Chapter

Nonconvulsive Status Epilepticus and Coma

Demet Ilhan Algın, Gülgun Uncu, Demet Ozbabalık Adapınar and Oğuz Osman Erdinç

Abstract

Nonconvulsive status epilepticus (NCSE) is common in patients with coma with a prevalence between 5 and 48%. Nonconvulsive status epilepticus (NCSE) is an electroclinical state associated with an altered mental status (AMS) but lacking convulsive motor activity. It is difficult to diagnose in the obtunded/comatose patients. Such patients have often other serious medical conditions, and the diagnosis of NCSE is frequently delayed in these patients. Diagnosing NCSE demands a high degree of clinical suspicion and for that reason likely remains under-recognized. The most important question, however, is whether the treatment of NCSE in coma improves the outcome of these patients or not. In this review, we aimed to summarize the EEG patterns in NCSE to further delineate the borders between comatose forms of NCSE and coma-epileptiform discharges and to evaluate modified EEG criteria for NCSE in a coma.

Keywords: coma, nonconvulsive status epilepticus (NCSE), EEG, periodic discharges, consciousness

1. Introduction

Coma is the disorder of consciousness because of the damage to diffused bilateral cerebral hemisphere corte or ascending reticular activation system (ARAS) [1].

This neural network starts from the dorsal part of the upper pons, continues in the mesencephalon, connects to the thalamus and diffuses widely from there to both hemispheres. In addition, ARAS is associated with some nuclei in the pons and mesencephalon, the posterior hypothalamus, and the basal forebrain. Communication in this network is established through neurotransmitters such as acetylcholine, noradrenaline, serotonin and dopamine [2]. Structural or biochemical damage or disruption of this neural network may cause unconsciousness. The most severe picture in the spectrum of consciousness disorders is coma. In a comatose patient, alertness and awareness are completely lost. Many causes of both intracranial and systemic origin can cause coma. In order to begin specific treatment as soon as possible, the underlying cause of the coma should be established as quickly as possible. For this purpose, the patient should be systematically approached and the possible causes of the mechanism should be considered in five major categories [3]:

1. Unilateral hemispheric mass lesions compressing diencephalon or brain stem.

2. Bilateral hemispheric lesions affecting the reticular formation and thalamocortical cycle fibers at thalamus level.

3. Infratentorial lesions that compress or damage the reticular formation in the brain system.

4. Diffuse lesions affecting the physiological function of the brain.

5. Psychiatric conditions mimicking coma.

The evaluation of coma patients falls within the responsibility of physicians working in many disciplines. Detecting the cause of the coma requires detailed investigation and deductive effort. The physician should consider the patient as a whole and be able to synthesize the information obtained from history, examination and diagnostic tools and theoretical information.

2. Nonconvulsive status epilepticus

Nonconvulsive status epilepticus (NCSE) which has higher morbidity and mortality is a treatable disorder when diagnosed properly. NCSE has special symptoms such as unexplained confusion or coma or vegetative status and aura which can distinguish from the normal conditions. NCSE is a continuous seizure activity with a minimum duration of 10–30 min on EEG [4]. In previous studies used different EEG criteria to identify the NCSE patients, the prevalence of NCSE ranges from 5 to 48% and the actual prevalence of NCSE is still unknown [5].

B Without prominent motor symptoms (i.e., nonconvulsive SE, NCSE)
B-1 NCSE with coma (including so-called subtle SE)
B-2 NCSE without coma
B-2.a Generalized
B-2aa: Typical absence status
B-2ab:Atypical absence status
B-2ac:Myoclonic absence status
B-2b. Focal
B-2ba: Without impairment of conciousness (aura continua, with autonomic, sensory, visual, olfactory, gustatory, emotional/psychic/experiential, or auditory symptoms)
B-2bb: Aphasic status
B-2bc: With impaired consciousness
B-2c. Unknown whether focal or generalized (Autonomic SE)
B-2ca:Autonomic SE

Table 1.
New ILAE classification of NCSE axis 1.

The new ILAE classification is based on 4 axes 1 being the semiology (**Table 1**); axis 2 is the etiology; axis 3 is EEG correlates, and axis 4 is the age of the patient. This concept takes account of the requirements for a classification supporting a clinical diagnosis, enabling research through standardization while ensuring an individualized treatment concept for the patient [6, 7].

