A Case Report and Literature Review:
Methylmalonate-Semialdehyde Dehydrogenase Deficiency With Cardiac Presentation: A Case Report With Literature Review

Morteza Alijanpour Aghamaleki[1], Masomeh Rezapour[2], Kazem Babazadeh[1], Hassan Zamani[3], Faeze Aghajanpour[4*]

1. Non-Communicable Pediatric Diseases Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran.
2. Department of Medical Sciences History, School of Traditional Medicine, Babol University of Medical Sciences, Babol, Iran.
3. Department of Pediatrics, Shahid Modarres Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
4. Department of Statistics, Faculty of Mathematics and Statistics, University of Mazandaran, Babolsar, Iran.

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ABSTRACT

Background: Methylmalonate-semialdehyde Dehydrogenase Deficiency (MMSDHD) is an uncommon autosomal recessive disorder. MMSDH is an enzyme encoded by the protein coding gene ALDH6A1 in humans.

Case Presentation: We present a 4-year-old boy with elevated liver enzymes, 3-hydroxyisobutyric aciduria (MMSDHD) and cardiac symptoms. He had a mutated ALDH6A1 gene, c.184c>G (p.Pro62Ala).

Conclusions: This is one of the rare case reports in the world and the first one in Iran that reports MMSDHD with cardiac disease.

1. Introduction

Methylmalonate-semialdehyde Dehydrogenase Deficiency (MMSDHD) is an uncommon autosomal recessive disorder characterized by the excessive excretion of S-2-(hydroxymethyl)butyric acid, 3-hydroxypropionic acid, beta-alanine, and R- and S-3-amino- and 3-hydroxyisobutyric acids. It is caused by deficient activities of malonic, methylmalonic and ethylmalonic semialdehyde dehydrogenases (1, 2). Methylmalonate-semialdehyde dehydrogenase (acylating), mitochondrial (MMSDH) is an enzyme encoded by the ALDH6A1 gene in humans (3).

Very few case reports have described patients with MMSDH deficiency and other metabolic abnormalities,

** Corresponding Author:*
Faeze Aghajanpour, BSc.
Address: *Department of Statistics, Faculty of Mathematics and Statistics, University of Mazandaran, Babolsar, Iran.*
Tel: *+98 (11) 32346963*
E-mail: *faezeaghajanpour@yahoo.com*

all of them have been in the context of increased urine levels of 3-hydroxyisobutyric acid (2, 4, 5). For the first time, Pollitt et al. (2) reported an asymptomatic child who was emphasized by high methionine levels on newborn screening. This child had 3-hydroxyisobutyric aciduria, and finally showed a homozygous missense mutation (c.1336G>A) in ALDH6A1 gene encoding MMSDH (4). Two unrelated children with 3-hydroxyisobutyric aciduria and different novel homozygous missense mutations in ALDH6A1 were described in a recent report (5). Considering the unstable behavior of methylmalonate-semialdehyde in enzyme assays, no report could illustrate the decrease in MMSDH enzyme activity. As such, the discovery of deleterious mutations in ALDH6A1 gene has until recently served as the only means of diagnosing MMSDH dysfunction (1).

Available reports indicate a highly variable clinical and biochemical phenotype, which can cause a challenge in diagnosis. Up to now, via identification of homozygous mutations in ALDH6A1, the gene encoding MMSDH, only three reported cases have been recorded at the molecular level. Confirmation by enzyme assay has until now not been possible, due to the extreme instability of the enzyme substrate (1).

The fates of intravenous loading tests of [2H8] valine (D8-valine) and [2H4] thymine (D4-thymine) in these patients show that this milder clinical form is likely due to a deficiency of methylmalonate- semialdehyde dehydrogenase affecting both the valine and the thymine pathways. This deficiency is different from other previous reported disorders, which influences multiple semialdehyde dehydrogenases (2, 6-8).

