Taiwanese Journal of Obstetrics & Gynecology 57 (2018) 137–140

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Case Report

Prenatal diagnosis of fetal glutaric aciduria type 1 with rare compound heterozygous mutations in GCDH gene

Hsiu-Huei Peng, Sheng-Wen Shaw, Kuan-Gen Huang*

Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital, Linkou Medical Center and Chang Gung University College of Medicine, Kwei-Shan, Tao-Yuan, Taiwan

ARTICLE INFO

Article history:
Accepted 27 June 2017

Keywords:
Glutaric aciduria type 1
GCDH gene mutation
Prenatal diagnosis
Compound heterozygous gene mutation

ABSTRACT

Objective: Glutaric aciduria type 1 is a rare disease, with the estimated prevalence about 1 in 100,000 newborns. GCDH gene mutation can lead to glutaric acid and 3- OH glutaric acid accumulation, with clinical manifestation of neuronal damage, brain atrophy, microencephalic macrocephaly, decreased coordination of swallowing, poor muscle coordination, spasticity, and severe dystonic movement disorder.

Case report: A 22-year-old female, Gravida 4 Para 2, is pregnancy at 13 weeks of gestational age. Her first child is normal, however, the second child was diagnosed as glutaric aciduria type I after birth. She came to our hospital for prenatal genetic counselling of her fetus at 13 weeks of gestational age.

We performed GCDH gene mutation analysis of maternal blood showed IVS 3 + 1 G > A heterozygous mutation, GCDH gene mutation analysis of paternal blood showed c. 1240 G > A heterozygous mutation, and the second child has compound heterozygous IVS 3 + 1 G > A and c. 1240 G > A mutations. Later, we performed amniocentesis at 16 weeks of gestational age for chromosome study and GCDH gene mutation analysis for the fetus. The fetal chromosome study showed normal karyotype, however, GCDH gene mutation analysis showed compound heterozygous IVS 3 + 1 G > A and c. 1240 G > A mutations. The couple decided to termination of pregnancy thereafter.

Conclusion: Glutaric acidemia type 1 is an autosomal recessive disorder because of pathogenic mutations in the *GCDH* gene. Early diagnosis and therapy of glutaric acidemia type 1 can reduce the risk of neuronal damage and acute dystonia. We report a case of prenatal diagnosis of fetal glutaric aciduria type 1 with rare compound heterozygous GCDH gene mutation at IVS 3 + 1 G > A and c. 1240 G > A mutations, which provide better genetic counselling for the couples.

Introduction

Glutaric aciduria is first described in 1975 [1], are a group of autosomal recessively inherited metabolic disorders that are characterized by abnormal excretion of glutaric acid due to a defect in amino acid or fatty acid metabolism pathways. Glutaric aciduria type 1 is caused by deficiency of Glutaryl-CoA Dehydrogenase (GCDH) enzyme, because of pathogenic mutations in the GCDH gene [2,3]. Deficiency of GCDH enzyme causes increased organic acid excretion of glutaric acid, 3-hydroxyglutaric acid and glutaconic acid in urine and elevated glutarylcarnitine (C5DC) in plasma. Clinical manifestation including of neuronal damage, brain atrophy, microencephalic macrocephaly, decreased coordination of swallowing, poor muscle coordination, spasticity, and severe dystonic movement disorder [4–6].

GCDH gene mutations are caused by different types of mutations such as missense, nonsense and frameshift mutations [7–9]. Different mutations have been reported from different ethnic groups [10–12]. Here, we present a case of prenatally diagnosed with rare compound heterozygous GCDH mutation at IVS 3 + 1 G > A and c. 1240 G > A mutations.

Case report

A 22-year-old female, Gravida 4 Para 2, is pregnancy at 13 weeks of gestational age. Prenatal and postnatal examination of her first

* Corresponding author. Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital, Linkou Medical Center and Chang Gung University College of Medicine, 5, Fu-Hsin Street, Kwei-Shan, 333, Tao-Yuan, Taiwan. Fax: +886 3 328 6700.

