Delirium and epilepsy

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Delirium (a state of usually reversible global brain dysfunction due to toxic, metabolic, or infectious causes) and epilepsy (a condition of spontaneous, recurrent paroxysmal electrical excitation or dysfunction) are becoming increasingly better understood, and hence easier to diagnose and treat. The clinical features of delirium predominantly involve subacute changes in cognition, awareness, and activity levels, behavioral disturbance, clouding of consciousness, and sleep–wake cycle changes. In contrast, epilepsy involves the acute interruption of brain function, often with convulsive activity, falls, and injury. States that may share the clinical features of both, such as nonconvulsive epileptic states, are also important: the cause of brain derangement is one of excessive and abnormal electrical brain activity. In such conditions, the clinical manifestations may resemble states of delirium and confusion, and the absence of convulsive clinical activity is significant. Electroencephalography remains the diagnostic test of choice: it is essential for differentiating these two conditions, enabling the distinctly different treatments for delirium and epilepsy. Ongoing research and investigation are essential to better understand the abnormal brain mechanisms underlying delirium, and to develop better tools for objective diagnosis.

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States of altered consciousness such as delirium and psychoses have long horrified humanity with the specter of loss of an individual's sovereignty and self-control, carrying with it the intimation of passage towards death. Agitated states with altered awareness and components of excitation and delusion have evoked the perception of visitation by demons, spirits, or even divine influence, but often with the consequence of ostracism from society. This has led, even in an age of enlightenment, to relegation to insane asylums. Only with Pinel and Esquirol in France, Chiarugi in Italy, and in institutions such as Bethlehem ("Bedlam") in England were there organized societal efforts toward addressing such conditions of insanity as forms of illness, which were identifiable even if not successfully treatable.[1] In the 20th century, scientific effort has been directed toward understanding delirium and researching its causes.

Epilepsy carried with it a similar societal view, also leading to incarceration and often draconian remedies. These conditions often are intertwined in terms of both clinical features and common substrates and triggers. A clearer distinction has been drawn between the two only by close clinical observation of phenomenology and, in the 20th century, by electroencephalography (EEG), enabling an electrophysiologic differentiation between them. But still they merge, as will be described.

The term epilepsy, derived from the Greek *epilambanein*, arose from the concept that the individual was "seized,"

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Selected abbreviations and acronyms

ASE	*absence status epilepticus*
CPSE	*complex partial status epilepticus*
GABA	*γ-aminobutyric acid*
NCSE	*nonconvulsive status epilepticus*
REM	*rapid eye movement*

gripped, or attacked by forces, thus presupposing a relatively circumscribed duration; while delirium comes from the Latin for "to leave the furrow," representing a "leave-taking" of one's senses.

Descriptions of such illnesses occur in ancient texts, with early accounts of delirium delineated as a mental disorder, and can be regarded as a model of physicians' efforts at understanding the diseased mind.[2,3] Hippocrates in his book *Epidemics* describes a condition characterized by restlessness, shifting moods, and visual hallucinations at night, but with lucid intervals.[4] Studies by Esquirol described maniacal attacks or *furor epilepticus* in which "raving fits" of lunatics were associated with epileptic symptoms.[5] Such observations were made by Tyson (1650-1708) as a physician to the Bethlehem Hospital.[6] Prichard went on to describe[7]:

The face is flushed, and the aspect of the patient is like that of a man under intoxication; he attempts to start from bed and run about and, on being withheld, reciprocates and endeavors to overcome resistance. Sometimes an appearance of maniacal hallucination displays itself, but more generally the disorder resembles frenetic delirium. It commonly continues 1, 2, or 3 days, during which the patient requires confinement in a strait waistcoat, and then gradually subsides, and the patient returns into his previous state.

At the end of the 18th century, Foderé described a "periodic delirium" that probably included cases of epileptic mania[8]:

These paroxysmals do not come on suddenly. Usually the patient feels their approach; they are preceded by a noise in the head and frightening dreams; then the patient feels something ascending from the lower parts of the body to the uppermost, almost as in the aura epileptica. He loses consciousness; he falls down; he is raised up again and is now raging.

Even as far back as 1808, an epileptic murderer was acquitted on the basis of diminished responsibility and placed in a workhouse. Falret, in France, described delirious types that could either precede or follow convulsive attacks. Such an "epileptic delirium" was seen in patients without acute convulsions. It "substituted" for the epileptic convulsions and was viewed as another manifestation of the same disease, but in a different form.[9] Delirium in this sense, represented "larval or masked epilepsy." Samt, in Germany, described patients "characterized by violence, fits and religious ecstasy."[10] Such prophesying epileptics had seizures followed by a state of mental twilight and confusion:

One patient before or after seizures, fell into an irritated and excited state, condemned his godless environment, mistook others for devils, thrashed, and wished to be crucified for the faith.

As noted by Krafft-Ebing[11]:

Consciousness is considerably dim during this delirious state, but still amenable to impressions from the external world. Accordingly, there does not exist any defective memory afterwards. The patient remembers his divine visions and does not correct them.

