

Nonconvulsive Status Epilepticus in Acute Brain Injury

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Summary: Whether or not nonconvulsive status epilepticus produces permanent brain damage is a source of controversy. Contributing to the controversy is the lack of clarity for classifying the clinical and electrographic phenomena that constitute nonconvulsive status epilepticus. Nonconvulsive status epilepticus commonly occurs in the context of an acute brain injury. For example, it commonly persists in generalized convulsive status epilepticus after convulsive activity has stopped, and it is not uncommonly associated with acute cerebral ischemia. Its clinical characteristics are ambiguous, subtle, and nonspecific making the diagnosis difficult. In the absence of EEG testing, it is likely to be missed or delayed. When acute brain injury and nonconvulsive status epilepticus occur concurrently, the severity of acute brain injury has traditionally been accepted as determining patient outcome. However, increasing evidence suggests that the two conditions are synergistically detrimental and increase brain injury. Guidelines remain to be established for the intensity and duration of anticonvulsant therapy in these patients. Evidence suggests that, in the absence of extreme and irreversible acute brain injury, early intensive intervention is necessary to improve the otherwise poor outcome of these patients. **Key Words:** Nonconvulsive status epilepticus—Nonconvulsive seizures—Status epilepticus—Continuous EEG monitoring.

It is generally agreed that nonconvulsive status epilepticus (NCSE) can cause significant and protracted morbidity. However, controversy exists regarding whether NCSE causes permanent or fatal cerebral injury (Aminoff, 1998; Young and Jordan, 1998). Consequently, uncertainty surrounds its treatment. Should intervention be as intensive and protracted as in generalized convulsive status epilepticus (GCSE), or should it be supportive and conservative?

There are methodologic and nosologic causes of this controversy. Traditionally, standard or serial EEGs have been used to diagnose NCSE and to classify it into either complex partial status epilepticus or petit mal status

epilepticus. Others have designated subtypes of NCSE, such as somatosensory status epilepticus, prolonged ictal fear, and elementary visual status epilepticus (McLachlan and Blume, 1980; Gasteau, 1983). Patients with acute brain injuries (ABIs) or critical systemic illnesses have generally been excluded from these classifications. Furthermore, when NCSE has been reported concurrent with ABI, poor outcomes have been attributed to the ABI. NCSE has been seen as an epiphenomenon, not a contributing cause of brain damage (Kaplan, 1996; Aminoff, 1998).

Only recently has continuous EEG monitoring (CEEG) been used to investigate the incidence and clinical spectrum of NCSE with ABI (Young et al., 1996; Treiman et al., 1998; Jordan, 1999; Vespa et al., 1999). Without CEEG, the diagnosis of NCSE can be missed, nor is it possible to determine its duration, natural history, or response to treatment. Recent evidence using CEEG suggests that, in selected patients with ABI,

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TABLE 1. *Electroencephalographic criteria for nonconvulsive seizures*

Guideline: To qualify at least *one* of primary criteria *and one or more* of secondary criteria, with discharges > 10 seconds

Primary criteria

1. Repetitive generalized or focal spikes, sharp waves, spike-and-wave, or sharp-and-slow wave complexes at >3/second.
2. Repetitive generalized or focal spikes, sharp waves, spike-and-wave or sharp-and-slow wave complexes at <3/second *and* secondary criterion No. 4.
3. Sequential rhythmic waves and secondary criteria 1, 2, *and* 3 with or without 4.

Secondary criteria

1. Incrementing onset: increase in voltage and/or increase or slowing of frequency.
2. Decrementing offset: decrease in voltage or frequency.
3. Postdischarge slowing or voltage attenuation.
4. Significant improvement in clinical state or baseline EEG after intravenous antiepileptic drug.

From Young et al., 1996 with permission.

NCSE significantly increases the vulnerability of the brain to permanent damage and death by mechanisms of secondary injury (Vespa et al., 1999).

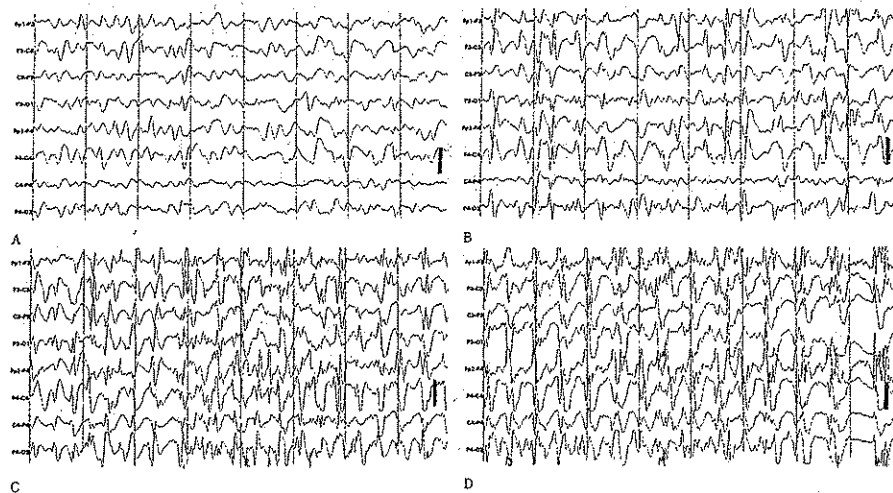
By definition, NCSE is an electroencephalographic not a clinical diagnosis. Although there is no established consensus, recommended EEG criteria for NCSE have been published (Young et al., 1996) (Table 1; Fig. 1). These have been used for purposes of this article. Nonconvulsive status epilepticus is diagnosed when EEG-recorded episodes of nonconvulsive seizures (NCS) are continuous or recurrent for greater than 30 minutes

