BMC Pediatrics

CASE REPORT

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Methylmalonic acidemia with recurrent hemophagocytic lymphohistiocytosis: a case report and review of the literature

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Abstract

Background Methylmalonic acidemia is a rare autosomal recessive disorder of propionate catabolism characterized by the accumulation of propionic acid and methylmalonic acid caused by methylmalonyl-CoA mutase deficiency. Clinical presentations range from acute deterioration in the neonatal period to later onset with a heterogeneous clinical course. Metabolite accumulation results in systemic involvement, affecting the nervous, gastrointestinal, and renal system functions and causing cardiomyopathy. Bone marrow dysfunction manifesting as neutropenia and anemia is a common hematological finding. Although rare, three cases of secondary hemophagocytosis were documented.

Case presentation An 18-year-old male patient diagnosed with methylmalonic acidemia presented with vomiting and altered mental status. He had a medical history of presumably hemophagocytic lymphohistiocytosis (HLH) at the age of 17 months. Physical examination, laboratory tests, and bone marrow aspiration results met the HLH-2004 diagnostic criteria, confirming a recurrent HLH. Although he recovered after intensive treatment, his cognitive function declined. Retrospective analysis revealed higher serum levels of ferritin during acute decompensations compared with nonattack periods. Correlation analysis revealed a strong relationship between serum ferritin and propionylcarnitine, one of the major propionyl-CoA-derived metabolites.

Conclusions HLH is a rare and underrecognized hematologic emergency in methylmalonic acidemia, and its early diagnosis and treatment are critical. Serum ferritin may be a useful clinical biomarker in the diagnosis of HLH-associated attacks in methylmalonic acidemia.

Keywords Methylmalonic acidemia, Secondary hemophagocytic lymphohistiocytosis, Metabolic attack, Ferritin

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Background

Methylmalonic acidemia is an autosomal recessive disorder of propionate catabolism, characterized by the accumulation of branched-chain amino acid metabolites such as propionylcarnitine (C3), 3-hydroxypropionic acid (3-OH-PA), methylcitric acid (MCA), and methylmalonic acid (MMA) in the plasma, urine, and other body fluids (Fig. 1). Isolated methylmalonic acidemia refers to the presence of excess MMA without homocysteine elevation, which is caused primarily by complete or partial deficiency of the enzyme methylmalonyl-CoA mutase (MUT) encoded by *MUT*. Other probable causes include a defect in the transport or synthesis of its cofactor, 5-deoxy-adenosyl-cobalamin, and deficiency of the enzyme methylmalonyl-CoA epimerase. The global incidence is believed to be 1:50,000 for isolated cases, whereas in Japan, the result of neonatal screening by tandem mass spectrometry revealed 1:120,000 [1]. Patients may present either shortly after birth with acute deterioration, metabolic acidosis, and hyperammonemia or later at any age with diverse clinical manifestations. Severe presentations can result in early mortality or progressive neurological comorbidities. Hematological abnormalities such as anemia, leukopenia, and thrombocytopenia are well-known complications of methylmalonic acidemia [2]. However, data on the development of hemophagocytic lymphohistiocytosis (HLH) in these patients are scarce [3, 4].

HLH is a rare but potentially fatal disease characterized by the proliferation and infiltration of over-activated macrophages and T-lymphocytes [5]. It is classified into primary and secondary forms according to etiologic difference. Primary HLH is an autosomal recessive disorder that affects infants and young children, with a classical onset within the first year of life. Causes of secondary HLH include severe infections, malignancies, rheumatologic disorders, and immune deficiency [5]. In rare cases, inborn errors of metabolism have also been implicated in secondary HLH. However, how the metabolites trigger HLH in inborn errors of metabolism is unclear. Herein, we present the case of a patient with methylmalonic acidemia who developed recurrent HLH complicated by metabolic attacks.

