Beware ictal activity that mimics psychiatric illness

How to detect and halt nonconvulsive status epilepticus

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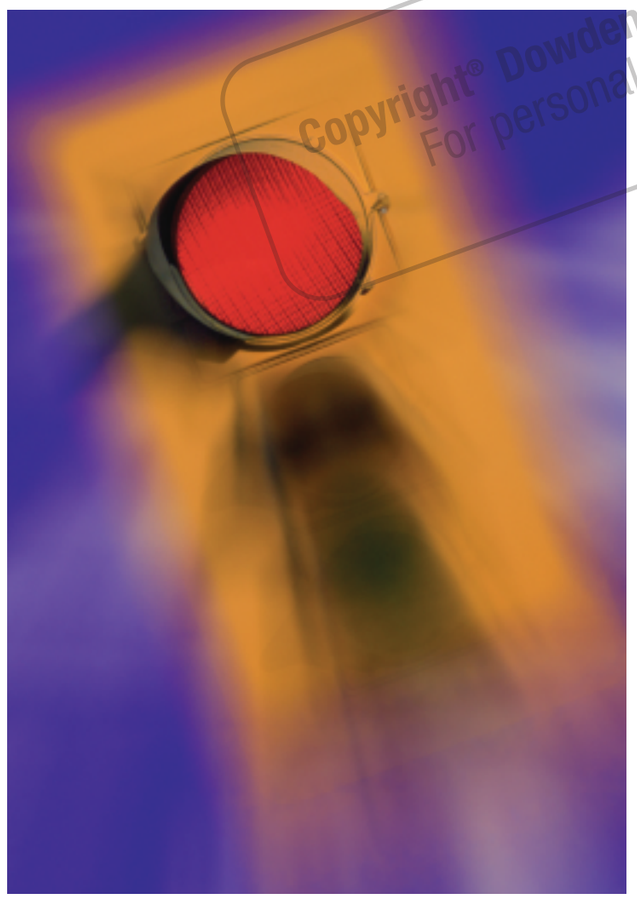

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Nonconvulsive status epilepticus (NCSE) is marked by neurobehavioral disturbances that resemble primary psychiatric disorders. Mistaken diagnosis and delayed treatment increase the risk of neurologic damage, so recognizing NCSE symptoms early is important.

To help you make a timely diagnosis, this article describes:

- neuropsychiatric manifestations of NCSE
- how to narrow the differential diagnosis by reviewing clinical symptoms and using electroencephalography (EEG)
- techniques used to rapidly halt ictal activity.

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Box

Status epilepticus: Risk of death, brain injury from nonconvulsive forms

Status epilepticus (SE) is an acute medical emergency. Both forms—convulsive (CSE) and nonconvulsive (NCSE)—require early recognition and treatment. In the United States, 60 SE cases occur per 100,000 population/year, with mortality rates of 20% in adults and 38% in the elderly.[1,2]

Mortality risk. Data suggest patients with NCSE are unlikely to die unless NCSE co-occurs with CSE or severe medical illness such as delirium or acute complications. Mortality risk does not appear linked with a type of EEG discharge.[3]

Neurologic injury risk. Prolonged NCSE may cause permanent neurologic damage.[4] Transient memory impairment has been reported after cessation of complex partial status epilepticus (CPSE).[5] CPSE also has resulted in prolonged neurologic deficits, although concomitant medical illnesses might have contributed to the deficits.[6] In one study, some patients gradually returned to baseline cognitive function after CPSE stopped, but they were not tested with standardized neuropsychological tools.[7]

No significant postictal memory impairment was observed on neuropsychological testing in patients with NCSE of frontal origin.[8] A >5-year follow-up study of absence status epilepticus (ASE) found no evidence of long-term cognitive or behavioral decline, even though most patients had recurrent ASE.[9] Similarly, no long-term sequelae were seen in patients with ASE.[10,11]

TRIGGERS, NEUROLOGIC SYMPTOMS

NCSE is an acute but treatable medical emergency that calls for assessing and supporting cardiac and respiratory function, monitoring vital signs, temperature reduction, and fluid replacement. Prognosis is usually good unless NCSE is associated with a serious medical illness (*Box*).[1-11]

Many metabolic, neurologic, pharmacologic, and medical abnormalities can precipitate NCSE (*Table 1*). The most common causes are hypoxia/ anoxia, stroke, infection, subtherapeutic antiepileptic levels, alcohol and benzodiazepine intoxication/withdrawal, and metabolic abnormalities.[4,7,10,12]

NCSE manifests as absence status epilepticus (ASE) or complex partial status epilepticus (CPSE). A generally accepted diagnostic definition is ≥30 minutes of behavioral change from base-