without improvement in the patient's clinical state, nor is there a return to a preictal EEG pattern between seizures. This article has chosen to exclude from this definition periodic lateralized epileptiform discharges, generalized periodic epileptiform discharges, and the clinical-EEG syndrome of anoxic myoclonic status epilepticus.

CASE PRESENTATION

A 48-year-old man underwent elective open-heart surgery for an atrial septal defect. During surgery, air bubbles entered the aortic cannula. Postoperatively, the patient was obtunded with left hemiplegia and occasional ocular deviation up and to the right. No convulsions were present. The initial diagnostic impression was air embolism with right cerebral infarction. A computerized tomography scan of the brain was normal. Continuous EEG was instituted and it identified NCSE arising from the right occipital region (Fig. 2). The patient was treated with intravenous lorazepam and loading doses of fosphenytoin. A propofol infusion was used to achieve a burst-suppression CEEG pattern with cessation of epileptiform discharges. Thirty-six hours later, the patient was weaned off the infusion and regained consciousness. His left-sided weakness resolved completely. A repeat computerized tomography scan of the head 5 days later showed no evidence of cerebral infarction. A follow-up EEG showed no epileptiform abnormalities (Fig. 2D). The patient went home with no neurologic deficits, maintained on high therapeutic levels of phenytoin. His NCSE was classified as inhibitory, focal motor NCSE with secondary generalization (Rubboli et al., 1998).

FIG. 1. Evolution of generalized nonconvulsive status epilepticus (NCSE) in a 54-year-old woman with multiorgan failure. (A) Generalized, low- to medium-voltage theta-delta activity. (B) Variable, but incrementing pattern of generalized spike, spike-wave, and sharp-wave discharges. (C and D) Progressively rhythmic and stereotyped spike, polyspike, and spike-wave generalized discharges. This activity was readily suppressed by diazepam injection. Thick vertical calibration bar is 50 μ V. Time interval between vertical dividing lines is 1 second. (From Young et al. 1996, with permission).



