Case Report

Journal Homepage: http://crcp.tums.ac.ir

# A Case Report of Isovaleric Acidemia without Acidosis

**Mahtab Ordooei[1,2], Razieh Fallah[1,3], Maryam Saeida-Ardekani[2], Fahimeh Soheilipour[4], Mahdieh Yavari[5,6], Mahta Mazaheri[2,7*]**

*1. Children Growth Disorder Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran*
*2. Mother and Newborn Health Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran*
*3. Department of Pediatrics, Shahid Sadoughi University of Medical Sciences, Yazd, Iran*
*4. Minimally Invasive Surgery Research Center, Iran University of Medical Sciences, Tehran, Iran*
*5. Dr. Mazaheri's Medical Genetics lab, Yazd, Iran*
*6. Division of Genetics, Department of Cell, Molecular Biology and Microbiology, Faculty of Science and Biotechnology, University of Isfahan, Isfahan, Iran*
*7. Department of Medical Genetics, School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran*

Use your device to scan and read the article online

**Citation** Ordooei M, Fallah R, Saeida-Ardekan M, Soheilipour F, Yavari M, Mazaheri M. A Case Report of Isovaleric Acidemia without Acidosis. Case Reports in Clinical Practice. 2024; 9(1): 3-5.

**Running Title** Isovaleric Acidemia without Acidosis

**Article info:**
**Received:** December 29, 2023
**Revised:** January 25, 2024
**Accepted:** February 11, 2024

**Keywords:**
Isovaleric acidemia; Leucine; Isovaleryl-CoA dehydrogenase; Autosomal recessive disease

## ABSTRACT

The deficiency of isovaleryl-CoA dehydrogenase leads to an inborn recessive error of leucine metabolism named isovaleric acidemia (IVA). Its presentation may be either in the neonatal period as an acute episode of metabolic acidosis or later as a "chronic intermittent form." Normal development is promoted by early diagnosis and treatment with a protein-restricted diet and supplementation with carnitine and glycine. The present case was a 35-day-old boy admitted with seizures, whose initial screening test was in favor of organic acidemia of the isovaleric acidemia type (Ammonia: 200 µmol/L). As the venous blood gas (VBG) analysis revealed no acidosis, newborn metabolic screening was repeated. Typical laboratory findings and elevated levels of C5 and C5/C2 confirmed isovaleric acidemia again. As the above patient had no acidosis while the other tests, including laboratory and genetic analysis, were in favor of IVA, he was considered to be a rare case.

## Introduction

Isovaleric acidemia (IVA), known as one of the "classical" organic acidemias/acidurias, is an autosomal recessive error of leucine metabolism resulting from a deficiency of isovaleryl-CoA dehydrogenase (IVD) [1]. Accumulation of derivatives of isovaleryl-coenzyme A, such as isovaleric acid, 3-hydroxyisovaleric acid, 4-hydroxyisovaleric acid, isovaleryl carnitine, and isovaleryl glycine (IVG), occurs due to IVD deficiency, which is toxic to the central nervous system [2]. IVA presentation may be either as an "acute neonatal form" that may lead to coma and death or a "chronic form" associated with developmental delay, with or without recurrent acidotic episodes during catabolic stress [3]. An acute episode of metabolic decompensation may occur during a catabolic state, such as an infection, in both acute and chronic intermittent forms [1].

*** Corresponding Author:**
***Mahta Mazaheri***
***Address:*** *Mother and Newborn Health Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran and Department of Medical Genetics, School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran*
***E-mail:*** *mazaheri54@yahoo.com*

**Copyright © 2024 Tehran University of Medical Sciences. Published by Tehran University of Medical Sciences**
**This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International license(https://creativecommons.org/licenses/by-nc/4.0/). Noncommercial uses of the work are permitted, provided the original work is properly cited.**

The clinical heterogeneity of IVA has progressively been emphasized by a large number of case studies [4,5]. Epidemiological studies of Asian IVA patients have shown the diversity of genotype-phenotype relationships in different populations and even within families [6-8]. The clinical outcome of most patients is improved by the early implementation of treatment through a timely diagnosis of IVA via newborn screening (NBS) programs around the world. The identification of IEM patients with an unexpectedly wide clinical presentation is due to the development of mass spectrometry for NBS [5,9].

