The minimally conscious state: Definition and diagnostic criteria

To the Editor: The definition of yet another dubious diagnosis, the minimally conscious state (MCS),¹ makes it apparent that a few members are hijacking the Academy to promote their own eugenic social agenda. The MCS diagnosis attempts to extend beyond the persistent vegetative state justification for terminating the brain-injured disabled.²⁻⁴ In the process, these social engineers are transforming neurologists into IQ police whose job it will be to interrogate their patients for the exact intelligence information required to avoid the death penalty. The warning of our fellow neurologist, Dr. Leo Alexander, who served on the staff of the Office of Chief Counsel for War Crimes at Nuremberg, holds true now as ever. Writing about the Holocaust, he states, "Whatever proportions these crimes [the Nazi war crimes] finally assumed, it became evident to all who investigated them that they had started from small beginnings. The beginnings at first were merely a subtle shift in emphasis in the basic attitude of the physicians. It started with the acceptance of the attitude, basic in the euthanasia movement, that there is such a thing as life not worthy to be lived. Gradually, the sphere of those to be included in this category was enlarged . . . but it is important to realize that the infinitely small wedged-in lever from which this entire trend of mind received its impetus was the attitude toward the nonrehabilitable sick."⁵

William J. Burke, MD, *St. Louis, MO*

To the Editor: The response engendered by the proposed criteria for the minimally conscious state by Giacino et al. is at once predictable and paradoxical.^{1,3,4} It is predictable in voicing concern that a new diagnostic category could be used to undermine the care of the severely disabled. Opponents contend that in the absence of an evidence base for these criteria, the consensus model used to generate these guidelines represents the consolidation of an ideological stance about the worth of these individuals. But is also paradoxical. This categorization could be a helpful tool in better understanding the continuum of brain states and designing research and therapies to improve and augment cognitive function.¹

By further distinguishing those in a persistent vegetative state from those we suspect have elements of consciousness, we can collectively make a stronger distributive justice claim for enhanced services and more research to address the needs of patients and families with brain injury. Practically, this regard should translate into better diagnostic precision. The staggering public health need posed by traumatic brain injury, coupled with society's marginalization of the disabled, makes this an ethical imperative as medicine seeks to provide the benefits of science to these historically underserved individuals.¹ In this, we disagree with Dr. Shewmon's assertion⁴ that, "there is no clinical or research need for, and strong reasons against, inventing a new diagnostic 'entity' that inherently cannot be meaningfully demarcated from 'severe disability.'"

While the concerns of Ms. Coleman³ are understandable and laudable, it would be more productive if she broadened her advocacy to bring therapeutic or palliative care advances to those with brain injury. Similarly, researchers and clinicians should seek out the diverse views of the disabled community. While we applaud advocacy for the disabled, it is important that it does not pre-empt the prerogative of properly authorized surrogates to make decisions to withdraw life-sustaining therapies in accord with the patient's previously expressed preferences.

Joseph J. Fins, MD, FACP, Nicholas D. Schiff, MD, *New York, NY*

To the Editor: Normal conscious behavior requires arousal that depends on the function of the ascending reticular activating system (ARAS) and awareness or content of consciousness that represents the sum of the cognitive, affective, and other higher brain functions related to "complex physical and psychologic mechanisms by which limbic systems and the cerebrum enrich and individualize human consciousness."⁷

Nonetheless, arousal cannot simply be related to the function

of the ARAS and awareness related to the function of the cerebral cortex because substantial interconnections among the brainstem, subcortical structures, and the neocortex are indispensable for both components of human consciousness. Hence, consciousness does not bear a simple one-to-one relationship with higher or lower brain structures.^{7,8}

Giacino et al.¹ stated that the vegetative state (VS) is "characterized by complete absence of behavioral evidence for self or environmental awareness . . ." and described the minimally conscious state as patients with "inconsistence but discernible evidence of consciousness." Most authors mention human consciousness without considering its two components. For example, higher brain theorists of death habitually describe the persistent or permanent VS as patients with "irreversible loss of consciousness" or "permanent unconscious," but in these patients arousal is preserved, while awareness is apparently lost.^{8,9}

VS patients reflect the only situation in which an apparent dissociation of both components of consciousness is found.⁸ I used the adjective "apparent" because of the following reflection. Can we deny the existence of internal awareness in VS because these patients apparently seem to be disconnected from the external world? The subjective dimension of awareness is philosophically impossible to test, but physiologically it seems conceivable that subjective awareness might continue.⁸

Karen Ann Quinlan's brain showed severe damage of the thalamus, with the cerebral hemispheres relatively spared.¹⁰ We can ask ourselves if in a case like this, other activating pathways, projecting to the cerebral cortex without relaying through the thalamus, could stimulate the cerebral cortex to provide internal awareness, even if physicians are unable to detect its manifestations.⁸

Hence, the paper of Giacino et al. represents a remarkable effort to identify and diagnose a new syndrome of consciousness impairment, along a continuum of brain damage. Nonetheless, I would use the term *minimally aware state* instead of *minimally conscious state*.