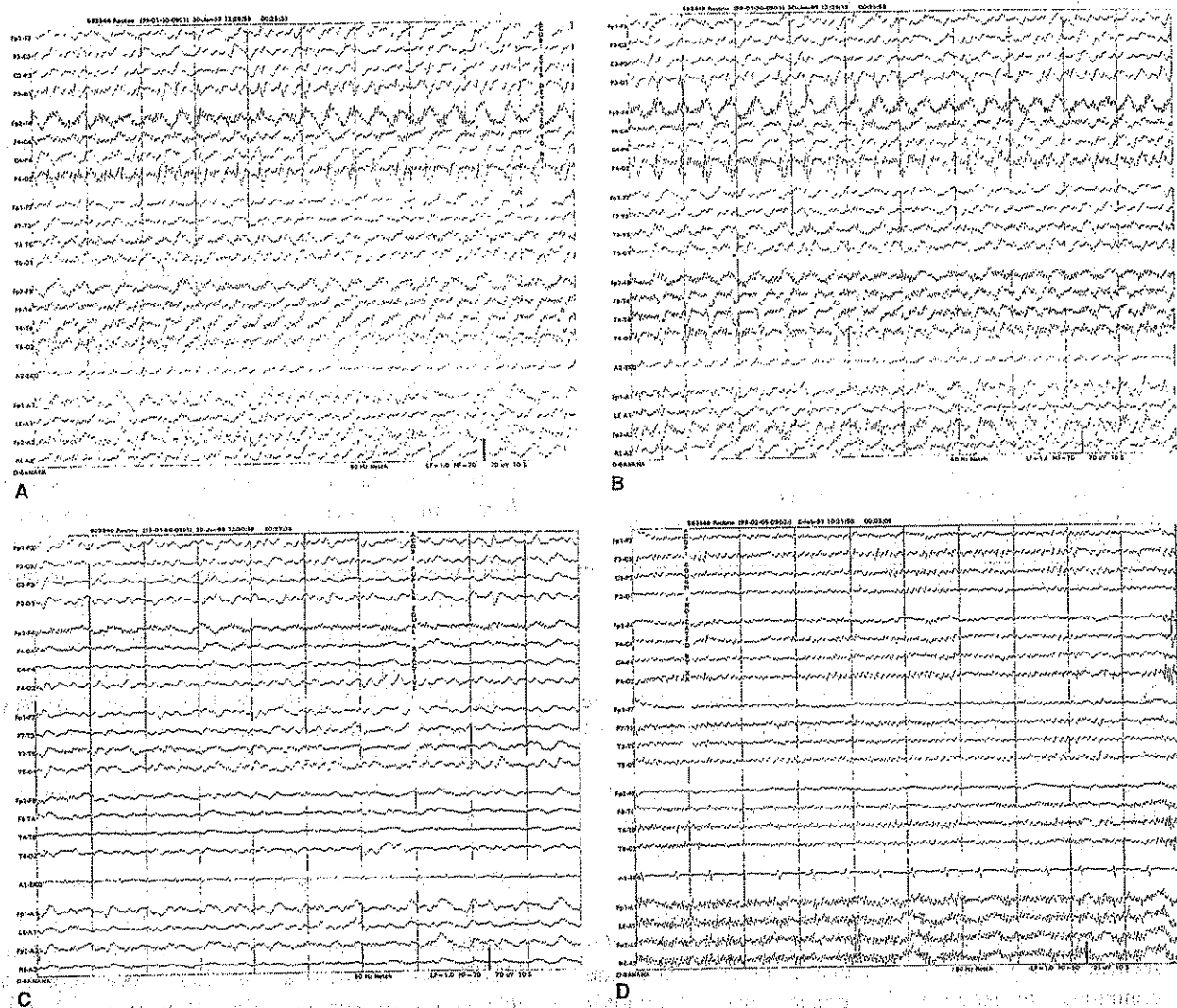


FIG. 2. Nonconvulsive status epilepticus (NCSE) arising in an obtunded patient after open-heart surgery for an atrial septal defect. During surgery, air bubbles were noted to enter the aorta. (A) Focal low-amplitude right occipital polysharp activity incrementing to produce rhythmic 2- to 3-Hz spike discharges with prominent spread over the ipsilateral hemisphere. As ictal buildup evolves, the patient's eyes deviate up and to the right, as an ipsiversive seizure phenomenon. (B) Spikes are seen in the contralateral posterior hemisphere, and the rhythmic activity is generalized. (C) Postictally, there is diffuse irregular theta-delta activity which is attenuated over the right hemisphere. Stereotyped episodes like this recurred every 5 minutes with no normal EEG intervening. (D) Routine digital EEG (DEEG) performed 5 days after the activity shown in panel C. Drowsy record with no epileptiform abnormalities. There is subtle attenuation of background activity in the right temporal region.

INCIDENCE AND CHARACTERISTICS OF NONCONVULSIVE STATUS EPILEPTICUS IN ACUTE BRAIN INJURY

Early convulsive seizures occur in 10 to 27% of patients with ABI (Engel, 1989). More than 50% of GCSE is associated with acute focal cerebral ischemia, acute severe head trauma, intracranial hemorrhage, cerebral hypoxia, hypoglycemia, drug intoxication, and withdrawal syndromes (DeLorenzo et al., 1992; Epilepsy Foundation of America, 1993; Lowenstein and Alldredge, 1993). Fifty-nine percent of status epilepticus (SE) patients with no

history of epilepsy have ABI (Barry and Hauser, 1993). Twenty-five percent of SE patients in those with known epilepsy is precipitated by ABI (Barry and Hauser, 1994).

ABI often alters consciousness and behavior and so can NCSE. Because NCSE, unlike GCSE, is not diagnosable by visual inspection, when it supervenes in ABI, the diagnosis is often unsuspected, even though it is surprisingly common among these patients (Drislane et al., 1998). Jordan found that 34% of 124 NICU patients monitored with CEEG had NCS, and 27% (33) had NCSE (Jordan, 1992). The admission diagnoses of these

TABLE 2. Clinical distribution of patients with nonconvulsive seizure

NCS	Admitting Dx (n)						
	ACI (43)	ICH (32)	SZ (16)	BT (11)	MC (10)	HT (7)	INF (6)
No. of PTS	11	7	9	6	6	2	2
% of (n)	26%	22	56	54	60	28	33

ACI, acute cerebral ischemia; BT, brain tumor; HT, head trauma; ICH, intracranial hemorrhage; INF, intracranial infection; MC, metabolic coma; NCS, nonconvulsive seizure; PTS, patients; SZ, seizure.

From Jordan KG, 1995 with permission.

patients included acute focal cerebral ischemia, intracranial hemorrhage, GCSE, metabolic coma, brain tumors, and acute severe head trauma. The highest incidence was in patients admitted with "controlled" GCSE and in unexplained "metabolic coma" (Table 2). The clinical features of these patients usually did not suggest an epileptic basis. The most common presentation was non-localizing coma. Others are listed in Table 3. In a study of NCSE in the emergency room, Kaplan (1996) found the most common clinical features to be delirium, agitation, aphasia, and "blank staring."

