Case Report

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A Case of Early Diagnosed Carnitine Deficiency Presenting with Respiratory Symptoms

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Key Words
Cardiomyopathy · Carnitine deficiency · Carnitine supplementation · Hypoketotic hypoglycemic encephalopathy · Primary carnitine deficiency

Abstract
Introduction: Carnitine deficiency is an autosomal recessively inherited disease characterized by a low carnitine concentration in plasma and tissues. Primary carnitine deficiency (PCD) is caused by a deficiency in the plasma membrane carnitine transporter, with urinary carnitine wasting causing systemic carnitine depletion. The most common presentation of PCD is hypoketotic hypoglycemic encephalopathy. Cardiomyopathy can also be seen. ***Case Report:*** A 9-month-old girl was admitted to our clinic with wheezing, respiratory distress and nighttime cough. She was pale, expirium was prolonged, breath sounds were coarse bilaterally and were increased in the right hemithorax. ***Results:*** She had hypochromic microcytic anemia and the serum CPK level was elevated. Cardiothoracic index was increased (0.62). In the chest X-ray there was hyperaeration especially in the upper regions of the left lung, and paracardiac infiltration in the right lung. The echocardiogram showed dilated cardiomyopathy. In pulmonary perfusion scintigraphy, perfusion of the right lung was 26% and of the left lung 74%. Cardiomegaly and dilatation in main the pulmonary artery was detected in the MR angiogram. Plasma carnitine and acylcarnitine levels were found to be significantly low. Fat accumulation in myocytes and rare atrophic fibers were detected in a muscle biopsy. Oral carnitine supplementation was started at a dose of 100 mg/kg. All the symptoms and findings regressed within a short period of time. ***Discussion:*** This case was presented to emphasize that carnitine deficiency can present with respiratory tract symptoms like wheezing and recurrent respiratory tract infections. Although PCD usually presents with hypoketotic hypoglycemia in infants, it also has to be suspected in the etiology of dilated cardiomyopathy. Treatment is very easy and lifesaving once the correct diagnosis is made, and the prognosis is excellent with lifelong carnitine supplementation.

Introduction

L-Carnitine is a naturally occurring hydrophilic amino acid derivate, produced endogenously in the kidneys and liver and derived from meat and dairy products in the diet [1]. It was first derived from meat (camus) in 1905. It plays an essential role in transfer of long-chain fatty acids to mitochondria for β-oxidation [2].

Carnitine deficiency is an autosomal recessively inherited disease characterized by low carnitine concentra-

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tion in plasma and tissues. It occurs in 1–5 cases per 10,000 population. It is most commonly seen between the age of 1 month and 7 years [3, 4].

Primary carnitine deficiency (PCD) (Online Mendelian Inheritance in Man 212140 [OMIM]) is caused by a deficiency in the plasma membrane carnitine transporter in muscle and kidney, with urinary carnitine wasting causing systemic carnitine depletion [5, 6]. This disorder arises from a mutation in the gene for PCD, *SLC22A5*, which encodes the carnitine transporter OCTN2 [7–10], and several mutations have been identified in affected patients [11]. Intracellular carnitine deficiency impairs the entry of long-chain fatty acids into the mitochondrial matrix. Consequently, long-chain fatty acids are not available for β-oxidation and energy production, and the production of ketone bodies (which are used by the brain) is also impaired [12–15]. Cardiac muscle, central nervous system and skeletal muscle are the affected organs. Secondary carnitine deficiency is caused by metabolic disorders like fatty acid oxidation disorders and organic acidemias or after pharmacological therapy. Carnitine depletion may be secondary to the formation of acylcarnitine adducts and the inhibition of carnitine transport in renal cells by acylcarnitines. The most common presentation of PCD is usually hypoketotic hypoglycemic encephalopathy. Cardiomyopathy, muscle weakness, gastrointestinal motility disorders, hypochromic anemia and recurrent infections can also be seen. In PCD, the plasma carnitine level is below 5% of normal [15]. The urinary carnitine level is elevated and the organic acid level is normal. Treatment with oral carnitine supplementation at a dose of 100–200 mg/kg/day, divided into 2–3 doses, is given. In early diagnosed cases, the prognosis of the disease is excellent with lifelong carnitine supplementation. This case is presented because of its rare presentation and good response to carnitine treatment.

