Clinical Case Report

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Carnitine-acylcarnitine translocase deficiency with c.199-10 T>G and novel c.1A>G mutation

Two case reports and brief literature review

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Abstract

Rationale: Carnitine-acylcarnitine translocate deficiency (CACTD) is a rare and life-threatening, autosomal recessive disorder of fatty acid β-oxidation characterized by hypoketotic hypoglycemia, hyperammonemia, cardiomyopathy, liver dysfunction, and muscle weakness; culminating in early death. To date, CACTD cases screened from the Chinese mainland population, especially patient with compound heterozygote with c.199-10T>G and a novel c.1A>G mutation in the SLC25A20 gene has never been described.

Patient concerns: Herein, we report 2 neonatal cases of CACTD identified from the mainland China. These 2 patients were presented with severe metabolic crisis and their clinical conditions deteriorate rapidly and both died of cardiorespiratory collapse in the first week of life. We present the clinical and biochemical features of 2 probands and a brief literature review of previously reported CACTD cases with the c.199-10T>G mutation.

Diagnoses: The acylcarnitine profiles by tandem-mass-spectrometry and the mutation analysis of SLC25A20 gene confirmed the diagnosis of CACTD in both patients. Mutation analysis demonstrated that patient No. 1 was homozygous for c.199-10T>G mutation, while patient No. 2 was a compound heterozygote for 2 mutations, a maternally-inherited c.199-10T>G and a paternally-inherited, novel c.1A>G mutation.

Interventions: Both patients were treated with an aggressive treatment regimen include high glucose and arginine infusion, respiratory, and circulatory support.

Outcomes: The first proband died 3 days after delivery due to sudden cardiac arrest. The second patient's clinical condition, at one time, was improved by high glucose infusion, intravenous arginine, and circulatory support. However, the patient failed to wean from mechanical ventilation. Unfortunately, her parents refused further treatment due to fear of financial burdens. The patient died of congestive heart failure in the 6th day of life.

Lessons: We report the first 2 cases of CACTD identified from the mainland China. Apart from a founder mutation c.199-10T>G, we identified a novel c.1A>G mutation. Patients with CACTD with a genotype of c.199-10T>G mutation usually presents with a severe clinical phenotype. Early recognition and appropriate treatment is crucial in this highly lethal disorder. This case series highlights the importance of screening for metabolic diseases including CACTD in cases of sudden infant death and unexplained abrupt clinical deterioration in the early neonatal period.

Abbreviations: CACT = carnitine-acylcarnitine translocase, CACTD = carnitine-acylcarnitine translocate deficiency, CK = creatine kinase, CPT2 = carnitine palmitoyltransferase-2, FAO = fatty acid β-oxidation, GC–MS = gas chromatography–mass spectrometry, LDH = lactate dehydrogenase, MCT = medium-chain triglycerides, MS/MS = tandem-mass-spectrometry.

Keywords: carnitine-acylcarnitine transferases deficiency, fatty acid β-oxidation, mutation analysis, SLA25A20

1. Introduction

Mitochondrial fatty acid β-oxidation (FAO) provides the major source of energy during prolonged fasting as well as for cardiac and skeletal muscle during long-term exercise.[1] The carnitine cycle is necessary to shuttle long-chain fatty acids from the cytosol into the intramitochondrial space where mitochondrial FAO takes place.[2] Carnitine-acylcarnitine translocase (CACT) is one of the crucial enzymes in the carnitine cycle, which mediates the transfer of the long-chain fatty acylcarnitine across the inner mitochondrial membrane in exchange of free carnitine.[3] Carnitine-acylcarnitine translocase deficiency (CACTD) is a rare and highly lethal mitochondrial FAO-disorder characterized by early onset of hypoketotic hypoglycemia, hyperammonemia, severe neurological damage, cardiomyopathy, liver dysfunction, and muscle weakness.[4] Most patients with CACTD develop severe metabolic decompensation in the

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neonatal period with a rapidly progressive deterioration and die in infancy or childhood despite aggressive treatment.[2,5]

