Successful Pregnancy in a Young Woman with Multiple Acyl-CoA Dehydrogenase Deficiency

Annalisa Creanza • Mariella Cotugno •
Cristina Mazzaccara • Giulia Frisso •
Giancarlo Parenti • Brunella Capaldo

Received: 07 March 2017 / Revised: 08 June 2017 / Accepted: 09 June 2017 / Published online: 07 July 2017
© SSIEM and Springer-Verlag Berlin Heidelberg 2017

Abstract Multiple acyl-CoA dehydrogenation deficiency (MADD) is an inborn disorder of fatty acid oxidation due to a defect in *electron transfer to the respiratory chain*. We describe the medical/nutritional management of a successful pregnancy in a 19-year-old woman with a known diagnosis of MADD. A high-carbohydrate, low-fat, six-meal diet supplemented with protein was prescribed to meet the nutritional needs during pregnancy. L-Carnitine supplementation was also progressively increased over the weeks. Serum acyl-carnitine profile revealed raised levels of chain-length C6-C14, which remained substantially unchanged during pregnancy. Serum amino acid profile was in the normal range indicating an adequate nutritional support. Pregnancy progressed uneventful and the patient gave birth to a healthy boy without any complication.

A careful clinical monitoring associated with an adequate medical/nutritional management may improve pregnancy outcome in women with MADD.

Introduction

Multiple acyl-CoA dehydrogenase deficiency (MADD), also known as glutaric aciduria type II, is an autosomal recessively inherited disease of fatty acid, some amino acid and choline oxidation, caused by a defect in the electron transfer flavoprotein (ETF) or the electron transfer flavoprotein dehydrogenase (ETF_{DH}), enzymes involved in the mitochondrial respiratory chain. This defect results in compromised fatty acid oxidation, with consequent impaired adenosine triphosphate (ATP) synthesis, insufficient gluconeogenesis and excessive lipid accumulation in different organs.

The clinical expression of MADD is highly heterogeneous ranging from severe neonatal-onset form, with or without congenital anomalies, to milder form with a late-onset, which is characterized by intermittent episodes of lethargy, metabolic acidosis, non-ketotic hypoglycaemia, muscle weakness, generally triggered by catabolic stress (Rhead et al. 1987; Turnbull et al. 1988; Mongini et al. 1992).

The clinical diagnosis of MADD is based on the presence of organic acid and acylglycine derivatives in the urine and increased levels of medium- and long-chain acyl-carnitines in the blood. Mutations in *ETF_A*, *ETF_B* or *ETF_{DH}* genes, encoding the alpha and beta subunits of electron transfer flavoprotein and the ETF-dehydrogenase, confirm the diagnosis.

The treatment of MADD consists of a high-carbohydrate, low-fat, low-protein diet associated with riboflavin and carnitine supplementation. Prevention of fasting and of other precipitating stresses is also essential. Riboflavin is precursor of flavin adenine dinucleotide (FAD), a cofactor of several mitochondrial enzymes, such as the acyl-CoA dehydrogenases. There is evidence of symptoms restoration

Communicated by: Robert Steiner

A. Creanza • M. Cotugno • B. Capaldo (✉)
Department of Clinical Medicine and Surgery, University of Naples
Federico II, Naples, Italy
e-mail: bcapaldo@unina.it

C. Mazzaccara • G. Frisso
Department of Molecular Medicine and Biotechnologies, CEINGE-
Biotechnologie Avanzate, University of Naples Federico II, Naples,
Italy

G. Parenti
Department of Translational Medicine (G.P.), University of Naples
Federico II, Naples, Italy

after riboflavin treatment particularly in patients with late-onset MADD (Olsen et al. 2007).

Advances in both nutritional therapy and management of acute attacks have considerably improved the outcome of MADD, particularly in patients with the milder forms of the disease (Williams et al. 2008; Trakadis et al. 2012). Thus, an increasing number of women long to have a baby. For most of the inherited diseases there is a lack of specific guidelines for the management during pregnancy; therefore, experience from isolated case reports is particularly valuable.

We present the case of a young woman with MADD who led to a successful pregnancy and her medical/nutritional management during pregnancy and delivery.

Case Description

The patient is a 19-year-old woman who was diagnosed with MADD at the age of 3 years, due to occurrence of lethargy and asthenia associated with anorexia. Routine

biochemical analyses showed remarkable increments in transaminases, lactic dehydrogenase, aldolase and creatine kinase. The chromatographic layout of urinary organic acids showed a typical dicarboxylic aciduria. MADD diagnosis was confirmed by molecular analysis, performed according to the standardized approach (Scolamiero et al. 2015), which showed a compound heterozygosity in the *ETFDH* gene (NM_001281737.1) for the mutations c.1074G>C (p.R358S) and c.1073G>A (p.R358K) in exon 9. Her parents were healthy carriers of one of the two mutations (Fig. 1).

