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Update article

France establishes guidelines for treating neurobehavioral disorders following traumatic brain injury

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ABSTRACT

This paper comments on the report by a committee of La Société Française de Médecine Physique et de Réadaptation (SOFMER) in response to the Haute Autorité de santé in France concerning the classification and clinical management of disorders of comportment following moderate to severe traumatic brain injury (TBI). In view of the large number of patients and families affected by these disorders, there is a strong rationale for these guidelines to ensure that clinical assessment and treatment is evidence-based. The report is viewed from the perspective of current research on disorders of comportment and in relation to recent reviews and meta-analyses on this topic. Comments on the classification draw on pathophysiology and brain imaging in addition to the clinical literature. The SOFMER report and recent projects in North America are compared for trends in the development of recommended assessment scales and standard, evidence-based treatment protocols for pharmacologic and non-pharmacologic interventions. Collaborative, multinational investigations of TBI are also noted, which are advancing progress toward guidelines for clinical management.

1. Introduction

A report prepared by La Société Française de Médecine Physique et de Réadaptation (SOFMER) in response to the Haute Autorité de santé in France provides clinicians and researchers with accessible, up-to-date, evidenced-based guidelines on the classification and clinical management of neurobehavioral disorders following severe traumatic brain injury (TBI). This consensus document synthesizes contributions by a multidisciplinary committee representing clinicians and investigators. Through their deliberations, this committee of TBI specialists achieved a common ground on the classification and clinical management of neurobehavioral sequelae (i.e., disorders of comportment during the post-acute and chronic stages of severe TBI). In this scholarly report, the committee has provided readers with clear definitions of the disorders.

Although a comparable document on this topic has not, to my knowledge, been disseminated in North America, the Brain Injury Association of America in association with Mount Sinai Medical Center in New York has initiated the project "Guidelines for the Rehabilitation and Chronic Disease Management of Adults with Moderate to Severe TBI". This project is currently compiling questions to be addressed by panels of rehabilitation experts concerning issues in the behavioral, cognitive, functional, medical, and participation/vocational domains. The project is soliciting feedback from the rehabilitation community to revise questions drafted in each domain and review additional questions (http://www.biausa.org/TBIGuidelines/tbi-rehabilitation-guidelines_feedback).

2. Recent North American projects related to the SOFMER report

Published reviews by groups working to develop guidelines or at least a consensus on clinical management of cognitive and behavioral problems from TBI include the 2006 Warden et al. [1] seminal review of pharmacologic therapy for neurobehavioral sequelae of TBI. The authors reviewed the evidence supporting specific drugs for treatment of poor attention and slowed processing speed, other cognitive deficits, aggression, depression, anxiety, and other psychiatric conditions after TBI. At the time of their review, Warden et al. [1] noted that the evidence was especially robust for treating attentional disturbance with methylphenidate, but they emphasized the general need for additional randomized clinical trials (RCTs) to provide a more evidenced-based approach to pharmacologic treatment. In contrast, the Frenette et al. [2] review of dopaminergic medications for

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treating neurobehavioral sequelae of TBI was more critical. The authors noted the heterogeneity in methods across clinical trials (e.g., different outcome measures) and were guarded concerning whether the current evidence supported clinical guidelines for the medications that they reviewed.

Recommendations from the recent review of pharmacologic management of cognitive impairment by Arciniegas and Silver [3] were similar to those by SOFMER, including caution about the use of neuroleptics, benzodiazapine, anticonvulsants, and anticholinergics. Arciniegas and Silver also highlighted the evidence for the effectiveness of amantadine in treating disorders of consciousness; they advocated for non-pharmacologic interventions such as environmental changes and cognitive training, a perspective consistent with SOFMER. The Wheaton et al. meta-analysis [4] focused on treating cognitive deficit and supported methylphenidate for treating attention and slowed cognitive processing. In 2011, the US National Academy of Science published a report by a multidisciplinary panel that evaluated the evidence for cognitive rehabilitation of TBI patients, with an emphasis on mild TBI [5]. The panel concluded that the evidence provided limited support for specific interventions to treat problems in attention, executive function, memory and communication. However, it also noted the need for clinical trials to standardize treatments using manuals that are accessible to other investigators, developing a common registry or linked registries of rehabilitation outcome data to facilitate meta-analyses, and bridging the gap between standard outcome measures and evaluation of everyday functioning.

