REVIEW

Insight into Delirium

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ABSTRACT

Delirium is a common and serious disorder with high morbidity and mortality. It occurs in 35 to 80 percent of critically ill, hospitalized patients. It may lead to mortality if not detected early. Studies show that delirium causes death in as many as 22 to 76 percent of patients who are hospitalized with delirium. It is often unrecognized and inadequately treated, and this may lead to poor outcome, including long-term care, longer length of stay in hospital, and high impact on health and social expenditure. There may be many reasons that delirium goes undetected, such as not understanding full pathophysiology and not having enough diagnostic tools to detect delirium in the early phase. A clear understanding of neurochemical equilibrium and pathways of the brain will help the clinician to understand the signs and symptoms of delirium. Pathophysiology of delirium is complex, and multiple theories have been proposed to explain its exact pathophysiology, but none of these mechanisms have been fully understood. Early detection of delirium and reduction of modifiable risk factors, along with better management, can result in better outcomes. This article discusses the pathophysiology and parts of brain involved in delirium as well as mood and psychotic symptoms of delirium.

INTRODUCTION

The word *delirium* is derived from Latin words *de* (away from, out of) and *lira* (the earth thrown up between two furrows) and is used to describe a condition in which an individual is performing at a lower level than normal and is not at the top of his or her conscious level.[1] The delirious state represents an acute change in concentration, attention, and cognition.

Delirium is defined as a transient, usually reversible, cerebral dysfunction that manifests clinically with a broad range of neuropsychiatric abnormalities. The hallmarks of delirium are waxing and waning signs, symptoms, and sensorium. Alertness and vigilance in the patient fluctuate. A delirious patient does indeed receive external information, but integrates it incorrectly, which produces behavioral responses that are inadequate to the environment.[2] Delirium is life threatening but can be prevented.

Despite the clinical impact delirium can have on patients, the pathophysiological mechanisms of delirium are still unknown.[3] The recognition rates of delirium are 12 to 43 percent, and delirium is inadequately treated in up to 80 percent of patients who exhibit it.[4] Delirium complicates the hospital stays of 20 percent of patients who are 65 years of age or older.[5]

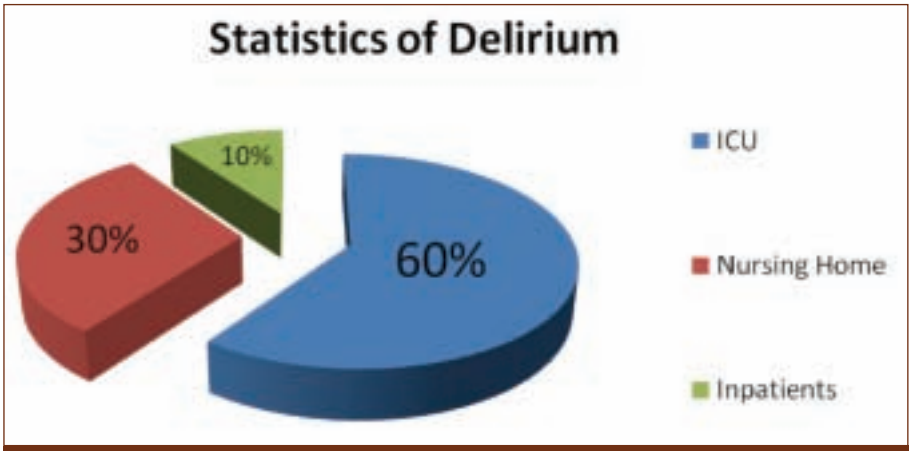

FIGURE 1. Prevalence of delirium in various clinical settings

Delirium is more commonly seen in surgical and medical wards than in psychiatric wards.[2] Patients with delirium have higher mortality, readmission, and long-term care rates compared to the general population.[6] Delirium costs approximately $38 billion to $152 billion per year in healthcare.[7] Delirium occurs in 60 to 87 percent of intensive care unit (ICU) patients, 15 to 60 percent of nursing home patients, and 14 to 56 percent of hospital inpatients (Figure 1).[7,8] Delirium occurs in 15 to 53 percent of older patients postoperatively. The prevalence of delirium increases with age and can occur in up to 14 percent of individuals who are over the age of 85 years, although the overall prevalence in the community is 1 to 2 percent.[5] In patients who are hospitalized with delirium, 22 to 76 percent die.[7] The yearly mortality rate worldwide for cases of delirium is 35 to 40 percent.[5]