Since the diagnosis, the patient was under follow up at the Paediatric Unit of AOU Federico II of Naples; she has been treated with a diet restricted in fat and protein associated with riboflavin, pyridoxine and carnitine supplementation. Over the years, the patient required sporadic hospitalizations for metabolic decompensations resolved with intravenous dextrose infusion and hydration.

At the age of 18, the patient was hospitalized for a severe episode of rhabdomyolysis (serum creatine kinase level: 69960 UI/L), which resolved with intravenous infusion of

Fig. 1 Pedigrees of the family with MADD defect. The electropherogram showing the mutation in the nucleotide sequence is under each symbol

Dextrose solution (initially 33%, then 10%), hydration and increased oral L-carnitine supplementation (100 mg/kg/day). Few months later, the patient unexpectedly became pregnant. She was not blood related to her partner. The genetic analysis of the partner did not reveal any mutations of *ETFA/ETFB/ETFDH* genes. At 8 week of gestation, the patient was in good clinical conditions and the results of her biochemical routine tests were normal. Echocardiographic examination evidenced a normal cardiac function. The medical and nutritional management for the whole gestation is reported in Table 1. A normocaloric (1,700 kcal) diet moderately restricted in fat and protein was recommended; an adequate intake of carbohydrate (>50% of total calories) was provided since it is the main energy substrate for foetal metabolism. The diet was divided into three main meals and three snacks in order to avoid prolonged fasting and to prevent the risk of hypoglycaemia. In addition, the patient was recommended to have a glucose supply (25–50 g) every 2 h in case of discomfort or episodic vomiting and to contact the hospital in case of persistence of symptoms, fever or acute illness.

In the second and third trimester, a protein supplementation was added to meet the increased protein requirement (Table 1). Riboflavin, pyridoxine and L-carnitine dosages were maintained constant. Folic acid, multivitamin and mineral supplements were started in the first trimester. At the beginning of the third trimester, L-carnitine was increased to 4,000 mg/day because of an increased sense of fatigue.

At the 22nd and the 36th week of pregnancy, the acyl-carnitine profile was analysed through spot extraction of blood on filter paper with chromatography liquid-mass tandem spectrometry (LC-MS-MS). Blood acyl-carnitine profile revealed raised levels of chain-length C6-C14, which remained substantially stable during pregnancy. Blood amino acid analysis performed at the same time

points showed amino acid levels within or slightly below the normal range (Table 2).

Periodic glucose home monitoring evidenced blood glucose levels within the normal range and no value was below 70 mg/dL throughout the gestation. Periodic obstetric ultrasound examination evidenced normal foetal growth. At the 39th, the patient underwent an elective cesarean section to reduce the risk of metabolic decompensation. During delivery and in the immediate postoperative period, she received intravenous carnitine (3,000 mg/day) and isotonic solution (with 10% dextrose) at variable rate to maintain normoglycaemia. She gave birth to a 3.1 kg healthy boy without any complication. The baby was breastfed for 2 months during which the patient continued the medical/nutritional therapy followed during pregnancy. At breastfeeding discontinuation, she returned to her usual dietary protein restriction and carnitine was reduced to the pre-gestation dose while continuing riboflavin and pyridoxine.

Discussion

Patients with MADD generate less energy from fatty acids and amino acids because of a defective transfer of electrons from flavoproteins to the mitochondrial respiratory chain. The reduced supply of energy is responsible for a number of clinical manifestations involving particularly those organs that have a high flux of beta-oxidation: the skeletal muscle, with consequent hypotonia, weakness and exercise intolerance; the heart with cardiomyopathy and arrhythmias; the liver with hepatomegaly and liver dysfunction; the brain with encephalopathy.

