Clinical Case Reports International

Case Report
Published: 08 Jan, 2026

Isovaleric Acidemia Associated Pancreatitis: Key Concepts Every Clinician Should Know

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Abstract

Background: Isovaleric Acidemia (IVA) is caused by Isovaleryl CoA dehydrogenase (IVD) deficiency, which results in impaired Leucine metabolism and toxic effects of Isovaleric acid metabolites in body. The patient presents with acute episodes of vomiting, abdominal pain, sweaty feet odor, encephalopathy, increased anion gap acidosis, Ketonuria and hyperammonemia. Acute abdominal pain and vomiting may lead the diagnosis of Pancreatitis and delay the identification of chronic form of IVA.

Case Presentation: We report a case of 6 years old male child presented with recurrent pancreatitis for 1 year of age. He was diagnosed pancreatitis with clinical symptoms, elevated pancreatic enzymes and imaging. Despite normalization of pancreatic enzymes and radiological findings, he did not show clinical stabilization that diverted our focus to investigate for Metabolic disorders. Investigations showed high anion gap acidosis, Ketonuria, hyperammonemia and elevated excretion of Isovaleric acid and its metabolites in urine. The treatment modified with leucine restricted diet and L- Carnitine supplements. The 2 years of follow up showed acute episodes of metabolic decompensation but normal pancreatic enzyme assays. Suspicion of Chronic Pancreatitis was raised as patient complained of malabsorptive stools. Later, diagnosis was confirmed with low fecal elastase level and fibrotic pancreas on imaging.

Conclusion: Our case discloses, the diagnostic Dilemma of Isovaleric Acidemia and Recurrent Pancreatitis due to coinciding symptoms. Further emphasizes to screen Isovaleric Acidemia patients for chronic pancreatitis with normal pancreatic enzymes.

Keywords: Isovaleric Acidemia, Chronic Pancreatitis, Metabolic disorder

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Received Date: *18 Dec 2025*
Accepted Date: *06 Jan 2026*
Published Date: *08 Jan 2026*

Citation:
Parkash A, Haleem A, Sughandi S, Akram M. Isovaleric Acidemia Associated Pancreatitis: Key Concepts Every Clinician Should Know. Clin Case Rep Int. 2026; 10: 1750.

Introduction

Isovaleric acidemia is autosomal recessive inherited disorder, first discovered by Tanaka in 1966. It is caused by absent or reduced activity of Isovaleryl- CoA Dehydrogenase (IVD), that results in impaired leucine metabolism and accumulation of isovaleric acid metabolites (3-hydroxyisovaleric acid, isovaleryl 5 carnitine and isovaleryl glycine) [1,2].

The systemic toxic effects are encountered by disruption of ATPase activity and failure of sodium potassium pump, that impairs neuronal cell membrane integrity resulting in oxidative stress induced encephalopathy. Neutropenia becomes evident due to downregulation of granulopoietic proliferation and Pancreatitis is manifested by toxic effect of ester substrates on acinar cells which alter calcium cellular levels and causes calcium depleted ATPase failure [1-3]. The symptoms are evident when Isovaleryl CoA level exceeds the glycine and carnitine esters formation [4]. Two phenotypes of IVA are discovered. Acute form presents with clinical manifestations like neonatal sepsis and Chronic form presents in infantile or early childhood age with abdominal pain, vomiting and encephalopathy. Mortality of acute and chronic forms is 33% and 3% respectively. Disease severity varies as per residual activity of enzyme [1,2,5].

Case Presentation

We report a case of 6 years old male patient, managed as case of recurrent pancreatitis secondary to idiopathic cause and had 18 hospitalizations since 1 year of age. He referred to our Gastroenterology

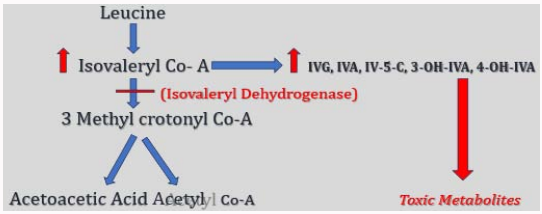

Figure 1: Leucine Metabolism.

department for the evaluation of frequent episodes of recurrent pancreatitis. He was thin lean boy, born of consanguineous marriage. He had significant muscle wasting, weight was 16 kg (<5th centile for age) and Height was 119 cm (at 50th centile for age). Family history was non-significant for any metabolic disorder and the systemic examination was normal. The treatment started with fat free diet as clinical symptoms, elevated pancreatic enzymes and radiologic findings [inflamed, enlarged pancreas and peripancreatic fat (Figure 2a) were consistent with acute pancreatitis.

