Detecting Delirium Using a Physiologic Monitor

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For the past 2500 years, delirium has been described based on the presence of behavioral symptoms. Each year, as many as 1 in 5 acute care and 80% of critically ill patients develop delirium. The United States spends approximately $164 million annually to combat the associated consequences of delirium. There are no laboratory tools available to assist with diagnosis and ongoing monitoring of delirium; therefore, current national guidelines for psychiatry, geriatrics, and critical care strongly recommend routine bedside screening. Despite the significance, health care teams fail to accurately identify approximately 80% of delirium episodes. The utility of conventional electroencephalogram (EEG) in the diagnosis and monitoring of delirium has been well established. Neurochemical and the associated neuroelectrical changes occur in response to overwhelming stress before behavioral symptoms; therefore, using EEG will improve early delirium identification. Adding EEG analysis to the current routine clinical assessment significantly increases the accuracy of detection. Using newer EEG technology with a limited number of leads that is capable of processing EEG may provide a viable option by reducing the cost and need for expert interpretation. Because EEG monitoring with automatic processing has become technically feasible, it could increase delirium recognition. Electroencephalogram monitoring may also provide identification before symptom onset when nursing interventions would be more effective, likely reducing the long-term ramifications. Having an objective method that nurses can easily use to detect delirium could change the standard of care and provide earlier identification.

Keywords: critical illness, delirium, EEG, electroencephalogram, geriatric

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DELIRIUM

For the past 2500 years, delirium has been described and understood based on the presence or absence of behavioral symptoms.[1] Not until 1983 was there an agreed upon definition when the American Psychiatric Association published the third edition of the *Diagnostic and Statistical Manual for Mental Disorders* (*DSM*). The American Psychiatric Association, in the *DSM*, defines delirium as "primarily a disturbance of consciousness, attention, cognition, and perception that can also affect sleep, psychomotor activity, and emotions." Since that time, *DSM* criteria have been revised several times, with the most recent being the *DSM-5*.

A growing body of literature demonstrates the significance of delirium in terms of mortality, reduced quality of life, and increased cost of care. Each year, hospitals are faced with as many as 1 in 5 acute care and 80% of intensive care unit (ICU) patients developing delirium.[2] As a country, the United States spends approximately $164 million annually to combat the consequences associated with delirium.[3] This amount is expected to increase dramatically over the next 20 years as the percentage of adults older than 65 years increases. This increase will result in an estimated 1 in 4 individuals falling into this age bracket.

Unlike many psychiatric conditions, there are no laboratory tools available to assist with diagnosis and ongoing monitoring of delirium.[4] Researchers have developed and evaluated more than 40 different clinical assessment tools and published more than 800 articles to assist clinicians in identifying the presence of delirium.[5] The current standard for diagnosis is a clinical examination including criteria from the *DSM-5*.[6] Their criteria are included in the Table.

Current national guidelines for psychiatry, geriatrics, and critical care strongly recommend routine screening for delirium. Although there are several systematic reviews describing ICU delirium screening tools, to date, there is no single review of available geriatric screening tools. Because of lack of enough evidence, neither the APA nor the American Geriatric Society has recommended a particular tool for delirium screening. Although numerous delirium assessment tools are used in hospitals, there remains tremendous subjectivity with such approaches. This subjectivity results in failure of nurses to identify as many as 80% of delirium cases.[7]

In 2013, the Society of Critical Care Medicine published the *Pain, Agitation, and Delirium Guidelines* recommending use of a validated tool for routine delirium screening. Although a definition for routine is not defined, 2 critical care screening tools were recommended: The Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist for delirium screening.[8] Both tools are clinical assessments to detect the behavioral symptoms resulting from delirium and have been well-validated in research settings. The CAM-ICU and Intensive Care Delirium Screening Checklist have been determined to be the most valid, reliable, and feasible delirium assessment tools for use in adult ICU patients. Between these 2 tools, only the CAM-ICU is considered validated in both geriatric and ICU patients. The CAM-ICU is the most studied and, as a result, has been described in the literature as the gold standard for assessing delirium in the ICU setting.

