Postoperative nonconvulsive encephalopathic status: identification of a syndrome responsible for delayed progressive deterioration of neurological status after skull base surgery

Clinical article

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Object. Over a 10-year period, the authors have observed a rare but recurring syndrome manifested by a delayed, postoperative, progressive decline in the level of consciousness to deep coma that is time-limited to several days with abrupt awakening. Extensive evaluation and workup demonstrated an abnormality on continuous electroencephalographic monitoring that implied nonconvulsive status epilepticus after the exclusion of structural, perfusion, infectious, or metabolic causes. This state has been very refractory to treatment with antiepileptic medication. In this article, the authors raise the awareness of this syndrome and its diagnosis, management, and outcome.

Methods. The authors reviewed the medical records of a cohort of 7 patients who exemplified this syndrome who were treated during the last 5 years.

Results. All 7 patients were women with a mean (± SD) age of 55 ± 15 years. The mean duration of surgery was 8.9 ± 1.8 hours. All patients had a stereotypical course of delayed progressive decline in their level of consciousness after surgery (average 3.3 ± 4.3 days) leading to deep coma. The unconscious state was time-limited, lasting on average 17.3 ± 13.7 days. Continuous electroencephalographic monitoring demonstrated a generalized abnormality with periodic discharges and abundant slow delta activity. A rather abrupt awakening occurred a few days after cessation of electrographic seizure activity. Structural, vascular, infectious, or metabolic causes were excluded based on an extensive workup.

Conclusions. In this study, the authors delineate and raise the awareness of an unusual syndrome. Recognition of this syndrome is important as a cause for delayed coma after surgery. The authors stress the need for respiratory, hemodynamic, and nutritional support for these patients until recovery. The origin of this syndrome remains enigmatic and is likely to be multifactorial with a prominent pharmacological role related to anesthetic agent or medication in a setting of craniotomy that is associated with alteration of the blood-brain barrier.

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Key Words • antiepileptic medication • coma • cranial surgery • postoperative nonconvulsive encephalopathic status • seizure • status epilepticus

Brain tumors and brain surgery may cause seizures and epilepsy. Status epilepticus has been defined as continuous seizure activity of ≥ 2 sequential seizures without full recovery of consciousness between seizures. In NCSE, electrographic changes consistent with continuous seizure activity are associated with coma or obtundation with minimal or no motor manifestations. Nonconvulsive status epilepticus accounts for ~ 20% of all cases of status epilepticus and is increasingly recognized in comatose patients who are admitted to a general ICU. Nonconvulsive status epilepticus is also well documented in patients with subarachnoid hemorrhage. This condition is easily missed among patients with altered consciousness after a craniotomy, especially if early continuous EEG evaluation is not performed because attention is focused on other causes.

A variety of EEG patterns have been described in patients with NCSE. The management of this condition may vary based on the clinical status of the patient. The recommended treatments include benzodiazepines and...
other longer-acting anticonvulsant medications to immediately halt and control abnormal electrical activity.\textsuperscript{2,27} The response to treatment with antiepileptic drugs has been inconsistent and disappointing.\textsuperscript{29} A poor outcome has been noted in patients in the ICU who were diagnosed with NCSE\textsuperscript{3,29,38} or associated with subarachnoid hemorrhage.\textsuperscript{7,31}

Our observations differed from the syndrome of NCSE in ill patients noted above in that prognosis for recovery was excellent. Patients with this new syndrome do not have an underlying systemic or neurological disorder, and despite a deep comatose stage, all examination results were negative.

**Methods**

Seven patients who underwent supratentorial craniotomies for skull base lesions suffered from a nearly identical pattern of postoperative deterioration in consciousness leading to coma. These patients underwent an extensive workup to find a cause, and constitute the cohort that we have gathered to recognize and analyze the syndrome that we have referred to as PONES. Hospital records, diagnostic studies, laboratory evaluations, and EEG examinations were retrospectively reviewed. All patients underwent craniotomies for resection of lesions located at the skull base, lasting a mean time of 8.9 ± 1.8 hours (Table 1).

No patient had a prior history of seizure. All surgical procedures were performed under general anesthesia. Isoflurane and fentanyl were the only anesthetic medications administered to every patient. The neuroanesthesia protocol included induction with a short-acting muscle relaxant, thiopental, fentanyl, and midazolam, sometimes along with propofol. Anesthesia was maintained during the procedure with the use of isoflurane as the inhalational agent, sometimes in combination with nitrous oxide and a continuous infusion of either fentanyl or propofol, and occasionally remifentanil. At induction, all patients received prophylactic antibiotics that were continued for up to 72 hours postoperatively. Our antibiotics of choice have been vancomycin and cefazidime due to their effectiveness against nosocomial infections caused by *Staphylococcus* and *Pseudomonas*. Six of the 7 patients received antiepileptic medications during surgery. Fluid overload during and after surgery was avoided to minimize potential brain edema.

