

# Late Onset Ornithine Transcarbamylase Deficiency Accompanying Severe Hyperammonemia After Cesarean Section: Case Report

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Received March 25, 2015; Revised April 04, 2015; Accepted April 16, 2015

**Abstract** Hyperammonemia is one of the common complications of porto-systemic shunt or liver failure. In patients without liver failure or porto-systemic shunt, hyperammonemia can be caused by urea cycle disorders. Nitrogen excretion pathway or enzyme deficiency disorder can result in any hyperammonemia, coma, or death that may cause severe clinical encephalopathy presenting with neurological symptoms. The most common cause of genetic disorders in the urea cycle is ornithine carbamoyltransferase deficiency. In this article, 28-year-old female patient who had late-onset ornithine carbamoyltransferase deficiency with severe acute hyperammonemia resulting coma and death after cesarean section is described. In addition, treatment of hyperammonemia including sodium benzoate, arginine, and hemodialysis were discussed.

**Keywords:** *ornithine carbamoyltransferase deficiency, urea cycle disorders, hyperammonemia, hemodialysis*

**Cite This Article:** Birsen Dogu, Nezir Yılmaz, Sabriye Ozcekic, and Hafize Oksuz, "Late Onset Ornithine Transcarbamylase Deficiency Accompanying Severe Hyperammonemia After Cesarean Section: Case Report." *American Journal of Medical Case Reports*, vol. 3, no. 5 (2015): 133-136. doi: 10.12691/ajmcr-3-5-4.

## 1. Introduction

Hyperammonemia is one of the common complications of porto-systemic shunt or liver failure. In patients without liver failure or porto-systemic shunt, hyperammonemia can be caused by urea cycle disorders. The amino acid products of endogenous and exogenous protein digestion are degraded by hepatic transamination and oxidative deamination to produce ammonia. Ammonia is converted to urea via the five different enzymes of the urea cycle (*carbamoyl phosphate synthetase*, *ornithine carbamoyltransferase (OTC)*, *argininosuccinic acid synthetase*, *argininosuccinase* and *arginase*) and is excreted through the kidneys [1].

Nitrogen excretion pathway or enzyme deficiency disorder can result in any hyperammonemia, coma, or death that may cause severe clinical encephalopathy presenting with neurological symptoms according to clinical trials. In adults, mild or partial deficiency of any of the urea cycle enzymes has been attributed to severe illness or stress-induced increases in protein catabolism or protein overload [2]. The most common cause of genetic disorders in the urea cycle is OTC deficiency [3] and shows heterogeneous clinical presentation [1]. Presentation of hyperammonemia and disease severity may vary depending on age of the patient. In infants, hyperammonemia can manifest itself as lethargy, poor feeding response, vomiting, hypotonia, and seizures [4]. In

adults, urea cycle disorders is the result of liver cirrhosis or chemotherapy rather than genetic defect. Partial or late-onset OTC deficiency can result from residual enzyme activity associated with peripheral mutations in the OTC gene. Adults can show severe symptoms or may be asymptomatic [5].

In this article, 28-year-old female patient who had late-onset OTC deficiency with severe acute hyperammonemia resulting coma and death after cesarean section is described. In addition, treatment of hyperammonemia including sodium benzoate, arginine, and hemodialysis were discussed.

## 2. Case Description

28-years-old, 39 weeks pregnant female patient was admitted to our hospital for cesarean section (C/S) operation under general anesthesia. Patient followed for 9 years with a diagnosis of epilepsy and mental retardation (MR) were in use valproic acid (400 mg/day). She has not used the drugs regularly over the past year.

In previous pregnancy histories, she has been twice of recurrent postpartum psychosis. On days after C/S operation, she had admitted to the emergency department with complaints such as agitation and mental confusion. She had been admitted to the neurology service with the diagnosis of seizures or/and psychosis and phenytoin 300 mg (100 mg at eight-hour intervals) was started. On the second day of admission, valproic acid was added to

treatment and administered haloperidol due to agitation. In the seventh day of service admission, the patient had unconsciousness and was admitted to intensive care unit (ICU) with a diagnosis of nonconvulsive status epilepticus and respiratory failure.

