Late-Onset Ornithine Transcarbamylase Deficiency: Treatment and Outcome of Hyperammonemic Crisis

abstract

Hyperammonemic crises in ornithine transcarbamylase deficiency (OTC) can be associated with devastating cerebral edema resulting in severe long-term neurologic impairment and death. We present an 8-year-old boy who had late-onset OTC deficiency in which early and aggressive management of hyperammonemia and associated cerebral edema, including therapeutic hypothermia and barbiturate-induced coma, resulted in favorable neurologic outcome. Our patient presented with vomiting and altered mental status, and was found to have a significantly elevated serum ammonia level of 1561 μmol/L. Hyperammonemia was managed with hemodialysis, 10% sodium phenylacetate, 10% sodium benzoate, L-arginine, intravenous 10% dextrose, intralipids, and protein restriction. He developed significant cerebral edema with intracranial pressures >20 mm Hg, requiring treatment with 3% saline and mannitol. Despite this treatment our patient continued to have elevated intracranial pressures, which were treated aggressively with non-conventional modalities including therapeutic hypothermia, barbiturate-induced coma, and external ventricular drainage. This therapy resulted in stabilization of hyperammonemia and resolution of cerebral edema. Molecular testing later revealed a hemizygous mutation within the OTC gene. Neuropsychological testing 1 year after discharge showed normal intelligence with no visual-motor deficits, minor deficits in working memory and processing speed, and slightly below average processing speed and executive functioning. Pediatrics 2014;133:e1072–e1076

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KEY WORDS
barbiturates, cerebral edema, hyperammonemia, induced hypothermia, intracranial hypertension, ornithine transcarbamylase deficiency

ABBREVIATIONS
CT—computed tomography
EVD—external ventricular drain
ICP—intracranial pressure
OTC—ornithine transcarbamylase deficiency
UCD—urea cycle disorder

Dr Bergmann conceptualized the case report, drafted the initial manuscript, and critically reviewed and revised the manuscript; Dr McCabe coordinated data collection and critically reviewed and revised the manuscript; Dr Smith critically reviewed and revised the manuscript; Dr Guillaume provided expertise in neurosurgical management and critically reviewed and revised aspects of the manuscript pertaining to neurosurgical intervention; Dr Sarafoglou provided expertise in endocrine and metabolic management and critically reviewed and revised aspects of the manuscript pertaining to endocrine and metabolic intervention; Dr Gupta conceptualized the case report and critically reviewed and revised the manuscript with emphasis on aspects pertaining to critical care medicine, and all authors approved the final manuscript as submitted.

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Ornithine transcarbamylase deficiency (OTC) is an X-linked urea cycle disorder (UCD) with an estimated incidence between 1/14,000 and 1/80,000. Although commonly diagnosed in neonates, patients can present at any age with hyperammonemic crisis owing to environmental stressors. Preceding symptoms are often nonspecific among late-onset cases and include vomiting, altered mental status, hyperammonemia, and cerebral edema in severe cases. As a consequence, the initial presentation may be associated with life-threatening complications owing to unrecognized hyperammonemia. Hyperammonemic crises account for most deaths, although survival has improved with the use of alternative pathway therapy such as sodium phenylacetate and sodium benzoate. Current estimates suggest that 53% to 91% of males and 74% to 98% of females who have OTC deficiency survive mild hyperammonemic episodes with prompt recognition of symptoms. Here we present a patient who had late-onset OTC deficiency, severe hyperammonemic crisis, and refractory cerebral edema, in whom early recognition and aggressive management resulted in a favorable neurologic outcome. The Institutional Review Board waived the need for informed consent.

**PATIENT PRESENTATION**

**Initial Presentation**

Our patient was an 8-year-old boy who had normal development, growth, and protein intake. Two days before admission he developed emesis and increasing somnolence. The following morning he displayed altered mental status with ataxia. There were no recent illnesses, diet changes, ingestions, travel, or animal exposure.

