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Case Report

Critical sample collection delayed? Urine organic acid analysis can still save the day! A new case of HMG-CoA synthase deficiency

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ABSTRACT

Mitochondrial 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) synthase (mHS) deficiency is an autosomal recessive disorder of ketone body synthesis caused by biallelic pathogenic variants in *HMGCS2*. Clinical symptoms are precipitated by prolonged fasting and/or intercurrent illness with onset before the first year of life. Clinically, patients may present with hypo−/ non-ketotic hypoglycemia, metabolic acidosis, hyperammonemia, lethargy, hepatomegaly, and encephalopathy. During periods of decompensation, elevations of 4-hydroxy-6-methyl-2-pyrone (4-HMP), several hydroxylated hexanoic and hexenoic acid species, and medium-chain dicarboxylic acids in the absence of significant ketonuria may be observed in the urine organic acid profile. Abnormalities may also be observed in plasma which includes elevated acetylcarnitine (C2) and 3-hydroxybutyryl/3-hydroxyisobutyryl (C4-OH) carnitine.

We report a patient who presented to the ED at 13 months of age with an undetectable point-of-care blood glucose level. Continuous infusion of dextrose-containing intravenous (IV) fluids were required to correct the hypoglycemia and routine chemistries were notable for an anion gap metabolic acidosis, transaminasemia, and elevated creatine kinase and lactate dehydrogenase. Urine and blood ketones were undetectable. Qualitative assessment of urine organic acids collected ~46 and ~ 99 h post-admission were significant for mild elevations of 4-HMP and hydroxy-hexanoic and hydroxy-hexenoic acid species with a notable absence of ketones. Previously, biochemical abnormalities in urine have been shown to normalize in as few as 27 h after treatment giving providers a narrow window with which to obtain a critical sample. Direct communication of laboratory findings to the ordering provider guided the molecular testing and assisted in results interpretation to confirm the molecular diagnosis.

Our case emphasizes the importance of collecting samples for biochemical analysis even if the critical period has been missed and acute metabolic decompensation seems to be resolved, as residual abnormalities observed in our patient greatly narrowed the differential diagnosis.

1. Introduction

Mitochondrial 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) synthase (mHS) deficiency (OMIM: 605911) is a disorder of ketone body synthesis caused by biallelic pathogenic variants in *HMGCS2*. mHS catalyzes the conversion of acetoacetyl-CoA and acetyl-CoA into HMG-CoA, a precursor to ketone bodies acetoacetate and 3-hydroxybutyrate. Enzymatic deficiency of mHS results in impaired ketone production and consequently clinical manifestations arise during episodes of prolonged fasting or illness.

The clinical presentation of mHS deficiency is characterized by episodes of hypoketotic hypoglycemia and metabolic acidosis. Diagnosis is often delayed due to non-specific symptoms. Seizure-like activity, or even coma have been observed [1,2]. If fasting is avoided, the prognosis is excellent, with intact development and normal life expectancy [3].

Laboratory findings may include metabolic acidosis, transaminitis,

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increased creatine kinase, absent (or low) ketones, and hypoglycemia. Urine organic acid profiles may show a characteristic pattern of dicarboxylic aciduria, and elevations of 4-hydroxy-6-methyl-2-pyrone (4-HMP), trans-3-hydroxyhex-4-enoic, trans-5-hydroxyhex-2-enoic, 3,5-dihydroxyhexanoic 1,5 lactone, 5-hydroxy-3-ketohexanoic, 3-hydroxy-5-ketohexanoic, and 3,5-dihydroxyhexanoic [4,5]. Acylcarnitine profile has been reported to be normal in a several cases [1,6–10]; however, there have also been reports of elevated acetylcarnitine (C2), and/or 3-hydroxybutyryl/3-hydroxyisobutyryl (C4-OH) carnitine, with reduced free carnitine (C0) [11]. Furthermore, biochemical abnormalities in the urine organic acid profile have been shown to normalize in as few as 27 h with treatment and remain normal during patient recovery [4], giving providers a narrow window with which to obtain a critical sample.

