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Case Report

The Ongoing Challenge of Diagnosing Non-convulsive Status Epilepticus: What About Generalized Non-reactive Rhythmic Alpha Activity in the Salzburg Criteria?

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Abstract

The ILAE Task Force on Classification released a report in 2015 to clarify the classification of status epilepticus. Non-convulsive status epilepticus (NCSE) was defined as SE without prominent motor symptoms, with or without coma. This diverse entity's electrophysiological diagnosis, which is more consistent in clinical recognition, may be challenging. Some classifications and revisions have been proposed recently, making NCSE diagnosis easier. There are, however, patients who remain in the 'grey zone'. The increasing evidence in patients, who do not meet the Salzburg Consensus Criteria for NCSE diagnosis of 'NCSE' or 'possible NCSE', but whose clinical and electrophysiological features are still suspicious for NCSE, may pave the way for developing more comprehensive criteria. Therefore, we present here the 'generalized non-reactive alpha activity' in the electroencephalogram (EEG) of an elderly patient with no known epilepsy before, who presented with acute confusional state of unexplained cause, which we suspected as NCSE and managed a ccordingly with success. Considering that 'time is brain', early and correct NCSE diagnosis is critical and the NCSE EEG criteria should be more inclusive for the patients in the 'grey zone like the one presented here with 'generalized non-reactive alpha activity'.

Keywords: Non-convulsive status epilepticus, alpha rhythm, Salzburg criteria, grey zone, generalized non-reactive alpha activity

INTRODUCTION

Non-convulsive status epilepticus (NCSE) was defined as SE without prominent motor symptoms, with or without coma.[1] Given the enormous heterogeneity of clinical presentations, diagnosing NCSE is difficult and its electroencephalogram (EEG) findings, also show prominent heterogeneity, are indispensable for diagnosis. Despite extensive collaborative efforts in classification and EEG definitions in the last two decades,[2-4] the diagnosis of NCSE is still challenging and requires paramount experience. New modifications are expected due to some challenging points, such as atypical EEG patterns, underestimation of lateralized periodic discharges, presence of false-negative patients, and lack of definition for the required time interval for the clinical improvement.[5,6] To support these new efforts, herewith we report a case of a suspected NCSE who presented with acute unexplained encephalopathy and had a 'generalized non-reactive rhythmic alpha activity' as an atypical EEG pattern.

CASE PRESENTATION

A 71-year-old, right-handed male patient was admitted to the emergency department with speech difficulties and blurred consciousness which was noticed when he woke up. He had limited cooperation and perseveration with otherwise normal physical and neurological examinations, and there were no neck stiffness and meningeal signs. His relatives denied using any drugs and he had no comorbid diseases, recent infectious disease including Coronavirus disease-19 or vaccination. His history was unremarkable except for mild head trauma at the age of 20 years. He had no family history of epilepsy. His cranial magnetic resonance imaging including diffusion-weighted imaging and computed tomography were unremarkable. There were 12 lymphocytes, 4 polymorphonuclear cells in cerebrospinal fluid (CSF). CSF protein was slightly increased (59 mg/dL), with normal glucose levels. Intravenous (IV) acyclovir 2250 mg/day was administered with a preliminary diagnosis of viral encephalitis, but the viral panel and all blood tests, including liver and renal function tests, ammonia, thyroid hormones turned out to be normal except for slightly increased C-reactive protein. The next day, he was still delayed in responding

and was disorientated. EEG showed spiky contoured, slightly high amplitude, continuous generalized rhythmic alpha activity, non-reactive to eye closure and it was evaluated as consistent with possible NCSE (Figure 1a). After IV diazepam administration, the patient was sedated and the frequency of the abnormal background activity gradually decreased to theta-delta waves (Figure 1b). Levetiracetam 2500 mg/day was administered intravenously and 1000 mg/day maintenance was prescribed. The control cranial magnetic resonance imaging was also normal. CSF cytology and cultures were unremarkable along with the autoimmune panel for anti-neuronal antibodies and paraneoplastic panel including anti-Hu, anti-Yo, anti-Ri, anti-amphyphisin, anti-Tr, anti-PCA-2, anti-Ma, anti CV2-1, anti-ANNA-3 antibodies. He tended to rapidly improve in the following days, correlated with the improvement of subsequent EEG (Figure 1c). On the fifth day, the patient's neurological examination was normal and he was discharged with peroral levetiracetam 1000 mg/day. His neurological examination and EEG (Figure 1d) were completely normal 4 months later.