Clinical evidence may vary greatly in NCSE. Negative and positive symptoms can be evaluated into two groups. Negative symptoms are anorexia, aphasia/mutism, amnesia, catatonia, coma, lethargy and negative symptoms are agitation, aggression, automatisms, twinkle, crying, delirium, echolalia, laughing, nausea-vomiting, nystagmus-eye deviation, perseveration, anxiety and psychosis [8]. Nonconvulsive status epilepticus is a treatable neurologic emergency when it is diagnosed properly. Diagnostic criteria depend on clinical status, EEG findings and response to treatment. During the initial evaluation, EEG recording is crucial for patients with acute confusion [6].

Although the etiologies of NCSE and coma intersect, NCSE is a distinct clinical picture and an electroclinic condition without convulsive motor activity. Diagnosis is difficult in a comatose patient. The diagnosis of NCSE is often delayed in those patients. Clinically, a high degree of suspicion is required for diagnosis. Ictal-interictal discrimination of activity on EEG is difficult despite the newly defined criteria and these criteria have practical application difficulties. Another important issue is how aggressive treatment of NCSE in comatose patients should be, because the positive or negative effect of NCSE treatment on the prognosis of those patients is not well known. A distinction should be made between patients with coma or other severe disorders and those with really epileptic mechanisms and treatment should be decided accordingly. Specific EEG patterns are not seen in a coma [9].

2.1 EEG patterns in comatose patients

2.1.1 Intermittent rhythmic delta activity

Among EEG findings in encephalopathy, intermittent rhythmic delta activity (IRDA) is considered to lie at the milder end of the spectrum of coma EEG patterns. IRDA may appear in patients who are awake or who are mildly lethargic or stuporous; IRDA patterns are not associated with deeply comatose states. IRDA tends to occur in the frontal regions in adults (frontal intermittent rhythmic delta activity, or FIRDA) and in the occipital regions in (occipital intermittent rhythmic delta activity, or OIRDA) [10].

2.1.2 Prolonged bursts of slow-wave activity

Prolonged bursts of slow-wave activity can occur in a variety of etiologies in coma. They are most often diffuse but can also be lateralized without any spatiotemporal evolution [11].

2.1.3 Stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIDs)

Stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIDs) are a relatively common phenomenon found on prolonged electroencephalogram (EEG) monitoring that captures state changes and stimulation of comatose patients. Common causes include hypoxic injury, traumatic brain injury, and hemorrhage and toxic-metabolic disturbances [12, 13].

2.1.4 Generalized periodic and rhythmic discharges

Generalized periodic discharges (**Figure 1**) (GPDs) with a triphasic morphology have been associated with nonepileptic encephalopathies.

2.1.5 Lateralized periodic discharges

PLEDs (**Figure 2**) are usually associated with obtundation in 95% of patients, focal seizures and focal neurological signs may occur in 80%, and *Epilepsia partialis continua* in 30% of the patients [14, 15].

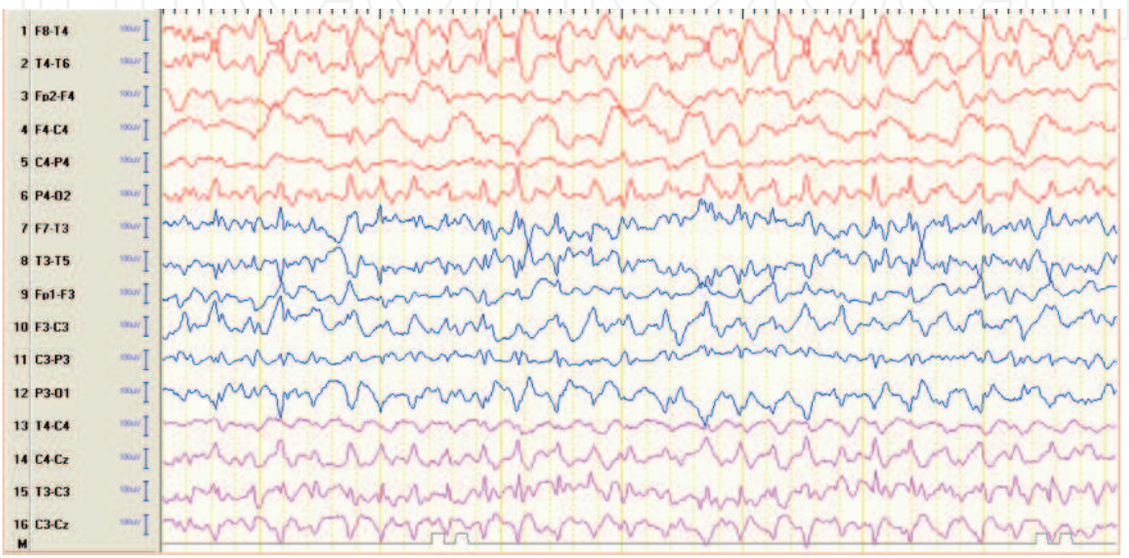

Figure 1.
A 45-year female patient coma due to intoxication with olanzapine continuous very regularly generalized 2–3/s spike and sharp wave activities.

