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Case Report

Nonconvulsive status epilepticus in the elderly associated with newer antidepressants used at therapeutic doses: A report of three cases☆,☆☆

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ABSTRACT

Classic antidepressants have been known to induce convulsive seizures and nonconvulsive status epilepticus (NCSE). On the other hand, many reports have emphasized the safety of novel antidepressants. However, we encountered three cases of NCSE in the elderly associated with the use of newer antidepressants at therapeutic doses.

All three patients were male and were 73 years of age or older. One patient was recently diagnosed with temporal lobe epilepsy and treated with low-dose lamotrigine. In all patients, newer antidepressants were initiated because of depressive symptoms. After titrating to therapeutic doses (paroxetine 20 mg/day, sertraline 50 mg/day, and combination of sertraline 50 mg/day and mirtazapine 30 mg/day in one patient each), impaired consciousness appeared. Electroencephalography (EEG) showed generalized slow waves with intermittent spike–slow-wave complexes. Intravenous injection of antiepileptic drugs improved EEG findings and clinical symptoms. After discontinuance of the abovementioned antidepressants, NCSE did not recur in any of patients. These reports raise the question of whether the newer antidepressants, like classic antidepressants, might also induce NCSE in the elderly, even when used at therapeutic doses. Physicians should consider monitoring for possible NCSE when using newer antidepressants in patients who may have low drug tolerability. Active continuous video-EEG monitoring is essential when behavioral and psychological symptoms or change in consciousness level is suspected.

1. Introduction

Nonconvulsive status epilepticus (NCSE) is clinically diagnosed as a prolonged epileptic condition with diminished level of consciousness and behavioral and/or mental abnormalities, but without major convulsive movements, accompanying epileptiform discharges on electroencephalography (EEG) [1,2]. Nonconvulsive status epilepticus may occur not only in patients with epilepsy but also in adults with no previous history of epilepsy [1,2]. According to some reports, a number of medications including cephalosporins, fluoroquinolones, penicillins, and psychotropics may induce NCSE [2–5].

Classic antidepressants have been known to induce NCSE and convulsive seizures [3,4]. On the other hand, many reports have emphasized the safety of novel antidepressants such as selective serotonin reuptake inhibitors (SSRI), serotonin and norepinephrine reuptake inhibitors (SNRI), and noradrenergic and specific serotonergic antidepressants (NaSSA) [6–8]. However, we encountered three cases of NCSE in the elderly associated with the use of newer antidepressants (paroxetine, sertraline, and mirtazapine) at therapeutic doses. We, therefore, reviewed the safety of antidepressant use in the elderly with respect to convulsive seizures and NCSE.

☆ Parts of this article are based on two case reports previously reported in Japanese in *Jpn. J. Psychiatr. Treat., 2013; 28: 365–372* and *J. Jpn. Epil. Soc., 2007; 25: 10–15*.
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2. Case presentation

2.1. Case 1 (this case report is based on a case report first reported in J. Jpn. Epil. Soc., 2007; 25: 10–15 in Japan)

A 76-year-old, previously neurologically healthy man with depression was treated with paroxetine 10 mg/day combined with quazepam 15 mg/day and alprazolam 1.2 mg/day. Two days after the paroxetine dose was increased to 20 mg/day, tremor of both upper limbs and episodic disturbance of consciousness accompanying impaired dexterity occurred. Conventional EEG recording showed frontal-dominant generalized slow-spike and slow-wave complexes on EEG, correlating with impaired consciousness (Fig. 1a). After intravenous injection of 2.5 mg of diazepam (DZP), spike–slow-wave complexes disappeared, and clinical symptoms were ameliorated (Fig. 1b). After paroxetine was discontinued, treatment with phenytoin (PHT) resulted in complete resolution of the disturbed consciousness and abnormal EEG, and these symptoms did not recur even after PHT was tapered and discontinued. We diagnosed this case as paroxetine-induced NCSE. During follow-up for 7 years, he has never had a relapse of NCSE.

