The Minimally Conscious State

A Diagnosis in Search of an Epidemiology

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Limited epidemiologic data undermine the identification of patients in a minimally conscious state (MCS) and needed health policy analysis. Based on the natural history of disorders of consciousness and the evolution of MCS, we propose 2 models to characterize MCS epidemiology: a severity model to integrate diagnostic and severity of injury codes, such as the Glasgow Outcome Scale (GOS) and the Glasgow Coma Scale (GCS) scores, and a venue model to track patient migration after hospital discharge through the acute, rehabilitative, and chronic care systems. We applied these analytics retrospectively to a New York State registry and the Centers for Disease Control and Prevention (CDC) 14-state study of traumatic brain injury (TBI). Extrapolations of national MCS incidence and prevalence depend on the severity marker used (GOS score vs GCS score); registry studied; discharge patterns; state variations; and life expectancy. The 14-state study modeled extrapolations (yield, 8844-25,088 patients <45 years) using GOS and GCS scores, respectively, as end points. Although these data are consistent with earlier estimates, the large variance points to the complexity of capturing evolving brain states and limitations of existing data sets as well as the conflation of general disability with disorders of consciousness in extant severity markers. These important concerns limit their generalizability and suggest an affirmative ethical obligation to prospectively collect reliable epidemiologic data to accurately characterize MCS demography.

The recent Schiavo case highlights the need to foster a better understanding of disorders of consciousness, specifically distinguishing the vegetative state (VS) from MCS.1 Objective, scientific data are needed to promote ethical clarity in a heavily value-laden debate. Yet, efforts to distinguish patients in MCS are obstructed by a paucity of epidemiologic and demographic data. Such basic information is essential to understand the natural history of MCS, develop diagnostic and prognostic markers, and engage in health policy analysis.2

Herein, we suggest methods to characterize MCS epidemiology and retrospectively apply these analytic methods to existing brain injury registries. Although estimates of MCS incidence and prevalence are presented, we caution that the results are not conclusive. Extrapolations from existing data sets will yield unreliable estimates of domestic incidence and prevalence. Instead, this work is intended to illustrate the complexity of tracking evolving brain states, limitations of available data sets, and need for systematic surveillance of this marginalized population.3

DISTINGUISHING MCS FROM VS

The MCS was first described in 2002 as a condition of severely altered unconsciousness in which minimal but definite behavioral evidence of environmental awareness is demonstrated.4
Patients may demonstrate attention and intention, purposefully track, and even communicate. The MCS should only be diagnosed when there is "clearly discernible evidence" of 1 or more of the following behaviors: simple command following; any gestural or verbal yes/no responses; intelligible verbalization; or movements or behaviors that are contingently responsive to environmental stimuli.

Minimally conscious state behaviors contrast with the "wakeful unresponsiveness" of VS in which there is no awareness of self, others, or the environment. Nonetheless, these 2 brain states can be conflated because of the episodic and intermittent failure of behavioral responsiveness in MCS. Behaviors distinguishing MCS from VS are noted in Table 1. Visual fixation, smooth pursuit tracking, and emotional or motor behaviors contingent on specific eliciting stimuli may be associated with lower levels of diagnostic certainty than inconsistent (but reproducible) command following, object manipulation, intelligible verbalization, and yes/no response. These later responses are understood as more diagnostically predictive. Emergence from MCS is signaled by the presence of functional object use or reliable communication.

Differentiating MCS from VS rests fundamentally on its historical and physical examination. The use of imaging and electrophysiologic studies remains investigational, though these modalities are evolving rapidly and are likely to influence diagnostic criteria. Imaging studies of patients in MCS conducted by Schiff et al indicated significant preservation of neuronal networks that selectively activate in response to spoken language. More recently, Owen et al reported similar findings in a woman who was behaviorally in VS 5 months after TBI. Functional magnetic resonance imaging revealed specific activations in response to verbal commands that were “indistinguishable” from normal controls. Her command following and functional magnetic resonance imaging findings suggest a transition to MCS, though her manifest behaviors were vegetative. Eleven months after injury she had progressed to visual tracking, a behavior consistent with MCS. To add to this complexity, electrophysiologic studies have suggested that a subgroup of patients in VS with preserved thalamocortical circuits have the ability for cortical information processing. The rapid evolution of these ancillary modalities will necessitate evaluation in population studies, further imparting an ethical obligation to characterize these patients.

AN ELUSIVE EPIDEMIOLOGY

Identifying patients in MCS is easier said than done because the demographic is inferential. Few studies have estimated this epidemiology and differentiated among brain states. The most frequently cited estimate of MCS prevalence uses extrapolations that may inaccurately capture actual epidemiology.

