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CASE REPORTS/CASE SERIES

Non-convulsive status epilepticus in the postanesthesia care unit following meningioma excision

État de mal épileptique non convulsif en salle de réveil après excision d'un méningiome

Jagan Devarajan, MD · Amira Mohammed Siyam, MD · Andreas V. Alexopoulos, MD · Robert Weil, MD · Ehab Farag, MD

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Abstract

Purpose *Non-convulsive status epilepticus (NCSE) is an underdiagnosed clinical entity in which electrical seizures occur with subtle or no overt clinical manifestations. It can cause delayed recovery from anesthesia and constitutes an important differential diagnosis for prolonged postoperative unconsciousness. This condition can be diagnosed only by electroencephalogram (EEG), and the institution of early treatment is associated with better prognosis. This case is presented to illustrate the occurrence of this rare clinical entity in a patient who had undergone extradural surgery.*

Clinical features *An elderly female with no history of seizures or predisposing factors for convulsions underwent an uncomplicated left frontotemporal craniotomy for excision of an extradural meningioma. She was unresponsive following surgery, which could not be explained by the imaging and laboratory investigations. A subsequent EEG demonstrated periodic epileptiform discharges in lateralized left hemispheric distribution characteristic of seizures. The seizures were not effectively prevented by prophylactic fosphenytoin; however, the patient responded slowly to intravenous levetiracetam, which is known to be a more effective treatment for NCSE. The patient had no predisposing factors for the development of seizures and was undergoing an extradural surgery.*

Conclusions *This case illustrates NCSE and emphasizes the importance of obtaining an electro-encephalogram early following craniotomy to diagnose any changes in the patient's mental status. This case also emphasizes that institution of early treatment is important to assure better prognosis.*

Objectif *L'état de mal épileptique non convulsif est une réalité clinique sous-diagnostiquée pendant lequel des crises électriques surviennent tout en ne présentant que peu de manifestations cliniques apparentes, voire aucune. Cet état peut entraîner un retard dans la récupération après l'anesthésie et constitue un diagnostic différentiel important d'inconscience postopératoire prolongée. L'état de mal épileptique non convulsif ne peut être diagnostiqué que par électroencéphalogramme (EEG), et un traitement précoce est associé à un meilleur pronostic. Ce cas est rapporté afin d'illustrer la survenue de cette entité clinique rare chez une patiente ayant subi une chirurgie extradurale.*

Éléments cliniques *Une femme âgée ne présentant aucun antécédent de crise épileptique ni aucun facteur prédisposant de convulsion a subi une craniotomie frontotemporale gauche simple pour exciser un méningiome extradural. Elle était non réceptive aux stimuli après la chirurgie, un état que l'imagerie et les examens de laboratoire n'ont pu expliquer. Un EEG réalisé postérieurement a révélé des décharges épileptiformes périodiques dans la distribution hémisphérique gauche latéralisée, caractéristiques de crises épileptiques. Les crises n'ont pas été prévenues de façon efficace avec l'administration prophylactique de fosphénytoïne; toutefois, la patiente a progressivement réagi au lévétiracétam par voie intraveineuse, un agent connu comme étant un traitement plus efficace pour les états de mal épileptique non convulsifs. La patiente ne présentait aucun facteur*

J. Devarajan, MD · A. M. Siyam, MD · E. Farag, MD (✉)
Anesthesiology Institute, Cleveland Clinic, Cleveland, OH, USA
e-mail: farage@ccf.org

A. V. Alexopoulos, MD
Epilepsy Center, Cleveland Clinic, Cleveland, OH, USA

R. Weil, MD
Brain Tumor and Neuro-Oncology Center (BTNC), Cleveland Clinic, Cleveland, OH, USA

prédisposant l'exposant à un risque de crise épileptique et subissait une chirurgie extradurale.

