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Long-Term Undiagnosed Nonconvulsive Status Epilepticus Identified by Urgent Electroencephalography with Hyperventilation Activation

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Keywords
Nonconvulsive status epilepticus · Hyperventilation activation · Urgent electroencephalography · Absence status epilepticus

Abstract
Nonconvulsive status epilepticus (NCSE) might be underdiagnosed in cases where clinical symptoms are ambiguous. If a patient exhibits ictal psychiatric symptoms such as NCSE presentation and is misdiagnosed as having a psychiatric disorder, the patient may be treated in psychiatry settings, where continuous electroencephalography (cEEG), the gold standard for NCSE diagnosis, is typically not used. Herein, we report our experience with a patient having NCSE who exhibited psychiatric symptoms and remained misdiagnosed for many years. We also included a brief review of the relevant literature. Our experience with this patient presents two clinically significant points: (1) clinicians should consider NCSE in the differential diagnosis of interictal psychosis when patients with epilepsy, in whom the seizure type is unknown, repeatedly present transient psychiatric symptoms, and (2) urgent EEG with hyperventilation activation during acute periods may help diagnose patients with suspected NCSE.

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Introduction

Nonconvulsive status epilepticus (NCSE), a condition of ongoing or intermittent clinical epileptic activity associated with electroencephalographic evidence of seizures but without overt convulsions [1], is a heterogeneous disorder, with its various subtypes having different presentations. NCSE can be classified into comatose and proper (NCSE without coma) forms according to the degree of impaired consciousness [1]. NCSE proper is often characterized by prolonged behavioral and cognitive changes as observed in focal NCSE with impairment of consciousness or absence status epilepticus (AS) [1]. NCSE can remain underdiagnosed in cases where clinical symptoms are ambiguous. There are several reports of NCSE patients being misdiagnosed with psychiatric disorders [2, 3]. In particular, if a patient exhibits ictal psychiatric symptoms as the NCSE presentation and is consequently misdiagnosed as having a psychiatric disorder, they may be treated in psychiatric settings, where continuous electroencephalography (cEEG) – the gold standard for NCSE diagnosis – is not typically used. Thus, patients misdiagnosed with psychiatric disorders, and not NCSE, subsequently receive inappropriate treatment. Therefore, practical approaches for accurate diagnosis of NCSE in psychiatry settings are needed. Here, we report our experience with a patient with NCSE exhibiting psychiatric symptoms who remained misdiagnosed for many years. Our report highlights the importance of considering NCSE in the differential diagnosis of interictal psychosis in patients with suspected epilepsy for whom seizure type (i.e., generalized vs focal) is unknown but not generalized tonic-clonic seizure (GTCS). Urgent EEG with hyperventilation (HV) activation may be useful in diagnosing some patients with suspected NCSE.

Case Presentation

A 38-year-old right-handed man with mild intellectual disability was admitted to our department with the primarily complaint being acute confusion. He had a history of two GTCS at 22 years of age. EEG and magnetic resonance imaging showed no evidence of epilepsy, but the patient was diagnosed with epilepsy based on the clinical course of his condition; valproate (VPA; 600 mg/day) was started (because carbamazepine induced skin eruptions). No obvious convulsive seizures were witnessed thereafter.

At 23 years of age, the patient presented with episodic mental alterations lasting from 30 min to 1 h and characterized by disoriented behavior followed by partial amnesia. These episodes were interpreted as focal impaired awareness seizures (FIAS) with subsequent postictal confusion. Thus, phenytoin (PHT; 250 mg/day) was added to the VPA.

At 24 years of age, the patient experienced acute confusion even without GTCS or FIAS. He exhibited agitation, visual hallucinations, and assaultive behavior toward his family members, for which he required psychiatric hospitalization. The onset of this behavior was abrupt and the confusional state lasted several days, following a fluctuating course until it gradually resolved. The patient had partial memory of his abnormal behavior and explained that family conflicts had triggered these episodes. The attending psychiatrist interpreted these transient confusional states as reflecting “acute interictal psychosis” or “brief reactive psychosis” and started the patient on risperidone (2 mg/day) to prevent the recurrence of the psychotic episodes. After discharge from the psychiatric ward, the patient had ideas of reference and subtle auditory hallucinations.