Patients with methylmalonic aciduria possess a more benign clinical course and no considerable increase in propionylcarnitine levels is observed. They ascertain the symptoms of developmental delay with or without seizures. Consideration of such patients cannot illustrate any abnormality of methylmalonyl-CoA mutase or cobalamin metabolism. The feasibility of a primary deficiency in the valine pathway at the level of methylmalonyl semialdehyde is a possible alternative explanation through the deletion of these two etiologies (9).

The clinical presentation related to the elevated levels of 3-hydroxyisobutyric acid may have different symptoms from severe microcephaly, neuronal migration abnormalities and early death, through a milder disorder with failure to thrive and chronic lactic acidosis to mild vomiting attacks with normal brain and cognitive development. Different dysmorphic anomalies indicate the biochemical abnormality (10). This case report is a presentation of a 4-year-old boy with MMSDHD and cardiac disease.

2. Case Presentation

A 4-year-old boy was diagnosed with MMSDHD. His weight and height were 14 kg (3% percentile) and 99 cm (10%-25% percentile), respectively. He had normal physical examination (without hepatomegaly), and normal feature and intelligence. For the first time, at 6 months of age elevated liver transaminases (SGOT: 157 U/L, SGPT: 115 U/L, Alp: 526 U/L) was noticed. Liver biopsy indicated no specific pathological results.

His brother died at 14 years of age due to probable cardiac disease with unknown etiology. Our patient had the history of normal growth and development. The patient was admitted with fever, fatigue and dyspnea for the first time in Amirkola Children Hospital (Babol City, North of Iran). Echocardiography was done due to dyspnea (Figure 1). After diagnosis of cardiac disease (mild dilatation of left ventricle and left atrium-mitral value regurgitation), he was transported to the cardiac ward.

Signs and symptoms of cardiac disease in this case included tachypnea, tachycardia, pallor, mild confusion, mild restlessness, delayed capillary filling, refill, filiform pulses, low blood pressure and muffled heart sounds. Moreover, left atrial enlargement and left ventricular enlargement, mild mitral regurgitation (tricuspid regurgitation and aortic insufficiency, and mild plural effusion were shown. Ejection fraction was 44%. Chest X-ray revealed cardiomegaly (CTR[1]>50%), elevated pulmonary blood flow and increased vascular markings.

According to the above findings, this case was considered to have dilated cardiomyopathy. His Laboratory results were as follows: AST: 157 IU/L; ALT: 115 IU/L; Ammonia: 59 µmol/L; Lactate: 9 mg/dL; Pyruvate: 0.3 mg/dL; T-chol: 160 mg/dL; TG: 140 mg/dL; HDL: 50 mg/dL, LDL: 100 mg/dL; CPK: 156 IU/L; T4: 11.8 µg/dL; TSH: 4 MIU/L.

Normal pattern of serum amino acid analysis was reported (Alanine level was 325 µmol/L, normal range: 157-481). LC/mass was checked two times with normal pattern (normal level of C5OH). In addition, urine GCMS was checked two times and 3-hydroxyisobutyrate was 197.4% and 574% (cutoff<13%) and 3-hydroxypropionate was 42% and 49.5% (cutoff<1.95%).