Suggested strategies for long-term treatment of IVA include reducing the production of toxic metabolites from leucine degradation using a protein- or leucine-restricted diet and enhancing the conversion of potentially neurotoxic free isovaleric acid into non-toxic carnitine and glycine conjugates, which are readily excreted in the urine by prescribing carnitine and/or glycine [3,4].

## Case Presentation

A 35-day-old was admitted to the hospital with seizures. He was born by cesarean section at the 38th week of pregnancy to Iranian parents in a consanguineous marriage. They were cousins, and there was no similar case in their familial history. His birth weight was 3.800 kg. There was no respiratory distress and no symptoms of lung involvement at the time of admission. On physical examination, his weight was 4 kg, and his height was 53 cm. The result of his newborn metabolic screening using MS/MS at 6 days of life revealed elevations of C5 (6.3 µmol/L) and C5/C2 (2.5 µmol/L) (reference value: C5: 0-2, C5/C2: 0-0.05 µmol/L). Results of biochemical analysis showed increased levels of ammonia (200 µmol/L). Additionally, urine analysis showed elevated 3-hydroxyisovaleric acid and isovaleric glycine. Since the blood gas analysis (VBG) at thirty-five days old revealed no acidosis during and after seizures, the primary metabolic screening was repeated. The results confirmed the previous tests. According to clinical and paraclinical signs, diet therapy for isovaleric acidemia, including a formula specific for IVA, supplementation with carnitine (100 mg/kg/day), and protein restriction, was started. The patient was also treated with anticonvulsant drugs. After diet therapy, he had seizures again. Due to the absence of acidosis during the seizures, the patient underwent genetic testing when he was 6 months old. Peripheral leukocyte DNA was extracted from the proband using a standard protocol. Whole exome sequencing was done on the DNA of the case to ascertain coding sequence variants. The quality of FastQ files was controlled using FastQC, then reads were mapped to the reference genome sequence (hg19) using BWA. The SAM file was converted to a BAM file by SAMtools. GATK tools (v2.2) were used to process the BAM files. SNPs and insertions and deletions were called by GATK tools. Then, shortlisted annotated variants were analyzed for the detection of pathogenic variants and phenotype-genotype correlation. The pathogenicity of the variants was determined by Varsome. The results showed a novel homozygous mutation of the IVD gene. After this step, we investigated his parents by Sanger sequencing. Exon 11 of the IVD gene (reference sequences: NM-000271.4) was PCR amplified using specific primers. The results of Sanger sequencing were analyzed using Finch TV 2.2 software and aligned to the human genome reference (hg19).

The exome analysis showed that the IVD gene (NM-000271.4) variant may be a possible candidate that explains Isovaleric acidemia (OMIM243500) with autosomal recessive inheritance. The outcome demonstrated a novel homozygous mutation (c.1132delG) in exon 11 of the IVD gene in the patient. After this observation, we performed Sanger sequencing for the proband and his parents. Parental sequence analysis showed that the parents were heterozygous at this locus. The variant (c.1132delG, p.G378fs) was not seen in population databases ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/), 1000G, and the local database. Based on ACMG guidelines, this variant can be classified as a pathogenic variant. Therefore, the diagnosis of IVD was confirmed, and the patient was sent home with medication and a scheduled follow-up. Moreover, we received written informed consent from the patient's father.

## Discussion

Isovaleric acidemia is a disorder in the subcategory of organic acidemia, characterized by early metabolic crises that often lead to coma, or it can result in a later chronic condition. Mild to severe mental retardation has been reported; however, patients may be developmentally normal [1]. Poor feeding, vomiting, seizures, and decreased levels of consciousness are symptoms of IVA [4].

In present study, we investigated a patient with IVA that had consanguineous parents and the diagnosis of IVD was made through newborn metabolic screening. While books and the reports of similar cases express acidosis as a remarkable sign of the disease, the present case had no acidosis during and after none of his seizures [2, 10, 11, 12, 13]. A case report by Pesce et al.,[14] presented an IVA case in the absence of hyperammonaemia or metabolic acidosis. Here, the

novel mutation, c.1132delG (a frameshift mutation in exon 11), was found in the proband, as a result of a frameshift mutation. The detected mutation in the case resulted in early termination (p.G378fs) of IVD production and might be the cause of isovaleric acidemia without acidosis in the patient

## Acknowledgments

The authors thank the patient's family for their cooperation in this study.