TABLE ***Diagnostic and Statistical Manual, 5th Edition*, Criteria for Delirium**

- Disturbance in *attention* (ie, reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced *orientation to the environment*)
- The disturbance develops over a short period (usually hours to a few days), *represents an acute change from baseline attention and awareness*, and tends to fluctuate in severity during the course of a day.
- An additional disturbance in cognition (eg, memory deficit, disorientation, language, visuospatial ability, or perception).
- *The disturbances in Criteria A and C* are not better explained by a preexisting, established, or evolving neurocognitive disorder and *do not occur in the context of a severely reduced level of arousal such as coma*
- There is evidence from the history, physical examination, or laboratory findings that the disturbance is *a direct* physiological consequence of another medical condition, *substance intoxication or withdrawal (ie, due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies.*

Despite the significance, health care teams fail to accurately identify about 80% of delirium episodes.[9] Delirium is often undiagnosed or mistaken for other conditions such as dementia and depression even when using a standardized bedside assessment. Some of the likely causes include the fact that delirium fluctuates throughout the day, assessments are either intermittent (usually once a shift) or retrospective over the previous 8 to 12 hours drawing on the clinicians recall, and components of the assessment are subjective and/or not clearly defined. Even when appropriately identified, delirium is often well established, further increasing the risk for poor long-term outcomes. Therefore, this review seeks to describe a potential alternative for identifying delirium in critically ill patients.

DELIRIUM AND BEDSIDE ASSESSMENT

Implementation research has shown that the limitations of the CAM-ICU assessment tool lead to low sensitivity and poor interrater reliability at 43% to 47%, meaning the CAM-ICU appropriately detected delirium less than half of the time.[10] The accuracy of delirium assessment using the CAM-ICU has been shown to be lower in patients with mild delirium (30%), baseline mild cognitive impairment (33%), and dementia (62%) as opposed to patients without cognitive impairments.[11] In patients with hypoactive

delirium, research has consistently shown significantly lower (31%-64%) sensitivities.[12] Further contributing to low sensitivities, the CAM-ICU requires extensive and frequent training to obtain and maintain interrater reliability. As many as 29% of patients have been found to be insufficiently vigilant to follow the instructions to complete a CAM-ICU assessment ($P < .001$), even after excluding moderately sedated patients.[13] Hypoactive delirium is more difficult to detect, resulting in significantly lower accuracy (31%-64%). The high prevalence of hypoactive delirium in patients who are 65 years or older is of particular concern for the older adult patient population. Ideally, assessment of older adults would include a measure capable of distinguishing "organic" from "functional" causes of acute mental status changes as well as differentiate delirium from dementia.[4] Organic means a disturbance caused by injury or disease affecting brain tissues as well as by chemical or hormonal abnormalities. As opposed to organic, functional causes are disturbances with no known associated organic or pathological tissue changes that can be found as causes for the symptoms. Further, it is recommended the measure provide a reliable method to indicate severity of illness and retain validity with repeated use. Electroencephalogram (EEG) with quantitative analysis has the potential to fulfill these requirements.

USE OF EEG

In 1875, Caton[14] discovered the fluctuating waveforms that constitute the EEG by reflecting a beam of light on the mirror of the galvanometer. When the electrodes were placed on 2 points, this beam of light was directed toward a large scale placed on the wall, allowing him to visualize currents of varying direction as they pass through a multiplier (pp 1-2).[15]

The use of conventional EEG in the diagnosis and monitoring of delirium has been well established since Romano and Engel's[16] work investigating the relationship between arousal and degree of abnormality on EEG among hospitalized delirious patients. They discovered a decrease in background EEG frequency while disorganization increased. As a result, it was determined that those changes were correlated with reduced arousal. Level of arousal is the patient's overall level of responsiveness to the environment. Impairment in the level of arousal signifies the presence of an underlying brain dysfunction. Arousal is a component of many delirium assessments, and level of arousal also seems to distinguish delirium from dementia. This work was extended by multiple researchers who replicated those findings, using computer-based quantitative EEG analysis.[17] Using these measures, research has shown adding EEG analysis to the current routine care and clinical assessment typically performed once or twice a day using a standardized delirium assessment tool significantly increased accuracy to greater than 95% ($P = .003$) when compared with the current practice identifying about 20% of delirium.[18]