Introduction

In brief, contemporary neurobiological understanding of delirium attributes it to a derangement in the correct functioning of cortical neuronal communication, largely caused by toxic influences of exogenous and endogenous substances. This is often consequent to internal organ dysfunction with toxic-metabolic effects on the neuronal substrates subserving the correct balance of pathways that support cognition, memory, and arousal. It is a perturbation of the mind, as much as of the brain.

Epilepsy, in contrast, is more of an acute and spontaneous, largely unpredictable, paroxysmal dysfunction of some, or most, of the brain functions, with a highly variable impact on subjective sensory perception, motor control, and—at its worst—consciousness and vital centers. With convulsive excitation of motor pathways, this leads to postictal exhaustion and variable unconsciousness. In almost all cases, this has been identified as being due to hyperexcitable and chaotic neuronal brain discharges, expressing themselves clinically, as an excited "exaggeration" of

the function of the part of the brain affected. In effect, epileptic excitation of a particular brain region, such as motor cortex, would lead to contralateral limb or axial movement represented by that cortex. As an example, chaotic neuronal bursts in the temporal lobe could lead to memory evocation of distant, isolated perceptions, and memories. This excitation has been delineated at the cellular and tissue levels by recording cellular discharges in vitro in brain slices, while noninvasive diagnostic EEG can record such synchronous discharges at the scalp surface in animals, and in humans affected with epilepsy.

Differentiation among delirium, dementia, psychosis, and seizures can sometimes be difficult, given the shared clinical features of many of these disorders. This article will include discussion of the pathophysiology and clinical features of delirium and epilepsy, provide indices for their diagnosis, and discuss the differentiating, as well as overlapping, features of seizures and delirium. It will also discuss transitions between the two, the role of medications and toxic influences, the ambiguity of EEG, and the concept of an ictal delirium, combining the elements of both states.

Definition and diagnosis

The *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R)* distinguishes between *organic mental disorders* and *organic brain syndromes*.[12] The criteria for organic brain syndromes do not refer to etiology, while those for organic mental disorders do. Delirium refers to transient "clouding of consciousness" with fluctuating attention, disordered thinking, and several other abnormal behaviors. One caveat in evaluating the literature relating delirium, psychosis, and epilepsy has been the broad inclusion of delirious and manic states under psychosis by some authors. Many do not define their inclusion criteria, and terminology varies from culture to culture. In the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*, postictal confusion or delirium is not included under psychosis, but there are strong resemblances with the similarity of symptoms, behavioral aberration, and confusion.[13]

Neurologists and psychiatrists often disagree on terminology: some authorities refer to a euphoric confusional state with hypervigilance and hyperactivity as delirium, while others refer to lethargy and psychomotor slowing in confusional states. Delirium tremens is characterized by hyperactivity and hypervigilance with EEG showing sparse normal alpha, but increased beta activity.

Clinical features of delirium

Delirium is the most frequently seen mental dysfunction in the critically ill.[14] Particularly prevalent in the elderly, it can be seen about 20% of hospitalized patients[15,16] as described by Lipowski[17]:

Delirium is a transient organic mental syndrome of acute onset, characterized by global impairment of cognitive functions, reduced level of consciousness, attentional abnormalities, increased or decreased psychomotor function, and a disordered sleep–wake cycle.

The clinical features of delirium predominantly involve impairment of cognition and awareness. Motor activity may be decreased or increased, but it often is characterized by agitation with behavioral disturbance. The clouding of consciousness typically impairs insight and a change in outlook, bringing the patient to medical attention. There is impaired orientation to time, place, and occasionally person, with the patient appearing to wander in space and time (usually in the past), confusing even close family members, the unfamiliar hospital surroundings, the seasons, and years. Nocturnal–diurnal sleep–wake cycles are often impaired and may be inverted, with sundowning characterized by agitation at the day's end, but lethargy or sleep during the daylight hours. It may engender lethargy or passivity with decreased eating and responsiveness during the day, alternating with agitation, anxiety, hallucinations, and hyperphasia at night. Any particular patient may have one or more of these disturbances, but the individual patient may have a highly variable temporal course and manifestations of these features. Physicians on their brief rounds may fail to note the fluctuating mental status so characteristic of delirium, while the nursing staff with a more prolonged observation bring the key signs to clinical attention.[18]

Delirium may be differentiated into two forms.[18,19] The first type is characterized by excitation, anxiety, anger, and changes in behavior with hypervigilance and typically signs of autonomic excess. This type follows benzodiazepine, alcohol, or barbiturate withdrawal, or the use of central nervous system–stimulating drugs such as cocaine or amphetamines. A second type is characterized by psychomotor retardation, indifference and apathy, impaired cognition, and physical activity with a decreased level of consciousness. The distinction may not

be clear, and one state may give way to the other, for example, following a period of excitation with alcohol withdrawal, a patient may pass over into a state of obtundation and lethargy.

