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Case Report

Intrahepatic Cholestasis Secondary to Citrin Deficiency

Rachel Chan Tzun* and Jorge Sales Marques

Pediatric department, Centro Hospitalar Conde S. Januário, Macau, China

***Corresponding Author:** Rachel Chan Tzun, Pediatric department, Centro Hospitalar Conde S. Januário, Macau, China.

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Abstract

Citrin deficiency (neonatal-onset type II citrullinemia), is an autosomal recessive metabolic disorder, caused by a mutation of the *SLC25A13* gene. Infants with citrin deficiency, have transient intrahepatic cholestasis, hepatic steatosis and parenchymal cellular infiltration associated with hepatic fibrosis, low birth weight, and growth retardation. Citrin deficiency as a cause of neonatal intrahepatic cholestasis occurs almost exclusively in Asian infants. Later in life, some of these patients may develop adult-onset citrullinemia type II which is characterized by fatty liver, hyperammonemia, and neurological symptoms, with sudden onset of disorientation, abnormal behavior, convulsions and coma due to hyperammonemia. Two cases of citrin deficiency are described first time in Macau-China. They both are male and showed intrahepatic cholestasis in the first 10 and 57 days of life. The alpha-fetoprotein was elevated as so as citrulline levels. Only one case has hyperammonemia. Molecular study confirmed mutation of the *SLC25A13* gene, homozygous in the case 1 and homozygous and heterozygous in the case 2. After lactose, free diet and vitamins, both cases showed normal development milestones until now.

Keywords: *Intrahepatic Cholestasis; Citrin Deficiency*

Introduction

Citrin deficiency (neonatal-onset type II citrullinemia), is an autosomal recessive metabolic disorder, caused by a mutation of the *SLC25A13* gene. The defective transport between the mitochondria and the cytosol, leads to insufficient substrate for argininosuccinate synthetase (ASS) and secondary functional deficiency of ASS activity [1]. Infants with citrin deficiency, have transient intrahepatic cholestasis, hepatic steatosis and parenchymal cellular infiltration associated with hepatic fibrosis, low birth weight, and growth retardation. Citrin deficiency as a cause of neonatal intrahepatic cholestasis occurs almost exclusively in Asian infants. The incidence is 1/19000 in Japan, 1/50000 in Korea and 1/17000 in China. The frequency of *SLC25A13* homozygotes in China, were calculated to be 1/9200 to the south of the Yangtze river and 1/3500000 to the north of the Yangtze river [2]. Later in life, some of these patients may develop adult-onset citrullinemia type II which is characterized by fatty liver, hyperammonemia, and neurological symptoms, with sudden onset of disorientation, abnormal behavior, convulsions and coma due to hyperammonemia [3]. Plasma amino acids analysis showed significant elevation of citrulline, methionine and threonine.

Cases Report

Case 1

Preterm male with 34 weeks of gestational age. Normal delivery. Birth weight: 1350g. Apgar 5/10/10. On physical examination showed hypospadia and ventricular septal defect. Feeding started on day 2 with breast milk. Tolerated well. No history of hypoglycemia or other event. Always yellow stools since them. The parents are young and unrelated. No family history of cholestasis, liver problem or psychiatric

disease. On day 10, found cholestasis with direct/total bilirubin > 30%. Alkaline phosphatase (AF) and G-Glutamyl transferase (GGT), were elevated. Alpha-fetoprotein levels (AFP) was very high: 125380.00 ng/ml (N: < 7.0). Acid-base, lactate, ammonia, glucose, TSH/FT4, reducing substance, alpha 1-antitrypsin and liver ultrasound were normal. Plasma amino acids showed elevated levels of methionine, threonine, citrulline and threonine: serine ratio. These results confirmed citrin deficiency and lactose-free formula was started imediately. The molecular study confirmed homozygous SLC25A13 NM _014251.2:c.852_855de 1TATG p.(Met285Profs*2), compatible with neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD.MIM#605814).

Now is under treatment with lactose free MCT riched formula, vitamin K, multiple vitamin, furosemide and spironolactone. The last two drugs for congenital heart disease. At 3 month of age, the weight is 3600 g. Development milestone according to the age. Blood test control, showed levels of AFP much better. (droped to 1566.00 ng/ml) (Table 1).