EEG WAVEFORMS

Electroencephalogram waveforms are generally classified according to their frequency, amplitude, shape, and position on the scalp. Frequency, measured in hertz (Hz), is the basic unit used to determine normal and abnormal rhythms. Electroencephalogram can be divided into different frequency bands. The familiar classification of waveforms, including alpha (8-12 Hz), beta (13-30 Hz), theta (4-8 Hz), delta (0.1-4 Hz), and gamma (30-100 Hz), are based on the signal frequency. Electroencephalogram signals are also classified based on the frequencies for different state/stimuli.[19] Amplitude is the measure of change. Amplitude is measured from the 2 most extreme values. Although the total range is much higher, a typical adult human EEG signal is about 10 to 100 μV in amplitude when measured from the scalp. The shape of the EEG waveform is assessed in spikes, sharpness, phases (ie, monophasic and polyphasic), and area of the brain or location. Certain patterns are considered normal at a specific age, state of alertness, or sleep. The EEG can be used along with other measurements including eye movement or electrooculography and finger and jaw clenching or electromyography to define sleep stages. Electrooculography and electromyography are considered artifact because they interfere with accurate recording of EEG. As a result, filters and other methods are routinely used to eliminate or reduce this artifact.

According to Maldonado's[20] pathoetiological model of delirium, the evolution of delirium begins with a stress response and the resulting neurochemical impact. His model describes multiple cellular level cerebral processes leading to microlevel chemical changes ultimately disrupting equilibrium. The stress response and resulting disequilibrium initiate multiple cascades that become a vicious cycle of competition between supply and demand. These changes are depicted as neuro-electrical changes on EEG. When the brain can no longer compensate, the individual begins to develop the behavioral symptoms associated with delirium such, as alteration in level of arousal and disorganized thinking. The pathoetiological model of delirium goes on to explain that neurochemical and their associated changes in neuro-electrical activity in response to overwhelming stress occurs before behavioral symptoms and how they can be monitored using EEG to improve early delirium identification.

One of the most prominent EEG waves is the alpha (8-12 Hz) wave, which is observed in all age groups and commonly found in adults who are awake but relaxed. In the awake state, particularly with the eyes closed, the alpha activity is maximal over the parieto-occipital lobes.[21] These waves are thought to reflect rhythmic, reciprocal

interactions between the thalamus and visual areas in the occipital and parietal cortices. Functionally, awake alpha has been associated with levels of arousal, relative cortical deactivation or inhibition, and attention and is thus an important factor in cognitive function. Measures of awake alpha have been found to be decreased in patients with cognitive deficits such as delirium, Alzheimer disease, and mild cognitive impairment.[21] Beta waves (13-30 Hz) are related to behavior and actions. These waves are located around cortical activity, seen in both sides of the frontal and parietal lobes but are most predominant in the frontal region. Beta waves are associated with thinking and assessing.[19] They tend to occur in conscious states like talking, problem solving, judgment, and decision making. Delta waves are the slowest waves (0.1-4 Hz) but have the highest amplitude. They are typically seen in all stages of sleep, especially stage 3 and 4 and are considered abnormal in adults who are awake. Theta waves range from 4 to 8 Hz and are typically present during deep relaxation and meditation. They are considered abnormal in adults but are normal under 13 years. Gamma waves fall around 30 to 100 Hz and require digital EEG techniques to for proper measurement. These waves occur during hyper-alertness and integration of sensory input. Gamma properly combines senses and memory experiences together.[19]

