Case Report/*Olgu Sunumu*

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# A Case of Tigecycline-Associated Nonconvulsive Status Epilepticus

## Tigesiklin İlişkili Nonkonvulsif Status Epileptikus Vakası

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**ABSTRACT**

Antibiotics, widely used in intensive care units, are generally well-tolerated but may cause adverse effects, including neurotoxicity. Nonconvulsive status epilepticus (NCSE) is a rare but severe neurotoxic effect of antibiotics, often requiring electroencephalogram (EEG) for diagnosis. This report presents an 80-year-old woman who developed NCSE after tigecycline administration for a suspected intra-abdominal infection. Despite initial antibiotic therapy, her condition deteriorated, presenting with confusion, mutism, and unresponsiveness. Neuroimaging showed no abnormalities, but EEG confirmed NCSE, characterized by generalized slow-wave activity and sharp wave discharges. Intravenous benzodiazepine was administered and clinical status and EEG findings improved rapidly. Tigecycline was discontinued, and antiepileptic therapy initiated, leading to a full recovery. This case underscores the importance of early recognition and management of NCSE in critically ill patients. Clinicians should remain vigilant for neurotoxic side effects of antibiotics like tigecycline, especially in vulnerable populations, as timely diagnosis and intervention are crucial for better outcomes.

**Keywords:** Tigecycline, nonconvulsive status epilepticus, electroencephalogram

**ÖZ**

Yoğun bakım ünitelerinde yaygın olarak kullanılan antibiyotikler genellikle iyi tolere edilir, ancak nörotoksisite de dahil olmak üzere yan etkilere neden olabilir. Nonkonvülzif status epileptikus (NCSE), antibiyotiklerin nadir ancak ciddi bir nörotoksik etkisidir ve genellikle tanı için elektroensefalografi (EEG) gerektirir. Bu rapor, olası bir intra-abdominal enfeksiyon nedeniyle tigecycline verilen 80 yaşındaki bir kadında gelişen NCSE vakasını sunmaktadır. Başlangıçta antibiyotik tedavisi uygulanmasına rağmen hastanın durumu kötüleşmiş; konfüzyon, konuşamama ve tepkisizlik belirtileri göstermiştir. Nörogörüntüleme incelemelerinde herhangi bir anormallik saptanmamış, ancak EEG'de yaygın yavaş dalga aktivitesi ve keskin dalga deşarjları ile karakterize NCSE tespit edilmiştir. Hastaya intravenöz benzodiazepin uygulanmış ve klinik durumu ile EEG bulgularında hızla düzelme sağlanmıştır. Tigecycline tedavisi kesilmiş, antiepileptik tedavi başlanmış ve hasta tamamen iyileşmiştir. Bu vaka, kritik hastalarda NCSE'nin erken tanı ve tedavisinin önemini vurgulamaktadır. Klinisyenler, özellikle hassas hasta gruplarında, tigecycline gibi antibiyotiklerin nörotoksik yan etkilerine karşı dikkatli olmalıdır, çünkü zamanında tanı ve müdahale, daha iyi sonuçlar için hayati öneme sahiptir.

**Anahtar sözcükler:** Tigesiklin, nonkonvulsif status epileptikus, elektroensefalogram

## INTRODUCTION

Antibiotics are widely used in intensive care units (ICU) in conjunction with other therapies. While these antimicrobial agents are generally well-tolerated, they can still cause side effects, which may be dose-dependent or idiosyncratic. Common adverse effects of many antibiotics include diarrhea and vomiting; however, the less frequent occurrence of neurotoxic effects on the central nervous system is not as widely recognized (1). One such example is nonconvulsive status epilepticus (NCSE), which is a rare neurotoxic effect of antibiotics (2).