In this case report, we describe the clinical presentation of a patient with a new diagnosis of mHS deficiency, later confirmed with molecular testing, and describe how the results of urine organic acid analysis guided the clinical work-up. Furthermore, we document persistent abnormalities in the urine organic acid profile up to 99 h after the first blood sample demonstrating hypoglycemia was obtained.

2. Methods

Review of the patient's medical record and clinical parameters was performed by the clinical team.

Urinary creatinine, urinary organic acid analysis, plasma acylcarnitine analysis, and plasma free and total carnitine analysis was performed by Duke University Health System's CLIA/CAP certified Biochemical Genetics Laboratory according to standard operating procedures.

Creatinine analysis was performed by alkaline picrate (Jaffe reaction) method. For the preparation of urine organic acids, a 2 mL volume of urine diluted to a fixed creatinine concentration of 1 mmol/L was spiked with undecanoic acid ($C_{11}H_{24}$) internal standard, derivatized at pH 8 using ethoxyamine hydrochloride and exhaustively extracted in ethyl acetate at pH 1. The ethyl acetate layer was removed, evaporated under a gentle stream of nitrogen, and tetracosane ($C_{24}H_{50}$) external standard was added before the final trimethylsilylation derivatization step using a mixture of *N*,*O*-bis(trimethylsilyl)-trifluoroacetamide and pyrimidine.

A Thermo Scientific TRACE ISQ LT/QD GC–MS system fitted with an Rxi-1 ms column 30 m DB-1 column (Restek), internal diameter 0.25 mm, film thickness 1.0 μm. One μL of derivatized extract was injected using a split ratio of 1:10 with initial temperature at 120 °C for 6 min, ramped at 8 °C/min to 300 °C, and then ramped at 10 °C to 315 °C at a carrier gas of 1.2 mL/min constant flow. The mass spectrometer operated in full scan mode from mass to charge 50 to 550. Peak identification was performed by spectral analysis.

Plasma acylcarnitine analysis was performed by flow injection analysis (FIA) of methyl-ester derivatives. In brief, a deuterated internal standard mixture and methanol were added to a fixed volume of plasma, mixed and centrifuged. An aliquot of the supernatant was filtered, dried under nitrogen stream, and derivatized at 50 °C for 15 min using methanolic HCl 3 N. Finally, samples were dried, reconstituted with a solvent matrix, and injected into the mass spectrometer (Waters Acquity-TQD coupled to an Acquity UPLC) for analysis. Acylcarnitine methyl ester derivatives were detected using a precursor-ion scan of *m/z* 99 from m/z 200 to 500.

Plasma free and total carnitine analysis was performed using two aliquots of the plasma sample, according to a published method [12]. Genetic testing for a Fatty Acid Oxidation Defects Panel consisting of 25 genes (Supplemental Table 1) was performed by Invitae®. Analysis of HMGCS2 included sequencing analysis of all coding regions with a mean coverage depth of 350× and up to 20 base pairs into the adjacent introns, as well as deletion/duplication analysis of coding regions.

3. Case report

3.1. Clinical presentation

The patient is a female of Vietnamese descent, who presented at 13 months of age with lethargy in the settings of acute gastroenteritis accompanied by a four-day history of decreased oral intake, vomiting and diarrhea. In the Emergency Department (ED), a seizure-like episode was witnessed. Her point-of-care blood glucose level was undetectable. She returned to her baseline following a 10% dextrose bolus, yet experienced a second hypoglycemic seizure-like episode a couple hours later due to blood glucose of <20 mg/dL (reference range: 70–99 mg/dL). Her hypoglycemia improved with the continuous infusion of dextrose-containing intravenous (IV) fluids (initially 5%, then 10%, Fig. 1). Routine chemistries, collected during the initial hypoglycemic event are shown in Table 1 and were notable for an anion gap metabolic acidosis and transaminitis, with elevations of creatine kinase and lactate dehydrogenase. A complete blood count showed findings suggestive of inflammation and the patient was found to be positive for both coronavirus HKU1 and astrovirus. Urine and blood ketones were undetectable. Lipid panel, total bilirubin, alkaline phosphatase, albumin, and uric acid were within the reference range.