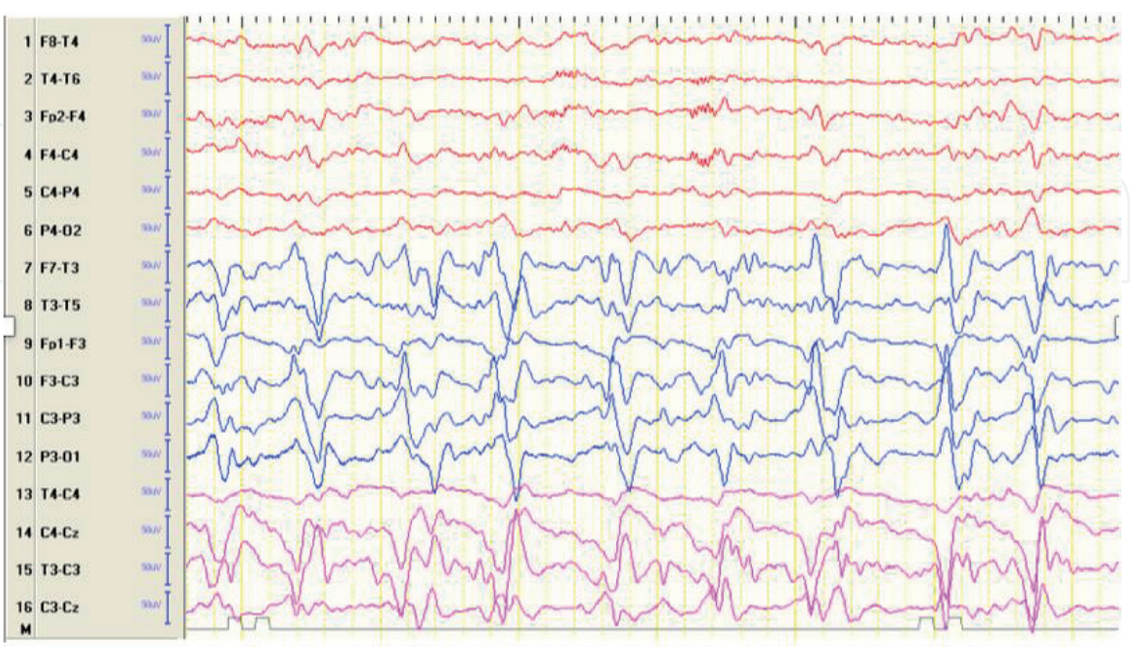

Figure 2.
A 40-year female, mentally retarded and epileptic patient admitted to our clinic with psychosis and diagnosed as limbic encephalitis. Lateralized periodic discharges left hemisphere. Flat periods with 1- to 2-second duration.

2.1.6 Triphasic waves (TWs)

Triphasic waves (**Figure 3**) are periodic and generalized, typically frontally predominant and not always epileptiform in appearance. This pattern can occur in any toxic-metabolic or structural encephalopathy although the early descriptions associated its presence to hepatic encephalopathy [16, 17].

2.1.7 Burst suppression patterns

Burst-suppression (**Figure 4**) in the electroencephalogram (EEG) is characterized by high amplitude events (bursts) alternated by periods of low or absent activity (suppressions). This pattern can be physiological, for instance during early development, or pathological, for example in almost half of comatose patients