He presented to an outside emergency department where he was minimally responsive and developed worsening mental status requiring intubation. Initial laboratory investigations were notable for an elevated serum osmolality and anion gap acidosis (Table 1). Head computed tomography (CT) scan demonstrated no hemorrhage, mass effect, or evidence of increased intracranial pressure (ICP) (Fig 1A). MRI on day 1 displayed restricted diffusion in the thalamus, suggesting possible infarct, normal venous flow, and no edema or structural abnormality. EEG at that time demonstrated diffuse slowing without epileptiform activity. His ammonia level returned significantly elevated to 1351 μmol/L, and on repeat, 1561 μmol/L. Metabolic studies obtained before initiation of therapy returned at a later date and were notable for significantly elevated urine orotic acid and glutamine levels (Table 1), and ketosis on urine organic acid screening. Continuous venovenous hemodialysis was initiated on day 1, with improvement of serum ammonia to 386 μmol/L at 1 hour, 98 μmol/L at 3 hours, and 89 μmol/L by 7 hours. He was treated with parenteral ammonia scavengers, including sodium phenylacetate (5.5 g/m²), sodium benzoate (5.5 g/m²), L-arginine (200 mg/kg), intravenous dextrose, and protein restriction. On day 2 he was transferred to our institution for management of a presumed UCD.

On presentation, he displayed upper extremity extensor posturing, positive Babinski sign, and normal pupillary light reflex. Initial laboratory values were notable for hypernatremia, elevated serum osmolality, and hyperammonemia, for which parenteral therapy was continued (Table 1). Head CT scan demonstrated early cerebral edema (Fig 1B). A Codman ICP monitor was placed, and his ICP varied from 16 mm Hg to 30 mm Hg during the first several hours.

**ICP Management**

Cerebral edema was managed with 3% saline continuous infusion, mannitol, sedation, maintenance of euthermia with a cooling blanket, and dopamine and norepinephrine to maintain cerebral perfusion pressure >50 mm Hg. He continued to have increased ICP (>20 mm Hg) refractory to conventional treatment. He was loaded with pentobarbital (5 mg/kg) on day 2 and a continuous drip was titrated to 5 mg/kg/h to induce coma. Therapeutic

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>ED Laboratory Values (reference range)</th>
<th>Post-HD Laboratory Values (reference range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mmol/L)</td>
<td>141 (135–145)</td>
<td>151 (133–143)</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.5 (3.5–5.5)</td>
<td>3.6 (3.4–5.3)</td>
</tr>
<tr>
<td>Chloride (mmol/L)</td>
<td>103 (98–106)</td>
<td>121 (98–110)</td>
</tr>
<tr>
<td>Bicarbonate (mmol/L)</td>
<td>11 (18–26)</td>
<td>19 (20–32)</td>
</tr>
<tr>
<td>Urea nitrogen (mmol/L)</td>
<td>8.9 (5.2–6.4)</td>
<td>5.4 (1.8–8.6)</td>
</tr>
<tr>
<td>Creatinine (μmol/L)</td>
<td>99.1 (30.5–65.6)</td>
<td>61.0 (13.3–46.5)</td>
</tr>
<tr>
<td>Glucose (μmol/L)</td>
<td>7.9 (3.3–5.8)</td>
<td>7.7 (3.2–5.5)</td>
</tr>
<tr>
<td>Anion gap (mmol/L)</td>
<td>25 (17–18)</td>
<td>11 (6–17)</td>
</tr>
<tr>
<td>Serum osmolality (mmol/kg)</td>
<td>350 (275–295)</td>
<td>320 (275–295)</td>
</tr>
<tr>
<td>White blood cell count (×10³/L)</td>
<td>10.6 (5.5–14.5)</td>
<td>11.6 (5.0–14.5)</td>
</tr>
<tr>
<td>Ammonia (μmol/L)</td>
<td>1561 (21–50)</td>
<td>93 (10–35)</td>
</tr>
<tr>
<td>Urine orotic acid (mmol/mol Cr)</td>
<td>3525 (&lt;40)</td>
<td>518.25 (0.4–2.32)</td>
</tr>
<tr>
<td>Glutamine (μmol/L)</td>
<td>1010 (823)</td>
<td>660 (50–740)</td>
</tr>
<tr>
<td>Citrulline (μmol/L)</td>
<td>24 (1–46)</td>
<td>8 (1–46)</td>
</tr>
<tr>
<td>Ornithine (μmol/L)</td>
<td>17 (10–163)</td>
<td>5 (10–110)</td>
</tr>
</tbody>
</table>