1. Cardiothoracic Ratio

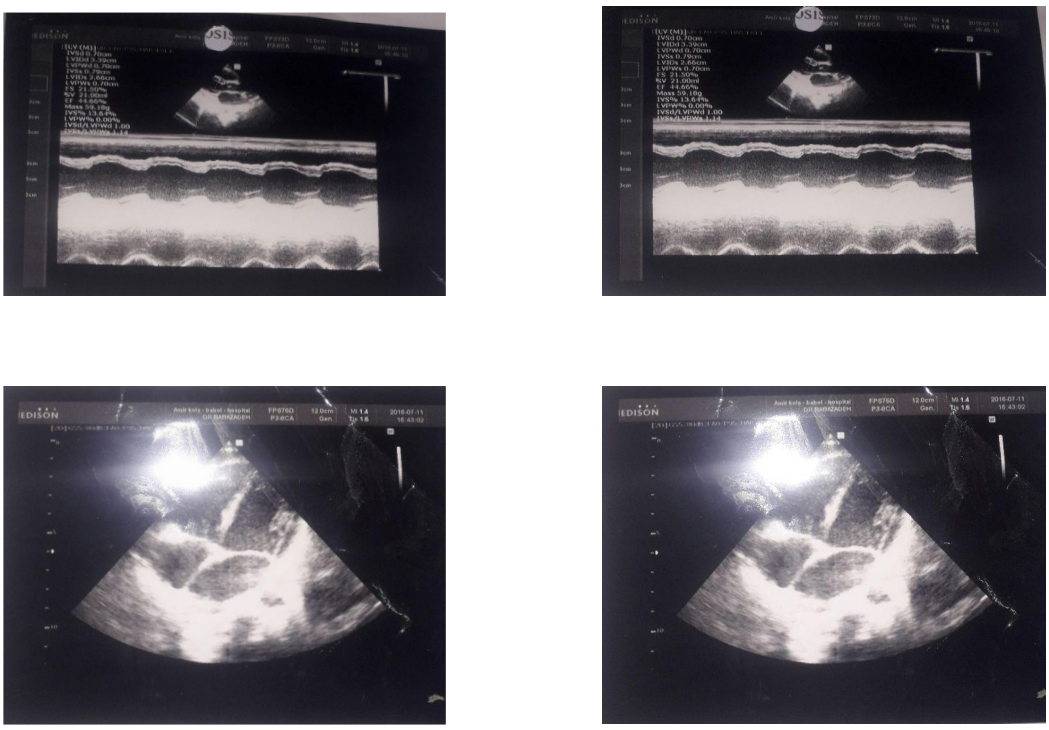

Figure 1. Echocardiography of case MMSDH

Finally, the blood sample was sent to CENTOGENE (a genetic diagnostic laboratory located in Germany) for genetic analysis and final confirmation of the disease. Then, his genetic mutation was reported c.184 c>G and gene analysis for ALDH6A1 gene, c.184c>G (p.Pro62Ala) was done. Thus, MMSDHD was genetically confirmed (Table 1). After treatment with specific drugs such as milrinone and dopamine, the EF reached 45% and the patient was discharged.

3. Discussion

In our report, we presented a 4-year-old boy with MMSDHD and cardiac disease. This is one of the rare case reports in the world and the first in Iran. There have been previous reports of MMSDH without cardiac disease. In the present study, the boy had no symptoms of vomiting, ketoacidosis, developmental delay, and malformation except for cardiac disease, unlike other reported cases in the world.

Marcadier et al. reported an 18-month-old infant with abnormal myelination found in brain MRI, which was accompanied with severe developmental delays, and transient/variable elevations in lactate, methylmalonic acid, 3-hydroxyisobutyric and 3-aminoisobutyric acids. This was the fourth case study in which Marcadier et al. explained about a child with defi-

Table 1. Summary results of genetic report of CENTOGENE (genetic diagnostic laboratory- Germany)

Steps	Results
ALDH6A1 (Sequencing: NM_005589.3)	Homozygous likely pathogenic variant c.184C>G (p.Pro62Ala) Homozygous variant of uncertain significance c.755C>T (p.Pro252Leu)
Results	A genetic diagnosis of methylmalonate semialdehyde dehydrogenase deficiency is confirmed. Further genetic testing is recommended.
Recommendations	1. Genetic counselling 2. Parental carrier testing

ciency of MMSDH due to the mutations in ALDH6A1 gene and concurrent deficiency of the enzyme level (1), elevated methylmalonic acid in urine, elevated 3-hydroxyisobutyric and 3-aminoisobutyric acids like the reported study; however, in the present study, the boy had no neurological disorders.

