

# Combination of Hyperammonaemia and Tachyarrhythmia in a Newborn with Carnitine-acylcarnitine Translocase Deficiency

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## Abstract

Carnitine-acylcarnitine translocase (CACT) deficiency is one of the fatty acid oxidation defects that presents early in the newborn period. It is known to be associated with a high mortality with a number of the earlier reported cases presenting as sudden infant death syndrome. Like most inborn errors of metabolism, presentation of CACT deficiency is rather non specific. Typical biochemical profile is one of hypoketotic hypoglycaemia with hyperammonaemia. While hyperammonaemia is a common feature for other IEMs like urea cycle disorders and organic acidurias, cardiac arrhythmias especially ventricular tachyarrhythmia are less commonly seen in them compared with fatty acid oxidation defects. Furthermore, patients with CACT deficiency may present without hypoglycaemia. We hereby reported a 5 day old male infant who was diagnosed to have CACT deficiency at post mortem examination. He presented with respiratory distress, deteriorated very rapidly and succumbed within 48 hours of presentation. Though hypoglycaemia was absent at initial presentation, hyperammonaemia and tachyarrhythmias were observed during the course of his rapid deterioration. We believe a combination of neonatal hyperammonaemia together with tachyarrhythmias should raise a strong clinical suspicion towards fatty acid oxidation defects. In Hong Kong CACT deficiency should be considered in this clinical context as it is one of the more commonly seen fatty acid oxidation defects among the Southern Chinese population.

## Key words

Carnitine-acylcarnitine translocase deficiency; Fatty acid oxidation defects; Hyperammonaemia; Neonatal; Tachyarrhythmia

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## Introduction

Carnitine-acylcarnitine translocase (CACT) is 1 of 10 closely related mitochondrial membrane carrier proteins that shuttle substrates between cytosol and intramitochondrial matrix space. It is essential for the entry of long-chain fatty acids (LCFA) into the mitochondrial matrix, transferring acylcarnitines across the inner mitochondrial membrane in exchange for free carnitine. CACT deficiency (OMIM 212138) is an inherited defect of this co-transport of free and esterified carnitine across the inner mitochondrial membrane leading to long-chain fatty acids being unavailable to get into the mitochondria for beta oxidation and ketogenesis.<sup>1</sup>

CACT deficiency is a severe disease that can cause neonatal or infantile sudden death.

## Case Report

The patient was a male infant born at 38 weeks of gestation by elective Caesarean section for breech presentation with birth weight of 2.94 kg. Apgar scores were 9 at 1 minute and 10 at 5 minute. Antenatal and perinatal course were uneventful. There was no infection risk. Parents were non consanguineous and family history was unremarkable.

Baby was noted to have respiratory distress and grunting on day 3 of life. Physical examination revealed signs of respiratory distress – grunting, subcostal insucking and tachypnoea with respiratory rate of 70 breaths per minute. Oxygen saturation was 100% in room air. Cardiovascular system examination was normal. There was no hepatosplenomegaly. Blood pressure was 74/37 mmHg.

After sepsis workup, baby was started empirically on intravenous penicillin and cefotaxime. Initial workup showed compensated metabolic acidosis with pH of 7.510, bicarbonate 17.2 mmol/L, and base deficit of 3.5 mmol/L. Complete blood picture, electrolytes and C-reactive protein

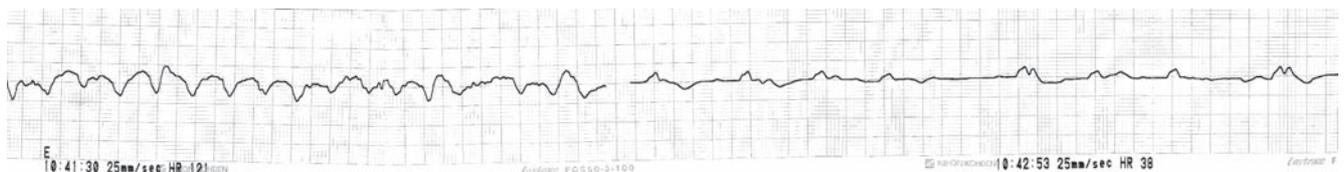
were normal. Random glucose was 4.7 mmol/L. Urine ketone was negative. Chest radiograph showed borderline cardiomegaly with clear lung fields.