MAIN POINTS

- Non-convulsive status epilepticus (NCSE) is an important neurological condition that needs to be diagnosed rapidly.
- Electrophysiological findings in the 'grey zone' could sometimes lead to challenges in the diagnosis of NCSE.
- In the presence of diffuse non-reactive alpha-like activity on electroencephalogram in the acute confusional state, we should also suspect NCSE in the differential diagnosis.

DISCUSSION

We present an intriguing case of acute confusional state, whose possible etiological causes were unidentified, with generalized rhythmic alpha activity on EEG that showed electrophysiological improvement after IV diazepam. Considering the modified NCSE criteria,[6] our patient had acute confusion lasting approximately 6 h and other possible causes were excluded as far as we could. His EEG showed generalized rhythmic alpha activity with some minor fluctuations in morphology and frequency, and these rhythms were replaced by delta waves after IV diazepam without rapid clinical improvement. After IV levetiracetam treatment, a gradual but complete clinical improvement was observed in the following days. Unfortunately, this case remained undiagnosed as NCSE with the current state of Salzburg Consensus Criteria for Non-convulsive Status Epilepticus (SCNC).

Defining accurate EEG criteria has become an important milestone for the diagnosis of NCSE. Many studies have been conducted to evaluate the sensitivity and specificity of the diagnostic approach after modification of the SCNC.[5,7] Although SCNC is successful in diagnosing 'Definite NCSE' and 'No-NCSE', it has been argued that there were gray zones in the 'possible NCSE' category.[8] The "continuous" spike-wave activity <10 sec but many epileptic paroxysms filling substantial parts of the epochs, persistent rhythmic delta/theta activity without fluctuations, the fluctuations that do not fully meet the criteria, lateralized periodic discharges, and <2.5 Hz epileptiform discharges (ED) that did not fulfill the secondary criteria could not be diagnosed as 'NCSE' or 'possible NCSE' all causing false negativity according to reports.[5,9]