Carnitine-acylcarnitine translocase deficiency (OMIN #212138) is an autosomal recessive disorder. The CACT protein is encoded by the SLC25A20 gene which has been mapped to chromosome 3p21.31, consists of 9 exons (NM_000387) and is widely expressed, particularly in heart, liver, and skeletal muscle.[3] The splicing mutation c.199-10T>G is most commonly encountered in patients from East Asia.[4,6,7] To date, CACTD with compound heterozygote with a novel c.1A>G and a c.199-10T>G mutation in the SLC25A20 gene has never been reported. Herein, we describe 2 probands identified from 153,789 newborns screened by tandem-mass-spectrometry (MS/MS) in Hunan province, China. Both patients were presented with severe metabolic crisis. To the best of our knowledge, these are the first reported CACTD disorders from the mainland China. The clinical features, genotype/phenotype correlation and management of patients with CACTD and c.199-10T>G mutation is discussed and the literature briefly reviewed.

2. Case description

This study was approved by the institutional review board of The Maternal and Child Health Hospital of Hunan Province. From January 2013 to June 2016, 2 cases of CACTD from 153,789 newborns using MS/MS neonatal screening have been identified. Both patients are from non-consanguineous marriages and are full-term normal weight infants with negative antenatal history.

2.1. Patient No. 1

A male born by spontaneous vaginal delivery. The Apgar score at 1 minute was 10. The patient experienced an episode of tachypnea and cyanosis (SpO_2 87%) 25 minutes after birth, but the situation improved when a nasal cannula was administrated. Physical examination revealed temperature of 36.6 °C, BP of 66/36 mmHg, and SpO_2 of 95% (on oxygen inhalation). The initial routine laboratory investigations showed mild hypoglycemia (1.9 mmol/L, normal 3.9–6.1), hyperammonemia (197 μmol/L, normal 0–70 μmol/L), elevated serum lactate dehydrogenase (LDH) (537 U/L, normal 135–214 U/L), creatine kinase (CK) (393.4 U/L, normal 24–195), and CK-MB (99.7 U/L, normal 0–24). Blood count, serum aminotransferases, lactic acid, and renal function tests were all within normal limits. The patient was treated initially with glucose at 6.5 mg/kg/min and arginine infusion. On the 3rd day of life, the patient abruptly experienced severe apnea and seizure, accompanied with low SpO_2 (82%) and progressive hyperammonemia (from 555 μmol/L to >715 μmol/L). He was treated with epinephrine and mechanical ventilation. However, the baby went into cardiac arrest 6 hours later and did not respond to cardiopulmonary resuscitation and succumbed 78 hours after his birth. He was the second child. His brother died at 2 days of age with sudden cardiac death. Urinary organic acids analysis by gas-chromatography–mass spectrometry (GC–MS) was normal. The newborn screening of dried blood spot using MS/MS showed a grossly increased level of long-chain acylcarnitine, especially C16, C18 acylcarnitine, and (C16+C18:1)/C2 ratio with a mildly decreased concentration of free carnitine (Table 1). The plasma acylcarnitine profiles were highly indicative of either CACT deficiency or carnitine palmitoyltransferase-2 (CPT2) deficiency. The mutation analysis of SLC25A20 gene from the cultured skin fibroblast of the patient disclosed a previously described homozygous c.199-10T>G mutation (Fig. 1). Moreover, sequence analysis of genomic DNA extracted from the peripheral blood of his parents identified a heterozygous status for the c.199-10T>G mutation (Fig. 1). These findings confirmed the diagnosis of CACTD.

Table 1

The acylcarnitine profiles in dried blood spots detected by tandem mass spectrometry.