At 28 years of age, VPA was discontinued because the patient developed liver dysfunction, and PHT monotherapy was prescribed.

He started to experience recurrent episodes of acute confusion at 30 years of age. The clinical symptoms and courses of these episodes were similar to those he had experienced at 24 years of age. Antipsychotics (risperidone 10 mg, propericiazine 150 mg, haloperidol 18 mg, levomepromazine 100 mg, olanzapine 10 mg) failed to resolve the acute confusion occurring at a yearly basis, and the patient required psychiatric admission every time.

None of the bedside EEG results were diagnostic, even though they were performed as soon as the patient had recovered from his agitation. Some EEGs showed excessive theta activity that may be explained by his antipsychotic medications; however, there was no evidence of epileptiform discharges. Additionally, he underwent several routine outpatient EEG examinations, but interictal EEGs during wakefulness and sleep did not reveal any diagnostic epileptiform abnormalities. HV activation provoked high-amplitude slow waves that were maximal bifrontally at diffuse regions, without clear clinical symptoms. EEG recovery times were sometimes slow, exceeding 60 s, but these findings were nonspecific.

On his most recent day of admission at 38 years of age, the patient was brought to the emergency room after an episode of acute confusion without an obvious trigger. Clinical examination showed no signs except for partial amnesia regarding his violent behavior toward his mother. His mother had witnessed him falling after hyperventilating, and the transient confusional state had begun after he arose. Based on this account and past EEG findings showing EEG slowing after HV activation, an urgent EEG was conducted to evaluate the patient's conscious state. During the first half of the recording, numerous alpha waves appeared in the occipital region, with frontal dominant theta/delta activities. However, voluntary HV triggered diffuse, high-amplitude slow waves that lasted 1 min post-HV and gave way to frontally predominant rhythmic delta activity (RDA) 1 min later (Fig. 1). Over time, some sharp waves were superimposed on RDA and RDA spread from the frontal region to the general region (Fig. 2, Fig. 3). The RDA with superimposed sharp waves lasted over 5 min, during which time the patient became restless and removed the electrodes without following instructions. The clinical interview performed by the EEG technician revealed that the patient was disoriented.

Given the patient's medical history, EEG findings (continuous RDA with "evolution" in frequency, morphology, and location [Fig. 1, Fig. 2, Fig. 3]) and clinical symptoms, we diagnosed the patient as having NCSE with impairment of consciousness and concluded that this condition had caused both his "acute confusion" and "prolonged FIAS-like episodes at the age of 23." Thus, PHT was discontinued and replaced with VPA (1,200 mg/day) as indicated in cases of AS, one of the subcategories of NCSE. The patient was prescribed monotherapy with VPA [4], but sporadic AS recurred. Therefore, levetiracetam (1,000 mg/day) was added. This drug combination has kept him seizure-free for 3 years. The cytogenetic study carried out on phytohemagglutinin-stimulated blood lymphocytes stained with trypsin-Giemsa banding technique showed no anomaly of chromosomes, such as ring chromosome 20.

Discussion/Conclusion

Our experience with this patient presents two clinically significant points: (1) clinicians, including psychiatrists, should suspect NCSE in the differential diagnosis of interictal psychosis in patients with epilepsy and repetitive transient psychiatric symptoms, even when lacking overt seizure symptoms different from those of GTCS; and (2) urgent EEG with HV activation during acute periods may help diagnose patients with suspected NCSE.