Other authors have also found high instances of NCSE in association with ABI. Grand'Maison et al. (1991) reported NCS in 55% of patients with acute or subacute lesions. Privitera et al. (1994) performed emergency EEGs on 198 patients with altered consciousness and found, as did Jordan (1992), that 27% (53 patients) had definite NCSE. In a recent Veterans Administration cooperative study examining treatment protocols for GCSE, Treiman et al. (1998) found that 20% who received "adequate treatment" continued to have NCS and NCSE on CEEG. Of 170 patients with GCSE, DeLorenzo et al. (1997) found that 12% continued in NCSE after their convulsions stopped. In a study by Jaitly et al. (1997) 53% of 180 GCSE patients had persisting NCSE after convulsive activity ceased. In a report by Vespa et al. (1999) of 56 patients with acute severe head trauma, 12.5% suffered NCS or NCSE.

TABLE 3. Clinical features of nonconvulsive seizures (n = 43)

	Percent
Coma	37
Aphasia	18
Mental dullness	14
Limb posturing	12
ABN eye movements	12
Automatisms	5
Cortical blindness	2
	100

ABN, abnormal.

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DIAGNOSIS OF NONCONVULSIVE STATUS EPILEPTICUS

In a series by Drislane et al. (1998), 77% of 89 patients with NCSE were not recognized as having seizures at the time of the diagnostic EEG. There was a median delay of 72 hours before the diagnosis of NCSE among those without antecedent clinical convulsions, compared to a delay of 24 hours in those who had observed clinical seizures. In the series by Young et al. (1996), 16% of NCSE patients were obtunded for more than 24 hours before EEG testing led to the correct diagnosis. Kaplan (1996) reported that of 23 patients with NCSE in the ED, only 13 were diagnosed in less than 24 hours. Seven patients required one to three days and three patients required four to five days for the diagnosis of NCSE to be made. In the study of NCSE in the emergency department by Jordan et al. (1995), the average time from patient arrival to diagnosis was 2.5 hours. Initial misdiagnosis occurred in 93% of patients. Combining both studies, NCSE was most often misinterpreted as a postictal state, psychiatric disorder, stroke, or metabolic encephalopathy (Fig. 3).

Although EEG is required to confirm the diagnosis, in many patients helpful clinical clues can raise the index of suspicion. Among 59 patients in whom attending neurologists suspected NCS, EEG confirmed the diagnosis in 83% (Young et al., 1996). The following characteristics should prompt consideration of NCSE:

- A prolonged "postictal state" after GCS or GCSE (Fig. 3). Postictal unawareness for more than 15 to 30 minutes should raise concern.
- A protracted state of reduced alertness after brain surgery (Fig. 4) or any other surgery where cerebral function is at risk (Case Presentation, Fig. 2).
- Unexplained onset of impaired consciousness, particularly if the level of consciousness fluctuates.
- Impaired consciousness or mentation associated with facial minimyoclonus or nystagmoid eye movements.

