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Case Report

A Rare Case of Malonyl-CoA Decarboxylase Deficiency with Novel Mutations in the MLYCD Gene in Two Indian Patients and Literature Review.

Radha Rama Devi*, Nalinikanth Panigrahi

Department of Medicine, All India Institute of Medical Science, Hyderabad, India

ABSTRACT

Malonyl-CoA decarboxylase deficiency causing isolated malonic aciduria is a rare inborn error of metabolism with heterogeneous phenotypic manifestations. The disease can be diagnosed in new-born screening. Early treatment prevents development of cardiomyopathy and intellectual disability. Tandem Mass Spectrometer (TMS) and urine Gas Chromatography Mass Spectrometry (GC-MS) and whole exome sequencing confirms the diagnosis. **Results:** Two patients from unrelated families were diagnosed with elevated C3DC acyl carnitine and increases excretion of malonic acid in the urine. The concentration of malonic acid in the urine was very high in case 1 as the test was done during acute crisis (423-fold elevation). Case 2 had 11-fold elevation (not in decompensation). No methyl malonic acid was detected in both the cases. Both the patients harbored novel mutations in the MLYCD gene. Case1 was homozygous c.C928T (p.Arg 310Ter) is stop gain mutation and case 2 was a compound heterozygote missense c.G1153A (p.Val385Met) and missense/exonic splicing c.G1175A (p.Arg392Gln) mutation in Exon 5. **Conclusion:** Two additional cases of malonic aciduria were reported adding to the 54 earlier reported cases. The disease is extremely rare, mainly characterized by hypoglycemia and metabolic acidosis cardiomyopathy is a later manifestation. Newborn screening can identify the presence of elevated C3DC. There are no recommendations regarding the appropriate treatment regimen. Both the patients have novel genetic variants.

Keywords: Malonic aciduria; Malonyl-CoA decarboxylase (MLYCD); Malonyl carnitine (C3DC); Mutation

INTRODUCTION

Combined malonic and methyl malonic aciduria due to Acyl-CoA Synthetase family member 3(ACSF3) deficiency and malonic aciduria (MIM 248360) without methylmelonic aciduria due to MLYCD are extremely rare inborn errors of metabolism with an autosomal recessive inheritance. Isolated malonic aciduria is caused by the deficiency of Malonyl-CoA Decarboxylase (MCD), (EC 4.1.1.9) that has an important role in regulating fatty acid metabolism. MCD catalyses the decarboxylation of malonyl-CoA to acetyl-CoA and CO_2. The enzyme deficiency causes accumulation of Malonyl-CoA and free malonic acid with increase in the excretion of urinary malonic acid and increased production of malonylcarnitine (C3DC).

The signs and symptoms of this disorder are heterogeneous with the disease manifesting in early childhood but symptoms can also develop in older infants and children. Symptoms may be triggered by fasting and illness. Almost all affected children have delayed development. Additional signs and symptoms include developmental retardation, epilepsy, hypotonia, hypertrophic cardiomyopathy, diarrhea, abdominal pain, constipation, vomiting, metabolic acidosis, hypoglycemia, ketosis, hyperlactatemia, etc. Cardiomyopathy can appear either early in life or later.

The MCD was first described by Hayaishi (1953) [1] and MCD deficiency (MCDD or MLYCDD) was first reported by Brown et al., (1984) [2]. Fifty-four cases have been reported in the literature until now [3]. The disease can be detected through new-born screening. In recent years, malonic aciduria has been included in newborn screening programs in several countries [4].

Malonyl-CoA Decarboxylase (MCD) is encoded by the MLYCD gene (MIM 606761), located on the long arm of chromosome 16

Correspondence to: Radha Rama Devi, Department of Medicine, All India Institute of Medical Science, Hyderabad, India, E-mail: radharamadevi@gmail.com

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(16q23.3) and contains five exons. MLYCD is highly expressed in heart, liver and kidney and weakly expressed in many other tissues such as brain, placenta and testis. The diagnosis of malonic aciduria can be made by detecting malonic acid in the urine and high levels of malonylcarnitine (C3DC) in the blood. The diagnosis is confirmed by demonstrating reduced enzyme activity in cultured skin fibroblasts and identification of the MLYCD gene mutation. The prognosis for patients is variable but the disease can be lethal in the neonatal period. The principle treatment is dietary, a low fat/high carbohydrate diet and carnitine supplements. Without treatment, episodes of hypoglycemia and metabolic acidosis may lead to delayed development, hypotonia, seizures and cardiomyopathy.