The core features of delirium are as follows:[9]

- Disturbance of consciousness (reduced clarity and awareness of the environment) with reduced ability to focus, sustain, or shift attention
- Change in cognition (e.g., disorientation, memory impairment, reduced problem-solving capability, and language disturbance) or perceptual disturbance
- Onset of hours to days with fluctuation during the course of day
- Disturbance directly linked to physiological consequences of a general medical condition with evidence from the history, physical examination, or laboratory findings.

Based on arousal disturbance and psychomotor behavior, the following three clinical subtypes of delirium have been described: 1) hyperactive (hyperaroused, hyperalert, or agitated), 2) hypoactive (hypoaroused, hypoalert, or lethargic), and 3) mixed (alternating features of hyperactive and hypoactive types).

The hyperactive type of delirium represents about 25 percent of cases and is known as the "classic" presentation of delirium; patients who exhibit the classic form of delirium are generally wildly agitated. The hypoactive type, also known as the "quiet" form of delirium, represents over half of all delirious patients.[1] The quiet form of delirium is more common in older patients than the other forms of delirium, but emergency physicians do not routinely screen for it, and thus it is not unusual for them to miss it.[4,10] The quiet form of delirium has a poorer prognosis than the classic and mixed forms.[1] Predisposing and precipitating factors of delirium are listed in Table 1.

Multiple theories have been proposed to explain the exact pathophysiology of delirium, but none of the mechanisms are fully understood (Figure 2). This article reviews the most important theories of pathophysiology of delirium.

PATHOPHYSIOLOGY OF DELIRIUM

Neurotransmitters involved in delirium. There are a number of neurotransmitters believed to be involved in the pathogenesis of delirium, including acetylcholine, serotonin, dopamine, and gamma-aminobutyric acid (GABA).[11]

Acetylcholine. Acetylcholine (Ach) is a neurotransmitter implicated in attention, memory, disorganized thinking, and perceptual disturbances.[11,12] The deficiency of this neurotransmitter leads to symptoms of delirium. Normal aging brings various physiological changes in the human body that lead to a decrease in Ach-producing cells and a decrease in oxidative metabolism in the brain, which ultimately leads to a decrease in Ach synthesis, putting elderly persons at high risk of developing delirium.[11] Any dysfunctions in the pathway of interaction between choline and acetyl coenzyme A (CoA) can reduce acetylcholine levels.[13]

Serum anticholinergic activity (SAA) has been used to assess the anticholinergic process. In several studies, SAA has been found to cross the blood brain barrier (BBB), which precipitates delirium.[14–16] A high level of SAA is strongly associated with delirium, whereas low levels lead to resolution of the delirious state.[13] As per the Confusion Assessment Method (CAM) for the ICU, those patients who had SAA greater than 20pmoL/mL were found to be delirious or were associated with a higher risk of delirium.[11]

In Alzheimer's disease, there is loss of cholinergic activity, which may contribute to cognitive decline and carry an increased risk of delirium. The risk of delirium is higher in patients using concomitant anticholinergic medications.[12,13]

Serotonin. Serotonin is a major excitatory neurotransmitter in the brain, and its production depends on the precursor tryptophan (TRP). It is postulated that a decrease in TRP levels may lead to a decrease in serotonin, which ultimately may lead to the development of delirium.[1,11] In a study by Robinson et al,[17] postoperative surgery patients who developed delirium had much lower levels of tryptophan than postoperative surgery patients who did not develop delirium.

