M. Therese Southgate, MD, *Section Editor*

Delirium (Acute Confusional States)

Z. J. Lipowski, MD, FRCP(C)

Delirium (acute confusional states), a common and often overlooked psychiatric disorder, can occur at any age, but elderly persons are especially prone to develop it. In later life, it is often a conspicuous feature of systemic or cerebral disease and drug (notably anticholinergic) toxicity, and it may constitute a grave prognostic sign. Its development in a hospitalized patient may interfere with his or her management, disrupt ward routine, and cause medicolegal complications as a result of patient injury. Acute onset of a fluctuating level of awareness, accompanied by sleep-wake cycle disruption, lethargy or agitation, and nocturnal worsening of symptoms, are diagnostic. Early recognition of delirium and treatment of its underlying cause are essential.

(*JAMA* 1987;258:1789-1792)

DELIRIUM is one of the most commonly encountered mental disorders in general hospital practice. It has been called *everyman's psychosis* to highlight the fact that everybody is potentially susceptible to it,[1] and it has been referred to as *reversible madness*, which "no doctor likes to miss."[2] In fact, he or she often does miss it, and the patient may suffer as a result.[3-5] While delirium can occur at any age, its incidence is highest among elderly persons, in whom it is probably most often missed.[6,7] To help clinicians recognize and manage it, its clinical features, etiology, pathogenesis, and treatment will be reviewed.

Definition of Delirium

Delirium (acute confusional states) is a transient disorder of cognition and attention, one accompanied by disturbances of the sleep-wake cycle and psychomotor behavior.[7,8] It is one of the so-called organic mental syndromes that constitute psychopathological manifestations of brain dysfunction.[8]

Frequency and Importance of Delirium

Few epidemiological studies of delirium have been reported to date. Two recent studies of elderly patients admitted to general medical wards found that 30% and 50%, respectively, of the patients aged 70 years or older showed evidence of delirium at some point during the index admission.[9,10] As elderly patients, those aged 65 years and older, occupy 38% of total hospital beds,[11] the frequency of delirium in the general hospitals is liable to be high. It is estimated that about 10% of hospitalized medical and surgical patients are delirious at any given time.[7]

Delirium is important clinically not merely because it is common. In elderly patients, it is often a presenting feature of acute physical illness, such as myocardial infarction or pneumonia, or of intoxication with medical (notably anticholinergic) drugs.[6,12] Failure to diagnose it and to identify and treat its cause could have serious, even lethal, consequences for the patient. Several studies have actually documented its high mortality.[4-6,13,14] Self-injury of the patient is a serious risk. Agitated, confused, and fearful, he or she may try to escape and fall and sustain a fracture or other injury. Tearing open of sutures and pulling out of intravenous lines may occur. Such a patient is often treated with injections of psychotropic drugs, such as chlorpromazine hydrochloride, and may develop hypotension, or he or she is physically restrained with consequent risk of deep vein thrombosis and pulmonary embolism.[9,10] Self-injury may lead to litigation, while legal and ethical complications may arise from the patient's inability to give informed consent.[15] Finally, delirium may present a difficult diagnostic problem and be mistaken for schizophrenia or dementia, for example, with consequent failure to identify and treat its organic cause.

Clinical Features

Global disorder of cognitive functions and attention (awareness, consciousness), disruption of the normal sleep-wake cycle, and either reduced or heightened activity and responsiveness constitute the cardinal features of the syndrome.[6-8,16] These symptoms develop acutely and tend to fluctuate in severity during the day, being most pronounced at night. Anxiety, restlessness, drowsiness, insomnia, and disturbing dreams may precede the development of the full-blown syndrome that often occurs during the night. The patient wakes up, confused and agitated, and may try to get out of bed and leave the ward.

Disorder of Cognition

Perception, thinking, and memory, ie, the main cognitive functions, are all impaired or abnormal to some extent and, hence, globally disordered. *Per-*

From the Department of Psychiatry, University of Toronto.

Reprint requests to Clarke Institute of Psychiatry, 250 College St, Toronto, Ontario, Canada M5T 1R8 (Dr Lipowski).

ception is disturbed, in that the patient has reduced ability to discriminate percepts and grasp the meaning of what he or she perceives. These deficits are partly responsible for what observers often refer to as *confusion*. The patient tends to misinterpret sensory stimuli and mistake an intravenous line for a snake or the sound of a falling glass for a pistol shot, for example. Such misinterpretations, ie, illusions, are mostly visual and auditory. Moreover, actual false perceptions, ie, hallucinations, that the patient typically believes to be real occur in many but not in all cases of delirium.[7] They are characteristically visual or visual and auditory, and they may range in complexity from simple sights and sounds to visions of animals in motion or whole scenes that involve people. Olfactory, kinesthetic, and tactile hallucinations are much less common. While frequently present, hallucinations are not necessary for the diagnosis. They are usually frightening; hence, the patient tends to react to them with attempts at flight or fight that may lead to injury.