Acylcarnitines	Concentration (μmol/L)		Normal value (μmol/L)
	Patient No. 1	Patient No. 2	
C0	7.28	9.08	9.5–40
C14	1.50	1.00	0.06–0.12
C14:1	0.19	0.22	0.01–0.16
C16	24.99	12.94	0.5–5.0
C16:1	1.71	1.34	0.01–0.11
C18	4.53	2.18	0.26–0.70
C18:1	6.33	3.03	0.3–2.6
C16/C2	3.31	1.12	0.04–0.30
C16/C3	36.75	7.03	0.35–0.40
(C16+C18:1)/C2	4.15	1.38	0.07–0.40

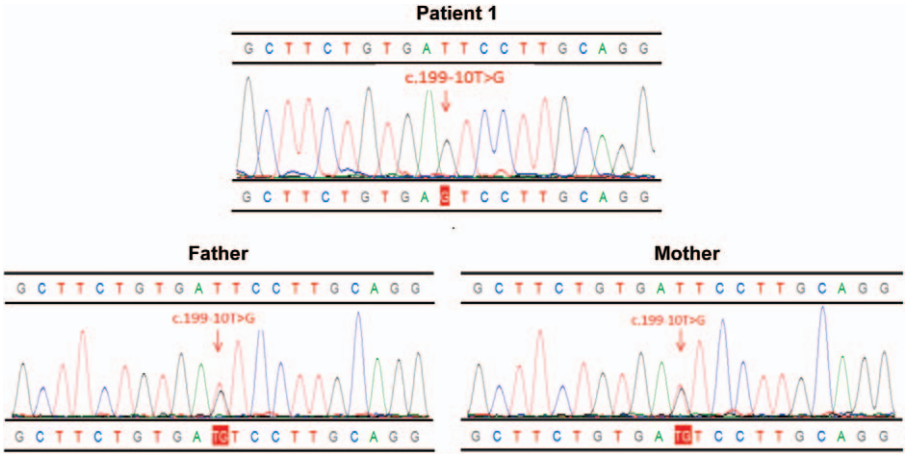

Figure 1. DNA sequence of intron 2 and intron 2 splice junction of the SLC25A20 gene. The patient No. 1 was homozygous for c.199-10 T>G mutation and his parents were a heterozygous status for c.199-10 T>G mutation (indicated by red arrows).

2.2. Patient No. 2

A female baby born by cesarean delivery. The Apgar score at 1 minute was 10. She was speedily transferred to the neonatal intensive care unit 52 hours after birth due to poor response and cyanosis (Fig. 2A). The physical examination revealed hypothermia (36 °C), hypotension (47/16 mmHg), bradypnea (30 beats/min), and low SpO_2 (45%). Routine laboratory tests showed pronounced hypoglycemia (0.9 mmol/L), hyperammonemia (380 μmol/L), and grossly elevated serum LDH (895.2 U/L), CK (689.4 U/L), CK-MB (146.0 U/L), and myoglobin (948 ng/mL, normal 0–90), consistent with skeletal muscle damage. Mechanical ventilation and arginine infusion was quickly administered. High glucose infusion at 6.5 mg/kg/min was also initiated to maintain a blood glucose level above 5.5 mmol/L. Circulatory disturbance was corrected after 2.5 hours of anti-shock therapy, and her plasma ammonia level decreased to 64 μmol/L after 3 hours of arginine infusion. Her clinical condition gradually improved (Fig. 2B) with stable vital signs; however, she was unable to wean from mechanical ventilation. Unfortunately, her parents refused further treatment due to fear of financial burdens. The girl died of congestive heart failure in the 6th day of life.

Urine analysis by GC–MS did not show elevated dicarboxylic-acids. However, MS/MS analysis of plasma acylcarnitines profile demonstrated a markedly abnormal accumulation of numerous long-chain acylcarnitine species (Table 1), in a typical pattern consistent with a diagnosis of either CACT or CPT2 deficiency. The results of the analysis of all SLC25A20 gene sequences, including intron and exon boundaries, revealed that this patient was compound heterozygous for 2 mutations: a novel c.1A>G mutation and a previously described c.199-10T>G mutation (Fig. 3). Sequence analysis of her parent's DNA extracted from blood indicated that the c.199-10T>G was derived from the maternal allele while the c.1A>G from the paternal allele (Fig. 3). Additionally, the subsequent DNA analysis of CPT2 gene was normal (data not shown). Taken together, these findings are consistent with the diagnosis of CACTD.

