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Renal donation from a donor with unrecognized ornithine transcarbamylase deficiency in adulthood

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Abstract

In this case report, we describe fatal hyperammonaemic coma caused by late-onset OCT deficiency in a 59-year-old male. On admission, he had hyperammonaemia (4489 mg/dL) and slightly elevated liver enzymes with no abnormality in INR, viral markers of acute hepatic failure and toxicology tests. Despite prompt introduction of plasmapheresis and continuous venovenous hemodiafiltration and implementation of further diagnostic work-up for urea cycle defect upon identification of a family member who died from type 2 citrullinemia in the detailed anamnesis, the clinical status rapidly deteriorated and brain death was confirmed at the 22nd hour of hospitalization. Donor kidneys from the patient were successfully transplanted into two recipients. Ornithine Transcarbamylase (OTC) deficiency was diagnosed based on demonstration of elevated ornithine, glutamine, lysine, aspartic acid and valine levels in plasma amino acid analysis. Late-onset OTC deficiency may be pre-existing with unknown hyperammonemic coma. Moreover, taking this into account in differential diagnosis, may provide early recognition and prevention of mortality.

Keywords

hyperammonaemia; adult urea cycle defect; ornithine transcarbamylase deficiency; renal transplantation

Introduction

Ornithine Transcarbamylase (OTC) deficiency is the most common and the only X-linked genetic disorder of the urea cycle, and caused by mutations in the OTC gene [1,2]. Depending on the effect of mutations on enzyme activity, two phenotypes exist in males including neonatal-onset and late-onset OTC deficiency [3-7]. No residual enzyme activity is evident in the neonatal-onset form leading to hyperammonaemic coma and death in the neonatal period, while the patients with late-onset disease have partial residual activity leading to onset of symptoms in later life in the presence of factors provoking hyperammonaemia [3-7]. Due to influence of X-inactivation pattern on the phenotype, female carriers are often asymptomatic [3,7,8].

Physiological stress, infection, excess protein intake, trauma, perioperative or postpartum state, prolonged hospital stay and anticonvulsant medications are considered amongst the factors that luxate hyperammonaemia which coincides with the clinical manifestation of late onset disease [6,7,9-11].

Symptoms of late-onset OTC deficiency mainly relate to hyperammonaemia, and include nausea, vomiting and altered mental state progressing from lethargy and confusion to coma and death if remain unrecognized, while rapidly fatal course is also likely due to intracranial edema in more severe attacks [7,11-13].

Accordingly, late-onset OTC deficiency is considered diagnostically challenging with the critical role of clinical suspicion and detailed investigation in early recognition of the disease enabling prompt treatment before progression into coma and death [2,3,7,11]. Herein, we report fatal hyperammonaemic coma caused by late-onset OCT deficiency in a 59 year-old male.

Case Presentation

A 59-year-old male was referred to our hospital for an investigation of prolonged unconsciousness started 15 days ago with disorganized speech, somnolence and muscle weakness. On admission, he was in a deep/semi-coma with Glasgow Coma Scale score of 6, post-intubation FiO2 was 65% with f15/min PEEP of 7 cm H_2O. His vital signs were stable, with a blood pressure of 112/61 mmHg, pulse rate of 104 bpm and body temperature of 36.1°C. Laboratory analysis revealed hyperammonaemia (4489 mg/dL) and slightly elevated liver enzymes (aspartate aminotransferase: 86 U/L; alanine aminotransferase: 122 U/L). INR was in the normal reference range and all viral markers of acute hepatic failure as well as toxicity tests were negative. There were no co-morbidities other than hypertension and no history of potential provoking factors for hyperammonaemia. He was diagnosed with acute hyperammonaemic encephalopathy and then plasmapheresis and Continuous Venovenous Hemodiafiltration (CVVHDF) were performed. At the 10th hour of hospitalization, serum ammonia levels were decreased to 3003 mg/dL without any observable improvement in his level of consciousness. Detailed anamnesis identified presence of a family member (his sister's grandson) who died from type 2 citrullinemia 2 years ago (3-yr-old) and thus a positive family history for inborn metabolic errors. Diagnostic doctors have indicated that the male members of the family can be sick and need to be investigated. However, the family did not have medical follow-ups and laboratory investigations. Accordingly, further diagnostic work up for a suspected diagnosis of a urea cycle defect was initiated including analysis of amino acid chromatogram and serum and urinary copper and ceruloplasmin levels, while the patient was also scheduled for urgent liver transplantation. However, his clinical status rapidly deteriorated with confirmation of the clinical diagnosis of brain death during follow-up neurological examination at the 22nd hour of hospitalization. Donor kidneys from the patient were successfully transplanted into two recipients. One of the recipients was end-stage renal disease caused by diabetic nephropathy, and the other was chronic pyelonephritis. Serum creatinine level was 1.2-1.5 mg / dL following 6 months of follow-up.