Following recovery from anesthesia and regaining consciousness after surgery, all patients were noted to be neurologically intact. After a latency period averaging 3.3 ± 4.3 days, an excessive drowsiness was first noted but patients continue to be easily arousable. These patients were progressively less responsive over the next 12–24 hours, falling into a comatose state without a focal neurological deficit. An extensive workup did not reveal a cause for this comatose state. Imaging modalities used included CT scanning, MR imaging with diffusion or perfusion/diffusion, and MR arteriography. A full laboratory workup evaluated electrolytes, metabolic profile, arterial blood gases, and antiepileptic medication levels. In addition, a lumbar puncture was performed to rule out an infectious cause. Transcranial Doppler ultrasonography was used to detect the presence of arterial vasospasm in the anterior and middle cerebral arteries. A 24-hour continuous video/ scalp EEG monitoring system was provided to assess patients for abnormal seizure activity. A neurology consultation was obtained to assist with the investigation and management of the possible causes of the diagnosis.

**Results**

Structural lesions were excluded based on serial imaging. Infectious causes were also excluded based on an evaluation of blood cultures, a CSF profile, or chest radiographs. Vasospasm or vascular occlusion was absent based on MR arteriography or transcranial Doppler ultrasonography assessment. Metabolic reasons were also eliminated after blood test results. The only consistent finding was continuous electrical discharges on electroencephalography consistent with NCSE (Table 2). On detailed video monitoring and review, some of these patients exhibited subtle ictal motor manifestations such as perioral twitching, finger twitching, or foot tapping.

Every patient was transferred to the neurosurgical ICU for a workup, close neurological observation, and support. Most patients required reintubation to protect their airway. Electroencephalograms of these patients showed generalized 1- to 3-Hz delta wave activity, with some patients

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs)</th>
<th>Diagnosis</th>
<th>Surgical Approach</th>
<th>Length of Op (hrs:mins)</th>
<th>Postop Latency</th>
<th>Duration of Coma (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>clival chordoma</td>
<td>middle fossa craniotomy</td>
<td>6:25</td>
<td>8 hrs</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>39</td>
<td>orbital cavernous hemangioma</td>
<td>lt supraorbital craniotomy</td>
<td>6:45</td>
<td>2 days</td>
<td>5.6</td>
</tr>
<tr>
<td>3</td>
<td>52</td>
<td>sphenoid wing adenocystic carcinoma</td>
<td>lt cranioorbital zygomatic</td>
<td>9:30</td>
<td>3 days</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>58</td>
<td>petroclival meningioma</td>
<td>rt anterior &amp; posterior petrosectomy</td>
<td>5:15 (stage I) 10:14 (stage II)</td>
<td>2 days</td>
<td>26</td>
</tr>
<tr>
<td>5</td>
<td>56</td>
<td>choroid plexus papilloma</td>
<td>rt suboccipital craniotomy</td>
<td>5:50</td>
<td>13 hrs</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>69</td>
<td>craniohypophysealgioma</td>
<td>rt petrosal approach</td>
<td>10:00</td>
<td>1 day</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>67</td>
<td>suprasellar meningioma</td>
<td>bifrontal craniotomy</td>
<td>11:15</td>
<td>4 days</td>
<td>1</td>
</tr>
</tbody>
</table>

* All patients were female, and all showed complete recovery after the coma.
The most frequent pattern was that of rhythmic generalized bursts of sharply contoured triphasic waves, with abundant delta activity.

Cephalosporins were withdrawn after the diagnosis of NCSE was made; additional antiepileptic medications were instituted. Antiepileptic medication levels were increased to supratherapeutic ranges, and a combination of multiple medications was used, including phenytoin, carbamazepine, phenobarbital, valproic acid, levetiracetam, and topiramate. Most patients received 2 or 3 antiepileptic medications concurrently with no improvement in their clinical status. This period of coma spontaneously and rather abruptly resolved days after its onset spontaneously.

