Delirium: Presentation, Epidemiology, and Diagnostic Evaluation (Part 1)

COLIN J. HARRINGTON, MD; KALYA VARDI, MD

ABSTRACT

Delirium is a highly prevalent and complex neuropsychiatric disorder marked by attentional dysfunction, disturbances in multiple cognitive domains, and changes in motor behavior, perception, sleep, and thought process. Delirium results from diverse toxic, metabolic, infectious, and structural etiologies and is associated with a number of adverse outcomes. Delirium pathophysiology involves perturbation of multiple neurotransmitter systems. Behavioral presentations of delirium are common and are often misattributed to primary psychiatric processes. Diagnostic assessment of delirium includes thorough physical examination, careful cognitive testing, appropriate metabolic and infectious studies, review of medications, and structural brain imaging and electroencephalography as indicated. Pharmacologic and non-pharmacologic interventions have been documented to reduce the incidence and severity of delirium. Antipsychotics are the treatment of choice for delirium-related agitation and psychosis.

KEYWORDS: Delirium, encephalopathy, cognitive disorder, agitation

INTRODUCTION

Delirium is a complex neuropsychiatric disorder marked by an alteration in level of consciousness, attentional dysfunction, disturbances in other cognitive domains including memory, orientation, and language, and associated changes in non-cognitive domains of motor behavior, perception, affect, sleep-wake cycle, and thought process.[1,2] Delirium results from diverse etiologies and is associated with a number of adverse clinical and systems outcomes including secondary infections, falls, violence, and increased hospital length-of-stay, healthcare costs, and mortality.[1-8] While the pathophysiology of delirium is poorly understood, the neurobehavioral syndrome likely represents a final common pathway of perturbation of multiple neurotransmitter systems operative across widely distributed neural networks.[1,9-11]

At its core delirium is a cognitive disorder and, as such, associated neurobehavioral changes and psychiatric signs and symptoms are considered *secondary*. Delirium has been described in the medical literature since antiquity and has acquired many diagnostic labels including acute confusional state, acute brain dysfunction, acute brain failure, acute organic brain syndrome, ICU psychosis, and metabolic encephalopathy, amongst others. The term *delirium* is derived from the Latin roots *de* (translated "away from") and *lira* (translated "furrow of a field") thus suggesting that one is derailed from the plowed or straight path.[11]

The term *encephalopathy* is often employed in place of or alongside delirium and allows for the proper grouping together of delirium and dementia as cognitive disorders – while also providing for the longitudinal course-based distinction between delirium and dementia, as acute and reversible, and chronic and progressive forms of encephalopathy, respectively. Use of this terminology also allows for description of the intermediate syndrome of sub-acute encephalopathy where cognitive dysfunction is often less obvious and neuropsychiatric symptoms predominate.

EPIDEMIOLOGY, RISK FACTORS, AND OUTCOMES

Delirium is a highly prevalent disorder estimated to occur in 10%-15% of general medical-surgical inpatients, in 25%-45% of hospitalized cancer patients, and in 80%-90% of terminally ill palliative care patients.[1,4,5,11,12] Rates of delirium are particularly high in the intensive care unit (ICU) where studies suggest that 30% of patients are delirious on admission and 60% develop delirium during the course of their critical illness.[1,3,5,13-15] Upwards of 80% of mechanically ventilated ICU patients are estimated to be delirious.[14-16]

Models of delirium etiology suggest predisposing, precipitating, and perpetuating factors.[1,2,4,11,17] Illness, pharmacologic, and environmental factors likely play roles in the development and persistence of delirium. Identification of modifiable factors is crucial to prevention and optimal management of delirium. Older age, premorbid cognitive dysfunction, medical illness burden, baseline poor functional status, and medication exposure are most highly predictive of delirium development.[1,2,4,5,11] Baseline cognitive dysfunction is the most robust predictor of incident delirium in the hospitalized patient with upwards of 60% of acute encephalopathy episodes thought to occur atop a baseline of cognitive impairment.[1,13,17,18] Delirium superimposed on dementia or other types of cognitive dysfunction appears more resistant to treatment.[1,19] Surgical patients, especially those undergoing total joint replacement and cardiac procedures requiring bypass, are at particularly high risk for the development of delirium.[4,20-22]