At admission to ICU, her general condition was poor, unconscious, lack of cooperation and orientation and Glasgow Coma Scale (GCS) was 5. On physical examination, body temperature 38.6°C, heart rate 138 beats/minute, respiratory rate 34/minute and blood pressure was 110/64 mmHg. The endotracheal intubation was performed by applying 2 mg.kg<sup>-1</sup> propofol and 0.6 mg.kg<sup>-1</sup> rocuronium with oral 7,5 numbered endotracheal cuffed tube due to unconsciousness. She was connected to a mechanical ventilator with BILEVEL ventilation mode. Mechanical ventilator settings has been set as FiO<sub>2</sub> 50%, Pressure support (PS): 13 cmH<sub>2</sub>O, PEEP: 5 cmH<sub>2</sub>O, I/E: 1/2, frequency: 12/minute. Antiepileptic (phenytoin 300 mg/day intravenously 100 mg at eight-hour intervals and valproic acid 1200 mg/day 400 mg at eight-hour intervals with nasogastric feeding) and antibiotic (ceftriaxone 2g, 1 g at twelve-hour intervals, intravenously) treatment was ordered. Midazolam intended to suppress seizure activity (5 mg.hr<sup>-1</sup>) and pentothal infusion (4 mg.kg<sup>-1</sup> hr<sup>-1</sup>) was applied.

In laboratory tests; hemoglobin 16.5 g.dL<sup>-1</sup>, white blood cell count of 6800/mm<sup>3</sup>, platelet count of 365000/mm<sup>3</sup>, hematocrit value was found as 50.5 %. In the analysis of serum electrolytes, severe hypernatremia (154 mEq.dL<sup>-1</sup>) was detected; serum potassium and chlorine levels were normal. C-Reactive Protein (CRP) value was determined as 121 mg.L<sup>-1</sup>. There were no abnormalities in coagulation and toxicological tests. Any brain lesion was observed in magnetic resonance imaging and computed tomography. After tracheal intubation, arterial blood gases values revealed such as PO<sub>2</sub>: 49 mmHg, PCO<sub>2</sub>: 132 mmHg, SpO<sub>2</sub> 97%, pH: 7.29, HCO<sub>3</sub>: 21.4 mmol.L<sup>-1</sup>. On the second day of admission, INR value rises 1.7, albumin values began to decline rapidly (from 3.8 g.L<sup>-1</sup> to 2 g.L<sup>-1</sup>). Ammonia levels were studied due to unconsciousness and history of valproic acid usage. Ammonia value of 532 mcg.dL<sup>-1</sup> (normal range of 10-80 mcg.dL<sup>-1</sup>) were measured. Due to high value of ammonia (see Figure-1), mental retardation and lack of liver failure that can explain hyperammonemia, urinary orotic acid levels were measured for the diagnosis of delayed urea cycle disorder. Urinary orotic acid level (809.5 mg/mg creatinine) were identified too high. Also in plasma amino acid analysis, high ornithine (223 μmol.L<sup>-1</sup>; [normal range 19-81 μmol.L<sup>-1</sup>]), glutamine (1893 μmol.L<sup>-1</sup> [normal range 500-750 μmol.L<sup>-1</sup>], and lysine (674 μmol.L<sup>-1</sup> [normal range 116-296 μmol.L<sup>-1</sup>]) with reduced citrulline (11 μmol.L<sup>-1</sup>; [normal range 19-62 μmol.L<sup>-1</sup>]) levels are viewed.

Because of unexplained/suspicious neurological situations (temporary postpartum psychosis) in earlier pregnancy and this time development of more severe neurologic situation (agitation and mental confusion), we had suspicion about the metabolic side of the event. Despite the absence of neurologic imaging findings, the usage of valproic acid for a long time has led to research metabolic aspects of the event (relationship between valproic acid and ammonia). Increase in ammonia levels, high levels of urinary orotic acid and plasma amino acids clearly revealed that this event caused from a urea cycle defect.