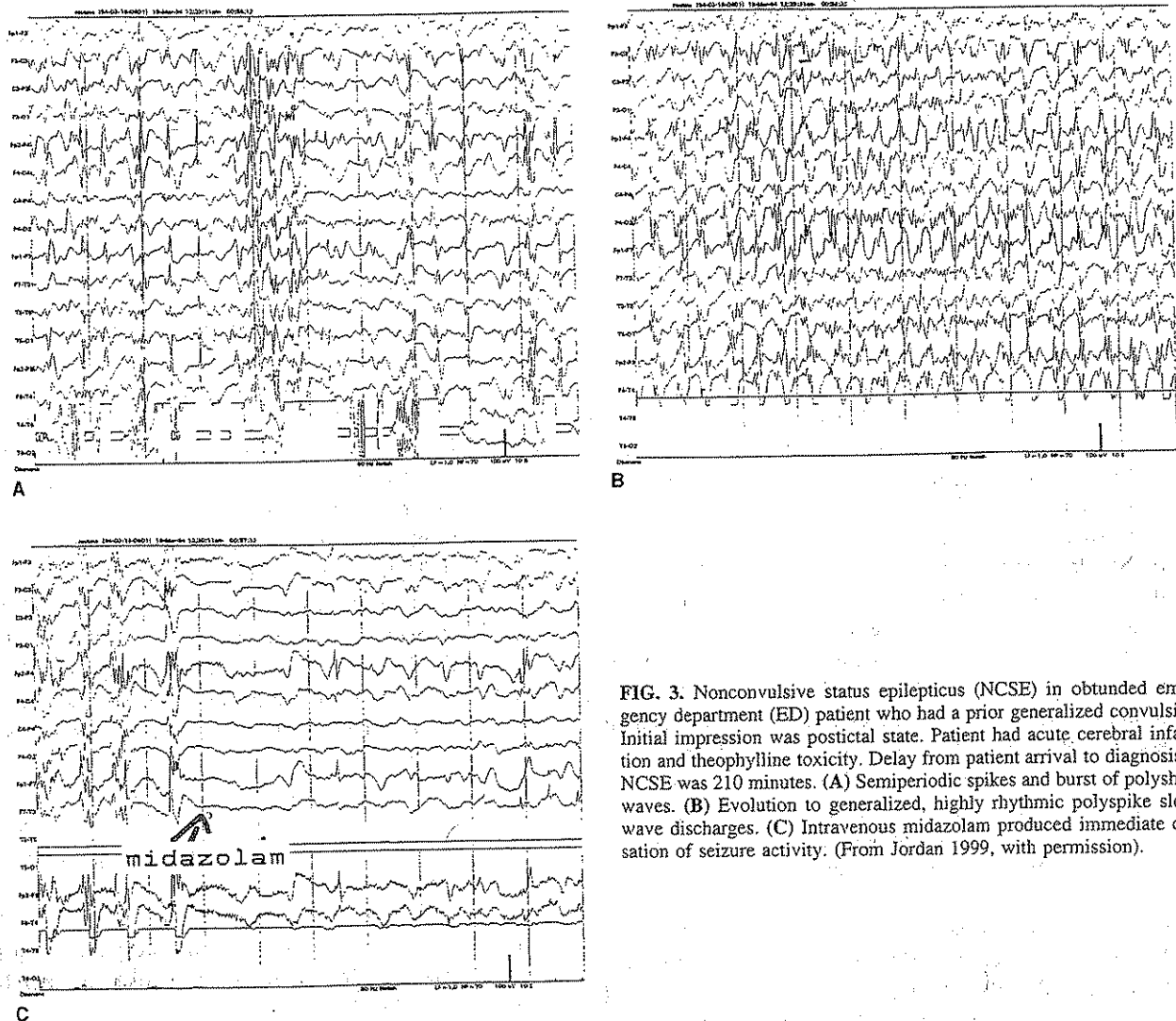


FIG. 3. Nonconvulsive status epilepticus (NCSE) in obtunded emergency department (ED) patient who had a prior generalized convulsion. Initial impression was postictal state. Patient had acute cerebral infarction and theophylline toxicity. Delay from patient arrival to diagnosis of NCSE was 210 minutes. (A) Semiperiodic spikes and burst of polyspike slow-wave discharges. (B) Evolution to generalized, highly rhythmic polyspike slow-wave discharges. (C) Intravenous midazolam produced immediate cessation of seizure activity. (From Jordan 1999, with permission).

- Episodic blank staring, aphasia, automatisms, or perseverative activity.
- Fluctuating aphasia in the absence of a structural lesion.

EFFECT OF DURATION AND DIAGNOSTIC DELAY ON MORTALITY

As in GCSE, the longer NCSE persists, the more difficult it is to treat and the higher the mortality rate (Fig. 5) (Young et al. 1996). In the study by Young et al., the effect of seizure duration of greater than 10 hours on mortality was highly significant (P value = 0.005; odds ratio = 18). Mortality attributable to NCSE was 57% compared to 9% in those with NCS only (P = 0.002). Only 22% of NCSE patients returned home compared to 60% of NCS patients.

Using multivariate logistic regression analysis, these authors found that seizure duration and delay to diagnosis, independent of etiology, were the most important variables increasing morbidity and mortality. Supporting their observations is a subsequent study by DeLorenzo et al. (1998) of 242 patients with GCSE. They found that delayed time to treatment and treatment responsiveness were independent predictors of outcome, after adjusting for the effects of etiology and age.

Nonconvulsive status epilepticus is more refractory to treatment and has a higher mortality than GCSE. Among 518 patients studied by Treiman et al. (1998), the first treatment regimen was successful in 55% with GCSE but in only 15% with NCSE; respective mortality rates were 27% and 65%. In the emergency department study by Jordan et al. (1995), only 25% of NCSE patients were