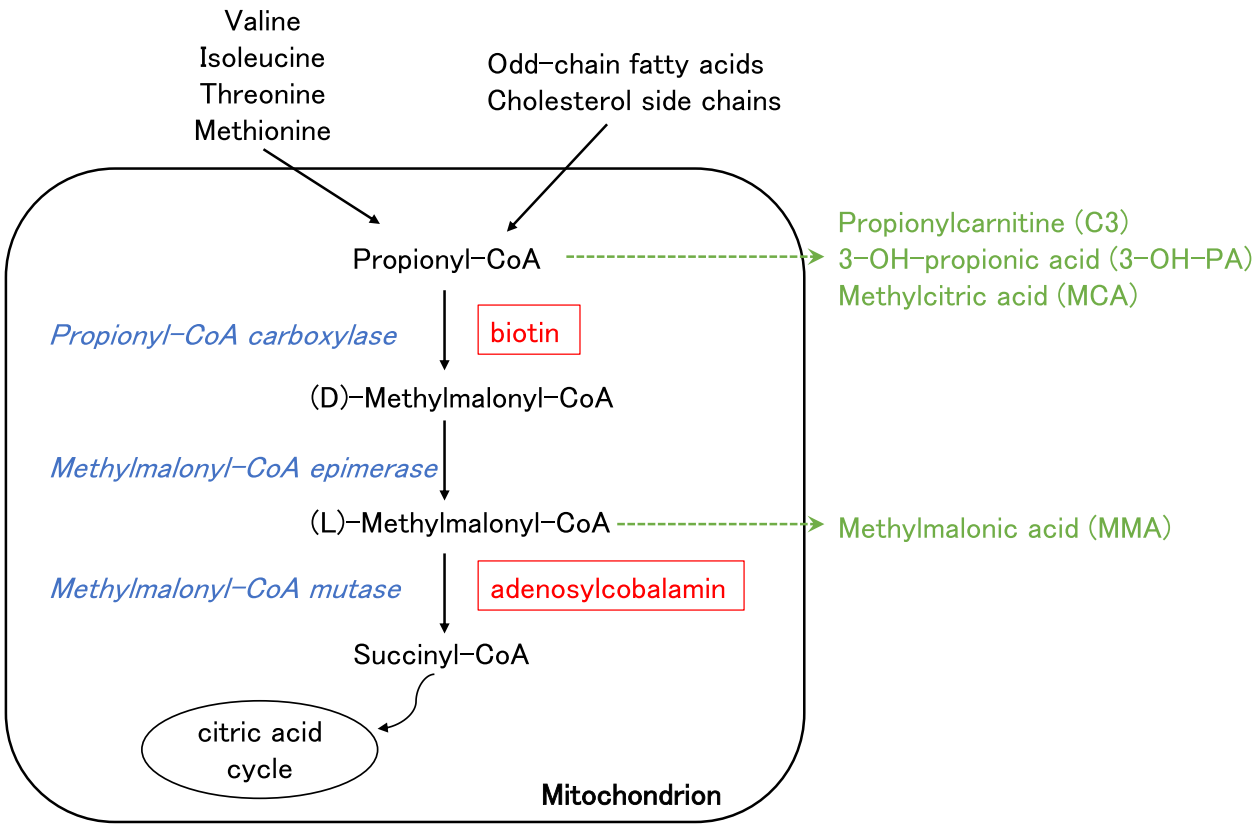

Fig. 1 Summarized pathways involving methylmalonic acidemia metabolism. A scheme showing the metabolic pathways involved in the mitochondrion. Enzymes are shown in blue characters. Boxes indicate the necessary cofactors in the metabolism. Metabolic products are shown in green characters

Case presentation

An 18-year-old male patient was born to healthy, nonconsanguineous parents. Pregnancy and delivery were uneventful. His birth weight, height, and head circumference were 3,020 g (+0.10 SD), 51.0 cm (+1.2 SD), and 32.0 cm (−0.80 SD), respectively. At the age of 17 months, he was referred to our hospital because of recurrent vomiting and altered consciousness. The urinary mass spectrometry analysis on organic acid metabolism using gas chromatography-mass spectrometry (GC–MS) detected increased excretions of MMA (23.03 mmol/molCr, +2.3 SD of normal controls), MCA (113 mmol/molCr, +7.7 SD), 3-OH-PA (29.3 mmol/molCr, +8.3 SD), and 3-OH-butyric acid (950 mmol/molCr, +7.1 SD). Acylcarnitine profile analysis detected increased levels of C3 (12.82 nmol/ml, reference values: < 3.5 nmol/ml) and C3/C2 (0.6, reference values: < 0.25, C2: acetylcarnitine). Plasma amino acid analysis did not reveal perturbed values of glycine, methionine, or homocysteine.

