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Case report

Late-onset urea cycle disorder in adulthood unmasked by severe malnutrition

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ABSTRACT

Urea cycle disorders (UCDs) most often involve inherited deficiencies in genes that code for enzymes normally used by the urea cycle to breakdown nitrogen. UCDs lead to serious metabolic complications, including severe neurologic decompensation related to hyperammonemia. Although the majority of UCDs are revealed soon after birth, stressful events in adulthood can lead to unmasking of a partial, late-onset UCDs. In this report, we describe a late-onset UCD unmasked by severe malnutrition. Early, specialized nutrition therapy is a fundamental aspect of treating hyperammonemic crises in patients with UCD. The case presented here demonstrates the importance of early recognition of UCD and appropriate interventions with nutrition support.

Introduction

The urea cycle and associated enzymes are responsible for the breakdown of nitrogen (Fig. 1); therefore, urea cycle disorders (UCDs) lead to elevated serum ammonia concentrations [1]. The primary enzymes involved in the urea cycle include carbamoylphosphate synthetase 1 (CPS1), ornithine transcarbamylase (OTC), argininosuccinate synthetase, argininosuccinate lyase, and arginase 1. Disorders involving these enzymes are usually inherited and most commonly result in symptoms of hyperammonemia, coma, and often death shortly after birth. However, clinical presentation of these disorders varies widely as either complete or partial deficiencies may be phenotypically expressed. Late-onset presentations of UCD associated with partial deficiencies may occur at any age, with up to 10% of UCD being diagnosed after the age of 16 y [2]. Late-onset UCDs are usually revealed following major stress from illness or surgery [1,2]. Reported mortality rates in patients with late-onset UCD range from 13% to 22%; therefore, it is essential that symptoms are recognized early to ensure prompt diagnosis and treatment [2,3]. This report describes a unique case of a late-onset UCD unmasked by severe malnutrition secondary to chronic alcoholism.

Case

Approval for publication was obtained by hospital and university institutional review boards. A 60-y-old black woman (height 165 cm, weight 48 kg) was admitted to the hospital on Jan. 30, 2013 for generalized weakness, failure to thrive, abdominal pain, and melanotic stools. She reported a 2-mo history of abdominal cramping with diffuse, non-radiating pain. This resulted in a decreased oral intake and a 22 kg weight loss (usual weight, 70 kg), leading to sarcopenia. Her past medical history was significant for depression, duodenitis, sigmoid diverticulitis, and alcohol abuse (up to 12 beers/d for an unknown duration). Omeprazole was the only home medication reported on admission. Examination of the oral cavity revealed severe gingival disease with significant bleeding. Neurologic examinations were normal with a Glasgow Coma Scale score of 15 upon admission. Radiologic tests included a brain computed tomography (CT), abdominal CT, and esophagogastroduodenoscopy (EGD). Brain CT showed mild, diffuse cerebral atrophy and periventricular ischemic changes. Abdominal CT revealed a possible pancreatic mass versus fluid-filled duodenal diverticulum measuring 10 mm in diameter; however, lipase levels were normal. EGD revealed non-specific antral and duodenal

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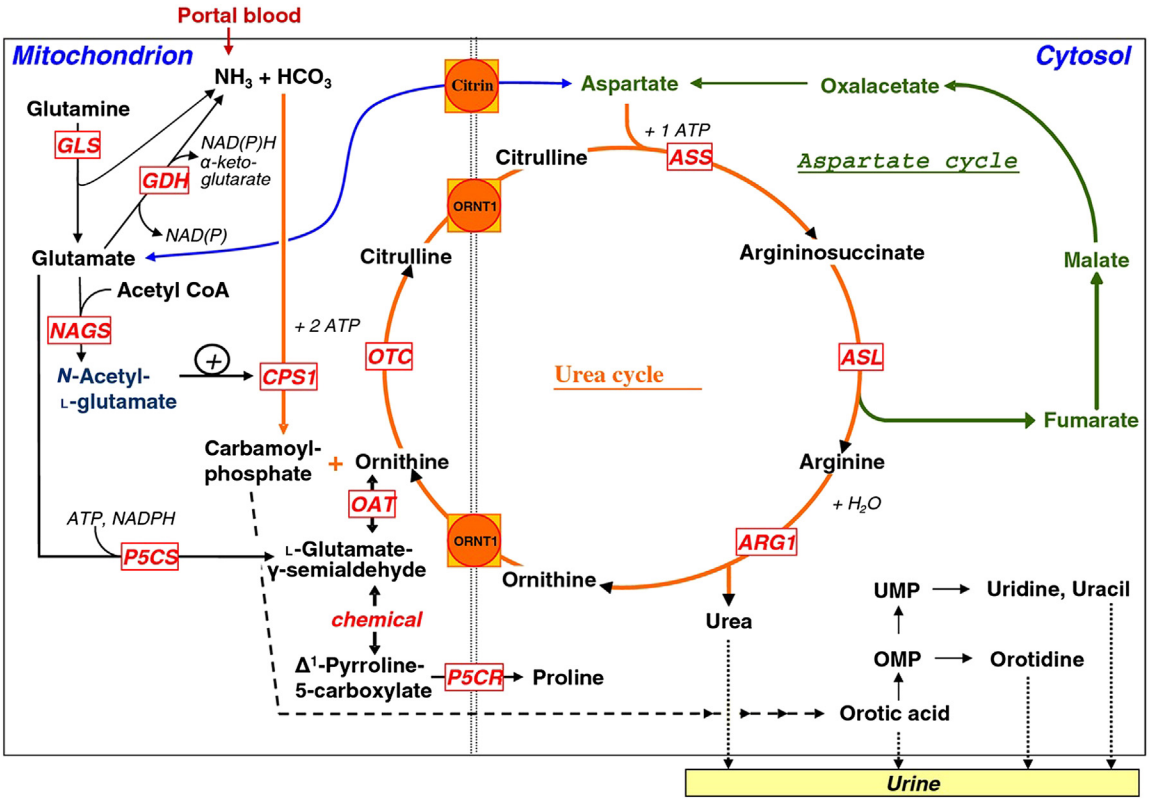

