

Case Report:

The Chronic Intermittent Form of Isovaleric Acidemia With Staphylococcal Scalded Skin Syndrome: A Case Report and Literature Review



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ABSTRACT

Isovaleric Acidemia (IVA) is an autosomal recessive Inborne Error of Metabolism (IEM), i.e., caused by the mutation of isovaleric-CoA dehydrogenase. Two phenotypes of IVA are reported; acute and chronic.

The case was a 3-year-old boy with chronic intermittent presentation. Elevated 3-hydroxybutyric acid and isovaleric glycine in urinary acid profile was reported. We also performed a brief review about the presented case; IVA in international databases for English language articles on children.

Several manners exist to screen IVA patients and the best one is GC-MS in urine analysis. The prognosis of the disease depends on the early interventions.

1. Introduction

Isovaleric Acidemia (IVA), as an autosomal recessive Inborne Error of Metabolism (IEM), is the first organic acidemia to be described (1). The disease is caused by the mutation of mitochondrial enzyme, Isovaleric-CoA Dehydrogenase (IVD) (1). IVD gene is located on the chromosome

15q14-15 (2, 3). Human IVD was extracted in 1987. Fibroblasts and lymphocytes are used to measure IVD activity for genetic analysis (4-12). IVA is an organic acidemia of branched-chain amino acid leucine. The prevalence of the disease was estimated to be 1/1000000 in Europe (1, 2, 9, 13).

IVA is classified in group 2 of IEM and has two forms of acute and chronic (14). During crises of the disease,

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urine contains isovaleric glycine, 3-hydroxyisovaleric acid, and other metabolites. Therefore, employing Gas Chromatography/Mass Spectrometry (GC-MS) became the mainstay for identifying organic academia in routine practice (15, 16). For practical purposes, the disease could metabolically be classified into mild, intermediate, and severe types. Both groups of acute and chronic IVAs are prone to an intermittent acute episodes of decompensation with minor illness (16). Additionally, a third type was described that may represent as a biochemical phenotype without clinical symptoms (16).

Infants with this condition appear well at birth; however, in the acute form, in first days or weeks of life, isovaleric-CoA derivatives cause nonspecific and variable clinical features. Such presentations include vomiting, lethargy, acidosis, ketosis, hyperammonemia, dehydration, failure to gain weight, seizures, odor of sweaty feet, progressing to coma, and death (4, 17-19).

In the late-onset form, recurrent attacks with dehydration and ketosis are triggered with infections and high protein. This type, combined with reactive hyperglycemia, is misdiagnosed as Diabetic Ketoacidosis (DKA) (2, 17, 20).

Staphylococcal Scalded Skin Syndrome (4S) occurs predominantly in infants and children aged <5 years. It includes a range of conditions from localized bullous impetigo to generalized cutaneous involvement with systemic illness. The onset of the rash may be preceded by malaise, fever, irritability, and exquisite skin tenderness. Scarletiform erythema develops diffusely and is accentuated in flexural and periorificial areas. The conjunctivae are inflamed and occasionally become purulent. The brightly erythematous skin may rapidly acquire a wrinkled appearance; in severe cases, sterile, flaccid blisters, and erosions develop, diffusely (21).

2. Case Presentation

A 34-month-old boy was admitted to the pediatric department due to altered consciousness and vomiting. Three day before admission, the patient started vomiting. First vomiting was nonbilious; however, it gradually increased in frequency and became bilious and forceful vomiting occurred with each meal. From the admission day, he was sleepy and had swelling and redness around eyes. There was no history of fever, abdominal pain, and diarrhea. He had normal defecation 5 days before admission. He was born by cesarean section. His birth weight was 3750 gr. He had a history of hospitalization, due to vomiting at the age of 10 and 16 months, as well as encephalitis at 25 months of age. In the disease