Subcutaneous injection of vitamin B12 for 5 consecutive days did not decrease the MMA level. Intracranial magnetic resonance imaging (MRI) detected T2 hyperintense signals over the bilateral basal ganglia. Accordingly, he was clinically diagnosed with vitamin B12 nonresponsive methylmalonic acidemia. He also presented with fever, pancytopenia (hemoglobin, 8.7 g/dL; leukocyte count, 2050 /μL; and platelet count, 35,000 /μL), hypertriglyceridemia (384 mg/dL), hypofibrinogenemia (60 mg/dL), and hemophagocytosis in the bone marrow. Ferritin, natural killer cell activity, and soluble interleukin-2 receptor (sIL-2R) data were unavailable. He received intravenous immunoglobulin and frequent blood transfusions for the suspicion of HLH and hematological abnormalities. His condition improved after treatment, and he was discharged 6 months later. After the initial acute decompensation with presumed HLH, management with standard therapy (low-protein diet, L-carnitine, and vitamin supplementation) led to a relatively good clinical course with limited acute attacks for 16 years. At the age of 9, he underwent gastrostomy to enable him to receive the strict dietary therapy for methylmalonic acidemia, because he developed feeding difficulties during occasional sick days. He was diagnosed with intellectual disability (IQ 46) and autism spectrum disorder according to the DSM-5 diagnostic criteria. With parental consent, targeted sequencing with the Sanger method in whole exons and introns (splice site) of *MUT* identified the heterozygous variants, namely, a splice donor variant (NM_000255.4: c.385+5G>A, Chr6: 49459077 on Assembly GRCh37) and a nonsense variant (NM_000255.4: c.1481T>A, p.Leu494Ter, Chr6: 49415462 on Assembly GRCh37). We could not validate the compound heterozygous mutations because parental consent of their analysis of *MUT* was not obtained. These variants were assumed to have the pathogenicity because these were two of the five most frequent variants in Japanese populations with isolated methylmalonic acidemia and presumed to result in the loss of function of *MUT* [6]. Although liver transplantation was discussed, parental consent was not obtained.

At the age of 18, despite adhering to the management with standard therapy, he was admitted for vomiting and altered consciousness. Laboratory tests revealed metabolic acidosis (pH 7.23, HCO_3^- 7.1 mmol/L, BE −18.1 mmol/L, anion gap 28.7 mmol/L), high transaminase levels, and hyperammonemia. Treatment for metabolic attack was commenced, including fluids, carnitine, and bicarbonate replacement in the intensive care setting. He had a fever and generalized erythema on day 3, and examination revealed high C-reactive protein levels, elongated prothrombin time, and activated partial thromboplastin time. Suspecting infection-associated disseminated intravascular coagulation, antibiotics and fresh-frozen plasma were administered. Fever persisted on day 6, and prominent bicytopenia [hemoglobin, 5.9 g/dL; leukocyte, 4,710 /μL (neutrophils, 68.4%); platelet 2,500 /μL) was observed. Other laboratory abnormalities included high levels of ferritin (2,293 ng/mL), interleukin-18 (1,709 pg/mL), and sIL-2R (1,720 U/mL) and a low level of natural killer cell activity (2.9%). Bone marrow aspiration revealed an increase in lipid-laden macrophages and hemophagocytosis (Fig. 2a). Thus, he was diagnosed with HLH after fulfilling six of the eight diagnostic criteria, and his clinical symptoms and laboratory data gradually improved after intravenous immunoglobulin and methylprednisolone pulse therapy. He had epilepsy during treatment and his seizures did not recur after the administration of oral levetiracetam at standard dose. His head MRI showed the progression of brain atrophy (Fig. 2b). Serum ferritin levels remained high and did not return to normal after recovering from HLH. Eight months after discharge, he had numerous acute decompensations without HLH development (Fig. 3). Cognitive function declined from an intelligence quotient of 46 (age 15) to 34 (age 19).