Over the course of several days, her symptoms gradually improved. The IV fluids were weaned slowly, and after demonstrating the ability to tolerate overnight fasts with blood sugar levels sustained above 70 mg/dL, she was discharged home with the plan for close outpatient follow-up.

Our patient's prior medical history was non-contributory; however, the family history was notable for distant consanguinity as parents are third cousins (Fig. 2). The results of the state newborn metabolic screen were normal and she passed the newborn hearing screen. Her growth parameters have been normal, with weight between 30 and 40%, length approximately 20–40%, and head circumference at 60th–70th percentiles. There was no prior history of hypoglycemia, perinatal distress, or neonatal intensive care unit stay.

Plasma acylcarnitine profile, plasma free and total carnitine, and urine organic acids were collected and a fatty acid oxidation gene panel were referred for testing approximately 37 h after the last documented hypoglycemic event.

3.2. Laboratory findings

Qualitative assessment of a urine organic acid profile collected on day 2 of admission showed mild elevations of 4-HMP, several hydroxyhexanoic and hydroxy-hexenoic acid species (3-hydroxy-4-hexenoate, 3,5-dihydroxyhexanoic 1,5 lactone, 5-hydroxy-2-hexenoate, and 3-hydroxyhexanoate), and medium-chain dicarboxylic acids (adipic, suberic, sebacic, and 3-hydroxydecanedioic acids), with a notable absence of ketones (Fig. 3). Semi-quantitative analysis of plasma acylcarnitines showed mild elevations of C2, C4-OH, hexadecenoylcarnitine (C16:1), and oleoylcarnitine (C18:1; Supplemental Table 2). Plasma total carnitine concentration measured within the normal reference range; however, the free carnitine (C0) concentration was decreased and an increase in the acyl to free ratio was observed (Supplemental Table 3). Urine organic acid analysis was performed on a repeat specimen collected just prior to discharge, four days after resolution of the patient's hypoglycemia and clinical symptoms, which continued to show mild elevations of 4-HMP, 3-hydroxy-4-hexenoate, 3,5-dihydroxyhexanoic lactone, 5-hydroxy-2-hexenoate, and 3-hydroxydecanedioic acids, without elevation of ketones.

A targeted gene panel for fatty acid oxidation defects with full coverage of *HMGCS2* identified two heterozygous pathogenic variants previously reported, c.1394del; p.Asn465Thrfs*10 (ClinVar accession VCV001327465.5) and c.1502G > C; p.Arg501Pro (ClinVar accession SCV001189983), confirming the diagnosis of autosomal recessive mHS deficiency.