Higher cortical function

Delirium is characterized by impairment of higher cortical functions, involving defective thinking, memory, and spatial, temporal, and personal orientation. The immediate environment may be misinterpreted or appear abnormal (illusions), and sights, sounds, or sensory stimuli may be perceived when not truly present (hallucinations); auditory hallucinations with voices, however, would suggest a psychosis rather than delirium.[3] Patients appear incoherent, unable to direct and sustain lines of thought, and unable to understand abstract ideas and use appropriate judgment. Learning, retention, and recall may be impaired with consequences on recent and long-term memory. There may be confabulation and emotional lability. Patients are easily distractible and cannot sustain directed mental efforts. Tasks are left unfinished, and there may be perseveration in thoughts, speech, and action.

Behavioral problems

Hyperactive delirium frequently manifests as anxiety, agitation, or even anger.[18-21] At the other end of the spectrum, lethargy, somnolence, or even catatonia may occur. Patients may exhibit both ends of the spectrum. Limbs or facial jerks, tremors, and voluntary or involuntary limb and face movements can occur with fluctuating intensity, making it difficult to differentiate from nonconvulsive status epilepticus (NCSE). It is the hypoactive patient whose diagnosis may be overlooked.

Prognosis

Delirium is usually considered to be a transient disorder of the mind, but it typically appears in the setting of more serious underlying dysfunction. The morbidity and mortality, therefore, stem more from the underlying conditions engendering delirium, rather than from the delirium itself. Mortality appears to range from a quarter to a third of patients, whether assessed at the time of admission or over 3 or 6 months from diagnosis.[22-24]

Pathogenesis

A number of causes for delirium have been identified *(Table I)*. Risk factors include prior cognitive impairment, advanced age, intercurrent infection, bone fracture, and medication use, particularly narcotics and neuroleptics. Postanesthesia delirium is common.[25] Nonetheless, many delirious patients have no clear toxic or metabolic abnormality. Some have attributed these states to environmental changes, particularly in the demented and elderly.

There are a number of mechanisms that may disrupt sleep–wake cycles and cognition. Arousal and cortical activation involves the ascending reticular activation system (ARAS), which modulates cortical excitability and wakefulness. Electrical stimulation of the ARAS may induce behavioral arousal in sleeping animals.[26] Conversely, lesions of the reticular system can induce a sleep-like state.[3,27] From such experiments, it appears that both sleep and coma are consequent to decreased inflow of tonic ascending impulses subserving wakefulness. A number of neurotransmitters have been suggested to be involved in this process.[28-32] Serotonergic input modulates slow-wave sleep and initiates rapid eye movement (REM) sleep. The serotonergic and catecholaminergic systems can also act antagonistically to produce wakefulness and slow-wave sleep alternately, but both induce REM sleep.[30] A highly complex but coordinated neocortical structure is "aroused" to consciousness by local circuit neurons, projections from ipsilateral and contralateral hemispheres, as well as by deeper structures in the pons and thalamus, and in basal forebrain.[3] Impairment of the integrity of this anatomical system (which is essential for self-awareness) can reduce attention and disrupt sleep or wakefulness.

In addition to the cholinergic hypothesis of delirium, which is supported by the observation that anticholinergic drugs frequently cause delirium, is the observation that delirium can be relieved by dopamine blockade. Observations of this reciprocal relationship between cholinergic and dopaminergic brain effects indicate a role for dopaminergic excess in delirium. The delirium associated with bupropion toxicity has been postulated to be due to excessive dopaminergic activity.[33] Delirium may also occur from serotonergic intoxication seen with serotonin syndrome,[34] resulting from concomitant use of serotonergic agents. Decreased γ-aminobutyric acid (GABA) activity has been implicated in delirium from sedative drug withdrawal, or toxic ictal delirium.[35] It has been suggested that, since the thalamus is rich in GABA, reduc-

tions in GABA affect thalamic gating stimuli. Similarly, antibiotics may induce delirium by reducing activity at the GABA receptors. More recent research has also centered on the role of glutamate, β-endorphin, and glucocorticoids in delirium, but further clarification is needed.

Strikingly, many of the symptoms of delirium resemble abnormal dream states, and experimental efforts have been directed at inducing delirium through manipulation of the sleep–wake cycle. Sleep-deprived volunteers can have visual and auditory hallucinations, as well as delusions, with poor cognition.[36,37] REM deprivation can induce fatigue, irritability, depersonalization, disorientation, and even visual illusions, but few behavioral changes.[38,39] It has been postulated, therefore, that disruption of sleep–wake cycles might, in turn, result in the inappropriate intrusion of elements of sleep and dreaming into wakefulness, or other waking state during sleep.[40] It is not clear, however, that sleep deprivation per se is an intrinsic trigger of delirium in hospitalized patients. It has been postulated that sensory deprivation alone, or on impaired brain homeostasis, such as with dementia or diffuse atrophy, may engender delirium. However, even in normal subjects, sensory deprivation can result in visual illusions, but without delirium. It has long been observed that patients in rooms