After conservative management, he showed decline in Pancreatic enzymes but had persistent vomiting, abdominal pain and notable sweaty feet odor. We screened for metabolic disorders, first tier Investigations showed High anion gap Metabolic acidosis, [PH =7.34, HCO3=13.4 mmol/L, CO2= 25.4 mmHg, AG=32], Ketonuria ++++, high Serum Ammonia level = 143ug/dl and Normal Plasma Lactate= 0.7 mmol/L. Second tier investigations showed nonspecific changes in Plasma Amino acids including mild decreased levels of Serine, Alanine, Citrulline, Cystine, Ornithine, Histidine, Arginine and Proline but Urine Organic acids including Isovaleric glycine, 3-hydoxy Isovaleric acid, 3-hydroxy butyric acid, 4-hydroxy Isovaleric acid and acetoacetic acid were markedly elevated. (Leucine Metabolism is elaborated in Figure 1 and All Investigation details are summarized in Table 1).

Metabolic acidosis with high ammonia, ketosis and normal lactate level revealed energy depleted disorder (Organic Acidemia with intact fatty acid oxidation and mitochondrial pathways respectively) and further Urine organic acids were suggestive of IVA. Patient treatment modified with leucine restricted- protein diet, essential amino acids and L- carnitine supplements started at 100 mg/kg/day in 2 divided doses.

In next 2 years, patient was observed to be non-adherent to diet and had 3 episodes of metabolic decompensation with normal reported pancreatic enzymes. Furthermore, patient complained of increased hunger and fatty stools which led us to screen the patient for pancreatic insufficiency and workup revealed fibrotic pancreas on computed tomography of abdomen (Figure 2b) and severe exocrine insufficiency with low fecal elastase 37.78 ug/ml (normal >200 ug/ml). Magnetic Resonance Cholangiopancreatography (MRCP) was done that excluded the structural anomaly and atrophic pancreas was visualized (Figure 2c).

Neutropenia was also documented with total leukocyte count of 2200/mm^3 and absolute neutrophil count of 1250. Patient treatment escalated with pancreatic enzyme replacement and strict adherence to leucine restricted-protein free diet and low-fat diet to further prevent myeloid precursor suppression and Diabetes mellitus.

In literature, it is stated that the high lipid diet due to restricted

Table 1: Summarized Investigations.

Investigation	Result at 6 years	Comments	Result at 8 years	Comments	Reference range
Hb - MCV	10.2 (78)	Normocytic Anemia	12.6 (84.6)	Normal	13-16g/dl
TLC (ANC)	9.8 (6370)	Normal	2.2 (1250)	Neutropenia	4,000 – 10,000
Platelets	550000	Normal	360000	Normal	1,50,000 to 6,50,000
RFTs & Electrolytes	Normal	Normal	Normal	Normal	------
Liver Function tests	Normal	-----	Normal	-----	------
Serum Amylase	216 U/L	Elevated	35 U/L	Normal	<80 U/L
Serum Lipase	498 U/L	Elevated	49 U/L	Normal	<51 U/L
Total Cholesterol	144 mg/dl	Normal	116 mg/dl	Normal	<200 mg/dl
Triglycerides	118 mg/dl	Normal	255 mg/dl	Elevated	<130 mg/dl
HDL	33 mg/dl	Low	24 mg/dl	Low	>40 mg/dl
LDL	87 mg/dl	Normal	55 mg/dl	Normal	<130 mg/dl
Serum Ammonia Level	143 ug/dl	Elevated	95	Elevated	<68 ug/dl
Plasma Lactate	0.7 mmol/L	Normal	1.2 mmol/l	Normal	<2.2 mmol/L Venous.
HBA1C	5.2%	Normal	4.8%	Normal	<6.4%
Fecal Elastase	240 ug/ml	Normal	37.78 ug/ml	Severe pancreatic insufficiency	>200 ug/ml
Urine Analysis	Ketonuria ++++	Ketosis	Normal	Normal	No sediments.
Plasma Amino Acids	Non-Significant	-----	-----	-----	-----
Urine Organic Acids	IVG, 3-OH IVA, 3-OH BA. 4-OH IVA and acetoacetate.	Ketosis And IVA esterification exceeds the limit.	-----	-----	-----
CT Abdomen-1	Enlarged pancreas with peripancreatic fat stranding.	Acute Pancreatitis	-----	-----	-----
CT Abdomen -2	-----	-----	Fibrotic Pancreas with fat staining	Chronic Pancreatitis	-----