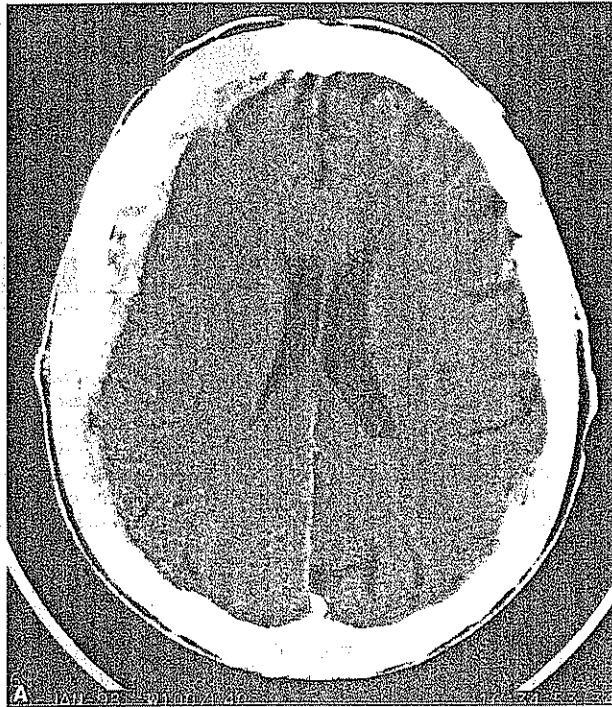


FIG. 4. Preoperative brain computed tomography (CT) scan and continuous EEG (CEEG) in patient with acute subdural hematoma (SDH) who suffered postoperative nonconvulsive status epilepticus (NCSE). (A) Extensive right hemisphere acute SDH. Cortical sulci are effaced, and there is mild mass effect. (B) Three days postoperatively, patient is obtunded with no convulsive activity. Prominent periodic lateralized epileptiform discharges (PLEDs) arising from the right hemisphere. (C) PLEDs evolve to focal nonconvulsive seizures (NCS) with spread to left frontal region. NCSE consisted of recurrent cycles of this ictal pattern. (From Jordan 1999, with permission).

controlled within 3 hours of initiating treatment, and by 5 hours only 50% were controlled. Jaitly et al. (1997) found that among 95 treated GCSE patients in whom NCSE persisted, mortality was 41%.

In spite of these statistics, patients with prolonged NCSE can respond to therapy and do well (Fig. 2). Drislane et al. (1998) found that, of 67 patients with NCSE due to nonanoxic causes, including 15 who were comatose, 46% (31) improved in alertness with anticonvulsant treatment.

CONCURRENT NONCONVULSIVE STATUS EPILEPTICUS AND ACUTE BRAIN INJURY SYNERGISTICALLY INCREASE MORBIDITY AND MORTALITY

Traditionally, in combined ABI and SE, the severity of the ABI has been considered the major determinant of mortality (Towne et al., 1994). However, there is recent evidence that concurrent ABI and SE are synergistically deleterious. When associated with ABI, GCSE is often

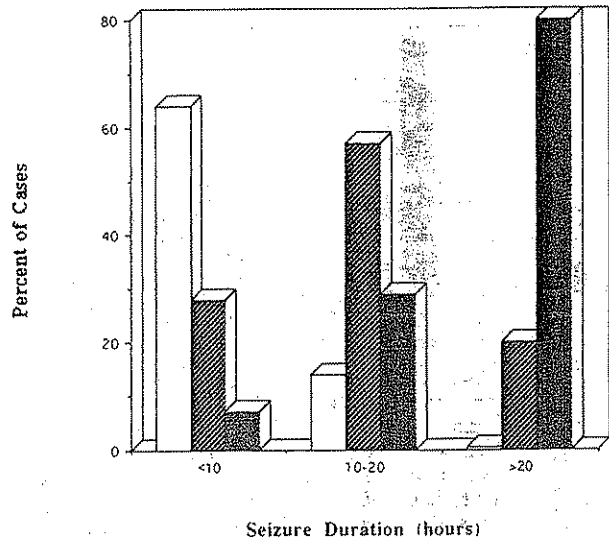


FIG. 5. Histogram showing relationship of nonconvulsive status epilepticus (NCSE) duration to outcome. A clear relationship between increasing duration and poor outcome (disabled and died) is seen. (□) Home; (▨) disabled; (■) died. (From Young et al., 1996, with permission).

resistant to frontline therapy and has a substantially higher morbidity and mortality than GCSE with non-acute brain injury (Lowenstein, 1998). In an important report, Waterhouse et al. (1998) found that when SE complicates acute ischemic stroke, mortality is three times higher than in stroke alone. In their prospective study, these investigators found a highly significant difference in mortality between these two groups which was not due to lesion size nor due to severity of the stroke itself. A logistic regression model indicated that the effects of SE and acute stroke on mortality were synergistic, not simply additive (Fig. 6).

A study by Bogousslavski et al. (1992) demonstrated that seizures can cause additional and permanent neurologic deficits after recent ABI. Ten of 48 patients who suffered focal seizures an average of 7 months after a stroke had persisting worsening of their previous neurologic deficit. None had additional strokes on magnetic resonance imaging or computerized tomography scan to account for the deterioration. The only significant factor differentiating these patients from the 38 who recovered was the prolonged duration of their seizures. The authors hypothesized that the additional neuronal injury was mediated by sustained excitatory amino acid toxicity produced by the protracted seizures. In the study by Treiman et al. (1998), patients who persisted in NCSE had a mortality rate twice as high as those in the "pure" GCSE group (30% versus 16%). In addition, in ABI,

