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 very rare condition, but this disease usually relates to severe neonatal outcomes. Recently, preimplantation genetic testing (PGT) has been a screening test that can be performed on embryos created via in vitro fertilization (IVF) to genetically analyze the embryos prior to transfer. Thus, PGT can eliminate the unhealthy embryo with inherited genetic disease. The aim of this case report was to provide data from PGT intervention in the management of SLC25A20 c.199-10T>G variation, particularly, in middle-income countries. A 26-year-old woman (G5P2) was hospitalized for a high-risk term pregnancy. The patient had a poor obstetric history (PARA 2010) with two suddend neonatal deaths after 28 hours and 31 hours of birth. Following a careful examination, the parental carrier testing showed heterozygous SLC25A20 c.199-10T>G variation in both mother and father. The subsequent pregnancy was terminated at 20 weeks of gestation due to homozygous SLC25A20 c.199-10T>G mutation. Consequently, the current pregnancy was successfully managed by IVF- selective embryo transfer. Carnitine–acylcarnitine translocase deficiency owing to SLC25A20 c.199-10T>G variation causes a sudden collapse in neonates. Thus, a high index of suspicion should be raised by the obstetricians in recurrent cases of unexplained early neonatal death. Parental carrier testing is necessary for prenatal management, and the selective embryo is a core treatment for the heterozygous SLC25A20 gene-carried parents 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] To date, at least 42 different pathogenic or possibly pathogenic variants of SLC25A20 have been identified that cause CACTD. In Asia, the c.199-10T>G splice site variation is the most frequently reported variant. This metabolic disease is very rare, but leading to a life-threatening condition. The estimated incidence of CACTD is 1/60,000 in Hong Kong.[3]

According to Ryder et al., approximately 87 cases relating to this metabolic disorder have been described in the literature.[4] Most patients present in the first 2 days of life, with hypoketotic hypoglycemia, hyperammonemia, cardiomyopathy or arrhythmia, hepatomegaly, and elevated liver enzymes.[4,5] Though the clinical manifestations of CACT deficiency are widely different, there are two distinct clinical subtypes: a neonatal-onset severe form and an infancy-onset milder form.[6] Extensive vascular degeneration was often observed in the heart and liver at autopsy and histopathological examination.[3,7] However, gene mutation detection is the gold standard for the diagnosis of CACTD.[7]

Along with the current state-of-the-art methods in genetic advances, preimplantation genetic testing (PGT) is a well-established alternative to invasive prenatal diagnosis and can be performed for monogenic disorders. PGT involves the biopsy of a single or few cells from *in vitro* fertilized embryos and testing of the biopsied samples for genetic aberrations followed by the selective transfer of embryos. Thus, PGT is an appropriate solution for couples at a high risk of transmitting a known genetic condition to their offspring.[8] However, this modality remains limited in low-resource settings.

Through this case report, the team would like to contribute to a rare disease relating to the SLC25A20 gene mutation and emphasize the importance of genetic screening, as well as embryonic selection related to this entity in a low-middle income country.

Case Report

A 26-year-old pregnant woman (G5P2) was admitted to our hospital due to a term pregnancy. Her medical record was unremarkable. Her obstetric history was particularly noted with 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. However, both newborn babies died suddenly within 2 days of birth with unexplained etiology. The clinical presentations deteriorated rapidly with poor response, low muscle strength and tone, cyanosis, cardiopulmonary collapse, and later cardiac arrest despite of resuscitation. Both parents denied consanguineous marriage and the family generation was investigated without the sudden death related to a similar circumstance. Thus, the parents were screened for normal karyotypes and genetic tests and both were heterozygous carriers of the SLC25A20 c.199-10T>G mutation (carnitine-acylcarnitine carrier deficiency). In addition, the father was detected with gene mutation of MBL2 and IDS and genetic analysis of the mother revealed variation of BCKDHB gene. However, the parents had asymptomatic symptoms. Two years ago, the patient was indicated for a medical termination of pregnancy at 20 weeks GA owing to the homozygous for the variant c.199-10T>G of the solute carrier family 25 member 20 (SLC25A20) gene. The confirmatory diagnosis was identified by amiocentesis. This pregnancy was conceived using artificial reproductive technology (ART) and preimplantation genetic testing (PGT).

At hospitalization, her vital signs were in stable. The patient was examined without signs of labor. The sonographic findings revealed a vital fetus corresponding to 39 weeks and 2 days GA. The fetal heart monitoring was normal. Laboratory tests were in the normal range. The patient was first scheduled for induction of labor (IOL), but she underwent cesarean section due to the failed IOL and bad obstetric history.

A male neonate was immediately assessed by the neonatologist at birth for strict monitor. The Apgar score was noted at 1 minute of 8 points and 5 minutes of 9 points. The newborn weighing 2900 grams was evaluated as normal in appearance. The serum bilan were normal, except for 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). However, this disturbance was rapidly recovered. He was uneventfully monitored at the newborn care unit during 7 days. Both mother and baby were later discharged to their home. The baby continued to be strictly monitored after birth. The heel blood and urine samples were collected for tandem mass spectrometry (MS/MS) and gas chromatography–mass spectrometry (GC/MS) analyses. Following GC/MS analysis of urine specimen (QP2020 system – Shimadzu – Japan), the results of glycolic acid and palmitic acid were slightly higher than the normal value of 5.65% (normal limit: <3.99%) and 43.27% (normal limit: <23.34%), respectively (Figure 1). However, none of metabolic diseases were detected in the blood specimen (Table 1).

Figure 1: Using Gas Chromatography Mass Spectrometry (GC/MS, QP2020 system – Shimadzu – Japan) analyzing urine specimen, the values of glycolic acid and palmitic acid were slightly higher than the normal limit.