In their important pioneering study, Strauss et al posited that between 112,000 and 280,000 adult and pediatric patients are in MCS. Their calculations are derived solely from a clinically heterogeneous group of pediatric patients, aged 3 to 15 years, who received services from the California Department of Developmental Services. Estimating adult MCS cases from a pediatric subset is problematic given the differing plasticity of the adult and pediatric cerebrum and the distinct age-related etiologies that contribute to MCS.

These problems are confounded by the potential for misdiagnosis in patients less carefully evaluated than those individually assessed by Strauss et al. Minimally conscious state is a relatively new diagnostic category and as yet not fully incorporated into clinical practice and diagnostic coding. These challenges are further complicated by the potential for brain states to evolve depending on their etiology and anatomical import in the brain. It is now appreciated that a persistent VS becomes permanent 3 months after anoxic injury and a year following traumatic injury. In the window between the persistent and permanent VSs, patients can progress to MCS.

Given the structure of our acute care system, most patients will be far from academic medical centers when—and if—they progress to MCS. This diagnostic progression can be missed in less medically intensive venues. Epidotic evidence of behavioral responsiveness in a nursing home may be insufficient to overcome an authoritative academic diagnosis that has become outdated. Notations by hopeful families who observe evidence of awareness can be dismissed as wishful thinking or denial.

Such was the well-published case of Terry Wallis who sustained a severe closed head injury after a motor vehicle crash in 1984. After 19 years in a nursing home, he regained functional communication. His first words were “mom” and “Pepsi.” He thought Ronald Reagan was still president. Though his family believed him aware for nearly 2 decades, their requests for neurological assessment were dismissed. Retrospective review of his medical record indicated he was comatose for 1 to 2 weeks, then recovered to VS and into MCS. Within months of injury, he grunted and nodded his head inconsistently, although still unable to gesture or communicate verbally. Since emergence from MCS in 2003, he continues to recover improved fluency and motor function. Recent diffusion tensor imaging reveals possible axonal re-
growth, postulated as a biological mechanism for his late recovery from MCS.18

As the Wallis case exemplifies, without careful longitudinal assessment, patients in MCS are prone to misdiagnosis because of episodic displays of behaviors and variable time frames of recovery.19 Empirical studies indicate diagnostic error rates of 30% to 40% of patients in VS who might be in MCS.20-22

**MODELS**

Assessing existing databases, we used multistate study of TBI and TBI registries from New York State. Two models were developed to approximate the number of severely injured patients who might eventually evolve to MCS: one based on diagnostic codes coupled with severity scores (Figure 1) and another recognizing the temporal nature of MCS evolution, based on patient migration through venues of care after hospital discharge (Figure 2).

In seeking to extract potential patients in MCS from the registries, our models draw on what is known about the natural history of MCS. First, late in the course of injury (after 1 year), patients who have evolved to the MCS are far more likely to have sustained traumatic vs anoxic brain injury.23,24 Finally, patients in MCS are more likely to have longer life expectancies than patients in a permanent VS because of their increased capacity to maintain homeostasis, manage bodily secretions, and thereby avoid deadly infections.15

**Severity Model**

With these parameters, we narrowed criteria to generate a more specific, albeit less sensitive, estimate of patients in MCS. To avoid overlap between patients with acquired injuries and early-onset degenerative disease, inclusion criteria were limited to patients younger than 45 years. By relying exclusively on TBI data sets, we sought to exclude patients with diffuse or anoxic brain injury, some of whom may be in MCS.

The data sets we relied on generally identified patients discharged from a hospital alive with 1 or more of the following diagnosis codes based on the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*: 800.0 to 801.9 (fracture of the vault or base of the skull); 803.0 to 804.9 (other and unqualified multiple fractures of the skull); 850.0 to 854.1 (intracranial injury, including concussion, contusion, laceration, and hemorrhage); and 959.01 (head injury, unspecified).

**Venue Model**

The venue model identifies patients whose impairments necessitate institutional care. In this way, venue of care would potentially correlate with the degree of cognitive dysfunction or disability. We cross-referenced the aforementioned scores with studies estimating the numbers of patients with TBI in skilled nursing care facilities (SNFs). From this yearly estimate, we calculated the cumulative number of incident cases using estimated survival times in long-term care. The numbers for survival are based on the average length of stay and existing literature delineating medical complications seen in institutionalized patients with severe brain injury (Figure 1).
Several data sets were compared and roughly aggregated to estimate the annual numbers of individuals with injury profiles that might eventually evolve to the MCS. A 14-state study of TBI reviewed 62,771 TBI-related hospital discharges and categorized patients by demographics, ICD code, medical records, and cause of injury.\textsuperscript{28} The study included an 11-state sample of 99,449 TBI-related hospital discharges for which supplemental GCS and GOS data were available.