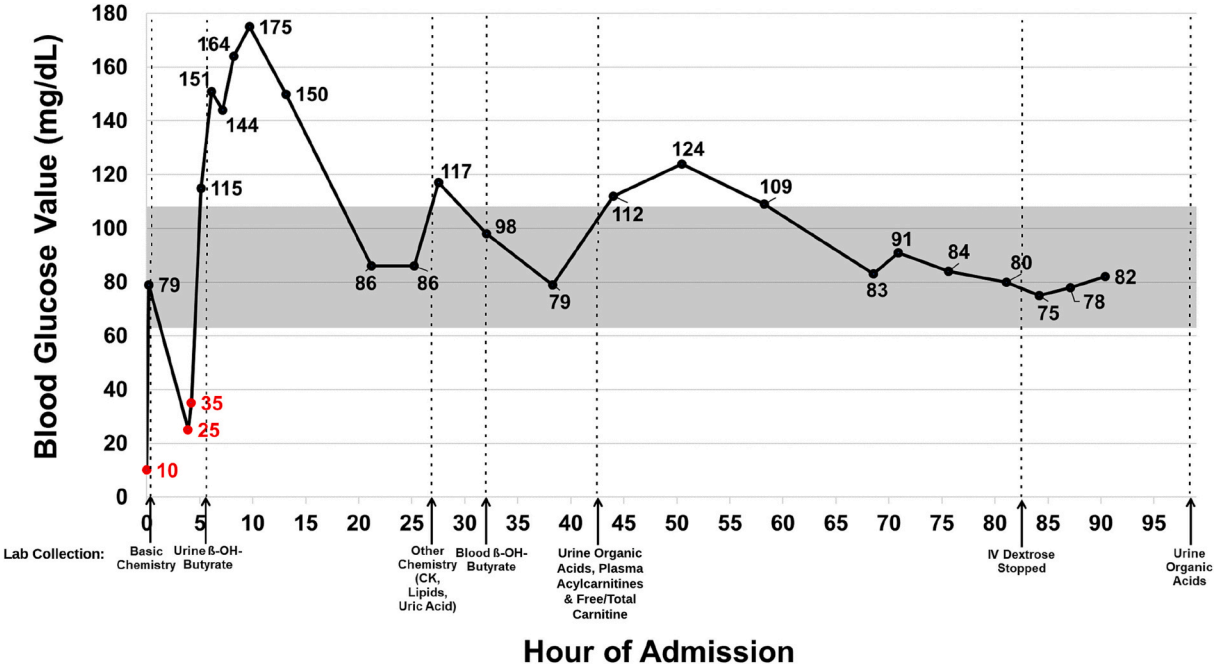

Fig. 1. Capillary blood glucose trend. Shaded grey region denotes the capillary blood glucose normal reference range. Vertical dashed lines denote collection of laboratory samples.

Table 1
Baseline laboratory findings.

Laboratory	Result	Status	Reference Range	Collection (hours after admission)
Absolute neutrophil count	12.2 K/μL	Elevated	1.5–8.5 K/μL	0.25
Carbon dioxide	16 mmol/L	Normal	22–32 mmol/L	
Anion gap	19	Elevated	5–15	
Potassium	3.9 mEq/L	Normal	3.5–5.1 mEq/L	
Sodium	131 mmol/L	Low	135–145 mmol/L	
Albumin	4.7 g/dL	Normal	3.5–5.0 g/dL	
Aspartate aminotransferase	238 U/L	Elevated	15–41 U/L	
Alanine transaminase	143 U/L	Elevated	0–44 U/L	
White blood count	21.3 K/μL	Elevated	6.0–14.0 K/μL	
Platelet count	635 K/μL	Elevated	150–575 K/μL	
C-reactive protein	0.7 mg/dL	Normal	<1.0 mg/dL	
Urine ketones	Negative		Negative	5.1
Creatine kinase	350 U/L	Elevated	38–234 U/L	27.5
Lactate dehydrogenase	545 U/L	Elevated	98–192 U/L	
Total cholesterol	110 mg/dL	Normal	0–169 mg/dL	
Triglycerides	79 mg/dL	Normal	<150 mg/dL	
Uric acid	3.5 mg/dL	Normal	2.5–7.1 mg/dL	
Beta-Hydroxybutyric acid	0.09 mmol/L	Low normal	0.05–0.27 mmol/L	32
Urine organic acids	Abnormalities consistent with mHS deficiency			46
Urine organic acids	Abnormalities consistent with mHS deficiency			99

4. Discussion

We describe the clinical presentation and diagnostic work-up of a patient with mHS deficiency and highlight the importance of urine organic acid analysis in the diagnosis of mHS, even when collected after the resolution of hypoglycemia. We also emphasize the persistent, albeit mild, elevations of 4-HMP and hydroxylated hexa(*e*)noic acids in samples collected in the post-recovery period. As these metabolites may be elevated secondary to ketosis, we emphasize the importance of recognizing the potential significance of mild elevations in the absence of ketones. Careful examination of the organic acid profile and correlation with the clinical history was critical in understanding the relevance of these mild abnormalities and guided the interpretation of the fatty acid oxidation defects gene sequencing panel.

This case report presents a patient with metabolic decompensation that developed in the setting of diminished oral intake associated with acute viral gastrointestinal illness. This presentation is typically associated with ketosis; however, in mHS deficiency, ketone body production is compromised. Moreover, on the contrary to persistent hypoglycemia observed in hyperinsulinism and accelerated development of hypoglycemia observed in other inborn errors of metabolism, such as glycogen storage disorders or fatty acid oxidation disorders, in mHS deficiency hypoglycemia develops predominantly in the setting of significantly prolonged fasting, as glycolysis and gluconeogenesis are not impaired [13]. Given the undisrupted beta-oxidation of fatty acids, metabolites of fatty acid oxidation can accumulate.

