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

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 (OMIM 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. Since then, six more cases have been reported. We diagnosed our first patient with CACT deficiency 5 years ago. 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 frontline clinicians to this inherited metabolic disease, a diagnosis that can easily be missed if this condition is not included in the differential diagnosis.

Case report

From 2002 to 2006, we diagnosed three cases of CACT deficiency. All the patients are Chinese. Patient 1 has been reported before. 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. For patient 2, initial investigations demonstrated hyperammonaemia and hypoglycaemia (Table 2). A glucose infusion was started at 5.8 mg/k/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 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,
his 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 mutation4 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, 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 hyperinsulism 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.

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

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Initial plasma glucose (mmol/L)</th>
<th>Maximum ammonia level (µmol/L)</th>
<th>Long-chain acylcarnitine profiles</th>
<th>Dicarboxylic acid in urine</th>
<th>Lactate (mmol/L)</th>
<th>Autopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Not done</td>
<td>Not done</td>
<td>Not done</td>
<td>Raised</td>
<td>Not done</td>
<td>Steatosis in myocardium and hepatocytes</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>455</td>
<td>Raised</td>
<td>Raised</td>
<td>5.2</td>
<td>Not applicable</td>
</tr>
<tr>
<td>3</td>
<td>1.3</td>
<td>216</td>
<td>Raised</td>
<td>Raised</td>
<td>8.9</td>
<td>Not done</td>
</tr>
</tbody>
</table>
A glucose infusion rate of 7 to 10 mg/kg/minute has been recommended. 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. 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. Hence, the use of carnitine in the treatment of patients with CACT deficiency has been questioned. 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. 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. 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.

References