Many neurotransmitters are linked to each other, so changes in the levels of various amino acids may play an important role in the development of delirium. For example, tryptophan competes with the amino acid phenylalanine for transport across the BBB, so when there is a change in the ratio of tryptophan to phenylalanine, the level of serotonin may increase or decrease, possibly leading to delirium.[1,18]

Dopamine. Elevation of dopamine has been associated with the development of delirium. Dopamine is associated with many metabolic pathways and calcium channels that lead to significant increases in dopamine under impaired oxidative conditions. The influx of calcium into cells leads to an increase in dopamine production and uncouples oxidative phosphorylation in brain mitochondria. The outcome is an increased production of toxic metabolites of dopamine and a decrease in production of ATP that inhibits the activity of cetechol-O-methyl transferase (COMT), which is a vital enzyme for synthesis and breakdown of dopamine in prefrontal cortex.[7,11,12] Thus, an increase in the level of dopamine may cause symptoms of the hyperactive type of delirium, including hallucinations and delusions.[12] Some studies have shown that suboptimal levels of dopamine cause atrophy of the midbrain and prefrontal cortex.[19,20] We believe dopamine is linked to the entire cascade of metabolic and behavioral events that may lead to delirium.

TABLE 1. Predisposing and precipitating factors of delirium

PREDISPOSING FACTORS
Extremes of age
Dementia
Functional impairment in activities of daily living
Medical comorbidity
History of alcohol abuse/dependence
Male gender
Sensory impairment (blindness, deafness)
PRECIPITATING FACTORS
Acute myocardial events
Acute pulmonary events
Bed rest
Fluid and electrolyte disturbances (including dehydration)
Hypoxemia due to any medical conditions
Drug withdrawal (sedatives, alcohol)
Infection (respiratory, urinar
Medications (wide range, especially psychoactive, anticholinergic, and opioid)
Uncontrolled pain
Urinary retention, fecal impaction
Indwelling devices (urinary catheters)
Severe anemia
Use of restraints
Intracranial events (stroke, bleeding, infection)

Gamma-aminobutyric acid (GABA) and glutamate. GABA and glutamate have both been implicated in the development of delirium.[11] Glutamate is metabolized into GABA, which is an inhibitory neurotransmitter. Hypnotic or sedative drug withdrawal may cause the level of GABA to drop, which in turn may cause delirium.[11]

Inflammatory processes involved in delirium. *C-reactive protein (CRP).* C-reactive protein (CRP) can stimulate the formation of reactive oxygen species, which cause disruption of BBB and manifest as delirium. Studies have shown that higher levels of CRP and interleukin (IL)-6 are associated with greater incidence of delirium in postoperative hip surgery patients.[21,22] In a prospective study by McGrane et al,[23] inflammatory biomarkers, procalcitonin and CRP, were measured in mechanically ventilated patients. Investigators found that higher levels of procalcitonin and CRP were associated with delirium and less coma-free days, implicating inflammation as an important