Calixto Machado, MD, PhD, *Ciudad de La Habana, Cuba*

Reply from the Authors: In response to Dr. Burke's letter, we reiterate that the primary objective of the Aspen Group was to distinguish individuals who demonstrate discernible, albeit limited, behavioral evidence of consciousness (i.e., minimally conscious state [MCS]) from those who are clinically unconscious (i.e., vegetative state [VS]). This project's impetus grew out of concern that clinical management of patients in acute MCS was often no different than for patients in VS. Consequently, some individuals with at least partial preservation of consciousness were not afforded the opportunity to receive aggressive rehabilitative treatment—a situation we believe that prevails. Our motivation was further bolstered by preliminary empirical evidence showing that although VS and MCS patients have similar degrees of neurobehavioral disability early after injury, functional outcome at 1 year is significantly more favorable in some MCS subgroups.^{11,12}

From a scientific standpoint, we are at a loss to understand Dr. Burke's portrayal of the MCS diagnosis as a mechanism for achieving "eugenics." The Aspen Group comprises largely clinicians who have been providing acute and long-term care for individuals with catastrophic brain injury for many years. The affiliations and experience of the authors of the MCS article¹ should be considered when judging Dr. Burke's allegations. We acknowledge that the definition and recommendations that we have proposed for MCS represent little more than a starting point, but one we hope will direct attention to this condition and facilitate further scientific inquiry.

We appreciate Dr. Machado's comments. He raises some issues that get at some key problems in understanding and defining consciousness and disorders of consciousness. One problem is semantics and how various terms are used in describing consciousness. He points out that consciousness is composed of two components, arousal and awareness, and suggests that the term *minimally aware state* be used in place of *minimally conscious state* because awareness but not arousal is the relevant component in this condition.

Different authors use the terms, *arousal*, *awareness*, and *consciousness* differently in relation to each other. Some emphasize the distinctness of arousal or wakefulness and consciousness.¹³ Some use the terms *awareness* and *consciousness* almost synonymously (e.g., consciousness = awareness of self and environment). Others consider awareness subordinate to consciousness. One author defined awareness as a state in which information is available for the individual to report on and act on.¹⁴ Another author observed that using this definition, computers may demonstrate awareness but not consciousness.¹⁵ Therefore, the appropriateness of one term over another may depend on the semantic nuances intended by the author. In order to avoid this problem, diagnostic terms such as VS and MCS require well-defined criteria so that there is some uniformity in their use for clinical and research purposes. The main goal of our paper was to propose such criteria for MCS.¹

J.I. Giacino, S. Ashwal, N. Childs, R. Cranford, B. Jennett, D. Katz, MD, J.P. Kelly, J.H. Rosenberg, J. Whyte, R. Zafonte, N.D. Zasler, *Braintree, MA*

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MRI measures of entorhinal cortex versus hippocampus in preclinical AD

To the Editor: Killiany et al. report that volumetric measures of the entorhinal cortex and, to a lesser extent, the hippocampus discriminate those elderly individuals in the Clinical Dementia Rating (CDR) 0.5 stage of cognitive impairment who progress to greater impairment from those who remain at the CDR 0.5 stage.¹ The authors propose that MRI measures detect preclinical pathologic change associated with AD and further suggest that AD pathology begins in the entorhinal cortex and later spreads to the hippocampus.¹ We applaud the careful work of this group, although the basis for their conclusion about the temporal spread of pathology can be challenged; because only a baseline MRI was obtained, the region in which volume loss first occurred cannot be resolved in this study.