Central nervous system	Systemic disease
Trauma Closed head injury/concussion Contusion Epidural, subdural, and intracerebral hemorrhage	Noncerebral nervous system disease • Metabolic/electrolytes • ↑Na; ↓Na • ↑Glucose; ↓glucose • ↑Ca; ↓Ca • ↑CO_2; ↓O_2
Cerebrovascular compromise • Transient ischemia: nondominant; thalamic: brain stem • Infarction: large hemisphere, thalamic; hematomas • Hemorrhage: subarachnoid or intracerebral	Systemic failure • Hepatic • Renal • Pulmonary • Cardiac • Endocrine • Hypothyroidism Hypoparathyroidism/hyperparathyroidism Hypocortisolemia/hypercortisolemia
Seizures/ictal states Nonconvulsive states • Complex partial status epilepticus • Absence status epilepticus • Postictal confusion • Paroxysmal lateralized epileptiform discharges (PLEDs) • Ictal encephalopathies (eg, intoxication with lithium, tiagabine)	Infection • Systemic • Organ • Lung • Kidney or urinary tract Fever Drugs, medication Drug abuse/alcohol Drug withdrawal Hypertensive encephalopathy/hypotension Paraneoplastic states
Neoplasia • Primary brain tumors • Metastases • Carcinoma	Immunological/endocrine dysfunction • Hashimoto's encephalopathy • Thyroid storm
Infection • Meningitis • Encephalitis	

Table I. Causes of delirium.

in surgical intensive care units without windows have a higher incidence of postoperative delirium.[41]

Other frequent causes include drug and alcohol withdrawal syndromes, probably representing the removal of depressant effects on downregulated systems, with rebound hyperexcitability. A REM-sleep rebound may follow drug withdrawal, intruding into waking states in the form of hallucinations, delusions, and psychotic phenomena.[3,42,43] Other pathophysiological explanations include decreased acetylcholine synthesis[21,44] and stress-induced augmentation of cortisol.[45,46] In hepatic and renal sufficiency, there may be abnormal elaboration of neurotransmitter substances that unbalance pathways subserving arousal and cognition, thus impairing sleep–wake cycles and normal cerebral processing.[47-49] Even in normal subjects, anticholinergic medications may produce delirium, disordered attention, impaired abstract thinking, temporal perception, and impaired memory.[50,51] The interplay among serotonergic, cholinergic, and noradrenergic mechanisms may thus be disrupted to impair the cognitive and arousal functions of the brain.[3]

There is increasing information to suggest that the neuronal dysfunction leading to delirium may occur from more focal cortical, subcortical, or combined dysfunction. Geschwind has suggested that focal lesions, for example, of the right hemisphere, may impair attention.[52] Evidence for this has come from structural and functional brain-imaging techniques, as well as from brain-lesion patients. Areas implicated include the caudate, and wider basal ganglial involvement, right subcortical strokes, right perimedian thalamic stroke, and stroke of the left caudate or right frontal cortex all indicate the involvement of thalamus and frontal regions in delirium.[53]

Differential diagnosis

Although delirium is frequently overlooked or misdiagnosed,[54] confusion is often the first sign to be noted, followed by waxing and waning cognitive function, incoherence, and an inversion of sleep–wake cycles. Once delirium has been identified, investigation is directed at underlying causes *(Table I)*. When hallucinations and agitation appear, but alertness and memory are relatively preserved, then a psychosis or drug-induced psychiatric condition may be present. Delirium can be accompanied by overactivity of the autonomic system, producing sweating, pupil dilatation, and tremor. Dementia usually occurs in a clear sensorium, without autonomic dysfunction, a little drowsiness, and inattention. Also, delirium has a more acute onset and greater fluctuation than simple dementia. Some fluctuation occurs in dementia, and delirium can appear in the setting of a chronic dementing process.[55] In psychosis, severe cognitive defects are rare, while auditory hallucinations are elaborate and frequent, and the EEG is normal.[56] Olfactory hallucinations, however, may be mistaken for epileptic aurae. As noted before, in delirium, cognitive deficits are marked with poorly organized and variable visual hallucinations. The EEG usually shows diffuse background slowing or intrusion of slower frequencies. Early studies by Engel and Romano correlated clinical, psychological, and EEG slowing in delirium, linking increasing lethargy with EEG desynchronization.[57,58] Progressive impairment in the Mini-Mental Cognitive Scores also correlates with slowing on EEG.[59] Conversely, with delirium following drug withdrawal, the EEG may show fast activity. Many of the typical differentiating features among psychosis, drug withdrawal, and delirium have been elaborated on by Lipowski.[3,60-62] Some investigators have reported intermittent bursts of bitemporal sharp activity on EEG in patients with rapid mood swings, psychotic episodes, depression, rage attacks, and suicide attempts,[63] as well as in bipolar disorders and rapid mood cycling.[64]

Problems of differentiating delirium and seizures can stem from the paroxysmal nature of the altered mental status and behavior that can occur with delirium, which may be mistaken for the confusion and agitation of complex partial seizures, postictal states of confusion, or even NCSE. A frequent presentation of delirium is in the elderly patient in the postoperative period, who appears feverish, agitated with sleep–wake cycle inversions, hallucinosis, and confusion. Here, there can be interplay of multiple organ system impairments or failures, including renal, hepatic, cardiac, respiratory, or endocrine.[65-69] Even when correctly identified, delirium may carry a high morbidity and mortality, but when misidentified as psychosis, seizure, or attributed to a dementing process, there may be inappropriate management. An agitated, confused, and uncooperative patient presents major management, and diagnostic dilemmas to nursing and medical staff.

