Altered mental status: a common complaint that led to a rare diagnosis - Ornithine Transcarbamylase Deficiency

Joshua J. White, OMS3
Charles C. Finch, D.O., FACOEP
Arizona College Of Osteopathic Medicine

Outline
- Introduction
- Case Presentation: Timeline of events, history and physical exam
- Discussion: Overview of Ornithine Transcarbamylase (OTC) Deficiency
  - What can we learn from this case?
  - Osteopathic Approach
  - Take away points for health care providers
- Questions
Introduction: Altered Mental Status

Invitation:
1. Throughout my presentation, compare what you would do to what was done.
2. Based on physical exam findings and lab results, what would your differential diagnosis include?
3. What can you do in the future to improve your evaluation of patients with altered mental status?

When a patient's clinical presentation and labs don’t fit the more common diagnosis, what is next in your workup?

HPI
7 year old Caucasian male presents to a small community hospital Emergency Department with “several episodes of vomiting and increased confusion.”

Per his father, he had a 2-day history of flu-like symptoms to include vomiting. Earlier in the day patient became confused, and was not responding appropriately to simple commands. This prompted father to bring him to the Emergency Department for evaluation. There is no history of any diarrhea or rashes. Father reports multiple episodes of non-bloody vomiting throughout the day.
HPI Con’t

- PMH: seasonal allergies, and periods of intermittent vomiting usually initiated of times of increased hunger.
- PSH: None
- FH: No relevant family history reported
- SH: Father admits to other family members with similar symptoms of vomiting and runny nose.
- Allergies: NKDA
- Medications: Flonase 50 mcg/inh nasal spray.
- Immunizations are up to date

Physical Exam

- Vitals:

<table>
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<th>Temperature (°C)</th>
<th>RR</th>
<th>BP</th>
<th>SpO2 on RA</th>
<th>HR</th>
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<tr>
<td>36</td>
<td>30</td>
<td>111/59</td>
<td>98%</td>
<td>96</td>
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- General: Patient is well developed, sleeping and arousable although appears to be slow to respond and confused.
- CV: Regular rate and rhythm. No murmurs, rubs, clicks or gallops.
- Respiratory: Clear to auscultation bilaterally in all fields. Chest expansion is equal bilaterally. No retractions or obvious respiratory distress.
- Abdomen: Soft, mild tenderness in the right lower quadrant with guarding present and no rebound. No distension appreciated and no other areas of focal tenderness. No organomegaly, masses or CVA tenderness.
- Neurologic: Awake, slow to respond and not acting appropriate during questioning. No focal deficits. Muscle strength is 5/5 in both upper and lower extremities. Sensation and reflexes are intact bilaterally. Meningitis is not suspected.
Timeline: workup decisions

- Arranged for life flight transfer to a pediatric hospital for further specialty care
- Head and abdominal CT, chest x-ray to look for cause of leukocytosis
- Labs showed a leukocytosis, and mild elevation in liver transaminases
- Patient became more confused, and a Lumbar Puncture was ordered.
- Abdominal Ultrasound due to concern for appendicitis
- IV Fluids and Labs

Lab Results

- Heme
  - WBC: 20.2 K/mcL
- Complete Differential
  - Neutrophil Absolute: 17.9 K/mcL
- Chemistries
  - AST: 99 unit/L
  - ALT 145 unit/L
  - Total Bilirubin: 1.5 mg/dL
- UA: negative
- Respiratory panel: Negative
  - Including: Influenza, RSV, Adenovirus, B. pertussis, Mycoplasma pneumoniae, C. Pneumoniae, Coronavirus, Human Metapneumovirus, parainfluenza.
En route to the Hospital

- En Route
  - Erratic breathing
  - Dilated Pupils
  - Clonus

- Due to patient’s worsening clinical presentation of encephalopathy:
  - Intubated for airway protection
  - Mannitol bolus
  - Ammonia level was checked

