CASE REPORT

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Successful Management by Selective Embryo in the Carnitine-acylcarnitine Translocase Deficiency with SLC25A20 C.199-10T>G Variation: The First Case Report from Vietnam and Literature Review

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ABSTRACT

Carnitine-acylcarnitine translocase deficiency with SLC25A20 c.199-10T>G variation is a rare condition, typically associated with severe neonatal outcomes. Recently, preimplantation genetic testing (PGT) has emerged as a screening test applicable to embryos produced through in vitro fertilization for genetic analysis before transfer. Thus, PGT allows for the identification and elimination of embryos carrying inherited genetic diseases. This case report aims to present data from PGT on intervention in the management of SLC25A20 c.199-10T>G variation, particularly in middle-income countries. A 26-year-old woman with a high-risk term pregnancy and a history of two sudden neonatal deaths underwent parental carrier testing, revealing heterozygous SLC25A20 c.199-10T>G variation in both parents. The subsequent pregnancy, identified as a homozygous for SLC25A20 c.199-10T>G mutation, was terminated at 20 weeks. The current pregnancy was successfully managed by in vitro fertilization-selective embryo transfer. Carnitine-acylcarnitine translocase deficiency owing to SLC25A20 c.199-10T>G variation can result in sudden neonatal collapse. Obstetricians should maintain a high index of suspicion in recurrent cases of unexplained early neonatal death. Parental carrier testing is crucial for prenatal management, and selective embryo transfer is a core treatment for heterozygous *SLC25A20* gene carriers in this highly lethal disorder.

Carnitine-acylcarnitine translocase deficiency (CACTD) is a rare and life-threatening autosomal recessive disorder of mitochondrial fatty acid β-oxidation (FAO) caused by a variation of the *SLC25A20* gene on chromosome 3p21.31.[1] The significantly increased acylcarnitine profiles are detected in dry blood spots by tandem mass spectrometry.[2] At least 42 different pathogenic or possibly pathogenic variants of SLC25A20 have been identified to date that cause CACTD. In Asia, the c.199-10T>G splice site variation is the most frequently reported. This metabolic disease is rare; it leads to life-threatening conditions, with an estimated incidence of 1/60 000 in Hong Kong.[3]

Ryder et al,[4] reported approximately 87 cases related to this metabolic disorder. Most patients present in the first two days of life, with hypoketotic hypoglycemia, hyperammonemia, cardiomyopathy or arrhythmia, hepatomegaly, and elevated liver enzymes.[4,5] Despite widely differing clinical manifestations of CACTD, two distinct clinical subtypes exist: a neonatal-onset severe form and an infancy-onset milder form.[6] Autopsy and histopathological examination often reveal extensive vascular degeneration in the heart and liver.[3,7] Gene mutation detection remains the gold standard for diagnosing CACTD.[7]

In the context of genetic advances, preimplantation genetic testing (PGT) has become a well-established alternative to invasive prenatal diagnosis, especially for monogenic disorders. PGT involves biopsying one or a few cells from in vitro fertilization embryos, testing the samples for genetic aberrations, and selectively transferring embryos without the identified genetic condition. While PGT is a suitable solution for couples at high risk of transmitting known genetic conditions, its application is currently limited in low-resource settings.[8]