Although the definition and classification of NCSE have evolved over the years, NCSE is often described as prolonged seizure activity without visible convulsions (3-6). In the recent classification by the International League Against Epilepsy (ILAE), NCSE is categorized based on altered consciousness levels and clinical and electroencephalogram (EEG) characteristics (3). Altered mental status may range from mild confusion to coma. In the ILAE classification, NCSE is subdivided into NCSE with coma and NCSE without coma (5). Continuous seizure activity may be accompanied by behavioral changes (6). These changes may be subtle, such as facial, trunk, or limb twitches, eye or head deviation, autonomic signs, au-

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tomatisms, and bizarre behaviors (wandering, hallucinations, fear, ecstasy, etc) (2-6). The diagnosis of NCSE requires EEG since the clinical symptoms are heterogeneous and often subtle (4,5). In most cases, a test-therapeutic intravenous anti-seizure medication (ASM) is useful to determine the uncertain EEG patterns.

Consequently, NCSE can be misdiagnosed as other intercurrent illnesses, results in delays in diagnosis and higher mortality rates. Early recognition and prompt treatment of this condition are essential for improving outcomes.

Tigecycline, a tetracycline-class antibacterial agent approved by the Food and Drug Administration in 2005, is used to treat polymicrobial multidrug-resistant infections, including both gram-positive and gram-negative bacteria (7). While generally well-tolerated, there are few reports in the literature of neurotoxic side effects associated with tigecycline.

This case report describes an 80-year-old woman who developed NCSE following tigecycline administration.

## CASE PRESENTATION

The patient, an 80-year-old woman with no known history of additional diseases, underwent surgery for ileus. On the fourth postoperative day, while under general surgery care, she was transferred to the intensive care unit due to a deterioration in her overall condition. Laboratory tests showed increased levels of C-reactive protein (>280 mg $L^{-1}$), procalcitonin (>40 ng $mL^{-1}$), and lactate (>5 mmol $L^{-1}$). Consequently, the antibiotics ceftriaxone and metronidazole were administered for four days, then discontinued, and meropenem was initiated.

The patient exhibited no clinical improvement despite a four-day course of meropenem treatment. An intra-abdominal infection was suspected, and the patient was prescribed tigecycline and fluconazole in addition to her existing regimen. Two days after initiating tigecycline and fluconazole, the patient's behavior deteriorated further, progressing to severe mutism. No meningeal irritation symptoms or lateralizing neurological symptoms were observed. The patient became confused, non-verbal, with her eyes open, and was unresponsive to commands.

A computed tomography (CT) scan of the cranium and diffusion-weighted imaging (DWI) revealed no acute neurological abnormalities. Liver function tests, kidney function tests, and electrolyte levels were all within normal ranges.

After obtaining a neurology consultation, an EEG was performed. The EEG revealed continuous generalized slow-wave activity and sharp wave discharges at approximately 3 Hz, prominent in bilateral temporal regions. The administration of intravenous benzodiazepines (10 mg) resulted in a substantial improvement in the EEG within a few minutes (Figure 1). Within two hours, the patient became alert and could respond to simple questions with a Glasgow Coma Scale of 15.

The patient was diagnosed with NCSE, subsequently, levetiracetam 1000 mg $day^{-1}$ was initiated. Tigecycline was discontinued, while fluconazole and meropenem were continued for the suspected intra-abdominal infection. The patient's clinical symptoms improved approximately six days after the diagnosis of NCSE, the discontinuation of tigecycline, and discharge from the ICU.

## DISCUSSION

The incidence and prevalence of NCSE vary across studies due to differences in study populations, diagnostic criteria, and access to EEG (8-11). On the other hand, patients in an intensive care unit have a higher incidence of NCSE. Seriously ill patients can develop NCSE with an acute condition such as electrolyte disturbances, endocrine abnormalities, acute ischemic stroke, intracranial hemorrhage, hypoxic-ischemic encephalopathy following cardiac arrest, and traumatic brain injury (11,12). The patient did not have a history of cardiac arrest, hypoxia, or electrolyte imbalances. Although brain CT and DWI imaging showed no acute abnormalities, these imaging results did not clarify the patient's clinical presentation.

