



Case Report

Analysis of Clinical and Pathological Features of a Case of Primary Carnitine Deficiency

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Abstract: In recent years, with the application of tandem mass spectrometry, an increasing number of patients with primary carnitine deficiency have been diagnosed in China. Because it is mainly concentrated in cities with good conditions, there are few reports of this disease in China. At present, the existing reports have mainly focused on screening and there are no reports addressing the degree of lesions in patients with primary carnitine deficiency. This article reports an pathological diagnosis upon autopsy of a patient with primary carnitine deficiency and describes and describes the pathological features of primary carnitine deficiency. The clinical data of the patient with primary carnitine were retrieved. A histologic analysis was performed on the liver. The autopsy pathology showed diffuse lesions in the patient's liver, interstitial pneumonia, pulmonary hemorrhage, pulmonary emphysema, and hilar lymphadenitis. The clinical response was characterized by abnormal liver function, fatty stool, abnormal renal function presenting as hematuria, and clinical manifestations such as elevated creatine kinase in the heart. Therefore, this pathological examination provides morphological diagnostic data for patients with primary carnitine deficiency and for the diagnosis of the degree of disease in these patients.

Keywords: Primary Carnitine Deficiency, Autopsy, Liver Enlargement, Chromosomal Genetic Disease

1. Introduction

Primary carnitine deficiency (PCD) causes low levels of carnitine in patients potentially leading to metabolic and cardiac symptoms [1]. It is caused by a mutation of the SLC22A5 gene leading to a defect in the function of the carnitine transporter. Clinical manifestations vary widely and mainly result in ketotic hypoglycemia, dilated cardiomyopathy, hepatomegaly, and muscle weakness. If not treated in a timely manner, the mortality is quite high. This study aims to report the clinical and autopsy pathological features of a child with primary carnitine deficiency at the age of 4 months.

2. Materials and Methods

A four-month-old infant was admitted to our hospital because of a cough for 10 days, wheezing, and gas promotion

for half a day. Ten days before admission, there was no occasional paroxysmal cough, cough, wheezing, gasp, fever, vomiting, or diarrhea. Four days before admission, the infant was treated with Cefixime granules and a Folcodine oral solution. However, the condition was not improved. Twelve hours prior to admission, the infant started wheezing and developed shortness of breath without cyanosis, convulsions, screaming, or confusion. A physical examination showed that the lungs were thick and the fine wet rales could be smelled; the lower right rib of the liver was 3.5 cm and the texture was soft. The infant was delivered by cesarean section at full term. His sister had died at the age of five months; the postmortem autopsy showed an enlarged heart and liver. After admission, the patient's blood biochemical was promptly examined, and the results showed 193 U/L alanine aminotransferase, 503 U/L aspartate aminotransferase, 644 U/L alpha-hydroxybutyrate dehydrogenase, 4.29 mmol/L blood glucose, 979 U/L lactate

dehydrogenase, 377 U/L creatine kinase, 39 U/LL creatine kinase CK-MB and 170.3 U/L aspartate aminotransferase isoenzyme. A routine stool examination revealed a 3+ fat ball and a conventional urinalysis revealed the presence of red blood cells (36.2/ μ l). Cardiac Doppler showed that the left heart was enlarged and the contraction function was decreased. Transabdominal ultrasound examination indicated that the liver was large and the echointensity was high. The chest X-ray showed a thickened texture in the lungs.

Immediately after admission, the patient was given oxygen. Wheezing, shortness of breath, and cyanosis were present. The patient's condition worsened. The infant was admitted to the pediatric intensive care unit (PICU). In the PICU, the infant was treated with tracheal intubation and ventilator-assisted breathing. Cefepime and oseltamivir were used for infection prophylaxis. Dopamine was used to improve cardiac function. Cardiac arrest occurred, leading to the death of the infant. An autopsy was performed after acquiring parental consent.