## Ethical Considerations

### Compliance with ethical guidelines

There were no ethical considerations to be considered in this article.

### Funding

No funding was received to assist with the preparation of this manuscript.

### Conflict of Interests

The authors have no conflict of interest to declare.

## References

[1] Haque N, Saha N, Alam MB, et al. Isovaleric Acidemia in a 5 Years of Boy: A Case Report. J Curr Adv Med Res. 2019;6(1):64-661. https://doi.org/10.3329/jcamr.v6i1.40788

[2] MP N. Isovaleric Aciduria a Case Report of Two Patients. Acta Sci Paediatr. 2019;2(8):45-482. https://doi.org/10.31080/ASPE.2019.02.0112

[3] Grünert SC, Wendel U, Lindner M, et al. Clinical and neurocognitive outcome in symptomatic isovaleric acidemia. Orphanet J Rare Dis. 2012;7(1):1-93. https://doi.org/10.1186/1750-1172-7-9

[4] Ensenauer JV and R. Isovaleric acidemia: new aspects of genetic and phenotypic heterogeneity. Am J Med Genet C Semin Med Genet. 2006;142c(2):95-1034. https://doi.org/10.1002/ajmg.c.30089

[5] Ensenauer R, Vockley J, Willard JM, et al. A common mutation is associated with a mild, potentially asymptomatic phenotype in patients with isovaleric acidemia diagnosed by newborn screening. Am J Hum Genet. 2004;75(6):1136-1142. https://doi.org/10.1086/426318

[6] Lin W De, Wang CH, Lee CC, Lai CC, Tsai Y, Tsai FJ. Genetic mutation profile of isovaleric acidemia patients in Taiwan. Mol Genet Metab. 2007;90(2):134-139. https://doi.org/10.1016/j.ymgme.2006.08.011

[7] Lee YW, Lee DH, Vockley J, Kim ND, Lee YK, Ki CS. Different spectrum of mutations of isovaleryl-CoA dehydrogenase (IVD) gene in Korean patients with isovaleric acidemia. Mol Genet Metab. 2007;92(1-2):71-77. https://doi.org/10.1016/j.ymgme.2007.05.003

[8] Vatanavicharn N, Liammongkolkul S, Sakamoto O, Sathienkijkanchai A, Wasant P. Phenotypic and mutation spectrums of Thai patients with isovaleric acidemia. Pediatr Int. 2011;53(6):990-994. https://doi.org/10.1111/j.1442-200X.2011.03488.x

[9] Dionisi-Vici C, Deodato F, Röschinger W, Rhead W, Wilcken B. "Classical" organic acidurias, propionic aciduria, methylmalonic aciduria and isovaleric aciduria: Long-term outcome and effects of expanded newborn screening using tandem mass spectrometry. J Inherit Metab Dis. 2006;29(2-3):383-389. https://doi.org/10.1007/s10545-006-0278-z

[10] Garg U and D.Smith L. Biomarkers in Inborn Errors of Metabolism: Clinical Aspects and Laboratory Determination. 1st edition. Amsterdam, Netherlands: Elsevier; 2017. https://doi.org/10.1016/B978-0-12-802896-4.00001-8

[11] Bissonnette B, Luginbuehl I, Marciniak B, J.Dalens B, editors. Syndromes: Rapid Recognition and Perioperative Implications. United States of America: McGraw-Hill Education; 2006.

[12] Kiliç M, Kaymaz N, Özgül RK. Isovaleric acidemia presenting as diabetic ketoacidosis: A case report. JCRPE J Clin Res Pediatr Endocrinol. 2014;6(1):59-61. https://doi.org/10.4274/Jcrpe.1181

[13] Zamanfar D, Keyhanian E, Ghazaiean M, Rostami Maskopaii S. The Chronic Intermittent Form of Isovaleric Acidemia With Staphylococcal Scalded Skin Syndrome: A Case Report and Literature Review. J Pediatr Rev. 2020;8(3):181-188. https://doi.org/10.32598/jpr.8.3.48.2

[14] Pesce F, Cerone R CU and RC. Acute neonatal isovaleric acidaemia presented without acidosis or ketonuria F. J Inher Metab Dis. 1991;14:111. https://doi.org/10.1007/BF01804400