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Case Report

Stealthy progression of type 2 diabetes mellitus due to impaired ketone production in an adult patient with multiple acyl-CoA dehydrogenase deficiency

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ABSTRACT

Background: Multiple acyl-CoA dehydrogenase deficiency (MADD) is an inherited metabolic disorder caused by biallelic pathogenic variants in genes related to the flavoprotein complex. Dysfunction of the complex leads to impaired fatty acid oxidation and ketone body production which can cause hypoketotic hypoglycemia with prolonged fasting. Patients with fatty acid oxidation disorders (FAODs) such as MADD are treated primarily with a dietary regimen consisting of high-carbohydrate foods and avoidance of prolonged fasting. However, information on the long-term sequelae associated with this diet have not been accumulated. In general, high-carbohydrate diets can induce diseases such as type 2 diabetes mellitus (T2DM), although few patients with both MADD and T2DM have been reported.

Case: We present the case of a 32-year-old man with MADD who was on a high-carbohydrate diet for >30 years and exhibited symptoms resembling diabetic ketoacidosis. He presented with polydipsia, polyuria, and weight loss with a decrease in body mass index from 31 to 25 kg/m^2 over 2 months. Laboratory tests revealed a HbA1c level of 13.9%; however, the patient did not show metabolic acidosis but only mild ketosis.

Discussion/conclusion: This report emphasizes the potential association between long-term adherence to high-carbohydrate dietary therapy and T2DM development. Moreover, this case underscores the difficulty of detecting diabetic ketosis in patients with FAODs such as MADD due to their inability to produce ketone bodies. These findings warrant further research of the long-term complications associated with this diet as well as warning of the potential progression of diabetes in patients with FAODs such as MADD.

1. Introduction

Multiple acyl-CoA dehydrogenase deficiency (MADD, MIM #231680), also known as glutaric acidemia type II, is caused by biallelic pathogenic variants in *ETFA*, *ETFB*, or *ETFDH* which encode electron transfer flavoprotein (ETF)-α, ETF-β, or ETF dehydrogenase (ETFDH) [1]. ETF, a heterodimer composed of ETF-α and ETF-β, is a highly conserved mitochondrial enzyme that receives electrons through dehydrogenase reactions [2]. The electron is transferred by ETFDH to ubiquinone in the mitochondrial respiratory chain [3]. Dysfunction of ETF and/or ETFDH can lead to the impairment of fatty acid oxidation and ketone body production [1]. Individuals with MADD are susceptible to hypoglycemia during prolonged fasting due to insufficient ketone production to compensate for energy deficits [4].

The bundle strategy, combining dietary modification and supplementation, is a practical and reasonable approach for managing MADD. The empirical dietary regimen consists of high-carbohydrate, low-fat, and low-protein meals while avoiding prolonged fasting [5]. Moreover, to dietary modification, oral supplementation of riboflavin has proven to be effective especially in mild forms [6]. D,L-3-hydroxybutyrate has been shown to provide clinical benefits [7]. Levocarnitine or coenzyme Q10 may also be administered [5], and bezafibrate is also a candidate

Abbreviations: BMI, body mass index; DKA, diabetes ketoacidosis; ETF, electron transfer flavoprotein; ETFDH, electron transfer flavoprotein dehydrogenase; FAODs, fatty acid oxidation disorders; MADD, Multiple acyl-CoA dehydrogenase deficiency; NAFLD, non-alcoholic fatty liver disease; T2DM, type 2 diabetes mellitus.

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drug [8]. While these interventions and intensive care may not result in improved outcomes for severe cases [9], mild forms of MADD can be managed and stabilized. Discontinuing dietary management, even after reaching adulthood with growth and metabolic stabilization, can still result in hypoglycemia, with devastating complications. While dietary management can provide lifesaving outcomes, long-term outcomes and the effects associated with appropriate dietary management remain unknown.

Herein, we present a case of a 32-year-old Japanese man with MADD who followed the MADD-specific diet for over 30 years and has exhibited diabetic ketoacidosis (DKA)-like symptoms as a manifestation of type 2 diabetes mellitus (T2DM).

2. Case presentation

The patient was first diagnosed with a mild form of MADD at the age of 12 months, presenting with hypoglycemia (1.0 mmol/L), hyperammonemia (434 μmol/L), metabolic acidosis, and loss of consciousness. The diagnosis was confirmed by urinary organic acid profiles which demonstrated hypoketotic, dicarboxylic aciduria and increased excretion of ethylmalonic acid, 2-hydroxyglutaric acid, and isovaleric glycine. Genetic analysis of the *ETFA* gene (NM_000126.4) revealed compound heterozygous pathogenic variants, c.[478del];[764G > T], p.[(Asp160Metfs*4)];[(Gly255Val)]. His clinical history up to childhood, the pathogenicity of these variants, and biomolecular details have been previously reported [10]. The patient was treated with dietary therapy, along with riboflavin and levocarnitine. Dietary therapy included avoidance of prolonged fasting and frequent meals that were high in carbohydrates but low in fat and protein. The patient experienced episodes of hypoglycemia due to fasting during infancy but has remained free of hypoglycemic events since the age of two and a half years.

