Pregnancy-related Type Citrullinemia Type 1: an Analysis of 14 Cases and Review of the Literature

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Abstract

Citrullinemia type 1 (CTLN1) is a rare autosomal recessive urea cycle disorder, without functional argininosuccinate synthase (ASS) enzyme, mostly occurring in newborns and infants, but it has been reported having an adult-onset in carriers of the pathogenic gene, and even more rarely, the onset of the disease is pregnancy related. The diagnosis and management process of pregnancy-related type citrullinemia 1 was found very challenging in the clinical practice. Citrullinemia type 1 was, often seen in newborns with a worldwide prevalence of 1:44,300–250,000, characterized by hyperammonemia and elevated citrulline levels in blood and urine as clinical features. Since 1980, only 14 cases with onset during pregnancy and puerperium have been reported. This review provides an overview of the relationship between Citrullinemia type 1 and pregnancy and discusses the mechanisms, clinical manifestations and genetic characteristics of pregnancy-related onset.

Background

Citrullinemia type 1 (CTLN1) is a type of urea cycle disorders (UCD) and inherited in an autosomal recessive manner with a worldwide prevalence of 1:44,300–250,000(1–4). Citrullinemia type 1 is caused by mutations in the argininosuccinate synthase 1 (ASS1), on chromosome 9q34.11, which is the only functional gene encoding argininosuccinate synthase (ASS) (5). The deficiency or absence of the rate-limiting enzyme ASS in the urea metabolism, in which citrulline is condensed with aspartate to form argininosuccinate, causing an abnormal accumulation of citrulline (see figure 1)(6). Citrullinemia type 1 has been found to be associated with more than 137 kinds of ASS1 mutations, mainly missense mutations, and a variant in the promoter sequence was found to be a cause of CTLN1(2, 7).

Most cases of CTLN1 are found in the neonatal period with acute hyperammonemia and progressive lethargy, poor feeding, and vomiting; in late-onset cases, the onset may occur at any time of life, and having milder clinical symptoms than the acute neonatal patients(8). Among these late-onset cases, pregnancy-related type CTLN1 have more special characteristics. There were only 14 pregnancy-related cases reported since 1980s(9–21). During pregnancy and the postpartum period, when women experience significant physical and psychological fluctuations, it is often difficult to diagnose and provide acute management, and the prognosis for patients may be worse(16, 19, 20). Through the analysis of this case series, this review outlines the relationship between CTLN1 and pregnancy and discusses the clinical manifestation, genetic characteristics, and treatment approach of pregnancy-related onset CTLN1.

Diagnosis

Establishing of the diagnosis of CTLN1 requires the following manifestations to be met, elevated plasma ammonia concentration, elevated plasma citrulline concentration and/or biallelic pathogenic variants in ASS1 on genetic testing(5). Molecular genetic testing approaches can include single-gene testing and use of a multigene panel(22).

Citrullinemia type I affects the urea cycle and is manifested by hyperammonemia and elevated citrulline concentration in blood and urinary, usually onset within a few days of birth with sleepiness, feeding difficulties, vomiting and shortness of breath(23, 24). Without timely interventions, an increase in intracranial pressure (ICP) secondary to hyperammonemia can lead to altered muscle tone, spasticity, epilepsy, stroke, loss of consciousness and result in newborn deaths(5, 25).

Neonatal probands often present with very early onset within the first week of life while on a full protein diet(26). There are typical initial symptoms, such as failure to feed, severe deficiency or total absence of activity, the related signs of lethargy, anorexia, hypothermia, seizures, neurologic posturing, and coma(26, 27).

The ASS1 mutations carriers may also have a milder late-onset or being asymptomatic for a lifetime. The delayed pathogenesis is unclear, which may be related to partial urea cycle enzyme deficiencies(28). The ammonia accumulation might be triggered at almost any time of life by illness or stress, resulting in mild elevations of plasma ammonia concentration(15, 18, 29). The patients with late onset generally have milder symptoms, however the late-onset type CTLN1 related to pregnancy often come along with rapid progression of the disease, with non-classic presentation like drowsiness, severe headache, convulsions, ataxia, migraine-like attacks, visual loss, intellectual disability and other neuropsychiatric symptoms(5).

