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# 3-HYDROXY-3-METHYLGLUTARYL-COENZYME A LYASE DEFICIENCY: A NARRATIVE REVIEW

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## ABSTRACT

3-Hydroxy-3-methylglutaryl-coenzyme A lyase deficiency is a rare autosomal recessive inborn error of leucine catabolism and ketogenesis. It is characterized by episodes of hypoketotic hypoglycemia, metabolic acidosis, and hyperammonemia, often precipitated by fasting or intercurrent illness. This narrative review summarizes current evidence on the molecular basis, clinical spectrum, diagnostic approach, and management of the disorder, with emphasis on the role of the clinical pharmacist. Literature indexed in PubMed, Scopus, and Google Scholar was reviewed, and the differential diagnosis, newborn screening, and prognosis are also considered. The disorder results from biallelic pathogenic variants in the gene encoding the enzyme, located on chromosome 1p36.11. Most patients present in the first year of life with acute metabolic decompensation. Diagnosis relies on urinary organic acid and plasma acylcarnitine profiles, confirmed by molecular analysis or enzyme assay. Management is based on prevention of fasting, early intravenous glucose during illness, moderate leucine and protein restriction, and carnitine supplementation. Neurological outcome depends largely on the number and severity of hypoglycemic episodes and on the speed of treatment. Evidence is limited to case series and expert consensus. Early

recognition and a structured emergency plan substantially reduce morbidity. Multidisciplinary care, including pharmacist-led medication review and caregiver education, is essential, and prospective registries are needed to define optimal long-term management.

**KEYWORDS:** 3-Hydroxy-3-methylglutaryl-CoA lyase deficiency; ketogenesis; leucine catabolism; organic acidemia; inborn errors of metabolism; clinical pharmacist.

## INTRODUCTION

3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) lyase deficiency (HMGCLD; OMIM 246450), also called 3-hydroxy-3-methylglutaric aciduria, is a rare autosomal recessive organic aciduria. It was first described in 1976 in a child with defective leucine metabolism.[1] The mitochondrial enzyme HMG-CoA lyase (EC 4.1.3.4; systematic name (S)-3-hydroxy-3-methylglutaryl-CoA acetoacetate-lyase) is required for the final step of ketone body synthesis and for the last step of leucine degradation. Its absence therefore removes the main alternative fuel the brain uses during fasting, and it explains the hallmark biochemical picture of severe hypoglycemia without an appropriate ketotic response.

Only a few hundred cases have been reported worldwide, yet the condition is clinically important because it mimics common neonatal and pediatric emergencies such as sepsis, Reye-like syndrome, and gastroenteritis, and because acute episodes are preventable and treatable.[2,3] This review summarizes the biochemistry, genetics, clinical features, diagnosis, and management of HMGCLD and highlights practical considerations for pharmacists and other members of the care team.

## METHODS

This narrative review was based on a search of PubMed, Scopus, and Google Scholar for articles on HMG-CoA lyase deficiency, 3-hydroxy-3-methylglutaric aciduria, *HMGCL*, and ketogenesis disorders. Case reports, case series, observational studies, and consensus guidance were considered. No formal risk-of-bias assessment was performed.

## BIOCHEMISTRY AND MOLECULAR GENETICS

### Enzyme function

HMG-CoA lyase catalyzes the cleavage of HMG-CoA into acetyl-CoA and acetoacetate. In liver mitochondria this reaction is the terminal step of ketogenesis, which supplies acetoacetate and 3-hydroxybutyrate to extrahepatic tissues during prolonged fasting.[4] The same reaction

completes leucine catabolism, so leucine-derived HMG-CoA accumulates when the enzyme is deficient. The crystal structure of the human enzyme has clarified the catalytic mechanism and the effect of disease-causing substitutions.[5]

### The *HMGCL* gene

The human gene is located on chromosome 1p36.11, and the cDNA was cloned in 1993.[6] A mitochondrial isoform carries out the principal metabolic function; a peroxisomal isoform has also been described.[3] More than 40 pathogenic variants (missense, nonsense, splice-site, and deletions) have been reported, with some variants clustering in particular populations, including cohorts from Saudi Arabia and the Iberian Peninsula.[3,7,8] Genotype-phenotype correlation is weak: patients with the same variant can differ in age of onset and severity.[3,9]

### Pathophysiology

Three mechanisms explain the clinical picture:

1. **Impaired ketogenesis.** During fasting, the liver cannot produce ketone bodies, the brain and heart depend entirely on glucose, and hypoglycemia develops early and is severe.
2. **Accumulation of organic acids.** HMG-CoA and its metabolites (3-hydroxy-3-methylglutaric, 3-methylglutaconic, 3-methylglutaric, and 3-hydroxyisovaleric acids) cause metabolic acidosis and interfere with mitochondrial function.
3. **Secondary hyperammonemia and carnitine depletion.** Accumulated acyl-CoA species inhibit urea-cycle activity and are conjugated to carnitine and excreted, lowering free carnitine.[3]

## EPIDEMIOLOGY

HMGCLD is extremely rare, and its true incidence is unknown. Higher numbers of cases have been reported from Saudi Arabia, Portugal, Spain, and Brazil, which is consistent with founder variants and consanguinity.[3,8] Because newborn screening panels vary and the elevated C5-OH acylcarnitine marker is not specific, case ascertainment remains incomplete.