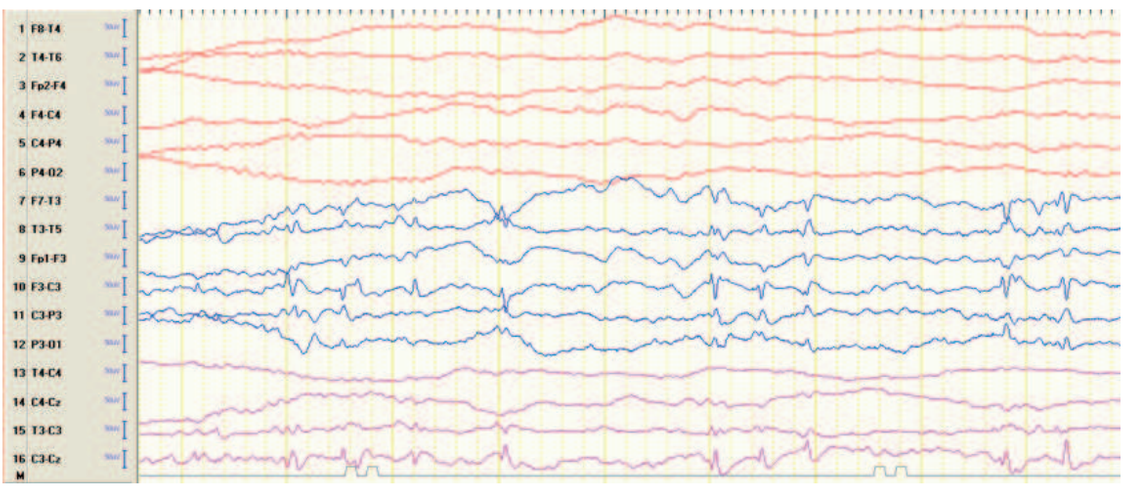

Figure 3.
A 61-year female patient, comatose state, had left-sided craniotomy after glioblastoma; EEG prominent in the left frontocentral region sharp waves with triphasic appearance.

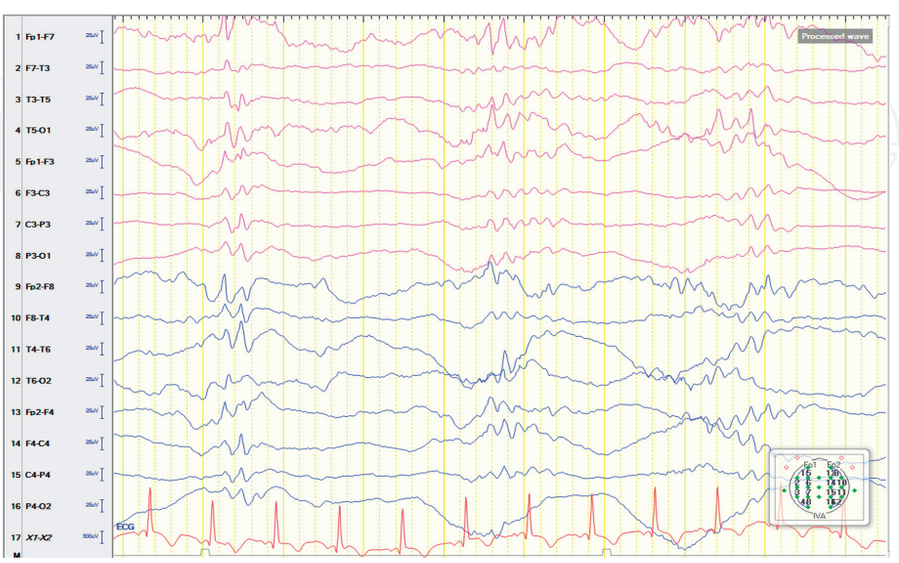

Figure 4.
A 70-year male patient, coma after cardiac arrest; EEG shows burst suppression pattern with bursts of mixed frequencies and interposed spikes and sharp waves. No response to treatment and died 7 days later.