Thinking is more or less disorganized and incoherent, as is evident from the patient's speech. Ability to use abstract concepts, solve problems, and direct thoughts at will is always impaired to some extent. As a result, the patient's responses and behavior tend to be erratic and lacking judgment, and he or she may deny being sick. Delusions, usually persecutory, are often, but not invariably, present. They are fleeting, poorly organized, and changeable in response to events in the patient's immediate environment. By contrast, in schizophrenia, mania, or paranoid psychosis, they tend to be well organized and consistently held.

Memory is impaired in all its key aspects: registration, retention, and recall. Immediate memory is defective due to short-attention span. Recall of recent events is faulty, and the patient may confabulate to make up for memory gaps. Some degree of amnesia for the experience of delirium remains after recovery.

Orientation is usually defective, especially for time, but may be intact in a mild case. In more severe delirium, the patient is disoriented for time and also for place and person; he or she typically mistakes unfamiliar surroundings and persons for to him or her familiar ones. In the most severe case, the patient may fail to recognize his or her next of kin.

Disorder of Attention

Attention is always disordered, in that the patient shows reduced ability to mobilize, shift, sustain, and direct it at will: he or she is distractible.[6,7,17] Clarity of awareness of self and environment is consequently blurred. The patient may be either hypoalert or hyperalert, ie, respond to stimuli with abnormally reduced or increased readiness, respectively. Attentional disturbance typically fluctuates during the day; hence, the patient is more or less lucid and accessible. Deficits of attention and awareness have been traditionally subsumed in the literature by the term *clouding of consciousness*. This obsolete and redundant concept is included among diagnostic criteria listed in the third edition of the *Diagnostic and Statistical Manual of Mental Disorders*[8]; however, it has been dropped from the recently revised version.[18]

Disorder of Sleep-Wake Cycle

Wakefulness is often reduced during the day, and the patient is drowsy and naps often, while at night he or she tends to be awake and agitated. The normal sleep-wake cycle is thus disrupted or may be actually reversed, or the patient may hardly sleep at all.[7] Such disorganization of the cycle appears to enhance cognitive-attentional deficits.

Psychomotor Behavior

A delirious patient may be hypoactive or hyperactive in regard to his or her movements and speech. He or she may be lethargic and respond slowly and hesitantly, or, on the contrary, may display excessive and semipurposeful activity and rapid, loud, pressured speech. It is such a hyperactive patient who is most likely to draw attention of the staff, while a hypoactive one may remain unnoticed and undiagnosed as he or she does not disturb anybody. It is a fallacy to view hyperactivity as a hallmark of delirium.[7,17,19] Some patients display involuntary movements, such as tremor or asterixis; an occasional patient may be mute or even catatonic.

Associated Features

Emotions that range from apathy or depression to fear or rage accompany the above diagnostic features. Signs of sympathetic nervous system arousal, such as tachycardia, sweating, pallor or flushing of the face, dilated pupils, and elevated blood pressure, may accompany fear and rage; they are typically present in delirium due to anticholinergic drugs or to alcohol and/or sedative-hypnotic drug withdrawal.

Prognosis

By definition, delirium is a transient disorder, one that ends in recovery after several days to weeks in most cases. In some patients, however, it may be a feature of terminal illness, such as cancer,[20,21] and be followed by death. In elderly patients, its development may be a grave prognostic sign.[13,14]

Etiology

Delirium represents an etiologically nonspecific syndrome due to widespread cerebral dysfunction that may be caused by a range of organic factors.[6,7,22] Elderly patients are especially prone to develop it as a result of the following factors: aging or disease of the brain; impairment of vision and hearing; reduced synthesis of neurotransmitters, notably acetylcholine; age-related changes in the pharmacokinetics and pharmacodynamics of drugs; high prevalence of chronic diseases and susceptibility to acute ones; and reduced capacity for homeostatic regulation.[6,7,22] Brain damage of any origin is also a predisposing factor. Sleep and sensory deprivation, immobilization, and psychosocial stress, such as bereavement or transfer to an unfamiliar environment, appear to facilitate the onset of delirium, especially in elderly patients.[6,7,22]

The causative organic factors may be grouped into four general classes[6,7,16,22]: (1) primary cerebral diseases, such as infection, neoplasm, trauma, epilepsy, and stroke; (2) systemic diseases that affect the brain, notably metabolic diseases, infections, and cardiovascular and collagen diseases; (3) intoxication with exogenous substances, ie, medical and recreational drugs, and poisons of industrial, plant, and animal origin; and (4) withdrawal from substances of abuse in a person addicted to them, mostly alcohol and sedative-hypnotic drugs.