2.2. Case 2 (this case is based on a case report first reported in Jpn. J. Psychiatr. Treat., 2013; 28: 365–372 in Japan)

A 73-year-old man with depression had a history of anxiety disorder since 69 years of age. Combination therapy of sertraline 50 mg/day and mirtazapine 15 mg/day was started for hypochondriac symptoms and severe insomnia. Five days after titrating the mirtazapine dose to 30 mg/day, his family noticed that he responded poorly to conversation and occasionally stopped during movement with a vacant stare. At presentation to the emergency room, examination showed disturbed consciousness, myoclonus, and tremor resembling catatonic symptoms. Conventional EEG demonstrated generalized slow waves with intermittent spike and slow-wave complexes. Intravenous injection of 5 mg of DZP improved EEG findings and resolved clinical symptoms. Because the effect of DZP was transient and the catatonic symptoms recurred, he was admitted to our hospital. After admission, long-term video-EEG recording was started, which showed continuous slow background activity and generalized, frontally predominant spike or polyspike-and-wave discharges during a catatonic episode (Fig. 1c). We obtained new information that he developed the same symptoms while taking amitriptyline 100 mg/day at the age of 69, albeit acting via a different neurotransmitter mechanism, which supports a diagnosis of NCSE triggered by antidepressant. Nonconvulsive status epilepticus was completely resolved with intravenous injection of phenobarbital 750 mg (Fig. 1d). Sertraline and mirtazapine were tapered and discontinued. The antiepileptic drug (AED) was then discontinued, and there has been no relapse during follow-up for 2 years.

2.3. Case 3

A 76-year-old man had onset of seizures at the age of 73, but the seizures were not evaluated, and he was treated for dementia. He presented at our hospital at the age of 76. Detailed clinical examinations and EEG led to a diagnosis of temporal lobe epilepsy. He was admitted to our hospital because of severe depressive symptoms. During titration of lamotrigine (LTG), depression deteriorated, and suicidal ideation also increased. Therefore, sertraline 25 mg/day was started. After titrating the sertraline dose to 50 mg/day combined with LTG 25 mg/day and nitrazepam 5 mg/day, he became markedly anorexic and appeared dazed, and his movements became more sluggish than usual. These symptoms suggested aggravated depressive symptoms. Two days after the sertraline dose was increased, EEG was obtained for differential diagnosis and revealed irregular unsteady alpha rhythms. The next day, EEG was performed again as the final screening for electroconvulsive therapy, which showed frontal, right temporal-dominant slow-wave rhythm gradually increasing in amplitude to form slow waves and spikes. Correlating with EEG changes, the level of cognition fluctuated between reduced awareness and complete unresponsiveness. His movements stopped when high-voltage slow waves and spikes became diffuse.

Intravenous DZP temporarily normalized the EEG findings and level of consciousness. The patient was diagnosed with NCSE (and electroconvulsive therapy was canceled), and he was monitored carefully with long-term video-EEG (Fig. 2).

Two days after sertraline was discontinued, clinical symptoms and EEG findings were resolved, while the LTG dose was increased to 200 mg/day for the purpose of treating his depressive mood. However, approximately one month after that episode, his depression worsened. The patient was treated with intravenous infusion of clomipramine 25 mg and oral mirtazapine 15 mg. Under careful observation, NCSE did not relapse, and depressive symptoms were ameliorated.