course, his clinical presentations progressed to 4S manifestations, like the recent admission. He was the second child of non-consanguineous Iranian parents. His older sister was 13 years old with healthy intelligence level. She presented no similar symptoms or known diseases. On physical examination, his weight was 14 kg (50th percentiles) and his height was 100 cm (90th percentiles), and he was lethargic. Tachycardia was also noted. Axillary body temperature of him was equal to 37.3°C. Oral mucosa was dry and his abdomen was soft and flat. His skin turgor and tonus was at low level. The laboratory analysis suggested the following values: WBC: 800/ μ L, (PMN=70%, LYMPH=17%, BASO=3%, monocyte=10%), RBC=4450000/ μ L, HB=10.5 gr/dL, MCV=75, MCH=21, PLT=183000, urea=44 mg/dL, Cr=0.7 mg/dL, Na=134 meq/lit, k=3.9 meq/L, Ca=8 mg/dL, ammonia=110, and lactate=3.84. The blood gas analysis data were as follows: PH: 7.29, PO₂:75 mmHg, PCO₂:27.8 mmHg, HCO₃:13.4 meq/L, and base deficit: -11. Liver function tests revealed normal result. Abdominal radiography and ultrasound sonography findings were normal. Brain CT and CSF analysis were also normal.

After 48 hours of admission, the patient presented high fever and tremor and was erythrodermic. Gradually, erythroderma was spread from the face to the trunk, i.e., accompanied by scaling and hair loss. In the laboratory analysis, the values were found as follows: WBC:800/ μ L (PMN=38%, lymph=50%, monocyte=4%, eosinophil=8%, RBC=3410000/ μ L, PLT=30000, NA=134 meq/L, K=2.3 meq/L, Ca=5.6 mg/dL, & P=2.5 mg/dL), According to the continuation of leukopenia, hypocalcemia, hypokalemia, metabolic acidosis; urine and plasma assessment for amino-acids were provided with the suspicion of IEM. Besides, the GC-MS of urine revealed grossly elevated (1325 time increase) isovaleric glycine suggestive of IVA. Special diet by formula specific for IVA and carnitine was started; his protein intake was restricted. The patient tolerated feed well and was discharged on a special diet. Surprisingly, in the third admission (after the last one), because of mild crisis, he demonstrated the same clinical presentation of 4S. However, because of his past history and vigorous management, these signs and symptoms did not progress.

3. Discussion

IVA is an autosomal recessive disorder caused by the mutation of IVD (16). It is a part of group 2 IEM, i.e., manifested as an acute (periodic vomiting, abnormal liver function) or chronic intermittent (failure to gain weight) (14). The attacks may be triggered by inter-current illnesses or other physiologic stressors, like fasting (16, 17).

We reported a case of a 3-year-old boy presented with the chronic intermittent form of IVA. Increased isovaleric glycine, as an indicator of IVA, was detected in the urine analysis with GC-MS method. Furthermore, ketosis was mentioned, i.e., because of elevated 3-hydroxy butyric acid. Variable clinical findings are originated from the amount of conjugated metabolites with genotype (4). For example, missense mutation, c.932C>T usually presented well without any cure (4, 16, 21). The patients may present dehydration, hypothermia, and the odor of sweaty feet. The laboratory findings were metabolic acidosis, hyperammonemia, hyper- or hypoglycemia, and hypocalcemia. Pancytopenia, due to bone marrow suppression, could occur as well as isolated neutropenia, and thrombocytopenia (16, 17, 22).

The odor is smelled because of the unconjugated metabolites in urine. The odor could be detected best in body fluids, especially by sweat or cerumen from the ear (1, 2, 13, 16, 23-27).

The characteristic smell of dirty socks may be present when the patient is acutely sick. Surprisingly, the urine has not odor; unlike other organic acidemias, i.e., because the unconjugated isovaleric acid responsible for the odor is inadequately excreted in urine. Secondary hyperammonemia is caused by the restraint of N-acetylglutamate synthetase activity with isovaleric-CoA and the evacuation of acetyl-CoA (28, 29). Patient's mental development depends on the age of diagnosis (30). Intellectual development may be affected by the frequency of attacks and the time of receiving cure. Globus pallidus may also be involved (31). The uncured patients are prone to intra-cerebral bleeding and edema that may lead to coma and death (16, 32).

Moreover, the disease presentations might be similar to diabetic ketoacidosis (33). Patients who survive a neonatal or other acute crisis at any time may be clinically indistinguishable from children diagnosed later in life, with more chronic conditions than the others.