The diagnosis of CTLN1 requires a combination of clinical manifestations and laboratory findings. According to the time of onset, severity of the disease and patient characteristics, CTLN1 can be classified into four types: ①neonatal (classic) type; ②milder late-onset (atypical) type; ③asymptomatic type; ④pregnancy-related type(5).

Citrullinemia type I is associated with genetic and environmental factors including diet, diagnosis and treatment(2, 23, 30). Since adult or late-onset metabolic genetic disorders lack specific manifestations, early detection, diagnosis, intervention or treatment is critical, and it is important to correlate these non-specific signs and clues to disease.

Differential Diagnosis

The diagnosis of pregnancy-related type CTLN1 is challenging because of the low incidence of CTLN1 and the necessity to differentiate CTLN1 not only from other urea cycle disorders but also from other disorders of pregnancy.

Women experience hormonal and physical function changes during pregnancy that bring along physical manifestations such as pregnancy sickness during early pregnancy, which can easily be confused with pathological changes of metabolic abnormalities(17, 20). The anxiety and depressive states, and behavioral changes in pregnancy and the postpartum period also tend to mask the altered neurological status of metabolic disease manifestations(16).

Pregnancy-related type CTLN1 requires distinguishing from specific diseases during pregnancy, including pre-eclampsia, HELLP syndrome, acute viral hepatitis, intrahepatic cholestasis of pregnancy, and acute fatty liver of pregnancy. ¶Pre-eclampsia encephalopathy: characterized by hypertension, proteinuria, convulsions, headache, blurred vision and vomiting. ¶HELLP syndrome(Hemolysis, Elevated Liver Enzymes, Lowered Platelets): mostly characterized by hypertension, proteinuria, hemolysis, elevated aminotransferases and reduced platelet count, and less frequently by impaired consciousness, occurs in the third trimester but can also start soon after delivery. ¶Acute fatty liver of pregnancy(AFLP): mostly occurs in late pregnancy, initially manifested by non-specific symptoms such as nausea, malaise, liver failure, progressive jaundice and coagulation dysfunction can occur. However, none of the above diseases showed elevated citrulline or ammonia concentrations, suggesting that blood ammonia testing is an important and necessary differential diagnostic test.

Genetic metabolic disorders need to be first considered after excluding other organic pathologies resulting in elevated blood ammonia(31). However, differential diagnosis between late onset urea cycle disorders is often difficult due to the fact that they share the similar presentation and laboratory findings, such as hyperammonia and non-specific psychoneurological symptoms. The clinical course in adults with citrullinemia type II (CTLN2, citrin deficiency) and ornithine transcarbamylase (OTC) deficiency is milder than that of CTLN1, with mild hyperammonemia and citrullinemia and higher incidence in adults, which are the reasons why these two diseases are more often considered first when making a diagnosis (32–34). Dihydrolipoamide dehydrogenase (DLD) deficiency has also been reported to display increased citrulline and ammonia(35). The application of genetic testing to identify mutated genes and GC-MS organic acid assays to analyze abnormal metabolites is important for diagnosis.

Clinical Features Of Pregnancy-related Type CtlN1

Pregnancy and puerperium are inducements of adult-onset urea cycle disorders(29, 36). Pregnancy-related type CTLN1 could be seen as even rarer cases of milder late-onset (atypical) type of CTLN1, while usually with more rapid disease progression. Physiological changes, like hormonal and metabolic status changes might be the important triggers for the onset of the disease and patients with pregnancy-related CTLN1, and can develop severe hyperammonemia, metabolic coma, and/or death during pregnancy or postpartum(5, 15, 30, 37). Patients can also be asymptomatic or have an acute onset during pregnancy or puerperium, associated with environmental factors, treatment, diet, and different gene mutations with different pathogenicity(14). It has been hypothesized that acute puerperal onset might be related to compensatory metabolism of maternal plasma ammonia by a healthy fetus, and that this unique "gene therapy" effect disappears after delivery, which may be a cause of puerperal onset(2, 14, 30). A multi-center study found that patients can developed psychiatric symptoms such as psychosis during pregnancy or postpartum, differentiated from perinatal psychiatric disorders(16).