Conclusion *Ce cas illustre un état de mal épileptique non convulsif et souligne l'importance de réaliser un électroencéphalogramme rapidement après une craniotomie afin de diagnostiquer tout changement dans l'état mental du patient. Ce cas souligne aussi que l'amorce précoce d'un traitement est importante afin de garantir un meilleur pronostic.*

Non-convulsive status epilepticus (NCSE) is characterized by ongoing brain seizures lasting for more than 30 min in the absence of overt clinical motor or sensory manifestations.[1] Subtle clinical features, such as myoclonic jerks or nystagmus may accompany the electrographic discharges of NCSE, and they are often difficult to appreciate. Non-convulsive status epilepticus can be diagnosed only with electroencephalography (EEG) and should be managed under continuous EEG monitoring. It is estimated that NCSE accounts for 20% of cases of status epilepticus.[2] However, the actual incidence is unknown, given that NCSE remains an underdiagnosed and misunderstood condition. Non-convulsive status epilepticus is commonly identified in critically ill patients, especially those who have suffered traumatic brain injury[3] and subarachnoid hemorrhage.[4] Non-convulsive status epilepticus has been increasingly reported in other populations of critically ill patients as well. Recent studies have estimated that approximately 8-48%[5-8] of comatosed patients in the intensive care unit may present with electrographic evidence of NCSE, depending on the group of patients studied. Delayed occurrences of this syndrome after several hours have been reported following skull base surgery;[9] however, the occurrence of non-convulsive seizures and NCSE in the immediate postoperative period is rare and may go unnoticed unless an EEG establishes the presence of seizure activity. These patients frequently present as having a depressed level of consciousness, abnormal behaviour, or perception disturbances. The latter could be confused easily with prolonged effects of volatile anesthetic agents, muscle relaxants, narcotics, postoperative ischemia/stroke, and other metabolic insults. The aim of this case report is to demonstrate the occurrence of this rare syndrome in the immediate postoperative period following extradural cranial surgery. The patient's Health Care Power of Attorney gave written informed consent for publication of this article.

Case presentation

An 83-yr-old 60 kg right-handed female presented to her primary care physician for workup of rapid cognitive decline. She was observed as having problems with her memory, speech, and executive functions, and changes in her personality, tantamount to reports by her children. Her medical history was negative for seizures or other neurological abnormalities, and her neurological exam was normal and revealed no signs of increased intracranial pressure. As part of workup for suspected dementia, a computed tomography (CT) scan and subsequent magnetic resonance imaging showed a 5.5-cm contrast-enhancing extradural tumour in the left fronto-temporal region with mass effect consistent with meningioma. The patient was referred for neurosurgical evaluation, and surgical intervention was recommended. On the day of surgery, the patient received a single "prophylactic" dose of fosphenytoin 1,000 mg intravenously. She received midazolam 2 mg as premedication, and anesthesia was induced with propofol 150 mg and fentanyl 50 μg. A onetime dose of rocuronium 50 mg was used for tracheal intubation. She did not receive additional rocuronium or fentanyl during the remainder of the surgery. Before incision, the patient received cefazolin 2 g, and she subsequently underwent an uneventful surgery under balanced anesthesia with sevoflurane supplemented by remifentanil. A phenylephrine infusion was used to maintain a mean arterial pressure (MAP) $\geq$ 70 mmHg, and her MAP was never $<$ 60 mmHg at any point in time during surgery. A left fronto-temporal craniotomy was performed without difficulty; the lesion was extradural in location, and the cortical brain surface was not manipulated. A gross total resection of the tumour was performed, which included a 1-cm circumferential rim of normal dura.

At the end of surgery and after elimination of the inhalational anesthetic agents, the patient remained unresponsive to commands; she was hemodynamically stable and breathing spontaneously. Her trachea was extubated and she was then transferred to the postanesthesia care unit for further management where she continued to be minimally responsive to painful stimuli. Initial laboratory tests revealed normal blood urea nitrogen, creatinine, liver function, coagulation panel studies, and ammonia level; the hematocrit was 31.7% and the phenytoin level was 10.1 $\mu g \cdot mL^{-1}$ (normal 10.0-20.0), which was measured one hour after surgery. Her ionized calcium was 1.19 $mmoL \cdot L^{-1}$ and her magnesium was 2.2 $mmoL \cdot L^{-1}$. She was neither hypoglycemic nor grossly hypercarbic. A head CT scan was obtained, which showed complete resection of the tumour and no intracranial lesions (Fig. 1); there was a minimal amount of air with no mass effect. The patient's EEG, which was performed later, showed paroxysmal activity lasting two to three minutes and occurring every three to five minutes (Fig. 2, Panels A-D). She was given an intravenous loading dose of levetiracetam 1,000 mg and a supplementary loading dose of fosphenytoin 300 mg phenytoin sodium equivalents.