To examine the usefulness of biomarkers in predicting metabolic attacks, serum ferritin and metabolites of methylmalonic acidemia were analyzed retrospectively. Serum ferritin levels were higher during metabolic attacks (median, 953 ng/mL; interquartile range, 781–1,354) than during nonmetabolic events (median, 642 ng/mL; interquartile range, 39–748) (Fig. 4a). However, the chi-squared test did not show a significant difference. Pearson's correlation analysis revealed a high correlation between C3 (also known as propionylcarnitine) and ferritin ($r=0.96$) and between 3-OH-PA and MMA ($r=0.94$)

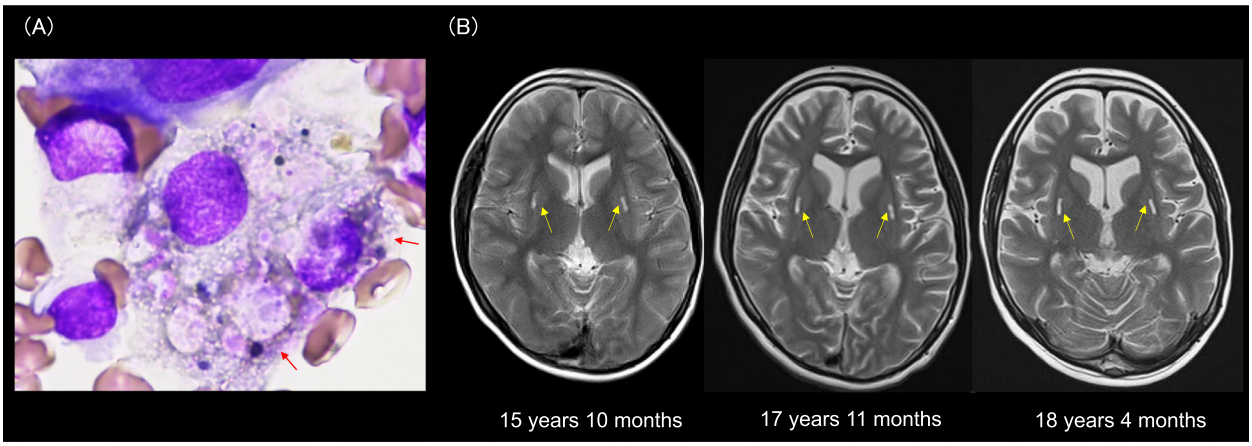

Fig. 2 Microscopic evaluation and neuroimaging. **a** Light microscopic image of bone marrow aspiration shows lipid-laden macrophages and hemophagocytosis of neutrophils (arrows). **b** Temporal changes in the axial T2-weighted image showing the progression of brain atrophy. Arrows indicate symmetric hyperintensities in the bilateral globus pallidus

