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 IVF 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 (G5P2) 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 homozygous for SLC25A20 c.199-10T>G mutation, was terminated at 20 weeks. The current pregnancy was successfully managed by IVF-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.

Keywords: c.199-10T>G variation, high-risk pregnancy, neonatal death, preimplantation genetic testing, SLC25A20, *in vitro* fertilization.

Introduction

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., reported approximately 87 cases related to this metabolic disorder. [4] 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 CACT deficiency, 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]

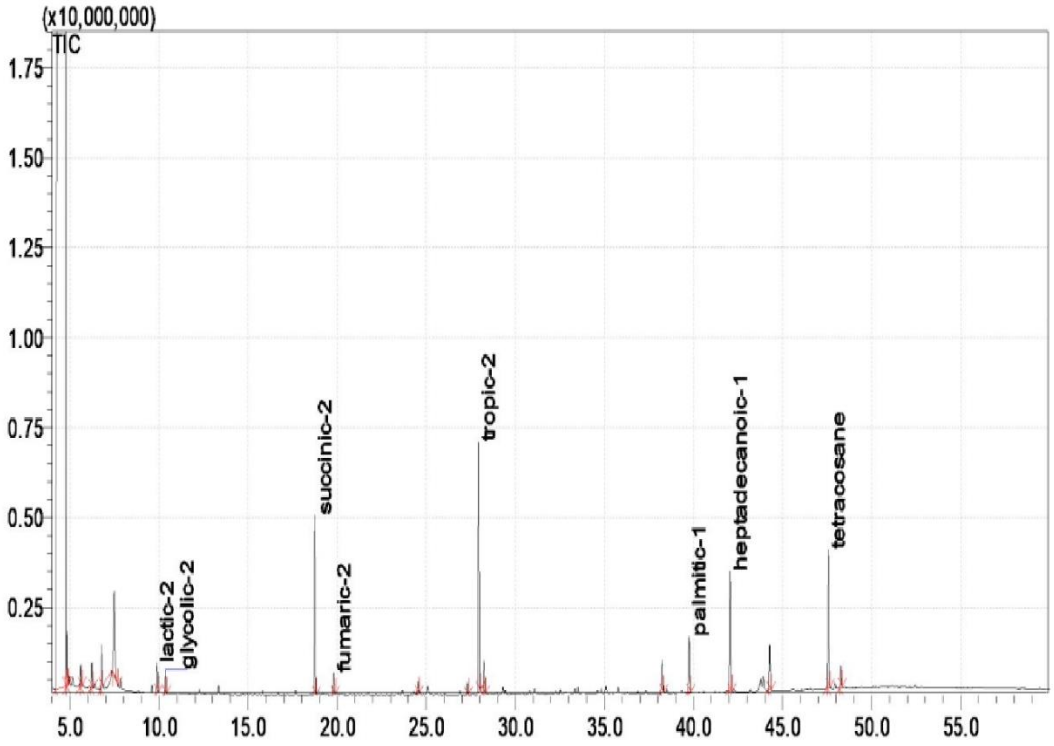
In the context of genetic advances, preimplantation genetic testing (PGT) has become a well-established alternative to invasive prenatal diagnosis, especially for monogenic disorders. PGT involves biopsing one or a few cells fromIVF embryos, testing the samples for genetic aberrations, and selectively 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]

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

Case report

A 26-year-old pregnant woman (G5P2) was admitted to our hospital for term pregnancy with an unremarkable medical record. Her obstetric history included one stillbirth at 8 weeks of gestation, two full-term deliveries by vaginal birth and cesarean section, with neonates weighing 3000 and 3100 grams, respectively. Unfortunately, both newborns died suddenly within 2 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 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 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 (ART) with preimplantation genetic testing (PGT).Upon hospitalization, the patient's vital signs were in stable, and she showed no signs of labor during examination. Sonographic findings revealed a vital fetus corresponding to 39 weeks and 2 days gestational age. Fetal heart monitoring was normal, and laboratory tests fell within the normal range. Initially scheduled for induction of labor (IOL), the patient underwent cesarean section due to failed IOL and a history of adverse obstetric events.A male neonate was promptly assessed at birth, with Apgar scores of 8 at 1 minute and 9 at 5 minutes. The newborn, weighing 2900 grams, 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. he neonate was monitored for seven days in the newborn care unit without complications. Both mother and baby were discharged, with the baby continuing to be strictly monitored postnatally. Blood and urine samples were collected for tandem mass spectrometry (MS/MS) and gas chromatography–mass spectrometry (GC/MS) analyses.

GC/MS analysis of urine (QP2020 system, Shimadzu, Japan) revealed slightly elevated values of glycolic acid and palmitic acid at 5.65% (normal limit: < 3.99%) and 43.27% (normal limit: < 23.34%), respectively [Figure 1]. However, no metabolic diseases were detected in blood samples [Table 1]. Subsequent blood tests for acylcarnitine, amino acids, hemoglobin abnormalities, and other rare metabolic pathologies showed normal results.



Item	Normal range	Result
Glycolic acid	< 3.99%	5.65%
Palmitic acid	< 23.34%	43.27%

Figure 1: GC/MS analysis of urine specimen, showing slightly higher values of glycolic acid and palmitic acid than the normal limit.

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.

