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Acute Respiratory Failure Revealing Carnitine Deficiency: A Case Report

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Abstract **Case Report**

L-carnitine deficiency is a rare metabolic disorder that results in defective fatty acid oxidation which leads to hypoglycemia, myopathy and severe cardiac dysfunction. It can be presented by an acute respiratory failure and the Carnitine supplementation appears to be effective in correcting the symptoms and improving the lung function. We report a case of a 10 months old infant admitted in the intensive care department for acute respiratory failure; an early intubation was necessary but the infant couldn't be weaned from the mechanical ventilation and a tracheostomy was performed after three months of failed extubation and weaning attempts. In addition to the persistence of the respiratory distress, recurrent hypoglycemia has been observed and a metablolic screening found an L-Carnitine deficiency. The supplementation allowed a rapid improvement.

Keywords: Carnitine deficiency -Metabolic disorders -Respiratory failure – Mechanical ventilation.

INTRODUCTION

Acute respiratory failure in children is the inability of the respiratory system to support oxygenation, ventilation, or both. In most cases, mechanical ventilation is required [1]. An early extubation is preferable but not always possible [2].

There are various reasons for extubation and weaning failures in children including respiratory, cardiovascular, neuromuscular, metabolic and psychological etiologies. To prevent and to treat these problems, different strategies have been described. Adjuvant therapies could be considered including a nutrition plan covering the metabolic needs [3].

L-carnitine deficiency is a rare metabolic disorder usually revealed by hypoglycemia, a progressive cardiomyopathy and muscle weakness [4]. Several reports showed that it could be presented by an acute respiratory failure [5-7].

The carnitine supplementation is approved for primary and secondary deficiencies and it has proven its efficiency in reversing the symptoms and preventing the complications [8]. The use of L-carnitine to treat and prevent respiratory problems has been suggested in different studies [5, 9, 10], but its use as a nutritional adjuvant in patients requiring long term intensive care and prolonged mechanical ventilation is yet to be explored.

In the case we report, we would like to present an unusual cause of persistence of respiratory distress, extubation and weaning failures and we would like to highlight the importance of metabolic screening and nutritional support in children under mechanical ventilation.

CASE REPORT

We report a case of a 10 months old infant who was admitted in the intensive care department of the children's hospital of Rabat for acute respiratory failure. He was born at term to nonconsanguineous parents, with a normal birth weight and had no medical or surgical history; he was exclusively breastfed and had a weight for age of 8 kg (under 1SD). Prior to this episode, the infant was active, showed no sign of dyspnea or muscle weakness.

Three days before his admission, he was asthenic, had a dry cough and a progressive dyspnea. The physical examination found an infant who was cyanotic with a nasal flaring and substernal retractions, an audible weezing, a respiratory rate of 50 per minute and a blood oxygen saturation level around 70%. He was intubated and treated initially for bronchiolitis and then for a bacterial pneumonia as he developed fever and signs of infection. His initial X-rays, bronchoscopic examination and echocardiogram were unremarkable.

During 3 months of treatment, even with successful spontaneous ventilation, 3 extubation attempts failed and a tracheostomy was performed. The patient was hypotrophic with no other signs but a recurrent unexplained hypoglycemia leading to a hypercaloric nutritional support. A metabolic screening revealed an acetyl-carnitine deficiency (C2-Carnitine level at 6.9 µmol/L, normal range 7.16 to 35.14) with mostly medium and short-chain acylcarnitine deficiencies (C3-Carnitine level at 0.19 µmol/L, normal range 0.48 to 2.46; C4-Carnitine level at 0.09 µmol/L, normal range 0.1 to 0.94; C5-Carnitine level at 0.06 µmol/L, normal range 0.07 to 0.33; C10-Carnitine level at 0.02 µmol/L, normal range 0.03 to 0.37; with C5-1 C3-DC C10-1 and C4-DC deficiencies). A supplementation was initiated with 10 mg/kg a day of exogenous carnitine. Eighteen days later, the patient was successfully weaned from mechanical ventilation and exited the intensive care department with a metal tracheostomy tube that was kept due to granulomatous inflammation found in his latest bronchoscopy. He was transferred to a department specializing in pediatric endocrinology and nutrition with prescribed exogenous carnitine and corticosteroid therapy.

DISCUSSION

L-Carnitine or β-hydroxy-γ-trimethylaminobutyric acid was first discovered in 1905 and got its name from the the latin word “Carnis” which means flesh [11]. The first cases of deficiency were described in 1973 [12].