Seizures and delirium

It may be often difficult to differentiate ictal from a delirious cause of agitation and altered mental status, particularly in psychiatric patients who are prone to both seizures and delirium, let alone psychosis.[70-77] An early delineation

of a personality type, the so-called "temporal lobe personality,"[78,79] underlies the concept of temporal-limbic abnormality that may lead to either psychosis or epilepsy.[80] The older literature describes an "epileptic delirium," which is characterized by hallucinations and delusions, a diminished level of consciousness, and a confusional state.[75] In the patient who may be delusional, agitated, or hypermanic, Landoldt described epileptiform discharges on the EEG with alternating dysphoria and psychosis.[81] Directed violence in the context of an epileptic "delirium" has been used as an "epilepsy defense" in patients accused of violent crimes, but a study by Treiman revealed little evidence of increased violence among people with epilepsy compared with the general population.[82] Violent behavior in this setting is usually of a "resistive" character with the confused patient trying to break away from physical restraint.

Among the different seizure types that may present with confusional states, those of complex partial seizures, whether repeated or prolonged, can result in marked agitation, at times with hypomania, hallucinations, illusions, and religiosity.[35,83-87] These rarely occur as the initial or heralding event of epilepsy, and there is almost invariably prior history of epilepsy. During the event, diagnosis cannot be made without observation of ongoing, usually lateralized, epileptiform activity on the EEG with waxing and waning patterns, and discharge frequency usually exceeding one per second. After isolated complex partial seizures, there may be a rise in prolactin level between 20 and 50 min after a single seizure in up to three-quarters of cases following temporal lobe seizures, and in slightly fewer after seizures with a frontal lobe origin.[88]

• Psychotic or other psychiatric symptoms appear within at least 7 days after a lucid interval following a seizure or, more commonly, a series of seizures
• The event may be characterized by psychosis, depression, elation, or anxiety-related symptoms
• The event is not simply an extension of the patient's previous mood or mental state prior to the onset of the seizure(s)
• The event is usually limited to days, rarely weeks
• The patient does not have significant clouding of consciousness as in delirium, and confusion—when present—can be attributed to the psychiatric symptoms (especially psychosis)
• The event cannot be attributed to other medical or other psychiatric causes (eg, drug intoxication, metabolic disturbances, head injury, or complex partial status)

Table II. Criteria for postictal psychiatric disturbances.
Adapted from reference 91: Logsdail SJ, Toone BK. Post-ictal psychoses: a clinical and phenomenological description. *Br J Psychiatry*. 1988;152:246-252. Copyright © 1988, The Royal College of Psychiatrists.

In the postictal or interictal periods, there may occasionally be acute psychosis in subjects without a prior psychiatric history. Such released automatisms may also engender bizarre movements or behavior. Left-sided foci have been associated with dysphoria, while right-sided discharges have been seen with laughter and hypomania.[89] Occasionally, with a relatively normal EEG, a postictal delirium can be seen after a flurry of seizures.[78] However, in most patients, psychosis is a postictal phenomenon *(Table II)*.[90]

Interictal and preictal delirium

As noted, components of delirium can be seen in the period between seizures, and also before seizures.[78,80,91,92] Some patients with a delirious encephalopathy have EEGs showing profuse, bilateral, synchronous spike, and slow-wave discharges.[35] Such discharges may at times resemble triphasic waves, particularly in the setting of a metabolic or toxic encephalopathy. Causes include raised ammonia, lithium, tricyclic antidepressant toxicity, tiagabine treatment, baclofen, metrizamide, ifosfamide, and other medications.[93] These patterns may be indistinguishable from the EEG perspective, from NCSE. In such cases, the EEG may normalize or at least show marked reduction in epileptiform morphologies, but the patient may remain clinically encephalopathic.[93] In other cases, both an epileptic and a triphasic encephalopathic state may coexist. One such case with raised ammonia and flurries of epileptiform triphasic waves showed resolution of this EEG activity following benzodiazepines, with a gradual normalization and improvement in state of consciousness over 12 h, but a further rise in serum ammonia.[94]

Ictal delirium

The transient encephalopathies or cortical impairment seen after seizures usually resolves over minutes to hours, although on some occasions, this may take days. Biton et al, however, have identified a more prolonged postictal encephalopathy lasting for 4 to 10 days after a cluster of seizures.[84] In this case, the EEG pattern was irregular in patients with borderline or mild mental retardation.

