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# EEG patterns compatible with nonconvulsive status epilepticus are common in elderly patients with delirium: a prospective study with continuous EEG monitoring

Naeije Gilles [a,*], Depondt Chantal [a], Meeus Claire [a], Korpak Keziah [b], Pepersack Thierry [b], Legros Benjamin [a]

[a] Dept of Neurology, Reference Center for the Treatment of Refractory Epilepsy, Hôpital Erasme Université Libre de Bruxelles, Belgium
[b] Dept of Geriatrics, Hôpital Erasme Université Libre de Bruxelles, Belgium

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ABSTRACT

*Introduction:* Delirium is a leading cause of hospitalization and morbidity in elderly persons. Nonconvulsive status epilepticus (NCSE) and delirium share many risk factors. We tested the hypothesis that NCSE plays an important role in delirium by performing continuous EEG (cEEG) monitoring in elderly patients with delirium of any cause.
*Material and methods:* Patients over 65 years old presenting with delirium in the emergency room were prospectively included and underwent either routine 20-minute EEG or cEEG within 24 h after admission.
Clinical, biological, and imaging characteristics, length of hospitalization, and outcome were compared between patients with possible NCSE and patients without epileptic discharges.
*Results:* There were 32 patients in each group. Continuous EEG detected patterns compatible with NCSE in 28% and focal interictal epileptiform discharges (IEDs) in 16% of the patients. Routine EEG detected patterns compatible with NCSE in 6% and focal IEDs in 16% of the patients. History of cognitive impairment and use of antibiotics and hypernatremia were significantly associated with the presence of possible NCSE. Delirium in patients with possible NCSE was initially attributed to another cause in over 80% of the cases. Patterns compatible with NCSE were associated with a longer hospitalization stay and a higher mortality rate.
*Conclusion:* Electroencephalographic patterns compatible with NCSE are found in 28% of elderly with delirium when cEEG monitoring is performed. No clinical or paraclinical parameter can reliably distinguish elderly patients with delirium with or without patterns compatible with NCSE in the absence of cEEG monitoring. Elderly patients with delirium and patterns compatible with NCSE have significantly higher mortality rates and longer hospital stays.



## 1. Introduction

Delirium, formerly known as acute confusional state, is one of the main causes of morbidity and mortality in the elderly. Delirium is a syndrome that complicates various medical conditions [1] and is, by definition, acute, transient, and potentially reversible. The extent of the range of acute medical conditions leading to delirium in the elderly remains unknown. Hypotheses on the pathophysiology of delirium include neurotransmitter deficiency, proinflammatory cytokines, acute stress responses, and neuronal injury, but definite evidence is lacking. Interestingly, many factors associated with delirium are also risk factors for epilepsy, such as electrolyte imbalances, hypoglycemia, systemic inflammatory response, and specific drugs [2,3].

Although well described in the literature [4,5], epileptic disorders are seldom considered as a potential cause of delirium. Acute confusional state may be an ictal or postictal symptom in various epilepsy syndromes. If ictal, delirium is generally the manifestation of a nonconvulsive seizure (NCS) or nonconvulsive status epilepticus (NCSE). Especially in the elderly, manifestations of NCSz can be subtle, with abnormal behavior, mood changes, and higher function impairment, or more pronounced, with clouding of consciousness and unresponsiveness [6,7]. These manifestations closely reflect the criteria used to diagnose delirium in the most widely used scale, the Confusion Assessment Method (CAM) [8].

Epileptic discharges are commonly identified in elderly patients with delirium of any cause [9,10], and NCSE is detected in 3% of the patients when EEG is performed [10]. The proportion of patients with EEG patterns compatible with NCSE increases to 15% when the delirium is not explained by biological or imaging findings [11]. Some studies claim that those epileptic discharges may play a role in the pathophysiology of delirium considering that treating them with antiepileptic drugs (AEDs) improves delirium symptoms [12,13]. In a small retrospective

* Corresponding author at: Department of Neurology, Hôpital Erasme, 808, route de Lennik, 1070 Bruxelles, Belgium. Tel.: +32 25558196; fax: +32 25553942.
*E-mail address:* gilles.naeije@erasme.ulb.ac.be (N. Gilles).

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study using continuous EEG (cEEG) monitoring, we found that 10/15 of elderly patients admitted for delirium of unexplained origin had NCSz or patterns compatible with NCSE, such as continuous multifocal spikes or periodic epileptiform discharges [14].