E-mail address: kghuang@ms57.hinet.net (K.-G. Huang).

https://doi.org/10.1016/j.tjog.2017.12.023

child is normal. Prental examination (including fetal ultrasound) of her second child has no significant abnormal findings, however, the second child was diagnosed as glutaric aciduria type I after birth by increased glutaryl (C5DC) carnitine on newborn screening. Urine organic acid analysis indicates the presence of excess 3-OH-glutaric acid, and urine acylcarnitine profile shows glutaryl carnitine as the major peak. The second child had developmental delay, cerebral palsy and epilepsy after birth. Magnetic resonance imaging at 1 year old revealed frontotemporal atrophy. This time, she came to our hospital for prenatal examination and genetic counseling of her fetus at 13 weeks of gestational age.

Maternal serum Down screening at 13 weeks of gestational age showed fetal nuchal translucency was 1.7 mm, free beta-HCG was 36.6 IU/L (0.794 MoM), PAPP-A was 1.650 IU/L (0.288 MoM), the risk of Down syndrome was 1/1777. We also performed GCDH gene mutation analysis for the couples and their second child to identify the gene mutation point. GCDH gene mutation analysis of maternal blood showed IVS 3 + 1 G > A heterozygous mutation, GCDH gene mutation analysis of paternal blood showed c. 1240 G > A heterozygous mutation (Fig. 1), and the second child has compound heterozygous c. 1240 G > A and IVS 3 + 1 G > A mutations.

Later, we perform amniocentesis at 16 weeks of gestational age for chromosome study and GCDH gene mutation analysis for the fetus. We obtained 30 ml of amniotic fluid from amniocentesis, including 20 ml for fetal karyotype and 10 ml for GCDH gene mutation analysis. The chromosome study of the fetus showed normal karyotype 46, XY, however, GCDH gene mutation analysis of amniotic fluid cells showed compound heterozygous c. 1240 G > A and IVS 3 + 1 G > A mutations (Fig. 2). Fetal ultrasound at 19 weeks of gestational age had no significant abnormal findings. The couple decided to termination of pregnancy thereafter. A male fetus weighting 470 gm was delivered through vagina.

Discussion

Glutaric acidemia type 1 is an autosomal recessive disorder of lysine, hydroxylysine, and tryptophan metabolism caused by deficiency of glutaryl-CoA dehydrogenase, because of GCDH gene mutation. Prenatal diagnosis and early treatment is important as about 80%–95% of untreated glutaric aciduria type 1 patients present with acute or insidious onset of a complex movement disorder with predominant dystonia during infancy and childhood [4,5]. Early diagnosis and therapy can reduce the risk of neuronal damage and acute dystonia.

GCDH gene, which consists of 11 exons located on 19p13.2, has more than 200 disease-causing mutations been identified [2,3]. Different GCDH gene mutations have been reported from different ethnic groups. The most frequent mutation in Europe is p. Arg402Trp accounting for 10%–20% of all alleles [3]. Other mutations are predominantly or even exclusively found in distinct populations such as p. Ala421Val in the Amish Community as well as Southern parts of Germany and Switzerland, the original settlement area of the Amish [3], IVS1 + 5G > T in the Oji-Cree First Nations [10], p. Pro248Leu and p. Glu365Lys in Turkey [11], and p. Arg227Pro and p. Val400Met in Spain [12].

The mutation of GCDH gene in IVS1 + 5G > T had been reported postnatally in 1995 [13]. The mutation of GCDH gene in c. 1240 G > A had been reported postnatally in 2008 [7]. However, compound heterozygous mutations of GCDH gene mutation at IVS 3 + 1 G > A and c. 1240 G > A had not been reported. To our knowledge, our case is the first report of prenatal diagnosis of fetal glutaric aciduria type 1 with compound heterozygous GCDH gene mutation at IVS 3 + 1 G > A and c. 1240 G > A.