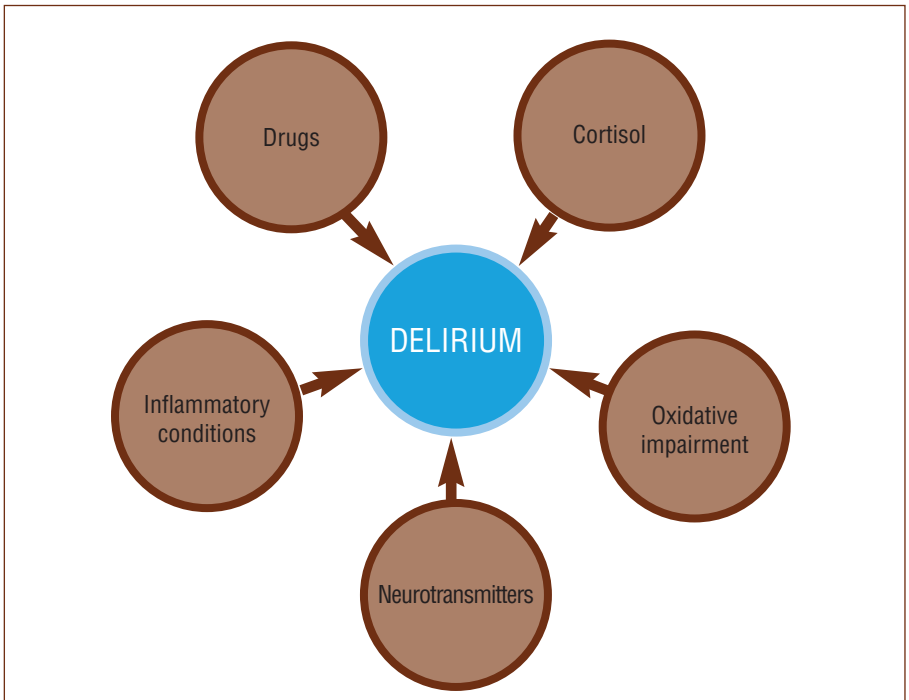

FIGURE 2. Common pathophysiological factors, processes, and conditions leading to delirium

mechanism in the pathophysiology of delirium and coma during critical illness.[23]

Proinflammatory cytokines. Proinflammatory cytokines, IL-1B, tumor necrosis factor-*alpha* (TNF-*a*, and, to a lesser extent, IL-6, are generated in the peripheral immune system and communicate with the brain.[24,25] The integrity of the BBB, a complex, heterogeneous, and dynamic tissue, is maintained by tight junction proteins, brain microvascular endothelial cells (BMECs), cerebral microvasculature, and cellular transport pathways. Aging, systemic disease, and ischemic injury can disrupt these processes, resulting in a decline in overall BBB function and integrity.[26]

Pneumonia and urinary tract infections may cause disruption of the BBB and activation of a cascade of events that may lead to delirium.[27] The BBB can also be disrupted by age-related changes, such as reduced cortical and white matter microvascular density,[28] fewer mitochondria per endothelial cell,[29] and smaller capillary lumen size with greater tortuosity. Infection activates the inflammatory cascade mediators, such as lipopolysaccharide (LPS), TNF-*a*, and IL-1, and thus these mediators stimulate other mediators and recruit other inflammatory cells to the injured site. The localized immune reaction then spreads causing high levels of cytokines to circulate.[7,27,30] When there is systemic inflammation, cytokines, such as TNF-*a*, enter the brain and stimulate the microglia, which further creates a neurotoxic response affecting neuronal functioning and thus potentially causing delirium (Figure 3).[31] It has been hypothesized that physical and surgical trauma play vital roles in the activation of the inflammatory cascade to a certain extent.[27]

Sepsis is associated with raised amounts of TNF-*a* and IL-1 and -6 in the cerebrospinal fluid (CSF), even in absence of meningitis.[32] Parenchymal neural cells are major producers of proinflammatory chemokine CC-motif ligand 2 (CCL2), and high peripheral levels of this chemokine may be reflective of BBB injury. There is evidence that high levels of CCL2, irrespective of the source, may play a primary role in BBB disruption and the inflammatory changes within the brain.[33,34]

In a study conducted in acutely medically ill, hospitalized, elderly patients (ages ≥65; n=185) with and without delirium, the authors examined the expression pattern of pro- and anti-inflammatory cytokines. The level of CRP and cytokines IL-*B* IL-6, TNF-*a*, IL-8, and IL-10 were taken from the subjects. A total of 34.6 percent of the subjects developed delirium. In patients who developed delirium, IL-6 and IL-8 levels were significantly higher (53% and 45% above detection levels, respectively) compared to those patients who did not develop delirium (31% and 22% above detection levels, respectively).[35]

It can be surmised that several conditions associated with acute systemic inflammation (e.g., septic shock and cardiac surgery) are associated with BBB dysfunction. Elevated blood levels of the *beta* subunit of S100 protein (S100 *B*), a marker of glial injury,[12] can be considered as evidence of increased BBB permeability.[27] BBB disruption during episodes of delirium has been suggested to occur in a recent study showing elevated serum levels of protein S100-*B* in acutely ill, elderly medical patients with delirium.[27] Another study done among elderly patients who underwent surgical repair of hip fractures showed that high levels S100-*B* were found in those patients with delirium and that S100-*B* was the strongest independent marker for delirium.[36]