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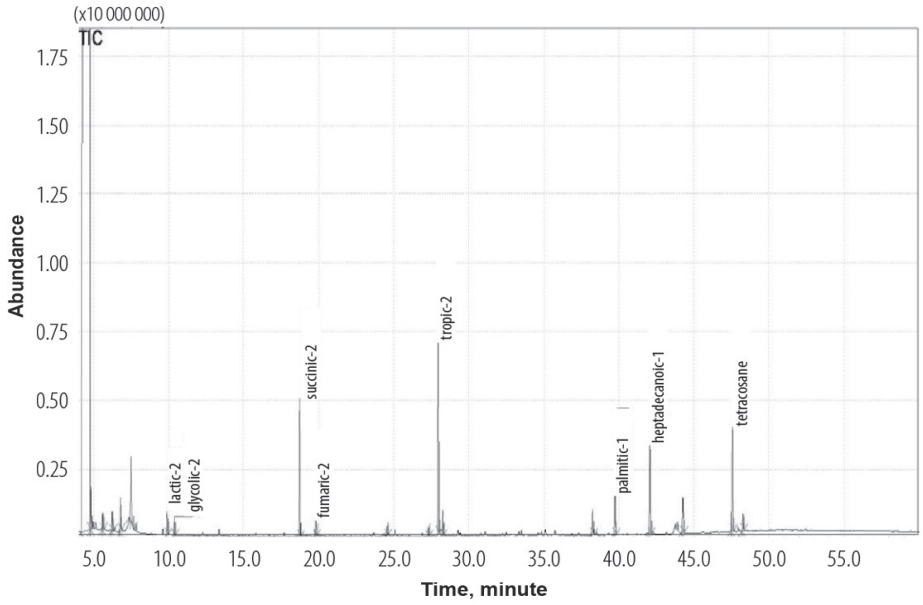

Item	Normal range	Result
Glycolic acid	< 4.0%	5.7%
Palmitic acid	< 23.3%	43.3%

Figure 1: Gas chromatography-mass spectrometry analysis of urine specimen, showing slightly higher values of glycolic acid and palmitic acid than the normal limit.

This case report contributes valuable insights into a rare disease associated with the *SLC25A20* gene mutation and highlights the significance of genetic screening and embryonic selection in low- and middle-income countries.

CASE REPORT

A 26-year-old pregnant woman (G5P2) was admitted to our hospital for a term pregnancy with an unremarkable medical record. Her obstetric history included one stillbirth at eight weeks of gestation and two full-term deliveries by vaginal birth and cesarean section, with neonates weighing 3000 and 3100 g, respectively. Unfortunately, both newborns died suddenly within two days of birth, and the etiology remained unexplained. The clinical presentations of the neonates included rapid deterioration, poor response, low muscle strength and tone, cyanosis, cardiopulmonary collapse, and eventual cardiac arrest despite resuscitation efforts. Both parents denied consanguineous marriage, and an investigation into the family history revealed no similar sudden deaths. Parental carrier testing showed a heterozygous SLC25A20 c.199-10T>G mutation in both mother and father. Additionally, the father had gene mutations in *MBL2* and *IDS*, and the mother had a variation in the *BCKDHB* gene. Despite these genetic findings, both parents were asymptomatic. Two years prior, the patient underwent a medical termination of pregnancy at 20 weeks of gestational age due to homozygosity for the c.199-10T>G variant of the *SLC25A20* gene. Confirmatory diagnosis was obtained through amniocentesis, and this pregnancy was conceived using artificial reproductive technology with PGT. Upon hospitalization, the patient's vital signs were stable, and she showed no signs of labor during examination. Sonographic findings revealed a vital fetus corresponding to 39 weeks and two days of gestational age. Fetal heart monitoring was normal, and laboratory tests fell within the normal range. Initially scheduled for induction of labor, the patient underwent cesarean section due to failed induction of labor and a history of adverse obstetric events. A male neonate was promptly assessed at birth, with Apgar scores of eight at one minute and nine at five minutes. The newborn, weighing 2900 g, appeared normal, and initial serum analyses showed a slight electrolyte imbalance (Na^+: 131 mmol/l, K^+: 6.02 mmol/l, Cl^-: 85.5 mmol/l, Ca^{2+}: 2.08 mmol/l, $NH3^-$: 109 umol/l), which were rapidly corrected. The neonate was monitored for seven days in the newborn care unit without complications. Both the mother and baby were discharged, with the baby being strictly

Table 1: Results of blood specimen tests indicating the absence of metabolic diseases related to acylcarnitine, amino acids, hemoglobin abnormalities, and other rare metabolic pathologies.