Prenatal diagnosis of fetal glutaric aciduria type 1 had been published and are summarized in Table 1. Prenatal diagnosis of

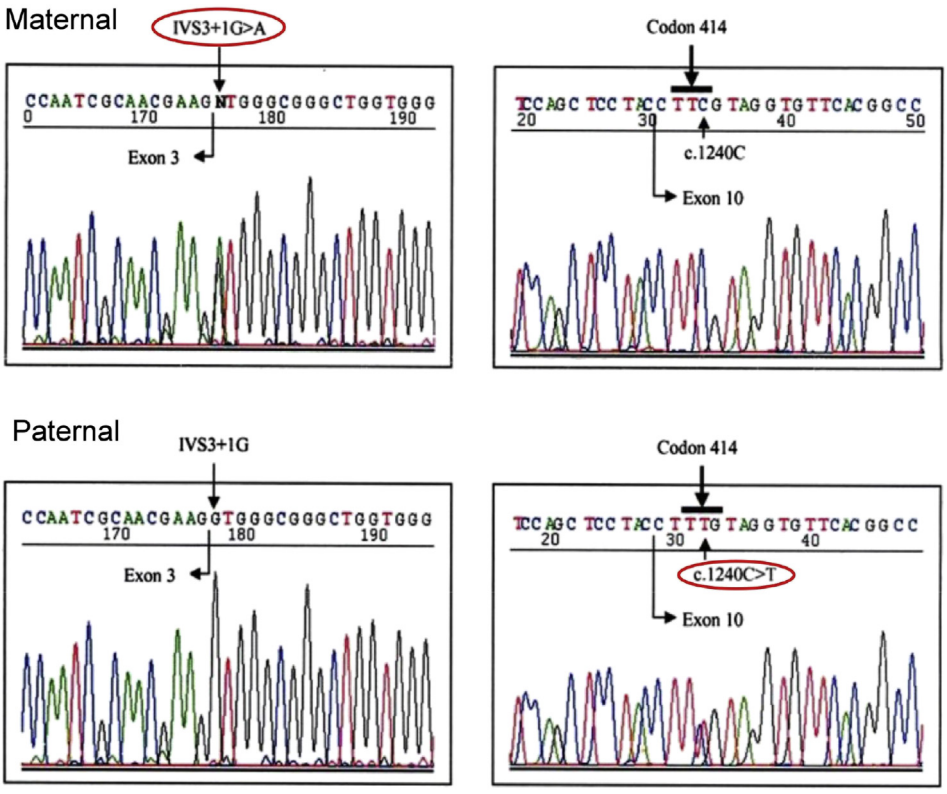

Fig. 1. GCDH gene mutation analysis of maternal blood (upper) showed IVS 3 + 1 G > A heterozygous mutation, GCDH gene mutation analysis of paternal blood (lower) showed c. 1240 G > A heterozygous mutation.

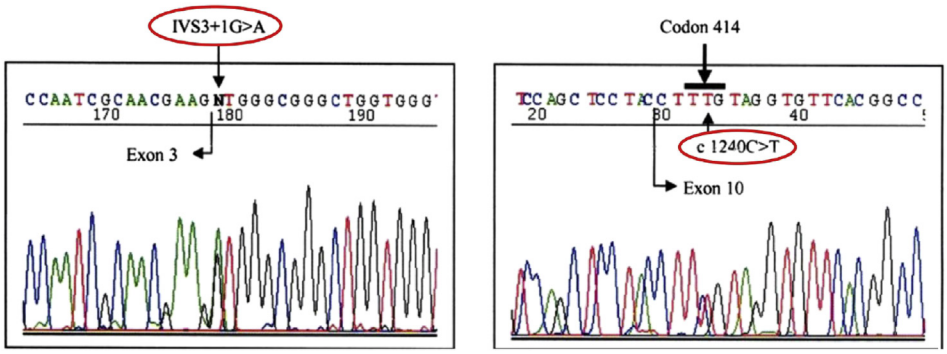

Fig. 2. GCDH gene mutation analysis of the fetal amniotic fluid showed compound heterozygous mutation with IVS 3 + 1 G > A mutation, and c. 1240 G > A mutation.