Twelve hours after presentation, baby suddenly developed four limbs twitching and intermittent hiccough. Another 10 hours later, he suddenly became apnoeic and was noted to have developed ventricular tachyarrhythmia. He was intubated, ventilated and required cardioversion, multiple doses of adrenaline, calcium gluconate and sodium bicarbonate for resuscitation. Echocardiogram showed normal cardiac structure and contractility.

Further laboratory investigations revealed elevated ammonia 883 (reference ranges <134 umol/L) and lactate 5.6 (reference range 0.7-2.1 mmol/L). Urea cycle disorder was suspected and baby was started on sodium benzoate and sodium phenylacetate (Ammonul) for control of hyperammonaemia. However, the infant continued to deteriorate, developed hypotension, multiorgan failure and persistent metabolic acidosis. In view of hyperammonaemia, anuria, persistent metabolic acidosis with elevated blood urea and creatinine to 12.9 mmol/L and 110 umol/L respectively, he was started on peritoneal dialysis. However, during insertion of the peritoneal catheter, he developed another episode of ventricular tachyarrhythmia (Figure 1) and despite aggressive resuscitation; baby did not respond and finally succumbed around 32 hours after his initial presentation of respiratory distress.

Post-mortem examination revealed hepatomegaly with marked steatosis. The heart was enlarged with marked fatty changes and there were prominent fatty changes in skeletal muscles and kidneys as well. Ultrastructural examination confirmed intracellular fat accumulation in liver, heart and renal tubules.

Other investigations included a normal plasma amino acid profile. This together with the normal excretion of orotic acid made urea cycle disorders unlikely. Gas chromatographic analysis of urinary organic acids showed elevation of dicarboxylic and 3-hydroxy dicarboxylic



**Figure 1** Run of ventricular fibrillation captured on rhythm strip.

acids including medium (C6-10) and long chain (C12-14) without ketone bodies. Carnitine studies showed a low serum free carnitine concentration 2.9 (reference range 19.3-53.9  $\mu\text{mol/L}$ ). There was a generalised increase in most of the acylcarnitines especially the C16:0 and C18:1 suggesting either carnitine palmitoyltransferase II deficiency or carnitine-acylcarnitine translocase deficiency.

Molecular genetic studies were performed using DNA material extracted from post-mortem splenic and liver tissues and analyzed by direct sequencing. Mutations in Carnitine-acylcarnitine translocase (CACT) gene, including two heterozygote mutations (one as [*SLC25A20*, IVS2AS, T-G, -10] and one as [*SLC25A20*, ARG37TERM CGA>TGA]) were identified. The first mutation represented a common mutation among the local population. The second mutation was a novel mutation that had not been reported before. Mutational analysis in the parents revealed the presence of one mutation [*SLC25A20*, IVS2AS, T-G, -10] in the father and the other mutation [*SLC25A20*, ARG37TERM CGA>TGA] in the mother confirming their carrier status.

## Discussion

CACT deficiency is among the most severe of fatty acid oxidation disorders which has a tendency to present early in the postnatal period. The severe phenotype frequently results in severe disability or death. The less severe phenotype can also cause significant disability from hypoglycaemia and/or hyperammonaemia at presentation. Affected infants present with multisystem involvement within days of birth. Neurological symptoms of seizures, hypotonia, vomiting, lethargy, pallor, apnea or coma are prominent. Hepatomegaly and liver failure occur with impaired gluconeogenesis, impaired ketogenesis, and hyperammonaemia during periods of starvation or infection. Dicarboxylic aciduria and lactic aciduria are variable. Plasma total carnitine concentrations are near or below normal. Cardiac involvement is prominent, presenting with conduction defects or cardiomyopathy. Most cases have proved to be fatal within the first few days or months of life.<sup>2</sup>

Our patient presented on day 3 of life and died within 48 hours of presentation. The two most prominent features observed were severe hyperammonaemia and ventricular tachyarrhythmia. Hypoglycaemia however was absent in our patient's presentation. Severe neonatal

hyperammonaemia in the absence of liver failure points strongly to an underlying inborn error of metabolism. Urea cycle defects, organic acidurias and fatty acid oxidation defects are top on the list of differential diagnoses.