Guidelines for the management of sports concussion have been published by the Fourth International Conference on Concussion in Sport [6] and the American Academy of Neurology [7]. Protocols for concussion management in North America are well established and widely followed but still lack support by rigorous RCTs. The international sports concussion literature suggests that concussion management protocols may be less widely implemented in Europe than in North America, but I am not aware of any surveys of trainers and physicians to compare practices across these continents.

The ongoing NIH-supported TRACK-TBI project is a multinational research consortium using advanced brain imaging and longitudinal follow-up of a large cohort to study the outcomes of TBI and the neural underpinnings of the sequelae [8]. In time, this approach may extend to rehabilitation and hopefully address guidelines for clinical management of post-acute and chronic, severe TBI [9].

3. Rationale for the SOFMER report

The premise that the neurobehavioral sequelae or problems of comportment are primary concerns for rehabilitation is supported by studies that reported cognitive and behavioral sequelae as the most frequent basis for disability at 6 months in two thirds of patients with severe TBI [10]. Similarly, interviews and rating scales given to families have documented that their concerns and burdens as caregivers focused more on behavioral issues than cognitive impairment and physical disability [11].

4. Classification of neurobehavioral disorders

In general, the classification of 4 types of neurobehavioral disorders agrees with clinical neuroscience research on post-acute and chronic stages of severe TBI. Disorders of excess behaviour (e.g., disinhibition, irritability, and aggression) and deficient behaviour such as apathy and depression involve distinct brain regions (e.g., orbitofrontal for disorders of excess) or systems (orbitofrontal-amygdala) and imbalance of neurotransmitters (e.g., dopaminergic for attention) or hormones. Identifying focal lesions in regions associated with disorders of comportment is informative clinically. However, functional imaging has disclosed that disruption of connectivity of key networks is an important mechanism in these conditions independent of focal lesions. For example, functional brain imaging studies [12] have implicated prefrontal-amygdala connections in emotional and behavioral regulation and their vulnerability to severe closed head trauma. Orbitofrontal and inferior frontal regions have been implicated in the capacity to inhibit inappropriate or irrelevant responses to situations [13]; reduced modulation of the amygdala by prefrontal cortex is also implicated in emotional memory and post-traumatic stress disorder [14].

The recognition of apathy and reduced motivation in the classification of disorders of comportment is consistent with the extensive literature documenting the high frequency of these problems following severe TBI. The document also presents a strong case for differentiating apathy from depression.

Disorders classified by the committee as "secondary" such as depression and anxiety are frequent after TBI and represent challenges to rehabilitation. The status of depression as a direct effect of TBI or in reaction to the resulting deficits and disability is not entirely clear. The independent status of suicide as a separate category can be questioned because it is a complex action that involves mechanisms in the disorders classified in categories I–III. Could suicide have been included in depression and perhaps agitation or aggression?

The SOFMER committee recognized that disorders of comportment are often chronic effects of severe TBI. Advances in research have characterized diffuse axonal injury, metabolic, and neurohormonal effects of TBI that contribute to evolving disturbances of affect and behavior. The discovery that subclinical seizures are more common than previously thought is another mechanism contributing to the late effects of severe TBI [15]. There is growing recognition that severe TBI triggers cellular processes that lead to neurodegeneration involving inclusion of hyper-phosphorylated tau and deposits of amyloid, which increase the risk of dementia or other neurodegenerative conditions [16]. The trajectory of age-related changes in cognition may be accelerated even in TBI patients who appear to evade a neurodegenerative disorder [17]. Individual differences in susceptibility to the chronic effects of severe TBI is also important to recognize. The committee addressed gender differences and alluded to genotype, a well-established factor in the risk of Alzheimer's disease in this population [18]. Alterations of behavior, mood, and cognition in the years following exposure to repetitive mild head trauma may be a harbinger of chronic traumatic encephalopathy [19]. Epidemiological evidence suggests that a single moderate to severe TBI increases the risk of dementia in people $\geq$ 55 years old [20].

5. Moderators of disorders of comportment

The SOFMER committee identified factors that increase the risk of disorders of comportment and alluded to factors that are protective. These "moderators" include genotype (e.g., APOE allele [18]), gender, education, and socioeconomic status. APOE 4 carriers are more vulnerable to poor outcomes after severe TBI, whereas education and an advantaged environment can be considered proxies for cognitive reserve [21] (i.e., the capacity to withstand or resist the adverse effects of neuropathology or other brain insults on cognitive decline) [21]. Similarly, resilience is increasingly being recognized as protective against post-traumatic stress disorder, depression, and other secondary effects of TBI.