Table 1
Prenatal diagnosis of Glutaric aciduria type 1.

	Goodman et al.[a]	Christensen [b]	Busquets et al.[c]	Lin et al.[d]	Our case
Case number	1	4	Family 1: 3 Family 2: 1 Family 3: 3	2	1
Gestational age	15 weeks	10–12 weeks	11–16 weeks	11 weeks	16 weeks
Diagnosis sample	amniotic cells	uncultured and cultured chorionic cells	chorionic villi biopsy or cultured amniotic fluid cells	chorionic villi	amniotic fluid cells
Diagnosis method	increase of glutaric acid, deficiency of glutaryl-CoA dehydrogenase	deficiency of glutaryl-CoA dehydrogenase	GCDH gene mutation analysis	GCDH gene mutation analysis	GCDH gene mutation analysis
Fetal ultrasound	not available	not available	not available	One case had dilatation of quadrigeminal cistern and suspicious macrocephaly at 30 weeks.	No significant abnormal findings at 19 weeks
Outcome	Termination of pregnancy	Termination of pregnancy	*Family 1*: 1 affected fetus spontaneous abortion, 2 carrier fetuses continue pregnancy *Family 2*: 1 carrier fetus continue pregnancy *Family 3*: 2 affected fetuses elective abortion, 1 carrier fetus continue pregnancy	One case continue pregnancy and delivery at 37 weeks	Termination of pregnancy

[a] Goodman, S. I., Gallegos, D. A., Pullin, C. J., Halpern, B., Truscott, R. J. W., Wise, G., Wilcken, B., Ryan, E. D., Whelan, D. T. Antenatal diagnosis of glutaric acidemia. Am. J. Hum. Genet. 1980, 32: 695–699.
[b] Christensen, E. Prenatal diagnosis of glutaryl-CoA dehydrogenase deficiency: experience using first-trimester chorionic villus sampling. Prenatal Diag. 1994, 14: 333–336.
[c] Busquets C, Coll MJ, Merinero B, Ugarte M, Ruiz MA, Martinez Bermejo A et al. Prenatal molecular diagnosis of glutaric aciduria type I by direct mutation analysis. Prenatal Diag. 2000, 20 (9):761–764.
[d] Lin, S. K., Hsu, S. G., Ho, E. S. C., Tsai, C. R., Hseih, Y. T., Lo, F. C., Lai, H. Y. and Chen, M. H. Novel mutation and prenatal sonographic findings of glutaric aciduria (type I) in two Taiwanese families. Prenat. Diagn. 2002, 22: 725–729.

fetal glutaric aciduria type 1 had been reported by the findings of elevation of glutaric acid in the amniotic fluid, together with deficiency of glutaryl-CoA dehydrogenase in amniotic cells [14]. However, since the description of patients with normal excretion of glutarate and significant residual activity, it is difficult to make precise prenatal diagnosis only depends on biochemical strategies. The first report of prenatal diagnosis of glutaric aciduria type 1 by GCDH gene mutation analysis were performed in chorionic villi biopsy or cultured amniotic fluid cells in three families at risk for glutaric aciduria type 1 [15]. Their results show that this strategy provides a fast and reliable method for prenatal diagnosis.

The combination of early diagnosis and an early start of metabolic treatment has dramatically improved the neurological outcome and survival of patients with glutaric acidemia type 1. Our case is an excellent example of prenatal diagnosis of glutaric acidemia type 1 with compound heterozygous GCDH mutations at IVS 3 + 1 G > A and c. 1240 G > A by GCDH gene mutation analysis, which provide better genetic counseling for the couples.

Conflict of interest

The authors declared no conflicts of interest.

