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Review Article

A neurologist's approach to delirium: Diagnosis and management of toxic metabolic encephalopathies

Vaishnav Krishnan *, Lester Y. Leung, Louis R. Caplan

Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Avenue, Boston, MA 02215, United States

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ABSTRACT

Toxic metabolic encephalopathies (TMEs) present as an acute derangement in consciousness, cognition and behavior, and can be brought about by various triggers, including endocrine and metabolic disturbances, exogenous toxins, pain and infection. Also referred to as "delirium" or "acute confusional states," TMEs are characterized by 1) an altered level of consciousness and activity, 2) global changes in cognition with inattention, 3) a fluctuating course with disturbances in the sleep-wake cycle, and 4) asterixis and myoclonus. The pathophysiology of this syndrome is poorly understood. Imbalanced neurotransmitter signaling and pathologically heightened brain inflammatory cytokine signaling have been proposed as candidate mechanisms. Focal brain lesions can also occasionally mimic TMEs. A neurological examination is required to identify the presence of focal findings, which when present, identify a new focal lesion or the recrudescence of prior ischemic, inflammatory or neoplastic insults. Diagnostic testing must include a search for metabolic and infectious derangements. Offending medications should be withdrawn. Magnetic resonance imaging, cerebrospinal fluid analysis and electroencephalography should be considered in select clinical situations. In addition to being an unpleasant experience for the patient and family, this condition is associated with extended hospital stays, increased mortality and high costs. In individuals with diminished cognitive reserve, episodes of TME lead to an accelerated decline in cognitive functioning. Starting with an illustrative case, this paper provides a neurologist's approach to the diagnosis, differential diagnosis and management of toxic metabolic encephalopathies.

1. Introduction

Toxic metabolic encephalopathies (TMEs), variously known as "acute confusional states," "sepsis-associated encephalopathy," "delirium," or "intensive care unit (ICU) psychosis" represent a serious and common neuropsychiatric syndrome associated with morbidity, prolonged hospitalization and financial costs, as well as increased psychological distress to the patient and family [1–3]. TMEs are canonical demonstrations of how distributed central nervous system circuits responsible for arousal, perception and focus are susceptible to systemic infectious, toxic or metabolic derangements. The brain's reaction to such derangements is often relatively acute, and a variety of different irritants often produce the same nonspecific behavioral reactions [4]. Nevertheless, perhaps due to heterogeneities in symptomatology and presentation, this condition remains under-recognized [5], and it has spurred the generation of several psychometric tools to assist with the rapid diagnosis of this condition [6]. TMEs often lead to persistent neurocognitive alterations even after offending triggers have been addressed effectively [7]. While serving on the neurology consult service in a multispecialty tertiary referral center, we obtained numerous consultations for "altered mental status." The specific questions ranged from concerns about nonconvulsive status or ischemic stroke to worries about the presence of undiagnosed dementia. In this clinical review designed for internists, we provide a neurologist's approach to the diagnosis and differential diagnosis of acute confusional states.

2. Case

A 91 year-old woman with systolic congestive heart failure presented to the cardiology clinic. At baseline, she is physically and cognitively independent. She was volume overloaded by examination, and so was electively admitted for diuresis. Over the next 48 h, high dose intravenous furosemide was administered with an appropriate treatment response. However, her serum creatinine increased from 1.0 to 1.8 mg/dL (estimated creatine clearance [CrCl] of 17 mL/min], and her systolic blood pressures reduced from the 130–140 mm range to 90–100 mm. She was transferred to the cardiac care unit (CCU) for milrinone therapy, which improved her renal function and blood pressures. However, on the second day of her CCU stay, she was noted to be confused, paranoid, and tremulous with intermittent jerking movements in all four extremities. When mobilized by physical therapy staff, she was unable to ambulate independently, and her knees appeared to intermittently give way. A noncontrast computed tomography scan of her head identified mild cerebral atrophy without hemorrhage, and a comprehensive laboratory investigation showed only an

* Corresponding author. Tel.: +1 617 667 4700.
E-mail address: vkrish@bidmc.harvard.edu (V. Krishnan).

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elevated creatinine (1.3, CrCl 22 mL/min). Neurology was consulted for "altered mental status with jerking movements." On exam, the patient was awake, alert and oriented only to her name. She was easily distracted and could not recall the months of the year backwards. She followed commands and did not display paraphasias. Cranial nerve examination was normal, and extremity movements were contaminated by intermittent myoclonic jerks that would affect one extremity at a time. The strength of individual muscle groups was normal, but she displayed an inconsistent and involuntary increase in tone. She had prominent bilateral asterixis. She was diagnosed with a toxic metabolic encephalopathy and no further diagnostic testing or neuroimaging was undertaken. Over the next several days, her mental status gradually improved as her cardiac and renal parameters returned to baseline. On the day of discharge five days later, her family noted that her responses were still delayed, but she was oriented and much less distractible.

3. Pathophysiology

Unraveling the basic biology of metabolic encephalopathy and delirious states remains the subject of active translational investigation. Hypoxia, hypoperfusion, infection, medications, alcohol withdrawal, and other triggers all appear to give rise to similar neurophysiological changes leading to global cognitive dysfunction of TMEs. Age and preexisting dementia are major risk factors for the development of delirious states, suggesting that diminished "cognitive reserve" remains a key vulnerability factor [8]. For simplification, we identify three main pathophysiological themes that deserve significant attention.