EEG CHANGES ASSOCIATED WITH DELIRIUM

Combining the pioneering work of Caton[14] and Romano and Engel[16] with research conducted by Jacobson et al[22] resulted in the acceptance that an increase in slow EEG activity (delta and theta) and a diminution of the occipital alpha rhythm characterize a delirium.[23] Early work attempting to associate waveform patterns found significant differences in the EEG spectra between delirious patients and healthy controls.[4] Specifically, they found that a reduction in the proportion of alpha activity and mean frequency were associated with declining cognitive status based on clinical assessment using the Mini-Mental Status Examination. When attempting to distinguish delirium for "normal" cases, researchers found that use of relative alpha power captured 96% of delirium and an association between proportions between delta activity and length of delirium and hospital stay. When patients were separated into delirious and nondelirious groups, EEG results showed a significant difference ($P < .001$).[24] Similar to previous studies using conventional EEG analysis, there was an association between spectral EEG changes and severity of cognitive deterioration in patients with delirium. A correlation between delta wave percentage and mean frequency has also been correlated with lengths of delirium and hospitalization.[4] Analysis of EEG power spectra comparing ICU patients on the same sedation medication regimen revealed significant differences in mean values for the delirium-negative patients, which were 55.6%, 29.5%, and 14.9% for the theta, alpha, and beta frequencies, respectively, and for the delirium-positive patients, 69.0%, 21.0%, and 10%, respectively.[25] The post hoc analysis revealed significantly higher power for the theta band ($P = .008$). A 3-way interaction analysis looking at delirium × frequency band × electrode site ($P = .033$) confirmed a reduction in fast and an increase in slower frequencies. Specifically, higher relative theta power and reduced alpha power for the delirium group compared to nondelirious patients at all 16 electrode sites and reduced beta power at frontocentral sites for the delirium group was observed. To emphasize the direction of the EEG changes, the alpha-theta ratio was calculated. The average ratio from all 16 electrodes values was 0.296 for the delirium group and 0.548 for the nondelirium group ($P = .039$). When comparing the EEG differences between those with delirium only, those with dementia only, and those with coexisting delirium and dementia, there are consistently greater abnormalities.[22] Evaluating theta activity and relative power of delta frequency bands and brain rate mapping (absolute power with scale maximum of 103 microvolts squared) resulted in accurate discrimination between delirium and dementia 90% to 95% of the time. The culmination of work has shown consistent and recognizable electrophysiological abnormalities with the presence of delirium readily detected by EEG, particularly when combined with quantitative analysis.

ADVANCES IN EEG RELATED TO DETECTING CHANGES

Over the last 15 or so years, studies have attempted to identify which EEG leads and potential methods of signal processing analysis of the waveforms were needed to discriminate delirium from nondelirium.[26] As the science related to EEG increased, a focus became reducing the number of leads required for monitoring. Therefore, researchers began to investigate which leads (or location of leads) were needed to detect various pathological states. In addition, scientists have begun to develop algorithms to process the EEG data and, therefore, detect meaningful changes consistent with specific conditions and disease states, including delirium. This has since led to a reduction in the number of leads required to monitor some conditions, such as level of awareness and wakefulness. Using this newer technology, limited leads with machine processed EEG may provide a viable option for routine EEG monitoring by reducing the burden and need for expert interpretation.

In 2015, Van der Kooi[27] used a bipolar-electrode derivation to determine EEG characteristics, showing large differences between patients with and without delirium

while also discriminating delirium from other causes to reduce the number of required EEG leads. In that study, and reaffirmed in a subsequent study, they determined that 2 leads, attached on the forehead between the center of the head and ear, distinguished delirium from nondelirium.[28]

Following on the success of several other studies using a variety of modified 2-electrode devices, researchers have confirmed identification of EEG changes consistent with delirium. Numan[26] conducted a study to determine if Ag/AgCl electrodes applied to the head using a headband would provide the data needed to determine delirium status. Bipolar recordings from an international 10 to 20 EEG system were used to obtain EEG data using 3 derivations.[26]

Based on a dichotomous classification by delirium experts—delirium and probably delirious—they examined several cutoff points of the relative delta power. Using a relative delta power of 1 to 4 Hz, they found fair accuracy (area under the curve [AUC] = 0.75) when attempting to discriminate delirium from probably delirium. When the relative delta range was widened to 1 to 6 Hz, accuracy improved slightly (AUC = 0.78). Although they deviated from the perfect discriminating test (AUC = 1.00), these results were significantly better than chance (AUC = 0.50). In the proof-of-concept study, the accuracy of the relative delta power to discriminate between definitely delirious patients and definitely nondelirious patients was significantly higher (AUC = 0.99).