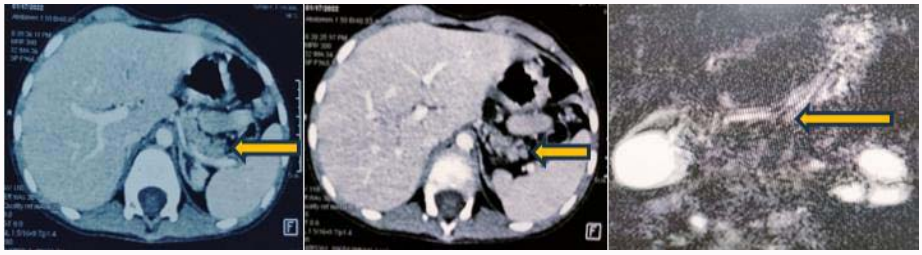

Figure 2: CT Abdomen shows inflamed pancreas with peripancreatic fat stranding suggestive of acute pancreatitis (6 years). B. Fibrotic pancreas (feathery appearance) revealed chronic pancreatitis (8years). C. MRCP shows intact pancreatic duct and atrophic pancreas.

protein can develop pancreatitis but our case highlights the toxic effect of leucine metabolites to pancreatic acinar cells and later lipemia interference with normal pancreatic enzyme assays and it is also first diagnosed case of IVA in recurrent pancreatitis.

Discussion

S G Kahler study in 1994 first identified organic acid disorders as cause of AP and reported 09 children among 108 patients of metabolic disorders. The diagnosis of Five, three and one cases were consistent With Methylmalonic Aciduria (MMA), IVA and maple syrup urine disease respectively.6 Woo Jin, et al in. 2021 further reported 6 patients of AP secondary to metabolic disorders, 2 cases of MMA developed Diabetes Mellitus by 20 years of age and one case of hyperornithinemia was diagnosed with gyrate atrophy at age 35 years [7].

No Global data is available about incidence of Pancreatitis in metabolic disorders. The toxicity of metabolites formed in energy depleted disorders can cause significant systemic morbidity in these patients.

Current treatment is with diet modification and L-Carnitine and/or Glycine supplements, which bind with isovaleryl-Co A and excrete it in the water soluble nontoxic Isovaleryl Carnitine and Isovaleryl Glycine forms [2]. Additionally, valproate can precipitate hyperammonemia and carnitine depletion and is generally avoided in organic acidemias [6]. Furthermore, early diagnosis of IVA can be best established by newborn screening and early intervention can lead to better outcome [8]. The advanced treatment of IVD gene induction may be implemented in human subjects in future [1].

Other way, The Pancreatitis is inflammation of pancreas, common etiologies include trauma, gallstones, tract malformation, autoimmune, infective, dyslipidemia and hereditary (SPINK1, PRSS1) mutated genes. Diagnosis of AP requires ≥2 of 3 features (compatible pain; amylase/lipase ≥3 × ULN; imaging findings) [7]. The diagnosis of Recurrent Pancreatitis requires two or more documented episodes and Chronic Pancreatitis is diagnosed, when there is evidence of endocrine or exocrine pancreatic insufficiency (HbA1c>6.5%, Low Fecal Elastase) or Radiologic findings suggestive of chronicity; fibrotic, calcified or atrophic pancreas. Acute Pancreatitis (AP) has incidence of 1 in 10,000 children, 2-5 % of AP patients have later Recurrent Pancreatitis and 2/100,000 children in a year develop chronic pancreatitis [2-4].

Our case had no documented AP episode for next 2 years but later atrophic pancreas was evident on computed tomography and Low fecal elastase levels also revealed Chronic damage. The treatment of acute episodes is early start of enteral feeds with fat free diet and chronic form with replacement of pancreatic enzymes or/and insulin whichever is depleted.

Conclusion

The concurrent diagnosis of Pancreatitis and chronic form of IVA is challenging. Our case emphasizes that every case of recurrent pancreatitis should be screened for metabolic disorders and normal pancreatic enzyme levels must be investigated for Chronic pancreatitis in IVA diagnosed cases to prevent long-term neurologic, hematologic as well as pancreatic endocrine and exocrine pitfalls. Genetic testing is limitation in our case due to cost issues.

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