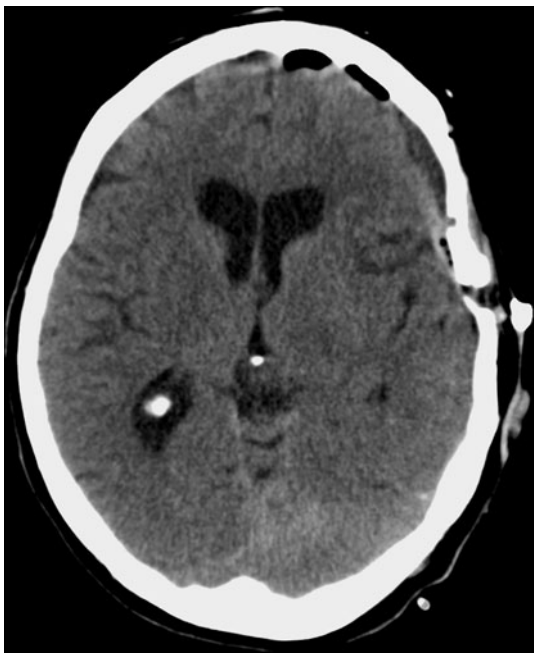

Fig. 1 Computed tomography scan of brain in the immediate postoperative period -1

She was also maintained on a levetiracetam 1,000 mg *iv* and fosphenytoin 100 mg every eight hours. After eight hours of initiating treatment, the seizures slowly decreased in intensity and duration. The seizures lasted 40-60 sec, occurred every 45-60 min, and persisted for another five hours. Paroxysmal lateralized epileptiform discharge-like patterns appeared occasionally over the left frontal region with evolving ictal patterns in the same hemisphere. Sharp wave activity was also present, which originated from the left frontal region. The patient had no clinically apparent seizure manifestations other than the aforementioned impaired level of consciousness. Her phenytoin level was measured at 18.8 $\mu g \cdot mL^{-1}$, and a level > 10 $\mu g \cdot mL^{-1}$ was maintained. Continuous EEG monitoring showed that the duration of electrographic seizure activity decreased to 40-60 sec, as did the frequency of seizures to once every 45-60 min until it gradually disappeared in the early morning of the first postoperative day. The morning after surgery, the patient was awake, alert, and followed commands, and she was ambulating by that afternoon. No seizures were noted 13 hr after surgery as a result of treatment with levetiracetam. The patient was monitored continually during the entire period using both video and electrical EEG. Levetiracetam was later changed to valproate delayed release 750 mg *po* in the morning and 1,000 mg at night due to a flushing reaction with the administration of a subsequent dose of levetiracetam. She was thereafter maintained on both phenytoin and valproate during the remainder of her hospital stay. At her one-month follow up, the patient and her family reported no symptoms that would indicate seizure activity.