Some patients have an onset early in pregnancy, usually in 10-14 weeks of gestation, which may be associated with an altered metabolic status or stress during pregnancy(9, 17, 20). High metabolic state during pregnancy, like hyperemesis gravidarum, increasing the protein breakdown, and the removing of nitrogen-containing metabolites beyond the maximum function of ASS, resulting in an elevated plasma ammonia, could be the initial of the episode(15, 30, 37). The recurrent vomiting (result in metabolic disorders) could be the potential inducement of CTLN1, yet also could be a psychoneurological symptom of high plasma ammonia(37).

Although, abnormal hepatic function does not occur as a major presenting feature in UCDs, impaired hepatic function with elevated transaminase (usually not significantly elevated) and/or coagulopathy (64.3%, 9/14, patient 1, 3, 4, 6, 10-14), as well as, behavioral & psychiatric illness (71.4%, 10/14, patient 1, 3, 4, 7-9, 11-14) are the two main initial manifestations in patients with pregnancy-related type CTLN1 (details in Table 1). Abnormal liver function can be mainly manifested as an increase in transaminase, and impaired coagulation due to abnormal hepatocyte function, resulting in impaired synthesis of coagulation factors. The underlying mechanism of hepatocellular impairment and abnormal liver function caused by pregnancy-related type CTLN1 is not well understood. However, some patients showed normal liver function and develop abnormal ALT/AST during disease progression(19).

The patients with CTLN1 might be asymptomatic probably due to low protein diet, and heterozygous mutations in ASS1(14). A dietary history of auto-selective vegetarianism, decreased protein intake, high carbohydrate intake and obesity (35.7%, 5/14, patients 4, 7-9, 13 in Table 1), as

well as, a history of behavioral and psychiatric illness, possibly resulting from chronic hyperammonemia, were other suggestive clues of CTLN1(29). Sleep disorders, delusions, hallucinations, and psychosis may occur as the hyperammonemic episode(38).

Genetic Characteristics

Characteristics of the patient's genetic background are still not adequately discussed. Although the correlations between genotype and phenotype was difficult to prove for the different environments and treatments(16). There are different phenotypes noticed for classic and milder late-onset type of CTLN1, suggesting that different mutation types have varying degrees of effect on structural changes in the protein, which in turn affects functional changes in ASS and influences the timing of onset and disease severity(22, 23). Despite the small number of reported cases, we have derived some patterns of patient genotype. Higher proportion of heterozygous (75.0%, 9/12) was found among reported pregnancy-related type cases (see Table 1), while patients with neonatal- or infantile-onset and severe disease had a higher proportion of homozygote (87%, 20/23), which suggested that late-onset or pregnancy-related type patients might be related to their genotype(30).

The severity of clinical symptoms is consistent with the degree of deficiency of ASS activity, homozygous pathogenic genotype would cause completely loss of function of ASS activity(28). In cases of pregnancy-related type CTLN1, considering no obvious clinical symptoms was found before pregnancy, we hypothesized that the apparent symptoms during pregnancy or postpartum might be related to the fact that there were some limited activities in their ASS function. On further analysis, if the patient was a homozygous pathogenic gene, then it could be determined that this particular mutation type might bring about a specific degree loss of function of ASS, whereas in patients with heterozygous genotype, it was difficult to determine the enzyme function because of the presence of a normal allele capable of encoding a normal function ASS, which can be proved with enzyme activity tests (5, 18).

Managements And Treatments

Hyperammonemia and its duration are highly correlated with patient prognosis and pregnancy outcome. Elevation of either above acceptable levels (ammonia >100 $\mu\text{mol/L}$ or plasma citrulline >~100 $\mu\text{mol/L}$) is sufficient evidence to initiate treatment. Once a diagnosis of a CTLN1 is made, treatment of acute manifestations can be started(8).