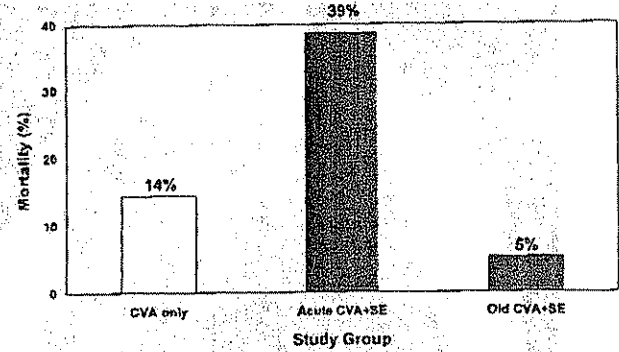


FIG. 6. Synergistic effect of status epilepticus (SE) and acute ischemic stroke on mortality. The mortality of acute cerebral vascular accident with status epilepticus (acute CVA [cerebrovascular accident] + SE) was significantly higher than acute CVA without SE (CVA only, $P < 0.001$) and also higher than remote CVA with SE (old CVA + SE, $P < 0.001$). A logistic regression model indicated that the effects of acute CVA + SE were synergistic, not simply additive. (From Waterhouse et al., 1998, with permission).

NCSE was 36% more likely to occur than GCSE and more than twice as likely to occur in association with acute systemic illness. There was an exponential increase in the mortality rate of ABI combined with prolonged NCSE in the emergency department study by Jordan et al. (1995) with an odds ratio of 23.8 for acute over remote brain injury. In addition, there was a highly significant difference in the mortality rate of NCSE

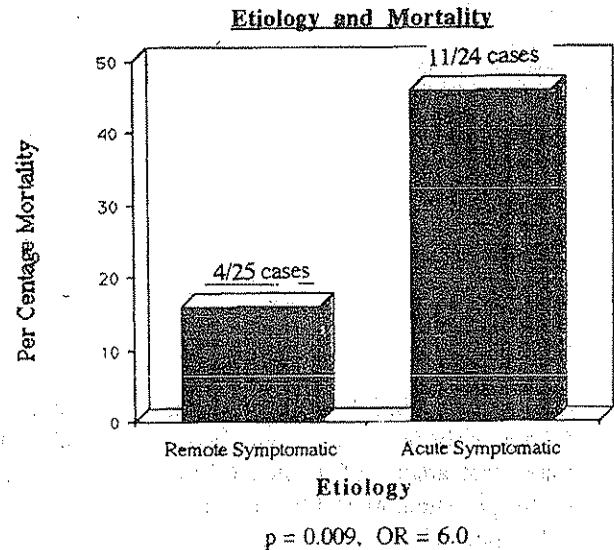


FIG. 7. Synergistic effect of concurrent nonconvulsive status epilepticus (NCSE) and acute brain injury (ABI). NCSE patients with ABI (labeled "acute symptomatic") showed a highly significant, nearly three-fold increase in mortality; P value and odds ratio as noted. (■) Mortality. (From Jordan 1999, with permission; modified from Young et al., 1996).