Fig. 1. The urea cycle and associated pathways. Reprinted from Häberle J, Boddaert N, Burlina A, Chakrapani A, Dixon M, Huemer M, et al. [1]. Copyright 2012, with permission from BioMed Central Ltd. ARG1, arginase 1; ASL, argininosuccinate lyase; ASS, argininosuccinate synthetase; CPS1, carbamoylphosphate synthetase 1; GDH, glutamate dehydrogenase; GLS, glutaminase; NAGS, *N*-acetylglutamate synthetase; NAD(P), nicotinamide adenine dinucleotide (phosphate); OAT, ornithine aminotransferase; OMP, orotidine monophosphate; ORNT1, ornithine transporter 1; OTC, ornithine transcarbamylase; P5 CR, pyrroline-5-carboxylate reductase; P5 CS, Δ^{1-} pyrroline-5-carboxylate synthetase; UMP, uridine monophosphate.

erythema and a Schatzki's ring-type stricture, although no source of bleeding was identified beyond the oral cavity. Stool was hemoccult-positive and hemoglobin was 6.3 g/dL (normal range, 11.5–15.5 g/dL) for which she received three units of packed red blood cells. Throughout her hospital stay there were no further signs of ongoing blood loss, and the remainder of her hospital course was uneventful. After 5 d, the patient was discharged home on hydrocodone/acetaminophen for abdominal pain and plans for a full mouth extraction. The source of abdominal pain was not determined, but her poor oral intake and weight loss were attributed to her history of alcohol abuse and significant gingival disease.

Approximately 1 wk later on Feb. 8, 2013, the patient was brought back to the emergency department (ED) by her family who reported that her mental status had progressively worsened since her hospital discharge, and she was found unresponsive that morning. In the ED, a neurologic examination revealed a Glasgow Coma Scale score of 7. The patient was admitted with acute mental status changes, malnutrition, and failure to thrive. Per family history, her oral intake had not improved, and the last time she consumed alcohol was before her previous hospital admission. The patient's blood alcohol level was undetectable as were acetaminophen, salicylate, and valproic acid levels; however, urine drug screen was positive for benzodiazepines. She was hypothermic and hypotensive after arrival on the floor and was subsequently transferred to the intensive care unit. Blood cultures were obtained to rule out infection and piperacillin/tazobactam was initiated for possible aspiration pneumonia. One of two sets of blood cultures (one of four bottles) drawn on hospital day 1 was positive for gram-positive cocci in clusters; therefore, contamination was suspected. Repeat blood cultures drawn on day 2 were negative. Questionable seizure activity was noted on admission for which levetiracetam was initiated. Electroencephalography was consistent with diffuse, nonspecific metabolic and/or hypoxemic changes; however, no epileptiform abnormalities were noted. Brain CT showed no changes from her previous admission. Magnetic resonance imaging of the brain showed an unusual pattern of diffusion restriction involving the cortical gray matter of the bilateral insular ribbon, most of the right temporal lobe, and most of the right parietal lobe, including the sensory motor strip.

After other causes of encephalopathy were ruled out, an ammonia level was drawn on hospital day 3; it was found to be elevated at 256 μmol/L (normal range, 9–35 μmol/L), and treatment with lactulose was initiated. Aside from mild transaminitis (i.e., more than three times the upper limit of normal) on admission, hepatic function was normal with no evidence of hepatomegaly or cirrhosis, and hyperammonemia could not be attributed to any of her home medications. Based on her clinical presentation and recent history of significant weight loss, a blood sample was obtained for evaluation of vitamin and trace element deficiencies, as well as late-onset UCDs. This patient's hospital course and therapy related to UCD is outlined in Figure 2. While the laboratory results were pending, empiric treatment for UCD was initiated on day 3, which included L-carnitine 500 mg intravenously (IV) every 4 h, L-arginine 200 mg/kg daily via continuous infusion, and sodium benzoate/sodium phenylacetate 175 mg/kg daily via continuous infusion with 10% dextrose