3. Discussion

Carnitine-acylcarnitine translocase deficiency is a rare and highly lethal inborn disorder that results in long-chain fatty acids being unavailable for mitochondrial β-oxidation and ketogenesis. The incidence of this clinical entity has been reported to be only 1:750,000 to 2,000,000 in Caucasia,[8] and approximately 1:60,000 in Hong Kong newborn populations, accounting for 33% of patients with FAO disorders.[9] During the last 2 decades, there have been no >60 patients described worldwide.[4] From 2013 to 2016, we screened 153,789 newborns in Hunan province, China and identified only 2 cases of CACTD. Thus, the incidence of this disorder in our region is about 1:76,894, which is similar to the rate in Hong Kong, China. To the best of our knowledge, these 2 cases are the first described CACTD disorders identified from the mainland Chinese population.

The clinical features of this entity reflect a combination of energy deprivation and endogenous toxicity of accumulation of long-chain acylcarnitines. The predominantly affected organs are the brain, heart, skeletal muscle, and liver. This explains the observed neurological abnormalities, cardiomyopathy, muscle damage, and liver dysfunction in CACTD patients.[2,3]

CACTD is classified into 2 phenotypes: a severe and mild form. The severe form is the more common phenotype with residual CACT enzyme activity <1% of normal level. It is usually present in the neonatal period and characterized by acute metabolic decompensation with a rapid deterioration, often presenting with acute cardiorespiratory collapse; the milder phenotype has residual enzyme activity of about 5% of controls and patients mainly present with episodes of hypoglycaemia and hyperammonemia during intercurrent illness.[3,10] Both cases we described herein presented with a severe clinical form.

As of February 2017, a total of 41 different mutations in the SLC25A20 gene have been described by Human Gene Mutation Database Professional. The mutation c.199-10T>G is a splicing mutation that resides in a conserved lariat branch sequence in intron 2 of the SLC25A20 gene.[11] This mutation was most commonly identified in patients from China, Thailand, Japan,

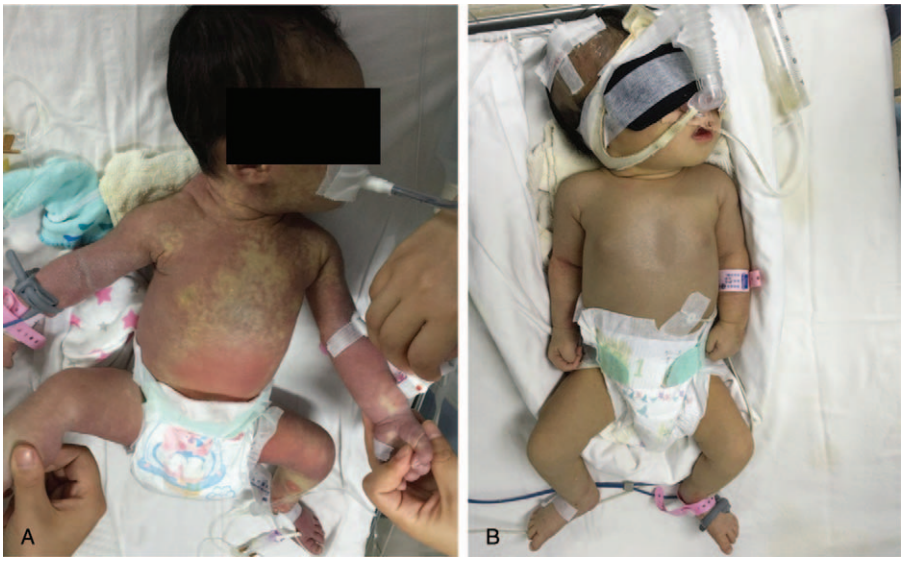

Figure 2. Comparison of the clinical condition pre- and posttreatment of patient No. 2. (A). Fifty-two hours after birth, the patient presented with circulatory collapse with severe cyanosis noted on the skin (B). After aggressive treatment, the patient's clinical condition significantly improved with cyanosis significantly alleviated.