**Illustrative Case**

This 39-year-old female (Case 2) underwent a supraorbital craniotomy with uneventful resection of an orbital apex cavernous hemangioma without intradural dissection. Total anesthesia time was 7 hours and 50 minutes. Medications administered during surgery included isoflurane, nitrous oxide, midazolam, fentanyl, cisatracurium, vancomycin, ceftazidime, propofol, dexamethasone, glycopyrrolate, neostigmine, albumin, furosemide, neosynephrine, and ondansetron. Immediately postoperatively the patient was awake, alert, oriented, and doing well. She became somewhat drowsy in the morning of the 1st postoperative day, but she continued to be arousable, follow commands readily, and interact while awake. A measurement of her blood electrolytes revealed a sodium level of 140 meq/L, potassium level of 4.0 meq/L, blood urea nitrogen of 12 mg/dl, creatinine level of 0.9 mg/dl, and osmolality of 290 mOsm/kg. Over the course of the day, she progressively became more lethargic. A head CT scan was unremarkable except for a mild pneumocephalus. On the 2nd postoperative day, she was no longer following commands. Later in the day, she was comatose and showed bilateral dilated pupils. An emergency repeat CT scan was unchanged from the previous day’s scan. The patient was subsequently reintubated for airway protection and electroencephalography performed on this day revealed generalized polymorphic slow wave activity, with frequent runs of hypersynchronous bilateral 2-Hz high-voltage delta activity with sharp waves, often exhibiting a triphasic configuration (Fig. 1). The patient was therefore placed on continuous EEG monitoring. At this time, the patient’s phenytoin level was 16.1 µg/ml, because she had received a loading dose of phenytoin on the 1st postoperative day. She subsequently received a loading dose of phenobarbital. A transcranial Doppler ultrasonography evaluation demonstrated normal flow velocities in all vessels.

During the 3rd postoperative day, her phenytoin level was 34.2 µg/ml and her phenobarbital level was 2.9 µg/ml. She remained comatose. Magnetic resonance imaging/arteriography with diffusion weighted imaging performed on this day showed no evidence of acute infract or vascular occlusion. A lumbar puncture revealed a normal CSF profile. Vancomycin and ceftazidime were discontinued. Electroencephalography showed generalized polymorphic slow wave activity, with persistent 1- to 2-Hz medium-voltage delta activity. The hypersynchronous delta activity from the day before had resolved. The 1- to 2-Hz medium-voltage delta activity continued to dominate the electroencephalography until the 9th postoperative day.

Over the next few days, the patient also started receiving carbamazepine; we maintained therapeutic to supratherapeutic antiepileptic drug levels. The patient became awake on the 8th postoperative day. She was discharged from the hospital a few days later, neurologically intact. On the day prior to discharge, her antiepileptic drug levels were 3.2 µg/ml of carbamazepine, 21.4 µg/ml of phenytoin, and 25.1 µg/ml of phenobarbital.

**Discussion**

**Identification of a Syndrome**

The almost identical clinical manifestation and course were striking and repetitive in the patients that we observed. This similarity warrants the awareness of this distinguishing syndrome from other disorders that lead to coma postoperatively, including NCSE by β-lactam antibiotics. Underlying causes of postoperative progressive decline in mental status include postoperative hematomas; epidural, subdural, and intracerebral hematomas; cerebral infarct, particularly venous or embolic; vasospasm; meta-

### TABLE 2: Summary of EEG findings

<table>
<thead>
<tr>
<th>Case No.</th>
<th>EEG Findings</th>
<th>EEG Seizure Classification</th>
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<tbody>
<tr>
<td>1</td>
<td>frequent prolonged runs w/ a gradual bilat (L&gt;R) predominantly anterior build up of rhythmic evolving slow waves (theta and delta)</td>
<td>generalized</td>
</tr>
<tr>
<td>2</td>
<td>bursts of high amplitude, generalized, repetitive triphasic waves of 1-2 Hz intermixed w/ rhythmic slow waves</td>
<td>generalized</td>
</tr>
<tr>
<td>3</td>
<td>bursts of generalized, irregular, mixed frequency activity w/ abundant repetitive sharp waves &amp; sharp/slow wave complexes</td>
<td>generalized</td>
</tr>
<tr>
<td>4</td>
<td>bursts of generalized, irregular, mixed frequency activity w/ abundant repetitive sharp waves &amp; sharp/slow wave complexes</td>
<td>generalized</td>
</tr>
<tr>
<td>5</td>
<td>brief runs of rt frontal sharp &amp; slow waves</td>
<td>focal</td>
</tr>
<tr>
<td>6</td>
<td>persistent sharp waves in a multifocal distribution</td>
<td>generalized</td>
</tr>
<tr>
<td>7</td>
<td>diffuse slowing w/ lt frontal sharp waves</td>
<td>focal</td>
</tr>
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</table>
another clinical syndrome that should be considered in the differential diagnosis. It is characterized by a progressive postoperative decline in mental status leading to deep coma. We have referred to this syndrome as PONES, which occurs in a delayed fashion after craniotomy and appears to resolve spontaneously with a good prognosis (Table 3).

