PEARLS

- Even when the cause of metabolic coma seems clear, consider an arterial ammonia level.
- Refractory status epilepticus may be due to acute hyperammonemia, and not the more commonly seen calcineurin inhibitor neurotoxicity.
- Hyperammonemia causes brain edema and requires multiple measures to lower it quickly.

CASE REPORT

A 64-year-old woman with familial pulmonary fibrosis underwent bilateral lung transplantation under general anesthesia with midazolam, propofol, and fentanyl. Her post-transplant immunosuppression regimen consisted of prednisone, azathioprine, and tacrolimus. She was initially alert and following commands but on postoperative day 3 became increasingly somnolent, necessitating reintubation. Sodium, renal and liver function tests, and CSF analysis (including opening pressure) were normal. Noncontrast CT scan of the head was unrevealing with no early evidence of cerebral edema. EEG showed diffuse delta with frequent 1- to 2-Hz triphasic waves. Her somnolence was attributed to her tacrolimus level (66.8 ng/mL) and the medication was held with normalization of the level by postoperative day 4. On postoperative day 5, she had persistent arrhythmic twitching of her left arm that within a minute generalized to a full-blown convulsive status epilepticus. Multiple doses of Ativan, totaling 10 mg, and 20 mg/kg PE of fosphenytoin were administered, with cessation of seizures. An ammonia level was obtained and was unreadable at greater than 1,200 μg/dL. AST was 36 U/L. Lactulose, rifaximin, and continuous venous-venous hemofiltration (CVVH) were initiated to normalize the ammonia level and continuous EEG monitoring was initiated. An intraparenchymal intracranial pressure (ICP) monitor was placed but the initial intracranial pressure was 4 mm Hg. Two hours after initial cessation of seizures, she had recurrent left arm twitching, which quickly generalized and was refractory to additional 4 mg/kg PE of fosphenytoin, maximal infusion rates of midazolam and propofol, and ultimately was controlled with pentobarbital infusion at a rate of 5 mg/kg/h, at which point the background changed from a pattern of generalized spike and waves to a completely suppressed background in the 1- to 2-Hz range without reactivity. Clinical seizures became under control within 1 hour after onset. Full resolution of electrographic status epilepticus took 6 hours longer. At that time, propofol and midazolam were stopped. Lactulose, rifaximin, and CVVH were continued and arterial ammonia declined gradually. After arterial ammonia had normalized, pentobarbital was slowly weaned. Her ICP remained below 10 mm Hg with the exception of 2 isolated spikes to 19 mm Hg lasting several minutes each on postoperative days 8 and 9. A repeat CT scan of the head on postoperative day 11 showed lack of gray–white matter differentiation and absence of sulci (pseudo-subarachnoid hemorrhage). When the pentobarbital was no longer detectable in her blood, the patient was declared brain dead.

DISCUSSION

Idiopathic hyperammonemic encephalopathy (IHE) is an uncommon complication of solid organ transplantation (table). It is characterized by abrupt alteration in mental status with mark-
Increased ammonia is a completely unexpected metabolic derangement in patients with organ transplantation other than liver transplantation. There was no evidence of intraoperative hypotension in our patient to explain the hyperammonemia. Seizures have traditionally been linked to IV loading with calcineurin inhibitors, explaining why neurotoxicity, despite trough levels within the anticipated range, was initially considered in our patient. The prevalence of this major complication leading to massive cerebral edema with refractory status epilepticus remains unclear and failure to measure arterial ammonia may lead to underdetection. Although the etiology of this syndrome is not yet fully elucidated, it appears to be multifactorial in nature. Potential contributing factors include pharmacologic agents, underlying enzymatic deficiencies, infection, or highly catabolic conditions. The rare occurrence of IHE in this population may suggest a preexisting defect in the urea cycle stressed by a major transplant procedure. While there are certainly specific anesthetic considerations in patients with a known enzymatic deficiency, hyperammonemia has not been reported to occur in enzymatically normal patients with the anesthetic agents our patient received. The cerebral edema may reflect the osmotic effect of accumulated intracellular glutamine, the primary metabolic product of ammonia metabolism in the brain. Optimal management remains to be formally established. While some patients do recover full neurologic function, the syndrome is frequently fatal. Whether early recognition and treatment of hyperammonemia (with prompt administration of lactulose and nonabsorbable antibiotics, aggressive management of cerebral edema with osmotic agents, hypothermia, and perhaps dialysis devices to accelerate the reduction in serum ammonia concentration) can change the devastating course of the most severe cases remains to be determined.

**AUTHOR CONTRIBUTIONS**

Dr. Hocker: drafting/revising the manuscript, acquisition of data. Dr. Rabinstein: drafting/revising the manuscript, study supervision. Dr. Wijdicks: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, study supervision.

**DISCLOSURE**

Dr. Hocker reports no disclosures. Dr. Rabinstein serves as section editor for Year Book Neurology and Neurosurgery and for Neurocritical Care; and receives research support from CardioNet and Boston Scientific. Dr. Wijdicks serves as the editor-in-chief of Neurocritical Care and receives royalties from The Comatose Patient (2008), Neurological Complications of Critical Illness (2009), and The Practice of Emergency and Critical Care Neurology (2010) (all published by Oxford University Press).

**REFERENCES**


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**Table: Neurologic presentation and outcome of IHE after solid organ transplantation**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Cases</th>
<th>Procedure</th>
<th>Days from transplant to presentation</th>
<th>Presentation</th>
<th>Seizures</th>
<th>Neurologic recovery</th>
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<tbody>
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<td>1</td>
<td>1</td>
<td>Lung transplant</td>
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<td>Agitation and somnolence</td>
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<td>RSE</td>
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<td>9</td>
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<td>Lung transplant</td>
<td>7</td>
<td>Lethargy followed by coma</td>
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<tr>
<td>3</td>
<td>1</td>
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<td>9</td>
<td>Agitation, followed by coma</td>
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<td>None reported</td>
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<tr>
<td>4</td>
<td>1</td>
<td>Combined heart/lung transplant</td>
<td>19</td>
<td>Altered mental status followed by myoclonus, seizures, and coma</td>
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<td>Focal motor Partial</td>
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<tr>
<td>5</td>
<td>6</td>
<td>Lung transplant</td>
<td>5–26</td>
<td>Encephalopathy followed by coma in all patients</td>
<td>3/6 patients</td>
<td>1 Complete; 5 deaths</td>
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<td>Lung transplant</td>
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<td>Confusion and agitation</td>
<td></td>
<td>None reported</td>
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<td>Renal transplant</td>
<td>4</td>
<td>Lethargy and difficulty following commands</td>
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<td>RSE</td>
</tr>
<tr>
<td>Case</td>
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<td>Lung transplant</td>
<td>3</td>
<td>Somnolence followed by coma</td>
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<td>RSE</td>
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</table>

Abbreviations: GCS—Glasgow Coma Scale; IHE—idiopathic hyperammonemic encephalopathy; RSE—refractory status epilepticus.


Pearls & Oy-sters: Status epilepticus from hyperammonemia after lung transplant  
Sara Hocker, Alejandro A. Rabinstein and Eelco F.M. Wijdicks  
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