Delirium is associated with numerous adverse outcomes including prolonged hospital length of stay,[1] increased rates of discharge to institutional care settings,[3] increased healthcare costs,[8] reduced quality of life,[1,11] increased short- and long-term mortality,[5-7] and long-term cognitive impairment.[9,13,14,18] Delirium in the ICU, after controlling for numerous confounders, is associated with an increase in ventilator dependent days and ICU length of stay, and is an independent predictor of increased mortality in mechanically ventilated patients.[16] Delays in diagnosis and treatment of delirium are associated with increased mortality in ICU patients.[23]

CLINICAL PRESENTATION, EXAMINATION, AND COURSE

There are many definitions of delirium in the literature. Factor analysis studies suggest that the broad and heterogeneous phenotype of delirium loads onto three core symptom domains including a "cognitive" domain (orientation, attention, short-term memory, long-term memory, and visuospatial ability), a "higher level thinking" domain (language and thought process), and a "circadian" domain (sleep-wake cycle and motor behavior).[24] Common to all definitions of delirium is a disruption in attention, often signaled by a frank alteration in level of consciousness or sensorium. On a spectrum between stupor and normal consciousness, delirium presentations can range from frank somnolence to more awake and alert states marked by subtle concentrational difficulty.[1] Intact attentional *function* includes the ability to focus, maintain, and shift attention according to environmental demands. Attentional *dysfunction* may manifest in clinical findings of obvious confusion with incongruent responses to the examiner's queries and in more subtle ways where patients can focus initially but are distractible, impersistent, or perseverative on bedside and formal neurocognitive testing. If basic attention and concentration are impaired, then more complex cognitive functions of language, orientation, memory, and thought process are secondarily disturbed. In cases of severe delirium, attentional impairment can frankly preclude adequate assessment of other higher order cognitive domains.

When attention and awareness are altered, the delirious patient's navigation of the environment is impaired. The surgical dictum to "look, listen, and feel" regarding the examination of the acute abdomen is applicable to the examination of the delirious patient as well. Observation of patients from a distance can provide clues about their cognitive function. Disheveled appearance, restless fidgeting, picking behavior, and talking out loud when alone in the room suggest inattention to self, disconnection from the environment, and response to internal stimuli. Just as palpation of the abdomen can alter the findings of auscultation, so too can more formal examination of delirious patients alter their cognitive performance. When engaged with a more structured cognitive assessment, the confused patient can sometimes "borrow the frontal lobe" of the organized examiner and respond more appropriately than expected – a particularly relevant issue in the assessment of the less obviously encephalopathic patient where proper diagnosis of abnormal behavior hinges on a comprehensive neuropsychiatric assessment. In this regard, the act of examining the patient may change the examined – and thus should come after a period of simple observation and casual engagement.

Delirium typically develops over hours to days. Subacute encephalopathies due to smoldering infection, slowly developing metabolic derangements, chronic lithium intoxication, and other drug toxicities can evolve over days to weeks. Cognitive and behavioral changes frequently fluctuate and follow a diurnal pattern. Assessment during periods of more lucid behavior can lead to the conclusion that patients are cognitively intact, making subsequent behavioral changes and agitation diagnostically difficult to understand.

Changes in motor behavior are common in delirium. Hypoactive and hyperactive subtypes of delirium have been identified. Different pathophysiologies have been proposed for the two motor subtypes but have not been supported to date. Patients often fluctuate between these two forms of delirium making single cross-sectional assessment diagnostically insufficient. Hyperactive delirium, often the result of drug intoxication and withdrawal states, can be associated with agitation and related patient and staff injury. Some studies suggest prognostic relevance to the motor subtypes, with hyperactive delirium more responsive to pharmacologic treatment and hypoactive delirium predictive of worse outcome.[1,2,11]

Psychiatric symptoms and neurobehavioral changes are common in delirium and range from frank agitation, to restlessness, anxiety, dysphoria, tearfulness, apathy, withdrawal, disinhibition, disordered thinking, and perceptual disturbances of hallucinations and delusions. In contrast to behavioral symptoms of *primary* psychiatric syndromes that occur in a clear sensorium, behavioral changes in delirium occur atop a substrate of clinically demonstrable abnormal brain function and are properly considered *secondary* phenomena. New onset psychiatric symptoms should trigger examination of cognitive *function* and evaluation for causes of cognitive *dysfunction* when it is demonstrated, especially in the elderly and medically ill.