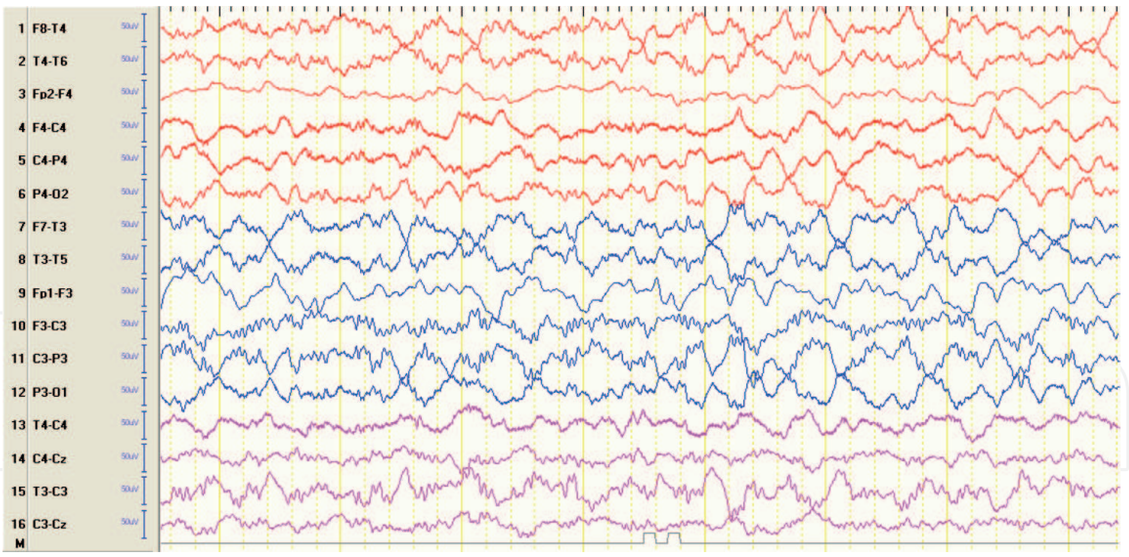

Figure 5.
A 45-year male patient, coma after traumatic brain injury; EEG shows 2-3 Hz delta slow waves with spindle prominent in the left frontocentral region.

within the first 48 h after cardiac arrest Burst suppression pattern can also be found in various etiologies (structural, toxic, and metabolic) or during hypothermia [18].

2.1.8 Alpha and theta coma patterns

Alpha coma can also be seen in intoxication (barbiturates, benzodiazepines, anesthetic agents, imipramine), brainstem lesions, locked-in syndrome and hypoxic-ischemic encephalopathy. Theta coma refers to the diffuse background activity of 4–7 Hz in coma. Theta coma patterns in patients with cortical dysfunction, such as in dementia or mild to moderate encephalopathy [19, 20].

2.1.9 Spindle coma patterns

Spindle coma patterns (**Figure 5**) in spindles, slow activity and K-complexes. They have been initially described in brain trauma but can be found also with other etiologies The etiology of spindle coma may be traumatic brain injury, intracerebral hemorrhage, post-ictal stages and intoxication [21, 22].

3. EEG criteria for NCSE in the comatose patients

Various EEG criteria have been used in previous studies to identify patients in comatose-NCSE, yielding a prevalence between 5 and 48%, but the true incidence of NCSE in coma is still not known. Nonconvulsive status epilepticus (NCSE) is a neurological emergency that is seen in a wide spectrum of cases. Diagnosis cannot be made without electroencephalography (EEG) due to the diversity of the clinical picture and the impaired consciousness due to the underlying primary damage, especially in intensive care patients. 4. In the London-Innsbruck Status Epilepticus meeting, the previous terminology was reviewed and Salzburg Criteria for the diagnosis of NCSE by Leitinger et al. reported [23–26] (**Table 2**).

In comatose patients, epileptiform discharges faster than 2.5 Hz or generalized periodic discharges (GPDs), lateralized periodic discharges (LPDs) and continuous 2/s GPDs with triphasic morphology of less than 2.5 Hz, as well as rhythmic

Patients without known epileptic encephalopathy

- EDs > 2.5 Hz, or
- EDs ≤ 2.5Hz or rhythmic delta/theta activity (>0.5 Hz) AN done of the following:
  - EEG and clinical improvement after IV AEDs, or
  - Subtle clinical ictal phenomena, or
  - Typical spatiotemporal evolution

Patients with known epileptic encephalopathy

- Increase in prominence or frequency when compared with baseline with
- Improvement of clinical and EEG features with IV AEDs

*If EEG improvement without clinical improvement, or if fluctuation without definite evolution, this should be considered possible NCSE

**Incrementing onset (increase in voltage and change in frequency), or evolution in pattern (change in frequency N1 Hz or change in location), or decrementing termination (voltage or frequency)

EDs: epileptiform discharges (spikes, polyspikes, sharp waves, and sharp-and-slow-wave complexes)

IV AEDs: intravenous antiepileptic drugs

** Typical spatiotemporal evolution.*

Table 2.
The Salzburz consensus criteria for nonconvulsive stress epilepticus (NCSE).

discharges (RDs) faster than 0.5 Hz were also taken into consideration as NCSE if they responded to benzodiazepine treatment with improvement in the EEG or mental status of patient (**Figure 6**) [26, 27].

NCSE with coma can be accompanied by generalized epileptiform discharges (coma-GED) and coma with lateralized epileptiform discharges (coma-LED). Etiologic factors and EEG patterns found in coma-GED and coma-LED are given in [19, 28] (**Table 3**).

4. Conclusion

NCSE is a disorder comprising a broad clinical spectrum that requires characteristic electroencephalographic changes to confirm the correct diagnosis. NCSE is an under-recognized cause of coma and traditionally involves the clinical picture of an altered mental status with diminished responsiveness, a diagnostic EEG and often a response to antiepileptic therapy [29].