People with epilepsy (PWE) often exhibit psychiatric symptoms. Psychotic states in PWE are less common than depression and anxiety, but the impact on life is greater; thus,

appropriate management is imperative. Psychotic states in PWE have been categorized into three primary types according to the temporal relationship to seizures or clusters of seizures: ictal, postictal, and interictal psychoses. This classification is important for acute and long-term management of psychosis [5]. Ictal psychosis (hallucinations, fear) has a sudden onset, lasts briefly (from seconds to minutes), and disappears as soon as the seizures cease [5]. It may occur in the context of NCSE, where patients may exhibit bizarre behaviors and thought incoherence, with or without loss of awareness [5]. NCSE can easily be overlooked if the seizures manifest exclusively or predominantly with episodes of psychosis. In the case of our patient, NCSE manifesting as acute confusional state was considered to represent an acute interictal psychosis for many years. The coexistence of NCSE and interictal psychosis may complicate the diagnosis of NCSE.

NCSE proper has been divided into two categories: AS (generalized NCSE) and focal NCSE [1]. Several case reports have described patients with recurrent and unprovoked focal NCSE with impairment of consciousness, exhibiting psychiatric symptoms as the main seizure type [3, 6]. AS has been subclassified as typical AS, occurring under a setting of idiopathic generalized epilepsy (IGE), or atypical AS, occurring in patients with symptomatic generalized epilepsy. Typical AS may occur sporadically as part of many IGE syndromes, but it can also occur in a recurrent fashion as the main seizure type [7]. In a group of 13 adult patients, Panayiotopoulos et al. [8] described an IGE syndrome characterized by phantom absences (mild ictal cognition impairment associated with brief, generalized spike-and-wave discharges), infrequent GTCS of usually late onset, and frequent AS episodes in about half of the cases. Genton et al. [4] described a series of 11 patients exhibiting recurrent AS as the primary seizure type, with onset in adolescence or adulthood. They referred to this condition as "absence status epilepsy" and reported good seizure control with VPA but stated that it was commonly misdiagnosed owing to its unusual clinical presentation and atypical EEG findings, which often led to the use of inappropriate drugs [4]. Our patient presented some clinical features overlapping with those of patients with Genton's "absence status epilepsy," although both the ictal and interictal EEG findings were not unusual in patients with the "absence status epilepsy" described by Genton et al. [4].

Clinicians, including psychiatrists, should consider NCSE in the differential diagnosis of interictal psychosis when patients with suspected epilepsy with unknown seizure type repeatedly present with transient psychiatric symptoms. Furthermore, the possibility of recurrent and unprovoked NCSE with late onset, such as AS, should be considered. The diagnosis should be confirmed with EEG findings of ongoing or repetitive nonconvulsive seizures. In the intensive care unit, the use of cEEG has been strongly recommended in critically ill patients [9]. Sutter et al. [10] reported that the sensitivity of cEEG for diagnosing NCSE increases over the first 48 h in the intensive care unit. However, the use of cEEG is challenging in psychiatry settings, since both EEG devices and staff familiar with the procedure are limited and patients with NCSE mimicking psychoses are not always able to cooperate during long-term monitoring. Routine EEGs arising from psychiatric referrals have limited value in clinical practice [11, 12]. A retrospective study of 187 consecutive EEG referrals from psychiatry found that only 1 EEG recording showed unequivocal evidence of an epileptogenic focus and that EEG results were not diagnostic in any of the 33 patients showing aggressive behavior [11]. Another retrospective study of 240 patients with acute psychotic episodes described that 7 patients had interictal spikes, but no ictal epileptiform activity was recorded [12]. The authors claimed that a routine EEG might not provide additional benefits to the clinician as a screening tool when evaluating patients with acute psychosis [12].

In our patient, urgent EEG with HV activation at the beginning of an acute confusional episode revealed ongoing seizure activity, although multiple prior routine EEGs (including bedside EEGs performed within 5 days of the presentation) failed to detect interictal or ictal epileptic discharges. The unfortunate timing of these routine EEGs during interictal phases or the lack of HV activation may explain these results (bedside EEGs at psychiatry wards in Japan are often performed without HV activation). It remains unclear whether the HV activation directly provoked the NCSE. However, there are several case reports of NCSE induced by HV activation [13–15], and the reproducible EEG findings (i.e., high-amplitude slow waves after HV activation) in our patient may explain the contribution of HV activation to the diagnosis of NCSE.