In a study of patients who underwent cardiac surgery, investigators examined postoperative changes in groups of inflammatory markers. Investigators found that six hours postoperatively, the patients who developed delirium had higher increases in cytokines and chemokines than patients who did not develop delirium.[30]

Other potential causes of delirium. *Cortisol.* Cortisol is an important hormone in the acute stress environment. It has been shown that cortisol, or glucocorticoid, has

delirious effects on memory and mood when secreted excessively.[12] The hippocampus is the part of the brain where learning and memory take place.[37] Excessive glucocorticoid levels seem to induce a vulnerable state in neurons. The hippocampus is a major target for these effects with its dense concentration of glucocorticoid receptors (GR).[12] Excess glucocorticoid causes cell death by various mechanisms, including hypoxia/ischemia, seizures, hypoglycemia, and energy failure of neurons. All of these effects cause a disruption of the hippocampal function.[12] High stress in patients in ICU can cause activation of the sympathetic nervous system, which leads to the increase of other stress hormones and serum cortisol.[13] Cortisol is also associated with apoptosis and mitochondrial dysfunction.[12] Hypothetically, patients with delirium have a disturbance in hypothalamic-pituitary-adrenal (HPA) axis and often fail a dexamethasone suppression test.[38] In a study by Pearson et al,[39] investigators found that CSF and plasma cortisol levels were significantly higher in hip fracture surgery patients with delirium compared to controls.[39] Starkman et al[40] found an association between hippocampal formations (HF) volume, memory dysfunction, and cortisol in patients with Cushing's Syndrome.

Oxidative impairment. Decrease in the oxygen supply to the brain causes inadequate oxidative metabolism, which leads to cerebral dysfunction.[12] Extrinsic factors, such as cardiac disease, intraoperative hypotension, intrinsic lung disease (e.g., pneumonia, acquired respiratory distress syndrome, pulmonary edema, and acute respiratory failure), and anemia lead to decreased oxygen exchange.[12] It has been hypothesized that patients are at high risk of cognitive dysfunction when there is drop in mean arterial pressure.[11] Many perioperative factors, such as anesthesia and adjuvant drugs, also play important roles in causing postoperative delirium.