Despite its high prevalence and associated morbidity and mortality, delirium often goes undetected. Behavioral changes of delirium are commonly attributed to primary psychiatric processes, leading to delays in diagnosis and treatment of its causes.[1,15,19,23] Hypoactive delirium is often mistaken for depression – where psychomotor slowing, poor oral intake, and limited engagement with family and staff are attributed to vegetative dysfunction and psychological withdrawal of a mood disorder. Restlessness and anxiety in the medically ill patient are often considered appropriate psychological responses to the illness experience (rather than symptoms

of delirium). Failure to cognitively probe these behavioral changes and to recognize them as manifestations of delirium often leads to delays in diagnosis of the causative medical-surgical illness, the introduction of unnecessary antidepressant medications, and the initiation of potentially deliriogenic benzodiazepines.

Hallucinations, illusions, and delusional ideation, typically paranoid, are particularly common in delirium and are highly distressing to patients, families, and staff.[12,25,26] These misperception symptoms result from cognitive misprocessing that leads to misinterpretation of sensory phenomena and misattribution of meaning to routine hospital events. Patients often report that they are being poisoned, experimented on, plotted against, or held captive (note, many *are* physically restrained and treated with injectable medications). Psychiatric consultation for a question of "psychosis" is often requested in these cases. Onset of primary psychosis in the elderly and medically ill is extremely unusual and new hallucinations or delusions in this population should be considered diagnostic of delirium or dementia until proven otherwise.

While considered a transient syndrome and indicative of typically reversible processes, recent data suggest that many delirium episodes last longer than initially presumed. As many as 30%-40% of patients discharged to nursing homes and skilled nursing facilities remain delirious at the time of transfer.[1] Delirium is a risk factor for long-term cognitive impairment, especially in survivors of critical illness and in cases of sepsis-related encephalopathy.[3,9,13,14,18,27]

RISK FACTORS AND CAUSES

Delirium is caused by a wide variety of etiologies including metabolic, toxic-pharmacologic, infectious, vascular, traumatic, and post-surgical conditions.[1,11,24] Though the vast majority of delirium episodes are not caused by structural disease, brain imaging is performed in most delirious patients as part of the initial evaluation. Structural causes of delirium are typically heralded by a history of trauma or a focal neurological exam. Delirium often evolves in hospitalized stroke patients and is typically the result of metabolic and infectious complications. Stroke as a direct cause of delirium is less common.

The pathophysiology of delirium is poorly understood. Inflammatory mechanisms are active in infectious, metabolic, traumatic, and other processes linked to delirium. Animal and human studies have documented numerous adverse mood, cognitive, and behavioral effects of various inflammatory mediators including interferon-alpha, interleukin-1, interleukin-6, and tumor necrosis factor-alpha. Illness-related *systemic* inflammation is thought to play a central role in delirium etiology of multiple causes.[28,29]

Dysfunction of various neurotransmitter systems has been implicated in the pathophysiology of delirium. Derangement of dopaminergic and serotonergic neurotransmitter function is likely causative in diagnoses of neuroleptic malignant

Table 1. Selected causes of delirium

Autoimmune	**Metabolic**
Acute graft versus host disease	Acidosis or alkalosis
Autoimmune encephalopathy (voltage-gated potassium channel, NMDA receptor)	Anemia
Central nervous system vasculitis	Hepatic failure
Hashimoto's encephalopathy	Hypercapnea
Systemic lupus erythematosus	Hypoalbuminemia
Cardiac	Hypo- or hypercalcemia
Acute myocardial infarction	Hypo- or hyperglycemia
Heart failure	Hypo- or hyperkalemia
Cerebrovascular	Hypo- or hypermagnesemia
Stroke (ischemic, hemorrhagic)	Hypo- or hypernatremia
Transient ischemic attack	Hypophosphatemia
Subarachnoid hemorrhage	Hypoxemia
Hypertensive encephalopathy	Uremia
Drug intoxication	Other (carcinoid, porphyria, etc)
Alcohol	**Neoplastic**
Bath salts	Carcinomatous meningitis
Cannabinoids (marijuana, synthetic)	Intraparenchymal brain tumor
Gamma-hydroxybutyrate	Lymphomatous meningitis
Hallucinogens	Parenchymal metastasis
Opiates	Paraneoplastic syndrome
Psychostimulants	**Systemic infection**
Sedative-hypnotics (benzodiazepines, barbiturates)	Bacteremia
Drug withdrawal	Cellulitis
Alcohol	Pneumonia
Sedative-hypnotics (benzodiazepines, barbiturates)	Sepsis
Endocrine	Urinary tract infection
Adrenal insufficiency or excess	**Traumatic brain injury**
Hypo- or hyperthyroidism	Diffuse axonal injury
Hypo- or hyperparathyroidism	Parenchymal contusion
Panhypopituitarism	Subdural hematoma
Intracranial infection	**Other**
Abscess	Central nervous system radiation
Encephalitis (HSV, arboviruses)	Disseminated intravascular coagulation, thrombotic thrombocytopenic purpura
Human immunodeficiency virus	Malignant hyperthermia, neuroleptic malignant syndrome, serotonin syndrome
Meningitis (bacterial, viral, fungal)	Postoperative state (cardiotomy, joint arthroplasty)
Neurosyphilis	Seizures

