Multiple acyl–coenzyme A dehydrogenase deficiency presenting with myopathy and hypoglycaemia: a case report

Sophie SL Yeow[1 †], MB, BS, MRCPCH, **TS Wong**[2 †], MB, ChB, FHKAM (Paediatrics), **Grace WK Poon**[1 *], MRCP, FHKAM (Paediatrics), **Gao Yuan**[3], PhD, FHKAM (Medicine)

[1] *Department of Paediatrics and Adolescent Medicine, Queen Mary Hospital, Hong Kong SAR, China*
[2] *Department of Paediatrics and Adolescent Medicine, Princess Margaret Hospital, Hong Kong SAR, China*
[3] *Department of Medicine, Queen Mary Hospital, Hong Kong SAR, China*

* Corresponding author: poonwkg@fellow.hkam.hk

† Equal contribution

This article was published on 14 Apr 2026 at www.hkmj.org.

This version may differ from the print version.

Hong Kong Med J 2026;32:Epub
https://doi.org/10.12809/hkmj2512906

Case presentation

Our patient was born full term, weighing 3.18 kg to consanguineous Chinese parents. Perinatal and family history were unremarkable and he had normal development and good past health. He reported intermittent periods of malaise from the age of 14 years. Random glucose level was 3.6 mmol/L and gamma-glutamyl transferase level was mildly elevated at 45 U/L (reference range, 13-44). No further investigations, including creatine kinase (CK) level, were performed for the hypoglycaemia, and no follow-up was arranged.

At the age of 22 years, he presented to Queen Mary Hospital in 2021 with a 3-month history of progressive malaise and generalised muscle weakness. He had no fever, constitutional symptoms, myalgia, rash or joint pain. Physical examination showed bilateral partial ptosis without fatigability. There was proximal and distal limb muscle atrophy and his weakness was at grade 4/5 on the Medical Research Council scale, with hypotonia and hyporeflexia. Cranial nerves, gait, cerebellar and sensory examinations were normal. There was no goitre, Cushingoid features, muscle tenderness or rash. Examination of other systems was unremarkable.

Initial blood tests revealed an elevated CK level of up to 867 U/L (reference range, 65-355), elevated liver transaminase level, fasting hypoglycaemia level of 3.3 mmol/L, hyperlactataemia level of 5.4 mmol/L, and high anion gap metabolic acidosis. Subsequent workup for myopathy, including thyroid function test, morning cortisol, myositis antibody panel, urine toxicology, nerve conduction velocity and electromyography, were unrevealing.

Metabolic myopathy due to an inherited metabolic disorder (IMD) was suspected. Plasma acylcarnitine profile detected elevation of multiple acylcarnitine species of all chain lengths and a low free carnitine level. There was urinary hyperexcretion of ethylmalonic acid, glutaric acid, 2-hydroxyglutaric acid and 4-hydroxyphenyllactic acid with isobutyrylglycine, hexanoylglycine and suberylglycine. Of note, at a fasting blood glucose level of 4.1 mmol/L, there was significant ketosis with beta-hydroxybutyrate level of 3.8 mmol/L. Ammonia level was elevated at 60 μmol/L. Lactate, lipid profile, insulin, and plasma amino acids were unremarkable. The patient was suspected to have multiple acyl–coenzyme A dehydrogenase deficiency (MADD).

Unfortunately, the patient was discharged before the acylcarnitine profile result was available and refused readmission for treatment. He presented 2 weeks later with decreased responsiveness. His CK level was over 14 000 U/L with markedly deranged liver enzymes (alanine aminotransferase level >1000 U/L). Urine myoglobin was weakly positive. He was treated with riboflavin, levocarnitine, coenzyme Q10 and intravenous fluids providing a glucose infusion rate of 3 to 4 mg/kg/min.

The muscle power, CK level, and liver enzyme level of the patient improved within 2 days. He was discharged on riboflavin and a low-protein, low-fat diet. At his latest follow-up at 25 years of age, his limb power was near normal and his malaise had improved.

Molecular testing was performed using next-generation sequencing with a genetic panel including the *ETFA*, *ETFB*, *ETFDH*, *SLC52A2* and *SLC52A3* genes. He was homozygous for the pathogenic variant c.250G>A in the *ETFDH* gene, the most common pathogenic variant causing late-onset MADD in Southern Chinese.[1] Muscle biopsy was not performed as a molecular diagnosis had been established using a peripheral blood sample.

Discussion

Multiple acyl–coenzyme A dehydrogenase deficiency, or glutaric aciduria type II, is an autosomal recessive IMD caused by mutations in either the *ETF* or *ETFDH* gene. This impairs electron transfer and affects oxidative phosphorylation. It also disrupts

fatty acid, amino acid and choline metabolism.[2] As an IMD, MADD is included in newborn screening in Hong Kong.[3] Nonetheless, most citizens in Hong Kong were born before newborn screening for IMDs was introduced (in all public birthing hospitals since 2020). In addition, false-negative screening results are possible, depending on disease severity and whether the patient is in a state of anabolism or catabolism. It is essential to maintain a high index of suspicion for MADD.