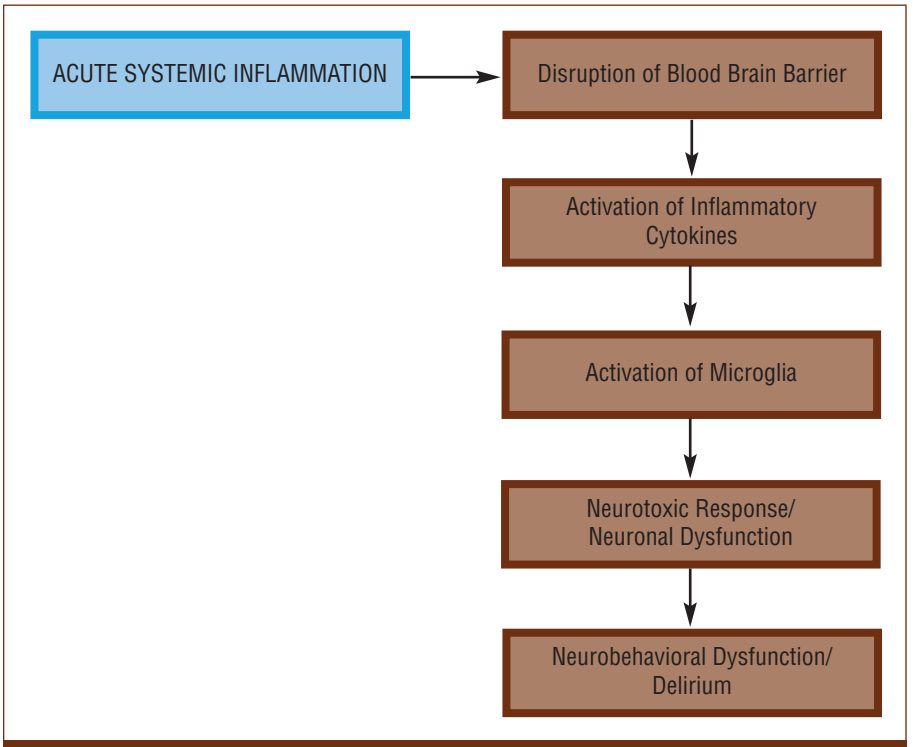

FIGURE 3. Different stages of inflammatory process resulting in delirium

Delirium after cardiac surgery has been shown to increase hospital and ICU stays and may even be life threatening.[41] A literature review by Koster et al[42] revealed 27 risk factors, 12 predisposing factors, and 15 precipitating factors for delirium after cardiac surgery. A low cardiac output and use of an intra-aortic balloon pump and ionotropic medication were the most relevant risk factors associated with postoperative delirium.

The normal aging process also causes a decrease in organ function, which affects oxygen supply, and this places the elderly at a higher risk for postoperative delirium than their younger counterparts.[43] In a study of 101 ICU patients by Seaman et al,[44] investigators found that delirium was more frequently precipitated by impaired oxidative metabolism, but was not linked to illness severity.

There is evidence that delirium may be caused by widespread brain dysfunction rather than localized disruption.[11] Neuroimaging studies conducted by Yokota et al[45] using xenon-enhanced computed tomography (CT) scans showed that patients with delirium have a 42-percent reduction in overall cerebral blood flow (CBF) compared with baseline and that occipital and subcortical regions have greater decrease in CBF than other regions. A study by Fong et al[46] also showed the same result of hypoperfusion with decreases in regional CBF in the brainstem and occipital lobe. In this study, 99mTc HMPAO single-photon emission computed tomography (SPECT) scans suggested that frontal and parietal cerebral perfusion abnormalities occur in delirium.[46]

When investigating the neuroanatomic correlation of delirium, CT and magnetic resonance imaging (MRI) scans have been used to examine structural abnormalities. A study by Koponen et al[47] using CT scans reported atrophy surrounding the cerebral ventricles in elderly psychiatric patients experiencing delirium when compared with matched controls.

According to Trzepacz,[48] certain specific brain structures, such as the thalamus and frontal and parietal cortex, are involved in delirium. CT

TABLE 2. Summary data for diagnostic accuracy of bedside instruments for diagnosing delirium

SOURCE	SAMPLE SIZE	DELIRIUM PREVALENCE %	EXAMINER SPECIALTY	95% CONFIDENCE INTERVAL	
				SENSITIVITY	SPECIFICITY
DOSS					
Van Germert and Schuurmans, 2007[67]	87	10	Nurse	89	88
Schuurmans et al, 2003[68]	92	20	Nurse	94	76
DRS					
Grassi et al, 2001[69]	105	63	Research psychologist	95	62
Rockwood et al, 1996[70]	67	37	Resident physician in geriatric medicine or psychiatry	82	94
Rosen et al, 1994[71]	791	9	Research clinician	94	82
Trzepacz et al, 1988[72]	47	43	Psychiatrist	98	98
MDAS					
Breitbart et al, 1997[73]	33	52	Psychiatrist	82	75
Kazmierski et al, 2008[74]	260	12	Psychiatrist	97	96
Matsuoka et al, 2001[75]	37	43	Psychiatrist	97	98
MMSE					
Grassi et al, 2001[76]	105	63	Trained research psychologist	96	38
Nu-DESC					
Leung et al, 2008[77]	100	25	Nurse	96	69

DOSS: Delirium Observation Screening Scale; DRS: Delirium Rating Scale; MDAS: Memorial Delirium Assessment Scale; MMSE: Mini Mental State Examination; Nu-DESC: Nursing Delirium Screening Scale

scan examination in patients with delirium have shown gross gray and white matter atrophy, ventricular enlargement, cortical and subcortical lesions, and white matter lesions with hyperintensities.[11] Interestingly, a study by Morandi et al[49] and a meta-analysis performed by Soiza et al[50] showed that findings from MRIs performed on subjects with delirium did not change the clinical treatment course.