Case Report

A 9-month-old girl was admitted to our clinic with wheezing, respiratory distress and nighttime cough that worsened in the morning. The symptoms started at 6 months of age after an upper respiratory tract infection. She had been treated with antibiotics and bronchodilators for the last 3 months but did not get any better. There was nothing remarkable in the prenatal, natal and postnatal history. The family history revealed bronchial asthma in the mother, grandmother, cousins and grandchildren of the father's siblings.

On physical examination, the patient's general condition was good, height and weight percentiles were consistent with age, she was conscious and active but rather pale. Heart rate was 120 bpm and rhythmic, BP 100/70 mm Hg, body temperature 37°C, respiratory rate 30/min, expirium was prolonged, breath sounds were coarse bilaterally and were increased in the right hemithorax. Cardiovascular and other system examination findings were normal.

Laboratory Data. Full blood count: Hb 9.3 mg/dl, Hct 28%, WBC 16,910/μl, platelets 273,000/μl, MCV 71.8 fl, Fe 356 mM, CRP 0.182 mg/dl, ESR 10 mm/h. Peripheral blood smear showed hypochromic microcytic anemia. There was no abnormality other than CPK 277 U/l (normal (N) 24–190 U/l) when biochemical parameters were checked. Urinanalysis was normal. PPD was negative. Cardiothoracic index was found to be increased (0.62) in the telegram. In the chest X-ray there was hyperaeration especially in the upper regions of the left lung, and there was paracardiac infiltration in the right lung. The echocardiogram showed dilated cardiomyopathy. In pulmonary perfusion scintigraphy, perfusion of the right lung was 26% and of the left lung 74%. Cardiomegaly and dilatation in the main pulmonary artery was detected in the MR angiogram. NH_3 and blood gas analysis, fundoscopic examination and urine organic acid levels were normal. In tandem mass spectrometry analyses, plasma carnitine levels were detected as follows: free carnitine level <0.1 μM/l (N 10–280 μM/l), total acylcarnitine level 2 μM/l (N 5–60 μM/l), and total carnitine level <2 μM/l (N 15–300 μM/l). Muscle biopsy was carried out and fat accumulation in myocytes and rare atrophic fibers were detected. These findings were consistent with muscle damage caused by carnitine deficiency. Oral carnitine supplementation was started at a dose of 100 mg/kg/day. All the symptoms and findings regressed within a short period of time. The patient has been followed up for the last 4 years under continuous carnitine supplementation and the symptoms have never recurred.

Discussion

Carnitine deficiency is a metabolic state in which carnitine concentrations in plasma and tissues are less than the levels required for normal function of the organism. Biologic effects of low carnitine levels may not be clinically significant until they reach less than 10–20% of normal. Carnitine deficiency may be primary and secondary.

PCD is an autosomal recessive disorder caused by a deficiency in the sodium-dependent plasma membrane carnitine transporter, with urinary carnitine wasting causing systemic carnitine depletion [5, 6]. The gene for PCD, *SLC22A5*, encodes the carnitine transporter OCTN2 [7–10], and several mutations have been identified in affected patients [11].

Three areas are involved in carnitine deficiency [16]. One of them is the cardiac muscle, which leads to progressive cardiomyopathy. The central nervous system is affected by encephalopathy caused by hypoketotic hypoglycemia, and the skeletal muscle is affected by myopathy.

The first clinical manifestation in asymptomatic individuals with PCD may be sudden death [17]. Patients with PCD may also develop progressive CMP that usually presents at a later age [18]. The cardiac function does not respond to inotropes or diuretics. Winter et al. [19] studied the clinical spectrum associated with secondary plasma carnitine deficiency in 51 patients, detecting cardiomyopathy in 9 of them. The other most common presentations were hypotonia in 34, failure to thrive in 27, recurrent infections in 27, encephalopathy in 6 and nonketotic hypoglycemia in 7 of the cases.

Acute encephalopathy accompanied by hypoketotic hypoglycemic episodes usually presents in younger infants with PCD. Periods of fasting in association with viral illness trigger these acute episodes. In our patient, the disease also occurred after a viral upper respiratory tract infection. Vikre-Jorgensen [20] also reported a case with PCD who presented with common cold and cardiomyopathy similar to our case, and emphasized the importance of early treatment in avoiding sudden death.