This syndrome is confirmed based on EEG changes and exclusion of other causes responsible for a decreased level of consciousness and coma. This syndrome is not caused by other common nonstructural causes of nonconvulsive seizures such as hypoxia or by metabolic disturbances such as hypocalcemia, hypoglycemia, hypomagnesemia, hyponatremia, and alcohol withdrawal. Early continuous EEG monitoring must be used for the recognition of PONES manifested by prolonged subclinical status epilepticus. Postoperative nonconvulsive encephalopathic status is similar to NCSE in that it can only be diagnosed with certainty using EEG recording. Therefore, electroencephalography is an indispensable test when PONES is clinically suspected. Short EEG studies may not be always sufficient; prolonged continuous recordings are often needed to diagnose this entity and to subsequently monitor the response to treatment. However, some EEG patterns encountered in the context of PONES as per NCSE may be nonspecific; the determination of whether they are actually ictal may be difficult. In such situations, correlation with the clinical scenario can help. In this patient series, the presence of abundant periodic sharply contoured triphasic waves, often organized in prolonged bursts, was attributed to likely NCSE after ruling out metabolic/hypoxic encephalopathies. We feel obliged to treat these symptoms with antiepileptic drugs, but the response is usually disappointing, even when using therapeutic levels of multiple antiepileptic medications. The clinical recovery also lags behind the EEG recovery.

Search for a Cause

The exact cause of this syndrome is still enigmatic

<table>
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<th>TABLE 3: Patient and treatment phases of PONES*</th>
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<tr>
<td>Phase</td>
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<tr>
<td>------</td>
</tr>
<tr>
<td>clinical</td>
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<tr>
<td>course</td>
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<tr>
<td>findings</td>
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<td>investigative</td>
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* BUN = blood urea nitrogen; TCD = transcranial Doppler.
despite an intense search. The cause is likely to be multifactorial, including blood-brain barrier breakdown or pneumocephalus, but we focused our search on possible pharmacological causes responsible for the syndrome as more known causes were ruled out. Postoperative nonconvulsive encephalopathic status may be a toxic reaction, as the patients make a full recovery that is not correlated in time with the institution and increase of the antiepileptic medications. The medications commonly administered to all of these patients during their hospital course, especially during surgery, included isoflurane, midazolam, sodium thiopental, dexamethasone, vancomycin, ceftazidime, and fentanyl.

Anesthetic Agents

Propofol in subanesthetic doses has been associated with an increase in electrocorticographic seizure activity, but this effect may terminate in minutes.19 Propofol was not used in all our patients who suffered from PONES. In patients with previously known epileptogenic abnormalities, etomidate may increase seizure risk, but this usually occurs among patients with known seizure disorders.20 Only 1 of the patients exhibiting PONES received etomidate.

Enflurane anesthesia may cause delayed postoperative seizures,21,26 but enflurane was not administered to our patients. The delayed effect of enflurane was related to the presence of fluorinated metabolites that may be measured in the urine up to 17 days.2 We used isoflurane in all of our patients suffering from PONES. Because ~ 8% of enflurane and 0.2% of isoflurane is metabolized by the body, the likelihood of isoflurane causing delayed problems due to its fluorinated metabolites is small. After the introduction of isoflurane as an inhalational anesthetic, 2 patients who suffered from generalized seizure activity after isoflurane administration were reported in the literature.18,22 In these cases nitrous oxide, a known epileptogenic drug, was also used. Neither of these 2 patients experienced any seizures during the immediate postoperative period. Subsequent studies in animals and humans demonstrated suppression of cerebral activity by isoflurane, leading to its recommended use in patients with refractory status epilepticus.15,35

Use of Fentanyl

Fentanyl was used for induction of anesthesia in all of our patients. This drug, or one of its congeners (usually remifentanil), was used for maintenance of anesthesia in 50% of our patients with PONES. Fentanyl is metabolized by the liver with subsequent renal excretion. The elimination half-life of fentanyl is between 3 and 4 hours. Remifentanil, on the other hand, is metabolized by plasma esterases, independent of hepatic metabolism or renal excretion, and has an elimination half-life of 8–20 minutes. The potency of remifentanil metabolites has been estimated at 1/2000–1/4000 of the potency of remifentanil itself. Ninety percent of the breakdown products are excreted by the kidney.17 Although originally fentanyl and its breakdown products were suspected, after investigating the pharmacokinetics of fentanyl and its congeners, our suspicion of fentanyl as a cause for PONES was reduced.