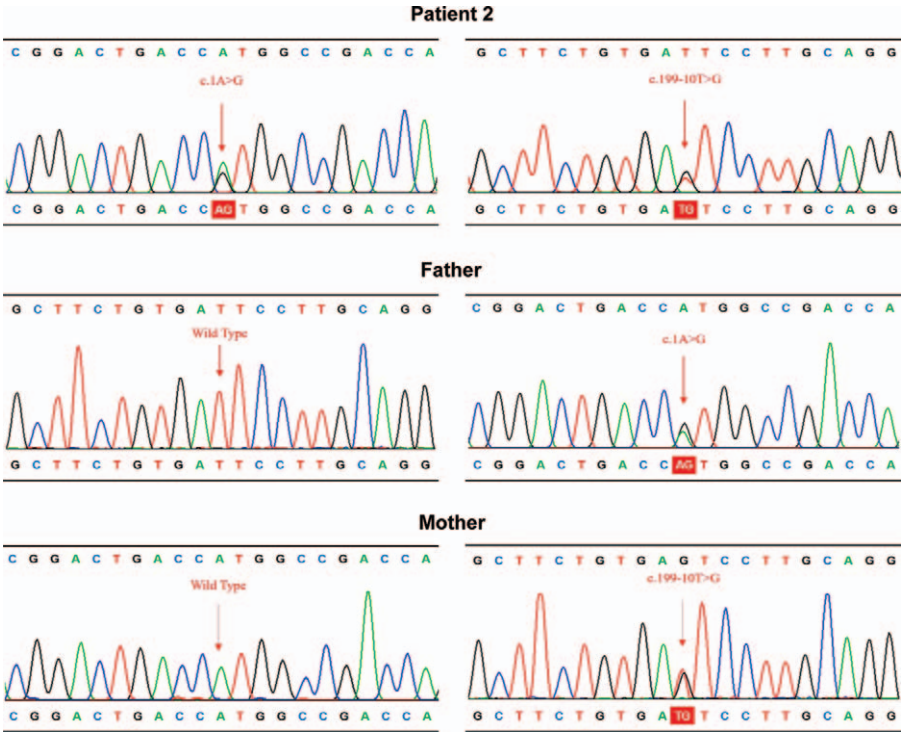

Figure 3. DNA sequence of SLC25A20 gene from patient No. 2 and her parents. The patient No. 2 was found to be heterozygous for a maternally-inherited c.199-10 T>G mutation and a paternally-inherited, novel c.1A>G mutation (marked with red arrows).

and Vietnam and probably represents a founder mutation in the Chinese population.[6,7,12–15] By searching the PubMed database, a total of 11 CACTD patients with c.199-10T>G mutation were found in previous literatures. Analysis of these literature showed that all patients presented with symptoms in the first 3 days of life. The most prevalent symptoms were sudden cardiac arrest, followed by apnea/respiratory distress, poor feeding, and lethargy. The mortality rate reaches up to 90.9%, and 63.6% patients died in the first 6 months of life. Cause of death mainly included cardiac arrest and respiratory failure (Table 2). Lee et al[13] described the outcomes of three Chinese Hong Kong neonates with CACTD with a homozygous c.199-10T>G mutation. All of them developed cardiac arrest within 2 days of age and only 1 patient survived. Vatanavicharn et al[7] also reported 2 cases of CACTD with homozygous c.199-10T>G mutation, the first identified in Thailand. Both patients developed cardiac arrest at third day of life. Similarly, the clinical condition of our 2 patients also deteriorated quickly and both died of cardiorespiratory collapse in the first week of life, despite an early and aggressive treatment. Taken together, these reports suggest that patients with CACTD and c.199-10T>G mutation have a high mortality rate during neonatal period. In 2001, Hsu et al[11] first examined the effect of the c.199-10T>G mutation on mRNA products and found that the lariat branch point sequence mutation at −10 position (T-10 → G-10) leads to either skipping of exons 3–4 or of exon 3 alone, which could perturb the second and third membrane domains of the translocase protein, causing premature protein truncation and a nonfunctional translocate enzyme (no activity). This may explain the severe consequence of the genotype of c.199-10T>G mutation, as in our patients.