Findings from plasma amino acids analysis revealed elevated ornithine, glutamine, lysine, aspartic acid and valine levels, while serum and urinary copper and ceruloplasmin levels were within the normal range. Genetic testing was coordinated for at-risk family members and 2 nephews were identified to have OTC deficiency along with up to 60% carrier status of an OTC gene mutation noted among female members. These findings confirmed that fatal hyperammonaemia in our patient was due to late-onset OTCD. Results were disclosed by a genetic counselor and symptomatic treatment with arginine and sodium phenylbutyrate, poor protein diet programs and appropriate follow-up were scheduled for the relevant family members.

Discussion

In this case report, we describe fatal hyperammonaemic coma caused by late-onset OCT deficiency in a 59-yr-old male who was referred to our clinic with a 15-day history of unconsciousness. Given the non-specific clinical presentation in our patient with no signs or symptoms suggestive of possible urea cycle defect or factors precipitating hyperammonaemia, consideration of serum ammonia analysis in diagnostic work-up of unexplained coma and then detailed anamnesis for family history of inborn metabolic errors in diagnostic work-up of unexplained hyperammonaemia seem crucial steps leading to suspected diagnosis of OCT deficiency.

Laboratory findings considered diagnostic for OCT deficiency include elevated plasma levels for ornithine, glutamine and decreased citrulline level along with identification of orotic acid and uridine in urinalysis [1,6,14]. Accordingly, the diagnosis of OCT deficiency in the etiology of hyperammonaemic coma in our patient was confirmed by demonstration of elevated ornithine, glutamine, lysine, aspartic acid and valine levels in plasma amino acid analysis and evidence on OTC deficiency in 2 males and carrier status of OTC gene mutations among female members upon genetic testing for at-risk family members.

Our findings support that the late-onset OCT deficiency can be associated with non-specific clinical presentation and unprovoked hyperammonaemic coma with no clues suggestive of an underlying urea cycle defect (i.e. voluntary protein avoidance, nausea/vomiting, dyspnea) or provoking factors (i.e. stress, infection, excessive protein intake, heavy exercise, medications) [2,3,7,14,15]. However, it should be noted that identification of hyperammonaemia is considered to narrow the differential diagnosis of coma in adults to Reye's syndrome, highdose chemotherapy, Proteus infection, glycine toxicity, liver failure, and late-onset urea cycle defects [7,13]. Besides, urea cycle disorders are considered to have a predictable pattern of laboratory abnormalities which can greatly assist in diagnosis such as hyperammonaemia without acidosis, respiratory alkalosis and an inappropriately low serum blood urea nitrogen [9,11], while hyperammonaemia without evidence of hepatic failure strongly suggests a urea cycle disorder amongst which OTC deficiency is the most prevalent one [16]. In our patient, laboratory findings revealed slightly elevated liver enzymes along with no abnormality in investigations for serologic markers of acute hepatic failure, co-morbid infection, serum ceruloplasmin levels, INR and toxicological tests. Thus, our findings emphasize importance of analyzing serum ammonia levels in patients with unexplained coma and the need to suspect OTC deficiency in patients with unexplained hyperammonaemia with guiding role of detailed anamnesis for family history for an inborn metabolic error in recognition of disease [3,11].