However, we agree that medial temporal lobe structures are most vulnerable to the earliest pathologic changes of AD. We find in our clinicopathologic studies that AD lesions develop initially in the entorhinal cortex and ultimately may be present in sufficient densities throughout the neocortex to meet criteria for neuropathologic AD, even in the absence of dementia.² We also have demonstrated that substantial entorhinal and hippocampal cortical neuronal loss occurs in CDR 0.5 individuals in comparison with nondemented elderly controls.³ Correspondingly, our MRI studies have shown that hippocampal measures of volume and shape discriminate CDR 0.5 individuals from nondemented individuals.⁴

We differ with Killiany et al. on two major issues. We use the term “preclinical AD” to indicate the presence of disease before it is clinically recognizable. This term characterizes cases with neuropathologic AD in the absence of cognitive symptoms, impairment, or decline.⁵ Thus, preclinical AD is before the CDR 0.5 stage. In contrast, Killiany et al. appear to use preclinical AD to designate CDR 0.5 individuals who already are symptomatic by virtue of their memory complaints. At least 21 of their cases progressed in CDR severity over 3 years, suggesting that the baseline memory complaints for these individuals reflected the initial clinical expression of AD. If so, these individuals might more accurately be considered to represent very early or very mild AD rather than preclinical AD. Postmortem studies performed by our group show that individuals with truly preclinical AD lack substantial neuronal or volume loss in the entorhinal cortex or hippocampus,³ suggesting that volumetric measures of medial temporal lobe structures would be unlikely to detect such cases.

It also appears that Killiany et al. operationalized the diagnosis of AD as equivalent to reaching the CDR 1 stage. This approach will miss many individuals who develop diagnosable AD

while still in the CDR 0.5 stage.^{6,7} Our experience indicates that pathologically verified AD can be clinically diagnosed even in CDR 0.5 individuals with a mean Mini-Mental State Examination score of 29,⁷ comparable with the “questionable” group of Killiany et al. Because they apparently do not recognize these early AD cases, the entorhinal measures reported by them may simply detect AD individuals within the CDR 0.5 stage who are more severely affected than others.¹ These individuals would be most likely to progress to a greater stage of AD severity (i.e., CDR 1) over a defined period, whereas less affected CDR 0.5 individuals with AD may require longer periods to progress. Rather than the presence or absence of disease, the MRI entorhinal measures may be detecting individuals who are relatively more advanced, and hence more likely to progress, within this group of very mildly impaired individuals. Should effective disease-modifying treatments be developed for AD, we suggest that it will be important that imaging and other surrogate markers identify the even less affected individuals with AD, as well as those at the earlier stage of preclinical AD, to permit optimal benefit of the interventions.

John C. Morris, MD, John Csernansky, MD, Joseph L. Price, PhD, *St. Louis, MO*

Reply from the Authors: The accompanying letter by Morris et al. raises three independent but interrelated issues important to those studying prodromal AD: 1) the nature of pathologic change seen earliest in the course of those destined to develop AD, 2) whether MRI measures have been identified that parallel this pathology, and 3) the nomenclature used to describe individuals in the prodromal phase of AD.

Pathologic studies have consistently reported that the parahippocampal gyrus is affected early in AD, and most studies show that entorhinal (and transentorhinal) cortex layer II neurons develop tangles even before the CA1/prosubicular neurons in the hippocampus.^{8,9} Both sites are affected early in the disease process without doubt.

Quantitative measures from MRI scan now clearly show in vivo what neuropathologic analyses have suggested from cross-sectional studies, i.e., that brain changes occur in specific brain regions long before overt dementia. The most commonly reported finding is that the entorhinal cortex and hippocampus show decreased volume among nondemented individuals with cognitive problems.^{10,11} Moreover, recent longitudinal data demonstrate a greater change over time in the entorhinal cortex than in the hippocampus during the prodromal phase of AD¹² that is consistent with pathologic findings.

The nomenclature used to describe individuals in the prodromal phase of AD is varied. In addition, the populations of nonde-

mented individuals with cognitive problems that have been studied differ in their range of impairment. We use the term "preclinical" to refer to individuals who do not yet meet clinical criteria for probable AD. These individuals clearly have clinical expression of AD, even though they are not demented. In our recent MRI study, there were 21 such "questionable" subjects who subsequently progressed to overt dementia. We used the Sum of Boxes from the CDR scale to quantify their degree of functional difficulty at baseline. Of the 21 questionable subjects (mean Sum of Boxes = 1.8), one had a Sum of Boxes of 3.0, while all others had a Sum of Boxes of 2.5 or lower. None had a box score of 3.5 or higher. Thus, our evaluation of these individuals indicated that they were not demented at the time the baseline MRI scans were obtained. Clearly, it will be important for groups studying such individuals to reach a consensus on terminology and methodology in order to facilitate examination of individuals with prodromal AD.