With current findings, urea cycle disorder was diagnosed and treatment was to be arranged such as; stopping protein catabolism, increased dextrose and lipids (1 g.kg<sup>-1</sup>day<sup>-1</sup>) for high energy support, sodium phenylbutyrate infusion (300 mg.kg<sup>-1</sup>day<sup>-1</sup>). Bromocriptine (30 mg, 10 mg at eight-hour intervals, orally), enemas, L-carnitine, metronidazole (3g, 1 g at eight-hour intervals, intravenously) was added to treatment in order to decrease high levels of ammonia. However, the ammonia levels remained high and patients were treated with dialysis and on the second day ammonia level decreased from 670 mg.dL<sup>-1</sup> to 430 mg.dL<sup>-1</sup>. However, the patient's general condition was deteriorating, hemodialysis treatment could not be continued because low blood pressure. The patient was administered dobutamine before (35 mcg.kg<sup>-1</sup>.min<sup>-1</sup>) and then noradrenalin infusion (0.04 mcg.kg<sup>-1</sup>.min<sup>-1</sup>) for inotropic support. Fluid replacement was achieved by calculating fluid deficit due to severe hypernatremia (Na: 157 mEq.dL<sup>-1</sup>).

Physical examination on the fourth day of admission; patient's general condition was poor, unconscious, GCS of 3 and fixed dilated pupil was viewed. Body temperature was 37.9°C, INR 1.72, white blood cell count of 20,000 mm<sup>3</sup>, CRP value of 209 mg.L<sup>-1</sup> and Na was 185 mEq.dL<sup>-1</sup>. Cardiopulmonary resuscitation (CPR) was performed to the patient who has developed cardiac arrest, patient not responding to CPR and died.

### 3. Discussion

The ornithine carbamoyltransferase gene is encoded on the X chromosome and is expressed in the mitochondrial matrix of the small intestine and liver, where it catalyzes the synthesis of citrulline from carbamoyl phosphate and ornithine. OTC deficiency has an estimated incidence of 1 in 14,000 and is the only urea cycle disorder that is X-linked [1].

Recent studies on the biochemical and molecular bases of OTC deficiency revealed a wide spectrum of genetic defects resulting in different phenotypes. Mutations predicted to abolish all enzyme activity were found in the neonatal onset group, while mutations causing partial or varying enzyme deficiency were found in the late onset group [6,7]. We also thought heterozygous in our patient because of adult age and lack of long-term complications.

Older patients are more often asymptomatic heterozygotes and are becoming symptomatic in the presence of a precipitating factor such as infection, trauma, surgery, childbirth, psychological stress, high protein diet or sodium valproate (as well as our patient) [8,9]. In the presence of stress factors such as pregnancy and long-term use of sodium valproic acid, clinical presentation occurred by triggering hyperammonemia.

Clinical manifestations are known as symptoms such as lethargy, hypothermia, hyperventilation, cerebral edema, seizures and coma [1]. In our patient after the second pregnancy, symptoms such as lethargy, seizures, confusion has occurred and decreased within a few days. After the recent pregnancy, the patient was admitted to the ICU with complaints like severe confusion, hyperventilation, hypothermia, status epilepticus, coma and cardiac arrest with GCS value of 3.