Mortality in nonconvulsive status epilepticus can be seen in 18–25%, and in severe patients with systemic disease followed by intensive care, this rate can increase to 50–52% [24]. It is important to decide how aggressive the treatment of NCSE in a coma should be. A distinction should be made between patients in coma and other severe illnesses and those in which epileptic mechanisms actually play a role, and treatment should be guided accordingly [30].

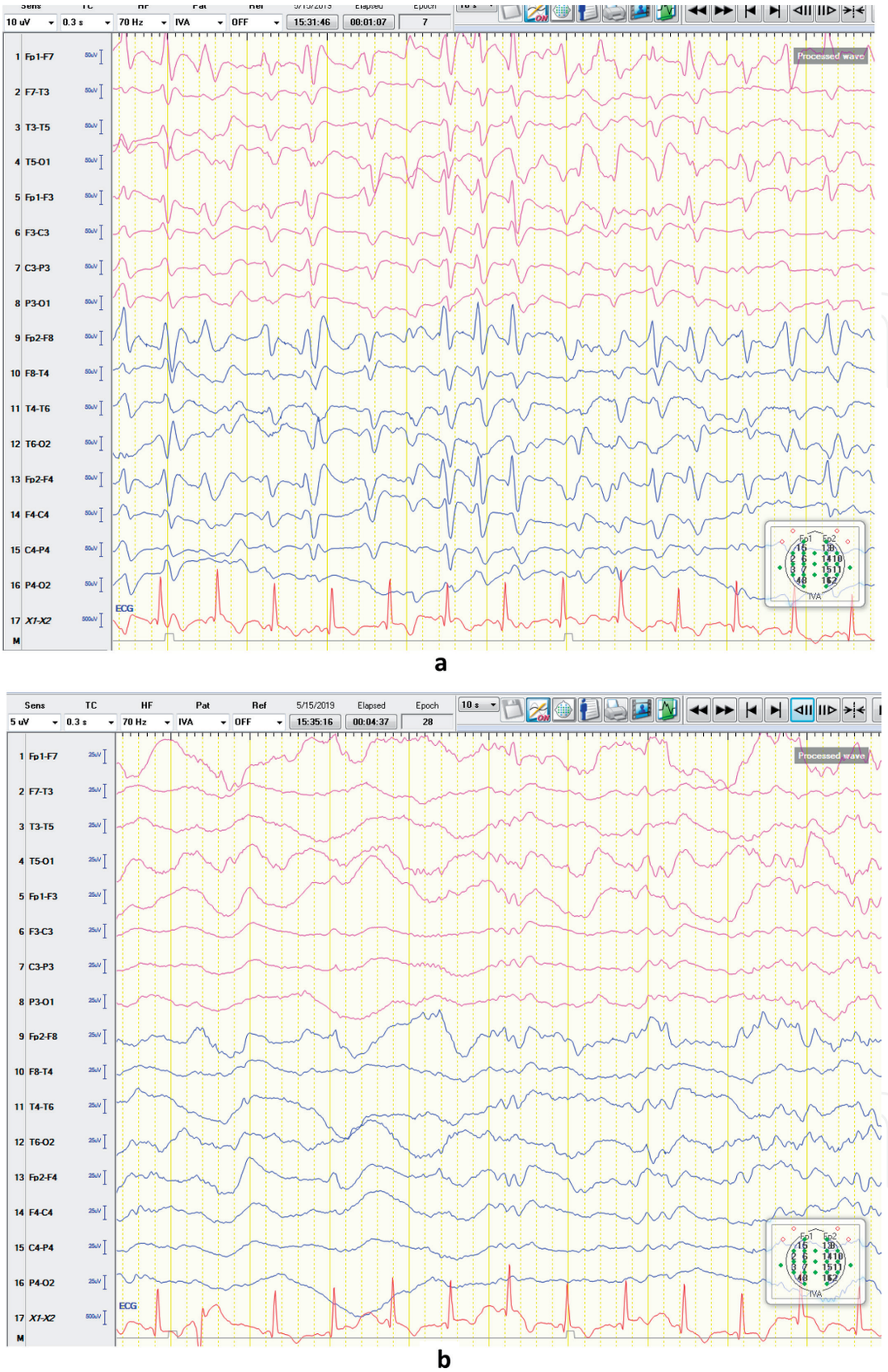

Figure 6.
(a) A 62-year female patient with breast cancer; confused; no abnormal movements; EEG shows repetitive generalized, >2.5/s spikes and slow waves with triphasic appearance. (b) Improvement of level of consciousness and EEG features following diazepam 10 mg IV.