Recognizing NCSE in elderly patients can be challenging, especially if they have no prior history of seizures. Disruption of the blood-brain barrier (BBB) has been observed in conditions such as uremia. This disruption facilitates the penetration of drugs into the central nervous system (CNS), which may result in CNS toxicity and conditions including NCSE (13). Despite this, the patient had no history of renal failure. We suspect that the patient's septic condition, secondary to an intra-abdominal infection, may have led to antibiotic toxicity through BBB disruption.

Electroencephalogram evaluation is crucial, as it is essential for accurate and timely diagnosis (14). In this case, NCSE was diagnosed based on EEG findings and clinical improvement after ASM administration. EEG patterns of NCSE can sometimes complicate the differentiation between NCSE and profound metabolic encephalopathy (15,16). The administration of intravenous benzodiazepines resulted in immediate clinical and EEG improvement of the confusional state. Positive responses to ASM treatment confirm the diagnosis of NCSE (17). Early detection and diagnosis are vital, as delays can increase morbidity or mortality (18).

Tigecycline has been approved for utilization in adult patients suffering from complicated skin and skin structure infections (excluding diabetic foot infections), complicated intraabdom-

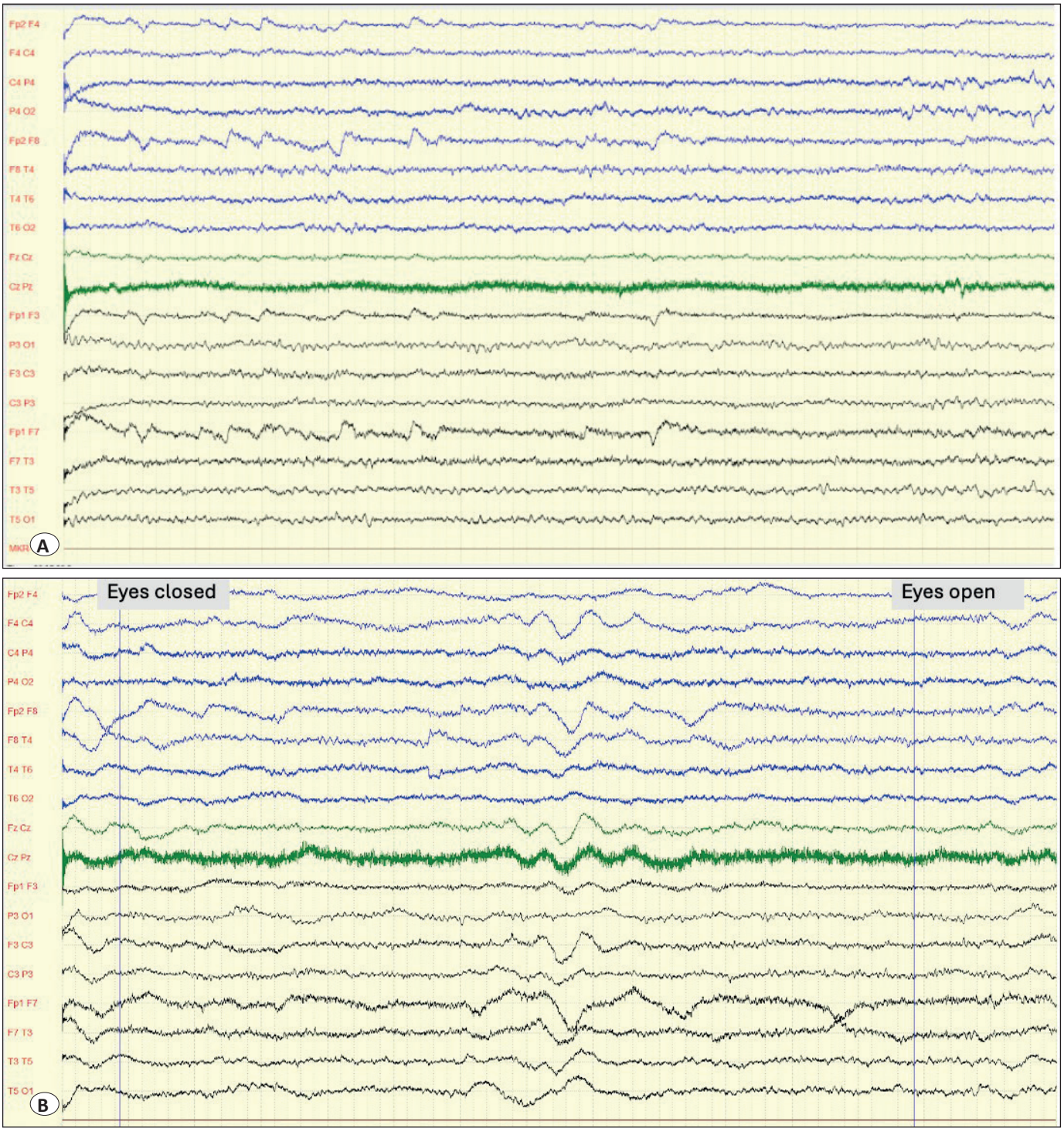


**Figure 1.** The Electroencephalograms of the case before **(A)** and after **(B)** diazepam injection. Electroencephalogram revealed continuous generalized slow-wave activity and sharp wave discharges at approximately 3 Hz, prominent in the bilateral temporal regions **(A)**. A few minutes after intravenous diazepam administration, the EEG showed a prominent alpha rhythm at 8-13 Hz observed with eyes closed, which is suppressed upon eye-opening **(B)**.

inal infections, and community-acquired bacterial pneumonia (19). The medication has been predominantly associated with gastrointestinal adverse effects, including nausea, vomiting, and diarrhea, particularly in adult patients aged 18 to 50 years (20). Other reported side effects include pancreatitis, acute generalized exanthematous pustulosis, local reactions at the injection site, liver enzyme