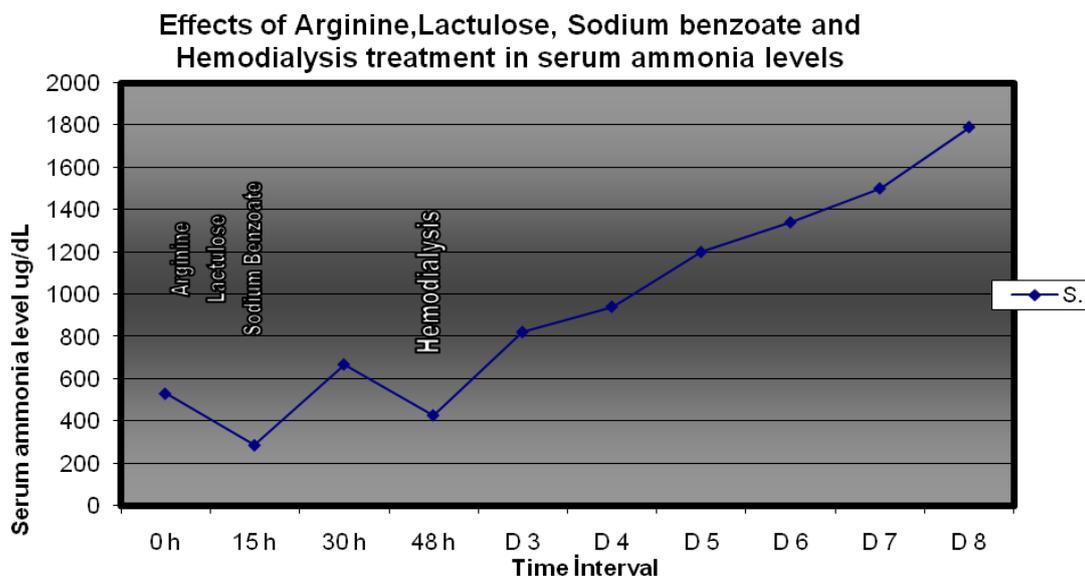
Ornithine carbamoyltransferase deficiency diagnosis based on demonstration of low plasma citrulline and arginine, increased plasma levels of glutamic acid and aspartic acid levels and increased urinary orotic acid levels [1]. However, no increase in plasma levels of ornithine was observed [10]. Definitive diagnosis can be obtained only by liver biopsy by measuring OTC enzyme activity and mutation analysis [2]. In our case, analysis of plasma amino acid levels and increased urinary orotic acid levels were consistent with OTC deficiency, allowing us to explain the etiology of his hyperammonemia and coma. No liver biopsy was performed in this case.

In general, the therapeutic principles for management of OTC deficiency include administration of urea cycle substrates that are lacking as a consequence of the enzymatic defect, administration of compounds that facilitate the removal of ammonia through alternative pathways, decreasing protein degradation by reducing nitrogen intake and minimalizing of protein catabolism. Arginine activates the urea cycle and should be administered as soon as the diagnosis is suspected [1]. Activation of alternative pathways with agents such as sodium benzoate (*as in our case*), sodium phenyl butyrate or glycerol phenylbutyrate will be useful in reducing serum ammonia level [11,12].

Liver transplantation should be considered only in patients with recurrent episodes of hyperammonemia and unresponsive to medical therapy. Levocarnitine is useful

in hyperammonemia associated to primary carnitine deficiency usually associated with hypoketotic hypoglycemia, cardiomyopathy, hepatomegaly, and increased transaminases serum levels. Levocarnitine may be also useful in cases with hyperammonemia due to administration of valproic acid [13,14].

There is not a definitive guideline as to when to initiate dialysis in a patient with hyperammonemia, However, if the blood ammonia level is more than three to four times from the upper limit or is increasing quickly, and/or if encephalopathic condition occurred, high-efficiency hemodialysis should be considered [15]. In encephalopathic patients, emergency dialysis should be applied immediately to prevent brain injury which may be caused by exposure to high blood ammonia levels. Quickly removal of ammonia from blood through dialysis is not associated with disequilibrium syndrome, because ammonia is a gas and is not osmotically active [16]. When normal blood ammonia level is reached, dialysis must be terminated and urea cycle medications must be applied. In our case, in the late stage of serum ammonia level of 670  $\text{mmol.L}^{-1}$ , dialysis performed. In Figure 1, effects of arginine, lactulose, dialysis treatment in decreasing serum ammonia levels have been shown. Although a little decrease in amount of ammonia levels, dialysis could not be continued due to unstable hemodynamics and coma. She lost her life because of increasing ammonia levels although receiving high-dose inotropic support.



**Figure 1.** Effects of arginine, sodium benzoate, lactulose and hemodialysis treatment in late-onset OTC deficiency

This case emphasize that late-onset OTC deficiency can occur in any age of the highlights and our case was 28-year-old patient. Serum ammonia levels should be measured in cases such as intravenous steroid usage, high-protein diets or amino acids, prolonged fasting, and of course extreme stress. Also drugs which contraindicate in late-onset urea cycle disorders such as valproic acid should be avoided.