Prognosis is better in patients with a history of epilepsy and prognosis in acutely symptomatic patients is related to the underlying disease. Convulsive and NCSE in patients with stroke, subarachnoid hemorrhage and traumatic brain injury worsen the prognosis by acting synergistically with acute brain pathology [31, 32].

	Etiology	EEG pattern
Coma-GED	Diffuse primary or secondary brain disturbances (anoxic, toxic, metabolic, infectious, degenerative) Space-occupying lesions with brainstem compression (direct or due to tentorial herniation) Known epilepsies?	Continuous generalized spiking Periodic spiking Burst suppression pattern in different variations
Coma-LED	Focal brain lesions (in most cases acutely acquired) In rare cases diffuse abnormalities (aminophylline intoxication, some forms of diabetic coma) Known epilepsies?	Continuous focal spiking PLEDs Bi-PLEDS Unilateral burst suppression pattern Unilateral triphasic waves
BI-PLED, bilateral periodic epileptiform discharges, GEDs, generalized epileptiform discharges; LED, lateralized epileptiform discharges; PLED, periodic epileptiform discharges.		

Table 3.
Etiologic factors and EEG pattern in comatose NCSE.

NCSE is a neurological emergency that can be treated if diagnosed properly. Diagnostic criteria depend on clinical status, EEG findings and response to treatment. EEG imaging is crucial for patients with acute confusion during the initial evaluation [33].

Acknowledgements

We would like to thank Neutec company for its support in publishing this section.

Author details

Demet Ilhan Algın[1], Gülgun Uncu[2*], Demet Ozbabalık Adapınar[3] and Oğuz Osman Erdinç[1]

1 Department of Neurology, Faculty of Medicine, Eskişehir Osmangazi University, Eskişehir, Turkey

2 Department of Neurology, Eskişehir City Hospital, Eskişehir, Turkey

3 Department of Neurology, Eskişehir Acıbadem Hospital, Eskişehir, Turkey

*Address all correspondence to: drgulguncu@gmail.com

References

[1] Posner J, Saper C, Schiff N. Plum and Posner's Diagnosis of Stupor and Coma. 4th ed. Oxford Unıversity Press; 2007

[2] Felten DL, Jozefowicz RF. Brainstem and cerebellum. In: Netter's Atlas of Human Neuroscience. Icon Learning Systems LLC; 2003

[3] Wijdicks E. Comatose. In: The Practice of Emergency and Critical Care Neurology. Oxford University Press; 2010

[4] Altindag E, Okudan ZV, Özkan ST, KrespiY,BaykanB.Electroencephalographic patterns recorded by continuous EEG monitoring in patients with change of consciousness in the neurological intensive care unit. Archives of Neuropsychiatry. 2016

[5] Towne AR, Waterhouse EJ, Boggs JG, et al. Prevalence of nonconvulsive status epilepticus in comatose patients. Neurology. 2000;**54**:340-345

[6] Rüegg S. Nonconvulsive status epilepticus in adults: Types, pathophysiology, epidemiology, etiology, and diagnosis. Neurology International Open. 2017;**01**(03):E189-E203. DOI: 10.1055/s-0043-103383

[7] Rüegg S. Non-convulsive status epilepticus in adults: An overview. Schweizer Archiv für Neurologie und Psychiatrie. 2008;**159**:53-83

[8] Brophy GM, Bell R, Claassen J, Alldredge B, Beleck TP, Glauser T, et al. Guidelines for the evaluation and management of status epilepticus. Neurocritical Care. 2012;**17**:3-23

[9] Bauer G, Trinka E. Nonconvulsive status epilepticus and coma. Epilepsia. 2010;**51**:177-119

[10] Husain AM. Electroence phalographic assessment of coma. Journal of Clinical Neurophysiology. 2006;**23**(3):208-220

[11] Kubicki S, Rieger H. The EEG during acute intoxication with hypnotics. Electroencephalography and Clinical Neurophysiology. 1968;**25**(1):94

[12] Johnson EL, Kaplan PW, Ritzi EK. Stimulus-induced rhythmic, periodic, or Ictal Dıscharges (SIRPIDSs). Journal of Clinical Neurophysiology. 2018;**35**:229-233