The severity of the clinical phenotype of MADD is explained by the type of mutation in the *ETFA/ETFB/ETFDH* genes, which results in different levels of residual enzyme activity (Olsen et al. 2003). Nonsense mutations

Table 1 Medical and nutritional management during the course of pregnancy

Week	Weight (kg)	Energy intake (kcal/day)	CHO g (%)	P g (%)	L g (%)	Protein supplement (g/day)	Therapy (mg/day)
8	63.8	1,700	257 (53)	80 (18)	59 (29)	0	L-Carnitine 3,000 Riboflavin 100 Pyridoxine 300
12	65.0	1,900	260 (53)	90 (19)	57 (28)	10	L-Carnitine 3,000 Riboflavin 100 Pyridoxine 300
24	70.0	2,100	263 (49)	110 (21)	60 (30)	30	L-Carnitine 4,000 Riboflavin 100 Pyridoxine 300
34	79.5	2,100	263 (49)	110 (21)	60 (30)	30	L-Carnitine 4,000 Riboflavin 100 Pyridoxine 300

CHO carbohydrate, P protein, L lipid

Table 2 Blood acyl-carnitine and amino acid profiles during the course of pregnancy

Blood acyl-carnitine levels (μmol/L)				Blood amino acid levels (μmol/L)			
Metabolite	Week 22	Week 36	Normal range	Metabolite	Week 22	Week 36	Normal range
C2	5	4.9	3.5–15.4	Aspartic acid	15	94	24–102
C3	0.28	0.32	0.07–0.65	Glutamic acid	73	298	67–223
C4	0.76	0.35	0.12–0.42	Serine	73	232	111–297
C5	1.35	0.65	0.05–0.24	Glutamine	429	401	432–871
C6	1.12	1.00	0.04–0.18	Alanine	298	554	193–597
C8	3.67	2.74	0.07–0.25	Glycine	145	401	240–460
C10	5.38	5.49	0.09–0.43	Threonine	133	195	109–268
C12	1.21	1.32	0.04–0.21	Arginine	23	76	36–172
C14	0.56	0.53	0.03–0.23	Histidine	87	119	72–131
C16	0.40	0.32	0.01–0.23	Taurine	78	212	50–270
C18	0.19	0.15	0.01–0.18	Tyrosine	46	69	45–107
				<i>Phenylalanine</i>	62	163	59–112
				Methionine	21	32	21–44
				Leucine	98	144	82–258
				Valine	190	237	187–411
				Isoleucine	57	62	42–111
				Lysine	147	195	150–286
				Proline	168	191	50–350
				Ornithine	46	75	63–133

are associated with fatal disease while missense mutations, particularly in the *ETFDH* gene, leaving a detectable residual enzyme activity, may account for the milder forms of the disease (Olsen et al. 2003; Goodman et al. 2002; Schiff et al. 2006; Yotsumoto et al. 2008). In the latter forms, symptoms are usually elicited by illness or catabolic stress, as physical exercise, prolonged fasting, irregular diet, although additional factors, not yet identified, such as cellular temperature, have been reported to modulate the enzymatic activity (Olsen et al. 2003).

Our patient had biallelic mutations in *ETFDH* gene, both in exon 9: c.1074G>C (p.R358S) and c.1073G>A (p.R358K). The former, already described in the homozygous state in three Palestinian siblings, was associated with early onset and milder forms of MADD (Olsen et al. 2005). The c.1073G>A (p.R358K) mutation was submitted just once to ClinVar database (rs796051959 in <https://www.ncbi.nlm.nih.gov/clinvar/>) as pathogenic allele, although lacking link to a specific clinical condition. However, familial segregation study and in silico analysis, performed by bioinformatics tools, confirmed that this substitution is likely pathogenetic.

Although the mutation identified in our patient cannot be linked with certainty to mild/late-onset MADD, she is likely to have a mild form of the disease in consideration of some important characteristics, i.e., the absence of congenital abnormalities, age at diagnosis and the relatively mild clinical course of the disease. Throughout the years, the patient suffered from sporadic episodes of vomiting, hypoglycaemia and muscle weakness, which were triggered by catabolic stress. Although pregnancy cannot be considered a strictly catabolic condition, it may precipitate metabolic decompensation in women with inherited disorders of energy metabolism. Nausea, recurrent vomiting or fasting may cause a shift of maternal metabolism towards ketosis and reduce glucose availability at a time of increased metabolic demand. Thus, the gestation in a woman with MADD may represent a high-risk condition both for the mother's health and for foetal growth. Hence, strict nutritional/medical surveillance is of paramount importance in pregnant women with MADD. At present, no guidelines are available for the care of pregnant women with this condition. Likewise, a clear management plan for delivery is warranted, as labour is associated with increased

energy requirements in addition to fasting and dehydration (Murphy 2015).