It is worth noting that when a patient appears to be compound heterozygous for 2 mutations, it is important to confirm that the 2 mutations are indeed on 2 different chromosomal strands and not on the same chromosomal strand/in the same gene copy. In the latter case, the patient is heterozygous for a double mutation, and the genotype does not confirm the disease.[19] In our patient No. 2, apart from c.199-10T>G, we have identified a novel heterozygous mutation c.1A>G, which has never been reported yet. This mutation causes the loss of the primary start codon ATG for methionine, which is replaced by a triplet GTG for valine (p. Met1Val). Direct sequencing of her parent's DNA revealed that the c.199-10T>G was derived from the maternal allele while the c.1A>G from the paternal allele.

The diagnosis of CACTD can easily be overlooked, especially in patients who initially present with unrevealing clinical features. Keeping a high index of clinical suspicion is crucial in establishing the diagnosis of this condition. When neonates suffer from a sudden deterioration with hypoglycemia or hyperammonemia for no apparent reason, we should raise the suspicion of CACTD or other fatty acid oxidation defects.[13,20] Newborn screening by MS/MS offers the important clue for the early detection of long-chain FAO disorders, helping neonatologists specify a metabolic treatment. An elevated concentration of long-chain fatty acid acylcarnitine esters (C16–18) and a secondary hypocarnitinemia is highly suggestive of the diagnosis of CACT or CPT-2 deficiency. However, due to these 2 disorders share the same characteristics in acylcarnitine profile, so definitive identification of CACTD requires measurement of CACT enzyme activity or mutation analysis of the SLC25A20 gene. The latter is expected to be a pivotal tool for differentially diagnosing these 2 disorders.[2] The metabolic decompensate noted in our 2 patients is typical: hypoglycaemia, hyperammonemia, skeletal muscle damage, and markedly elevated long-chain acylcarnitine with low free carnitine concentration. Sequence analysis of the

Table 2

Summary of the clinical features of previous reported carnitine-acylcarnitine translocate deficiency patients with splicing mutation c.199-10T>G.

Patient No.	Sex	Reference (y)	Ethic origin	Consanguineous parents	Previous deceased siblings	Genotype	Onset time	Presenting symptoms	Outcomes
1	M	Stanley et al 1992[16]	Chinese (father)	No	Old brother died at 4 y of age (sudden cardiac death)	Heterozygous c.199-10T>G +c.120delT	At 36 h after birth	Seizure, severe apnea, hypotension	Deceased at 37 mo of age. (respiratory failure)
2	F	Chalmers et al 1997[17]	Chinese (father)	No	Not mentioned	Heterozygous c.199-10T>G +c.326delG	At 27 h after birth	Sleepy, poor feeding	Deceased at 31 h of age (cause unknown)
3	F	Hammond et al 1998[18] Costa et al 2003 (case No. 5)[6]	Vietnamese	No	Not mentioned	Homozygous c.199-10T>G	At 2 days of age	Hypothermia, hypoglycaemia	Deceased at 6 mo of age (respiratory arrest)
4	M	Costa et al 2003 (case No. 6)[6]	Vietnamese	No	Not mentioned	Homozygous c.199-10T>G	<3 d after birth	Hypopnea, hypothermia, hypoglycaemia	Deceased (time not mentioned) (sudden death)
5	M	Costa et al 2003 (case No. 7)[6] Brivet et al 1996[15]	Vietnamese	No	Two siblings had died previously at 24 h and 48 h of life, respectively	Homozygous c.199-10T>G	<3 days after birth	Not mentioned	Deceased at 2 mo of age (sudden death)
6	M	Fukushima et al 2013 (case No. 1)[14]	Japanese	No	None	Heterozygous c.199-10T>G +c.576G>A	At 2 d of age	Respiratory failure, asphyxia	Deceased at 33 mo (Reye syndrome)
7	F	Lam et al 2003[12] Lee et al 2007 (case No. 1)[13]	Chinese (Hong Kong)	No	First child	Homozygous c.199-10T>G	At 41 h after birth	Sudden cardiac arrest	Deceased at 3 d of age (sudden cardiac arrest)
8	M	Lee et al 2007 (case No. 2)[13]	Chinese (Hong Kong)	No	Not mentioned	Homozygous c.199-10T>G	At 32 h after birth	Sudden cardiac arrest	Alive at 32-m follow-up
9	F	Lee et al 2007 (case No. 3)[13]	Chinese (Hong Kong)	No	Not mentioned	Homozygous c.199-10T>G	28 h after birth	Sudden cardio-respiratory failure	Deceased at 38 h of age (sudden cardiac arrest)
10	M	Vatanavicharn et al 2015 (case No. 1)[7]	Thailand	Yes	First child	Homozygous c.199-10T>G	At 10 h of age	Hypothermia and developed cardiac arrest at 60 h after birth	Deceased at the age of 2 y and 8 mo (upper gastrointestinal bleeding and metabolic decompensation)
11	F	Vatanavicharn et al 2015 (case No. 2)[7]	Thailand	No	First child	Homozygous c.199-10T>G	At 2 d after birth	Lethargy, poor feeding, and cardiac arrest	Deceased at 4 mo of age (sudden cardiac arrest)