Malonic acid pathway

Malonyl-CoA is formed by carboxylating acetyl-CoA (catalyzed by the acetyl-CoA carboxylase enzyme) provides 2-carbon units to fatty acids for fatty acid chain synthesis. The long-chain fatty acids undergo mitochondrial beta oxidation to provide energy. Free fatty acids are activated and form long-chain acyl-CoAs and are transported into the mitochondria through the carnitine shuttle: Acyl-CoA molecules are conjugated to carnitine by Carnitine Palmitoyl-Transferase I (CPT-I). This is the limiting step of beta-oxidation. Acylcarnitines are transported across the inner mitochondrial membrane by the carnitine-acyl carnitine translocase. Acylcarnitines are converted into acyl-CoAs and released into the mitochondrial matrix *via* carnitine palmitoyl transferase II (CPT-II). Subsequently, acyl-CoAs undergo beta-oxidation with the release of one molecule of acetyl-CoA at each cycle of oxidation [5]

Acetyl-CoA is used to produce ketone bodies or to fuel the Krebs cycle (or tricarboxylic acid cycle), which yields NADH and FADH2, providing the respiratory chain substrates for the production of ATP. Malonyl-CoA regulates the limiting step in beta-oxidation by inhibiting CPT-I, playing an important role in the regulation of mitochondrial beta-oxidation of fatty acids in fed conditions. Increased malonyl-CoA and malonic acid due to MCD deficiency result in the inhibition of the carnitine palmitoyl-transferase I (CPT-I) and of the Krebs cycle.

The present report describes the first report of two cases from India. In view of the rarity of the disease, a comprehensive literature review of the reported cases is included.

CASE PRESENTATION

Case 1

The first case is a 5month old girl child, born at 40 weeks of gestation. She was the first child of a consanguineous couple. Postnatally, she remained well until 30 months and developed diarrhea. She was admitted at a private hospital where she was found to have metabolic acidosis. She continues to have loose stools and was referred for genetic evaluation to rule out cystic fibrosis. Her developmental milestones at six months were appropriate. No history of seizers or hypotonia. Cardiac evaluation by 2-D Echo was normal. In view of the metabolic acidosis, TMS screening and urine organic acids, plasma amino acids by High Performance Liquid Chromatography (HPLC), liver function tests, serum lactate and ammonia were tested seen in Table 1. Exome sequencing was done and a homozygous likely pathogenic stop gain variant in MLYCD gene was identified. The child was started on carnitine 100mg/kg/day, high carbohydrate diet and low fat diet with Medium Chain Triglycerides (MCT) oil supplementation. On follow up, the child remained well until a readmission with diarrhea and no metabolic acidosis four months after starting the diet. Follow up urine malonic acid levels in urine was still high (203 fold elevation). At this time, fat restricted, high carbohydrate diet was continued and the child is stable at present aged 2yrs.

Case 2

A one-year-old male child born to non-consanguineous patient presented with persistent vomiting, failure to thrive and has been evaluated for inborn errors of metabolism and cyclic vomiting syndrome. On clinical evaluation, mile stone were normal, weight and height is <30th centile. There was no specific systemic involvement with normal cardiac function. In view of a suspected inborn error of metabolism, biochemical evaluation (Table1) was carried out for inborn errors of metabolism and whole exome sequencing was done. A compound heterozygous variant in MLYCD gene was identified. The child was advised to start on carnitine and low fat diet. Subsequent follow up was not possible during the covid outbreak and the family was lost for follow up.

	TMS	Lactate	Ammonia	LFT	Plasma Amino Acids	Urine Malonic acid (GC-MS)
Case 1						
FC	18 uM					
C3DC	3.4 uM	1.2mg	35 umol/l	N	N	423 (fold elevation)
Case 2						
FC	24 uM					
C3DC	1.9 uM	2.2 mg	56 umol/l	N	N	11 fold elevation

Note: TMS: Tandem Mass Spectrometry; GC-MS: Gas Chromatography- Mass Spectrometry; LFT: Liver Function Test.

Table 1: Biochemical evaluation was carried out for inborn errors of metabolism by Tandem Mass Spectrometry (TMS) screening and urine organic acids, plasma amino acids by High Performance Liquid Chromatography (HPLC), liver function tests, serum lactate and ammonia were tested.

Molecular study

Case 1: By whole exome sequencing, a homozygous variant of MLYCD gene was identified in exon 4. The c.C928T (p.Arg 310Ter) is stop gain mutation and the variant was not observed in 1000 Genome database, but in ExAC database at 0.000008 minor allele frequency (Healthy populations database frequency <0.05). The variant is deleterious with no protein production as it is a stop gain mutation.

Case 2: The patient showed a heterozygous missense c.G1153A (p.Val385Met) and missense/exonic; splicing c.G1175A (p.Arg392Gln) mutation in Exon5 of MLYCD gene. The c.G1153A (p.Val385Met) variant was not observed in 1000 Genome database, but in ExAC database at 0.0002 minor allele frequency (Healthy populations database frequency <0.05).The variant is predicted to be deleterious by bioinformatics algorithms such as Mutation Taster_pred, FATHMM_pred, M.CAP_pred, fathmm. MKL_coding_pred and Phenolyzer. The c.G1175A (p.Arg392Gln) variant was not observed in 1000 Genome database, but in ExAC database at 0.00009 minor allele frequency (Healthy populations database frequency <0.05). The variant is predicted to be deleterious by bioinformatics algorithms such as FATHMM_pred, M.CAP_pred and phenolyzer. The findings indicate a compound heterozygous variation in the MLYCD gene.