In elderly patients, more than one causative factor is often implicated, and it may involve therapeutic doses of commonly used drugs, such as diuretics, digoxin, antiparkinsonian and antipsychotic drugs, antidepressants, sedative-hypnotic agents, and cimetidine.[6,7,16,22] Drugs with anticholinergic activity are especially liable to induce it.[23] Other common causes of delirium in later life include congestive heart failure, pneumonia, urinary tract infection, cancer, uremia, hypokalemia, dehydration and/or sodium depletion, and cerebral infarction.[24-28] General surgery in an elderly patient has been reported to be followed by delirium in 10% to 14% of cases[29,30]; it may reach 50% after surgery for hip fracture.[31]

Pathogenesis and Pathophysiology

Even though delirium has been known and frequently described since Hippocrates,[7] it has been largely ig-

Differential Diagnosis of Delirium and Dementia

Feature	Delirium	Dementia
Onset	Acute, often at night	Insidious
Course	Fluctuating, with lucid intervals, during day; worse at night	Stable over course of day
Duration	Hours to weeks	Months or years
Awareness	Reduced	Clear
Alertness	Abnormally low or high	Usually normal
Attention	Lacks direction and selectivity, distractibility, fluctuates over course of day	Relatively unaffected
Orientation	Usually impaired for time, tendency to mistake unfamiliar for familiar place and persons	Often impaired
Memory	Immediate and recent impaired	Recent and remote impaired
Thinking	Disorganized	Impoverished
Perception	Illusions and hallucinations usually visual and common	Often absent
Speech	Incoherent, hesitant, slow or rapid	Difficulty in finding words
Sleep-wake cycle	Always disrupted	Fragmented sleep
Physical illness or drug toxicity	Either or both present	Often absent, especially in Alzheimer's disease

nored by researchers. As a result, knowledge of its pathogenesis and pathophysiology is scanty. Classic studies by Engel and Romano[19] in the 1940s resulted in the most influential pathogenetic hypothesis. Those investigators carried out a series of investigations that involved electroencephalographic (EEG) recordings and concluded that general reduction in cerebral oxidative metabolism accounted for both the cognitive impairment and the concurrent slowing of the EEG background activity. Thus, any disease or toxic agent that caused reduction of the supply, uptake, or utilization of substrates for brain metabolic activity could lead to delirium. More recently, Blass and Plum[32] proposed that a reduced rate of cerebral oxidative metabolism resulted in reduction of acetylcholine synthesis, and the consequent cholinergic deficiency constituted a common denominator in metabolic-toxic encephalopathies, one of whose manifestations is delirium. This interesting hypothesis has considerable empirical support. Numerous studies carried out in the 1960s showed that delirium could be readily induced in experimental subjects by administration of various anticholinergic agents and be reversed by physostigmine salicylate, a cholinesterase inhibitor.[7,33] Itil and Fink[33] postulated that imbalance of central cholinergic and adrenergic mechanisms underlies delirium. Thus, reduced cerebral oxidative metabolism and consequent reduction in the synthesis of certain neurotransmitters, notably acetylcholine, their imbalance, or both, appear to play a major pathogenetic role. One needs to apply such techniques as positron emission tomography to the study of delirium to clarify its pathophysiology.

Two other hypotheses are worth mentioning. Kral[34] proposed that acute confusional states in elderly patients represent a reaction to acute stress, one mediated by elevated levels of plasma cortisol and its deleterious effects on anatomical substrates of attention and information processing. There is actually some evidence that hypercortisolemia may follow exposure to any type of stress, including psychosocial stress, and be associated with cognitive impairment.[35,36] Further studies are needed to test this hypothesis.

Finally, Geschwind[17] hypothesized that acute confusional states should be viewed as *global disorders of attention* and reflected acute lesions in the anatomical substrates of attention. He based this opinion on the observation of the frequent occurrence of these states in right hemisphere infarctions and on the postulated dominance of that hemisphere for attention. The issue of a localized vs global or widespread brain pathologic condition in delirium remains unresolved.