## CLINICAL PRESENTATION

In the largest published series, most patients presented within the first year of life, and a substantial proportion presented in the neonatal period.[9] Late-onset and asymptomatic cases have also been described.

**Acute decompensation** typically follows fasting, vomiting, diarrhea, or infection and may include:

- Vomiting, lethargy, hypotonia, and poor feeding
- Hypoketotic hypoglycemia
- Severe metabolic acidosis with an increased anion gap
- Hyperammonemia
- Hepatomegaly with elevated transaminases (Reye-like picture)
- Seizures, coma, and, if untreated, death[2,3,9]

**Chronic and extra-metabolic manifestations** reported in some patients include developmental delay, epilepsy, white-matter abnormalities on magnetic resonance imaging, pancreatitis, and cardiomyopathy or arrhythmia.[3,9] Neurological outcome appears to depend largely on the number and severity of hypoglycemic episodes and on the speed of treatment.

## DIAGNOSIS

Biochemical investigations

The typical laboratory findings are summarized in Table 1. Urinary organic acid analysis during a crisis is the key diagnostic test, and the pattern may be less pronounced between episodes.[3]

**Table 1: Typical biochemical findings in 3-hydroxy-3-methylglutaryl-coenzyme A lyase deficiency.**

| Investigation | Typical finding in HMGCLD |
|---|---|
| Blood glucose | Low during crisis |
| Blood/urine ketones | Absent or inappropriately low for the degree of hypoglycemia |
| Blood gas | Metabolic acidosis, high anion gap |
| Plasma ammonia | Often elevated |
| Liver enzymes | Elevated |
| Urine organic acids (GC-MS) | Increased 3-hydroxy-3-methylglutaric, 3-methylglutaconic, 3-methylglutaric, and 3-hydroxyisovaleric acids |
| Plasma acylcarnitines (MS/MS) | Elevated C5-OH and C6DC; low free carnitine |

*C5-OH, 3-hydroxyisovalerylcarnitine; C6DC, dicarboxylic hexanoylcarnitine (including 3-methylglutarylcarnitine); GC-MS, gas chromatography-mass spectrometry; HMGCLD, 3-hydroxy-3-methylglutaryl-coenzyme A lyase deficiency; MS/MS, tandem mass spectrometry.*

### Confirmatory testing

Diagnosis is confirmed by sequencing of *HMGCL* (with deletion/duplication analysis where needed) or by enzyme activity assay in fibroblasts or leukocytes.[3,7] Molecular confirmation also enables carrier testing and prenatal or preimplantation diagnosis.

### Newborn screening

Elevated 3-hydroxyisovalerylcarnitine (C5-OH) is the screening marker, but it is shared with several other disorders. Positive screens therefore require second-tier urine organic acid analysis and genetic testing.[3]

### Differential diagnosis

The main conditions to be distinguished from HMGCLD are listed in Table 2.

**Table 2: Differential diagnosis of 3-hydroxy-3-methylglutaryl-coenzyme A lyase deficiency.**

| Condition | Distinguishing features |
|---|---|
| **3-Methylcrotonyl-CoA carboxylase deficiency** | **Raised C5-OH and 3-hydroxyisovaleric acid; no 3-hydroxy-3-methylglutaric acid** |
| **Beta-ketothiolase deficiency** | Ketotic acidosis with 2-methylacetoacetate and **tiglylglycine** |
| HMG-CoA synthase **deficiency** | Hypoketotic hypoglycemia; no HMG-related organic acid excretion |
| Fatty acid oxidation disorders | Hypoketotic hypoglycemia with characteristic acylcarnitine profile |
| Multiple carboxylase deficiency | Broader organic aciduria; biotin responsive |
| Hyperinsulinism | Hypoglycemia with inappropriately high insulin; normal organic acids |

*C5-OH, 3-hydroxyisovalerylcarnitine; CoA, coenzyme A; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A.*

## MANAGEMENT

Management is based on expert opinion and case series. No randomized trials exist.[9,10]

### Acute metabolic decompensation

- **Stop fasting and give glucose early.** Start intravenous dextrose promptly to suppress lipolysis and reduce protein catabolism; the infusion rate should be titrated to maintain normoglycemia, following the metabolic center's protocol.
- **Correct acidosis.** Sodium bicarbonate may be required for severe acidosis; monitor

electrolytes and fluid status.

- **Treat hyperammonemia** according to organic acidemia protocols. Extracorporeal removal is reserved for severe cases not responding to medical therapy.[10]
- **Give L-carnitine** to replace depleted stores and promote excretion of organic acid conjugates.[3,9]
- **Look for and treat the trigger** (infection, dehydration, prolonged fasting).
- **Avoid** ketogenic regimens and prolonged fasting, because they are contraindicated in a disorder of ketogenesis.