A case with developmental delay (without any episodes of metabolic acidosis), which was related to the excretion of remarkable amounts of methylmalonate, without any relationship with the increased excretion of malonate, ethylmalonate, 3-hydroxypropionate, or b-alanine and propionylcarnitine in blood or urine was reported by Roe et al. Furthermore, the activity of methylmalonyl-CoA mutase and the pathway for cobalamin metabolism were intact (9) in the patient of the present study, who did not show high excretion of methylmalonic acid in urine sample.

Gray et al. indicated a metabolic defect in intact fibroblasts using 14C-labeled valine or β-alanine and that malonic semialdehyde dehydrogenase activity was deficient in disrupted cells (7). Like the current study, some studies reported increased levels of 3-hydroxyisobutyric acid (5-7, 10-12). Unlike the present study (with cardiac symptoms), there was persistent pulmonary hypertension in the first case reported by Loupatty et al. (11). Roe et al. did not report any clinical symptoms in their case (9), but our case showed the delayed manifestation of clinical symptoms at 4 years of age.

Elevated laboratory findings (beta-alanine, 3-hydroxypropionic acid, R- and S-3-amino- and 3-hydroxyisobutyric acids and S-2-(hydroxymethyl)butyric acid in the report of Pollitt et al., age and sex of the patient (male, 4 years old) are similar to the current study (2). Gibson et al. reported two cases indicating the deficient MMSDH enzymatic activity. The first case was presented in a 6-year-old male diagnosed with lethargy, failure to thrive, vomiting and metabolic acidosis (6). But in our case, the patient did not show these symptoms.

Two unrelated patients were reported by Sass et al. (2012) with increased urinary concentrations of 3-hydroxyisobutyric acid and developmental delay. Mutation analysis of the ALDH6A1 gene of the second patient demonstrated a different missense mutation, c.184 C>T (P62S), which was also identified in 1/530 control chromosomes. Both mutations had influence on conserved amino acids of the methylmalonate-semialdehyde dehydrogenase protein. In one case of their study, the immediate death was shown due to hepatic encephalopathy which was secondary to liver failure. Case one demonstrated metabolic acidosis and cerebral edema. His care provider found him while breathing but febrile and cyanotic, with liver failure and disseminated intravascular coagulation. At birth, case 2 was a girl with bilateral microphthalmia with cataracts and hypotonia (5). In addition, the increased urinary concentrations of 3-hydroxyisobutyric acid and genetic results are consistent with the present study, but heart symptoms were observed only in our case. Moreover, in agreement with the current study, some other studies have reported gene mutation results of ALDH6A1 (1, 13, 14).

This case report demonstrated the first Iranian case with MMSDH deficiency. He had elevated liver enzymes and cardiac disease, while cardiac manifestation is an unusual presentation of MMSDH deficiency in other reports. This case report develops the understanding about clinical and biochemical aspects of this very uncommon condition, and it can be significantly underdiagnosed, considering the numerous biochemical abnormalities initially observed in our patient.

Ethical Considerations

Compliance with ethical guidelines

The patient and his family were informed about the aim of this study. Also, in article's writing, ethical principles were considered.

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Conflict of interest

The authors declared no conflict of interest.

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References

[1] Marcadier JL, Smith AM, Pohl D, Schwartzentruber J, Al-Dirbashi OY, Majewski J, et al. Mutations in ALDH6A1 encoding methylmalonate semialdehyde dehydrogenase are associated with dysmyelination and transient methylmalonic aciduria. Orphanet Journal of Rare Diseases. 2013; 8:98. [DOI:10.1186/1750-1172-8-98] [PMID] [PMCID]

[2] Pollitt RJ, Green A, Smith R. Excessive excretion of beta-alanine and of 3-hydroxypropionic, R- and S-3-aminoisobutyric, R- and S-3-hydroxyisobutyric and S-2-(hydroxymethyl) butyric acids probably due to a defect in the metabolism of the corresponding malonic semialdehydes. Journal of Inherited Metabolic Disease. 1985; 8(2):75-9. [DOI:10.1007/BF01801669]