The clinical presentation of MADD varies widely. The severe form presents in the neonatal period with life-threatening metabolic crisis. The milder or late-onset form can present at any time from infancy to adulthood with intermittent metabolic decompensations, often triggered by catabolic events. Patients may also present with lipid storage myopathy with muscle weakness and rhabdomyolysis. Concomitant hypoglycaemia should raise suspicion of lipid storage myopathy due to fatty acid oxidation defects (FAOD). Unexplained hypoglycaemia, as in our patient at 14 years of age, should not be ignored.

Classically, FAOD leads to non-ketotic hypoglycaemia as beta-oxidation of fatty acids is impaired, resulting in reduced formation of ketone bodies. Nonetheless, significant ketosis has been reported in FAOD and MADD,[4] and was also observed in our case. The mechanism underlying significant ketosis in FAOD remains unclear, but clinicians should be aware that the presence of ketosis alone is insufficient to exclude FAOD.

Although IMDs are often considered rare, particularly in adults, studies have shown that late-onset MADD due to the c.250G>A variant in the *ETFDH* gene is not uncommon in the Southern Chinese population.[1,5] Wang et al[1] estimated a c.250G>A carrier frequency of 1.35% in the Han Chinese population, implying an incidence of approximately 1:22 000. Like our patient, all patients carrying *ETFDH* variants in the cohort reported by Wang et al[1] showed riboflavin responsiveness. The treatable nature of this disease with riboflavin supplementation underscores the importance of recognising affected patients. With the increasing availability of next-generation sequencing, molecular testing of the *ETFDH* gene should be considered when investigating patients with unexplained myopathy in our locality. This may spare patients invasive procedures such as muscle biopsy.

Recognising MADD may be challenging due to its non-specific presentation. In appropriate clinical settings, investigation of myopathy should include plasma acylcarnitine profile, ammonia, lactate, glucose, and urine organic acids to evaluate for IMD-related myopathy. Elevated plasma acylcarnitine species of all chain lengths and urinary organic acids such as glutaric acid, are seen in patients with MADD.[6]

Late-onset MADD, like many other IMDs, may present with non-specific features that overlap with more common conditions. This case illustrates the importance of considering metabolic myopathy even in adolescents or adults, and that unexplained hypoglycaemia should not be overlooked. A prolonged diagnostic odyssey may be avoided, and targeted treatment can markedly improve disease control.

Author contributions

Concept or design: SSL Yeow, TS Wong.
Acquisition of data: SSL Yeow, TS Wong.
Analysis or interpretation of data: SSL Yeow, TS Wong.
Drafting of the manuscript: SSL Yeow, TS Wong.
Critical revision of the manuscript for important intellectual content: TS Wong, GWK Poon, G Yuan.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

Funding/support

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethics approval

The patient was treated in accordance with the Declaration of Helsinki. The patient provided informed verbal consent for the treatment/procedures, and consent for publication of this case report.

References

1. Wang ZQ, Chen XJ, Murong SX, Wang N, Wu ZY. Molecular analysis of 51 unrelated pedigrees with late-onset multiple acyl-CoA dehydrogenation deficiency (MADD) in southern China confirmed the most common ETFDH mutation and high carrier frequency of c.250G>A. J Mol Med (Berl) 2011;89:569-76.
2. Nilipour Y, Fatehi F, Sanatinia S, et al. Multiple acyl-coenzyme A dehydrogenase deficiency shows a possible founder effect and is the most frequent cause of lipid storage myopathy in Iran. J Neurol Sci 2020;411:116707.
3. Hospital Authority. Newborn Screening Programme for Inborn Errors of Metabolism (IEM). June 2025. Available from: https://www.smartpatient.ha.org.hk/docs/default-source/disease-pdf/newborn-screening-programme-for-iem_2025.pdf?sfvrsn=71d35ccb_8. Accessed 3 Mar 2026.
4. Olpin SE. Implications of impaired ketogenesis in fatty acid oxidation disorders. Prostaglandins Leukot Essent Fatty Acids 2004;70:293-308.
5. Lan MY, Fu MH, Liu YF, et al. High frequency of *ETFDH* c.250G>A mutation in Taiwanese patients with late-onset lipid storage myopathy. Clin Genet 2010;78:565-9.
6. Prasun P. Multiple Acyl-CoA Dehydrogenase Deficiency [Internet]. In: Adam MP, Ardinger HH, Bick S, Mirzaa GM, et al, editors. GeneReviews. Seattle (WA): University of Washington; 1993. Available from: https://www.ncbi.nlm.nih.gov/books/NBK558236/. Accessed 3 Mar 2026.

