadic PD. This preclinical period is, at present, poorly understood in its pathobiological features. Moreover, such features may differ according to other factors, such as the underlying etiology, age, sex, and concomitant medication. Again, it is not surprising that PET results vary in subjects presumed to be "preclinical" PD cases. In support of this statement, even victims of accidental MPTP exposure show fairly diverse interindividual evolutions of clinical features and longitudinal 18-fluorodopa PET data, ranging from a normal to a definite parkinsonian state.10

Furthermore, the assumption that the entire period between the age at onset in the index twin and the time point at which the primarily asymptomatic cotwin becomes clinically affected represents his or her "preclinical" stage is not proved for the PD twins. Our earlier PET data6 and those of Piccini et al.1 show heterogeneity in the metabolism of 18-fluorodopa in motor-asymptomatic cotwins, with even normal values in some asymptomatic MZ cotwins. Given the current knowledge and despite methodologic inconsistencies of such an interpretation cannot be exclusively attributed to the limitations of the PET method. It is useful to remember that PET technology per se does not and cannot prove that the metabolic differences between MZ and DZ pairs or within familial PD are genetic in origin.

P. Vierregge, MD, J. Hagenah, MD, I. Heberlein, MD, Lübeck, Germany; C. Klein, MD, Charlestown, MA; H.-P. Ludin, MD, St. Gallen, Switzerland

References
Reply from the Authors: We appreciate the interest and comments of Drs. Bogousslavsky and Ghika on our work. We think it is difficult to distinguish between catalepsy and motor persistence. The latter implies the inadequate maintenance of a posture or position upon the examiner’s command, whereas catalepsy has been defined as the tendency to maintain postures induced by the examiner. Our patients maintained postures passively applied to them, without any verbal command. Furthermore, three of them were aphasic (unable to understand commands). One interesting feature of most of our patients was that they had left-sided hemispheric lesions, whereas motor persistence was described mostly with lesions of the right prefrontal and premotor regions. An update of our series of catalepsy in stroke showed that six out of seven patients had left-sided lesions (unpublished data).

Nevertheless, even taking into account these differences, we may be looking at the same motor phenomenon, regardless of lateralization or way the posture is induced. We believe that both the phenomenon named motor persistence by Drs. Bogousslavsky and Ghika and the cataleptic postures we found are commonly overlooked in clinical practice. We agree that further studies are needed to better understand the mechanisms underlying these phenomena.

G. Saposnik, MD, J.A. Bueri, MD, R.C. Rey, MD, R.E.P. Sica, MD, Buenos Aires, Argentina

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References

Corrections

In the article “Rate of functional decline in Huntington’s disease” (Neurology 2000;54:452–458) by Marder et al., one of the participating sites was omitted from the Appendix. William Mallonee, MD, David Palmer, MD, Gregory Suter, Hereditary Neurological Disease Centre, Wichita, KS, should have been included. The authors apologize for the error.

In the article “Frequency and duration of hospitalization of patients with AD based on Medicare data: CERAD XX” (Neurology 2000;54:740–743) by Fillenbaum et al., the percentages for race in the first numeric column of table 1 were reversed. They should read: white 87.0, black 13.0. The authors apologize for the error.

In the article “Long-term treatment with vagus nerve stimulation in patients with refractory epilepsy” (Neurology 1999;53;1731–1735) by Morris et al., several individuals were omitted from the Vagus Nerve Stimulator Study Group Appendix. Brad Vaughn, Chapel Hill, NC; Adrian Upton, Hamilton, Ontario, Canada; Jack Wilberger, Pittsburgh, PA; H. Stefan, Erlangen, Germany; and Edward Faught, Birmingham, AL, should have been included. The publisher apologizes for the error.
Long-term treatment with vagus nerve stimulation in patients with refractory epilepsy

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