Does the FOUR Score Correctly Diagnose the Vegetative and Minimally Conscious States?

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Wijdicks and colleagues[1] recently presented the Full Outline of UnResponsiveness (FOUR) scale as an alternative to the Glasgow Coma Scale (GCS)[2] in the evaluation of consciousness in severely brain-damaged patients. They studied 120 patients in an intensive care setting (mainly neuro-intensive care) and claimed that "the FOUR score detects a locked-in syndrome, as well as the presence of a vegetative state."[1] We fully agree that the FOUR is advantageous in identifying locked-in patients given that it specifically tests for eye movements or blinking on command. This is welcomed given that misdiagnosis of the locked-in syndrome has been shown to occur in more than half of the cases (see Laureys and colleagues[3] for review).

As for the diagnosis of the vegetative state, the scale explicitly tests for visual pursuit, and hence can disentangle the vegetative state from the minimally conscious state (MCS). The diagnostic criteria for MCS have been proposed[4] only recently, but Wijdicks and colleagues[1] do not mention the existence of this clinical entity in their article. As for the vegetative state, MCS can be encountered in the acute or subacute setting as a transitional state on the way to further recovery, or it can be a more chronic or even permanent condition. The MCS refers to patients showing inconsistent, albeit clearly discernible, minimal behavioral evidence of consciousness (eg, localization of noxious stimuli, eye fixation or tracking, reproducible movement to command, or nonfunctional verbalization).[4] The FOUR scale does not test for all of the behavioral criteria required to diagnose MCS.[4] It is known from the literature (see Majerus and colleagues[5] for review) that about a third of patients diagnosed with vegetative state are actually in MCS, and this misdiagnosis can lead to major clinical, therapeutic, and ethical consequences.

We tested the ability of the newly proposed FOUR scale to correctly diagnose the vegetative state in an acute (intensive care and neurology ward) and chronic (neurorehabilitation) setting. Patients were assessed using the GCS,[2] FOUR scale,[2] and Coma Recovery Scale-Revised (CRS-R)[6] in randomized order. The latter scale was specifically developed to differentiate vegetative patients from MCS and to identify patients that have emerged from MCS. The basic structure of the CRS-R is similar to the GCS and the FOUR scale, but its subscales are much more detailed, targeting more subtle signs of recovery of consciousness. This increased attention to subtle but potentially important clinical signs lengthens the administration time of the CRS-R and makes it more challenging to use in the intensive care setting.

Sixty severely brain-injured, postcomatose (ie, GCS $\leq$ 8) patients were prospectively studied (15 in New Jersey and 45 in Liège). Mean age was 50 years (range, 18–86 years); 39 patients were men. Cause was traumatic brain injury (24 patients), postanoxic-ischemic encephalopathy (14 patients), ischemic or hemorrhagic stroke (9 patients), aneurysmal subarachnoid hemorrhage (4 patients), metabolic encephalopathies (3 patients), status epilepticus (3 patients), encephalitis (2 patients), and craniotomy for brain tumor (1 patient). All patients were assessed free of sedative agents or neuromuscular function blockers, and 22 acute patients were intubated. Thirty patients were studied in the acute setting (ie, within 4 weeks after their brain insult; mean, 11 days; range, 1–24 days), and 30 patients were studied in a chronic setting (ie, more than 4 weeks after the insult; mean, 23 months; range, 1 month to 16 years).

Overall, 29 patients (16 acute and 13 chronic patients) were considered as being in a vegetative state based on the GCS (ie, GCS subscores showed spontaneous or stimulation-induced eye opening [$E > 1$]; absence of verbalization [$V < 3$]; and absence of localization of pain [$M < 5$]). The FOUR scale identified 4 of these 29 patients (1/16 acute and 3/13 chronic patients) as not being vegetative given that these patients showed visual pursuit (FOUR scale subscore $E = 4$). This finding confirms the authors' claim that the FOUR scale is superior to the GCS in detecting a vegetative state "where the eyes can spontaneously open but do not track the examiner's finger."[1]

However, the CRS-R identified an additional seven patients (four acute and three chronic) showing visual fixation (ie, eyes change from initial fixation point and refixate on a new target location for more than 2 seconds on at least two of four trials), and hence meeting the criteria for MCS set forth by the Aspen Workgroup.[4] Therefore, of the 25 patients identified as being in a vegetative state by the FOUR scale, 7 were diagnosed as being in a MCS by the CRS-R (4/15 acute and 3/10 chronic patients). All seven of these patients showed visual fixation, a clinical sign heralding recovery from the vegetative state,[4] but not included in the FOUR eye response score.