Discussion

The delayed recovery from anesthesia could be attributed to several causes. In this case, we were able to rule out common causes such as hypothermia, prolonged effects of muscle relaxants, and opioids. The patient was administered only 50 μg of fentanyl and 50 mg of rocuronium at the induction of anesthesia, and remifentanil and sevoflurane were used for the rest of the surgery, which lasted 265 min. Moreover, at the time of recovery, three half-lives were elapsed since the administration of fentanyl and midazolam. Neuromuscular monitoring showed complete recovery from muscle relaxants. Remifentanil was stopped about 45 min before the patient was transferred to the recovery room, and sevoflurane was at 0% ten minutes after the end of surgery. Her final temperature was 35.6, which changed to normal as soon as she arrived in the recovery room. The patient was not given centrally acting anticholinergic medications to suspect anticholinergic syndrome. There were no episodes of hypoxia and prolonged durations of hypotension to suspect cerebral hypoxia or hypoperfusion. As she had cranial surgery, she was not given flumazenil or naloxone so as to avoid precipitating seizures. Moreover, at the time of recovery, three half-lives were elapsed since the administration of fentanyl and midazolam. The next differential diagnosis was an intracerebral event due to thrombosis or hemorrhage, which was subsequently ruled out by CT scan. The CT scan showed expected postoperative changes consisting of a small amount of left frontal pneumocephalus and a small amount of high attenuation blood by-products subjacent to the craniotomy. The findings were not consistent with her unconsciousness. An EEG was later obtained that showed evidence of non-convulsive status epilepticus in the patient.

Non-convulsive status epilepticus is a condition that has raised considerable controversy amongst physicians and researchers regarding its definition and classification. Due to the heterogeneity of its clinical symptomatology and the polymorphism of its EEG presentation, this syndrome is often missed and is generally underdiagnosed. The critically ill[6] and the elderly[10,11] are two distinct groups of patients that have been cited repeatedly in the literature as being prone to developing NCSE. There also seems to be a gender predilection towards females. The diagnosis of NCSE is difficult in the geriatric population since it is often a diagnosis of exclusion; however, early detection is essential to prevent further medical and neurological sequelae. A high degree of suspicion and early intervention is important, as delay in diagnosis and initiation of treatment has been associated with poor prognosis.

Symptoms of NCSE range from subtle muscle twitches to generalized coma, which might be confused with prolonged action of anesthetic agents. Generalized