Table 1

Clinical factors that may precipitate NCSE

Medical	**Recent infection, hyperventilation, trauma, menstruation, pregnancy, renal dialysis, postoperative period, sleep deprivation**
Metabolic	**Hypoparathyroidism, renal failure, hyper/hyponatremia, hyper/ hypoglycemia, hypocalcemia**
Neurologic	**Mental retardation, dementia, stroke**
Pharmacologic	**Low serum levels or abrupt discontinuation of anticonvulsants, alcohol intoxication/withdrawal, benzodiazepine withdrawal lithium and neuroleptic use, psychotropic overdose**

Source : References 9,10,12,16

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Promising New Investigator: Joseph S. Goveas, MD

This paper was among those entered in the 2006 Promising New Investigators competition sponsored by the Neuroleptic Malignant Syndrome Information Service (NMSIS). The theme of this year's competition was "New insights on psychotropic drug safety and side effects."

Current Psychiatry is honored to publish this peer-reviewed, evidence-based article on a clinically important topic for practicing psychiatrists.

NMSIS is dedicated to reducing morbidity and mortality of NMS by improving medical and psychiatric care of patients with heat-related disorders; providing support information for medical professionals, patients and families; and improving scientific understanding of these conditions through research.

line, with diagnostic EEG findings.[4,13] EEG is indispensable because the clinical manifestations of NCSE are predominantly behavioral, with minimal or no motor activity.

ASE, a primary generalized process, is characterized by confusion or diminished responsiveness; it may be associated with occasional blinking or other minor motor activity and can last for hours to days. It usually occurs in patients with known epilepsy, particularly absence seizures.

ASE is reported primarily in children, although de novo cases have been described in elderly patients with no history of epilepsy.[10,14]

CPSE is usually associated with a history of focal epilepsy and vascular disease. CPSE has a focal onset, with subsequent secondary generalization. Onset is usually temporal in origin but also can be extratemporal.

Patients with CPSE often cycle between an "epileptic twilight state" with confusion and complete unresponsiveness with stereotyped automatisms. It can present with marked behavioral fluctuation or a change in mental status and

Table 2

Differential diagnosis of NCSE

Metabolic disorders	**Hypo/hyperglycemia, hypercalcemia, Addison's disease, Cushing's disease, uremia**
Neurologic disorders	**Stroke, CNS tumors, closed head trauma, transient global amnesia, seizures, inflammatory and infectious encephalopathies**
Psychiatric disorders	**Schizophrenia, mood disorders, catatonia, malignant catatonia, somatoform disorders, conversion disorder, Asperger's syndrome, malingering**
Toxic disorders	**Toxic encephalopathy, neuroleptic malignant syndrome, serotonin syndrome, alcohol and sedative-hypnotic withdrawal, drugs (lithium toxicity, tricyclics, baclofen, tiagabine, overdose)**

Source: Reference 17,18

is generally followed by a prolonged postictal state.[4,7,13-15] Several NCSE cases have occurred in patients with no history of seizures.[9,10,16]

Historically, CPSE was reported to be less common than ASE, but this misconception was most likely caused by failure to recognize CPSE's clinical presentation and rapid generalization on EEG.[7,15]

NEUROPSYCHIATRIC FEATURES

Patients with NCSE may be referred for evaluation of an array of behavioral changes commonly seen in psychiatric practice. The differential diagnosis is extensive (*Table 2*) and includes neurologic and medical conditions often associated with catatonic syndrome.[17,18]

In a retrospective study, Kaplan[12] assessed clinical presentations and reasons for diagnostic delay in 23 adults eventually diagnosed with NCSE. Presenting symptoms included:

- confusion, agitation, aggressive behavior
- lethargy, mutism, verbal perseveration, echolalia
- delirium, blinking, staring, chewing or picking behaviors
- tremulousness or myoclonus
- bizarre behavior (inappropriate laughing, crying, or singing)
- rigidity with waxy flexibility
- delusions, hallucinations.

Clinicians mistook hallucinations and mood lability for a primary psychiatric condition in 7 patients, presumed catalepsy was psychogenic in 3 patients, and thought obtundation was caused by alcohol or drug intoxication in 4 cases.