In patients with prior structural abnormalities, such as strokes, there may be periods of diminished level of con-

sciousness and abnormal behavior in association with an EEG pattern of periodic lateralized epileptiform discharges (PLEDs).[91] Such borderline states between intraictal "irritability" around an epileptogenic zone can result in pseudoperiodic lateralized discharges varying from one every 5 to 10 seconds, through the entire range to more than one per second. It becomes exceedingly difficult to decide whether such a state is representative of an interictal state, cortical irritability, or an ongoing status epilepticus. The cutoff has long been somewhat arbitrary at between 0.5 and 1.5 Hz, but more recent studies have suggested that, with limb movements, adversive gaze deviation, nystagmus, or documentation of increased cerebral flow or metabolism using single photon emission computed tomography (SPECT), positron emission tomography (PET), or perfusion weighted magnetic resonance imaging (MRI), an ictal state is present.[95] Such differentiation has led to recommendations of more aggressive suppression of seizures in the form of status epilepticus on the assumption that there was a danger of ongoing neuronal exhaustion and added brain insult.[82] This finding and conclusion have not been supported by other investigators.

	ASE	CPSE
Attitude	Unreactivity to threat	Anxious
	Lack of initiative	Aggressive
	Inability to plan	Irritable
	Withdrawal	
Affect	Indifference	Fearful
	Perplexity	"Ironic" appearance
	Crying	"Puzzled"
	Laughing	Smiling
	Aggressivity	
Memory/cognition	Variable amnesia	Diminished consciousness
	Slow ideation	Confabulation
	Disorientation	Amnesia
		Disorientation
Speech	Verbal perseveration	Verbal automatisms
	Monosyllabic answers	Speech arrest
	Lack of spontaneous speech	Mumbling
	Interrupted speech	Aphasia
	Clicking noises in mouth	Abnormal vocalizations
		Mutism
		Humming
Motor	Hippus	Complex motor automatisms
	Clumsy motor performance	Oroalimentary automatisms
	Motor perseveration	Motionless staring
	Automatisms (chewing;	Perseverative gesticulations
	compulsive handling of objects)	Head and eye deviation/nystagmus
	Rhythmic blinking	Limb extension
	Eye rolling	Blinking
	Small amplitude jerking of face or arms	Myoclonic jerks of face, mouth and limbs
	Quivering of lips	
	Tonic neck spasms	
	Ataxic gait/pseudoataxia	
	Wandering	

Table III. Clinical features of nonconvulsive status epilepticus (NCSE): differentiation between absence status epilepticus (ASE)[98] and complex partial status epilepticus (CPSE) (presented at the ECNS Meeting; Baltimore, Md; September 2002).

Continued on page 195

NCSE also presents in various forms as a delirious state. It has been traditionally classified into (i) absence status epilepticus (ASE); and (ii) a lateralization-related NCSE complex partial status epilepticus (CPSE), which has, in turn, been further subdivided into frontal and temporal subtypes.[96] Each of these varieties has somewhat different behavioral aspects, although there is overlap among the different types.[97] A classification of NCSE in terms of ASE and CPSE is given in *Table III*.[98] NCSE is one of the great imitators and the only way to differentiate these ictal states from types of encephalopathy and delirium of nonictal cause, is an EEG. These ictal states are more frequently seen in particular settings, as noted in *Table III*. Some general distinctions can be made between ASE and CPSE. For example, anxiety, aggression, fear, and irritability are more frequently seen with CPSE than with ASE, as are stereotyped automatisms.[97] Eye deviation, nystagmus, and lateralized automatisms are also seen with CPSE. With both types, however, agitation, aggressivity, violent behavior, and hallucinations occur.[99,100] Some of the striking behavioral/delirious manifestations seen in these nonconvulsive states are given in *Table IV*.[97] The cardinal features of ASE may be only mild obtundation, withdrawal, and confusion, but there is often paucity of speech with halting monosyllabic answers, variable amnesia, but frequent eyelid, perioral, and limb myoclonia. The patient may complain of visual hallucinations or go into a dreamy state and interact in a vague and inappropriate manner.[101] Patients appear disoriented and quiet, and give a description of "closeness" or "heat." The patient may present with hostility and aggression, agitation, and impulsive behavior.[102,103] Of particular interest has been the recent delineation of CPSE into frontal lobe subtypes. Recent work by Thomas et al elucidated a more frequent variety characterized by affective disinhibition, indifference, and mood disturbances with subtle impairment of cognitive functions associated with unilateral frontal seizure activity (type 1), while there was a less frequent variety (type 2) with bilateral, asymmetric frontal foci and more marked behavioral disturbances, temporospatial disorientation, confusion, and perseveration.[104] These recent descriptions have highlighted the fact that nonconvulsive states are characterized less by

	ASE	CPSE
Behavior	Inappropriate for situation with preserved alertness Infantile behavior Fugue states Catatonia	Wandering Violent behavior Agitated unresponsiveness Psychotic behavior
Psychiatric	Hallucinations Paranoid persecution	
Experiential	Feeling of oppression Uncontrollable rush of thoughts Desire to (but inability to) perform simple motor acts (motor apraxias) Dreamy state: "feels vague" "In a different world" "Drifting away" "Drunk" Worried; edgy Dizzy Missing pieces of conversation Central vision "vibrates"	Visual "bright spots"/dancing colors "Structures that change shape" Movement Paranoia Déjà vu
Other	Incontinence Diarrhea Headache Frontal release signs Babinski reflex	

Table III. Continued.