Drugs. The physiologic changes associated with aging may increase the development of drug-induced delirium, and anticholinergic toxicity and polypharmacy are very common in elderly people.[51] Use of drugs with high anticholinergic activity, especially with muscarinic receptor activity, are considered to be a risk factor for delirium.[50] The use of sedatives[52,53] and analgesics[54] has also been associated to delirium. Drugs that may contribute to the presence of delirium include those with anticholinergic properties, tranquilizers, analgesics, and narcotics.[55] The medications may cause delirium by several mechanisms via an increase in the production of dopamine and glutamate and a decrease in anticholinergic activity.[51] Some drugs also produce a potent neurotoxic metabolite, which may cause delirium.[2,11]

DELIRIUM AND PSYCHOTIC SYMPTOMS

Sleep is essential for maintenance of memory circuits, and without it, the brain may suffer progressive synaptic weakening due to molecular turnover.[56] When sleep is disrupted, such as by delirium, memory circuits may deteriorate and subsequent activation of incompetent circuits may generate psychotic symptoms.[56] Impairment of cognitive performance and change in mood are the earliest manifestations of sleep deprivation, and as delirium progresses, it may cause other symptoms of sleep deprivation, such as visual and tactile hallucinations.[48,57] Visual hallucinations are more common than auditory hallucinations in patients with delirium. In a study that investigated the incidence of hallucinations in delirium, researchers

TABLE 3. Testing for causes of delirium

• Complete blood cell count and differential, serum electrolytes, glucose, urea, creatinine, calcium, albumin, vitamin B12, thyroid stimumlating hormone
• Oxygen saturation
• Urinalysis
• Chest x-ray
• Electrocardiogram
• Liver enzymes and function tests
• Blood cultures
• Lumbar puncture
• Computer tomography scan of head

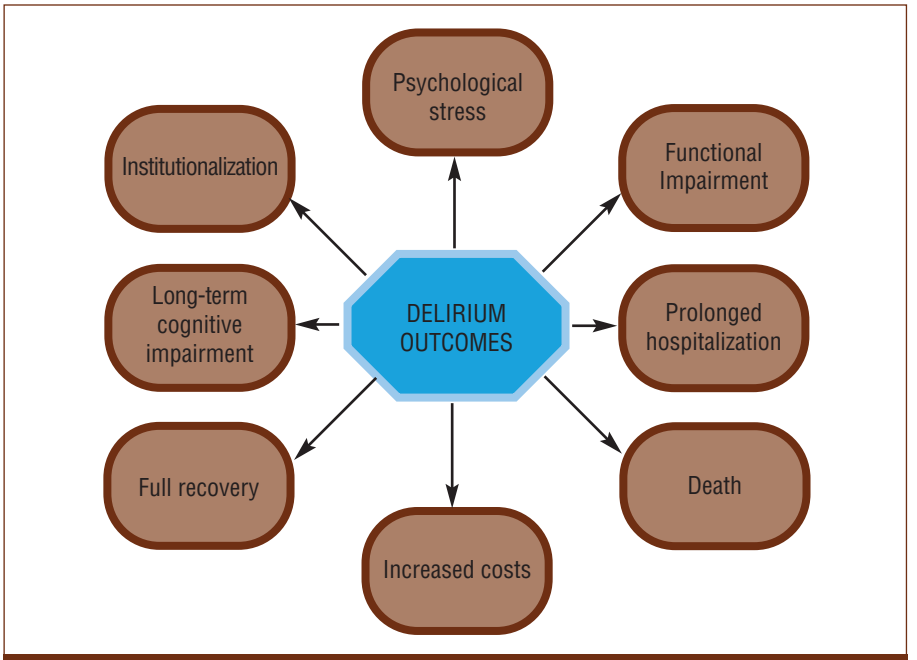

FIGURE 4. Outcomes of delirium

found 30 percent of the hallucinations to be visual and 15 percent to be auditory.[58]