A prospective study of 22 patients with NCSE found that 7 had a history of psychotic depression, schizophrenia, self-mutilation, bipolar disorder, or episodic severe aggression; 12 of 18 with ASE had a history of epilepsy, and 3 of 4 with CPSE had experienced seizures associated with cerebrovascular accident, right cerebral embolus, and thiazide-induced hyponatremia, respectively.[16]

NCSE in the elderly can be difficult to diagnose, especially in patients with comorbid severe medical illnesses and other confusional states.[4] CPSE with possible generalization is more common than ASE in the elderly. Hyperreligiosity, intermittent agitation, motor perseveration, ictal fear, catatonic signs, delusional preoccupation, and auditory and visual hallucinations have been observed during NCSE in the elderly and misdiagnosed as primary psychiatric conditions.

Cerebrovascular disease, tumors, and trauma are the most common causes of late-life NCSE.[4,19] De novo NCSE occasionally presents:

- after benzodiazepine withdrawal
- with neuroleptic, tricyclic antidepressant, or lithium treatment[10,16]
- with metabolic abnormalities and nonpsychotropic medications.[10]

Table 3

Clinical features that raise suspicion of NCSE

Domain	Features
Cognitive changes	**Prolonged confusion, executive dysfunction, obtundation, attention/memory difficulties, lack of initiative, perseveration, stupor**
Speech	**Poverty of speech with monosyllabic answers, verbal perseveration, echolalia, palilalia, aphasia, paraphasic errors, confabulation, mutism**
Affective	**Prolonged fear, affective indifferent state with blank facial expression, hypomania, psychotic depression, inappropriate laughing and crying, anxiety states**
Psychosis	**Visual, auditory and cenesthetic hallucinations, delusions**
Impulse control	**Hostility, agitation, violence, groping, genital manipulation, picking, posturing**
Others	**Catatonic signs, autonomic disturbances**

Source: References 5,7-9,12,15-17,20-23

CLINICAL SYMPTOMS

Clinical features of NCSE include cognitive changes, speech abnormalities, affective disturbances, psychosis, poor impulse control, and bizarre behaviors (*Table 3*). Some patients develop ictal phenomena resembling catatonia or clinical and EEG changes that mimic neuroleptic malignant syndrome (NMS).[20-23]

Catatonia. Lim et al[24] described three patients with EEG-confirmed NCSE that manifested as ictal catatonia. A prolonged, trance-like, stuporous state during epilepsy has been reported, as has CPSE presenting with psychogenic unresponsiveness. Drury st al[25] described a patient who presented with catatonia and increased muscle tone but had prominent EEG abnormalities implicating an organic cause.

Among 29 patients with acute catatonic syndromes, epileptic activity was identified in 4. One patient with absence status was diagnosed with NMS during the catatonic period.[26] Conversely, the commonality of clinical features has led to misdiagnosis of psychogenic catatonia as NCSE. EEG is necessary to exclude NCSE in these cases.

NMS. Yoshino et al[27] described two patients taking neuroleptics who met criteria for NMS and had EEG changes consistent with NCSE. They later reported another patient with NCSE complicating NMS; the point at which NCSE developed was unknown, however, because EEG activity was not recorded at NMS onset.[28] Based on NMS diagnostic criteria proposed by Caroff et al,[29] these patients could have developed NCSE mimicking NMS.

EEG FOR DIAGNOSIS

Candidates. Because differentiating NCSE from similar conditions can be difficult, use EEG to confirm your clinical observations. No guidelines exist, but consider EEG when the patient's history suggests NCSE. Ask the patient or family about:

continued

Table 4

EEG findings that support a clinical diagnosis of NCSE

Clear-cut criteria

Frequent or continuous focal seizures, with ictal patterns that wax and wane with change in amplitude, frequency, and/or spatial distribution

Frequent or continuous generalized spike wave discharges:

- **in patients without history of epilepsy**
- **in patients with epilepsy, when discharges show significant changes in intensity or frequency compared with baseline EEG**

Periodic lateralized epileptiform discharges ("PLEDs") or bilateral periodic epileptiform discharges ("biPEDs") occurring in patients with coma from generalized tonic-clonic status epilepticus (subtle SE)

Probable (equivocal) criteria

Patients with acute cerebral damage who also show frequent or continuous EEG abnormalities without previous similar findings

Patients with epilepsy who show frequent or continuous generalized EEG abnormalities and similar interictal EEG patterns but whose clinical symptoms suggest NCSE

Source: References 4,12-14,17

- changes in mental status from baseline, especially new-onset catatonia or unexplained altered consciousness
- duration of events
- presence or absence of motor activity
- behavioral fluctuations
- presence or absence of automatisms or blinking.

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List the patient's medications, ask about illicit substance or alcohol use, and gather a comprehensive history of medical, neurologic, and psychiatric illnesses. Include NCSE in the differential diagnosis of elderly patients with acute prolonged confusion. Try to obtain EEG early to differentiate focal from secondary generalized seizures.