Acknowledgement

This study was supported by the following grants: NSC97-2314-B-182-024 (HH Peng) from National Science Council, Taiwan; CMRPG 340201, CMRPG371611, CMRPG371612 and CMRPG371613 (HH Peng).

References

[1] Goodman SI, Markey SP, Moe PG, Miles BS, Teng CC. Glutaric aciduria; a "new" disorder of amino acid metabolism. Biochem Med 1975;12:12–21.
[2] Goodman SI, Stein DE, Schlesinger S, Christensen E, Schwartz M, Greenberg CR, et al. Glutaryl-coa dehydrogenase mutations in glutaric acidemia (type i): review and report of thirty novel mutations. Hum Mutat 1998;12:141–4.
[3] Zschocke J, Quak E, Guldberg P, Hoffmann GF. Mutation analysis in glutaric aciduria type i. J Med Genet 2000;37:177–81.

[4] Strauss KA, Puffenberger EG, Robinson DL, Morton DH. Type i glutaric aciduria, part 1: natural history of 77 patients. Am J Med Genet C Semin Med Genet 2003;121C:38–52.
[5] Kölker S, Garbade SF, Greenberg CR, Leonard JV, Saudubray JM, Ribes A, et al. Natural history, outcome, and treatment efficacy in children and adults with glutaryl-coa dehydrogenase deficiency. Pediatr Res 2006;59:840–7.
[6] Gitiaux C, Roze E, Kinugawa K, Flamand-Rouvière C, Boddaert N, Apartis E, et al. Spectrum of movement disorders associated with glutaric aciduria type 1: a study of 16 patients. Mov Disord Off J Mov Disord Soc 2008;23:2392–7.
[7] Keyser B, Mühlhausen C, Dickmanns A, Christensen E, Muschol N, Ullrich K, et al. Disease-causing missense mutations affect enzymatic activity, stability and oligomerization of glutaryl-CoA dehydrogenase (GCDH). Hum Mol Genet 2008;17(24):3854–63.
[8] Liu Q, Chen Y, Chen W. Mutation analysis of GCDH gene in four patients with glutaric academia type I. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 2015;32(2):187–91.
[9] Wang Q, Li X, Ding Y, Liu Y, Song J, Yang Y. Clinical and mutational spectra of 23 Chinese patients with glutaric aciduria type 1. Brain Dev 2014;36(9):813–22.
[10] Greenberg CR, Prasad AN, Dilling LA, Thompson JR, Haworth JC, Martin B, et al. Outcome of the first 3-years of a DNA-based neonatal screening program for glutaric acidemia type 1 in manitoba and northwestern ontario, Canada. Mol Genet Metab 2002;75:70–8.
[11] Kölker S, Garbade SF, Boy N, Maier EM, Meissner T, Mühlhausen C, et al. Decline of acute encephalopathic crises in children with glutaryl-coa dehydrogenase deficiency identified by newborn screening in Germany. Pediatr Res 2007;62:357–63.
[12] Busquets C, Merinero B, Christensen E, Gelpí JL, Campistol J, Pineda M, et al. Glutaryl-coa dehydrogenase deficiency in Spain: evidence of two groups of patients, genetically, and biochemically distinct. Pediatr Res 2000;48:315–22.
[13] Greenberg CR, Reimer D, Singal R, Triggs-Raine B, Chudley AE, Dilling LA, et al. A G-to-T transversion at the +5 position of intron 1 in the glutaryl CoA dehydrogenase gene is associated with the Island Lake variant of glutaric acidemia type I. Hum Mol Genet 1995;4(3):493–5.
[14] Goodman SI, Gallegos DA, Pullin CJ, Halpern B, Truscott RJ, Wise G, et al. Antenatal diagnosis of glutaric acidemia. Am J Hum Genet 1980;32(5):695–9.
[15] Busquets C, Coll MJ, Merinero B, Ugarte M, Ruiz MA, Martinez Bermejo A, et al. Prenatal molecular diagnosis of glutaric aciduria type I by direct mutation analysis. Prenat Diagn 2000;20(9):761–4.