Obtaining a critical sample (i.e. collection of the specimens at the time of presentation, prior to initiation of treatment) is recommended and highly valued during the diagnostic work-up of patients presenting with hypoglycemia [13,14]; however, it is often deferred when profound hypoglycemia is unexpected and requires immediate management, as occurred in our patient. Whenever possible, it is recommended to collect a critical sample when the serum blood glucose is below 50 mg/dL, as metabolic derangements are usually most pronounced in the presence of hypoglycemia. Besides the blood glucose, critical sample specimens often include serum bicarbonate, insulin, c-peptide, beta-hydroxybutyrate, lactate, cortisol, growth hormone, free fatty acids, ammonia, urine organic acids, free and total carnitine, and an

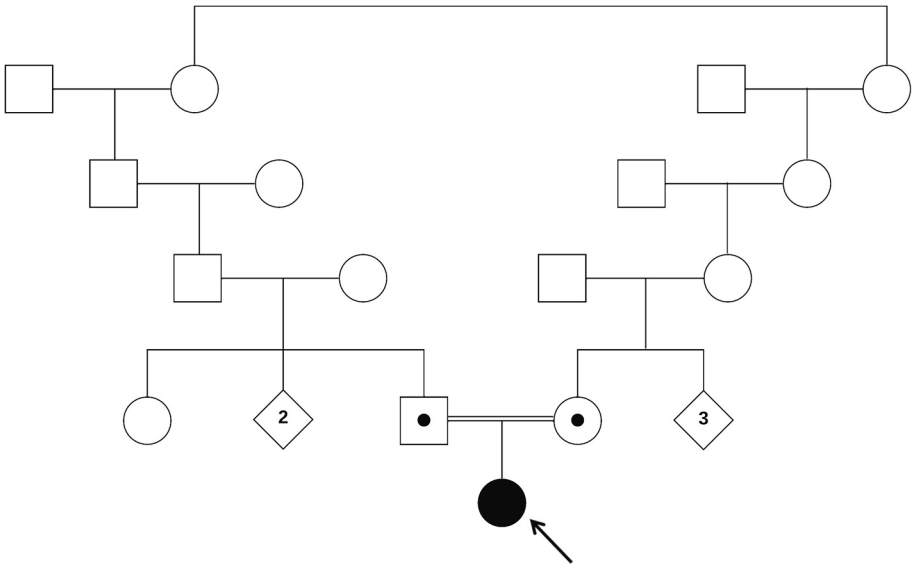

Fig. 2. Family pedigree with mHS deficiency. The arrow indicates the proband. Filled in symbols represent affected individuals.

acylcarnitine profile. Even though samples for organic acid analysis, acylcarnitine analysis, and free and total carnitine analysis were not collected during our patient's hypoglycemic events (Table 2), abnormalities were still noted which allowed for differentiation of mHS from other disorders of ketone synthesis, such as 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) lyase deficiency. In contrast to previously published reports, which document normalization of urine organic acids as soon as 27 h after treatment [4], our patient displayed persistent elevations of 4-HMP and hydroxylated hexa(*e*)noic acids up to 99 h after the first documented hypoglycemic event, even though blood glucose concentrations had normalized within the first five hours of dextrose-containing IV fluids, and remained within the normal ranges throughout the rest of the admission. The persistent elevation of 4-HMP has also been documented in another patient at a 1 year follow-up [15]. Furthermore, in contrast to published findings, triglycerides measured within the normal reference range in our patient and glutaric acid was not detected in the urine organic acid profiles [2].