In the literature, there is only one case report on pregnancy and delivery in women with MADD (Trakadis et al. 2012). This case refers to a successful pregnancy in a young woman with an atypical presentation of MADD; indeed, no detail of the nutritional management is provided. We planned a close nutritional follow up throughout pregnancy. A six-meal diet high in fibre, very low in fat, but supplemented with protein (10 g/day in the 2nd trimester and 30 g/day in 3rd trimester) was prescribed to meet the increased protein demand during pregnancy. Serum amino acid analysis showed that the amino acid availability was adequate for foetal growth (Elango and Ball 2016). Serum acyl-carnitine concentrations remained stable throughout pregnancy through adequate nutritional therapy along with carnitine, riboflavin and pyridoxine supplements.

The clinical and biochemical stability preserved by the patient during pregnancy demonstrates the safety of the nutritional/medical therapy adopted, which proved to guarantee a good outcome for both mother and baby.

Acknowledgments We thank Dr. Angela Giacco for nutritional counseling.

Synopsis

A successful pregnancy was achieved in a woman with MADD through a careful clinical monitoring associated with an adequate nutritional/medical management.

Authorship Contribution

Annalisa Creanza analysed the data and wrote the first draft, Mariella Cotugno cared for the patient and collected the clinical data, Giulia Frisso and Cristina Mazzaccara performed the genetic test and wrote the part of the manuscript dealing with molecular diagnosis, Giancarlo Parenti cared for the patient during childhood and Brunella Capaldo cared for the patient and revised the manuscript.

Corresponding Author

Brunella Capaldo.

Funding

None.

Compliance with Ethics Guidelines

Conflict of Interest

Annalisa Creanza, Mariella Cotugno, Cristina Mazzaccara, Giulia Frisso, Giancarlo Parenti and Brunella Capaldo declare that they have no conflict of interest.

Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from patient for being included in the study. Additional informed consent was obtained from all patients for which identifying information is included in this article.

Animal Rights

This article does not contain any studies with human or animal subjects performed by the any of the authors.

References

- Elango R, Ball RO (2016) Protein and amino acid requirements during pregnancy. *Adv Nutr* 7:839S–844S
- Goodman SI, Binard RJ, Woontner MR, Frerman FE (2002) Glutaric acidemia type II: gene structure and mutations of the electron transfer flavoprotein:ubiquinone oxido reductase (ETF:QO) gene. *Mol Genet Metab* 77:86–90
- Mongini T, Doriguzi C, Palmucci L et al (1992) Lipid storage myopathy in multiple acyl-CoA dehydrogenase deficiency: an adult case. *Eur Neurol* 32:170–176
- Murphy E (2015) Pregnancy in women with inherited metabolic disease. *Obstet Med* 8:61–67
- Olsen RK, Andresen BS, Christensen E, Bross P, Skovby F, Gregersen N (2003) Clear relationship between ETF/ETFDH genotype and phenotype in patients with multiple acyl-CoA dehydrogenation deficiency. *Hum Mutat* 22:12–23
- Olsen RK, Andresen BS, Christensen E et al (2005) DNA-based prenatal diagnosis for severe and variant forms of multiple acyl-CoA dehydrogenation deficiency. *Prenat Diagn* 25:60–64
- Olsen RK, Olpin SE, Andresen BS et al (2007) ETFDH mutations as a major cause of riboflavin-responsive multiple acyl-CoA dehydrogenation deficiency. *Brain* 130:2045–2054
- Rhead WJ, Wolff JA, Lipson M et al (1987) Clinical and biochemical variation and family studies in the multiple acyl-CoA dehydrogenation disorders. *Pediatr Res* 21:371–376
- Schiff M, Froissart R, Olsen RK, Acquaviva C, Vianey-Saban C (2006) A novel gross deletion caused by non-homologous recombination of the PDHX gene in a patient with pyruvate dehydrogenase deficiency. *Mol Genet Metab* 88:153–158

- Scolamiero E, Cozzolino C, Albano L et al (2015) Targeted metabolomics in the expanded newborn screening for inborn errors of metabolism. *Mol BioSyst* 11:1525–1535
- Trakadis Y, Kadlubowska D, Barnes R et al (2012) Pregnancy of a patient with multiple Acyl-CoA dehydrogenation deficiency (MADD). *Mol Genet Metab* 106:491–494
- Turnbull DM, Barlett K, Eyre JA et al (1988) Lipid storage myopathy due to glutaric aciduria type II: treatment of a potentially fatal myopathy. *Dev Med Child Neurol* 30:667–672
- Williams SF, Alvarez JR, Pedro HF et al (2008) Glutaric aciduria type II and narcolepsy in pregnancy. *Obstet Gynecol* 111:522–524
- Yotsumoto Y, Hasegawa Y, Fukuda S et al (2008) Clinical and molecular investigations of Japanese cases of glutaric acidemia type 2. *Mol Genet Metab* 94:61–67