3. Results

The autopsy showed that the skin was slightly yellow. A transverse position of the heart was present (cardiothoracic ratio 1:2), the heart size was $4.6 \times 4.5 \times 3.5$ cm, the heart weight was 51.7 g, and the left ventricular wall thickness was 1.2 cm. The double lung lobe was normal with a plaque appearance and sinus bronchia secretion. Bleeding was present at a point on the surface of the thymus. The liver was enlarged ($19 \times 12 \times 6$ cm) with a gray-yellow surface and multiple congestion and bleeding points. The small intestine was flatulent.

Pathological findings are described below.

First, the liver was enlarged and the hepatic lobular structure was disrupted and had extensive diffuse translucent, vacuolar-like, and fatty-like degeneration of the hepatocytes (negative glycogen staining). Combined with clinical and laboratory test findings, the hepatic enlargement was considered to be caused by a congenital inherited metabolic disorder, such as a fatty acid metabolism disorder or another metabolic disease that can cause liver damage.

Second, translucent, vacuolar-like and fat-like degeneration of the proximal convoluted tubules were detected in the kidney.

Third, the left ventricular wall was slightly hypertrophied.

Fourth, signs of systemic inflammation were present, including interstitial pneumonia, pulmonary hemorrhage, pulmonary edema, emphysema, hilar lymphadenitis, interstitial myocarditis, interstitial inflammation, intestinal interstitial inflammation, and sinusitis.

Fifth, signs of hypoxia were present such as hepatic, renal, and intestinal bleeding.

After two weeks, the genetic test results detected a mutation in the SLC22A5 gene.

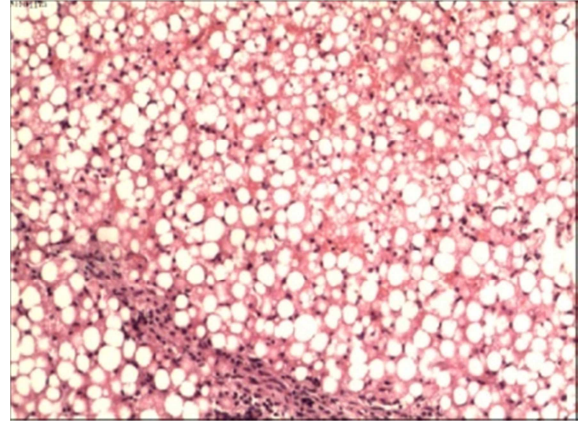


Figure 1. Liver histopathology. (Microscope magnification $\times 100$ times).

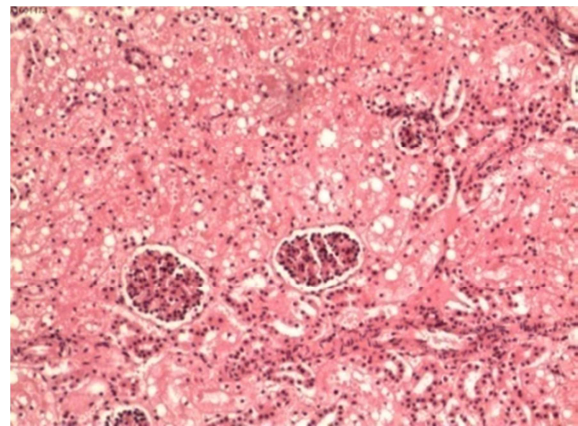


Figure 2. kidney histopathology (Microscope magnification $\times 100$ times).

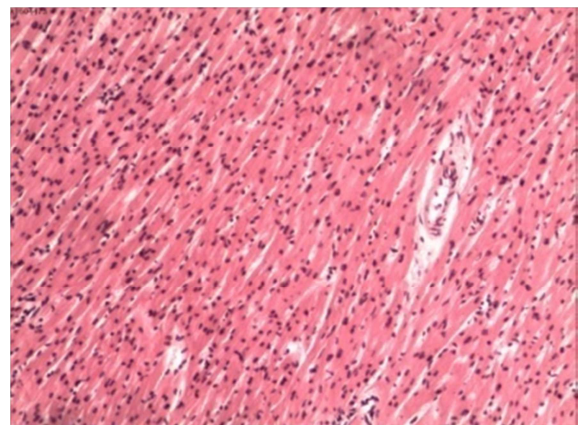


Figure 3. Cardiac histopathology (Microscope magnification $\times 100$ times).