abnormalities, thrombophlebitis, pruritus, fever, mitochondrial dysfunction-related acute metabolic acidosis, abdominal pain, headache, cholestasis, jaundice, and Stevens-Johnson syndrome (21-23). Neurological side effects associated with tigecycline have not been widely reported, making our case particularly instructive. We believe that disruption of the BBB, potentially exacerbated by the patient's septic condition, may have contributed to the neurological effects observed in our patient.

Awareness of the potential neurotoxic effects of various antibiotics, including tigecycline, is crucial for early detection and management of such complications. Vigilance in critically ill patients is essential to identify potentially serious but reversible adverse effects of antibiotic therapy, especially with antimicrobial agents.

The symptoms of NCSE often manifest several days after the initiation of antibiotic treatment, with a median delay of four days, and can be easily overlooked in ICU patients. These symptoms can worsen if appropriate strategies to facilitate drug removal are not employed (e.g., discontinuation, interruption, or dialysis) or if interventions such as antiepileptic medication are not implemented. Clinicians should maintain a high index of suspicion to ensure timely detection, especially in patients with predisposing factors. Inflammatory conditions, organic acid accumulation, and renal dysfunction may increase the risk of BBB disruption, allowing greater CNS penetration of antibiotics (24,25).

In conclusion, changes in mental status in patients with postoperative complications and medical illnesses may indicate or lead to toxic metabolic changes, infections, hypoxia, or cerebral stroke. Nonconvulsive status epilepticus should be considered when evaluating mental status changes, and its underlying causes should be thoroughly investigated.

## AUTHOR CONTRIBUTIONS

**Conception or design of the work:** SA
**Data collection:** SA
**Data analysis and interpretation:** BG
**Drafting the article:** BG
**Critical revision of the article:** KC
**Other (study supervision, fundings, materials, etc):** KC
The author (SA, BG, KC) reviewed the results and approved the final version of the manuscript.

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