Item	Value	Normal range	Unit	Result
Glucose-6-Phosphate Dehydrogenase (G6PD)	118.74	> 41	µM NADH	Normal
Thyroid Stimulating Hormone (TSH)	0	< 30	µIU/mL	Normal
17-hydroxyprogesterone (17-OHP)	3.6	< 30	ng/mL	Normal
Phenylalanine (PHE)	1.41	<3.9	mg/dL	Normal
Total Galactose (TGAL)	1.42	< 13	mg/dL	Normal
T_4	13.5	4–22.6	µg/dL	Normal
Galactose-l-Phosphate Uridyltransferase (GALT)	4.15	> 2.0	U/g Hb	Normal
Biotinidase (BIOT)	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
3-Hydroxy-HexadecenoyIcarnitine (CI OH)	0.03	0–0.08	μmol/L	Normal
Hexadecadienoylcarnitine (Cl 6:2)	0	0–0.03	μmol/L	Normal
3-Hydroxy-HexadecanoyIcarnitine (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-OctadecenoyIcarnitine (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

At the time of this report, the baby remained in good condition without notable complications, and the family expressed gratitude for the positive outcomes. Ethics 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 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 FAO disorders, which are immediately the direct cause of death, while 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, describe late-onset cases emerging 61 days after birth.[3]

Table 2: Cases of CACTD 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. (2017), China[11]	-G3P3 -First baby (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. (2020), China[3]	-G4P3 -the second child (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 grams	61 days
Li et al. (2021), China[6]	-G2P1 -The first child 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. (2022), China[7]	Primipara	At 2 days of birth	- Hypnesthesia, convulsions, hypothermia and bradypnea -Severe metabolic crisis -Deteriorated rapidly	The parents were carriers of 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	3 days

							pts at one min	
Zhang et al. (2023), China[5]	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 -the M1 variant was paternal -the M2 variant was maternal.	Cardiopulmonary resuscitation for 1 hour	-37 wks 6 days -CS -Male-female twin -3490-3490 grams	1.5–3.5 days
Carmona et al. (2023), Philippines [12]	-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 -2400gr -Good cry	33rd hour 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 -2600gr -good cry	On the 61st hour of life

CS: cesarean section; P:parity; G: gravida; VB: vaginal birth; wks: weeks.

In assisted reproductive techniques, preimplantation genetic diagnosis (PGD) offers couples with heritable genetic disorders a means to avoid the birth of diseased offspring.[13] In this case, IVF 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. also agreed that the reproductive choices through pre-implantation genetic testing or through early confirmatory testing for CACTD in the neonates and anticipatory management could help improve severe neonatal outcomes.[12]

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 carnitine–acylcarnitine translocase deficiency, 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.

Declaration statements

Conflicts of interest

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

Ethical approval

Ethical approval was naturally waived for case report from Ethics Committee of Tu Du Hospital.

Informed consent

Informed consent was obtained from the patient.

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References

1. Palmieri F, Scarcia P, Monné M. Diseases caused by mutations in mitochondrial carrier genes SLC25: a review. Biomolecules 2020 Apr;10(4):655.

2. Habib A, Azize NA, Rahman SA, Yakob Y, Suberamaniam V, Nazri MI, et al. Novel mutations associated with carnitine-acylcarnitine translocase and carnitine palmitoyl transferase 2 deficiencies in Malaysia. Clin Biochem 2021 Dec;98:48-53.

3. Chen M, Cai Y, Li S, Xiong H, Liu M, Ma F, et al. Late-onset carnitine-acylcarnitine translocase deficiency with SLC25A20 c.199-10T>G variation: case report and pathologic analysis of liver biopsy. Front Pediatr 2020 Oct;8:585646.

4. Ryder B, Inbar-Feigenberg M, Glamuzina E, Halligan R, Vara R, Elliot A, et al. New insights into carnitine-acylcarnitine translocase deficiency from 23 cases: management challenges and potential therapeutic approaches. J Inherit Metab Dis 2021 Jul;44(4):903-915.

5. Zhang L, Hu Y, Xie M, Zhang Y, Cen K, Chen L, et al. Carnitine-acylcarnitine translocase deficiency caused by SLC25A20 gene heterozygous variants in twins: a case report. J Int Med Res 2023 Apr;51(4):3000605231163811.

6. Li X, Shen J. One potential hotspot SLC25A20 gene variants in Chinese patients with carnitine-acylcarnitine translocase deficiency. Front Pediatr 2022 Nov;10:1029004.

7. Li X, Zhao F, Zhao Z, Zhao X, Meng H, Zhang D, et al. Neonatal sudden death caused by a novel heterozygous mutation in SLC25A20 gene: a case report and brief literature review. Leg Med (Tokyo) 2022 Feb;54:101990.

8. De Rycke M, Berckmoes V. Preimplantation genetic testing for monogenic disorders. Genes (Basel) 2020 Jul;11(8):871.

9. Gagnier JJ, Kienle G, Altman DG, Moher D, Sox H, Riley D; CARE Group*. The care guidelines: consensus-based clinical case reporting guideline development. Glob Adv Health Med 2013 Sep;2(5):38-43.

10. Tang C, Liu S, Wu M, Lin S, Lin Y, Su L, et al. Clinical and molecular characteristics of carnitine-acylcarnitine translocase deficiency: experience with six patients in Guangdong China. Clin Chim Acta 2019 Aug;495:476-480.

11. Yan HM, Hu H, Ahmed A, Feng BB, Liu J, Jia ZJ, et al. Carnitine-acylcarnitine translocase deficiency with c.199-10 T>G and novel c.1A>G mutation: two case reports and brief literature review. Medicine (Baltimore) 2017 Nov;96(45):e8549.

12. Carmona SM, Abacan MA, Alcausin MM. Carnitine-acylcarnitine translocase deficiency with c.199-10T>G mutation in two Filipino neonates detected through parental carrier testing. Int J Neonatal Screen 2023 Jan;9(1):4.

13. Van der Aa N, Zamani Esteki M, Vermeesch JR, Voet T. Preimplantation genetic diagnosis guided by single-cell genomics. Genome Med 2013 Aug;5(8):71.