Different brain regions, such as primary calcarine, occipital, parietal lobe, and temporal cortex, contribute to visual hallucinations.[48] Delirium reflects cognitive impairment rather than a psychotic process. Lesions on basal ganglia, thalamus, temporal, and parietal areas have been shown to contribute to delusion.[48] Symptoms of delirium may be similar to functional psychosis (e.g., acute mania), and delirium may present as distractible attention, fearful and labile emotions, jumbled speech, hallucinations, and delusions. But the presence or absence of disorientation and clouding of consciousness may be the only symptoms that help the clinician to differentiate between psychosis and delirium in a patient.[56,59]

DIAGNOSING DELIRIUM

The diagnosis of delirium can be made on the basis of clinical history, behavioral observation, and cognitive assessment. Different screening tools have been used to diagnose delirium, but the most widely used bedside screening tool is the Confusion Assessment Method (CAM).[60] It is a standardized tool that provides a brief, validated algorithm for diagnosing delirium. The CAM has a sensitivity of 94 to 100 percent and a specificity of 90 to 95 percent.[60] A meta-analysis demonstrated that the CAM has a sensitivity of 94 percent and specificity of 89 percent.[61] The CAM is composed of four criteria: acute onset and fluctuating course, inattention, disorganized thinking, and altered level of consciousness. A review of 11 bedside instruments used to identify the presence of delirium in adults concluded that the CAM was the most accurate test for delirium and the Mini Mental State Examination (MMSE)[62] was the least accurate test.[63]

There are several other instrumental tools that are used to diagnose delirium (Table 2).[64–74] Delirium Observation Screening Scale (DOSS)[65,75] is a 25-item scale based on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) criteria for delirium.[9] A score of 3 or more points indicates delirium. It takes less than five minutes to complete this test.

The Delirium Rating Scale (DRS)[69] is a 10-item observational scale (range, 0–32) that rates patients on characteristic symptoms of delirium. This scale is generally used by clinicians with psychiatric training.

The Memorial Delirium Assessment Scale (MDAS)[70] is a 10-item, 4-point clinician-rated scale (range, 0–30) designed to measure the severity of delirium.

The Nursing Delirium Screening Scale (Nu-DESC)[76] is designed to be administered by a nurse and is based on clinical observation in routine practice.

Electroencephalography (EEG) is useful in patients with altered consciousness in order to exclude nonconvulsive or subclinical seizures.[77] Nonconvulsive status epilepticus (NCSE) may cause continuous fluctuating impairment of consciousness. An individual exhibiting NCSE lacks motor manifestations or convulsions, and this condition is often under-recognized, particularly in older patients. NCSE requires an EEG to make the diagnosis. One report evaluating use of EEGs for diagnosis of delirium found that in 198 EEGs performed on patients for the indication of altered consciousness without convulsions, 74 (37%) of the patients had definite or probable

NCSE.[78] Thus, an EEG evaluation should be obtained for any patient with altered consciousness of unknown etiology.[79]

Once the diagnosis of delirium is made, the search must begin for the underlying etiology. Table 3 shows the tests that should be performed to help determine the etiology of the delirium.

OUTCOME

Delirium can result from multiple etiologies, and outcome is usually unfavorable. Delirium may lead to aspiration pneumonia, inadequate fluid intake, physical injury, permanent cognitive impairment, and electrolyte imbalance. Studies have shown that outcome depends on the severity of delirium.[80] Figure 4 shows the possible outcomes of delirium.

CONCLUSION

Delirium is a critical illness and a serious complication of hospitalization. Delirium is associated with high morbidity and mortality. It is potentially preventable and treatable, but poor understanding of its pathophysiology and the complexities that occur in the brain during delirium have limited the development of successful treatment. The role of impaired cholinergic transmission, inflammation, and impaired oxidative metabolism have been implicated in the development of delirium. Use of neuroimaging and neuroanatomic correlation in delirium have been studied.

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