In conclusion, clinicians should consider NCSE in the differential diagnosis of interictal psychosis when patients with epilepsy whose seizure type is unknown repeatedly present with transient psychiatric symptoms. Additionally, urgent EEG with HV activation performed during an acute episode may help detect NCSE.

Statement of Ethics

The patient has provided written informed consent for the publication of this case report.

Disclosure of Statements

The authors of this study have no conflicts of interest to disclose.

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Author Contributions

All authors made substantial contributions to the study. G. Taniguchi examined the patients, participated in the treatment of the patient, and drafted the manuscript. K. Masaki performed urgent EEG and seizure interview. S. Kondo participated in the treatment and reviewed the manuscript. M. Yumoto and K. Kasai revised the manuscript for important intellectual content.

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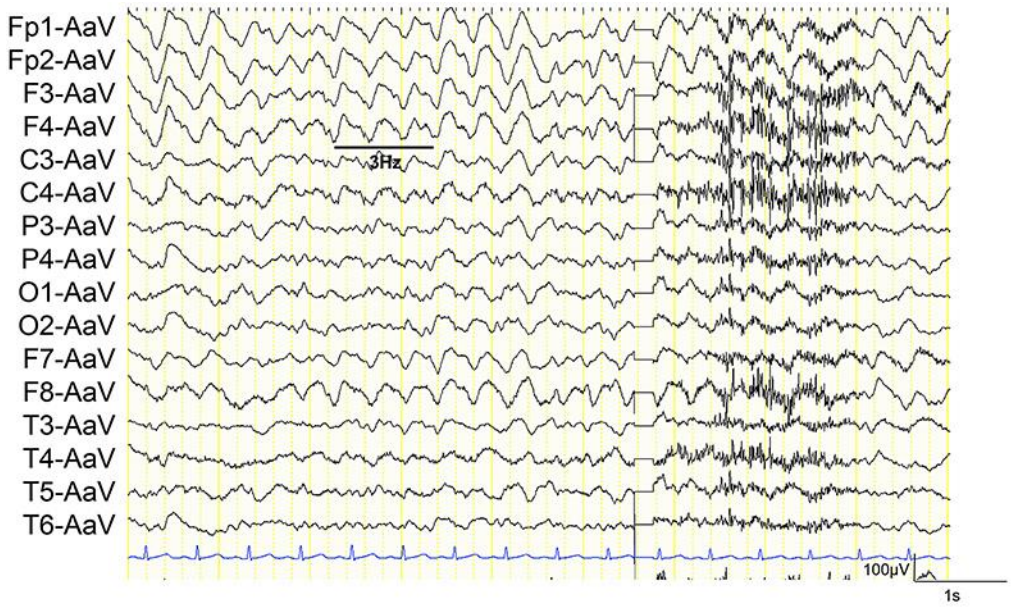

Fig. 1. EEG showing 3-Hz rhythmic delta activity at 2 min post termination of hyperventilation activation. The average of the two earlobe electrodes, A1 and A2, is taken as reference. Slow waves appear predominantly in the bi-frontal region.