Figure 1 shows that hepatocytes are widely diffuse, vacuolated, and fatty-like. Figure 2 shows that renal proximal convoluted tubules are vacuolated and fatty degeneration. Figure 3 shows that there is no myocardial degeneration.

4. Discussion

The most common age of onset for primary carnitine deficiency is between 1 and 7 years old. This is a potentially fatal disease in this age group, and it is a common disease of fatty acid oxidative metabolism [2, 3]. Domestic and

international reports of the prevalence of neonatal primary carnitine deficiency range from 1:4000 to 1:12000 [4, 5]. The highest incidence of primary carnitine deficiency (1:300) is in the Faroe Islands, an archipelago in the North Atlantic that remained geographically isolated for many centuries, where about 5% of the population is carrier for an abnormal allele [6, 7]. In 1998, Wu et al [8], confirmed that the gene SLC22A5, which encodes the OCTN2 protein is located on autosome 5q31 [9]. To date, a variety of mutations in this gene have been reported, and the mutation sites involve exons 1-9 and introns 3, 7 and 8. The mutation types include missense mutations, nonsense mutations, frameshift mutations and splicing mutations. Approximately 70% of patients with primary carnitine deficiency have at least one mutation site in the SLC22A5 gene [10]. Incomplete statistical data in Japan and the United States show that the SLC22A5 mutation rate in the general population is 0.5% to 1.0% [5]. A coding mutation of the SLC22A5 gene leads to decreased function of the carnitine transporter [11]. Because carnitine in food cannot be absorbed into the bloodstream from the gastrointestinal tract, the plasma and intracellular carnitine and acylcarnitine levels are reduced. Due to the defective expression of OCTN2, the carnitine intake in the tissue is continuously reduced and carnitine storage in the myocardium and skeletal muscle is reduced. Furthermore, the reabsorption of free carnitine by the kidney is reduced and a large amount of carnitine is discharged from the urine, eventually causing reduction or depletion of carnitine in the body [12]. Carnitine in the body mainly comes from dietary meat. The main function of carnitine is to assist the transport of long-chain fatty acids to the mitochondria to participate in β -oxidation. A lack of intracellular carnitine causes long-chain fatty acids to enter the mitochondria and accumulate in the cytoplasm. Concomitantly, the energy production of fatty acid oxidative metabolic pathways is reduced, particularly in situations of hunger and stress, resulting in insufficient energy production. This mutation indirectly affects other metabolic pathways, such as glucose aerobic oxidation, gluconeogenesis, and ketone body formation, thereby affecting the oxidation energy supply of fatty acids, and subsequently, a series of biochemical abnormalities [13].

Different mutations in SLC22A5 cause different forms and severity of disease. Previous studies on primary carnitine deficiency mainly focus on the myocardium, skeletal muscle and central nervous system abnormalities, which manifest as progressive cardiomyopathy, hypoglycemia and low ketosis encephalopathy and muscle disease. Liver enlargement is mainly indicated by physical examination and ultrasound. However, pathologic findings are rarely reported. Our case showed elevated liver metastasis enzymes and organ damage. Liver pathology showed that liver cells were widely diffuse, vacuolated, and fatty-like. Liver enlargement was 3.5 cm under the ribs on clinical examination, liver function was impaired, and bile secretion was insufficient. In the clinical manifestation, there appeared to be fat in the stool. Alanine aminotransferase and aspartate aminotransferase were increased. The skin was yellow. Cardiac pathologic findings