The latter group presentations are relatively non-specific, such as failure to thrive, developmental delay, or intellectual disability. Accordingly, a specific diagnosis for these children is suggested; it must be considered in all patients with this clinical picture. During crisis, acute pancreatitis, myeloproliferative syndrome, Fanconi syndrome, and cardiac arrhythmias, and ketoacidosis were reported (16).

Several methods are available to evaluate IEM patients. These approaches include blood and urine analysis, genetic counseling, diet assessment, and obtaining

family history. Elevated lactate, pyruvate, and ammonia may manifest mitochondrial involvement (14). Newborn screening, by MS/MS, demonstrate the elevations of the C5 acylcarnitine metabolite markers in dried blood spots. Through this method, the majority of patients are diagnosed pre-symptomatically. Furthermore, C5 acylcarnitine represents a mixture of isomers (isovaleric carnitine, 2 methylbutyryl carnitine, & pivaloyl carnitine); thus, for confirming diagnosis, further diagnostic evaluation is required (16).

In differential diagnosis by biochemical laboratory, pivaloyl carnitine must be considered as derived from a component of several antibiotics named pivalic acid; and the elevation of 2-methylbutyryl glycine urine due to an inborn error of leucine catabolism caused by a deficiency of Short/Branched-Chain Acyl-CoA Dehydrogenase (SBCAD), through the deficiencies of the electron transfer flavoprotein and its dehydrogenase, isovaleric-CoA intermediates could be observed (16). The hallmark metabolites of IVD in plasma and urine, i.e., elevated regardless of patient's metabolic condition are isovaleric carnitine and isovaleric glycine (16). The Gas Chromatography (GS-MS) and Mass Spectrometry (MS-MS) are used for diagnosing IVA patients to detect organic acid in urine and acylcarnitine in blood (4, 34, 35). These metabolites in blood and urine are also used to diagnosis between IVA and DKA conditions (5). There is no way to detect sickness period; only protein restriction could be evaluated by measuring prealbumin and albumin. Amniotic fluid analysis, cultured amniocytes, and detecting acylcarnitine by MS/MS are used to prenatal screening (16, 36). In addition, β -oxidation impairments, urea cycle impairments, and other organic acidemia should be considered for the differential diagnosis (16, 37). There are different approaches for IVA treatment.

Three goals must be addressed in the treatment of IVA, regardless of the IVA type (16, 37). The first is preventing metabolic decompensation. The key point is a clinical observation of the patient. During metabolic stress, achieving anabolism is the main therapeutic approach (16). This situation must be preserved with high-calorie intake and decreased protein level, especially leucine intake to approximately 50% of patient's usual daily minimum; with the promotion of protein anabolism, this condition returns to normal after 24 hours (16, 17). Next step is consuming oral solutions, containing simple sugars, leucine free formula (if oral intake is interrupted), and IV glucose infusion; thus, this goal could be easily accomplished (11, 16, 18, 23, 24, 38, 39). The second goal is reducing the production of isovaleric-CoA from leucine catabolism in long time by controlling patients' dietary.

Children need an adequate intake of protein and calorie for healthy growth; accordingly, in many cases, lower protein intake of approximately 1.5 gr/kg/day with natural foods may be sufficient (16). Protein intake should be regulated according to the patient's age necessity (30). For this reason, daily requirement after restricting leucine, especially in patients with recurrent clinical symptoms, natural proteins provided with leucine-free formula (LFAA) is recommended (16). Generally, treatment with carnitine, glycine, and a restricted protein diet (with or without LFAA), especially after the early childhood years (39, 40), could lead to a relative metabolic stability (41). Additionally, companies that produce LFAA for IVA only supply a limited range (41).