The study noted that detailed sample weighting programs and methods were developed and applied to the abstracted data to permit the merging of state-specific data. The study estimated that 6.3% of TBI-related hospital discharges during 1997 had severe disability, less than 1% in “persistent coma” by GOS score.\textsuperscript{28} (We interpret “persistent coma” to mean VS, although this erroneously conflates the eyes-open VS and MCS.)

Using GCS discharge data, the 14-state study estimated severe injury in 9.8% (6152 patients) of total 1997 TBI-related hospital discharges. Of those, approximately 4516 were younger than 45 years based on the age distribution of TBI.\textsuperscript{28} This would extrapolate to a yearly national prevalence of 25,088 cases younger than 45 years. Using weighted GOS score estimates of the 62,771 live TBI-related hospital discharges reviewed for 14 states, approximately 3952 had severe GOS scores.\textsuperscript{28} Of those, 1592 were younger than 45 years, based on percentage of injury data and age distribution of severe GOS score.\textsuperscript{28} Extrapolating these GOS data to a national incidence yields 8844 yearly cases of severe TBI in patients younger than 45 years. These national extrapolations are based on 2000 US census data and assume comparability of national and 14-state age-based severe TBI incidence (Table 2).

**Table 2. Estimated National Extrapolations From Available Registries\textsuperscript{a}**

<table>
<thead>
<tr>
<th>Sample</th>
<th>Cases &lt; 45 y</th>
<th>National Extrapolation at 1 y</th>
<th>National Extrapolation at 5 y</th>
<th>National Extrapolation at 10 y</th>
</tr>
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<tbody>
<tr>
<td>New York State severe GCS score</td>
<td>301\textsuperscript{b}</td>
<td>4493</td>
<td>22,465</td>
<td>44,930</td>
</tr>
<tr>
<td>14-State study severe GCS score</td>
<td>4516\textsuperscript{c}</td>
<td>25,088</td>
<td>125,440</td>
<td>250,880</td>
</tr>
<tr>
<td>14-State severe GOS score</td>
<td>1592\textsuperscript{c}</td>
<td>8844</td>
<td>44,220</td>
<td>88,440</td>
</tr>
</tbody>
</table>

Abbreviations: GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; SNF, skilled nursing home facility; TBI, traumatic brain injury.

\textsuperscript{a}Extrapolated cases over time do not take into account variable rates of population change, death, recovery, or annual variations in severe TBI rates, all of which could affect results.

\textsuperscript{b}An average of the range (estimated 207-395 SNF population) found for the age group younger than 45 years was used for calculating incident cases. The SNF range presented reflects the use of the New York State Minimum Data Set and Hospital Discharge Data as end points in describing the potential range of applicable patients. National extrapolation results considered that the New York State population constituted approximately 6.7% of the total US population in 2000.

\textsuperscript{c}The 14-state study data were extrapolated using US population numbers for the 11 states from which data were obtained: Alaska, Arizona, Colorado, Louisiana, Minnesota, Nebraska, New York, Oklahoma, Rhode Island, South Carolina, and Utah for using GOS and GCS score. These 11 states constituted approximately 18% of the US population in 2000.

**MODELED ANALYSIS**

**Estimated Annual Incident Cases of MCS: Severity Model**

Studying the MCS population also requires knowledge of discharge status, which may be to home, rehabilitation, or long-term care. Disposition is primarily determined by functional status, although socioeconomic factors like family support and insurance coverage also play a role (Figure 2).

To quantify the TBI nursing home population, we used New York State Department of Health (DOH) Bureau of Injury Prevention data collected since 1997. As part of the CDC-funded multistate Central Nervous System Injury Surveillance Prevention System project, the New York State DOH conducts surveillance of TBI-related hospitalizations and deaths and analyzes random samples of TBI hospital records to further categorize TBI risk factors, severity, and outcomes. The New York State DOH conducted a preliminary analysis of these records from 1996 through 1999 (J. Eisele, PhD, written communication, unpublished data used with the permission of the New York State DOH Bureau of Injury Prevention, June 7, 2004).

The New York State DOH identified 11% of patients with TBI with “severe” injuries based on GCS score and levels of consciousness information.\textsuperscript{29} Extrapolating to statewide incidence for 2000, the New York State DOH estimated 1530 individuals would sustain severe TBI. We found conflicting estimates for SNF information. A preliminary review of the 2002 New York State Minimum Data Set (MDS) provided by the New York State DOH Division of Home and Community-Based Care found approximately 532 cases where a resident was admitted with an ICD-9-CM diagnosis of 854.00 (TBI unspecified) in 2002. Of these cases, 27% (144 cases) were between 26 and 45 years of age and 12% (64 cases) were 25 years or younger, for a total of 207 New York residents younger than 45 years with TBI who were discharged to an SNF.