Our initial working diagnosis for this baby was urea cycle disorders. Yet there were a few atypical features for urea cycle defects here. Firstly the plasma urea level was not particularly low and secondly there was severe metabolic acidosis rather than alkalosis even from the early stage of presentation. What added further to the atypical presentation of urea cycle defects was the development of ventricular tachycardia.

Neonatal arrhythmias are uncommon and occur in only 1-5% of newborns during the first 10 days of life. Most of these arrhythmias are premature supraventricular beats that usually disappear over the first month of life. Neonatal tachyarrhythmias (supraventricular tachycardias (SVTs) and ventricular tachycardias (VTs)) are much rarer. Arrhythmias may occur either in the structurally normal heart or in the setting of congenital heart disease. Other important etiologies of arrhythmia include myocarditis, rare cardiac tumours (haematomas and rhabdomyomas), post myocardial infarction, electrolyte and metabolic abnormalities, drug toxicity and channelopathies like long QT syndrome.

Inherited metabolic disorders in particular fatty acid oxidation defects are increasingly recognised as an important cause of neonatal arrhythmias.<sup>3</sup> Cardiac involvement is frequent in fatty acid oxidation defects manifesting either as isolated arrhythmias, cardiomyopathy, conduction defects per se or a combination of these problems.<sup>3</sup> Fatty acid oxidation defects and disorders of mitochondrial oxidative phosphorylation account for about 15% of cardiomyopathies in infants.<sup>4</sup> In addition, sudden or unexpected death has also been recognised as a presenting symptom of fatty acid oxidation defects. The prevalence of fatty acid oxidation defects in different reported series of sudden infant death varies greatly and diagnosis is usually retrospective.<sup>5</sup> Severe ventricular arrhythmias have been postulated as the cause of sudden infant death syndrome or unexpected death in young children harbouring these defects. The accumulation of arrhythmogenic intermediary metabolites of fatty acids, such as long-chain acylcarnitines is thought to be responsible for these arrhythmias.<sup>6</sup>

Among the 107 confirmed cases of fatty acid oxidation defects in Bonnet's series,<sup>6</sup> 24 had arrhythmias or conduction defects as their predominant presenting

symptom. The types of arrhythmias they presented with included ventricular tachycardias, atrial tachycardias, sinus node dysfunction with episodes of atrial tachycardia, atrioventricular blocks and left bundle – branch blocks.

Though the precise incidence of fatty acid oxidation defects in Hong Kong is still unknown, the 3 conditions that have been reported and are perhaps more prevalent locally include carnitine transporter defect,<sup>7</sup> multiple acylCoA dehydrogenase deficiency<sup>8</sup> and CACT deficiency.<sup>9,10</sup> The more common Medium chain acyl-CoA dehydrogenase deficiency among the Caucasian population has not been reported among the local Hong Kong Chinese. Most of the reported local CACT deficiency cases died early in the neonatal period and their diagnosis was made retrospectively. It is highly possible that the number of CACT deficiency patients is even more than what we know of and is a significant fatty acid oxidation defect locally.

## Conclusion

Neonatal hyperammonaemia and tachyarrhythmia are each individually rare. Despite the absence of hypoglycaemia, the combination of these two rare but potentially serious life threatening conditions in an otherwise low risk newborn infant should prompt one to the consideration of fatty acid oxidation defects and in particular CACT deficiency in the Southern China region of Hong Kong.

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