The IVA E-IMD guidelines recommend that natural protein intake should be restricted to reduce the isovaleric acid level; however, at least the safe levels of protein intake advocated by WHO/FAO/UNU 2007 must be supplied (42). An over-restriction of natural protein could lead to catabolism and metabolic instability (43). Leucine is an essential amino-acid; thus, it significantly impacts the regulation of metabolism. This process occurs by signaling an increase in translation, promoted global protein synthesis, promoted insulin release, and inhibited autophagic protein degradation (44-46). There is a potential for adverse side effects, including anorexia, triglyceride lipolysis, weight loss, amino-acid imbalance, and muscle wasting from the rigorous restriction of leucine; i.e., because of the specific role of this amino-acid in protein synthesis promotion (16, 47-49). Leucine provides 10% of amino-acid content of animal protein and only 6% of plant protein (49). Indeed, in IVA, the emphasis is on protein intake; however, the maintenance of energy intake may be as essential as protein restriction. Moreover, it demonstrated the main cause for producing toxic metabolites in IVA, i.e., the turnover of endogenous protein, rather than dietary protein intake (4, 38).

Eliminating harmful metabolites is the third goal of treatment (16, 50, 51). This purpose could be achieved by standing isovaleric-CoA. Conjugated materials should be used, such as glycine and carnitine for isovaleric-CoA toward reactions that produce presumed nontoxic metabolites that could be easily excreted. Isovaleric-CoA is enzymatically conjugated to glycine. This reaction could be augmented by supplementation with exogenous glycine to supra-physiologic levels. This supplementation decreases the accumulation of toxic metabolites of IVA following a leucine load and reduces the severity of symptoms during intercurrent illness or may be prevented from these morbidities (16). Initial dosing in the range of 150 mg/kg/day to 250 mg/kg/day (150-600

mg/kg/day) given orally in divided 3-4 equal doses led to a dose sensitive increase in the excretion of urinary isovaleric glycine. The optimum dose is unclear, i.e., because at least in one report, high doses decreased the excretion of toxic metabolites. This is presumably due to the inhibition of glycine-N-acylase by glycine that also may result in secondary hyper ammonia (13, 16, 52-54).

Toxic metabolites conjugate with carnitine in blood and urine; accordingly, the secondary deficiency of carnitine could be detected. Treatment with carnitine supplementation has promoted in these patients. Moreover, combined therapy with glycine and carnitine is more effective than therapy with one medication (16, 50, 51, 55, 56). However, the clinical benefits of this manner were not established in the collected studies (56-58). The recommended dose of carnitine is 100mg/kg/day divided in two or three equal parts (16). Furthermore, controlling age-appropriate weight gain, growth, and development, as well as avoiding specific protein malnutrition in the patients with protein restriction is of importance. There is also no established laboratory marker for monitoring disease state or controlling therapy; however, the analysis of amino-acids, albumin, and prealbumin in plasma is recommended. Even without treatment, due to irreversible oxidative decarboxylation occurring earlier in the leucine degradation pathway, the plasma levels of leucine in IVA were not elevated (16). For monitoring and determining the necessity of carnitine supplementation analysis of plasma, free carnitine concentration may be helpful (16).

4. Conclusion

IVA is a type of group 2 IEM that could be presented acute or chronic. The key point is the age of diagnosis. Delayed diagnosis and treatment could lead to severe complications, such as coma or death. Thus, the identification of spectrum signs and symptoms could help clinicians to extent the definite diagnosis in a patient with the unusual presentation or course of the disease; also, among those with poor response to routine managements for a routine or unusual presentation. This is because the late onset of the disease may be progressed to coma and death by trigger factors, including high protein intake and infections.

Ethical Considerations

Compliance with ethical guidelines

The relevant Ethics Code was obtained for this study (Code: IR.IUMS.FMD.REC.1396).

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Authors' contributions

All authors contribute in preparing this article.

Conflicts of interest

The authors declared no conflicts of interest.