According to the New York State Hospital Discharge Data (HDD) for 2000, however, of the 13,907 patients hospitalized for TBI during that year, 1015 (7.3%) were discharged to an SNF.\textsuperscript{30} The difference between the MDS and HDD data may be the lack of sensitivity of the MDS for detecting the full TBI population. The MDS data rely on the ICD code 854.00 to identify patients with TBI, whereas, in fact, not all patients with TBI receive this code. If the same percentages applied as uncovered by the MDS study, approximately 395 of the New York SNF residents would be younger than 45 years.

National population estimates for April 1, 2000, are 281,421,906, with New York having 18,976,457, or about...
6.7% of the national population. Given the potential for significant differences among states, the small percentage of total New York residents with severe TBI, and differences between the periods measured, extrapolating to national levels provides only a rough estimate of the number of TBI cases in 2000: between approximately 7940 and 15 159, including between approximately 3090 and 5896 for people younger than 45 years (based on SNF numbers and using the MDS and the HDD data, respectively, as end points) or approximately 22 836 based on patients with GCS scores (using 2000 US census data and assuming that national percentages for SNF residents with severe TBI and patients with severe GCS scores would be identical to that of New York).

ESTIMATED TOTAL INCIDENT CASES

Patients with MCS may follow a survival time course distinguishable from other brain-injured patients. It has been suggested that patients in VS due to TBI have a lower mortality rate and longer survival compared with those with anoxia.22 Survival in MCS depends on age; quality of care; comorbid illness and injury; and decisions to withhold or withdraw life-sustaining therapy. Survival estimates with severe brain injury are variable.31 32 Young patients with MCS retain limited mobility and have longer life spans; 81% have an 8-year survival.22

Using these estimates, we modeled the number of MCS cases expected over time, assuming a constant annual incidence. These calculations include patients in VS as well as those who have emerged from MCS and do not consider that patients in MCS experience variable rates of emergence, natural death, or palliative care plans.

COMMENT

This retrospective analysis has limitations that call for prospective data collection to accurately characterize MCS epidemiology. These limitations include imprecise and variable data collection, patient evaluation, sampling methods, extrapolations, and projections.

Variation in state TBI census data—use of GOS, GCS, or both scales—may have affected our MCS estimates.28 Beyond that is the incompleteness of the data set: 40% of abstracted 14-state cases lacked GCS scores. Scores were inferred based on admission information about level of consciousness. Similarly, SNF placement does not differentiate between need due to physical or cognitive disability. Sampling and weighting methods used in the data sets also may inadequately capture patients with MCS. The 14-state study relied on severity data from 11 states, with 7 providing data based on stratified weighted random samples drawn proportionately from 3 groups: predischARGE data; admission and small and large hospitals, respectively. These strata are not necessarily reflective of the likelihood of MCS; furthermore, states used varying formulas to generate samples. Finally, patient venation discharge home. Using these outcomes as a severity indicator, CDC data suggest a range of 10 000 to 22 000 patients with a potentially severe TBI-related disability. This conclusion is consistent with our extrapolation from the 14-state study of between 8844 and 25 088 patients younger than 45 years with severe TBI, using GOS and GCS data, respectively. Although these ranges are comparable, differences occur within data sets depending on which instrument is used.

CONCLUSIONS

The seminal article by Jennett and Plum5 described VS as “a syndrome in search of a name.” Decades later, MCS has a name but remains a diagnosis in search of an epidemiology. Without reliable epidemiologic measures, patients in this condition remain silent victims, unheard and uncounted.2 Therapeutic advances will require knowledge of MCS natural history only obtainable through prospective epidemiologic studies. In tandem with in-depth longitudinal neuroimaging and electrophysiologic studies of individual patients, epidemiologic assessment14 will help expand the range of therapeutic35 36 and neuropsychiatric options16 necessary for patient-centered care.

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Author Contributions: Drs Fins and Gerber and Ms Master had full access to all of the data in the study and take

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responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Fins, Master, and Gerber. Acquisition of data: Fins and Master. Analysis and interpretation of data: Fins, Master, Gerber, and Giacino. Drafting of the manuscript: Fins, Master, and Giacino. Critical revision of the manuscript for important intellectual content: Fins, Master, Gerber, and Giacino. Statistical analysis: Fins, Master, and Gerber. Obtained funding: Fins. Administrative, technical, and material support: Master and Gerber. Study supervision: Fins, Gerber, and Giacino.

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