It is a small water soluble molecule, obtained mainly from exogenous sources (essentially meat) and synthetized endogenously from lysine and methionine [4]. Aside from transporting long chain fatty acids to the mitochondria for β-oxidation, this molecule has different important physiological roles including modulation of the acyl-CoA/CoA ratio [14], storage of energy as acetyl-carnitine [14, 15], excretion of toxic metabolites [16] and anti-oxidant activity [17]. Different carnitine derivates, such as acetyl-carnitine and propionyl-L-carnitine, have been considered for metabolic therapies to increase myocardial ATP levels and to prevent the emergence of insulin-resistance in heart and skeletal muscle [18, 19].

Long term fasting is usually the trigger of the symptom onset [13]. In fact, when glucose is consumed, the adipose tissue releases fats to be metabolized to produce ketones, an alternative source of energy, and acetyl-CoA activates pyruvate carboxylase in the liver leading to gluconeogenesis. When β-oxidation is defective, fats accumulate in the liver, heart and muscle, and glucose doesn’t regenerate by gluconeogenesis [20].

Different etiologies have been described to L-carnitine deficiency, including:

- Primary carnitine deficiency, an autosomal ressecive disorder due to the lack of functional OCTN2 carnitine transporters;
- Secondary carnitine deficiencies caused by: prematurity, pregnancy, malnutrition, kidney or liver failure, Jamaican vomiting sickness, some medications like valproic acid or Zidovuldine…
- β-oxidation abnormalities dues to enzyme deficiencies;
- Organic acidurias.

These different etiologies are associated to heterogenous clinical and biochemical results. In some cases, like the case we report, carnitine deficiency exists even with normal levels of free carnitine (C0) [21].

The described infantile presentation of carnitine deficiency is heterogeneous, it’s mostly metabolic with hypoketotic hypoglycemia, hyperammonemia, hepatomegaly, elevated transaminases, and hepatic encephalopathy; it could include cardiomyopathy, muscle weakness and elevated creatine kinase [4, 13].

In our case, different tests have been made including viral, bacterial, toxic, metabolic and blood enzymes; and the only explanation found to the persistent hypoglycemia and muscular weakness leading to weaning difficulties was the carnitine deficiency.

The increase of energy need caused by sepsis and mechanical ventilation may have caused an important solicitation of the various sources of energy in the body revealing the deficiency. The clinical improvement under 10 mg/kg a day of exogenous carnitine was rapidly seen.

The dose recommended for primary carnitine deficiency is 100-400 mg/kg/day [20]. Apart from this specific case, different dosages are reported in the literature including 10 to 20 mg/kg a day with improvement of the lung function as a result of the treatment [22, 23].

The deficiency we found was minor; it allowed us to start with a low dose of supplementation which proved to be efficient with a rapid favorable evolution.

Carnitine supplementation may have various benefits especially on neonates and infants. In fact, their endogenous production of carnitine is insufficient and they rely mostly on exogenous supply that may be poor (formulas based on soy milk, human milk with mother suffering from carnitine deficiency…) [24].

Cases of L-carnitine deficiency presenting initially with respiratory symptoms were reported [5-7], and several studies linked the improvement of lung function to the carnitine supplementation.

Ozturk *et al*., suggest that premature infants with respiratory distress syndrome should benefit from an early carnitine therapy; it may reduce the duration of mechanical ventilation, the use of surfactant and the occurrence of bronchopulmonary dysplasia [9].

Iafolla *et al*., reported three cases of siblings suffering from apnea and periodic breathing, one of the siblings died of Sudden Infant Death Syndrome which started the family investigation, the mother was found to be carnitine deficient and the surviving infants had abnormal acylcarnitine concentrations. A rapid resolution of both respiratory and metabolic abnormalities was seen after carnitine supplementation [5].

In a study published on the journal of allergy by Al-Biltagi *et al*., two groups of 50 children were investigated, a group with moderate persistent Asthma and a healthy group, the asthmatic group of children had lower carnitine levels compared to the control healthy group, and the patients supplemented with carnitine showed significant improvement of childhood-asthma control test (C-ACT) and pulmonary function tests (PFT) [10]. Other studies showed that carnitine levels were lower in asthmatic children during exacerbation of Asthma compared to stable asthmatics and controls [25, 26].

Aside from the respiratory benefits, carnitine supplementation proved to be effective against multiple diseases: it may be used to prevent and treat mild to severe cardiac disorders [27]; it may reduce insulin-resistance in diabetes mellitus [28, 29], it may also have neuroprorective effects (especially on neonates and infants) [30] or even reduce autism severity [31].

CONCLUSION

In case of long term respiratory distress in intensive care, hypotrophy and recurrent unexplained hypoglycemia, the measurement of plasma L-carnitine should be considered in children even with normal cardiac function. Untreated, this rare metabolic disorder's complications could be lethal. Further studies should be performed on children under mechanical ventilation, the existence of the deficiency and the impact of carnitine therapy may be underestimated.

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