To confirm these results, we performed a prospective study to assess the prevalence of EEG patterns compatible with NCSE in elderly patients with delirium of any cause and to assess the yield of cEEG in that context.

## 2. Methods

All patients over 65 years old meeting the criteria of delirium in the emergency room were prospectively included.

Delirium was considered in patients fulfilling CAM criteria for delirium [8]: (1) acute onset and fluctuating course, (2) inattention, (3) disorganized thinking, and (4) altered level of consciousness. Delirium is diagnosed when features 1, 2, and either 3 or 4 are present.

Patients were included and underwent either routine 20-minute EEG or cEEG in the first 24 h after admission, depending on the availability of a portable cEEG machine. Electroencephalography and cEEG were recorded using 21 scalp electrodes placed according to the international 10–20 system.

The study was powered to demonstrate that cEEG could detect EEG patterns compatible with NCSE in over 20% of the elderly patients with delirium in comparison with the 3% detection rate of routine 20-minute EEG published in the literature.

Routine EEG and cEEG were reviewed by the same electroencephalographers (BL, CD, and GN) trained in cEEG reading. Findings were classified according to published consensus criteria [15]. Continuous EEGs were read at least twice a day.

Electroencephalography patterns were classified as follows:

- Focal spikes
- Multifocal spikes
- Periodic epileptiform discharges (PEDs)
- Occurrence of clear-cut seizures.

Patterns that were considered to be compatible with possible NCSE included the following:

- Repetitive clear-cut seizures
- Continuous multifocal spikes
- PEDs (either generalized or lateralized).

In case of possible NCSE, cEEG was extended until 24–36 h after clinical recovery or EEG improvement.

Clinical, biological, and imaging characteristics and length of hospitalization were compared between patients with EEG patterns compatible with NCSE and patients without.

The AED treatment was managed at the discretion of the treating physician and individualized according to the type of status/seizure, comorbidity, and comedications. Our institution protocol for the treatment of NCSE has been described elsewhere [16].

### 2.1. Statistics

Data were stored in an Excel database, and statistical analyses were performed using Stata 11.2 software (Texas, USA). Results were presented as means (±SD) or medians with range. Unpaired Student's *t*-test was used to compare means between groups, and Chi-square test was used to assess group differences in proportions of the conditions.

For all statistical analyses, $p < 0.05$ was considered to be statistically significant.

The study was approved by the Ethics Committee of Hôpital Erasme, Brussels, Belgium: EudraCT/CCB: B406201213738.

## 3. Results

### 3.1. Study cohort

Thirty-two patients were included in each group. Mean age was 82 years (range: 67–95), and 70% of the patients were women. History of seizure was noted in one patient in the EEG group and in 4 patients in the cEEG group ($p = 0.039$). Other baseline characteristics are comparable and detailed in Table 1.

### 3.2. Electroencephalography results

In the cEEG group, focal spikes were found in 5 (16%) patients, continuous multifocal spikes in 1 patient, absence status in 1 patient, and periodic discharges in 7 patients (Table 2). Thus, EEG patterns compatible with NCSE were seen in a total of 9 (28%) patients.

Before EEG patterns compatible with NCSE were detected by EEG, more than 80% of the patients had another presumed diagnosis to explain delirium (Table 2). General medical management and AED treatment improved the EEG in 90% of the cases and led to delirium resolution in 60%.

In the routine EEG group, focal spikes were found in 5 (16%) patients and periodic discharges in 2 (6%) (Table 2).

### 3.3. Overall comparison of characteristics of patients with EEG patterns compatible with NCSE and those without

Clinical parameters significantly associated with EEG patterns compatible with NCSE were as follows: history of cognitive impairment (7/11 (64%) vs 13/53 (25%), $p = 0.011$), antibiotic use (2/11 (18%) vs 0/53 (0%), $p = 0.002$), and higher serum sodium concentrations (145 mEQ/L vs 140 mEQ/L, $p = 0.027$).

Patients with EEG patterns compatible with NCSE had worse outcomes with significantly longer hospital stays (21 vs 11 days, $p = 0.004$) and a ninefold higher mortality rate (36% (4/11) vs 4% (2/53), $p = 0.001$).