References

1. Tanaka K, Budd MA, Efron ML, Isselbacher KJ. Isovaleric acidemia: A new genetic defect of leucine metabolism. *Proceedings of the National Academy of Sciences of the United States of America*. 1966; 56:236-42. [DOI:10.1073/pnas.56.1.236] [PMID] [PMCID]
2. Tanaka K. Isovaleric acidemia: Personal history, clinical survey and study of the molecular basis. *Progress in Clinical And Biological Research*. 1990; 321:273-90.
3. Parimoo B, Tanaka K. Structural organization of the human isovaleryl-CoA dehydrogenase gene. *Genomics*. 1993; 15(3):582-90. [DOI:10.1006/geno.1993.1111] [PMID]
4. Ensenauer R, Vockley J, Willard J-M, Huey JC, Sass JO, Edland SD, et al. A common mutation is associated with a mild, potentially asymptomatic phenotype in patients with isovaleric acidemia diagnosed by newborn screening. *American Journal of Human Genetics*. 2004; 75(6):1136-42. [DOI:10.1086/426318] [PMID] [PMCID]
5. Kleijer W, Van der Kraan M, Huijmans J, Van Den Heuvel C, Jakobs C. Prenatal diagnosis of isovaleric acidemia by enzyme and metabolite assay in the first and second trimesters. *Prenatal Diagnosis*. 1995; 15(6):527-33. [DOI:10.1002/pd.1970150605] [PMID]
6. Mohsen A-WA, Anderson BD, Volchenboum SL, Battaile KP, Tiffany K, Roberts D, et al. Characterization of molecular defects in isovaleryl-CoA dehydrogenase in patients with isovaleric acidemia. *Biochemistry*. 1998; 37(28):10325-35. [DOI:10.1021/bi973096r] [PMID]
7. Vockley J, Parimoo B, Tanaka K. Molecular characterization of four different classes of mutations in the isovaleryl-CoA dehydrogenase gene responsible for isovaleric acidemia. *American Journal of Human Genetics*. 1991; 49(1):147.
8. Hyman DB, Tanaka K. Isovaleryl-CoA dehydrogenase activity in isovaleric acidemia fibroblasts using an improved tritium release assay. *Pediatric Research*. 1986; 20(1):59-61. [DOI:10.1203/00006450-198601000-00017] [PMID]
9. Rhead WJ, Tanaka K. Demonstration of a specific mitochondrial isovaleryl-CoA dehydrogenase deficiency in fibroblasts from patients with isovaleric acidemia. *Proceedings of the National Academy of Sciences*. 1980; 77(1):580-3. [DOI:10.1073/pnas.77.1.580] [PMID] [PMCID]
10. Shih VE, Mandell R, Tanaka K. Diagnosis of isovaleric acidemia in cultured fibroblasts. *Clinica Chimica Acta*. 1973; 48(4):437-9. [DOI:10.1016/0009-8981(73)90425-7]
11. Tajima G, Sakura N, Yofune H, Febriani ADB, Nishimura Y, Sakamoto A, et al. Establishment of a practical enzymatic assay method for determination of isovaleryl-CoA dehydrogenase activity using high-performance liquid chromatography. *Clinica Chimica Acta*. 2005; 353(1-2):193-9. [DOI:10.1016/j.cccn.2004.11.007] [PMID]
12. Yoshida I, Søvik O, Sweetman L, Nyhan WL. Metabolism of leucine in fibroblasts from patients with deficiencies in each of the major catabolic enzymes: branched-chain ketoacid dehydrogenase, isovaleryl-CoA dehydrogenase, 3-methylcrotonyl-CoA carboxylase, 3-methylglutaconyl-CoA hydratase, and 3-hydroxy-3-methylglutaryl-CoA lyase. *Journal of Neurogenetics*. 1985; 2(6):413-24. [DOI:10.3109/01677068509101427] [PMID]
13. Budd MA, Tanaka K, Holmes LB, Efron ML, Crawford JD, Isselbacher KJ. Isovaleric acidemia: Clinical features of a new genetic defect of leucine metabolism. *New England Journal of Medicine*. 1967; 277(7):321-7. [DOI:10.1056/NEJM196708172770701] [PMID]
14. Cleary M, Green A. Developmental delay: When to suspect and how to investigate for an inborn error of metabolism. *Archives of Disease in Childhood*. 2005; 90(11):1128-32. [DOI:10.1136/adc.2005.072025] [PMID] [PMCID]
15. Tanaka K, Isselbacher KJ. The isolation and identification of N-isovalerylglycine from urine of patients with isovaleric acidemia. *Journal of Biological Chemistry*. 1967; 242(12):2966-72.
16. Vockley J, Ensenauer R. Isovaleric acidemia: New aspects of genetic and phenotypic heterogeneity. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics*. Wiley Online Library; 2006. [DOI:10.1002/ajmg.c.30089] [PMID] [PMCID]
17. Sweetman L, Williams J. Branched chain organic acidurias. In: Scriver CR, Sly WS, Valle D, editors. *The Metabolic and Molecular Bases of Inherited Disease*, 8th ed. New York: McGraw Hill; 2001.
18. Sezer T, Balci O. Infantile spasms during acute metabolic decompensation in an infant with isovaleric acidemia. *Journal of Clinical Neurology*. 2016; 12(3):376-7. [DOI:10.3988/jcn.2016.12.3.376] [PMID] [PMCID]
19. Grünert SC, Wendel U, Lindner M, Leichsenring M, Schwab KO, Vockley J, et al. Clinical and neurocognitive outcome in symptomatic isovaleric acidemia. *Orphanet Journal of Rare Diseases*. 2012; 7(1):9. [DOI:10.1186/1750-1172-7-9] [PMID] [PMCID]