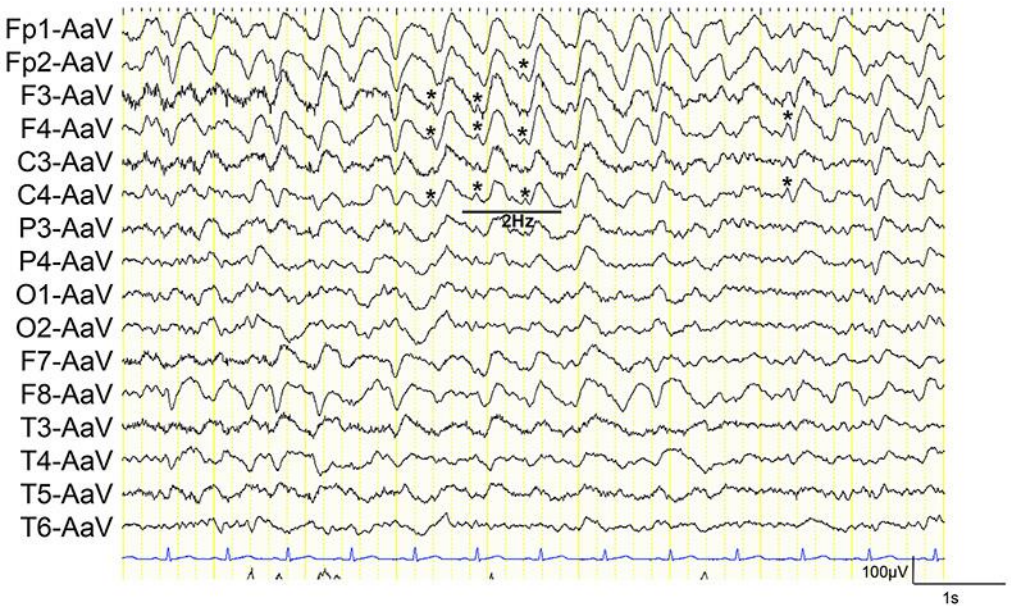

Fig. 2. EEG showing 2-Hz rhythmic delta activity with superimposed sharp waves (several marked with asterisks) at 3 min post termination of hyperventilation activation. The average of the two earlobe electrodes, A1 and A2, is taken as reference. The amplitude of the sharp wave is small and monophasic.

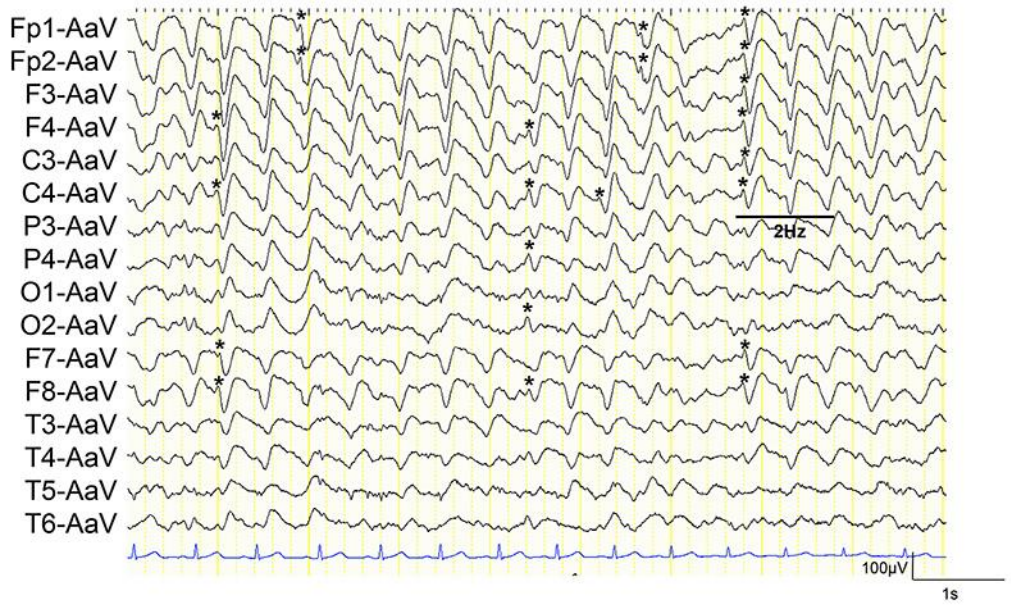

Fig. 3. EEG showing 2-Hz generalized rhythmic delta activity with superimposed sharp waves (several marked with asterisks) at 5 min post termination of hyperventilation activation. The average of the two earlobe electrodes, A1 and A2, is taken as reference. The morphology changed to biphasic while the peak-to-peak (i.e., negative peak to positive peak) amplitude increased.