"a confusional state" than by a "mood disturbance," where affective disinhibition, hypomania, and fear predominate over significant obtundation. The behavioral aspects of NCSE have been extensively reviewed recently.[98]

ASE and CPSE may present as a delirious state, and may be overlooked unless an EEG is obtained. However, in other wandering states with amnesia, the EEG may be unrevealing. Episodes of confusion with amnesia although without dissociative features can occur with NCSE. Typically, though, automatisms, muscle twitching, confusion, and waxing and waning verbal responsiveness are noted.

Some authors describe classic mania of limited duration in the postictal period. Such patients had right temporal lobe foci.

Perez and Trimble[105] noted that 50% of patients with psychosis and epilepsy were diagnosed as having schizophrenia. One report by Dongier et al found that of 516 patients, 12.8% had ASE, 24.4% had slow delta activity with confusion, and 24.4% had forced normalization; epileptiform activity regressed during this psychotic period.[106] It has long been noted that there is a reciprocal relationship between epilepsy control and abnormal psychiatric states, which led to the treatment of schizophrenia by electroconvulsive therapy. Some patients with paradoxical normalization have anxiety, insomnia, and social inversion.

Patients with a clinical diagnosis of psychosis have occasionally been found to have pure unilateral limbic status epilepticus,[107] as may patients with ASE.[108] Patients report hallucinations, intense panic, apathy, anxiety, delusions, and a change in personality. A series of 52 cases of "epileptic clouded states" were described by Levin.[109] Logsdail and Toone established criteria for postictal psychosis, including a clouding of consciousness and delirium with disorientation, hallucinations, and delusions, but a clear sensorium, lasting up to 3 months.[90] This may occur shortly after a seizure, or after a return to normal mental status. One case report by So et al demonstrated that postictal psychosis is not necessarily an "epileptic equivalent" of the limbic system.[110] During an admission for epilepsy surgery,

	Percentage of affected cases		
	ASE/AASE	TCPSE	FCPSE
Cognition			
Impaired consciousness	≥90%	51% to 90%	51% to 90%
Fluctuating level of consciousness	≥90%	26% to 50%	26% to 50%
Slowness	26% to 50%	<10%	26% to 50%
Verbal automatisms	<10%	11% to 25%	<10%
Confabulation	<10%	<10%	11% to 25%
Paranoia	<10%	26% to 50%	<10%
Mood			
Indifferent; brooding	11% to 25%	<10%	11% to 25%
Puzzled; mute	11% to 25%	<10%	26% to 50%
Ironic	<10%	<10%	26% to 50%
Smiling; laughing	<10%	<10%	26% to 50%
Anxious; frightened	<10%	26% to 50%	<10%
Angry	<10%	11% to 25%	<10%
Aggressive; irritable		51% to 90%	
Agitated	11% to 25%	<10%	<10%
Movements			
Simple automatisms	11% to 25%		
Complex automatisms	<10%	26% to 50%	<10%
Wandering	<10%	11% to 25%	<10%
Facial/global myoclonia	50% to 90%	<10%	<10%

Table IV. Behavioral distinctions between absence status epilepticus (ASE), atypical absence status epilepticus (AASE), temporal lobe complex partial status epilepticus (TCPSE), and frontal lobe complex partial status epilepticus (FCPSE).

Adapted from reference 97: Rohr-le-Floch J, Gauthier G, Beaumanoir A. Etats confusionelles d'origine épileptique: interêt de l'EEG fait en urgence. *Rev Neurol* (Paris). 1988;144:425-436.

• Lethargy and confusion attributed to a postictal state
• Ictal confusion mistaken for metabolic encephalopathy
• Unresponsiveness and catalepsy presumed to be psychogenic
• Obtundation thought to be due to alcohol or drug intoxication
• Hallucinations and agitation mistaken for psychosis or delirium
• Lethargy presumed secondary to hyperglycemia
• Mutism attributed to aphasia
• Laughing and crying ascribed to emotional lability

Table V. Clinical examples in which the diagnosis of nonconvulsive status epilepticus (NCSE) was missed or delayed according to experience at Johns Hopkins Bayview Medical Center, Baltimore, Md.
Adapted from reference 98: Kaplan PW. Behavioral manifestations of nonconvulsive status epilepticus. *Epilepsy Behav*. 2002;3:122-139. Copyright © 2002, Academic Press.