20. Erdem E, Cayonu N, Uysalol E, Yildirmak ZY. Chronic intermittent form of isovaleric acidemia mimicking diabetic ketoacidosis. *Journal of Pediatric Endocrinology and Metabolism*. 2010; 23(5):503-5. [DOI:10.1515/jpem.2010.082] [PMID]
21. Lindner M, Gramer G, Haege G, Fang-Hoffmann J, Schwab KO, Tacke U, et al. Efficacy and outcome of expanded newborn screening for metabolic diseases-Report of 10 years from South-West Germany. *Orphanet Journal of Rare Diseases*. 2011; 6(1):44. [DOI:10.1186/1750-1172-6-44] [PMID] [PMCID]
22. Kelleher JF, Yudkoff M, Hutchinson R, August CS, Cohn RM. The pancytopenia of isovaleric acidemia. *Pediatrics*. 1980; 65(5):1023-7.
23. Levy HL, Erickson AM, Lott IT, Kurtz DJ. Isovaleric acidemia: Results of family study and dietary treatment. *Pediatrics*. 1973; 52(1):83-94.
24. Lott IT, Erickson AM, Levy HL, Kennedy JP. Dietary treatment of an infant with isovaleric acidemia. *Pediatrics*. 1972; 49(4):616-8.
25. Mendiola J Jr., Robotham JL, Liehr JG, JC W. Neonatal lethargy due to isovaleric acidemia and hyperammonemia. *Texas Medicine*. 1984; 80(1):52-4.
26. Worthen H, Al Ashwal A, Ozand P, Garawi S, Rahbeeni Z, Al Odaib A, et al. Comparative frequency and severity of hypoglycemia in selected organic acidemias, branched chain amino acidemia, and disorders of fructose metabolism. *Brain and Development*. 1994; 16(1):81-5. [DOI:10.1016/0387-7604(94)90100-7]
27. Yoshino M, Yoshida I, Yamashita F, Mori M, Uchiyama C, Tatibana M. Neonatal isovaleric acidemia associated with hyperammonemia. *Urea Cycle Diseases*: Springer; 1982. pp. 141-6. [DOI:10.1007/978-1-4757-6903-6_19] [PMID]
28. Coude F, Sweetman L, Nyhan W. Inhibition by propionyl-coenzyme A of N-acetylglutamate synthetase in rat liver mitochondria. A possible explanation for hyperammonemia in propionic and methylmalonic acidemia. *Journal of Clinical Investigation*. 1979; 64(6):1544-51. [DOI:10.1172/JCI109614] [PMID] [PMCID]
29. Stewart PM, Walser M. Failure of the normal ureagenic response to amino acids in organic acid-loaded rats: Proposed mechanism for the hyperammonemia of propionic and methylmalonic acidemia. *The Journal of Clinical Investigation*. 1980; 66(3):484-92. [DOI:10.1172/JCI109879] [PMID] [PMCID]
30. Zschocke J, Hoffmann GF, AG M. *Vademecum metabolism: Manual of metabolic paediatrics*. 2nd ed. Friedrichsdorf: Milupa; Stuttgart: Schattauer; 2004.
31. Sogut A, Acun C, Aydin K, Tomsac N, Demirel F, Aktuglu C. Isovaleric acidemia: Cranial CT and MRI findings. *Pediatric Radiology*. 2004; 34(2):160-2. [DOI:10.1007/s00247-003-1049-8] [PMID]