First, two main neurotransmitter systems have been implicated in the clinical manifestations of acute confusional states. Reduced central acetylcholinergic signaling can directly result in cognitive impairment: this is exemplified by the iatrogenic development of delirium in vulnerable individuals following the administration of medications with prominent anticholinergic activity. These include first generation antihistamines (e.g., diphenhydramine, meclizine), tricyclic antidepressants (e.g., imipramine, amitriptyline) and antispasmodic agents for overactive bladder (e.g., tolterodine, oxybutynin). A rat model of low dose atropine administration recapitulates the neurocognitive impairments, electroencephalographic slowing and sleep impairments of typical anticholinergic encephalopathic states [7,9], but has not yet been implemented more extensively to identify specific cholinergically innervated brain regions that are responsible for behavioral impairments in metabolic encephalopathies [10]. The success of antidopaminergic agents in addressing the hyperactivity and agitation of delirium have led some to propose that excess dopaminergic signaling also plays a role. In support of this theory is the observation that excess dopamine supplementation in patients with Parkinson's disease can result in delirium. Overall, both of these neurotransmitter systems are best thought of as modulators rather than primary mediators of inattention and disorientation.

Second, serum levels of a variety of proinflammatory cytokines (e.g., interleukin-8 and tumor necrosis factor alpha) and anti-inflammatory cytokines (e.g., interleukin-10) appear to be elevated in patients with acute confusional states [7]. Recent work has identified specific panels of cytokines that seem to distinguish encephalopathy in "inflamed" (i.e., those with infection or sepsis) versus "noninflamed" patients [11]. Cytokines are thought to act on neurons through humoral routes (by directly activating macrophages in regions that lack a functional blood brain barrier, such as the circumventricular organ) or through the activation of cytokine receptors on vagal afferent neurons [12,13]. Pro-inflammatory cytokines may act directly on endothelium to result in impaired cerebrovascular autoregulation in sepsis [14]. Cytokines do cross the blood brain barrier, but with the advent of more sensitive and quantitative cytokine assays, we are just beginning to collect data on how cerebrospinal fluid cytokine levels may predict the occurrence of delirium [15,16]. Preliminary experiments using a model of polymicrobial sepsis in mice have shown that persistent brain elevations TNF-α (tumor necrosis factor-α) and IL-6 (interleukin-6) may be responsible for long-term neuropsychological sequelae following bacterial infections [17].

Encephalopathy associated with kidney or liver failure is likely related to an accumulation of unexcreted medications or toxic physiological metabolites (many of which have not yet been identified). Hepatic encephalopathy has traditionally been conceptualized as a direct consequence of elevated ammonia levels [18], which itself is sufficient to enhance glycolysis and depress mitochondrial function [19]. Patients with minimal hepatic encephalopathy (MHE, cirrhotic patients who have subtle impairments in cognitive function only detected with neuropsychological testing) have been the subjects of functional magnetic resonance imaging studies. MHE patients demonstrated altered functional connectivity in a number of "resting state networks" [20]. Resting state networks are interconnected cortical and subcortical brain regions that are activated when a subject is awake and at rest and demonstrate abnormal connectivity in a number of neurodegenerative conditions including early Alzheimer's disease. In contrast to ammonia, the encephalopathy associated with renal failure ("uremic encephalopathy" or "dialysis dementia") may be related to the accumulation of "guanidino" compounds (including guanidinosuccinic acid and methylguanidine) [21]. Associated electrolyte and acid-base derangements may also contribute, though less significantly [18].

For a given patient, one or many of these factors may be contributory. A premorbid dementia resulting in diminished cognitive reserve [22], sensory deprivation (e.g., lack of hearing aids), together with environmental triggers that result in pain and involuntary immobilization (e.g., use of restraints, urinary catheters), may all combine with the above medical and iatrogenic etiologies to raise the risk and prolong the course of metabolic encephalopathy [1].

4. Clinical manifestations and approach to physical examination

A relatively acute onset of new behavioral symptoms with a fluctuating course remains the key distinguishing feature between dementia and toxic metabolic encephalopathies; hence, neurologists prefer the term "acute confusional state." The American Psychiatric Association formally identifies delirium as having i) core features of rapid and abrupt onset of impaired attention and altered sensorium, together with ii) changes in "at least one cognitive domain" (e.g., recent memory and orientation.) and iii) "associated features" (e.g., changes in sleep wake cycle, worsening in the evening) [23].

Rather than describing patients as "altered," it is preferable to report specific alterations in i) activity (ranging from hypoactive abulia to agitated delirium), ii) *arousal* (ranging from alertness to stupor), and iii) *cognition*, which occurs within specific domains (attention, memory, language, etc.) [24]. Perceptual disturbances such as audiovisual hallucinations and delusions may be prominent features. Subtle difficulties with focus and attention are often the first sign of an ensuing encephalopathy, and are characterized by delayed reaction time and easy distractibility. Global inattention typically contaminates other abnormalities on mental status testing, such as difficulties with calculation, short-term recall and incorrect responses to simple orientation questions.

Inattentiveness is typically followed by diminished arousal or changes in the level of activity (ranging from severe agitation and hyperactivity to *abulia*, a hypoactive state with diminished spontaneity). There have been efforts to distinguish between "hypoactive" and "hyperactive" delirious states. From studies of patients with focal lesions, abulia has been linked to dysfunction within circuits connecting the frontal lobes to basal ganglia structures, including the caudate and accumbens nuclei, thalamus and midbrain [25]. In contrast, focal lesions in hyperactive patients typically disturb posterior circuits connecting occipitoparietal cortices to limbic structures within the mesial temporal lobe [26]. In patients without focal lesions, this distinction simply reflects a spectral response to the same underlying neurological insult