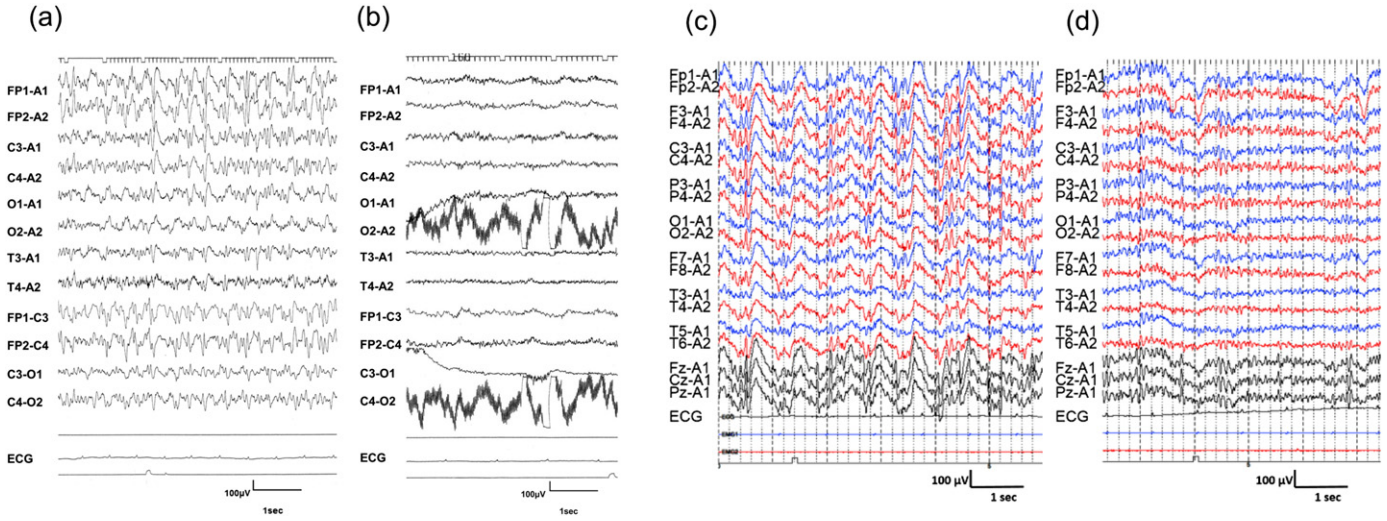

Fig. 1. Electroencephalograms (EEG) before and after treatment with antiepileptic drug treatment in Cases 1 and 2. (a) Case 1 while on paroxetine 20 mg/day. EEG was recorded during altered state of consciousness. Spike and slow-wave complexes are observed. (b) Case 1 recorded approximately 170 s after starting intravenous injection of 2.5-mg diazepam. Spike and slow-wave complexes are no longer observed. (c) Case 2 while on sertraline 50 mg/day and mirtazapine 30 mg/day. EEG was recorded during a catatonic-like episode. Continuous slow background activity and generalized, frontally predominant spike or polyspike-and-wave discharges are observed. (d) Case 2 after intravenous injection of 750-mg phenobarbital. Epileptiform discharges are no longer observed.

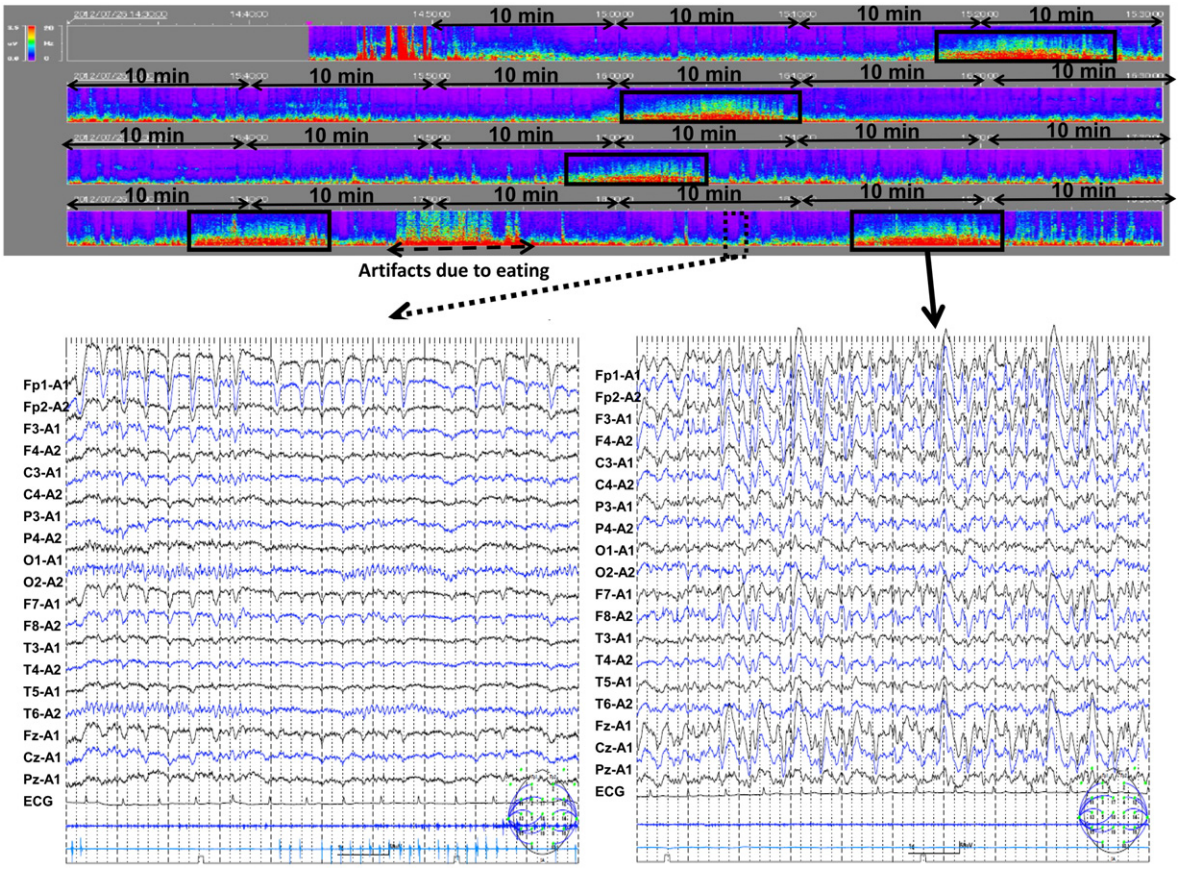

Fig. 2. Color density spectral array (CDSA) for the EEG data of Case 3. On the CDSA, time is shown on the X axis and frequency (range: 0 to 20 Hz) on the Y axis. The frequency-specific power from 0 to 3.5 Hz was visually represented using a color scale, with blue representing low power and light blue, green, yellow, and red representing successively higher power. In this case, seizure activity (emphasized in square) typically lasts 8–10 min and recurs every 30–50 min.