Blood tests	Value	Normal range	Unit	Result
Glucose-6-phosphate dehydrogenase	118.74	> 41	µM NADH	Normal
Thyroid stimulating hormone	0	< 30	µIU/mL	Normal
17-hydroxyprogesterone	3.6	< 30	ng/mL	Normal
Phenylalanine	1.41	< 3.9	mg/dL	Normal
Total galactose	1.42	< 13	mg/dL	Normal
Thyroxine	13.5	4–22.6	µg/dL	Normal
Galactose-l-phosphate uridyltransferase	4.15	> 2.0	U/g Hb	Normal
Biotinidase	91.14	> 36	MRU	Normal
Pathologies relating to hemoglobin (Thalassemia and variation of hemoglobin disease (≥ 5 diseases)	Low risk			
Amino acid				
Alanine	120.6	0–550	µmol/L	Normal
Arginine	12.2	0–36	µmol/L	Normal
Aspartic	83.25	0–810	µmol/L	Normal
Citruline	11.53	3.5–40	µmol/L	Normal
Glutamic acid	322.86	0–1000	µmol/L	Normal
Glycine	136.49	0–470	µmol/L	Normal
Leucine	175.39	30–280	µmol/L	Normal
Methionine	19.13	3.5–30	µmol/L	Normal
Ornithine	109.93	20–245	µmol/L	Normal
Phenylalanine	46.78	0–125	µmol/L	Normal
Proline	218.01	60–410	pmol/L	Normal
Tyrosine	126.67	0–210	µmol/L	Normal
Valine	109.83	20–200	µmol/L	Normal
Free carnitine and acylcarnitine				
Free carnitine (CO)	19.83	8–110	µmol/L	Normal
Acetylcarnitine (C2)	11.95	2.3–45	µmol/L	Normal
Propionylcarnitine (C3)	0.86	0.3–6	µmol/L	Normal
Butyrylcarnitine (C4)	0.12	0–0.61	µmol/L	Normal
C3DC + C40H	0.02	0–0.14	µmol/L	Normal
C4DC + C50H	0.06	0–0.5	µmol/L	Normal
Isovalerycarnitine (C5)	0.07	0–0.5	µmol/L	Normal
Tyglycarnitine (C5: I)		0–0.06	µmol/L	Normal
C5DC + C60H	0.12	0–0.45	µmol/L	Normal
Hexanoylcarnitine (C6)	0.03	0–0.14	µmol/L	Normal
Octanoylcarnitine (C8)	0.03	0–0.2	µmol/L	Normal
Octenoylcarnitine (C8:l)	0.03	0–0.25	µmol/L	Normal
Decanoylcarnitine (CIO)	0.03	0–0.17	µmol/L	Normal
Decenoylcarnitine (Cl O: l)	0.02	0–0.16	µmol/L	Normal
Decadienoylcarnitine (CI 0:2)	0.02	0–0.09	µmol/L	Normal
Dodecanoylcarnitine (Cl 2)	0.03	0–0.25	µmol/L	Normal
Dodecenoylcarnitine (Cl 2:1)	0.01	0–0.26	µmol/L	Normal
Tetradecanoylcarnitine (C14)	0.11	0–0.5	µmol/L	Normal
Tetradecenoylcarnitine (C14:l)	0.04	0.01–0.3	µmol/L	Normal
Tetradecandienoylcarnitine (C14:2)	0.01	0–0.05	µmol/L	Normal
3-hydroxy-tetradecanoyIcarnitine (C140H)		0–0.03	µmol/L	Normal
Hexadecanoylcarnitine (Cl 6)	1.46	0.3–6	µmol/L	Normal
Hexadecenoylcarnitine (C16: I)	0.08	0.01–0.4	µmol/L	Normal

Table 1: Results of blood specimen tests indicating the absence of metabolic diseases related to acylcarnitine, amino acids, hemoglobin abnormalities, and other rare metabolic pathologies.