Ronald Killiany, PhD, Bradley T. Hyman, MD, PhD,
Marilyn S. Albert, PhD, *Charlestown, MA*

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Homocysteine, vitamin B₆, and vascular disease in patients with AD

To the Editor: We read with interest the article by Miller et al. about plasma homocysteine (Hcy) levels in patients with AD.¹ They found that high Hcy levels are not associated with AD, whereas, in AD and controls, they are related to vascular disease. These conclusions fit well with our on-going study carried out on a consecutive series of patients with AD and controls. One hundred and six patients with AD and 186 age- and gender-matched controls have been enrolled so far. All subjects performed a standardized clinical and laboratory workup including plasmatic levels of vitamin B₁₂, folate, and Hcy. Patients and controls were classified into two subgroups (vascular vs nonvascular) according to the presence of hypertension, diabetes, history of stroke or TIA, cerebrovascular lesions on CT, myocardial infarction, angina, congestive heart failure, coronary artery disease, or peripheral vascular disease. No significant difference in Hcy levels was found between patients with AD and controls (16.2 ± 8.3 vs 17.1 ± 9.1 ; $p = 0.37$), whereas, within each group, vascular subgroups showed higher Hcy levels. In particular, within the AD group, there was a significant difference for Hcy levels between vascular AD and nonvascular AD (18.0 ± 8.0 vs 13.8 ± 7.9 , $p < 0.02$), but not for vitamin B₁₂ or folate. Through a multivariate analysis entering vascular condition, Mini-Mental State Examination scores, demographic, and laboratory variables, only vascular disease ($\beta = 0.258$) and folate ($\beta = 0.210$) were found to independently predict Hcy levels ($R = 0.16$, $p < 0.02$).²

In agreement with the findings by Miller et al., these results support the strong association between Hcy values and vascular pathology in AD, thus arguing against the claim of a direct relation between Hcy and AD.³ This view is further substantiated by the lack of association between Hcy levels and dementia severity. Moreover, Hcy levels are likely dependent on nutritional factors as shown by the association with folate in our series and with pyridoxal-5-phosphate in the sample reported by Miller et al. We agree with the authors that further studies are required to elucidate the role of Hcy in AD progression, as vascular damage is likely to contribute to the course of dementia. The recent literature has focused the attention on vascular changes related to AD as a consequence of A β peptide toxicity and its deposition.⁴ The published article underlines the need to understand which measures of vascular damage are involved in AD pathology and how they relate with concomitant vascular risk factor(s) whereby dementia course could be faster.

B. Borroni, MD, C. Agosti, MD, A.F. Panzali, PhD, *Brescia*;
M. Di Luca, PhD, A. Padovani, MD, PhD, *Milan, Italy*

Reply from the Authors: The data presented by Borroni et al. replicate our finding that elevated plasma Hcy concentrations are associated with vascular disease but not AD.¹ It is interesting to note that the same conclusion was reached in our study and that of Borroni et al. despite a clear difference between the two study samples in the range of Hcy values observed. In our study, mean Hcy levels for the study sample subgroups ranged from 9.3 to 13.8 $\mu\text{mol/L}$, whereas in the Borroni et al. study they ranged from 13.8 to 18.0 $\mu\text{mol/L}$. The likely explanation for this difference is folic acid fortification, which has been instituted in the United States and has successfully lowered Hcy levels in the general population.⁵ As far as we know, folic acid fortification has not been instituted in Italy, the location of the Borroni et al. study. Consistent with this supposition is that Borroni et al. found that the only significant independent predictors of Hcy levels were vascular disease and folate. In our study, folate was not a significant predictor of Hcy levels, because overall folate status of our study sample was relatively high, and Hcy is only expected to become elevated when folate status is below a certain threshold.⁶

Nonetheless, the consistent finding in both studies that vascular disease, but not AD, is an independent predictor of Hcy levels has potentially important implications. It has recently been reported that elevated Hcy levels predicted dementia and AD incidence in the Framingham Heart Study population.⁴ Though this suggests that Hcy is a causative factor in dementia and AD, it remains possible that Hcy is simply a marker for vascular disease and that vascular disease is the important risk factor for dementia. This implies that blood Hcy levels become elevated as a consequence of vascular disease. A mechanism by which this may occur has been postulated.⁷

Two final points: first, as reported by Borroni et al., we too did not observe a significant association between Hcy and dementia severity in our patients with AD as indicated by Mini-Mental State Examination scores. Though this could be viewed as substantiating the conclusion that there is no direct relation between Hcy and AD, as suggested by Borroni et al., it must be noted that both our study and theirs were cross-sectional in design. It is difficult to ascertain in such a design the length of time a person has had dementia, certainly a critical factor in considering the severity of the disease. Last, Borroni et al. have mistakenly said that we found an association between pyridoxal-5'-phosphate (vitamin B₆) and Hcy in our study sample, which we in fact did not. What we did find was that low B₆ status conferred a significant odds ratio for AD independent of Hcy and vascular disease. We are currently trying to replicate this finding and to determine the ramifications of low B₆ status in patients with AD.