Emergency treatment should be used, in the case of acute hyperammonemia, such as stopping protein intake, along with the use of nitrogen scavenger therapy, such as sodium benzoate, sodium phenylacetate, and L-arginine to remove excess nitrogen. intravenous glucose to maintain energy supply, L-arginine supplementation and hemodialysis(HD) if necessary(19). Chronic management includes lifelong dietary management to maintain plasma ammonia concentrations below 100 $\mu\text{mol/L}$ and plasma glutamine concentrations near normal; administration sodium phenylbutyrate or glycerol phenylbutyrate; a long-term low-protein diet with L-arginine and other essential amino acids needs to be maintained(5).

In patients carrying the pathogenic gene, the genotype of the fetus can be analyzed by direct or indirect measurement of chorionic ASS enzyme activity at 12 weeks of gestation, or direct analysis of amniotic fluid cells at 16 to 18 weeks of gestation(39). Citrulline concentration or citrulline to ornithine + arginine ratio in amniotic fluid at 15-16 weeks of gestation can be used as a complementary test(40). The prognosis of newborns with CTLN1 remains poor even in centers with abundant medical resources(24), and patients may choose to continue their pregnancy and deliver in a hospital with newborn care capabilities(30). The failure to diagnose and treat at an early stage is a major cause of poor prognosis in newborns(6). Blood ammonia testing, GC-MS screening of blood and urine should be performed as early as possible.

There are no specific guidelines on how women who have a physician-managed pregnancy should choose their delivery method. Delivery might be an inducing factor of CTLN1(19). During vaginal delivery, the patient expends a lot of energy and protein catabolism increases, which can lead to citrulline accumulation and increased blood ammonia levels due to reduced or deficient ASS enzyme activity in CTLN1 patients, thus triggering the disease. A delivery method that minimizes the patient's stress level and results in a calmer condition seems to be a safe delivery method for CTLN1 patients.

Learning Points For Physicians

1. Some patients show a present of gestational hyperemesis. Avoiding metabolic stress or crisis during pregnancy and puerperium is the key to avoid the onset or progression of CTLN1.
2. Unexplained abnormal hepatic function, coagulopathy, vomiting and behavioral disorders might be important clues and early symptoms of UCDs. Plasma ammonia should be tested as soon as possible.

3. Rare genetic metabolic diseases might be considered if hyperammonemia is detected, after ruling out hepatic dysfunctions, neuropsychiatric disorders and infectious diseases. Genetic testing and GC-MS organic acid testing are important for diagnosis.
4. A multi-disciplinary team is important for diagnosis and managements, for CTLN1 during pregnancy, continuous plasma ammonia monitoring, aggressive ammonia-lowering therapy, neurological monitoring and protection are required.