EEG patterns. *Table 4* summarized NCSE diagnostic criteria. NCSE shows characteristic patterns in ASE and CPSE,[9,10,16,23] and EEG changes can be continuous or nearly continuous in both.

In ASE, a generalized, bilaterally synchronous, rhythmic, 3- to 3.5-second spike with a bifrontal maximum is seen in 40% of cases.[30] Also described in ASE are fragmented spike waves, multiple spikes and waves, and generalized bilateral discharges with focal predominance. This last pattern might suggest an underlying focal origin of the epileptic discharge with secondary generalization.[31,32]

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In CPSE, less-synchronous epileptiform activity has been described, including rhythmical slow, rhythmic spikes, or rhythmic spike and slow waves. Two types of CPSE of frontal origin have been described:

- Type 1 presents clinically with mood disturbance and minimal confusion. EEG shows a frontal focus with a normal background.
- Type 2 presents clinically with confusion. EEG shows bilateral asymmetric frontal discharges.[8]

Not always clear. Making a clear distinction between primary and secondary generalization on EEG is not always possible.[15] In a large series of NCSE cases,[31] ictal discharges on EEG were:

- generalized in 69%
- diffuse with focal predominance in 18%
- focal in 13%.

Although most EEGs showed a generalized pattern, many cases probably started focally with immediate generalization. Morphologies seen—in descending order of frequency—were atypical spike and wave, multiple spike waves, rhythmic delta with intermittent spikes, and typical spike and wave patterns. Ictal discharge frequency also was variable and <3 Hz in 79% of cases.

When possible, obtain EEG early to differentiate focal from secondary generalized seizures

Distinguish between ictal and interictal EEG findings with epileptiform activity, because only the former is diagnostic for NCSE. Intravenous benzodiazepines might be necessary during EEG to verify the diagnosis.[33]

NCSE has developed after electroconvulsive therapy (ECT), but a cause-effect relationship is debatable. Interictal and abnormal EEG findings after ECT may be misdiagnosed as NCSE.[34]

Neuroimaging has limited clinical value because of the need for patient cooperation and specialized equipment.[4] Head CT or MRI can exclude structural abnormalities. PET and SPECT show increased metabolism and blood flow, respectively, in NCSE. MR spectroscopy shows elevated lactate and decreased N-acetyl aspartate.

HALTING ICTAL ACTIVITY

To rapidly stop ictal activity—the main goal of treatment—recognizing and correcting precipitant factors is vital:

- Consider discontinuing medications that could lower the seizure threshold.
- Order a complete blood count, serum electrolytes, calcium, arterial-blood gas, liver and renal function tests, urine toxicology screen, and serum antiepileptic drug concentrations.
- When possible, obtain neuroimaging and EEG in the emergency room for accurate diagnosis and prompt treatment.[12]

Medications. Benzodiazepines such as lorazepam, diazepam, and clonazepam are used most often to interrupt seizure activity. Use them cautiously in medically fragile patients, however, to prevent hypotension and respiratory depression.

Response to benzodiazepines might be transient, lasting only hours or days. For instance, diazepam's anticonvulsant effect may last <20 minutes and lorazepam's ≤12 hours. Longer-term agents include phenytoin, valproic acid, carbamazepine, and phenobarbital.

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Bottom Line

Neurobehavioral disturbances without prominent motor activity could suggest nonconvulsive status epilepticus (NCSE). Order an EEG to support clinical observation and confirm the diagnosis. Suspect NCSE in patients with acute altered mental status and behavioral changes of uncertain cause. Early, rapid resolution of ictal activity can prevent long-term neurologic injury.

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Related resources

- Epilepsy Foundation. www.epilepsyfoundation.org
- Neuroleptic Malignant Syndrome Information Service. Hotline for health professionals (888) 667-8367. www.nmsis.org

DRUG BRAND NAMES

Carbamazepine • Tegretol, Carbatrol
Clonazepam • Klonopin
Diazepam • Valium
Lamotrigine • Lamictal
Levetiracetam • Keppra
Lithium carbonate • Lithobid, Eskalith CR
Lorazepam • Ativan
Phenobarbital • Luminal
Phenytoin • Dilantin
Tiagabine • Gabitril
Topiramate • Topamax
Valproic acid • Depakote

DISCLOSURE

The authors report no financial relationship with any company whose products are mentioned in the article or with manufacturers of competing products.

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Newer antiepileptics—such as lamotrigine, levetiracetam, or topiramate—have been used with varying results, and their role in first-line treatment of NCSE is evolving. Rarely, the antiepileptic tiagabine precipitates or worsens NCSE.[4,13, 14]

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