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Blood tests	Value	Normal range	Unit	Result
3-hydroxy-hexadecenoylcarnitine (CI OH)	0.03	0–0.08	µmol/L	Normal
Hexadecadienoylcarnitine (Cl 6:2)	0	0–0.03	µmol/L	Normal
3-hydroxy-hexadecanoylcarnitine (CI 60H)	0.01	0–0.05	µmol/L	Normal
Octadecanoylcarnitine (C18)	0.58	0.18–1.9	µmol/L	Normal
Octadecenoylcarnitine (C18:I)	0.77	0.38–2.5	µmol/L	Normal
3-hydroxy-octadecenoylcarnitine (Cl 8:101-1)	0.01	0–0.05	µmol/L	Normal
Octadecadienoylcarnitine (C18:2)	0.13	0.03–0.8	µmol/L	Normal
3-hydroxy-Octadecadienoylcarnitine (CI 8:201-1)	0.01	0–0.04	µmol/L	Normal
3-hydroxy-Octadecanoylcarnitine (CI 80H)		0–0.03	µmol/L	Normal

monitored postnatally. Blood and urine samples were collected for tandem mass spectrometry and gas chromatography-mass spectrometry analyses.

Gas chromatography-mass spectrometry analysis of urine (QP2020 system, Shimadzu, Japan) revealed slightly elevated values of glycolic acid and palmitic acid at 5.7% (normal limit: < 4.0%) and 43.3% (normal limit: < 23.3%), respectively [Figure 1]. However, no metabolic diseases were detected in the blood samples [Table 1]. Subsequent blood tests for acylcarnitine, amino acids, hemoglobin abnormalities, and other rare metabolic pathologies showed normal results.

At the time of this report, the baby remained in good condition without notable complications, and the family expressed gratitude for the positive outcomes. Ethical approval was waived for publication, all patient details were de-identified, and written informed consent was obtained from the parents. This case report adheres to the CARE guidelines.[9]

DISCUSSION

In this case, the recurrence of two unexplained neonatal sudden deaths led to a comprehensive genetic analysis, revealing an autosomal recessive disorder associated with the *SLC25A20* gene, confirming the diagnosis of CACTD. The severe phenotype observed in the neonatal deaths aligns with the typical clinical manifestations of CACTD, characterized by hypoketotic hypoglycemia, hyperammonemia, liver function damage, and elevated creatine kinase.[5] Pathological changes include heart failure, arrhythmia, respiratory collapse, and cardiac arrest relating to the accumulation of long-chain fatty acids in multiorgan due to mitochondrial fatty acid β-oxidation disorders, which are immediately the direct cause of death. At the same time, gene mutation is the underlying cause of death [Table 2]. Neonatal death has mostly been noted after delivery or in the first week of life.[5,10,11] Rare reports, such as Chen et al's,[3] describe late-onset cases emerging 61 days after birth.

In assisted reproductive techniques, preimplantation genetic diagnosis offers couples with heritable genetic disorders a means to avoid the birth of a diseased offspring.[13] In this case, in vitro fertilization with selective embryo transfer successfully avoided the birth of homozygous genetic carrier fetuses, resulting in a newborn carrying a heterozygous *SLC25A20* gene without severe symptoms after birth. Carmona et al,[12] also agreed that the reproductive choices through preimplantation genetic testing or through early confirmatory testing for CACTD in the neonates and anticipatory management could help improve severe neonatal outcomes.

The multidisciplinary approach, incorporating molecular diagnosis, prenatal screening, and neonatal care, represents the current standard for managing CACTD. Timely intervention is crucial in limiting neonatal morbidity and mortality associated with this life-threatening disorder.[4]

CONCLUSION

Obstetricians should maintain a high index of suspicion of CACTD, particularly in cases of recurrent unexplained neonatal deaths. Parental carrier testing is essential for prenatal management, and the use of selective embryos provides a viable option for heterozygous *SLC25A20* gene-carried parents in this highly lethal disorder.

Table 2: Cases of carnitine-acylcarnitine translocase deficiency with SLC25A20 c.199-10T>G variation in the last five years.