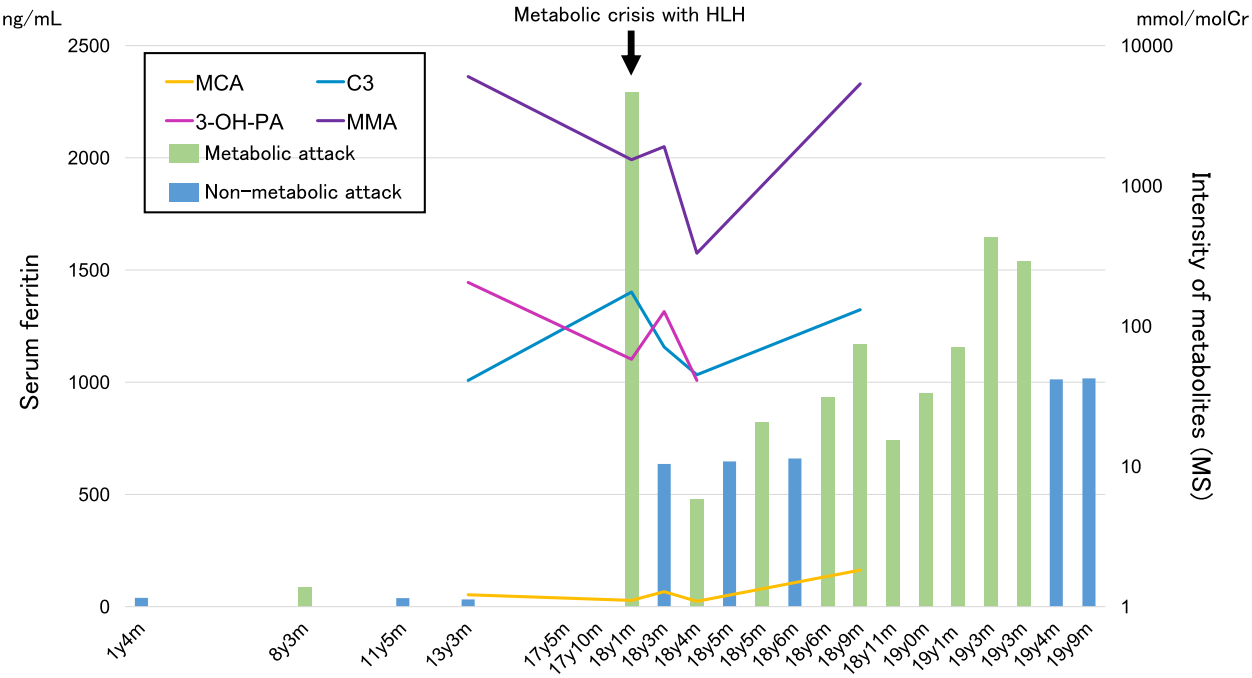

Fig. 3 Clinical course and trend of serum ferritin levels. Green bars indicate the values of serum ferritin obtained during metabolic attacks, and blue bars represent the serum ferritin during nonattacks. The highest value was obtained during acute decompensation complicated by hemophagocytic lymphohistiocytosis (arrow). Line graphs show the value of metabolites concurrently obtained. Abbreviations: 3-OH-PA, 3-hydroxypropionic acid; C3, propionylcarnitine; HLH, hemophagocytic lymphohistiocytosis; MCA, methylcitric acid; MMA, methylmalonic acid; MS, mass spectrometry

(Fig. 4b). Statistical analyses were conducted using R (ver 4.3.2; https://cran.r-project.org/).

Discussion and conclusions

Herein, we report the first case of methylmalonic acidemia in a patient with recurrent HLH complicated by acute metabolic decompensations (Table 1). Early recognition and treatment of HLH lead to his recovery. The diagnosis of HLH is established by meeting more than five of the eight criteria, including fever; splenomegaly; cytopenias in ≧2 cell lineages; hypertriglyceridemia (> 265 mg/dL) and/or hypofibrinogenemia (< 150 mg/dL), hyperferritinemia (> 500 ng/mL); high sIL-2R levels (> 2,400 U/mL or higher than laboratory-defined