Nonetheless, despite the recognition of OTC on the same day of hospitalization, along with implementation of hemodiafiltration and a schedule for urgent liver transplantation, the clinical status of our patient rapidly deteriorated with identification of brain death at the 22nd hour of hospitalization. Although the clinical status rapidly deteriorated after admission to our clinic, diagnostic work up could only be performed late in the course of the disease, which delayed the diagnosis of OCT deficiency in our patient. Indeed, prolonged ICU stay itself is considered amongst the factors likely to luxate hyperammonaemia in late-onset OTC deficiency [3,14,15], while the prognosis of disease is also strongly influenced by the duration of coma and peak ammonia levels [14,17]. Hence, the fact that the disease

remained undiagnosed and untreated for a long-term in our patient seems to be associated with poor prognosis and rapid deterioration, by limiting the efficacy of available therapeutic measures like to enable full recovery if the disorder had been recognized in time. Accordingly, early diagnosis and prompt treatment of late-onset OTC deficiency associated with hyperammonaemia was reported to be resulted in full recovery in past case reports by means of hemodialysis and arginine and benzoate administration in a 59-year-old male patient [6], long-term hemodialysis coupled with administration of L-arginine and lactulose in a 69 year-old male patient [18], hemodialysis, protein elimination and ammonia scavenging medications in a 47-year-old male [19], CVVHDF and intravenous sodium benzoate in a 32year old female [16], aprotidic diet in a 35-year old male [20] and intermittent hemodialysis and intravenous sodium phenylacetate and sodium benzoate in a 53-year-old male [7]. Authors indicated early diagnosis of adult-onset OTC deficiency to be essential to avoid serious complications and to increase the likelihood of treatment to effectively lower the patient's plasma ammonia level and to result in full recovery [6,7,16,18-20]. However, similar to our findings, failure to timely recognize the disease and thus delay in treatment was reported to be associated fatal hyperammonaemia due to late-onset OTC deficiency in past case reports, including a 45-year-old male post-transplant patient who developed cerebral edema [21], a 60-year-old female patient with severe malnutrition and consequent development of respiratory distress [22] a 67-year-old male with pneumonia with consequent development of generalized seizures and diffuse cerebral edema [3] and 5 patients (1 female, 4 males) aged 21 to 66 years who developed unexpected fatal encephalopathy [2]. Hence, it seems crucial to increase clinicians' awareness of the possibility of OCT deficiency in patients with unexplained hyperammonaemic coma, given that disease may manifest with non-specific clinical presentation, the rapid deterioration and incidentally the fatal outcome, while the diagnosis relies mainly on clinical suspicion and careful investigation [2,3,11,21].

Our findings support the importance of obtaining ammonia levels in all patients with unexplained coma, especially in patients in the ICU or in an otherwise catabolic state [3] and consideration of urea cycle disorders in the differential diagnosis of acute hyperammonaemia in adult patients [3,11]. The relevance of recognizing OCT deficiency lies in the reversibility of hyperammonaemia and prevention of mortality by means of several measures available if only the disorder is recognized in time [3,6,23].

In conclusion our findings indicate fatal hyperammonaemic coma caused by late-onset OCT deficiency in a 59-year-old male with a 15-day history of unconsciousness preceding referral to our hospital. Possibly linked to long-term delay in diagnosis and treatment, rapid deterioration was noted in clinical status despite implementation of therapeutic measures within this first 24 hours of current hospitalization with identification of hyperammonaemia and suspected diagnosis of urea cycle disorder. Our findings indicate that late-onset OTC deficiency can present with an unprovoked fatal hyperammonaemic coma and emphasize the consideration of serum analysis for ammonia levels in patients with unexplained coma and OTC deficiency in the differential diagnosis of patients with unexplained hyperammonaemia, given the likelihood of reversibility of hyperammonaemia and prevention of mortality with timely recognition and prompt initiation of definitive therapy.

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