#### 4. Conclusion

Unexplained neurological symptoms in a patient with no history of liver disease should raise the suspicion of a

urea cycle disorder. Late-onset OTC deficiency can be successfully treated with hemodialysis, arginine and sodium benzoate administration. In our case, despite appropriate treatment, poor general condition, severity of encephalopathy and deep coma were the reasons of treatment failure. Therefore, it should be noted that mortality and neurological sequelae due to late-onset urea cycle disorders can be reduced with early diagnosis and appropriate treatment.

#### References

- [1] Brusilow SW, Maestri NE. "Urea cycle disorders: diagnosis, pathophysiology, and therapy". *Adv Pediatr* ; 43. 127-70. 1996.

- [2] B.C. Lanpher, A. Gropman, K. A. Chapman, U. Lichter-Konecki, Urea Cycle Disorders Consortium, and M. L. Summar, "Urea cycle disorders overview," in GeneReviews [Internet], R.A.Pagon, T. D. Bird, C. R. Dolan, K. Stephens, and M. P. Adam, Eds., University of Washington, Seattle, Wash, USA, 1993-2003.
- [3] Applegarth DA, Toone JR, Lowry RB. Incidence of inborn errors of metabolism in British Columbia, 1969-1996. *Pediatrics* 2000; 105: e10.
- [4] Kang ES, Snodgrass PJ, Gerald PS. "Ornithine transcarbamylase deficiency in the newborn infant". *J Pediatr.* 82(4): 642-9, Apr.1973.
- [5] McCullough BA, Yudkoff M, Batshaw ML, Wilson JM, Raper SE, Tuchman M. "Genotype spectrum of ornithine transcarbamylase deficiency: correlation with the clinical and biochemical phenotype". *Am J Med Genet.* 93(4). 313-9. Aug.2000.
- [6] Tuchman M, McCullough BA, Yudkoff M. "The molecular basis of ornithine transcarbamylase deficiency". *Eur J Pediatr.* 159(Suppl 3). S196-8. Dec.2000.
- [7] Tuchman M, Morizono H, Rajagopal BS, Plante RJ, Allewell NM. "The biochemical and molecular spectrum of ornithine transcarbamylase deficiency". *J Inherit Metab Dis.* 21(Suppl 1): 40-58. 1998
- [8] Gordon N. "Ornithine transcarbamylase deficiency: a urea cycle defect" *Eur J Paediatr Neurol.* 7(3). 115-21. 2003.
- [9] Ellaway CJ, Bennetts B, Tuck RR, Wilcken B. "Clumsiness, confusion,coma, and valproate". *Lancet.* 353(9162). 1408. Apr24.1999.
- [10] Choi D.E, Lee K.W, Shin Y.T, and Na KR, "Hyperammonemia in a patient with late-onset ornithine carbamoyltransferase deficiency," *Journal of Korean Medical Science.* 27(5). 556-9. May.2012.
- [11] Diaz G.A, Krivitzky L.S, Mokhtarani M. et al., "Ammonia control and neurocognitive outcome among urea cycle disorder patients treated with glycerol phenylbutyrate," *Hepatology.* 57(6), 2171-9. Jun.2013.
- [12] Maillot F and Crenn P. "Urea cycle disorders in adult patients," *Revue Neurologique,* 163(10). 897-903. Oct.2007.
- [13] Magoulas PL and El-Hattab AW, "Systemic primary carnitine deficiency: an overview of clinical manifestations, diagnosis, and management," *Orphanet Journal of Rare Diseases.* 7. 68. Sep 18.2012.
- [14] Mock CM and Schwetschenau KH, "Levocarnitine for valproic-acid-induced hyperammonemic encephalopathy," *Am J Health Syst Pharm.*, 69(1).35-9. Jan1.2012.
- [15] Mathias RS, Kostiner D, Packman S. "Hyperammonemia in urea cycle disorders: role of the nephrologist." *Am J Kidney Dis.* 37(5). 1069-80. May. 2001.
- [16] Wiegand C, Thompson T, Bock GH, Mathis RK, Kjellstrand CM, Mauer SM. "The management of life-threatening hyperammonemia: a comparison of several therapeutic modalities". *J Pediatr.* 96(1). 142-4. Jan.1980.