Table 1: None of metabolic diseases relating to acylcarnitine, amino axit, hemoglobin abnormalities, and others rare metabolic pathologies were detected on the blood specimen.

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

Thyroxine (T4)	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 (HEMO) (Thalassemia and variation of Hemoglobin disease (≥ 5 diseases)	Low risk			
Acid amin				
Alanine (Ala)	120.6	0-550	µmol/L	Normal
Arginine (Arg)	12.2	0-36	µmol/L	Normal
Aspartic (Asp)	83.25	0-810	µmol/L	Normal
Citruline (Cit)	11.53	3.5 - 40	µmol/L	Normal
Glutamic acid (Glu)	322.86	0- 1000	µmol/L	Normal
Glycine (Gly)	136.49	0- 470	µmol/L	Normal
Leucine (Leu)	175.39	30 - 280	µmol/L	Normal
Methionine (Met)	19.13	3.5 - 30	µmol/L	Normal
Ornithine (Orn)	109.93	20 - 245	µmol/L	Normal
Phenylalanine (Phe)	46.78	0- 125	µmol/L	Normal
Proline (Pro)	218.01	60 - 410	pmol/L	Normal
Tyrosine (Tyr)	126.67	0-210	µmol/L	Normal
Valine (Val)	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 was in good condition without any notable complications. The family felt grateful for the good outcomes of both mother and baby.

The ethics approval was naturally waived for publication of this case report. All patient details were de-identified. Written informed consent to publication were obtained from the parents. The reporting of this study conforms to CARE guidelines.[9]

Discussion

In the present case, the recurrence of two neonatal sudden death was initially unexplained. Nevertheless, following the genetic analysis from the parents, a life-threatening autosomal recessive disorder in association with the SLC25A20 gene was detected as the gold standard for the confirmed diagnosis. These findings are in line with the diagnosis of CACTD. Moreover, the rapid deterioration of neonatal conditions was suitable for a severe phenotype. The neonatal death was mostly noted after delivery 2-3 days or in the first week of life in several sporadic reports.[5,10,11] CACTD has severe clinical manifestations and a progressively poor prognosis, which presents rapidly as hypoketotic hypoglycemia, hyperammonemia, liver function damage and elevated creatine kinase.[5] The 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). Rarely, Chen et al., reported a late-onset of CACTD cases with homozygous c.199-10T>G variation emerging 61 days after birth.[3]

Table 2: Some cases related to carnitine-acylcarnitine translocase deficiency with SLC25A20 c.199-10T>G variation in the last 5 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]	-G2P2 -the first baby (boy)died at 2 days of age with sudden cardiac death.	At 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 2 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 1 min	6 days
Chen et al. (2020), China[3]	-G4P3 -the second child (boy) died on the day of birth of an unknown cause. -The	At 61 days of birth	- severe metabolic crisis, - clinical condition rapidly deteriorated - respiratory insufficiency	Homozygous	Both parents and older sister were heterozygous	Several resuscitation attempts failed	-36 wks -female -CS -2200 grams	61 days

	third child (girl) is in good health.		and cardiac arrest					
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 5mins	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 pts at 1 min	3 days
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 h	-37 wks 6 days -CS -male-female twin -3490-3490 grams	1.5–3.5 days
Carmona et al. (2023), Philippines [13]	-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	-37wks -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, NICU: neonatal intensive care unit, P:parity, G: gravida,VB: vaginal birth, wks: weeks

In the era of assisted reproductive technique, preimplantation genetic diagnosis (PGD) aims to help couples with heritable genetic disorders to avoid the birth of diseased offspring.[12] In this pregnancy, the patient received in vitro fertilization (IVF) with the selective embryo, thus avoiding the homozygous genetic carrier fetuses. The newborn carried a heterozygous SLC25A20 gene, and the severe symptoms were not present after birth. However, the neonate needs to be carefully monitored. Similar to our case, 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 the severe neonatal outcomes if warranted.[13]

Currently, a timely approach with a multidisciplinary team including the advances in molecular diagnosis, prenatal screening, and neonatal care is an appropriate management of CACTD, thus neonatal morbidity and mortality are limited.[4]

Conclusion

In conclusion, a high index of suspicion of carnitine–acylcarnitine translocase deficiency owing to SLC25A20 c.199-10T>G variation should be made by the obstetricians in recurrences of sudden neonatal death with unknown reason. Parental carrier testing is necessary for prenatal management, and the selective embryo is an acceptable option for the heterozygous SLC25A20 gene-carried parents in this highly lethal disorder.

***List of abbreviations*:** CACTD: Carnitine–acylcarnitine translocase deficiency, in IVF: *in vitro* fertility, FAO: fatty acid β-oxidation.

References

1. Palmieri F, Scarcia P, Monné M. Diseases Caused by Mutations in Mitochondrial Carrier Genes SLC25: A Review. Biomolecules 2020;10(4).

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;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;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;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;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;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;54:101990.

8. De Rycke M, Berckmoes V. Preimplantation Genetic Testing for Monogenic Disorders. Genes (Basel) 2020;11(8).

9. Gagnier JJ, Kienle G, Altman DG, Moher D, Sox H, Riley D. The CARE Guidelines: Consensus-based Clinical Case Reporting Guideline Development. Glob Adv Health Med 2013;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;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;96(45):e8549.

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

13. Carmona SM, Abacan MA, Alcausin M. Carnitine-acylcarnitine Translocase Deficiency with c.199-10T>G Mutation in Two Filipino Neonates Detected through Parental Carrier Testing. Int J Neonatal Screen 2023;9(1).