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Case Report

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Innocent Adult-onset type II citrullinemia complicating pregnancy

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Abstract

Type II citrullinemia (CTLN2) is a rare autosomal recessive disorder characterized by hyperammonaemic encephalopathy, resulting from mutations in the SLC25A13 gene. It has age-related clinical manifestations, including neonatal intrahepatic cholestasis and adult-onset presentations. This case report presented a pregnant woman diagnosed with innocent CTLN2**.** A 22-year-old pregnant woman was diagnosed with CTLN2 after presenting with mental fog, agitation, and elevated ammonia levels. Her pregnancy was terminated, and she subsequently had three more successful pregnancies, during which she was treated with sodium benzoate, L-Arginine, and a protein-poor diet. Her symptoms and liver function tests improved with treatment. This was the first case report of a pregnant woman with CTLN2. Timely diagnosis and appropriate management strategies are crucial for both maternal and fetal health in cases of liver disease during pregnancy. CTLN2 should be considered in the differential diagnosis of coma in pregnancy, particularly when elevated liver enzymes and hyperammonaemia are present.

Keywords: citrullineamia, coma, L-arginine, pregnancy

1. Introduction

Citrin deficiency has two main age-related clinical manifestations neonatal intrahepatic cholestasis (NICCD), presenting in the first year of life, and type II citrullinemia in adulthood (CTLN2)(1). CTLN2 is a rare autosomal recessive adult-onset disorder characterized by episodes of hyperammonemic encephalopathy. It results from mutations in the *SLC25A13*, which is localized on chromosome 7q21.3 and encodes the liver-specific isoform of the mitochondrial aspartate–glutamate carrier (AGC2), also known as citrin (2). It is mostly developed by patients aged between 11 and 79 years. Unlike other types of citrullinemia, in citrullinemia, no primary defect has been found within the argininosuccinate synthetase (ASS) locus. Patients with CTLN2 present with various neurologic manifestations resembling those of hepatic encephalopathy closely (3). CTLN2 can cause premature death, and it manifests with frequent attacks of hyperammonaemia, neuropsychiatric symptoms, liver steatosis, and brain oedema (4).

CTLN2 patients usually present with hyperammonaemia and citrullinemia. Hyperammonaemia develops in patients with liver disease or if the urea cycle cannot control the ammonia load (5). Pregnancy itself is an important risk factor for this disease because it creates protein load. A spontaneous attack during pregnancy can cause diagnostic confusion with many other serious diseases and lead to overtreatment.

CTLN2 is also characterized by an unexplained liver-specific reduction in argininosuccinate synthetase, which is a key enzyme in the urea cycle, leading to decreased activity (6). The purpose of the urea cycle is to remove ammonia produced by deamination reactions in the mitochondrial matrix and to convert it to urea, which is excreted to achieve detoxification. Ammonia is very toxic to tissues, especially to neuronal tissues including the brain, and its accumulation can result in brain edema and neuropsychiatric symptoms (7).

According to detailed literature review results, type II citrullinemia cases diagnosed during pregnancy have not been previously reported in the literature. In this case report, a case with previously undiagnosed type II citrullinemia, who had an attack due to pregnancy and presented with coma, was presented, and the approach to such rare cases during pregnancy was summarized.

2. Case Report

A 38-year-old pregnant woman (Gravida 3, parity 2) was admitted for further evaluation of maternal citrullinemia type II to the high-risk pregnancy unit. The patients gave informed consent.

In 2006 (at the age of 22), she was referred to the current clinic for further evaluation of new-onset mental fog and agitation in the 16th gestational weeks of pregnancy. Sudden blurring of consciousness occurred after the patient was admitted to the hospital. In the physical examination, blood pressure was found to be 100/60 mmHg, and the patient was unconscious. In the laboratory investigation, she was negative for toxicology, serology (Hepatitis C Virus, Hepatitis B Virus, and human immunodeficiency virus, etc), autoimmunity, hormonal, and imaging studies, while the levels of aspartate

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aminotransferase (AST), alanine aminotransferase (ALT) and ammonia were elevated. The patient was intubated and referred to another hospital with the presumed diagnosis of liver failure. She was diagnosed with type 2 citrullinemia (CTLN2) there. Her first pregnancy was terminated due to poor health and a life-threatening condition. After pregnancy termination, the patient was administered L-Arginine and sodium benzoate and a protein-poor diet. With this treatment, liver function tests and general condition improved

Based on abdominopelvic sonography findings in 2012, all findings were normal except for mild hepatomegaly. The patient stopped the treatment in 2013 due to the absence of complaints, and the drugs she used caused nausea and fatigue.