32. Fischer AQ, Challa VR, Burton BK, McLean WT. Cerebellar hemorrhage complicating isovaleric acidemia: A case report. *Neurology*. 1981; 31(6):746-8. [DOI:10.1212/WNL.31.6.746] [PMID]
33. Attia N, Sakati N, Al Ashwal A, Al Saif R, Rashed M, Ozand P. Isovaleric acidemia appearing as diabetic ketoacidosis. *Journal of Inherited Metabolic Disease*. 1996; 19(1):85-6. [DOI:10.1007/BF01799353] [PMID]
34. Burke D, Halpern B, Malegan D, McCairns E, Danks D, Schlesinger P, et al. Profiles of urinary volatiles from metabolic disorders characterized by unusual odors. *Clinical Chemistry*. 1983; 29(10):1834-8. [DOI:10.1093/clinchem/29.10.1834] [PMID]
35. Tanaka K, Hine DG, West-Dull A, Lynn TB. Gas-chromatographic method of analysis for urinary organic acids. I. Retention indices of 155 metabolically important compounds. *Clinical Chemistry*. 1980; 26(13):1839-46. [DOI:10.1093/clinchem/26.13.1839] [PMID]
36. Knerr I, Vockley J, Gibson KM. Disorders of leucine, isoleucine, and valine metabolism. *Physician's guide to the diagnosis, treatment, and follow-up of inherited metabolic diseases*. United Kingdom: Springer; 2014. p. 103-41. [DOI:10.1007/978-3-642-40337-8_7]
37. Hoffmann GF, Nyhan WL, Zschocke J, Mayatepek E, Kahler SG, Hoffmann, et al. *Inherited metabolic diseases*. United Kingdom: Springer; 2002.
38. Millington DS, Roe CR, Maltby DA, Inoue F. Endogenous catabolism is the major source of toxic metabolites in isovaleric acidemia. *Journal of Pediatrics*. 1987; 110(1):56-60. [DOI:10.1016/S0022-3476(87)80288-3]
39. Pollitt RJ. Endogenous catabolism as source of toxic metabolites in isovaleric acidemia. *Journal of Pediatrics*. 1987; 111:477-8. [DOI:10.1016/S0022-3476(87)80488-2]
40. Collins J, Umpleby A, Boroujerdi M, Leonard J, Sonksen P. Effect of insulin on leucine kinetics in maple syrup urine disease. *Pediatric Research*. 1987; 21(1):10. [DOI:10.1203/00006450-198701000-00004] [PMID]
41. Pinto A, Daly A, Evans S, Almeida M, Assoun M, Belanger-Quintana A, et al. Dietary practices in isovaleric acidemia: A European survey. *Molecular Genetics And Metabolism Reports*. 2017; 12:16-22. [DOI:10.1016/j.ymgmr.2017.02.001] [PMID] [PMCID]
42. WHO, University UN. *Protein and amino acid requirements in human nutrition*. Geneva: World Health Organization; 2007.
43. Kölker S, Cazorla AG, Valayannopoulos V, Lund AM, Burlina AB, Sykut-Cegielska J, et al. The phenotypic spectrum of organic acidurias and urea cycle disorders. Part 1: The initial presentation. *Journal of Inherited Metabolic Disease: Official Journal of the Society for the Study of Inborn Errors of Metabolism*. 2015; 38(6):1041-57. [DOI:10.1007/s10545-015-9839-3] [PMID]