SLC25A20 gene helped us reach a final diagnosis for these 2 patients.

Early appropriate treatment is crucial in this disease and, if promptly administrated, may reverse the metabolic decompensation. It is generally agreed that the basic principle of managing CACTD is to maximally inhibit tissue lipolysis. The treatment regimen during the acute deterioration includes intravenous glucose to suppress the mobilization of fat and fatty acid oxidation, and ammonia detoxification along with other supportive measures depending on the clinical features.[2,21] In patients with severe cardiomyopathy or acute heart failure, extracorporeal membrane oxygenation or ventricular assist devices offer the potential for patient survival during diagnostic workup and in initiating a specific metabolic therapy.[22] In addition, triheptanoin (UX007), a novel investigational drug composed of synthetic medium-chain triglycerides (MCT), has recently been used as a compassionate use protocol for the emergency management of patients with several FAO disorders and severe cardiomyopathy. Mahapatra et al[23] described a case of an infant with CACTD admitted in severe metabolic crisis that devolving into cardiogenic shock who was successfully treated by triheptanoin.

In our patient No. 2, medical treatment with high glucose infusion was quickly started to keep the blood glucose level about 6.0 to 7.0 mmol/L and arginine was administrated intravenously to lower blood ammonia level, while mechanical ventilation and anti-shock therapy was provided to maintain the respiratory and circulatory function. Such an aggressive treatment regimen had resulted in good clinical and biochemical response in this patient. L-carnitine was not supplemented initially because its use in CACTD remains controversial. Carnitine therapy may cause a further accumulation of toxic long-chain acylcarnitines and thus, precipitating ventricular arrhythmias. The long-term diet therapy of this disorder includes avoidance of fasting with frequent meals, high-carbohydrate intake, MCT supplementation, and restriction of long-chain fats.[21,24] Important prognostic factors of CACTD could be the genotype, residual activity, prompt medical intervention during acute episodes and the duration and type of long-term treatment used. Of note, early therapeutic intervention together with good dietary compliance could significantly alter the natural history and improve the prognosis of this disorder. For example, Pierre et al[25] reported a quite distinct outcome of 2 siblings with CACTD. One of the siblings has resulting profound developmental delay and epilepsy, while the another was prospectively treated with a low fat/high-carbohydrate diet formula and MCT supplementation. The patient responded well to treatment and had no episodes of metabolic decompensation with normal development. Vitoria et al[4] also described the outcomes of 4 patients with CACTD and 2 of them were survived and show normal psychomotor and growth development at 4 and 16 years of age under the similar treatment regimen mentioned above.

4. Conclusion

In summary, we report the first 2 cases of CACTD identified from the mainland China. Apart from a founder mutation c.199-10T>G, we have identified a novel c.1A>G mutation. Patients with CACTD with a genotype of c.199-10T>G mutation usually presents with a severe clinical phenotype. Early recognition and appropriate treatment is crucial in this highly lethal disorder. Due to early onset, poor prognosis and increasing incidence, we urge pediatricians working with a Chinese population to pay more attention to CACTD.

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