At a routine follow-up appointment at the age of 32 years, the patient reported symptoms of polydipsia, polyuria, frequent muscle spasms, fatigue, and decreased appetite. One month before the episode, his levels of HbA1c, insulin, CPR, and HOMA-R index were 8.5%, 13.9 μU/mL, 2.68 ng/mL, and 4.5, respectively, which suggested the existence of T2DM. The diagnosis of T2DM and starting interventions and treatments had been just planned at the appointment. The patient was engaged in physical labor and had an estimated energy intake of over 2000 kcal/day with a macronutrient composition of 14% protein, 20% fat, and 66% carbohydrate. The patient had a long-standing habit of consuming 500–1000 mL of soft drinks daily since the age of 13; however, during this period, his intake increased to 1500–2000 mL/day to alleviate thirst. His weight had decreased from 90.9 kg to 74.7 kg in two months with a resultant decrease in body mass index (BMI) from 31 to 25 kg/m^2.

Laboratory examination included the following results: postprandial blood glucose, 382 mg/dL; HbA1c, 13.9% [normal: < 6.5], total ketone bodies, 2.5 mmol/L; 3-hydroxybutyrate, 1.4 mmol/L; serum cholinesterase, 293 U/L [normal: 240–486]; creatine kinase, 176 U/L [normal: 59–248]; urea nitrogen, 13 mg/dL [normal: 8–20]; and creatinine, 0.56 mg/dL [normal: 0.65–1.07]. A venous blood gas was pH, 7.42; $HCO3^-$, 26.5 mmol/L; pCO2, 42.5 mmHg; anion gap, 4.4 mmol/L. Urinalysis was positive for glucose and ketone bodies. Insulin level was 3.9 μU/mL. AST, ALT, and GGT levels were significantly lower on this day (Fig. 1). His acylcarnitine profile did not show significant fluctuation in acylcarnitine values (Table 1). CT scans showed a fatty liver (Fig. 2) and a visceral and subcutaneous fat area of 103.90 cm^2 and 129.36 cm^2 at the level of the navel, respectively.

The patient was managed with intravenous saline and a short-acting insulin infusion. Following 11 days of intensive insulin therapy using insulin lispro, glargine, and liraglutide, the patient's blood glucose levels stabilized. The patient was transitioned to a once-daily liraglutide injection and has been well-controlled since. Dietary management has been changed to 1700 kcal/day with a macronutrient composition of 17% protein, 27% fat, and 56% carbohydrate.

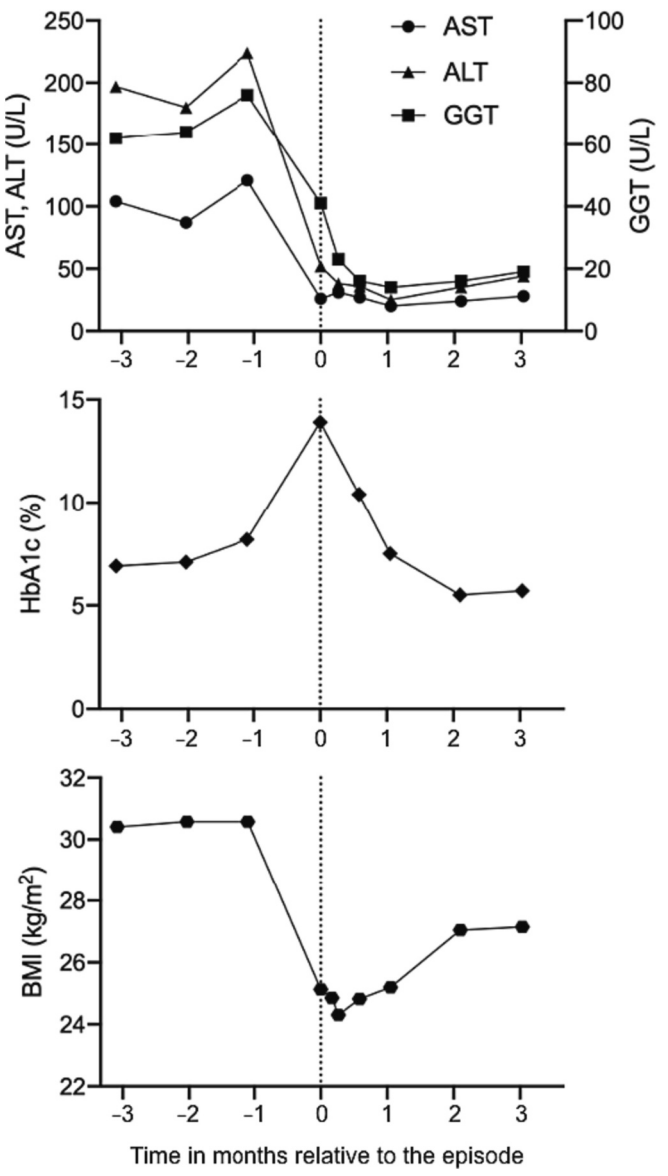

Fig. 1. Temporal changes in AST, ALT, GGT, HbA1c, and BMI preceding and following the described episode.