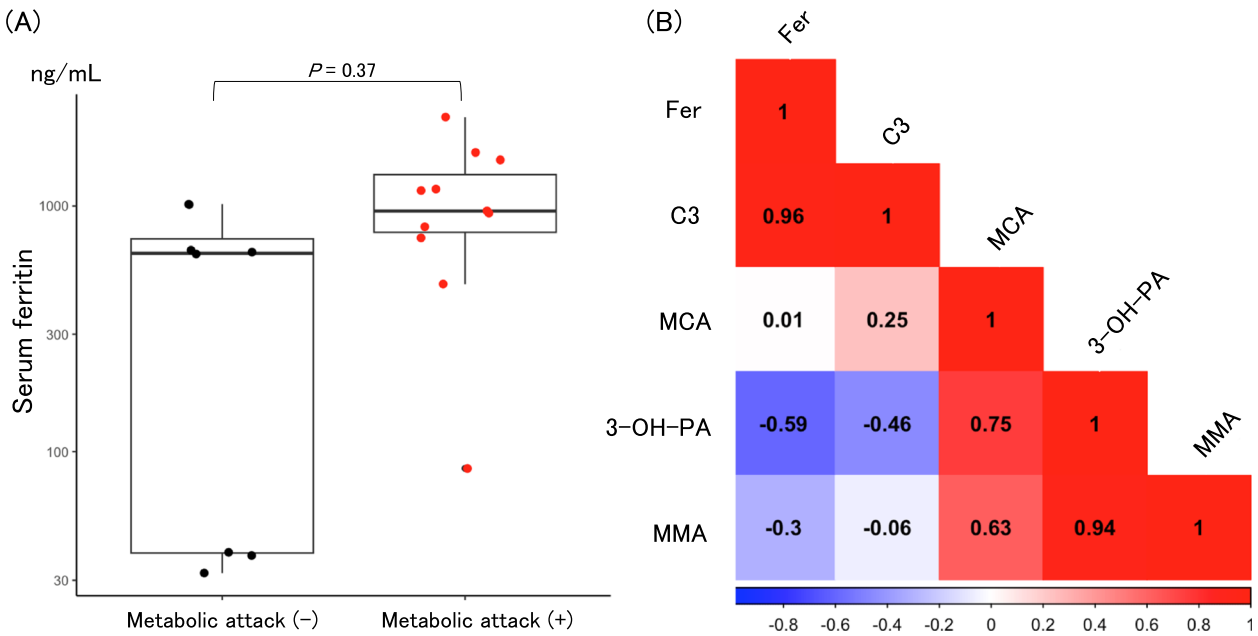

Fig. 4 Interrelationship between ferritin and metabolites of methylmalonic academia. **a** Serum ferritin levels were higher in samples obtained during metabolic attack. **b** Pearson correlation analysis shows the strongest correlation between ferritin and C3. Abbreviations: 3-OH-PA, 3-hydroxypropionic acid; C3, propionylcarnitine; Fer, ferritin; MCA, methylcitric acid; MMA, methylmalonic acid

Table 1 Clinical profile of patients with methylmalonic acidemia presenting with HLH

	Patient 1	Patient 2	Patient 3	Present case	
Country	Turkey	Saudi Arabia	Saudi Arabia	Japan	
Reference number	3	4	4	NA	
Gender	Male	Female	Male	Male	
MUT variations	p.N625V/p.N625V	p.Y110C/p.Y110C	p.Q37X/p.R108C	c.385 + 5C > T/p.L494X	
Age at first metabolic attack (y)	0	NA	NA	1	
Age at onset of HLH (y)	4	17	16	1	18
Acute presentation					
Respiratory distress	No	Yes	No	No	No
Altered level of consciousness	Yes	No	No	Yes	Yes
Vomiting / Decreased fluid intake	Yes	Yes	No	Yes	Yes
Criteria for HLH [Normal range]					
Fever (℃)	38.0	< 37.0	< 37.0	39.0	38.5
Splenomegaly	No	Yes	Yes	No	No
Cytopenia	3 cell lineages	3 cell lineages	3 cell lineages	3 cell lineages	2 cell lineages
Triglycerides [40–234] / Fibrinogen [200–400] (mg/dL)	2219 / 214	340 / 200	592 / 222	384 / 60	210 / 275
Ferritin [40–465] (ng/mL)	645	494	4124	NA	2292
Soluble interleukin-2 receptor [157–475] (U/mL)	NA	1572	1090	NA	1720
Natural killer cell activity [17–48] (%)	NA	NA	NA	NA	2.9
Bone marrow hemophagocytosis	Yes	Yes	Yes	Yes	Yes
Number of fulfilled criteria for HLH	5/8	5/8	6/8	?/8	6/8
Treatment	IVIG, CyA, DEX, PE	Abx	Abx, PSL, GCSF	IVIG	Abx, PSL, IVIG
Response	Progressive	Recovery	Recovery	Recovery	Recovery
Neurological comorbidity	Deceased	ID	ID	ID, ASD, Epilepsy	

Abbreviations: *Abx* antibiotics, *ASD* autism spectrum disorder, *CyA* cyclosporin A, *DEX* dexamethasone, *GCSF* granulocyte colony stimulating factor, *HLH* hemophagocytic lymphohistiocytosis, *ID* intellectual disability, *IVIG* intravenous immunoglobulin, *NA* not available, *PE* plasmapheresis, *PSL* prednisolone

normal ranges); hemophagocytosis in the bone marrow, spleen, or lymph nodes; and low or absent natural killer cell activity, according to clinical trials of HLH-2004 diagnostic criteria [5, 7]. Central nervous system involvement was not included in the criteria; however, it can be found in approximately 50% of patients with HLH, bearing worse outcomes [8].