As previously mentioned, patients with mHS deficiency typically have a normal acylcarnitine profile; however, low free carnitine and elevations of C2, C4-OH, and the C2/C0 ratio have been reported [2,10,16]. In addition to elevated C2 and C4-OH in our patient, elevated C16:1 and C18:1 were also observed without an elevation of the C2/C0 ratio. Elevations of C2 and C4-OH, with or without increased long-chain species, can be observed secondary to ketosis; however, our patient was non-ketotic and these analytes may be elevated secondary to the prolonged fasting duration. While these mild abnormalities in plasma are not observed in all patients with mHS deficiency, they should raise concern if associated with a clinical presentation compatible with mHS deficiency [2,17]. One possibility for the origin of these ketotic markers in the plasma acylcarnitine profile is that alternative sources of ketones is mobilized in mHS deficiency, such as those derived from leucine and isoleucine metabolism [4]. Another possibility is that only one of the two D/L 3-hydroxybutyrylcarnitine isomers may be affected. Considering the methodology for acylcarnitine analysis employed by our laboratory does not involve the use of a column to separate isomers, it is possible that only one of the isomers is detected, thus leading to a profile similar to ketosis. It has been suggested that the use of ratios (plasma D-3-hydroxybutyrate/free fatty acid or urine D-3-hydroxybutyrate/adipic acid) may provide a more accurate measurement of ketosis and aid in the diagnosis of mHS deficiency [4].

The history of distant consanguinity in our patient raised the suspicion of an inborn error of metabolism; however, results of genetic testing surprisingly revealed two heterozygous pathogenic variants in *HMCS2* gene. The c.1394del; p.Asn465Thrfs*10 variant has been previously reported in a female patient of Chinese descent [5] and the c.1502G > C; p.Arg501Pro pathogenic variant has been previously reported in three patients of Chinese/Thai descent [18,19]. This case highlights that urine organic acid findings were helpful in making the diagnosis and guiding the patient management and molecular diagnosis by allowing for a targeted gene panel as opposed to exome sequencing. These findings, combined with results of genetic testing, provided an explanation for the patient's clinical presentation.

At the time of discharge, recommendations included avoidance of fasting, maintenance of a well-balanced diet, and periodic glucose monitoring via a prescribed point-of-care blood glucose monitoring kit (especially when symptomatic or at the time of illness). The family was provided with an emergency letter outlining the management and care in case of the recurrence of hypoglycemia. Six months post-discharge, she is thriving with no further episodes of hypoglycemia documented. Her development is normal.

5. Conclusion

The presented case highlights the importance of communication between the providers and laboratory team. The clinical history, including the fact that the patient continued middle-of-the-night feeds, and this episode represented the first prolonged fast experienced by the patient, in addition to the associated nonketotic hypoglycemia, provided the crucial insight into the interpretation of the biochemical laboratory findings. On the other hand, suspicion of mHS raised through biochemical testing, and direct communication with the providers, guided the molecular confirmatory testing initiated by the clinical team.

Moreover, our case stresses the importance of collecting samples for biochemical analysis even if the critical period has been missed and acute metabolic decompensation seems to be resolved, as residual abnormalities greatly narrowed the differential diagnosis in our patient.

CRediT authorship contribution statement

Monika Williams: Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Conceptualization. **Iskren Menkovic:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Pamela Reitnauer:** Writing – review & editing, Investigation. **Eileen Gilbert:** Writing – review & editing, Formal analysis. **Dwight**