RESULTS

Malonic Aciduria (MA) is extremely rare with an estimated prevalence of less than 1 in 400,000 newborns occurring worldwide [6]. To the best of our knowledge, 54 patients have been described in the literature so far, in 26 articles or abstract on literature survey. Reporting two more cases from this report adds to the number of reported patients to 56. Hypertrophic cardiomyopathy is a common finding in 40% of patients [7]. However, cardiomyopathy is absent in both the patients in this study. A regular follow up is important as cardiomyopathy can develop at any age [8]. Two out of seven patients reported by Fitzpatrick et al., [8,9] developed cardiomyopathy and the other five without cardiomyopathy had elevated level of malonic acid only during acute illness. So they concluded that cardiomyopathy may occur only after prolonged exposure to high levels of malonic acid. These patients should be regularly screened for cardiomyopathy even when they are asymptomatic in order to ensure early therapy. Occurrence of hypoglycemia and metabolic acidosis is explained by impaired fatty acid oxidation and inhibition of CPT1 enzyme.

Malonic aciduria is diagnosed by New-Born Screening (NBS) in countries doing routine NBS. The C3DC is elevated on the AA/AC screen and abnormal levels of the related markers C3DC/C10 and C5DC/C3DC also compliment the suspected diagnosis. In the absence of NBS, all sick children with metabolic acidosis and children with cardiomyopathy should be routinely tested for acyl carnitine levels. Although no development delay is noticed in both the patients at present as they are still below 2years, a follow up is essential to look for development of other symptoms. The spectrum of phenotypes of the reported cases and the present two cases is given in Table 2.

The phenotype of malonic aciduria overlaps with fatty acid oxidation disorders because of the role of MCD in the fatty acid metabolic pathway. Metabolic acidosis and hypoglycemia is explained by MLYCD pathophysiology-oxidation *via* the inhibition of CPT-I by malonyl-CoA, of pyruvate carboxylase secondary to dicarboxylic aciduria and of the tricarboxylic acid cycle *via* the inhibition of succinic acid dehydrogenase by malonic acid [10].

Spectrum of phenotypes	Reported patients		present cases	
	Present	Absent	Present	Present
Consanguinity	16	14	1	1
Failure to thrive	8	19	1	1
Digestive symptoms	7	0	1	0
Development delay	36	11	0	2
seizure	15	22	0	2
Cardiomyopathy	24	14	0	2
C3DC	17	0	2	0
Metabolic acidosis	18	11	1	1
Hypoglycemia	0	0	2	0
Urine malonic acid	38	0	2	0
Abnormal brain MRI	12	0	0	0

Note: MRI: Magnetic Resonance Imaging.

Table 2: Phenotype of reported malonic aciduria cases and present cases.

DISCUSSION

Forty seven unique variants are reported in the literature in the MLYCD gene until now. The three variants reported now are novel bringing the total to 50 MLYCD variants. Among the reported variants, majority are misssense (15), large deletions, including a complete gene deletion (7), 6 nonsense, 11 small insertions/deletions (indels) with a frameshift, 1 without, 2 variants concerning the first codon and 5 intronic variants, with 2 different substitutions at the same position (c.949-14A). Forty-eight% (n = 19) of punctual variants are located in the first

exon. Except for large deletions (deletion of the first 3 exons, deletion of all 5 exons and exon 5 deletion) that have been described in two distinct index cases, all variants are private mutations. The three novel variants described in this study, one is nonsense and one is missense and one is exonic splicing. While 48% are located in exon 1, the novel variants reported now are located in exon 4 and 5.

Although there is no specific dietary recommendations to treat MCD deficiency a low fat, high carbohydrate diet would lead to near normalization of the urinary organic acid excretion [11-13].

By giving L-Carnitine load (100 mg/Kg body weight), it stimulates beta oxidation of fatty acids through CPT1, brings down the level of malonyl-CoA thereby controlling hypoglycemia and metabolic acidosis. Presently, case 1 is on carnitine and high carbohydrate, low fat diet, did not develop any decompensation after this treatment. She is also developing normally.

CONCLUSION

MCD is a rare metabolic disease, can be diagnosed by new-born screening. Early intervention results in prevention of cardiomyopathy and other neurological manifestations. Screening of newborns may be possible through detection of elevated blood levels of malonylcarnitine using electrospray ionisation tandem mass spectrometry (ESI-MS/MS). Prenatal screening is theoretically possible through enzyme or DNA analysis of amniocytes or chorionic villus samples. However, a close monitoring is important to prevent complications. The principle treatment is dietary, with patients being recommended to follow a low fat/high carbohydrate diet. Carnitine supplements may also be recommended.

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