showed that the important channel produced by cardiac ATP was derived from the oxidation of fatty acids, which may have caused the cardiomyopathy due to the lack of carnitine or the dysfunction of the required enzymes. The age of a patient at disease onset is determined by the activity of residual enzymes that act on beta-oxidation. Primary carnitine deficiency heterozygotes may develop cardiac hypertrophy with aging [4]. Myocardial damage in patients with primary carnitine deficiency is more insidious and not easily detected at the onset of the disease. Some patients present only with palpitations, which are observed when symptoms such as syncope and dyspnea appear. Other clinical manifestations are related to energy metabolism disorders and biochemical abnormalities induced by fatigue, cold stimulation, hunger and infection. The heart of this patient showed a slight hypertrophy of the left ventricular wall. An autologous heart position (cardiothoracic ratio 1:2), heart size of $4.6 \times 4.5 \times 3.5$ cm, or standardized data of infant heart size have not been reported; therefore, this case can only provide the cardiothoracic ratio indicating an enlarged heart. There was no obvious abnormality in the myocardium that could be observed using a light microscope, which may indicate a need for effective pathological support using electron microscopy. However, an electron microscope requires a fresh tissue specimen; therefore, a more detailed diagnosis could not be made in this case. ECG monitoring showed tachycardia. Impaired cardiac function in children is characterized by elevated creatine kinase and alpha-hydroxybutyrate dehydrogenase. This child's sister had died at home at 5 months of age, presumably related to arrhythmia or another disease of the heart. The renal pathology of this infant revealed translucent, vacuolar-like, and fatty-like degeneration of the proximal convoluted tubules of the kidney. Due to reabsorption of the proximal convoluted tubules, energy consumption requirements, low blood sugar and reduced blood supply, cellular hypoxia, and carnitine deficiency led to an accumulation of cytoplasmic fatty acids, causing tubule steatosis. The clinical manifestations included hematuria under hemorrhage on urine examination without creatinine abnormalities on biochemical examination. These findings may be related to the age of the patient. Substantial damage or renal compensation were not found.

Primary carnitine deficiency is an inherited metabolic disease. If early diagnosis and standardized treatment can be performed before irreversible organ damage occurs, patients can achieve the same quality of life as that of people without this deficiency [14]. Once a diagnosis of carnitine deficiency is established, a series of tests should be performed for baseline evaluation, such as echocardiography for cardiomyopathy, an electrocardiogram for arrhythmia, detection of creatine kinase and transaminases and fasting. The blood sugar concentration has been observed to affect muscle, liver function and hypoglycemia. Clinical supplementation with L-carnitine is a life-saving treatment. In the acute phase, 100~500 mg/d L carnitine is administered intravenously or orally. The maintenance dosage is 30~100

mg/d. In addition, diet therapy is also very important, including the consumption of food sources (from cows and sheep) of L-carnitine, nutritional support, and vitamin B2, B6, C and iron supplementation to ensure the patient's own carnitine synthesis [15]. Infection can increase catabolism and aggravate the consumption of carnitine in the body. Even in the case of unclear infection, active control of the infection is recommended, which can also be used for clinical treatment of the primary disease. In this case, the infant had an acute metabolic crisis induced by an upper respiratory tract infection, resulting in damage to multiple organs, such as the myocardium, brain, liver and skeletal muscle, resulting in respiratory failure and cardiac arrest. A diagnosis is often difficult due to the lack of specific clinical manifestations or routine laboratory tests. Although the patient underwent high-performance liquid chromatography-tandem mass spectrometry to screen for carnitine after admission, his condition rapidly deteriorated and cardiac arrest occurred after 7 hours as there was insufficient time to treat the primary disease. Improving the level of understanding of primary carnitine deficiency is necessary for the diagnosis and treatment of patients.

5. Conclusion

The clinical manifestations of this case were nonspecific and mainly included symptoms of pulmonary infection with a lack of clinical manifestations or affected organs characteristic of systemic carnitine deficiency. Functional impairment and organ failure manifestations included muscle weakness, acute encephalopathy, and renal failure. Biochemical tests indicated only nonspecific changes. Therefore, the diagnosis of primary carnitine deficiency requires reliable evidence through pathological examination, which can further determine the extent of the disease. Clinicians must be provided with a basis for choosing appropriate treatments, for improving the recognition of primary carnitine deficiency and achieving a knowledge level that is conducive to the diagnosis and treatment of patients.

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