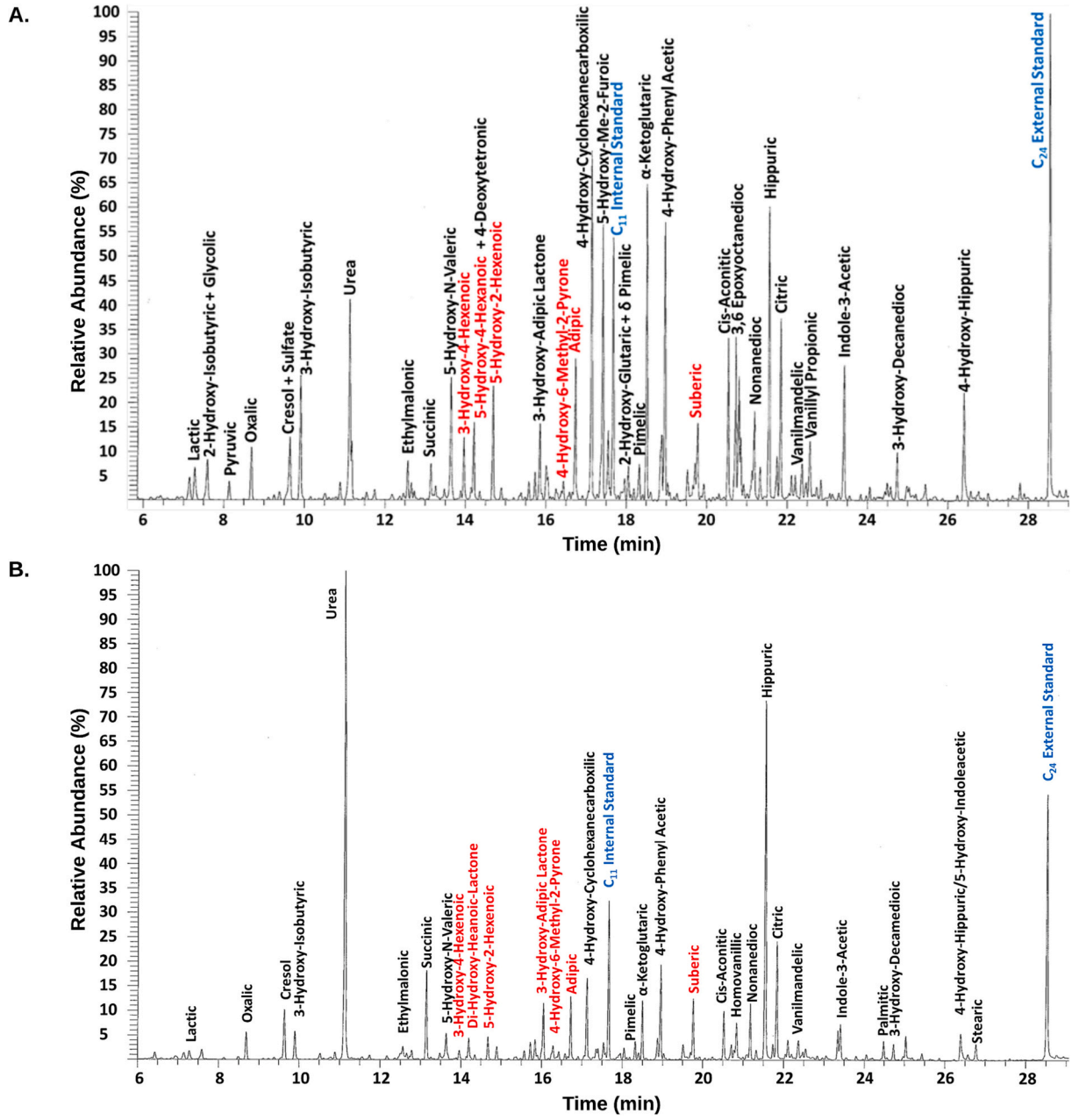

Fig. 3. (A) Total ion chromatogram of urine organic acids collected approximately 46 h and; (B) a repeat urine collected at 99 h after the presentation of a severe hypoglycemic event. Metabolites in red were previously reported in patients diagnosed with mHS deficiency (Table 2) [4]. Internal and external standards are indicated in blue.

Table 2
Previously reported organic acid abnormalities [4] identified in our patient.

Metabolite	46 h	99 h
3-Hydroxy-4-hexenoic acid	+	+
3,5-Dihydroxyhexanoic 1,5 lactone*	+	+
5-Hydroxy-2-hexenoic acid	+	+
4-Hydroxy-6-methyl-2-pyrone	+	+
5-Hydroxy-3-ketohexanoic acid	–	–
3-Hydroxy-5-ketohexanoic acid	–	–
3,5-Dihydroxyhexanoic acid*	–	–
cis-5-Hydroxyhex-2-enoic acid	–	–

* 2 peaks.

Koeberl: Writing – review & editing. **Sarah P. Young:** Writing – review & editing, Visualization, Supervision, Conceptualization. **Ashlee R. Stiles:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Conceptualization.

Declaration of competing interest

None.

Data availability

The authors do not have permission to share data.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgmr.2024.101062.

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