CASE REPORT

Carnitine-acylcarnitine translocase deficiency in three neonates presenting with rapid deterioration and cardiac arrest

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We report on three Chinese neonates with carnitine-acylcarnitine translocase deficiency. They presented within the first 48 hours of life. Two neonates were found in cardiac arrest; one of them survived after resuscitation. The third neonate suddenly developed cardiorespiratory insufficiency and succumbed eventually. The clustering of three cases in 5 years suggests that carnitine-acylcarnitine translocase deficiency is not rare in our Chinese population. We advocate that investigation for metabolic diseases including carnitine-acylcarnitine translocase deficiency should be performed in cases of sudden infant death and unexplained abrupt clinical deterioration in the early neonatal period. Non-ketotic hypoglycaemia is an early clue. The mainstay of initial treatment is glucose infusion at a rate greater than 7 mg/kg/minute, which inhibits beta-oxidation of fatty acids (the defective enzymatic steps in carnitine-acylcarnitine translocase deficiency) and thus prevents the accumulation of toxic long-chain acylcarnitines.

Introduction

Carnitine-acylcarnitine translocase (CACT) is part of the fatty acid transport system located in the mitochondrial membrane. It is essential for the transport of long-chain acylcarnitines into the mitochondria, where β-oxidation of long-chain fatty acids to acetyl-CoA and ultimately the generation of energy takes place. The body relies on fat as the main source of energy during prolonged fasting. Therefore, a deficiency of CACT leads to an accumulation of cardio-toxic long-chain acylcarnitines when lipolysis is activated in the fasting state. The heart is therefore frequently affected during metabolic decompensation and cardiorespiratory failure, arrhythmia, and sudden cardiac arrest may be expected. Newborns with CACT deficiency are especially vulnerable in the first few days of life when their oral intake tends to be small and their glycogen reserves low, forcing them to rely heavily on lipolysis and the metabolism of fatty acids to meet their energy needs.

Carnitine-acylcarnitine translocase deficiency (OMIN 212138) is an autosomal recessive condition. The *CACT* gene has been mapped to chromosome 3p21.31. It is a rare disorder. Before 2003 only 24 cases had been reported in the literature.[1] Since then, six more cases have been reported.[2,3] We diagnosed our first patient with CACT deficiency 5 years ago.[4] Since then, we have diagnosed another two patients. We therefore suspect that CACT deficiency is not rare in our Chinese population. We report these cases to alert paediatricians and other front-line clinicians to this inherited metabolic disease, a diagnosis that can easily be missed if this condition is not included in the differential diagnosis.

Key words
Carnitine acyltransferases; Deficiency; Sudden infant death

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Case report

From 2002 to 2006, we diagnosed three cases of CACT deficiency. All the patients are Chinese. Patient 1 has been reported before.[4] The clinical features and laboratory findings are summarised in Tables 1 and 2, respectively.

Patients 1 and 2 had sudden cardiac arrests in the early postnatal phase before discharge from hospital. They were immediately resuscitated. Patient 1 did not respond and the diagnosis was confirmed after death as described.[4] For patient 2, initial investigations demonstrated hyperammonaemia and hypoglycaemia (Table 2). A glucose infusion was started at 5.8 mg/kg/minute and increased to 7.6 mg/kg/minute by increasing the glucose concentration in the intravenous fluid from 10 to 18%. The plasma ammonia level decreased from 455 μmol/L to 175 μmol/L after 1 hour and fell to 138 μmol/L in 4 hours. Carnitine therapy (50 mg/kg/d) was started on day 13 after the diagnosis of CACT deficiency was made. He was put on a high carbohydrate and low fat diet supplemented with medium-chain triglycerides. He responded well

to treatment and had no further episodes of metabolic decompensation. He is now 32 months old and has mild developmental delay. A recent echocardiogram revealed hypertrophic cardiomyopathy but he has no cardiovascular symptoms.

Patient 3 was born in a hospital 6 km away from our hospital. At 28 hours after birth she was found to have cardiorespiratory insufficiency of abrupt onset. She was cyanotic, had poor peripheral circulation and hypotension. She went into cardiac arrest 1 hour later. She responded to cardiopulmonary resuscitation and was then transferred to our hospital for intensive care. Initially, her blood pressure was maintained with dopamine. Later, she developed recurrent ventricular tachycardia that responded to intravenous doses of lidocaine. Eventually she developed bradycardia, then cardiac arrest and did not respond to further cardiopulmonary resuscitation. She succumbed 10 hours after admission to our unit.

The presence of dicarboxylic acid in patient 3's urine (measured by gas chromatography-mass spectrometry) and/or typical serum acylcarnitine profiles with increased serum acylcarnitines of C16:1, C16:0, C18:2, C18:1 and C18:0 (measured by liquid chromatography-mass spectrometry) raised the possibility of CACT deficiency. The diagnosis was confirmed by the demonstration of homozygous mutations in her *CACT* gene. The same IVS2-10T–>G mutation[4] was found in all three patients. We lost contact with the parents of patient 1; the parents of patient 2 and 3 were heterozygous for the mutation.

Discussion

Most patients with CACT deficiency deteriorate rapidly during the neonatal period,[1,5] although a milder presentation during the postneonatal period has been reported.[6] Sudden neonatal death is the most extreme presentation,[7] and this happened in our patients 1 and 2 (or 'near missed sudden death' to be exact for patient 2). The metabolic derangement noted in our patients is typical: hypoglycaemia, increased serum lactate levels, hyperammonaemia, increased dicarboxylic aciduria, low free carnitine level, and raised long-chain acylcarnitines. Urine ketostix was not performed in our patients. Had this been done, the urine ketones would have been low. The detection of hypoketotic hypoglycaemia is helpful in the initial management of patients with hypoglycaemia, as this can narrow the differential diagnosis down to either hyperinsulinism or fatty acid oxidation defects.