[13] Hirsch LJ, Claassen J, Mayer SA, EmersonRG.Stimulus-inducedrhythmic, periodic, or ictal discharges (SIRPIDs): A common EEG phenomenon in the critically ill. Epilepsia. 2004;**45**:109-123

[14] Chatrian GE, Shaw CM, Leffman H. The significance of periodic lateralized epileptiform dischages in EEG: An electrographic, clinical and pathological study. Electroencephalography and Clinical Neurophysiology. 1964;**17**:177-193

[15] Gandelman-Marton R, Rabey JM, Flechter S. Periodic lateralized epileptiform discharges multiple sclerosis: A case report. Journal of Clinical Neurophysiology. 2003;**20**(2):117-121

[16] Brigo F, Storti M. Triphasic waves. American Journal of Electroneurodiagnostic Technology. 2011;**51**:16-25

[17] Brenner RP, Schaul N. Periodic EEG patterns: Classification, clinical correlation and pathophysiology. Journal of Clinical Neurophysiology. 1990;**7**:249-267

[18] Hofmeijer J, Tiepkema-Cloostermans MC, van Putten MJ. Burst-suppression with identical bursts: A distinct EEG pattern with poor outcome in postanoxic

coma. Clinical Neurophysiology. 2014;(5):947-954

[19] Kaplan PW, Genoud D, Ho TW, et al. Etiology, neurologic correlations, and prognosis in alpha coma. Clinical Neurophysiology. 1999;**110**:205-213

[20] Berkhoff M, Donati F, Bassetti C. Postanoxic alpha (theta) coma: A reappraisal of its prognostic significance. Clinical Neurophysiology. 2000;**111**:297-304

[21] Coma BG, Death B. In: Niedermeyer E, Lopez Da Silva F, editors. Electro-Encephalography: Basic Principles, Clinical Applications, and Related Fields. 4th ed. Baltimore: Williams and Wilkins; 1999. pp. 459-475

[22] Sutter R, Kaplan PW. Electroencephalographic patterns in coma: When things slow down. Epileptologie. 2012;**29**:201-209

[23] Hirsch LJ, Brenner RP, Drislane FW, So E, Kaplan PW, Jordan KG, et al. The ACNS subcommittee on research terminology for continuous EEG monitoring: Proposed standardized terminology for rhythmic and periodic EEG patterns encountered in critically ill patients. Journal of Clinical Neurophysiology. 2005;**22**(2):128-135

[24] Hirsch LJ, LaRoche SM, Gaspard N, Gerard E, Svoronos A, Herman ST, et al. American clinical neurophysiology Society's standardized critical care EEG terminology: 2012 version. Journal of Clinical Neurophysiology. 2013;**30**(1):1-27

[25] Leitinger M, Beniczky S, Rohracher A, Gardella E, Kalss G, Qerama E, et al. Salzburg consensus criteria for non-convulsive status epilepticus: Approach to clinical application. Epilepsy & Behavior. 2015;**49**:158-163

[26] Leitinger M, Trinka E, Gardella E, Rohracher A, Kalss G, Qerama E, et al. Diagnostic accuracy of the Salzburg EEG criteria for non-convulsive status epilepticus: A retrospective study. Lancet Neurology. 2016;**15**:1054-1062

[27] Mesraoua B, Deleu D, Hail Al H. et al. Nonconvulsive Status Epilepticus in Patients with Altered Mental Status Admitted to Hamad. DOI: 10.5772/intechopen.83580

[28] Trinka E, Cock H, Hesdor er D, et al. A definition and classication of status epilepticus—Report of the ILAE task force on classification of status epilepticus. Epilepsia. 2015;**56**:1515-1523

[29] Naravanan JT, Murthy JM. Nonconvulsive status epilepticus in a neurological intensive care unit: Profile in a developing country. Epilepsy. 2007;**5**:900-906

[30] Young GB, Jordan KG, Doig GS. An assessment of nonconvulsive seizures in the intensive care unit using continuous EEG monitoring: An investigation of variables associated with mortality. Neurology. 1996;**47**(1):83-89

[31] Litt B, Wityk RJ, Hertz SH, Mullen PD, Weiss H, Ryan DD, et al. Nonconvulsive status epilepticus in the critically ill elderly. Epilepsia. 1998;**39**(11):1194-1202

[32] Trinka E, Leitinger M. Which EEG patterns in coma are nonconvulsive status epilepticus? Epilepsy & Behavior. 2015;**49**:203-222

[33] Baykal B, Ebru A, editors. Nonconvulsive Status Epilepticus. Istanbul: Cortex Publishing; 2018