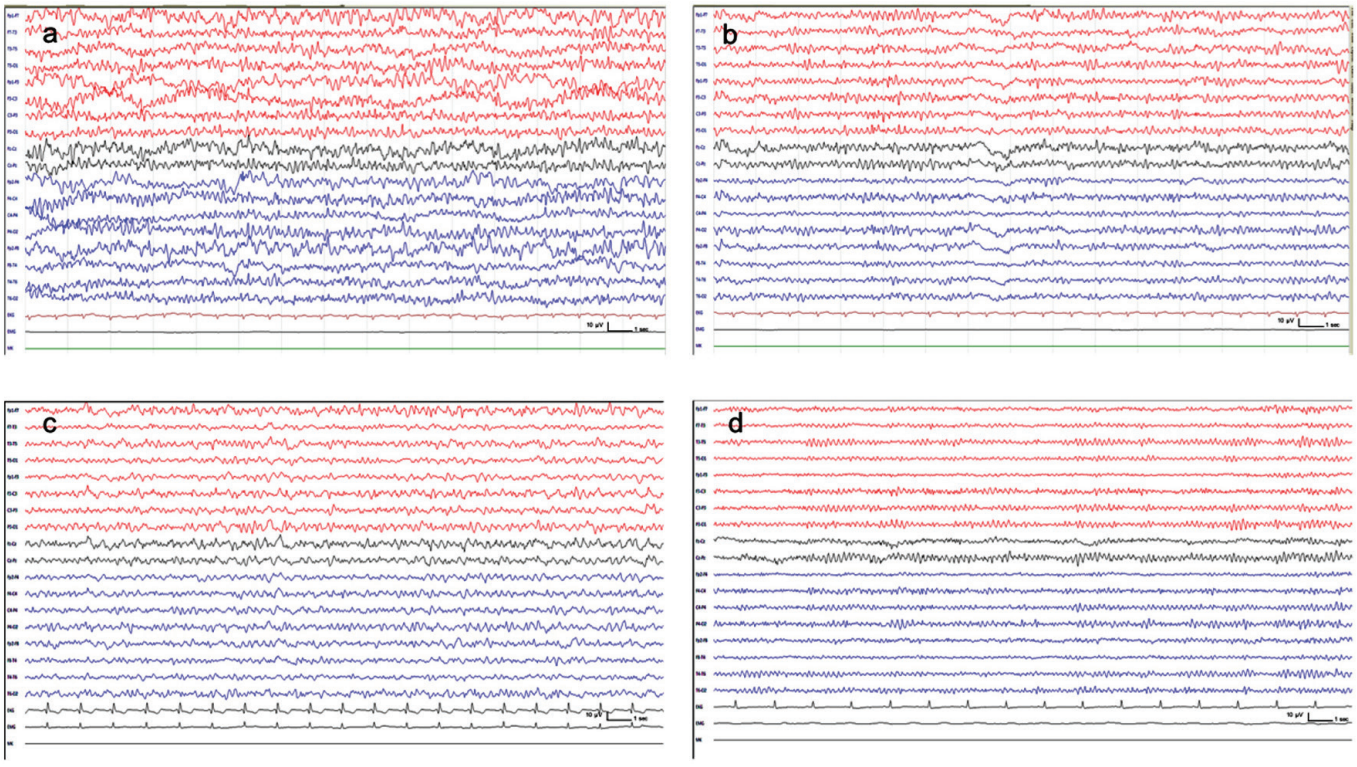

Figure 1. In EEG (high pass filter 0.5 Hz, low pass filter 70 Hz, bipolar longitudinal montage), generalized non-reactive rhythmic alpha activity was detected on the day of admission (a), these rhythms were replaced by theta-delta frequency background activity after IV diazepam without any clear clinical improvement (b). A gradual improvement of the EEG patterns was observed along with clinical improvement on day 2 after levetiracetam treatment (c) and 4 months later, EEG was normal (d)

Ictal generalized rhythmic alpha activity is a rare phenomenon in NCSE. Bauer et al.[6] reported two adult NCSE patients with generalized alpha activity who had known epilepsy but different syndromes. One of them was a 55-year-old male patient with generalized tonic-clonic seizures and impaired cognition and disturbed behavior episodes, which were accompanied by generalized alpha activity in ictal video-EEG recordings. The second patient was a 29-year-old mentally retarded female with a history of infantile spasm; she had episodes of tonic posture in the legs, irregular subtle myoclonia in the arms, hypersalivation and oral automatism, lasting 1-3 days. During these periods, generalized 11-13 Hz ictal activity and sometimes interposed spike and wave complexes in the frontal regions were detected and these episodes were considered NCSE.

It may be wondered why generalized rhythms of alpha frequency were observed instead of well-known ED of the NCSE. Many studies have shown that the sources of electrical events reflected in the scalp EEG as α waves are located in not only the occipital cortex, but also the extra-occipital cortical generators.[10] However, our patient had generalized alpha pattern instead of posterior dominant alpha rhythms of wakefulness. The most well-known cause of generalized alpha-pattern is alpha coma, in which the alpha pattern is located more posteriorly with variability and reactivity in patients with brainstem lesions, whereas the alpha pattern in hypoxic encephalopathies due to cardiac arrest tends to be diffuse spread and non-reactive, more prominent in the frontal regions.[11,12] Some hypotheses have been proposed for the pathophysiological processes of this heterogeneous clinic entity such as the deafferentation of thalamo-cortical circuits releasing autonomous cortical alpha frequency generation in the alpha pattern associated with brainstem lesion, s and a direct effect on cortical alpha frequency generators in the drug intoxication.[13] The neuroimaging findings and metabolic screening were normal, however, a direct or indirect pathophysiological effect of frontal structures on other cortical structures, such as deafferentation of the thalamocortical pathways, may be responsible for this generalized non-reactive 'alpha-like activity' suggestive of NCSE. This speculation needs to be supported by experimental studies and functional imaging techniques.

As a result, our elderly patient is the first case with no epilepsy history before, who was pre-diagnosed with viral encephalitis but unsupported by additional tests such as CSF results and neuroimaging, recovered gradually after antiepileptic treatment along with the symptoms, and diagnosed with NCSE with this unique generalized non-reactive alpha activity.

NCSE's EEG diagnostic criteria have revised several times considering experience and knowledge. Despite this, there are still NCSEs whose diagnosis is doubtful or undiagnosed. Considering that 'time is brain', early and correct NCSE diagnosis is vital and it is inevitable that the guidelines should be more inclusive for patients in the 'grey zone like the one presented here with 'generalized non-reactive alpha activity'.

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Ethics

Informed Consent: Written informed consent was obtained from the patient.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: İ.İ.K., B.B., Design: İ.İ.K., B.B., Data Collection or Processing: İ.İ.K., B.B., Analysis or Interpretation: İ.İ.K., B.B., Literature Search: İ.İ.K., B.B., Writing: İ.İ.K., B.B.

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