[3] Kedishvili NY, Popov KM, Rougraff PM, Zhao Y, Crabb D, Harris R. CoA-dependent methylmalonate-semialdehyde dehydrogenase, a unique member of the aldehyde dehydrogenase superfamily. cDNA cloning, evolutionary relationships, and tissue distribution. Journal of Biological Chemistry. 1992; 267(27):19724-9. [PMID]

[4] Chambliss KL, Gray RG, Rylance G, Pollitt RJ, Gibson KM. Molecular characterization of methylmalonate semialdehyde dehydrogenase deficiency. Journal of Inherited Metabolic Disease. 2000; 23(5):497-504. [DOI:10.1023/A:1005616315087] [PMID]

[5] Sass JO, Walter M, Shield JPH, Atherton AM, Garg U, Scott D, et al. 3-Hydroxyisobutyrate aciduria and mutations in the ALDH6A1 gene coding for methylmalonate semialdehyde dehydrogenase. Journal of Inherited Metabolic Disease. 2012; 35(3):437-42. [DOI:10.1007/s10545-011-9381-x] [PMID]

[6] Gibson KM, Lee CF, Bennett MJ, Holmes B, Nyhan WL. Combined malonic, methylmalonic and ethylmalonic acid semialdehyde dehydrogenase deficiencies: An inborn error of beta-alanine, L-valine and L-alloisoleucine metabolism? Journal of Inherited Metabolic Disease. 1993; 16(3):563-7. [DOI:10.1007/BF00711682] [PMID]

[7] Gray RG, Pollitt RJ, Webley J. Methylmalonic semialdehyde dehydrogenase deficiency: Demonstration of defective valine and beta-alanine metabolism and reduced malonic semialdehyde dehydrogenase activity in cultured fibroblasts. Biochemical Medicine and Metabolic Biology. 1987; 38(1):121-4. [DOI:10.1016/0885-4505(87)90069-7]

[8] Manning NJ, Pollitt RJ. Tracer studies of the interconversion of R-and S-methylmalonic semialdehydes in man. Biochemical Journal. 1985; 231(2):481-4. [DOI:10.1042/bj2310481]

[9] Roe CR, Struys E, Kok RM, Roe DS, Harris RA, Jakobs C. Methylmalonic semialdehyde dehydrogenase deficiency: Psychomotor delay and methylmalonic aciduria without metabolic decompensation. Molecular Genetics and Metabolism. 1998; 65(1):35-43. [DOI:10.1006/mgme.1998.2737] [PMID]

[10] Shield J, Gough R, Allen J, Newbury-Ecob R. 3-Hydroxyisobutyric aciduria: Phenotypic heterogeneity within a single family. Clinical Dysmorphology. 2001; 10(3):189-91. [DOI:10.1097/00019605-200107000-00007] [PMID]

[11] Loupatty FJ, van der Steen A, Ijlst L, Ruiter JP, Ofman R, Baumgartner MR, et al. Clinical, biochemical, and molecular findings in three patients with 3-hydroxyisobutyric aciduria. Molecular Genetics and Metabolism. 2006; 87(3):243-8. [DOI:10.1016/j.ymgme.2005.09.019] [PMID]

[12] Podebrad F, Heil M, Beck T, Mosandl A, Sewell AC, Bohles H. Stereodifferentiation of 3-hydroxyisobutyric- and 3-aminoisobutyric acid in human urine by enantioselective multidimensional capillary gas chromatography-mass spectrometry. Clinica Chimica Acta. 2000; 292(1-2):93-105. [DOI: 10.1016/S0009-8981(99)00210-7]

[13] Vasiliou V, Nebert DW. Analysis and update of the human aldehyde dehydrogenase (ALDH) gene family. Human Genomics. 2005; 2(2):138-43. [PMID] [PMCID]

[14] Vasiliou V, Pappa A, Petersen DR. Role of aldehyde dehydrogenases in endogenous and xenobiotic metabolism. Chemico-Biological Interactions. 2000; 129(1-2):1–19. [DOI:10.1016/S0009-2797(00)00211-8]