Authors, year report, country	Obstetric history	Timing onset	Clinical symptoms	Type of variation on newborn	Parental gene analysis	Interventions	This pregnancy (GA, sex, newbornweigh, delivery)	Time of death after birth
Yan et al,[11] 2017, China	-G3P3 -First infant (boy) died at 2 days with sudden cardiac death	25 minutes after birth	- Severe metabolic crisis -Clinical conditions deteriorate rapidly - Both died of cardiorespiratory collapse in the first week of life	Homozygous	Heterozygous status for the c.199-10T>G mutation	- High glucose and arginine infusion - Respiratory and circulatory support	- Male - Spontaneous VB	78 hrs
	-	At 52 hours after birth	- Poor response and cyanosis -Died of congestive heart failure	A compound heterozygous for two mutations: a novel c.1A>G mutation and a previously described c.199-10T>G mutation	The c.199-10T>G was derived from the maternal allele while the c.1A>G from the paternal allele	- Antishock therapy - Arginine infusion - Mechanical ventilation	- Female - CS - Apgar score of 10 pts at one minute	6 days
Chen et al,[3] 2020, China	-G4P3 -the second infant (boy) died on the day of birth of an unknown cause. -The third child (girl) is in good health	At 61 days of birth	- Severe metabolic crisis, -Clinical condition rapidly deteriorated - Respiratory insufficiency and cardiac arrest	Homozygous	Both parents and older sister were heterozygous	Several resuscitation attempts failed	- 36 wks - Female - CS - 2200 g	61 days
Li et al,[6] 2021, China	-G2P1 -The first infant died at two days old from asphyxia, arrhythmia, and cardiac arrest	After 28 hours of birth	- Sleepy, no need of breastfeeding - Ventricular tachycardia, bradycardia, and complete right bundle branch block between the ages of 47 and 51 hours	Homozygous	Both parents were heterozygous carriers of the variation	Resuscitation	- Full-term - CS - Apgar score 10 pts at 5 mins	3 days
Li et al,[7] 2022, China	Primipara	At two days of birth	- Hypnesthesia, convulsions, hypothermia and bradypnea -Severe metabolic crisis - Deteriorated rapidly	The parents were carriers of the gene mutation	A compound heterozygote with c.199–10 T>G and a novel c.1A> T mutation in the *SLC25A20* gene	Resuscitation	- Full-term - Spontaneous VB - Male - Normal birth weight - Apgar score of 10 pts at 1 min	3 days
Zhang et al,[5] 2023, China	G1P2	a poor response, hypoglycemia, hypotonia, arrhythmias and sudden cardiorespiratory arrest on day 1.5	Hypoglycemia, arrhythmia, and sudden death	Two heterozygous variants of the *SLC25A20* gene in the two infants: paternal variant M1:c.706_707insT: p.R236L fs*12 and maternal variant M2: c.689C>G:p.P230R	-Heterozygous status - M1 variant was paternal - M2 variant was maternal.	Cardiopulmonary resuscitation for 1 hr	- 37 wks 6 days - CS - Male-female twin - 3490-3490 g	1.5–3.5 days

Table 2: Cases of CACTD with SLC25A20 c.199-10T>G variation in the last five years.

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Authors, year report, country	Obstetric history	Timing onset	Clinical symptoms	Type of variation on newborn	Parental gene analysis	Interventions	This pregnancy (GA, sex, newbornweigh, delivery)	Time of death after birth
Carmona et al,[12] 2023, Philippines	- G2P2 - Twice recurrent neonatal deaths	On 17th of life	- Sleeping until the 21st hour of life without waking to feed - No spontaneous eye opening and had fair cry - Generalized cyanosis and subsequently went into cardiac arrest	Missed	Both parents were identified to be heterozygous carriers of a pathogenic variant c.199-10T>G in the *SLC25A20* gene.	Resuscitation	-37 wks -CS due to non-reassuring fetal status - Male - 2400 g - Good cry	33rd hr of life
		On 19th hour of life	- No spontaneous eye opening with fair cry and fair suck - Cyanosis and sudden hypotonia	Missed		Admission at NICU and was given 10% IV dextrose infusion	- 38 wks - CS - female - 2600 g - good cry	On the 61st hour of life

CS: cesarean section; P: parity; G: gravida; VB: vaginal birth; wks: weeks; hr: hours; NICU: neonatal intensive care unit; IV: intravenous.

Disclosure

The authors declare no conflicts of interest. Ngoc Bich Trinh and Phuc Nhon Nguyen contributed equally to this paper and should be considered as co-first authors.

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