In conclusion, we welcome this new scale and its effort to more accurately and expeditiously diagnose the locked-in syndrome by specifically assessing voluntary eye movements. The FOUR scale also adds assessment of eye tracking, which allows it to differentiate vegetative from MCS patients, but it should be noted that both acute and chronic patients may solely show visual fixation, an item not evaluated by the FOUR scale.

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Reply

Does the JFK Revised Coma Recovery Scale Complement the FOUR Score?

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The FOUR score (Full Outline of Unresponsiveness) has been well received in and outside the United States and has been implemented at the Mayo Clinic Saint Mary's Hospital.[1] What is notable is that the nursing staff has enthusiastically embraced the new coma scale. Studies on its usefulness outside the boundaries of the Neurological-Neurosurgical Intensive Care Unit are under way.

The FOUR score has been developed to assess the depth of coma in a more detailed manner than the Glasgow Coma Scale. The FOUR score was not devised to assess long-term severely disabled or permanently unconscious patients as much as the JFK revised coma recovery scale (JFK CRS-R) was not devised to assess acutely comatose patients. The JFK CRS-R lacks important parts of the neurological examination, tests six components, and requires considerable time of observation to be certain of the behavioral responses of the patient. The FOUR score was also not developed to *diagnose* a vegetative or minimally conscious state. That requires a comprehensive neurological evaluation and observations over time. Nonetheless, Schnakers and colleagues[2] note that the FOUR score recognizes important clinical components of these conditions when tested in a new set of patients. We believe the answer to their question is a tentative yes.

Does the JKFCRS-R complement the FOUR score? In patients who remain unconscious or show possible early signs of awareness, the JFK CRS-R may have additional value in differentiating vegetative from minimally conscious states. The JFK CRS-R may identify visual fixation, but that is a difficult test that requires careful and prolonged observation and is a clinical sign that has to be differentiated from a visual orienting reflex in vegetative state. Visual fixation may also occur in akinetic mutism, and thus may not indicate emergence from a comatose state. Visual fixation for those reasons has not been included in the FOUR score. Moreover the JKF CRS-R will have to be validated in large group of patients using physicians and nursing staff who manage acutely comatose or stuporous patients as raters. However, Schnakers and colleagues' study is interesting and suggests that perhaps a FOUR score assessment followed by a JFK CRS-R assessment (if warranted) may be a useful combination in certain instances.

We are pleased that the rehabilitation community has an interest in the FOUR score. Cross-pollination of scales may be useful, and the FOUR score is currently tested in the rehabilitation setting in our institution.

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Tomographic Visualization of Cholinesterase

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Kuhl and colleagues[1] used 1-[^{11}C] methyl-4-piperidinyl n-butyrate ([^{11}C]BMP) to visualize butyrylcholinesterase (BuChE) in normal subjects and Alzheimer's disease (AD) patients. They found no increase in synaptic BuChE in AD, but a number of issues arise when analyzing this conclusion.

It is stated that [^{11}C]BMP is not a substrate for acetylcholinesterase (AChE), but no evidence is presented to verify this possibility, such as a biochemical characterization of BMP. Instead, the report by Snyder and colleagues,[2] who synthesized [^{11}C]BMP and examined it as a substrate for cholinesterases (ChEs), is quoted, but that study used eel AChE and horse serum BuChE. It is thus assumed that [^{11}C]BMP is specific for human synaptic BuChE, but this cannot be done without direct evidence because it is well established that ChEs from different species have different biochemical properties, including substrate specificity, affinity, and inhibitor sensitivity.[3]

The isoforms of ChEs expressed in AD are poorly understood, especially with regard to their origin, compartmentalization, and subcellular localization. Biochemical observations show convincingly that there is an increase in the levels of BuChE in AD,[4] and histochemical evidence shows that this increase is due in part to its deposition in neuritic plaques and neurofibrillary tangles.[5] The imaging study did not corroborate this established change in the levels of BuChE between control subjects and patients, because the methodology used does not visualize lesion-bound BuChE. Given the inability of this method to detect established patterns of BuChE alterations in AD, it is uncertain whether the pattern visualized can be attributed to synaptic BuChE.

Many histochemical studies have visualized the distribution of AChE and BuChE in the human brain.[5] Most of these assess the distribution of ChEs at the light microscopic level, and comments can be made only about the enzymes located in cell bodies and their processes. Evaluating the synaptic distribution of ChEs usually requires resolution at the electron microscopic level, but no evidence is provided regarding the ability of positron emission tomography imaging to visualize the contents of synapses. Because the spatial resolution of this imaging technique is several orders of magni-