ED, emergency department; HD, hemodialysis.

* Outside records returned ∼1 week after initial presentation. Post-HD metabolic studies returned ∼1 week after presentation to our institution.
Hypothermia was initiated on day 3, with temperatures ranging between 34.7°C and 35.6°C. MRI was performed on day 6 for prognostic purposes and demonstrated improving sulcal effacement with patent basal cisterns, suggesting residual but improved edema (Fig 1C). Diffusion-weighted imaging displayed reduced diffusivity in the hippocampi bilaterally (Fig 1D). With favorable findings on imaging despite increases in ICP, the ICP monitor was replaced with an external ventricular drain (EVD), which resulted in improved ICP control (Fig 1E).

On day 5, ~48 hours after initiating pentobarbital, he developed an elevated lactate level to 5.4 mmol/L with no evidence of decreased tissue perfusion, organ dysfunction, or impaired oxygen delivery. Infectious workup was unrevealing. Pentobarbital level was supratherapeutic to 286.3 μmol/L. Lactic acidosis was attributed to propylene glycol toxicity from pentobarbital, and resolved with discontinuation of the infusion.

**Endocrine Abnormalities**

By day 4 our patient’s serum sodium level was 169 mmol/L, with an osmolality of 349 mmol/kg, which was partially attributable to hypertonic fluid administration. He had dilute urine output with a specific gravity of 1.005, urine sodium level of 42 mmol/L, and urine osmolality of 185 mmol/kg, suggestive of central diabetes insipidus. He was effectively treated with a vasopressin infusion. On day 6, random cortisol level returned low at 104.8 mmol/L. Repeat cortisol level was 151.7 mmol/L with a low adrenocorticotropic hormone level of <0.5 pmol/L, suggestive of secondary adrenal insufficiency. He was treated with stress dose hydrocortisone (50 mg/m²/day). Morning and nighttime thyroid function tests revealed low thyroid stimulating hormone, with normal free thyroxine and reverse triiodothyronine. Loss of thyroid stimulating hormone diurnal rhythm and normal reverse triiodothyronine were consistent with central hypothyroidism and he was started on levothyroxine (2 μg/kg).

**Remainder of Hospital Course**

Our patient was warmed over 48 hours starting on day 7 without increases in ICP or worsening hemodynamics. Amino acid-modified nasogastric feeds and enteral ammonia scavengers were started on day 8. He advanced to full feeds by day 10. Ammonia levels remained <9 μmol/L. Metabolic studies, after initiation of therapy, were notable for an elevated urine orotic acid level with normal glutamine and citrulline levels (Table 1). He was extubated on day 13 and the EVD was removed on day 16. Thyroid function tests on day 20
returned normal and levothyroxine was discontinued. He was weaned off hydrocortisone by day 23. Low-dose cosynotrop stimulation test on day 29 showed 30- and 60-minute post-test cortisol levels of 618.0 nmol/L (normal >413.8 nmol/L) and 405.5 nmol/L, respectively. He displayed complete recovery of his hypothalamic-pituitary-thyroid axis, and was discharged on oral phenylbutarate, L-citrulline, and arginine after a 30-day hospital stay.