Table 1
Cases of pregnancy-related type CTLN1

Patient	Mutation type	Mutation	Year	Initial symptoms and clinical course	Outcome	Country (origin)	Reference
1	Homozygote	c.794G>A	1980	Altered level of consciousness, at week 13 gestation, hypertransaminasemia.	N.R.	Japan	Yamada et al.(9)
2	Heterozygote	c.352G>A, c.IVS15+1_+13del13	1996	Repeatedly induced by pregnancy.	N.R.	Japan	Ohta et al.(10)
3	Heterozygote	c.257G>A, c.1168G>A	1993	Occasionally experienced headache, dizziness during walking, and consciousness disturbance, fulminant hepatic failure at week 19 gestation.	Pregnancy terminated, died 7 months later.	Bolivian	Ito et al. (12)
4	Heterozygote	c.929A>G, c.892delG	2005	Abnormal ALT, coagulopathy, ammonia and psychiatric symptoms, postpartum.	Returned to normal neurologic status.	USA	Enns et al.(13)
5	Heterozygote	c.928A>C, c.IVS15-1G>C	2004	Asymptomatic with elevated plasma and urine citrulline.	Normal outcome.	Canada	Potter et al.(14)
6	Heterozygote	c. 352 G>A, c. 1168 G>A	2010	Acute liver failure, nausea and scleral icterus, at week 19 gestation.	Delivery with a healthy baby at week 37 gestation; Well on treatment	USA	Salek et al.(15)
7	Homozygote	p.A118T	2010	Irritability and difficulties in oral speech, 2 days after delivery, then movement disorder, progression to coma.	Died on day 7 after delivery.	Switzerland	Harbrle et al.(16)
8	Homozygote	c.773+49C>T	2010	Headaches, dizziness and disorientation 4 days after delivery, then generalized tonic seizures, progression to coma.	Full recovery after 6 months	Switzerland	Harbrle et al.(16)
9	Heterozygote	c.1088G>A	2010	Disorientation and drowsiness, 4 days after delivery, then rapid progression to coma.	Well on treatment.	Switzerland	Harbrle et al.(16)
10	N.R.	N.R.	2014	Vomiting, initial presentation with 'hyperemesis gravidarum', acute liver failure (hypoglycemia, abnormal ALT, coagulopathy, hyperammonemia), at week 14 gestation.	Delivery with a healthy female baby at week 36 gestation; Well on treatment	Australia	Sinclair et al.(17)
11	Heterozygote	N.R.	2018	Altered mental status, acute liver failure at week 22 gestation.	Delivery with a healthy male baby; ammonia level decreased with treatment but increased peripartum.	USA	Randall et al.(18)
12	Heterozygote	c.422T>G, c.431C>G	2020	The appearance of altered mental status, abnormal ALT, coagulopathy, hyperammonemia, 10 hours after delivery, then rapid progression to coma.	Died on day 6 hospitalized.	China	Ai et al. (19)

N.R. not reported;

Patient	Mutation type	Mutation	Year	Initial symptoms and clinical course	Outcome	Country (origin)	Reference
13	Heterozygote	c.421-2A>G, c.1046>G	2020	Sleep disorders, depression, poor response, sudden generalized convulsion, vomiting, coagulopathy and hyperammonemia at week 12 of gestation.	Died on day 14 hospitalized.	China	Wang et al.(20)
14	Homozygote	N.R.	2021	Altered mental status 4 days after delivery, hyperammonemia, then acute liver failure (elevated ALT/AST and INR)	Well on treatment, mental status improved, AST/ALT and INR normalized.	USA	Wykowski et al.(21)
N.R. not reported;							

Abbreviations

CTLN1: Citrullinemia type 1; ASS: argininosuccinate synthase; ICP: intracranial pressure; CPS I: Carbamyl phosphate synthetase I; OTC: Ornithine transcarbamylase; ASS: Argininosuccinate synthase; ASL: Argininosuccinate lyase; HELLP: Hemolysis, Elevated Liver Enzymes, Lowered Platelets; AFLP: Acute fatty liver of pregnancy; CTLN2: citrullinemia type II; DLD: Dihydrolipoamide dehydrogenase; ALT: Alanine transaminase; AST: Aspartate transaminase; UCD: Urea Cycle Disorder; HD: hemodialysis; GC-MS: Gas Chromatography-Mass Spectrometry;

Declarations

ETHICS APPROVAL AND CONSENT TO PARTICIPATE:

According to the ethical guidelines of the Human Ethics Committee of Shengjing Hospital of China Medical University, written ethics approval was not required.

CONSENT FOR PUBLICATION:

Not applicable.

AVAILABILITY OF DATA AND MATERIALS:

All data generated or analysed during this study are included in published articles.

COMPETING INTERESTS:

Authors have no competing interests to declare.

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AUTHORS' CONTRIBUTIONS:

JL, LZ and FL contributed to design of study and manuscript writing. RC, MFA, LH and QC contributed to critically analyzing the manuscript and providing important intellectual contents. All authors read and approved the final manuscript.

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Figures

CPS I: Carbamyl phosphate synthetase I

OTC: Ornithine transcarbamylase

ASS: Argininosuccinate synthase

ASL: Argininosuccinate lyase

Figure 1

Urea Cycle and Related Enzymes