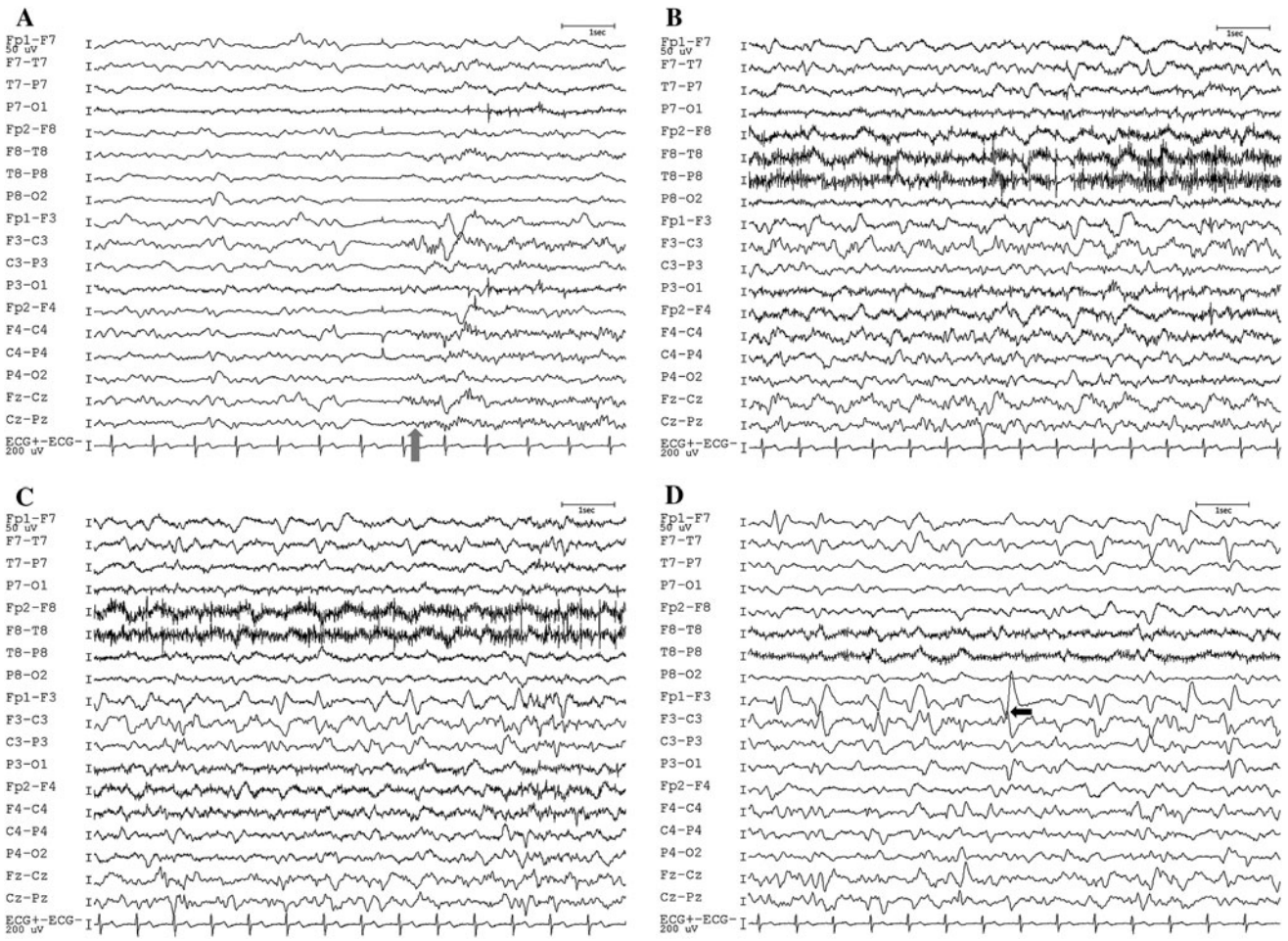

Fig. 2 *Panel A* Ten-second scalp electroencephalogram (EEG) tracings (longitudinal bipolar montage) obtained during the patient's initial EEG recording on postoperative day 0. Onset of an electrographic seizure in the middle of this ten-second page, punctuated by the appearance of low amplitude fast activity in the midline as well as left and right predominantly central derivations (gray arrow). This is preceded by a one-second diffuse attenuation of the preceding EEG activities – note, the diffuse slow activity at the beginning of the page with additional continuous polymorphic delta waves slowing in the left hemisphere, maximum in the left frontal region, consistent with the presence of a structural lesion in this area. *Panel B* Evolving ictal pattern 60 sec after onset (continuation of the same electrographic seizure displayed in panel A) characterized by the presence of a rhythmic high amplitude delta wave slowing seen bilaterally, but with a left hemisphere preponderance, along with an overriding alpha activity seen in the midline as well as the left and right central regions. *Panel C* Continuation of the same electrographic seizure six minutes after onset (electrographic status epilepticus). The record is characterized by a sharply contoured high amplitude slow activity that now appears more sequestered within the left hemisphere in the presence of diffusely slow abnormal EEG background activities. *Panel D* Continuation of the same electrographic seizure 12 min after EEG onset, with appearance of semi-periodic broad-based epileptiform activity (paroxysmal lateralized epileptiform discharge-like pattern, "periodic lateralized epileptiform discharges") in the left hemisphere, maximum over the left frontocentral region (dark arrow), in the presence of a diffusely slow abnormal EEG background

spike-and-wave and generalized polyspike-and-wave discharges are the most common EEG manifestations. However, several other EEG patterns have also been associated with NCSE,[12] including typical spike-and-wave, atypical spike-and-wave, multiple spike-and-wave, rhythmic delta waves with intermittent spikes, periodic epileptiform discharges, and triphasic waves. Even so, in some cases, excessive and overly aggressive treatment of seizures has also been reported to result in worsening of outcomes.[10] Several studies in animals have clearly shown the importance of treating non-convulsive seizures, which may be associated with increased metabolic, oxidative, and excitotoxic stress on brain at-risk,[13-15] and thus may result in irreversible neuronal injury. The management of NCSE is less clear in patients in whom NCSE presents as a manifestation of a serious underlying illness. A poor prognosis following NCSE is often due to the concurrent underlying illness, and the additional effect of NCSE is supplemental if not additive. Certain subsets of patients with NCSE may be more easily treatable, such as our

patient who presented in the immediate postoperative period and had no intracranial lesions at the time of seizures; therefore, rapid intervention may prevent subsequent neurological damage and intensive care unit complications.