Monitoring patients at risk for delirium in clinical practice is more feasible using a bipolar derivation as compared to full EEG.[28] Researchers have also discovered alterations in the relative delta power capable of delirium detection using a bipolar derivation. Unlike previous studies that evaluated results based on relative powers over all EEG channels, researchers have determined that the discriminative accuracy of the EEG features was high, with high importance values for relative delta, alpha, and beta power to distinguish between hypoactive delirium and controls. Distinction between patients with hypoactive delirium patients and those who are sedated was mainly based on betweenness centrality in the alpha frequency band. Although full EEG is not practical on all patients in routine daily practice, functional network measures have been found to contribute to the distinction between hypoactive delirium and recovery from anesthesia. These findings suggest that these conditions can be distinguished with EEG.[28]

Further research may help determine device usefulness for selecting appropriate prevention and treatment strategies to decrease morbidity and mortality, improve patient outcomes, and reduce cost of care. Future studies may potentially eliminate the need for frequent intermittent nurse delirium assessments by providing an objective method to ascertain which nurse-driven interventions are most effective in preventing and treating delirium. To improve recognition above the current state, a new diagnostic tool for the purpose of identifying developing delirium should increase sensitivity to greater than 50%. If processed EEG data accurately identify delirium in critically ill patients, this would potentially allow for assessment of 58% of patients currently not accurately identified.

CONCLUSION

It has been known for decades that background EEG slowing occurs during delirium.[29] Use of routine full EEG monitoring for daily delirium screening is time-consuming and impractical because these studies can be performed and interpreted only by specifically trained personnel. Because EEG monitoring with automatic processing has become technically feasible, detection protocols with a limited number of electrodes and automatic processing could increase recognition of delirium.[29] Recent studies using a 2-electrode EEG system showed significant differences between patients with and without delirium. Although cognitive testing has been the historic gold standard for the identification of delirium, if EEG-based detection shows usefulness, this approach may better fit the need for objective evaluation of patients, which is less dependent on observer interpretation of patient response.[30] However, the EEG technique for detection must be validated.

Delirium is an acute disorder of attention and global cognitive function characterized by fluctuating symptoms. Many of those who survive an episode of delirium will be left with persistent cognitive impairment. There are no effective and scalable recovery models to remediate ICU-acquired cognitive impairment. The routine use of early delirium identification and preventive measures in the ICU is widely endorsed given the high prevalence of delirium, its deleterious effects on patient outcome, and the high costs related to these effects. The routine use of a physiologic method for delirium detection may facilitate early recognition in those patients at greatest risk at a point when interventions are more likely to be effective.

Earlier detection of delirium in the older adult ICU patient population may facilitate use of early preventive strategies, but a physiologic objective method for delirium detection is unclear. The biochemical pathways for attention and cognition are still being characterized. Based on the previous work and the pathophysiologic mechanisms described above, evaluating the use of physiologic methods for early detection represents a major step forward in the field of delirium. Unfortunately, a limited number of studies have evaluated these devices for analyzing EEG waveform analysis to detect delirium.

APPLICATION TO NURSING

Delirium is complex, may be subtle, and is highly underdiagnosed.[31] Despite our best efforts to prevent delirium,

it inevitably strikes most of our patients. Currently, nurses do not have the necessary equipment at the bedside to provide early identification of delirium. Earlier detection, when nursing interventions would be more effective, could likely reduce the long-term ramifications.

Having an objective method that nurses can easily use could change the standard of care by providing earlier identification. Physiologic monitoring may also provide identification before symptom onset, especially in the setting of hypoactive delirium, allowing for the greatest impact on patient outcomes. Because a physiologic monitor is lacking, nurses are hampered in providing optimal patient care and conducting research on this pervasive problem.

Until such a time when physiologic monitoring is available, nurses need to understand the pathophysiology of delirium so they can identify patients at increased risk of delirium. Because prevention and early identification are key to improving patient outcomes, nurses should remain proficient in the use of bedside clinical assessment tools such as the CAM-ICU. Most importantly, it is critical that nurses continue to be strong patient advocates by providing high quality basic nursing care because this is the best method of delirium prevention and treatment.

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