Several inborn errors of metabolism are rarely complicated by HLH. Previously reported representative rare metabolic disorders included galactosialidosis [9], biotinidase deficiency [10], Wolman's disease [11], lysinuric protein intolerance [12], Niemann–Pick disease [13], Gaucher disease [14], propionic acidemia [3], Pearson syndrome [15], and multiple sulphatase deficiency [16]. HLH developed in most of these patients during infancy. Among those who reported propionic acidemia and our review of methylmalonic acidemia cases showed a later onset of HLH (median age, 16 years; range, 1–18 years). The exact mechanisms underlying the pathophysiology are not yet fully elucidated and are likely to be multifactorial. The accumulation of nondegraded metabolites, as a consequence of the disrupted metabolic pathways, may lead to inflammasome activation triggering macrophage overactivation. This mechanism offers a potential explanation for HLH development. Micronutrient deficiencies and dysfunctional mitochondria associated with impaired energy production and oxidative stress are probable reasons for the observed hematological complications in methylmalonic acidemia [2].

For the first time, this report shows the alteration of serum ferritin levels at metabolic attacks and non-metabolic events in a patient with methylmalonic acidemia. No significant difference was obtained, although a tendency toward higher ferritin levels was noted during acute decompensation events. Serum ferritin levels also did not normalize after HLH resolution, indicating a subclinical persistent hyperinflammatory state. These observations might suggest ferritin as a probable biomarker for HLH-associated attacks. Serum ferritin functions as an acute-phase reactant in response to inflammation or infection, modulates the immune response and provides protection against oxidative stress [17]. Further analysis shows a correlation between ferritin and C3, which might indicate a similar trend in the dynamics of ferritin and MMA metabolism. Larger studies are needed to test the usefulness of ferritin as a potential biomarker for metabolic attacks.

This study has several limitations. First, we were unable to obtain samples for comprehensive analyses of serum ferritin and urinary and/or serum organic acid for every metabolic and postmetabolic attack. This is expected in dealing with acute onset of diseases with varying severity and clinical progression. Second, we could not exclude the effects of age and dietary factors on the interpretation of the results. Identifying clinically useful disease biomarkers is beneficial for the early recognition and management of acute decompensation. However, our novel approach provides suggestions for future research avenues in the management of rare inborn errors of metabolism.

Abbreviations

3-OH-PA	3-Hydroxypropionic acid
C3	Propionylcarnitine
C2	Acetylcarnitine
HLH	Hemophagocytic lymphohistiocytosis
MCA	Methylcitric acid
MMA	Methylmalonic acid
MUT	Methylmalonyl-CoA mutase
sIL-2R	Soluble interleukin-2 receptor

Acknowledgements

We thank the patient and his family for their participation.

Authors' contributions

FY, SA, PFC, YS, and RK conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. KM, SK, SYL, and MI provided care for the patient, performed the initial analyses, and reviewed the manuscript. KM conducted the genetic analysis and critically reviewed the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

Funding

This work was supported in part by JPJS KAKENHI number JP22K15913 (Akamine); a research grant from the Ministry of Health, Labor and Welfare of Japan (JP22HA1003 to Chong and Kira); and the Morinaga Foundation for Health & Nutrition (Chong).

Data availability

All datasets for this study are included in the manuscript.

Declarations

Ethics approval and consent to participate

The studies involving human participants were reviewed and approved by the ethics committee of Fukuoka Children's Hospital (number 2022–131).

Consent for publication

Written informed consent for publication of this study was provided by the participants' legal guardians.

Competing interests

The authors declare no competing interests.

Received: 7 January 2025 Accepted: 20 March 2025
Published online: 31 March 2025

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