44. Anthony TG, McDaniel BJ, Byerley RL, McGrath BC, Caver DR, McNurlan MA, et al. Preservation of liver protein synthesis during dietary leucine deprivation occurs at the expense of skeletal muscle mass in mice deleted for eIF2 kinase GCN2. *Journal of Biological Chemistry*. 2004; 279(35):36553-61. [DOI:10.1074/jbc.M404559200] [PMID]
45. Lynch CJ, Hutson SM, Patson BJ, Vaval A, Vary TC. Tissue-specific effects of chronic dietary leucine and norleucine supplementation on protein synthesis in rats. *American Journal of Physiology-Endocrinology and Metabolism*. 2002; 283(4):E824-E35. [DOI:10.1152/ajpendo.00085.2002] [PMID]
46. Jonker R, Engelen MP, Deutz NE. Role of specific dietary amino acids in clinical conditions. *British Journal of Nutrition*. 2012; 108(S2):S139-S48. [DOI:10.1017/S0007114512002358] [PMID] [PMCID]
47. Cheng Y, Meng Q, Wang C, Li H, Huang Z, Chen S, et al. Leucine deprivation decreases fat mass by stimulation of lipolysis in white adipose tissue and upregulation of uncoupling protein 1 (UCP1) in brown adipose tissue. *Diabetes*. 2010; 59(1):17-25. [DOI:10.2337/db09-0929] [PMID] [PMCID]
48. Zhu X, Krasnow SM, Roth-Carter QR, Levasseur PR, Braun TP, Grossberg AJ, et al. Hypothalamic signaling in anorexia induced by indispensable amino acid deficiency. *American Journal of Physiology-Endocrinology and Metabolism*. 2012; 303(12):E1446-E58. [DOI:10.1152/ajpendo.00427.2012] [PMID] [PMCID]
49. Paul A, Southgate DA, Russell J. First supplement to McCance and Widdowson's the composition of foods: Amino acids, mg per 100 g food, fatty acids, g per 100 g food. London: The Stationery Office; 1980.
50. Low L. Inborn errors of metabolism: Clinical approach and management. *Hong Kong Medical Journal*. 1996; 2:274-81.
51. Van den Hout JM, Kamphoven JH, Winkel LP, Arts WF, De Klerk JB, Loonen MCB, et al. Long-term intravenous treatment of Pompe disease with recombinant human α -glucosidase from milk. *Pediatrics*. 2004; 113(5):e448-e57. [DOI:10.1542/peds.113.5.e448] [PMID]
52. Shigematsu Y, Sudo M, Momoi T, Inoue Y, Suzuki Y, Kameyama J. Changing plasma and urinary organic acid levels in a patient with isovaleric acidemia during an attack. *Pediatric Research*. 1982; 16(9):771. [DOI:10.1203/00006450-198209000-00013] [PMID]
53. Ito T, Kidouchi K, Sugiyama N, Kajita M, Chiba T, Niwa T, et al. Liquid chromatographic-atmospheric pressure chemical ionization mass spectrometric analysis of glycine conjugates and urinary isovalerylglycine in isovaleric acidemia. *Journal of Chromatography B: Biomedical Sciences and Applications*. 1995; 670(2):317-22. [DOI:10.1016/0378-4347(95)00174-3]
54. Martin-Hernandez E, Lee P, Micciche A, Grunewald S, Lachmann R. Long-term needs of adult patients with organic acidemias: Outcome and prognostic factors. *Journal of Inherited Metabolic Disease*. 2009; 32(4):523. [DOI:10.1007/s10545-009-1191-12] [PMID]
55. Fries MH, Rinaldo P, Schmidt-Sommerfeld E, Jurecki E, Packman S. Isovaleric acidemia: Response to a leucine load after three weeks of supplementation with glycine, L-carnitine, and combined glycine-carnitine therapy. *The Journal of Pediatrics*. 1996; 129(3):449-52. [DOI:10.1016/S0022-3476(96)70081-1]
56. Itoh T, Ito T, Ohba S, Sugiyama N, Mizuguchi K, Yamaguchi S, et al. Effect of carnitine administration on glycine metabolism in patients with isovaleric acidemia: Significance of acetylcarnitine determination to estimate the proper carnitine dose. *The Tohoku Journal of Experimental Medicine*. 1996; 179(2):101-9. [DOI:10.1620/tjem.179.101] [PMID]
57. Roe C, Millington D, Maltby D, Kahler S, Bohan T. L-carnitine therapy in isovaleric acidemia. *Journal of Clinical Investigation*. 1984; 74(6):2290-5. [DOI:10.1172/JCI111657] [PMID] [PMCID]
58. Mayatepek E, Kurczynski TW, Hoppel CL. Long-term L-carnitine treatment in isovaleric acidemia. *Pediatric Neurology*. 1991; 7(2):137-40. [DOI:10.1016/0887-8994(91)90011-9]

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