Mild hepatomegaly was found on abdominal ultrasonography again in her second pregnancy in 2015. AST was found to be 18 IU/l, ALT to 21 IU/ L, and ammonia to 93.8 mc/l, and vitamin B12 replacement was started due to low serum vitamin B12 (95 pg/mL). At the 33rd gestational week of the patient, ammonia was found as 60.8 pg/mL, ALT as 78 IU/ L and AST: 68 IU/L. Treatment with sodium benzoate and a protein-poor diet was initiated. The patient delivered a 2850 g healthy male baby with APGAR 9 at the 1st minute and 10 at the 5th minute by normal vaginal mode at the 38th gestational week. Postpartum ammonia and liver function tests were within normal limits.

The patient had her third pregnancy under L Arginine and sodium benzoate treatment in 2017 and gave birth by normal vaginal route without any antenatal or postnatal complications. The patient did not receive postpartum sodium benzoate and L arginine treatment.

The patient was admitted to the current clinic at the 26th week of gestation in her fourth pregnancy in November 2022. She was 38 years old when presenting to the current clinic. In the examinations of the patient, ammonia was 58. 7 mc/L, AST 598 IU/L, and AST: 758 IU/L. Serologic and autoimmunity studies were all negative. The patient was consulted with the gastroenterology department, and treatment with sodium benzoate, L-arginine, and ursodeoxycholic acid (total daily dose of 750 mg) was initiated. Liver function tests and ammonia levels improved with treatment The patient gave birth to a healthy male baby with a birth weight of 3240 g, Apgar score 6 at 1 min. and 8 at 5 min by vaginal route spontaneously at 38 weeks of gestation. There were no postpartum maternal and neonatal complications. Postpartum ammonia (42.9 μmol/L (range 6-47)) and liver function tests (ALT 19 IU/L (range, 0-45), AST 19 IU/L (range 0-35)) were within normal limits.

3. Discussion

Adult-onset CTLN2 is known to be one form of citrin deficiency in urea cycle enzymes and results from mutations in the citrin gene. The other manifestations of CTLN2 include disorientation, abnormal behaviour, seizures, coma, and brain oedema (8). Citrin deficiency was described for the first time in Japan. However, subsequent cases were identified in Korea, Israel, Czech, China, England, and the United States, suggesting that citrin deficiency may be seen worldwide.

Presentation of CTLN2 is sudden and usually between 20 and 50 years of age. Our patient was diagnosed with CTLN2 when she was 22 years old. The diagnosis of citrin deficiency is established in a person with characteristic findings, including increased blood or plasma concentration of ammonia (hyperammonaemia). In our case, the level of ammonia was elevated. In one study investigating Type II (adult onset) citrullinemia, four of 10 patients had hyperammonaemia (9).

Urea cycle enzyme disorders result in the accumulation of toxic levels of ammonia in the blood due to deficient or absent enzymes involved in the urea cycle. Liver transplantation is considered an ideal treatment for these disorders, as the liver is the main site of urea cycle activity. However, conservative treatments such as a low-protein diet, dietary arginine supplementation, and medication can provide temporary relief by reducing ammonia levels. These treatments include sodium citrate, sodium benzoate, lactulose, non-absorbed antimicrobial agents, and branched-chain amino acid infusion. These treatments do not address the underlying enzyme deficiency and are only temporary solutions. For severe cases, liver transplantation may be necessary (10).

Recent studies have highlighted the importance of diet in CTLN2. It was demonstrated that a Medium-chain triglycerides supplement with a low–low-carbohydrate formula supplementation has a revolutionary effect on the treatment of CTLN2. It promptly decreases blood ammonia levels in six patients and improves hepatic enzyme expression and steatosis in one patient after long-term treatment (11). Our patient received a protein-poor diet, and her symptoms resolved over time.

Liver diseases during pregnancy pose a significant clinical challenge because they may affect both the mother and unborn baby. Abnormal liver tests are encountered in 3% to 5% of pregnancies due to numerous potential causes, and clinical symptoms range from self-limiting to rapidly fatal. In our case, the patient had mild hepatomegaly with elevated levels of AST and ALT that were returned to normal values with medical therapy. Timely diagnosis of liver disease during pregnancy is of great importance in order to establish appropriate management strategies. CTLN2 should be kept in mind in the differential diagnosis of liver diseases, especially in the presence of elevated liver enzymes and hyperammonaemia. To the best of our knowledge, this is the first case reported in the literature on a pregnant woman with CTLN2.

Informed consent

Informed consent was obtained for publication of this case report.

Conflict of interest
Authors indicated that they have not any financial relationship with the organization that sponsored this case report.

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Authors' contributions
Concept: M.A., Design: M.A., Data Collection or Processing: M.A., E.S.G.G., Analysis or Interpretation: M.A., S.G., E.S.G.G., Literature Search: M.A., S.G., Writing: M.A., S.G.

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