Diagnostic Issues

No specific diagnostic test for delirium exists, and diagnosis is made on the basis of its essential clinical features. Cognitive and attentional deficits are elicited and observed at the bedside. A commonly used test, such as the "Mini-Mental State," may help to elicit them, but it cannot distinguish delirium from dementia and is of limited value in the case of older and poorly educated patients.[37] Mental status evaluation is best done unobtrusively while taking the history of the present illness and hospitalization that will reveal memory gaps, inconsistencies, distractibility, bewilderment, disorganized thinking, and impaired orientation.[19] The patient is asked to subtract serially seven or three from 100, to repeat three words and three objects, to count from 20 backward, to repeat a few familiar proverbs, and to give the date, day of the week, and time of the day. These bedside tests will bring out attentional deficits and impairment of memory and abstract thinking. In general, *acute onset of cognitive and attentional deficits and abnormalities, whose severity fluctuates during the day and tends to worsen at night, is practically diagnostic.*

Delirium needs to be distinguished from dementia, functional psychosis (schizophrenia, mania), and a psychogenic dissociative state. Differential diagnosis from dementia is particularly important (Table) and may be difficult, especially when delirium is superimposed on Alzheimer's disease or multi-infarct dementia.[6,22] A history of intellectual decline, long antedating the onset of the acute cognitive disorder, is crucial for the differential diagnosis. A demented patient is usually normally alert and aware of his or her surroundings, fails to show an irregularly fluctuating level of awareness during daytime, and shows defective knowledge of commonly known facts. Acute deterioration of cognitive and attentional processes in a known demented patient suggests delirium and calls for full investigation to determine its cause (or causes).

An acutely schizophrenic or manic patient may appear to be confused but, on careful questioning, fails to show cognitive deficits and is likely to have auditory (voices) rather than visual hallucinations and elaborate rather than poorly systematized and sustained delusions. In a doubtful case, an EEG may help: in delirium, but not in a functional psychosis, it is usually diffusely slowed, roughly proportionately in degree to the severity of cognitive impairment.[19,38,39] Delirium due to sedative-hypnotic drug and alcohol withdrawal does not, however, feature EEG slowing but rather excessive low-amplitude fast activity.[39,40] In a dissociative state, the patient may complain of being confused and unable to recall personal data, including even his or her own name; an EEG is normal.

Management

Once delirium is diagnosed on clinical grounds, its organic cause (or causes) must be sought and treated. Especially in elderly patients, all drugs, notably the anticholinergic ones, taken by the

patient are suspect and should be discontinued or their dose be reduced. Polypharmacy should be avoided. If despite these measures, delirium continues, a careful medical and neurological reevaluation is in order. A psychiatric consultation should be sought, since liaison psychiatrists in particular are well familiar with the syndrome and its many disguises and causes.[3]

Symptomatic and supportive therapy is important. Fluid and electrolyte balance, nutrition, and adequate vitamin supply need to be ensured. The patient is best cared for in a quiet, well-lit room, with a few familiar objects and a visible calendar and clock. These measures help to reduce anxiety, agitation, and disorientation. Good nursing care is crucial and aims at orienting and reassuring the patient.[6,7,31] Nurses should be trained to recognize early symptoms of delirium and report them at once; the night staff's observations are particularly important. Sedation may be necessary to relieve severe agitation, insomnia, or both. Haloperidol (Haldol) is usually the safest and most effective drug for this purpose.[6,7,23,41] It may be given parenterally or orally in doses of 2 to 10 mg initially until the patient calms down. In alcohol withdrawal, delirium benzodiazepines are the drugs of choice.[42] In severe anticholinergic intoxication, physostigmine salicylate, 1 to 2 mg, should be given slowly intravenously or intramuscularly and repeated after 15 minutes. Contraindications to its use include a history of heart disease, asthma, diabetes, peptic ulcer, and bladder or bowel obstruction. It needs to be given cautiously to avoid seizures and cardiac arrhythmia.[7,43,44] In hepatic encephalopathy, oxazepam or lorazepam may be used.[45]

Conclusion

Delirium is a common syndrome, especially in elderly patients, and occurs in all clinical settings. It may develop at any age and be a serious prognostic sign. It is often overlooked, yet every clinician and nurse should learn to diagnose it early in an attempt to prevent ward disruption, lethal outcome, and medicolegal complications. This long known yet neglected organic mental syndrome is practically and theoretically important and badly in need of research.

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