Challenges In Treatment of NCSE

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NCSE
- Definition & Classification
- Diagnosis
- Issues in specific age groups
- Treatment
- Prognosis & Outcome

Definition
- A state of ongoing or non-recovery between seizures without convulsion including altered cognitive or behavioral change, usually for more than 30 minutes along with evidence of seizures on EEG recording.

**Definition**

- A term used to denote range of condition in which electrographic seizure activities is prolonged and results in nonconvulsive clinical symptoms.
  - Clinical symptoms are dependently largely on the level of cerebral development, epileptic syndrome, and location of epileptic activities
  - Electrographic activity can take various forms

Shorvon S. Epilepsia 2007;48(suppl 8):35-8

**Classification**

- Various types of classifications according to age-groups, clinical presentations, and EEG
- Practical classification
  - Absence NCSE
  - Simple NCSE
  - Complex partial NCSE
  - Subtle NCSE

Chang AC, Shinnar S. Emerg Med Clin N Am 2011;29:61-72

**Classification of NCSE**

1. NCSE occurring in the neonatal and infantile epileptic syndromes
   - Infantile spasms
   - Severe myoclonic epilepsy of infancy (M. Beall’s syndrome)
2. NCSE in other forms of neonatal or infantile epilepsy
   - Persistent intractable epilepsy
   - Postnatal syndromes
   - Neonatal seizures and status epilepticus
   - Infants with non-feeding or feeding difficulties
   - Infants with acute encephalopathy
   - Postnatal metabolic disorders

3. NCSE occurring in childhood syndromes
   - Benign childhood epilepsy with centrotemporal spikes
   - Benign childhood epilepsy with centrotemporal spikes and focal seizures
   - Childhood absence epilepsy
   - Childhood absence epilepsy with centrotemporal spikes
   - Childhood absence epilepsy with centrotemporal spikes and focal seizures
   - Childhood absence epilepsy with centrotemporal spikes and focal seizures

4. NCSE occurring in later childhood
   - Focal seizures with centrotemporal spikes
   - Focal seizures with centrotemporal spikes and focal seizures
   - Focal seizures with centrotemporal spikes and focal seizures
   - Focal seizures with centrotemporal spikes and focal seizures

5. NCSE occurring in the adult syndromes
   - Focal seizures with centrotemporal spikes
   - Focal seizures with centrotemporal spikes and focal seizures
   - Focal seizures with centrotemporal spikes and focal seizures
   - Focal seizures with centrotemporal spikes and focal seizures

6. NCSE occurring in the elderly
   - Focal seizures with centrotemporal spikes
   - Focal seizures with centrotemporal spikes and focal seizures
   - Focal seizures with centrotemporal spikes and focal seizures
   - Focal seizures with centrotemporal spikes and focal seizures

*Secondary syndromes: cases in which it is not clear to what extent the continuous electrographic abnormalities are contributing to the clinical impairment

Shorvon S. Epilepsia 2007;48(suppl 8):35-8
Epidemiology

- Incidence: 5.6 – 18.3 per 100,000 individuals per year
- 4 – 25% of convulsive SE
- Up to 58% of patients did not have history of epilepsy
- 8 – 40% of comatose patients in ICU
  - High percentage in patient with infection, CVD, acute traumatic brain injury
  - 32% in children with critically ill
  - Subtle NCSE: not well documented

Narayan T, Murphy JM. Epilepsia 2003;44:99-6
Chang AK, Shnier S. Emerg Med 2011;29:65-72

NCSE in Infants & Children

- Determination of significant changes in cognitive function or behavior is not straightforward as in adults
  - Children with preexisting delayed development
  - Children with intractable epilepsy and specific syndrome
- EEG issue
  - Chaotic base-line EEG

NCSE in Infants & Children
Suggested Criteria for Diagnosis of NCSE in Children

Clear and persistent clinical changes in behavior (including cognition, memory, arousal or motor behavior), confirmed by comparisons with previous functioning observation and/or by neuropsychological examination, in the presence of continuous paroxysmal electrographic activity, and in the absence of clonic, tonic or tonic-clonic seizures

Diagnosis

• Diagnosis is based on awareness of this condition, clinical suspicion
• Clinical presentation
• EEG monitoring
• Exclusion of other causes