3. Discussion

3.1. NCSE precipitated by antidepressants

We have presented three cases of elderly men with NCSE associated with the newer antidepressants at therapeutic doses. Most antidepressants are considered to have a propensity to lower the seizure threshold. Classic antidepressants (clomipramine, maprotiline, bupropion, mianserine, and amitriptyline) are known to induce NCSE and convulsions in some patients [2–5]. By contrast, a PubMed search found only a few case reports of seizures associated with newer antidepressants [9–11]. To the best of our knowledge, this is the first case report of proven NCSE associated with the newer antidepressants.

People with epilepsy are well known to have a high rate of depressive symptoms [8]. Moreover, the presence of depressive symptoms may have a greater adverse effect than epileptic seizures on the patient's quality of life [12]. Therefore, there is growing interest regarding depression in people with epilepsy. As a result, an increasing number of reports support the view that patients with epilepsy with depression should be treated actively with antidepressants [7,8]. Considering the effect on seizure threshold, these reports recommend novel antidepressants such as SSRIs, SNRIs, and NaSSAs instead of classic agents such as tricyclic antidepressants [7,8]. Furthermore, a report even proposed that novel antidepressants possess anticonvulsant rather than proconvulsant actions [6].

However, in the absence of reports evaluating the seizure threshold in clinical studies of elderly patients or using aged animal models, the safety of novel antidepressants regarding their effects on epileptic seizure threshold in the elderly remains debatable. Currently, it is considered desirable to use these newer agents with caution. This view is supported by a cohort study investigating the safety of antidepressants for treating depression in elderly patients, which has indicated that newer antidepressants are not necessarily safer than classic agents [13].

3.2. Difficulty in diagnosing NCSE in elderly patients

The diagnosis of NCSE is particularly challenging in elderly patients because clinical symptoms may be very subtle and, sometimes, difficult to differentiate from usual behaviors or psychiatric disorders [1]. Furthermore, many elderly persons already have comorbidities that cause “stupor”, “amnesia”, “delirium”, and “confusional episodes”. In particular, concurrent psychiatric diseases such as depression and dementia may complicate the diagnosis [1,14]. As there are no specific clinical and radiographic findings for NCSE, a diagnosis often relies on EEG findings [2]. A standard routine EEG may not always detect NCSE because of the variability of electrographic seizure patterns. Electrographic and clinical seizure activity may occur not only continuously but also intermittently [15]. As Fig. 2 illustrates (Case 3), some types of NCSE in older patients occur at relatively constant intervals. Additionally, postictal confusion lasts for 1–2 h or occasionally longer in an elderly patient without any other clinical signs suggestive of NCSE. Therefore, the rate of diagnosis of NCSE might be increased greatly if continuous video-EEG monitoring were used in suspected cases. The analysis of such monitoring can be facilitated by techniques such as color density spectral array (CDSA), also termed a color spectrogram, which is a quantitative EEG display tool that permits easy recognition of NCSE in prolonged EEG recording. In CDSA, fast Fourier transformation (FFT) is used to convert raw EEG into a time-compressed and color-coded display.

As shown in Fig. 2 and illustrated in the report of Friedman et al. [15], CDSA is a useful tool for identification of NCSE in older patients.

Because of the difficulty in diagnosing NCSE, this condition is most probably underrecognized in clinical practice. Delay in NCSE diagnosis and prolonged seizure activity may lead to aspiration pneumonia, falls, and other accidents, which are associated with increased mortality [2,14].

4. Conclusion

Like classic antidepressants, newer antidepressants also may be associated with NCSE in the elderly, even when used at therapeutic doses. In view of the apparent association between NCSE and the commencement of newer antidepressant drugs that has been illustrated by these three case reports, it is recommended that when such medication is commenced in the elderly, that the patient be monitored closely for impaired awareness and, if this is observed, that EEG monitoring be performed to determine whether this is attributable to NCSE.

Disclosures

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

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