Blood test	Total bilirubin (micromol/L) N: 0-24	Direct bilirubin (micromol/L) N: < = 5	GGT (U/L) N: < 60	AF (U/L) N: < 449	AFP (ng/ml) N:	Citrulline (mmol/l) N: 14-32
1m	82	23.2	151	669	125380	379
3m	7	-	103	770	1566	173

Table 1: *Blood test at the diagnosis and 3 month of age – case 1.*

Case 2

A 57 days old male, was found to have cholestasis. Feeding well, no frequent vomiting with yellow color of the stools. He was borned by normal delivery, with 40 weeks of gestational age Birth weight: 3520 g.Apgar 10/10/10. The parents are young and non-consanguineous. No family history of liver disease, seizure or psychiatric disorders.

On physical examination, despite mild jaundice, all the rest was unremarkable.

Blood test revealed high ammonia in two occasions: 99 and166 micromol/L. Lactate was also high: 4.8 nmol/L. Direct/total bilirubin > 65%. The liver function showed high levels of ASL, AST, AF and GGT. The AFP was increased: 114003.48 ng/ml. Plasma amino acids was compatible with citrin deficiency with high levels of citrulline, threonine and threonine: serine ratio. The molecular study revealed apparent homozygous SLC25A13 NM_014251.2: c.1638_1660dup23.p(Ala554Gycfs*17). Heterozygous IVS16ins3kb was also detected. We started lactose free MCT riched formula, vitamin K and multiple vitamin.

Now, at 5y 6m of age, the development is unremarkable. Blood test showed normal liver function, AFP and ammonia levels (Table 2).

Blood test	Total bilirubin (micromol/L) N: 0-24	Direct bilirubin (micromol/L) N: < = 5	GGT (U/L) N: < 60	AF (U/L) N: < 449	AFP (ng/ml) N	Ammonia (mmol/L) N: 16-60	Citrulline (mmol/l) N: 14-32
1m	227	158.7	149	661	114013	99	445
8m	5	-	13	153	10.9	52	67
5 y	-	-	10	223	3.31	36	26

Table 2: *Blood test at the diagnosis, 8 months and 5 year of age – case 2.*

Discussion

The two cases are typical presentation on neonatal onset of citrin deficiency. In both situations, the patients showed intrahepatic cholestasis. In Asia, all newborns and infants with this kind of presentation associated or not with hepatic steatosis, metabolic and genetic studies for citrin deficiency, should be performed.

We need to exclude other causes of intrahepatic cholestasis, like biliary atresia, alpha 1 – antitrypsin or carbohydrate degradation glycoprotein, but in those cases, plasma citrulline is normal.

Citrin deficiency showed high levels of amino acid citrulline. Argininosuccinate synthetase(ASS) and argininosuccinate lyase (ASL), both deficiency of urea cycle disorder(UCD), can appear also with citrulline elevated in plasma, but argininosuccinic acid in urine is absent in the former and is low in the latter. In UCD, ammonia levels are high, more than 200 mmol/L at diagnosis. In our 2 cases of citrin deficiency, only in case 2, the ammonia levels were high, but less than 200 mmol/L. The case 1 was homozygous and case 2 homozygous and heterozygous for *SLC25A13* gene. IVS16ins3kb was described first in 2008 by Tabata., *et al*. in Japan. After, in all East Asian patients tested were also found, suggesting that these mutations may have occurred very early in some area of East Asia [4].

Prenatal diagnosis and genetic counseling was proposed for the parents in future pregnancy.

Breast milk, which is high in carbohydrates, is not suitable diet for these patients. Dietary macronutrient formula types with higher protein levels are good source of food. Symptoms remit with fat-soluble vitamin supplementation and the use of lactose free formula or formulas containing medium-chain triglycerides [5]. Most patients show spontaneous improvement by one year of age. Some of them may have a progressive course with continued failure to thrive and dyslipidemia, chronic or fatal liver disease [6]. In those cases, without clinical improvement, the most effective treatment is this situation is liver transplantation.

In our two cases, so far the clinical evolution is good and the blood test controls are in desirable levels of citrulline in case 2. Growth and development milestones are normal for the age and sex of the affected children.

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