Only one of our three patients survived; this high mortality rate accords with experience elsewhere.[1,5] Nevertheless, the importance of early initiation of appropriate treatment should be recognised as the treatment is simple and, if promptly introduced, may reverse the metabolic decompensation.[8] The mainstay of treatment is to minimise the mobilisation of fat and fatty acid metabolism by providing adequate glucose infusion.

三名新生兒因卡丁尼脂肪酸轉移缺乏症導致情況急變及心跳停頓

本文報告三名華籍新生兒患有卡丁尼脂肪酸轉移缺乏症，他們都是出生後48小時內發病。當中兩人心跳停頓，經搶救後其中一人存活；第三名新生兒突然出現心肺功能不足，最終死亡。這三宗在五年內出現的病例，顯示卡丁尼脂肪酸轉移缺乏症在華籍人口中並不罕見。若有嬰兒突然死亡，而在出生初期出現無法解釋的臨床病情急劇惡化，便應研究是否患有代謝性疾病，包括卡丁尼脂肪酸轉移缺乏症。此症的早期病徵是非酮症性血糖過低，初期治療的主要方法為葡萄糖注射，劑量須超過7 mg/kg/minute，藉此抑壓脂肪酸的二次氧化（即卡丁尼脂肪酸轉移缺乏症的不完整酵素性過程），防止有毒的長鏈性脂肪酸積聚。

TABLE 1. Clinical features of the three patients diagnosed with carnitine-acylcarnitine translocase deficiency

Patient No.	Sex	Gestation (weeks)	Birth weight (kg)	Consanguinity	Feeding	Time at presentation (hours)	Initial symptoms	Survived
1	M	38.4	2.41	No	Formula	41	Sudden cardiac arrest	No
2	M	35.6	2.71	No	Breast-feeding	32	Sudden cardiac arrest	Yes
3	F	37.4	2.3	No	Formula	28	Cardiorespiratory failure	No

TABLE 2. Laboratory findings of patients with carnitine-acylcarnitine translocase deficiency at presentation and autopsy findings

Patient No.	Initial plasma glucose (mmol/L)	Maximum ammonia level (μmol/L)	Long-chain acylcarnitine profiles	Dicarboxylic acid in urine	Lactate (mmol/L)	Autopsy
1	Not done	Not done	Not done	Raised	Not done	Steatosis in myocardium and hepatocytes
2	1.5	455	Raised	Raised	5.2	Not applicable
3	1.3	216	Raised	Raised	8.9	Not done

A glucose infusion rate of 7 to 10 mg/kg/minute has been recommended.[9] We speculate that the provision of adequate glucose (7.6 mg/kg/minute) might account for the survival of patient 2.

Carnitine therapy is commonly used to treat secondary carnitine deficiency occurring in CACT deficiency and recent clinical reports strongly support its administration as it is thought to be safe and effective.[10] Our patient was given carnitine in line with this view. However, there is a theoretical risk that carnitine therapy can cause a further accumulation of toxic long-chain acylcarnitines, which have been found to be arrhythmogenic in experimental situations.[11] Hence, the use of carnitine in the treatment of patients with CACT deficiency has been questioned.[1,5] Carnitine was initiated on day 13 of life in patient 2 and we are not sure if arrhythmia could have been induced had it been used during the initial presentation. Perhaps, the question of whether carnitine therapy is beneficial or detrimental in patient 2 and other patients similarly treated can only be answered if we compare patients receiving carnitine with those receiving a placebo in a randomised control trial.

The raised urine dicarboxylic acids and classical acylcarnitine profiles as described above, limited the differential diagnosis to either CACT deficiency or carnitine palmitoyl transferase-2 deficiency. Both conditions yield indistinguishable levels of dicarboxylic acid in urine and plasma acylcarnitine levels. A definitive diagnosis of CACT deficiency can be made using enzyme assays of CACT in muscles, liver or skin fibroblasts.[5] However, due to the rapid demise of patients 1 and 3, we did not manage to save live tissue from these patients. As a result, we resorted to DNA sequencing, which does not require live tissue.

To date, there have been 30 patients with CACT deficiency reported in the literature. The clustering of three cases in 5 years in our hospital, which serves a region with a birth rate of around 5000 per year, is obviously much greater than expected, given its global rarity. This suggests that CACT deficiency is not rare in our Chinese population or at least not as rare as in other populations. At present, we are aware of two other cases of CACT deficiency diagnosed in other hospitals in Hong Kong in the past 5 years. Therefore, we urge paediatricians and other front-line clinicians working with a Chinese population to look out for CACT deficiency.

When resuscitating neonates suddenly deteriorating for no apparent reason, the detection of hypoketotic hypoglycaemia at the bedside should raise the suspicion of CACT deficiency (or other fatty acid oxidation defects). Plasma ammonia and lactate, which are typically raised, should be checked. Under these circumstances, a glucose infusion of at least 7 mg/kg/minute is imperative.[9] This may be overlooked as sick neonates are not uncommonly fluid-restricted and often prescribed 10% dextrose, which falls short of the glucose infusion rate required to obviate the need for utilisation of fats. We should also perform the appropriate investigations leading to a diagnosis, which should be diligently pursued as the opportunity to save specimens may be lost if patients die. Each hospital should have a peri-mortem protocol for suspected metabolic diseases. When CACT deficiency is suspected, blood should be tested for acylcarnitine profiles, and urine tested for organic acids as the results can support this diagnosis. Further definitive tests to confirm the diagnosis should then be performed.

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