**Table 1**
Study cohort. Characteristics of the patients according to the presence of single (N = 32) or continuous EEG record (N = 32).

| | EEG N = 32 | cEEG N = 32 | p |
|---|---|---|---|
| | % or mean (SD) | % or mean (SD) | |
| Age (years) | 83 (8) | 81 (8) | 0.358 |
| % females | 24/32 (75%) | 21/32 (66%) | 0.412 |
| History of stroke | 8/32 (25%) | 10/32 (31%) | 0.578 |
| History of epilepsy | 1/32 (3%) | 4/32 (13%) | **0.039** |
| Cognitive impairment | 10/32 (31%) | 10/32 (31%) | 1 |
| >3 comorbidities | 24/32 (75%) | 25/32 (78%) | 0.768 |
| Tramadol use | 1/32 (3%) | 3/32 (9%) | 0.302 |
| Psychotropic substance use | 19/32 (59%) | 18/32 (56%) | 0.800 |
| Antibiotic use | 1/32 (3%) | 1/32 (3%) | 1 |
| Use of >5 drugs | 21/32 (66%) | 24/32 (75%) | 0.412 |
| Focal neurological sign | 3/32 (9%) | 4/32 (13%) | 0.689 |
| Myoclonus | 0% | 0% | – |
| Na (mEq/L) | 141 (10) | 140 (5) | 0.605 |
| Na < 137 | 19% | 25% | 0.545 |
| Na > 145 | 9% | 6% | 0.641 |
| Urea/creatinine ratio > 40 | 78% | 72% | 0.564 |
| Osmolality (mOsm/L) | 307 (26) | 309 (15) | 0.801 |
| CRP (mg/L) | 35 (57) | 65 (64) | 0.057 |
| Hb (g/dL) | 12.9 (1.5) | 13.4 (1.9) | 0.267 |
| Acute brain lesion | 5/32 (16%) | 5/32 (16%) | 1 |
| Chronic brain lesion | 10/32 (31%) | 8/32 (25%) | 0.578 |
| LOS (days) | 11 (9) | 14 (12) | 0.335 |
| Death | 2/32 (6%) | 4/32 (13%) | 0.391 |

Na: sodium; CRP: C-reactive protein; Hb: hemoglobin; LOS: length of stay.
Boldfaced value means it is statistically significant.

**Table 2**
Electroencephalography results. Epileptiform activities found in older patients with delirium with continuous EEG and routine EEG.

| | Continuous EEG N = 32 | 20 minutes routine EEG N = 32 |
|---|---|---|
| Epileptiform activities (percent of patients) | **44%** | **22%** |
| NCSE | **28% (n = 9)** | **6% (n = 2)** |
| GPEDs | 16% (5) | 6% (2) |
| Mean frequency Hz [range] | 1.6 [1–3] | 3 [2–4] |
| 3-Hz SW | 3% (1) | – |
| PLEDS + | 3% (1) | – |
| BI-PLEDS + | 3% (1) | – |
| Continuous multifocal spikes | 3% (1) | |
| IEDs | 16% (n = 5) | **16% (n = 5)** |
| Initial ER diagnosis of patients with NCSE | | |
| Infection | 60% | 50% |
| Suspected seizures | 20% | – |
| Concussion | 10% | 16% |
| Stroke | – | 16% |
| Subdural hematoma | – | 16% |
| Unknown | 10% | – |
| Outcome of NCSE | | |
| Clinical recovery | 60% | 50% |
| EEG improvement | 90% | 50% |

NCSE: nonconvulsive status epilepticus; GPEDs: generalized periodic epileptiform discharges; 3-Hz SW: 3-Hertz spike–waves; PLEDs+: periodic lateralized epileptiform discharges plus; BI-PLEDs+: bilateral periodic lateralized epileptiform discharges plus. IEDs: interictal discharges; ER: emergency room.

## 4. Discussion

Using cEEG monitoring, we found patterns compatible with NCSE in 28% of the elderly patients with delirium when cEEG monitoring was performed in the first 24 h after admission in the emergency room. In comparison, routine 20-minute EEG detected EEG patterns compatible with NCSE in only 6%. These results highlight the fact that, although labor-intensive, cEEG monitoring is useful in the work-up of elderly patients with delirium.

The higher percentage of patients with a history of seizures in the cEEG group could have biased the results towards a higher proportion of patients with EEG patterns compatible with NCSE; however, history of seizures was not statistically different between patients with and without EEG patterns compatible with NCSE in the cEEG group (data not shown).