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Dementia with Lewy bodies and AD are not associated with occipital lobe atrophy on MRI

To the Editor: Middlekoop et al.¹ examined whether occipital lobe hypoperfusion and hypometabolism, observed in dementia with Lewy bodies (DLB) and sometimes in AD, are associated with occipital lobe atrophy. They found normal occipital lobe volumes in both diseases.

We studied 15 patients with probable AD, 15 patients with probable DLB (14 patients with DLB and 1 patient with AD with visual hallucinations) and 12 controls using a similar protocol. The groups had comparable ages (70.4 ± 8 , 70.1 ± 9.1 , 66 ± 5.9 ; means $\pm$ SD; $p = 0.23$, Kruskal-Wallis ANOVA). Length of history of dementia (DLB 2.9 ± 2.5 , AD 2.4 ± 1.4 years; $p = 0.22$) and Mini-Mental State Examination scores (DLB 21.0 ± 4.8 , AD 18.1 ± 5.2 ; $p = 0.85$, Mann-Whitney *U* test) were comparable. The study was performed on a Siemens (Munich/Erlangen, Germany) Magnetom Vision plus 1.5 Tesla MRI unit using T1-weighted, three-dimensional MPRAGE sagittal sequences (slice thickness 1.2 mm, TR 9.7 msec, TE 4 msec, flip angle 12 deg. Matrix 200×256 mm, pixel size 1.2×0.94 mm) and an Allegro workstation (ISG Technologies, Canada). Forebrain, occipital lobe, and supratentorial subarachnoid space volumes were measured by one experienced person blinded to the diagnosis using a semiautomated segmentation process.

Because of different intracranial volumes (DLB 1262.2 ± 95.9 , DAT 1154.2 ± 149.7 , controls 1136.1 ± 87.2 cm³; $p = 0.009$), occipital lobe (DLB 120.2 ± 12.7 , DAT 111.1 ± 13.1 , controls 121.6 ± 9.6 cm³) and forebrain volumes (925.8 ± 101.9 , AD 817.6 ± 110.3 , controls 897.6 ± 93.86 cm³) were normalized (divided by intracranial volumes). Normalized forebrain volumes (NFV) were significantly smaller in AD (0.71 ± 0.1 , $p = 0.003$) and insignificantly smaller in DLB (0.73 ± 0.09 , $p = 0.057$) than

in controls (0.79 ± 0.09) and similar in DLB and AD ($p = 0.39$). Normalized occipital lobe volumes (NOV) were smaller in DLB (0.095 ± 0.01) and AD (0.096 ± 0.01 , $p = 0.02$) than in controls (0.107 ± 0.01 , $p = 0.007$) and similar in DLB and AD ($p = 0.85$). NFV minus NOV (DLB 0.64 ± 0.1 , AD 0.61 ± 0.1 , control 0.68 ± 0.05) were significantly smaller in AD ($p = 0.0031$) and insignificantly smaller in DLB ($p = 0.072$) than in controls and similar in DLB and AD ($p = 0.37$). NOV divided by NFV minus NOV were similar in all groups (DLB 0.149 ± 0.02 , AD 0.155 ± 0.01 , controls 0.156 ± 0.02 ; $p = 0.39$).

Our study, performed in smaller collectives than those of Middlekoop et al.,¹ corresponds to previous publications demonstrating forebrain atrophy in AD and mild atrophy also in DLB.^{2–4} In contrast to Middlekoop et al.,¹ occipital lobe atrophy was found, which was similar in DLB and AD, and does therefore not explain occipital hypometabolism and hallucinations in DLB.

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Corrections

Time is money—or is it? Estimating the costs of informal caregiving

In the article, “Time is money—or is it? Estimating the costs of informal caregiving” by Douglas J. Lanska (*Neurology* 2002;58:1718–1719), there was an error in the second sentence of the third paragraph. The sentence should read as follows: “They are based on mathematical models, without various (often unstated and untested) assumptions, that estimate “societal” dollar costs for services presently provided with remuneration, and that include different components in the modeled costs.” The author apologizes for this error.

Experience, competency, and education: Graduating neurology residents' experience with tPA

In the letter to the editor, “Experience, competency, and education: Graduating neurology residents' experience with tPA” (*Neurology* 2002;59:1863), an author's name was spelled incorrectly. The author's name should read Richard M. Dasheiff, MD. The publisher apologizes for this error.

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