Neuromuscular Blocking Agents

Neuromuscular blocking agents used for induction in these procedures included succinylcholine, rocuronium, vecuronium, cisatracurium, and pancuronium. Succinylcholine exhibits an ultra-short duration of action and is metabolized by plasma cholinesterase.8 Pancuronium has a long duration of 120–180 minutes and is excreted by the kidney.21 Pancuronium does have a tendency to redistribute, resulting in lower plasma levels of the drug after first administration, but in the 1 case in which pancuronium was used there was no repeat dosing. Vecuronium and rocuronium are both of intermediate duration, and are both cleared by the liver after a period of ~ 60 minutes. The metabolites of these agents do contain about half the activity of the parent compound, however, these metabolites are also rapidly cleared.36 On the other hand, cisatracurium undergoes Hoffman elimination, which is organ dependent and has a half-life of 25 minutes. The patients in this group all began to have neurological deficits long after the expected elimination time of these agents, and all patients exhibited recovery from these agents, as exhibited by neuromuscular stimulation.

Use of Antibiotics

Penicillin-based antibiotics may be associated with a slightly increased risk of postoperative seizures.34 The seizures presumably caused by this drug occurred within 24 hours after administration, usually terminating in 12 hours. The epileptogenicity of this type of antibiotic may be due to its competitive inhibition against γ-aminobutyric acid.25 The convulsant potential of β-lactam antibiotics including cephalosporins has been investigated by injecting increasing concentrations of these antibiotics into the ventricles of rats while measuring the threshold for seizure activity. In that study, cefazolin was found to have the lowest convulsant dose, about one-fourth of the dose required of benzylpenicillin. The ceftazidime epileptogenic dose fell between ampicillin and meropenem, about 6 times as large as the dose required of benzylpenicillin.10 In renal failure, competitive inhibition of the active transport by a build-up of toxic organic acids may increase antibiotic concentrations in the CSF and induce epileptogenesis.15

Interestingly, ceftazidime and other third- and fourth-generation cephalosporins have rarely been implicated in encephalopathy and NCSE.11,22,25,37 Ceftazidime used for our patients is excreted unchanged by glomerular filtration. This drug may cause NCSE in patients with impaired renal function due to its abnormally high plasma and CSF levels, because the CSF level of ceftazidime is ~ 23% of its blood level. Patients reported in the literature with presumed ceftazidime toxicity underwent a clinical course very similar to that reported in our series. Other studies have reported a decline in patients’ mental status 24–36 hours after administration of ceftazidime. In at least 1 study, similar to our findings, patients presented with progressive disorientation, sometimes associated with mild facial or limb myoclonus, that began 1–10 days after administration of cephalosporin treatment.33

A lack of response to antiepileptic medication has also been documented by other studies. In a report of 10 patients with renal failure who suffered from a syndrome similar to PONES, only 2 patients improved immediately after clonazepam administration whereas 8 others improved
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2–7 days afterward. The reason for a lack of satisfactory response to antiepileptic medication is not clear, however; encephalopathic features of this syndrome may persist despite disappearance of its epileptic features on electroencephalography. This focus on the role of ceftazidime was suspected in retrospective analysis, but unfortunately we have no blood or CSF levels for ceftazidime in our patients. If continuation of antibiotic therapy is necessary in some patients, tobramycin was recommended as a reasonable choice if cephalosporin treatment needed to be halted.

Despite our emphasis on the possible role of β-lactam antibiotics, our patients have a different presentation because none of our patients were in renal failure. All of the patients in this study recovered completely and the period of coma varied significantly.

Electroencephalography Findings

Making the diagnosis of NCSE may be difficult, because the EEG patterns are not typical and may overlap with EEG findings of encephalopathic states. The atypical spike and wave complexes with a triphasic aspect may be confused with the EEG pattern of encephalopathy. Nonconvulsive status epilepticus can only be diagnosed with certainty using EEG recording. Therefore, electroencephalography is an indispensable test when NCSE is clinically suspected. Short studies may not be always sufficient; prolonged continuous recordings are often needed to diagnose this entity and to subsequently monitor the response to treatment. However, some EEG patterns encountered in the context of NCSE may be nonspecific; the determination of whether they are actually ictal may be difficult. In such situations, correlation of the EEG patterns with the clinical scenario can help determine the diagnosis.

Conclusions

Postoperative nonconvulsive encephalopathic status is a rare but distinct syndrome of delayed postoperative coma. After other causes have been ruled out, this syndrome must be considered. It is important, however, to initiate continuous EEG monitoring early, provide full support (hemodynamic, respiratory, and nutritional) during the comatose period, and to realize that, despite the apparent poor condition of the patient, there is a good chance for an excellent recovery.

Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

References


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