Electroencephalography patterns compatible with NCSE consisted of periodic discharges in 9 out of 11 patients. Published criteria to consider those periodic discharges as being "ictal" include clinical manifestations consistent with NCSE lasting over 30 min, PEDs lasting over 10 s, and either a PED frequency over 2.5 Hz or significant evolution in field/morphology/frequency or clinical focal motor symptoms or improvement after a trial of rapid-onset intravenous antiepileptic drugs [17]. We found these criteria impractical because every single patient with periodic discharges had at least one of them. Moreover, response to AEDs is difficult to assess in these patients, since concomitant medical problems (infection and ionic disturbances) were corrected as well. Therefore, although the vast majority of patients with PEDs showed some clinical or EEG improvement with AED treatment, we recognize that this does not prove a causal relationship, nor that those discharges truly represent NCSE in all patients.

Even if two patients had periodic lateralized epileptiform discharges (PLEDs), which may be of ictal origin in patients with symptoms, most PEDs were generalized periodic epileptiform discharges (GPEDs), which are not specific of NCSE and may be found in other conditions. The differential diagnosis of such discharges is broad and includes diffuse metabolic/toxic encephalopathy, postanoxic coma, as well as rare diseases like Creutzfeldt–Jakob disease (CJD) [18]. In our study, there were no cases of CJD or postanoxic coma, but metabolic/toxic disturbances are common in this population. Nevertheless, in our study, elderly with delirium and EEG patterns compatible with NCSE had a ninefold higher mortality rate and longer hospital stays. Therefore, we conclude that these EEG patterns constitute a marker of the severity of the underlying disease, regardless of its pathophysiological origin. One controlled study compared the outcome of patients with similar acute medical conditions with or without PEDs and also showed a significant increase in mortality rate in the group of patients with PEDs [19]. So far, there is no compelling evidence on whether treating those PEDs may improve the clinical outcome of these patients or not. Studies found that NCSE and PEDs increase mortality rate [20,21], aggravate existing brain lesions [22], and may affect brain metabolism [23]. Those findings, in combination with experimental studies in which NCSE leads to structural damage and cognitive impairment, argue strongly for active treatment of NCSE and PEDs when they are found in patients with altered mental states regardless of the underlying cause.

In accordance with previous work on the association of NCSE and unexplained delirium in the elderly, no clinical or paramedical parameter could be identified that predicts the occurrence of EEG patterns compatible with NCSE and thereby helps in distinguishing between elderly patients with delirium but without such EEG patterns with EEG patterns compatible with NCSE and elderly patients with deliriumbut without such EEG patterns [11,23]. In our study, patients with EEG patterns compatible with NCSE had significantly more cognitive impairment. Cognitive impairment is a known risk factor for seizures [24], and the higher proportion of patients with preexisting cognitive impairment in the group with EEG patterns compatible with NCSE probably reflects their increased liability to acute symptomatic seizures. However, the predictive value of cognitive impairment is unlikely to be clinically useful because of the high prevalence of various degrees of cognitive impairment in the elderly population. Patients with EEG patterns compatible with NCSE also had significantly higher serum sodium concentrations. Both hypernatremia and hyponatremia [25] are known to increase the potential for seizures, but the difference in serum sodium concentrations between patients with and without EEG patterns compatible with NCSE in our study (5 mEq/L), although statistically significant, does not seem to be clinically relevant. Similarly, use of antibiotics is also a risk factor for seizures and NCSE [18], and although there were more patients treated with antibiotics in the group with EEG patterns compatible with NCSE, this proportion is too small to be useful in practice.

## 5. Conclusions

Patterns compatible with NCSE are found in 28% of the elderlypatients with delirium when cEEG monitoring is performed in the first 24 h after admission to the emergency room. Since no clinical or paraclinical parameter can distinguish elderly with delirium with or without patterns compatible with NCSE, prolonged EEG monitoring has a role in the care of elderly with delirium, especially when the cause of delirium is unclear and 20-minute routine EEG is inconclusive. Elderly with delirium and patterns compatible with NCSE have significantly higher mortality rates and longer hospital stays. Further studies are needed to assess the role of treating epileptic discharges in the prognosis of delirium when associated with EEG patterns compatible with NCSE.

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Thierry Pepersack did the statistics and contributed to the editing of the paper.

Benjamin Legros supervised the study and contributed to the editing of the paper.

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## Conflict of interest

None of the authors has any conflict of interest to disclose.

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