Clinical Features of NCSE

- Functional changes
  - Slow mentation
  - Responses
  - Disorientation
  - Confusion
  - Psychosis
  - Unresponsiveness
  - Altered behavior

- Motor manifestations
  - Gross movement i.e. positioning, raising, limb flexion or extension, head deviation
  - Rhythmic myoclonia
  - Twitches

- Automatism
  - Gestural
  - Verbal
  - Mimicry

Clinical Features of NCSE in Infants & Children

- Apathy
- Absentmindedness
- Aggressiveness
- Decreased alertness
- Restlessness
- Pseudodementia
- Mutism
- Inappropriate verbal outbursts

- Oral automatism
- Perioral or facial twitching
- Regression
- Infantile behavior
- Head nodding
- Increased salivation
- Decreased eye contact
- Eye blinking, eye staring

Kaplan PW. Epilepsy Behav 2002;3:122-139
Missed or Delayed Diagnosis of NCSE: Examples of Clinical Presentations

- Lethargy and confusion attributed to post-ictal state
- Ictal confusion mistaken of metabolic encephalopathy
- Unresponsiveness & catalepsy presumed to be psychogenic
- Hallucination and agitation secondary to hyperglycemia
- Mutism attributed to aphasia
- Laughing & crying ascribed to emotional liability

Red-flag for Recognition of NCSE

- Patient with generalized tonic-clonic seizure with prolonged postictal state
- Altered sensorium with subtle signs or fluctuation of mental status
- Stroke patients with clinical worsening than expected
- Elderly with unexplained stuporous or confusion
- Infant and child with intermittent altered vital signs and deterioration of consciousness

Etiology

- Primary CNS pathology: remote & acute
  - Infection
  - Cerebrovascular diseases
  - Trauma
  - Ischemia
  - Pre-existing epilepsy
- Metabolic derangement
- Intoxication & drug induced
- Hormonal disturbance
**Differential Diagnosis of NCSE**

- **Neurologic**
  - Mitochondrial encephalopathies
  - Transient global amnesia
  - Posttraumatic amnesia
  - Confusional migraine
  - Vascular compromise

- **Toxic/metabolic**
  - Toxic encephalopathy
  - Drugs
  - Intoxications
  - Metabolic derangement
  - Withdrawal syndromes

- **Epilepsy/seizure-related**
  - Typical absence epilepsy
  - Atypical absence epilepsy
  - LGS with encephalopathy
  - Altered mental status with PLEDs/BPEDs/BiPLEDs
  - Prolonged postictal confusion
  - Postictal psychosis

- **Psychiatric**
  - Acute psychotic reaction
  - Dissociative conversion reaction
  - Malingering

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**Drug-induced NCSE: Tiagabine**

**Case Report**

Non-convulsive status epilepticus induced by tiagabine in a patient with pseudotumor.


**Diagnosis: Electrographic Criteria**

**Clear-cut criteria**

- Frequent or continuous focal electrographic seizures with patterns that change in amplitude, frequency, or localization
- Frequent or continuous generalized spikes-and-waves in patients without prior history of epilepsy
- Frequent continuous generalized spikes-and-waves, significantly different in amplitude or frequency as compared to previous finding, in patients with a history of epileptic encephalopathy
- Periodic lateralized epileptiform discharges (PLEDs) in comatose patients after convulsive status epilepticus

Diagnosis: Electrographic Criteria

Equivocal patterns
- Frequent or continuous electroencephalographic abnormalities in patients with acute cerebral injuries whose EEG showed no previous similar findings
- Frequent or continuous generalized spike-and-waves, not significantly different in amplitude or frequency as compared to previous findings, in patients with a history of epilepticencephalopathy whose clinical symptoms suggest NCSE


NCSE in Elderly
- Risk from multiple co-morbidities and baseline cognitive impairment in elderly
- Unusual causes of NCSE: antibiotics
- Frequent subtle signs
  - Slight motor manifestation: eyelid myoclonia, automatism, nystagmus, dystonia, interrupted speech
  - Psychological manifestation: depression
- Risk of delayed treatment
- High morbidity & mortality: up to 57%