*See Table 2 for drugs causing delirium

Adapted from:Trzepacz PT, Meagher DJ, and Leonard M. (2011). Delirium. In Levenson JL (Ed), *Textbook of Psychosomatic Medicine*. Arlington, VA: American Psychiatric Publishing, Inc.

syndrome and serotonin syndrome, respectively. Deficient gamma-aminobutyric acid (GABA) function and glutamate hyperactivity have been implicated in the encephalopathy of sedative-hypnotic withdrawal. The anti-cholinergic properties of numerous medications (**Table 2**) play a role in the development of delirium. Opiate narcotics drive delirium via both their opioid and anti-cholinergic effects.

Causes of delirium cut across all organ systems. Derangements in sodium and calcium metabolism, hypoalbuminemia, hypoxemia, hypercapnea, hepatic and renal insufficiency, hyper and hypoglycemia, drug intoxication and withdrawal, infection, and primary central nervous system diseases including stroke, seizure, and traumatic brain injury have all been associated with delirium.[1,11] (**Table 1**).

Medications from multiple classes, via both well-understood and more idiosyncratic mechanisms, have been associated with delirium (**Table 2**). Antimicrobials (antiviral acyclovir, macrolide antibiotics including clarithromycin, fluoroquinolones such as ciprofloxacin, penicillins, cephalosporins, and metronidazole), anticonvulsants (phenytoin, phenobarbital, valproic acid), corticosteroids, antiparkinson agents (amantadine, levodopa), cardiac drugs (digitalis, lidocaine, quinidine, and beta-blockers), and various antineoplastic agents (5-fluoruracil, methotrexate, procarbazine, vincristine, interferon alpha, and ifosfamide) have all been implicated in the development of delirium. Opioid analgesics and benzodiazepines are especially common causes of delirium in hospitalized medical-surgical patients.

Acute *intoxication* with virtually any abuseable prescription or illicit drug can drive a delirium. Drug *withdrawal* delirium, however, is more specifically associated with use of sedative-hypnotic agents (i.e., alcohol, benzodiazepines, and barbiturates) that share a GABA-ergic mechanism of action and drive a delirium tremens-like encephalopathy syndrome. While there are case reports of delirium associated with abrupt discontinuation of opioid narcotics (methadone), these agents typically do not produce a withdrawal delirium. Presumption of opioid withdrawal as the cause of delirium in opioid abusers or medical-surgical patients exposed to prolonged courses of narcotic analgesics is ill advised as these patients are often affected by and at risk for multiple delirium-related conditions.

Emergency department presentations for acute mental status change are extremely common and have given rise to protocol driven empiric treatment of frequently occurring reversible causes of delirium. Emergency protocols, in parallel with appropriate diagnostic testing, include the administration of supplemental oxygen, intravenous dextrose, intravenous normal saline, naloxone, and thiamine targeting, respectively, hypoxemia, hypoglycemia, hypovolemia, opioid intoxication, and Wernicke's encephalopathy. Flumazenil, a benzodiazepine reverse agonist, is sometimes administered for suspected benzodiazepine intoxication, but reports of benzodiazepine withdrawal-induced seizures have led to more cautious use of this agent.