This is a rare case of NCSE occurring in the immediate postoperative period that presents as acute encephalopathy following intracranial but extradural surgery in a patient with no known history of seizures. Upon literature review, a case was reported of multiple focal neurological deficits occurring two days after intracranial surgery for gross total resection of an oligodendroglioma, which carried the resection to the sulcus anterior to the motor strip.[16] Based on EEG findings, that patient was also thought to have NCSE.

In our case, NCSE manifested with unresponsiveness and impaired level of consciousness, manifestations that were clearly distinct from the patient's preoperative presentation. Her symptoms of depressed sensorium in the postoperative period that were far in excess of what one might generally expect, coupled with a normal appearing CT scan and essentially normal intraoperative and postoperative laboratory values, including normal sodium, blood urea nitrogen, creatinine, and carbon monoxide levels in serum, led us to diagnose subclinical status epilepticus. Her recovery of consciousness and responsiveness following treatment with phenytoin and levetiracetam, which correlates directly with cessation of EEG seizure activity on continuous EEG monitoring, further supports the diagnosis of NCSE. Non-convulsive status epilepticus may be (relatively) difficult to treat with anticonvulsant medications, especially in elderly patients.[17] Indeed, it took about 12 hr for the disappearance of abnormal electrical discharges after appropriate therapy was instituted, despite an initial therapeutic postoperative level of phenytoin. A single bolus dose of phenytoin had been given preoperatively for "prophylaxis" as per our standard neurosurgical protocol. This case also illustrates that a single adequate dose of phenytoin may not completely prevent the development of seizures.

Delayed occurrence of NCSE has also been recorded after skull base surgery;[9] therefore, the above manifestations could have been triggered secondary to the actual surgery. One could argue that EEG appearance could have resulted from various types of acute or subacute insults, such as ischemia, trauma, or hypoxic injury. This argument, however, is not supported by the neuroimaging data and the patient's subsequent clinical course – namely the disappearance of paroxysmal EEG patterns and electrographic seizures, which was accompanied by improvement in the patient's mental status following antiepileptic medications. There are also reports in the literature of NCSE secondary to administration of tramadol and cephalosporin antibiotics in renal failure patients.[18] Our patient did receive one gram of cefazolin as surgical antibiotic prophylaxis at the beginning of the case. Nevertheless, cephalosporin-induced NCSE is highly unlikely in this case since the patient exhibited symptoms several hours following single-dose administration. Furthermore, her renal function was normal pre- and postoperatively.

With regard to treatment options, many patients with NCSE show response to an initial treatment with benzodiazepines such as lorazepam. A retrospective study performed in Germany compared the course of NCSE in a group of patients treated with intravenous levetiracetam with a "control" group of patients[19] who received the conventional intravenous medications (including benzodiazepines) that have been used traditionally for the management of NCSE. Similar outcomes in terms of symptom improvement and cessation of seizure activity were noted in the two groups. Notably, the group treated with levetiracetam suffered from considerably fewer side effects. Furthermore, the use of parenteral levetiracetam has been beneficial in the treatment of benzodiazepine-refractory status epilepticus.[20] Intravenous anesthetics, such as pentobarbital, midazolam, and propofol,[17] are the next line of defence in some refractory NCSE treatment algorithms. In any event, optimal recovery is more likely due to early consideration, diagnosis, and treatment.

We have described a case of *de novo* NCSE in an elderly female with no history of seizures. The entity occurred in the immediate postoperative period after uncomplicated resection of a convexity meningioma without any overt direct brain manipulation. NCSE may be more common than reported and should be considered early in the differential diagnosis of any patient with unexplained impairment of consciousness after intracranial surgery. Early recognition and treatment is more likely to improve outcomes.

Competing interests None declared.

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