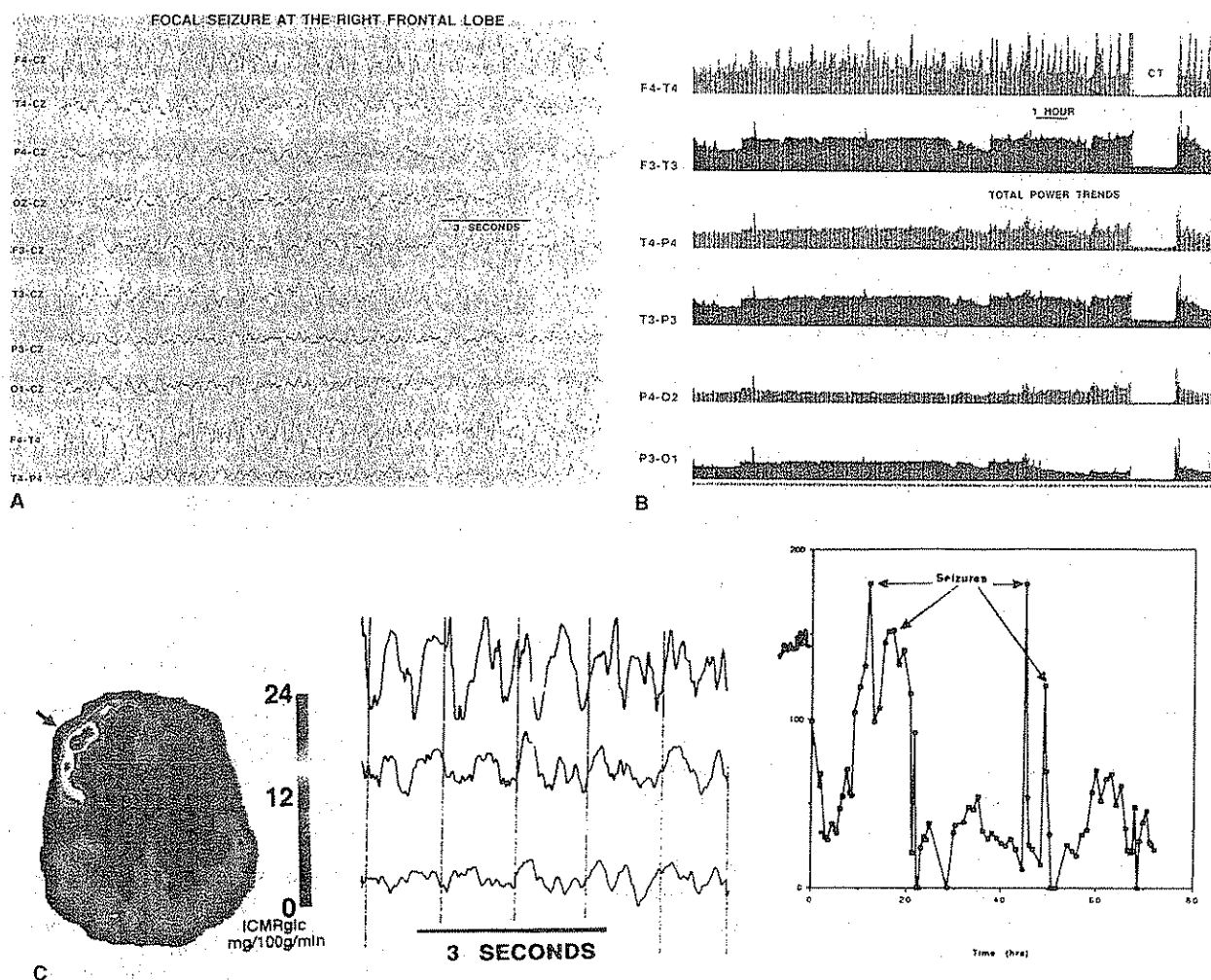


FIG. 8. Posttraumatic nonconvulsive status epilepticus (NCSE) associated with elevated regional cerebrospinal fluid (CSF) glutamate concentrations. (A) Raw digital EEG showing focal nonconvulsive seizures (NCS) in the right frontal region. (B) Quantitative EEG showing frequent, repetitive focal seizures in the right frontotemporal region, consistent with NCSE. (C) (Left) Positron emission tomography (PET) scan showing hypermetabolic activity in the right frontal region (arrow). (Center) Three-second epoch of EEG showing ongoing right frontal seizure. (Right) Profile of CSF microdialysate showing sudden peaks of increased glutamate concentration coinciding with seizure episodes. (Courtesy of Paul Vespa, M.D., Division of Neurosurgery, Department of Neurology, UCLA Medical Center, Los Angeles, California.)

patients with ABI versus those with remote brain injury in the ICU study by Young et al. (1996) (Fig. 7). Severe disability or death was seen in 75% of NCSE patients with ABI versus 38% without the condition (Jordan et al., 1995). There is biochemical evidence supporting this deleterious synergy. In a study of unselected SE patients, DeGiorgio et al. (1995) found that the highest levels of serum neuronal enolase, a marker of neuronal injury, occurred in patients with combined SE and ABI.

These data are consistent with the accepted concept of secondary neuronal insult described by Miller and Becker (1982). Acutely injured neurons are more likely than intact neurons to suffer irreversible in-

jury or death when exposed to comparable levels of ischemic, metabolic, or hypoxic insults. Waterhouse et al. (1998) draw an analogy with the head injury literature in which the combination of two acute traumatic brain injuries produces a worse outcome when compared with either injury alone. These observations suggest that the initial injury sets up a process in the brain making it more susceptible to the second injury. Figure 8 suggests a potential explanation for the deleterious interaction between NCSE and ABI. Synergistic brain injury is likely to be mediated by excitotoxic neurotransmitters released during repetitive seizures.

SUMMARY AND CONCLUSION

The context of ABI highlights the confusing and heterogeneous symptomatology of NCSE, as well as limitations of our current classification schemes. Further studies are needed to subclassify NCSE by clinical phenomena, electroencephalographic characteristics, underlying etiology, and patient outcomes.

Nonconvulsive status epilepticus is a common complication of many kinds of ABI. It often persists in GCSE after convulsive activity responds to treatment or spontaneously stops. The clinical characteristics of NCSE are ambiguous, subtle, and nonspecific, making the diagnosis difficult and uncertain. In the absence of CEEG monitoring, or fortuitously timed standard EEG, the diagnosis is likely to be missed or delayed. Because the morbidity and mortality of NCSE are largely determined by duration and delay to diagnosis, improving its outcome will require the availability and timely use of EEG testing. An awareness of certain clinical signs and contexts can heighten suspicion that NCSE is present.

When they are concurrent, the relative contributions of ABI and NCSE to patient outcomes can be problematic. Increasingly persuasive evidence suggests that these two conditions act synergistically to augment and accelerate brain damage through the release of excitatory neurotransmitters, among other mechanisms.

Guidelines remain to be established for the intensity and duration of anticonvulsant therapy in these patients. This author's interpretation of the evidence suggests that, unless the underlying ABI is extreme and irreversible, prompt recognition and early intensive intervention is appropriate and necessary to improve the otherwise poor outcome of these patients.

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