Molecular testing revealed a mutation in codon 159 of exon 5 of the OTC gene, which has been previously reported as causative for late-onset OTC. Our patient’s brother, mother, maternal grandfather, and maternal uncle were also screened, and his grandfather had the same mutation.

Neuropsychological testing 1 year after discharge showed no visual-motor deficits (Rey-Osterrieth Complex Figure Test), normal intelligence (Woodcock-Johnson III Tests of Achievement – Normative Update), average working memory, and slightly below average processing speed (Wechsler Intelligence Scale for Children – Fourth Edition) and executive functioning (Delis-Kaplan Executive Functioning System).

**DISCUSSION**

Hyperammonemia associated with OTC deficiency results from urea cycle dysfunction within the mitochondria of hepatocytes and inability to convert carbamyl phosphate and ornithine to citrulline. Glutamine synthetase catalyzes the formation of glutamine from ammonia and glutamate in cerebral astrocytes, leading to increased intracellular osmolarity, cell loss, and cytokine release, and oxidative stress resulting in cytotoxic cerebral edema. Impaired cerebral autoregulation and increases in cerebral blood flow may also contribute. Despite aggressive medical management, morbidity and mortality from associated hyperammonemia remain significant. Plasma ammonia levels ≥200 μmol/L to 500 μmol/L are associated with poor neurologic outcomes and death. Current treatment strategies for hyperammonemic crisis aim to reduce ammonia production and absorption and facilitate elimination. In cases of uncontrolled hyperammonemia, hemodialysis is an effective treatment. Our patient’s initial ammonia level was 1561 μmol/L and was effectively managed with parenteral ammonia scavenger therapy after continuous veno-venous hemodialysis. Post-dialysis, our patient developed refractory increases in ICP, hypernatremia, and mildly reduced serum osmolality. The decrease in osmolality after dialysis may have contributed to cerebral edema. However, the decrease was small and over an extended time period, suggesting that fluid and electrolyte shifts were not a major contributing factor.

Conventional and nonstandard therapies for ICP reduction should be aggressively used to control cerebral edema. Although there are no verified predictive measures to determine who develops cerebral edema, the degree of hyperammonemia is a commonly cited measure of irreversible neurologic changes. Recent investigation found that cerebral edema or increased ICP was present in 16 out of 49 patients who had UCDs who died while undergoing therapeutic hypothermia for ICP control is an effective treatment of brain injury of various etiologies. However, beneficial effects on mortality and morbidity in traumatic brain injury are not clearly demonstrated. Recent investigation among neonates who have UCDs has been promising, showing that hypothermia is a feasible and safe therapeutic adjunct in the treatment of hyperammonemia-induced cerebral edema. It is unclear whether any benefit would be attributable to decreased ammonia production, slowing of metabolism, or cerebral blood flow alteration. Induction of barbiturate coma may also be useful for refractory ICP management, however this is not standard and efficacy has been debated. The length of pentobarbital therapy was significant, considering our patient’s drug level was elevated 5 days after discontinuation, but we cannot conclude that barbiturate use contributed to a favorable outcome. Indeed, pentobarbital administration may have led to propylene glycol toxicity, which has been previously reported. Earlier EVD placement may have provided benefit and avoided the need for barbiturates. Additionally, decompressive craniotomy could have been used, as this has been shown to assist with successful treatment of cerebral edema associated with OTC deficiency.

Our patient demonstrated minor neurocognitive deficits at 1-year follow-up. Similar deficits among heterozygous OTC-deficient females have been described. Additionally, recent investigation using diffusion tensor imaging and fMRI among patients who have OTC deficiency has shown alterations in white matter tracts involved in working memory and executive functioning and impaired frontal lobe processing when performing attentional tasks.

**CONCLUSIONS**

Aggressive management of hyperammonemia and resultant cerebral edema with conventional and nonstandard therapies may improve outcomes among those who have UCDs.
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