Chang ML. J Formosa Med Assoc 2013;102:1012.e102-3
Chang ML. J Formosa Med Assoc 2013;102:1012.e102-3

Treatment of NCSE

<table>
<thead>
<tr>
<th>NCSE type</th>
<th>Treatment</th>
<th>Prognosis</th>
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<tbody>
<tr>
<td>Absence status epilepticus</td>
<td>Oral clonazepam, intravenous lorazepam or intravenous valproic acid</td>
<td>Good</td>
</tr>
<tr>
<td>Simple partial status epilepticus</td>
<td>Oral clonazepam, Intravenous lorazepam or intravenous valproic acid</td>
<td>Good</td>
</tr>
<tr>
<td>Complex partial status epilepticus</td>
<td>Treatment of the underlying etiology, Oral clonazepam, intravenous lorazepam, intravenous felbamate or intravenous valproic acid</td>
<td>Uncertain; depends on etiology</td>
</tr>
<tr>
<td>NCSE in patients with learning difficulties</td>
<td>Oral clonazepam, oral steroids. Surgery (multiple subpial transection)</td>
<td>Uncertain; you’re at risk for seizures and electrographic abnormalities</td>
</tr>
<tr>
<td>NCSE in coma</td>
<td>Intravenous lorazepam, intravenous fosphenytoin, general anesthetics</td>
<td>Poor</td>
</tr>
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Treatment

- Initial therapy: Benzodiazepines
- Second line
  - ASE: VPA
  - SPSE: less aggressive than generalized form
  - CPSE: similar to convulsive SE
  - Subtle NCSE: PHT, VPA and other AEDs
- New AEDs: levetiracetam, lacosamide
- Others: ketamine, topiramate, KD

Treatment of NCSE

- New generation AED: Levetiracetam

Treatment of NCSE

- New generation AEDs: Lacosamide
Treatment of NCSE

- Stepwise treatment 24 – 48 hrs in each step

<table>
<thead>
<tr>
<th>Step</th>
<th>Medication</th>
<th>Time</th>
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<tbody>
<tr>
<td>I</td>
<td>Lorazepam</td>
<td></td>
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<tr>
<td></td>
<td>+ Phenytoin</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Midazolam</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Valproic acid</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Levetiracetam</td>
<td></td>
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<tr>
<td></td>
<td>Lidocaine</td>
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</tbody>
</table>


Types | Response to AEDs | Recurrence |
---    |------------------|------------|
1. Etiological/orientating factors: 
1a. Absence status epilepticus (ASE) 
   i. Typical absence status epilepticus (TASE) Excellent Frequently
   ii. “on set” absence status in the elderly Good, few recurrences occasionally transmitted Risk triggers can be identified Frequent
2. Absence status with progressive generalized epilepsy, juvenile myoclonic epilepsy Relatively refractory (when seen in the setting of a syncopal event or electrolyte/substrate abnormality) Frequent
3. Simple Partial resistant status epilepticus (SPRSE) Excellent Frequent
4. Complex Partial status epilepticus (CPSE) 
   i. Complex partial status epileptics of frontal lobe origin (CPFE) Good to very good, but often delayed Frequent
   ii. Complex partial status epileptics of temporal lobe origin (TCPSE) Good to very good, but often delayed Frequent

Kaplan PW. Neurologist 2005;11:348-381

Types | Response to AEDs | Recurrence |
---    |------------------|------------|
III. NCSE Presentation by Age: 
Electrical status epilepticus during sleep (SEMS) Landau-Kleffner (acquired epileptic encephalopathy) Relatively refractory (when seen in the setting of encephalopathy: normal development) Frequent
Minor epileptic status of Brett Poor Few

IV. Electrophysiological Seizures and Coma: 
1. Subtle status usually postconvulsive status epilepticus (PCSE) Poor Few
2. With major CNS damage, often with audiogenic failure, (with facial, perioral, and/or (and hypoxic ischemia), but without apparent preceding SE Poor Few

Kaplan PW. Neurologist 2005;11:348-381
Ketamine & NCSE


Ketamine in Refractory SE

Intravenous ketamine for the treatment of refractory status epilepticus: A retrospective multicenter study

Nicole Gaspard, Hermann Frenen, Uthliph Judd, James N. Bonnans, Bernard R. Nathan.


title

Retrospective multicenter study of medical, neurosurgical, and/or interventional neurology (MNI) centers in FR, academic medical centers in North America and Europe, examining patients with refractory status epilepticus (RSE) for intravenous ketamine (IV-K) as a therapy option. The study was designed as a retrospective analysis of data obtained from 24 centers, including 496 patients with RSE. The primary outcome was the proportion of patients who achieved seizure-free status after IV-K treatment, with the secondary outcome being the proportion of patients who achieved a modified Rankin Scale (mRS) score of 0 or 1 at 3 months.