Table 2. Selected drugs causing delirium

Analgesics	**Antiparkinsonian drugs**
Opiates	Amantadine
Salicylates	Bromocriptine
Antimicrobials	Dopamine agonists
Acyclovir, gancyclovir	(ropinirole, pramipexole)
Aminoglycosides	Levodopa
Amphotericin B	**Cardiac drugs**
Antimalarials	Beta-blockers
Cephalosporins	Captopril
Ethambutol	Clonidine
Interferon	Digoxin
Isoniazid	Lidocaine
Macrolides (clarithromycin)	Methyldopa
Metronidazole	Procainamide
Quinolones (ciprofloxacin)	Quinidine
Rifampin	Tocainide
Sulfonamides	**Sedative-hypnotics**
Vancomycin	(intoxication or withdrawal)
Anticholinergic	Barbiturates
Antihistamines (H_1)	Benzodiazepines
Antispasmodics	**Stimulants**
Atropine and atropine-like drugs	Amphetamines
Benztropine	Epinephrine, phenylephrine
Phenothiazines	Pseudoephedrine
Tricyclics (amitriptyline, doxepin, imipramine)	Theophylline
Trihexiphenidyl	**Miscellaneous**
Anticonvulsants	Antihistamines (H_2)
Phenobarbital	Baclofen (intoxication or withdrawal)
Phenytoin	Bromides
Valproic Acid	Disulfiram
Anti-inflammatory drugs	Ergotamine
Corticosteroids	Lithium
Nonsteroidal anti-inflammatory drugs	Propylthiouracil
Antineoplastic drugs	Quinacrine
Asparaginase	Timolol (ophthalmic)
Dacarbazine	
Diphosphamide	
5-Fluorouracil	
Methotrexate	
Procarbazine	
Vinblastine	
Vincristine	

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EVALUATION

Delirium evaluation begins with a thorough physical examination with particular attention paid to findings suggestive of metabolic derangement, infection, and neurologic focality. Routine metabolic studies should be checked and urinalysis and chest X-ray obtained. Brain imaging is often performed in the assessment of delirium, but is typically unrevealing. Brain computed tomography (CT) scanning is indicated for evaluation of intraparenchymal or subdural hemorrhage in patients with a history of trauma or focal neurologic examination findings. Magnetic resonance imaging (MRI) is more sensitive in evaluating for space occupying lesions, white matter disease processes, and new ischemic stroke as causes of delirium.

Electroencephalography (EEG) in delirium typically reveals diffuse bilateral background slowing in the delta to theta range. These EEG changes are non-specific and common to encephalopathies of diverse etiologies. Certain causes of delirium are associated with specific EEG findings including triphasic waves in hepatic encephalopathy, excess beta-range activity in benzodiazepine intoxication, and periodic discharges and burst suppression in prion diseases.

EEG is not particularly helpful when neuropsychiatric assessment is consistent with a diagnosis of delirium and physical examination and laboratory investigation suggest its cause(s). In contrast, even non-specific background slowing on EEG can be very helpful in distinguishing between abnormal behavior of psychiatric disease and that of more subtle, subacute encephalopathy where cognitive dysfunction is *less obvious* – as the EEG in most psychiatric disorders is normal.

When patients are *obviously* encephalopathic but evaluation for toxic, metabolic, infectious, and structural causes is unrevealing, EEG is indicated to evaluate for non-convulsive status epilepticus (NCSE). Recent studies have documented unexpectedly high rates of NCSE in critically ill and ICU patients.[30] This is a notable finding that argues for more liberal use of EEGs in encephalopathic critically ill patients who typically have multiple non-epileptic processes driving their delirium and in whom EEG has previously been thought to be less indicated.

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Authors

Colin J. Harrington, MD, is the Director, Consultation Psychiatry and Neuropsychiatry Education, Rhode Island Hospital, and Associate Professor (clinical), Clinician Educator, Departments of Psychiatry and Medicine, Alpert Medical School of Brown University.

Kalya Vardi, MD, is a Resident in Psychiatry, Department of Psychiatry and Human Behavior, Alpert Medical School of Brown University.

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The authors have no financial disclosures to report.

Correspondence

Colin J. Harrington, MD
Director, Consultation Psychiatry and Neuropsychiatry Education
Rhode Island Hospital, APC 9
593 Eddy St.
Providence RI 02903
401-444-5480
Fax 401-444-3492
Colin_Harrington@Brown.Edu