**Long-term management**

The components of long-term care are summarized in Table 3. The degree of dietary protein restriction varies between centers, and over-restriction should be avoided because of its effect on growth.[3,9]

**Table 3: Components of long-term management.**

| Component | Principle |
|---|---|
| Dietary | Avoid fasting; frequent feeds; age-appropriate, moderately leucine-restricted (protein-controlled) diet; limit high-fat intake; slow-release carbohydrate at night in selected patients |
| Carnitine | Maintenance L-carnitine supplementation guided by plasma free carnitine |
| Sick-day plan | Written emergency protocol with early oral glucose/carbohydrate, and a low threshold for hospital admission and intravenous dextrose |
| Monitoring | Growth, developmental assessment, liver function, pancreatic enzymes if symptomatic, and cardiac assessment where indicated |
| Education | Caregiver training; emergency letter for health-care facilities |

**The clinical pharmacist's role**

- **Medication review** to avoid or minimize drugs that can precipitate decompensation or deplete carnitine (for example, valproate), and to check that any intravenous lipid in parenteral nutrition is appropriate.
- **Dose verification and compounding** of carnitine and other supportive therapy, and counseling on gastrointestinal adverse effects and adherence.
- **Sick-day protocol support**, including ensuring that caregivers have glucose sources, emergency contact numbers, and a written plan.
- **Interprofessional communication** between emergency, pediatric, nutrition, and metabolic teams.
- **Pharmacovigilance**: reporting of adverse drug reactions and medication errors in this

vulnerable population.

## PROGNOSIS

Outcome has improved with earlier diagnosis and structured prevention of fasting. In the published series, patients diagnosed early and managed with emergency plans tend to have better neurodevelopmental outcomes, whereas recurrent or prolonged hypoglycemia is associated with cognitive impairment and epilepsy.[3,9] Death during the first decompensation remains a risk in unrecognized cases.

## FUTURE DIRECTIONS

Priorities include international patient registries, standardized definitions of dietary and carnitine regimens, long-term neurological and cardiac outcome studies, and the use of genome sequencing in infants with unexplained hypoketotic hypoglycemia. Preclinical work using animal models may inform future gene-based or enzyme-based approaches, although no clinical therapy of this type is currently available.

## LIMITATIONS

This is a narrative review and is subject to selection bias. The literature consists mainly of case reports and small case series, and heterogeneity in reporting limits comparison between studies.

## CONCLUSION

HMGCLD is a rare but treatable disorder of ketogenesis and leucine catabolism. A high index of suspicion in infants with hypoketotic hypoglycemia and metabolic acidosis, rapid urine organic acid and acylcarnitine analysis, and early intravenous glucose are the foundations of care. Long-term outcomes depend on prevention of fasting, carnitine supplementation, structured emergency plans, and multidisciplinary follow-up in which the clinical pharmacist has a defined role.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## REFERENCES


1. Faull K, Bolton P, Halpern B, Hammond J, Danks DM. Patient with defect in leucine metabolism. N Engl J Med., 1976; 294(18): 1013.
2. Gibson KM, Breuer J, Nyhan WL. 3-Hydroxy-3-methylglutaryl-coenzyme A lyase deficiency: review of 18 reported patients. Eur J Pediatr, 1988; 148(3): 180-6.
3. Pié J, López-Viñas E, Puisac B, et al. Molecular genetics of HMG-CoA lyase deficiency. Mol Genet Metab, 2007; 92(3): 198-209.
4. Fukao T, Mitchell G, Sass JO, Hori T, Orii K, Aoyama Y. Ketone body metabolism and its defects. J Inherit Metab Dis., 2014; 37(4): 541-51.
5. Fu Z, Runquist JA, Forouhar F, et al. Crystal structure of human 3-hydroxy-3-methylglutaryl-CoA lyase: insights into catalysis and the molecular basis for hydroxymethylglutaric aciduria. J Biol Chem., 2006; 281(11): 7526-32.
6. Mitchell GA, Robert MF, Hruz PW, et al. 3-Hydroxy-3-methylglutaryl coenzyme A lyase (HL): cloning of human and chicken liver HL cDNAs and characterization of a mutation causing human HL deficiency. J Biol Chem., 1993; 268(6): 4376-81.
7. Menao S, López-Viñas E, Mir C, et al. Ten novel HMGCL mutations in 24 patients of different origin with 3-hydroxy-3-methyl-glutaric aciduria. Hum Mutat., 2009; 30(3): E520-E529.
8. Al-Sayed M, Imtiaz F, Alsmadi OA, et al. Mutations underlying 3-hydroxy-3-methylglutaryl CoA lyase deficiency in the Saudi population. BMC Med Genet, 2006; 7: 86.
9. Grünert SC, Schlatter SM, Schmitt RN, et al. 3-Hydroxy-3-methylglutaryl-coenzyme A lyase deficiency: clinical presentation and outcome in a series of 37 patients. Mol Genet Metab, 2017; 121(3): 206-15.
10. Baumgartner MR, Hörster F, Dionisi-Vici C, et al. Proposed guidelines for the diagnosis and management of methylmalonic and propionic acidemia. Orphanet J Rare Dis., 2014; 9: 130.