Prognosis

- Various outcomes due to multiple confounding factors
  - Identifications of patients
  - Unavailable diagnostic tool (EEG) and proper interpretation
  - Correct classification of NCSE types
  - Lack of baseline data
  - Differentiating morbid effects of treatment from the morbidity of underlying cause of NCSE

Kaplan PW. Neurologist 2005;11:348-381
Prognosis

- Poor outcomes in those with multiple medical problems, traumatic head injury, anoxia, refractory status epilepticus
- Morbidity varies with
  - Concomitant brain injury 27%
  - NCSE due to epilepsy 3%
  - Initial level consciousness (7% in obtundation VS 9% in deep lethargy)
- Types of NCSE
- Response to Treatment

Types | Prognosis | Outcome
--- | --- | ---
1. Concomitant nonconvulsive status epilepticus (NCSE) | Excellent | No mortality or mortality
2. Absent status epilepticus (AIE) | Excellent | Excellent
3. Tonic absence status in the setting of a preceding NCSE | Excellent | Excellent
4. Absent status with a previously generalized seizure, progressive | Graded to fair | Graded to fair
5. Absent status with a previously nonconvulsive status | Fair to poor | Fair to poor
6. Apoapical absence status epilepticus (AASE) | Usually good to excellent, occasionally poor | Usually good to excellent, occasionally poor
7. Status partialis nonconvulsive status epilepticus (SPN) | Usually good to excellent, occasionally poor | Usually good to excellent, occasionally poor
8. Complex partial status epilepticus (CPSE) | Usually good to excellent, occasionally poor | Usually good to excellent, occasionally poor
9. Complex partial status epilepticus of temporal lobe origin (TLPSE) | Usually good to excellent, occasionally poor | Usually good to excellent, occasionally poor
10. Complex partial status epilepticus of non-temporal lobe origin (NLPSE) | Usually good to excellent, occasionally poor | Usually good to excellent, occasionally poor

Kaplan PW. Neurologist 2005;11:348-361

Types | Prognosis | Outcome
--- | --- | ---
11. NCSE: Prognosis by Age
   a. Electrical status epilepticus during sleep (ESEDS)
   b. Lennox-Gastaut (acquired epileptic encephalopathy)
   c. Minor epileptic status of Drett
   d. Status partialis usually progressive status epilepticus (CPSE)
   e. Absent status usually progressive status epilepticus (AIE)
   f. Absent status usually progressive status epilepticus (AIE)
   g. With major CNS damage, often with subdural bleeding (with focal, partial, and/or subacute), but without apparent preceding CNS disease
   h. With major CNS damage, often with subdural bleeding (with focal, partial, and/or subacute), but without apparent preceding CNS disease

Kaplan PW. Neurologist 2005;11:348-361
Markers for NSE

Neuron-specific enolase is increased after nonconvulsive status epilepticus.

Department of Neurology, University of Southern California School of Medicine, Los Angeles, USA.

Abstract

Serum neuron specific enolase (s-NSE), a marker of brain injury and acute seizures, was increased in 2 patients with nonconvulsive SE. Neither patient had an acute neurologic insult other than nonconvulsive SE (NCSE) accounting for s-NSE changes. Increase in s-NSE provides further in vivo evidence of transient brain injury after NCSE.

NCSE

- Often overlooked and frequently can be mistaken for other medical condition
- Diagnosis is based on awareness of this condition, clinical suspicion, EEG monitoring, and response to AED
- AED is effective at the right time
- NCSE must be included in D/Dx of coma
- High concern should be exercised in elderly, infant and young children especially in those with unexplained acute confusional state