their patients, were implanted with electrodes, and after nine complex partial seizures over several days, followed by a 9-hour lucid interval, psychosis appeared. Recording showed frequent bitemporal, independent, epileptiform discharges over the mesial limbic structures, but without electrographic seizures.[110] Logsdail and Toon suggest criteria to distinguish postictal psychiatric disturbances and other syndromes *(Table II)*.[90]

Conclusion

Delirium and epilepsy may be difficult to differentiate, and there may be considerable overlap between the two states. One imitates the other because of the commonly fluctuating level of consciousness, abnormal behaviors, and subtle motor manifestations. ASE and CPSE can be mistaken for delirium, encephalopathy, or psychiatric diseases *(Table V)*.[98] Seizures may present with ictal, interictal, or postictal delirium. Many of the conditions resulting in delirium may also induce seizures, including hepatic and renal failure, electrolyte and metabolic abnormalities, drug intoxications, intracranial infections, and occasionally lateralized acute cerebrovascular events. In some overtreated patients with epilepsy, there may be intoxication with anticonvulsants and delirium. Other patients may have both delirium and epilepsy. Moreover, borderline states between the two have been delineated. There is an increasing understanding of the different nonconvulsive states and borderline ictal states that continue to evade diagnosis and appropriate treatment in the absence of an EEG.

Some broad differences, albeit with exceptions, can be noted. Delirium typically begins more gradually and persists longer than seizures, or even NCSE. Most patients with NCSE have a prior history of seizures, but a recently delineated entity of de novo NCSE in the elderly is being increasingly recognized.[111] Aside from medication or toxic screening of blood and urine, the single most helpful test is EEG, but interpretation may be problematic. At one end of the spectrum, clear electrographic epileptiform activity in a rapid waxing and waning pattern suggests seizures, but certain metabolic and particularly toxic encephalopathies may also have sharply contoured morphologies on EEG, such as triphasic waves, which may strongly resemble—or indeed be indistinguishable from—electrographic seizures. In cases in which one of the entities is thought to be present, there should be an immediate stopping of possible delirium-causing medications, an investigation for underlying organ failure, a high index for seizures, and particularly nonconvulsive status with an EEG. Incorrect or delayed diagnosis of either entity may increase morbidity and mortality. ❑

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Delirium y epilepsia

El delirium (un estado de disfunción cerebral global, usualmente reversible debido a causas tóxicas, metabólicas o infecciosas) y la epilepsia (una condición espontánea, recurrente de disfunción o excitación eléctrica paroxística) cada día se comprenden mejor, por lo que resultan más fáciles de diagnosticar y de tratar. Las características clínicas del delirium incluyen predominantemente cambios subagudos de tipo cognitivo, en la conciencia reflexiva, en el nivel de actividad, trastornos de conducta, obnubilación de conciencia y cambios del ciclo sueño vigilia. En oposición, la epilepsia significa la interrupción aguda del funcionamiento cerebral, a menudo con actividad convulsiva, caídas y heridas. También son importantes los cuadros clínicos que pueden compartir características de ambas patologías, como los estados epilépticos no convulsivos, en que la causa del trastorno cerebral es una actividad eléctrica anormal y excesiva. En tales condiciones, las manifestaciones clínicas pueden simular cuadros de delirium y confusión, y es significativa la ausencia de convulsiones clínicamente manifiestas. El electroencefalograma se mantiene como la prueba diagnóstica de elección y resulta esencial para diferenciar entre las dos condiciones y adecuar los distintos tratamientos para el delirium y la epilepsia. La experimentación y las investigaciones en curso son esenciales para una mejor comprensión de los mecanismos cerebrales anormales que subyacen al delirium y para desarrollar mejores herramientas para un diagnóstico objetivo.

Délire et épilepsie

Le délire (un état de dysfonctionnement cérébral global habituellement réversible, d'origine toxique, métabolique ou infectieuse) et l'épilepsie (un état spontané récurrent de dysfonctionnement ou d'excitation électrique paroxystique) sont de mieux en mieux compris et donc plus faciles à diagnostiquer et à traiter. Le tableau clinique du délire est marqué essentiellement par des modifications subaiguës de la cognition, de la connaissance, et des niveaux d'activité, des troubles comportementaux, une obnubilation et des changements des rythmes veille-sommeil. À l'opposé, l'épilepsie entraîne l'interruption brutale de la fonction cérébrale, qui s'accompagne souvent de convulsions, chutes et blessures. Les pathologies pouvant associer des aspects propres à ces deux tableaux cliniques, comme les épilepsies sans convulsions, sont également importantes : la cause du trouble cérébral est une activité cérébrale électrique anormale et excessive. Dans ce cas, les signes cliniques peuvent être semblables dans les états de délire et de confusion et l'absence de convulsions cliniquement manifestes est significative. L'électroencéphalogramme reste le test diagnostique de choix : il est indispensable pour différencier ces deux pathologies, et donc spécifiquement adapter le traitement, soit au délire, soit à l'épilepsie. La recherche et les investigations en cours sont essentielles pour une meilleure compréhension des mécanismes cérébraux anormaux sous-jacents au délire et le développement de meilleurs outils de diagnostic objectif.

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