No sexual predilection exists for primary or secondary carnitine deficiency. The mean age at onset of PCD is 2 years, with onset ranging from 2 months to 7 years. Infants typically present with hypoketotic hypoglycemia, whereas older children present with skeletal or cardiac myopathy. Hypoketotic hypoglycemic encephalopathy is accompanied by hepatomegaly, elevated liver transaminases, and hyperammonemia. The ketone bodies in urine are decreased or absent. There can be metabolic acidosis. The patient can have hyperuricemia as carnitine competes with uric acid in renal excretion. Our patient was 9 months old and apart from the classical knowledge, she had no symptoms of hypoketotic hypoglycemic encephalopathy but symptoms related with cardiac failure that started at 6 months of age. If patients present with cardiomyopathy, onset may occur with rapidly progressive heart failure or murmur. A gallop rhythm can be found. However, our patient presented with cough and wheezing caused by dilatation in the pulmonary artery.

Squarcia et al. [21] reported a case of PCD who presented at 3.5 years of age with congestive heart failure and dilated cardiomyopathy. Hou [22] reported a case of PCD who presented at 6 years of age. Her major clinical features were neonatal metabolic acidosis, epilepsy, recurrent infections, acute encephalopathy and dilated cardiomyopathy with heart failure that occurred before 4 years of age. There was an excellent improvement in cardiac functions and clinical condition after oral carnitine therapy.

Measurements of free carnitine and total carnitine in plasma are important in the diagnosis and clinical management of patients with carnitine deficiency [2]. In PCD, unlike the other forms of carnitine deficiencies, plasma carnitine level is below 5% of normal [15]. Plasma acylcarnitine levels are proportionately reduced. The urinary carnitine level is elevated and organic acid levels are normal. In our patient, plasma-free carnitine level was <0.1 μM/l (N 10–280 μM/l), total acylcarnitine level 2 μM/l (N 5–60 μM/l), and total carnitine level <2 μM/l (N 15–300 μM/l). Urine organic acid analysis, NH_3 and blood gas analysis were found to be normal and these findings led us to think that the deficiency was primary rather than secondary.

Carnitine deficiency may be a cause of gastrointestinal dysmotility, with recurrent episodes of abdominal pain and diarrhea. Hypochromic anemia and recurrent infections are other manifestations of the disease. Our patient also had hypochromic microcytic anemia and recurrent respiratory tract infections.

Serum creatinine kinase level can be elevated in PCD, as our patient also had a moderately elevated creatinine kinase level.

In imaging studies, the cardiothoracic index can be found to be elevated and an echocardiogram may reveal cardiac enlargement and increased thickness of the right ventricular wall. CTI of our patient was 0.62 and echocardiogram revealed dilated cardiomyopathy. Besides these findings, she also had hyperaeration in the left upper pulmonary region and paracardiac infiltration in the right pulmonary region. Due to these findings, lung perfusion scintigraphy was carried out and perfusion of the left lung was found as 26% whereas in the right lung it was 74%. MR angiography also revealed dilatation in the main pulmonary artery and cardiomegaly.

The invasive diagnostic procedures are skin and muscle biopsy. A muscle biopsy was carried out in our patient and fat deposition in myocytes and rare atrophic fibers were detected and these findings were consistent with muscle damage as a result of carnitine deficiency.

We immediately began oral carnitine supplementation in our patient at a dose of 100 mg/kg/day as soon as the diagnosis was confirmed. Cardiac and respiratory symptoms resolved very quickly. The patient no longer needed anti-inflammatory and bronchodilator treatment. Anticongestive treatment was also stopped at the end of first year as the patient no longer had wheezing attacks. In many studies it is remarked that oral carnitine replacement improves fasting ketogenesis, cardiac function, growth and cognitive performance, especially in

PCD. The fast and excellent improvement in cardiac functions of our patient also made us think that the deficiency was primary. There are many case reports about the importance of early treatment and how good the prognosis is with continuous carnitine supplementation [11, 20–23]. If PCD diagnosis is confirmed, carnitine can also be administered intravenously.

In order to make a certain diagnosis, a molecular work-up that provides information on the gene for the carnitine transporter defective in PCD and mutational screening is necessary. Although clinical and laboratory findings support that our case had PCD, we were not able to carry out a genetic work-up.

This case was presented to emphasize that carnitine deficiency can present with respiratory tract symptoms like wheezing and recurrent respiratory tract infections. The etiology of dilated cardiomyopathy also has to be kept in mind. Moreover, we wanted to overlook the pathogenesis, anamnestic, physical, laboratory and diagnostic features of this rare disease in which the treatment is very easy and lifesaving once the correct diagnosis is made, and the prognosis is excellent with lifelong carnitine supplementation.

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