Hospital Course

- Given an ammonia level was checked and found to be severely elevated at 381 (15-45 µ/dL).
- Treatment:
  - Aggressive IV fluid hydration was continued to prevent further catabolism.
  - The patient was given an ammonul IV bolus (sodium phenylacetate + sodium benzoate) to treat his hyperammonemia.
  - Nephrology was consulted, and dialysis was started due to the hyperammonemia.
  - The diagnosis of OTC deficiency was initially suspected based on his clinical presentation and hyperammonemia, and confirmed through genetic testing and liver biopsy.
  - The patient’s mental status did not improve despite aggressive therapy. An EEG was performed and results were significant for global encephalopathy. Given evidence of brain death, the parents withdrew life support and patient was pronounced dead.
What Is Ornithine Transcarbamylase (OTC) Deficiency?

Ornithine Transcarbamylase is a mitochondrial enzyme responsible for the 2nd step of the urea cycle, where ornithine and carbamoyl phosphate are turned into citrulline.
Urea Cycle Disorders

Elevated levels of Ammonia in the brain:

Usually presents first with: Vomiting, altered mental status, and poor feeding.

Can progress to: coma, seizures, encephalopathy.
Patient Presentation

- OTC Deficiency is an x-linked recessive disorder and patients present with either a full or partial deficiency.
- Patients who have OTC deficiency are males with full deficiency of the enzyme and present with symptoms shortly after birth, or males and/or females with a partial deficiency who can present at any time from infancy through adulthood.

Epidemiology

- The prevalence of OTC deficiency is estimated to be at a range of 1/14,000 to 1/80,000.
- Mortality rates in the past have been as high as 50%. Recent estimates of mortality note a rate of 24% for neonatal presentation, and 11% for those affected after the neonatal period.
- This improvement is due to early diagnosis and improved treatment.
Diagnosis

- Laboratory findings of elevated plasma ammonia levels with a normal glucose and anion gap suggests OTC deficiency.
- The diagnosis for neonatal onset (full deficiency) OTC deficiency is made by finding elevated glutamine, low/absent citrulline, and elevated urinary orotic acid levels.
- Late onset (partial deficiency) requires genetic testing and/or liver biopsy to confirm the diagnosis.

Treatment

- Treatment for OTC deficiency is mainly focused on treating hyperammonemia.
  - It includes a pharmacological intervention that targets ammonia elimination, which is typically a combination of intravenous sodium phenylacetate and sodium benzoate.
  - A nutritional supplementation is also given with the amino acids L-citrulline or L-arginine; and a low-protein diet is maintained to avoid further catabolism.
  - Patients presenting with severely elevated levels require dialysis to filter nitrogen from the blood.
  - The only definitive treatment for OTC deficiency is liver transplantation.
  - Prompt recognition and treatment is key for the best clinical outcome.
Ammonia Level

- Early diagnosis and treatment is crucial to successful outcomes of patients that present with OTC deficiency.
- In patients who present with altered levels of consciousness, clinicians should consider checking an ammonia level, as the consideration of OTC deficiency is a concern.
- If elevated, nitrogen scavenger therapy should be initiated immediately to prevent further complications.

Family History/Genetic Counseling

- Since OTC deficiency is known to be x-linked recessive, prenatal testing can be done through chorionic villus sampling or amniotic fluid cell analysis.
- Newborn screening is limited, as it provides low specificity and limited benefit.
- Genetic testing is recommended to help families identify patients at risk, and to assist families with the preparation and early treatment OTC deficiency.
Osteopathic Approach

- Treating the patient as a whole
- This patient had a history of intermittent idiopathic vomiting for the past 2 years, how does that fit into this clinical picture?
- His vomiting in periods of increased hunger was likely due to ammonia buildup triggered by increased catabolism.
- The deficiency manifested itself in subtle ways for 2 years prior to the acute event. What would it take to have been caught earlier?

What can we learn from this case?

1. If a patient presents with an altered mental status that cannot be explained by anything else, consider checking an ammonia level.
2. For patients with OTC deficiency or other genetic disorders, encourage genetic counseling, family education and potentially prenatal screening.
3. When the clinical and laboratory findings are not matching up to the most common presentations, think about the more rare life threatening diseases for your differential diagnosis.
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References

Questions?