Table 1
Acylcarnitine profiles in dried blood spots.

Acylcarnitine (μmol/L)	Reference*	Months relative to the episode				
		−4	−2	0	+2	+4
C0	20–70	57.75	49.91	32.2	57.2	73.15
C2	5–45	5.18	4.39	11.95	10.84	7.83
C4	<1.4	0.52	0.47	1.05	1.21	1.1
C5	<0.7	0.67	0.57	1.49	1.03	2.35
C6	<0.15	0.24	0.43	0.33	0.59	0.52
C8	<0.3	0.74	1.64	0.48	0.88	0.76
C10	<0.25	0.37	0.75	0.27	0.41	0.33
C12	<0.3	0.07	0.11	0.07	0.08	0.09
C14:1	<0.3	0.04	0.11	0.06	0.09	0.04
C16	<0.4	0.52	0.56	0.68	0.56	0.61

* Yamada et al. [11].

3. Discussion and conclusions

This case highlights the potential for an atypical presentation of T2DM in the presence of fatty acid oxidation disorders (FAOD) such as

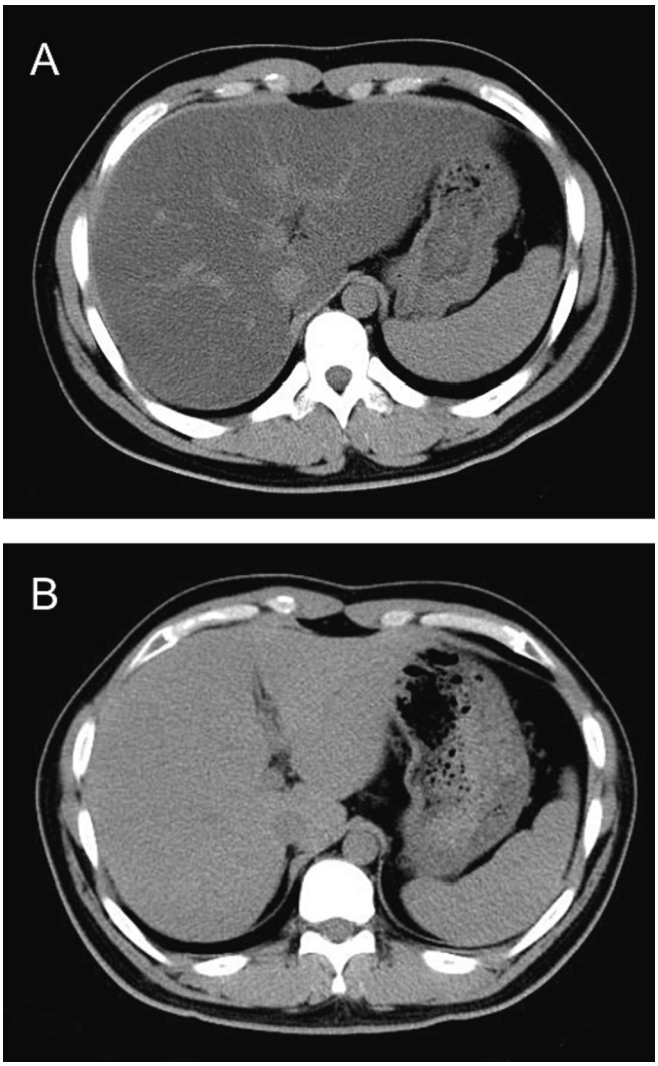

Fig. 2. Axial CT scans of the liver. A) 12 years prior to the episode. B) Near the time of the episode.

MADD, which presents a challenge in recognizing and diagnosing diabetic metabolic decompensation involving ketosis. This may be attributed to the patient's inherently limited capacity to produce ketones despite the severe and worsening nature of T2DM. In cases with significantly elevated HbA1c levels, it is plausible that DKA might possibly ensue, as reported mean HbA1c levels in patients with DKA-onset DM range from 13.1% to 13.3% [12,13]. However, despite our patient experiencing substantial weight loss and presenting with a notably high HbA1c value of 13.9%, he did not manifest the typical signs of DKA, as his total ketone body level was only 2.5 mmol/L. Additionally, our patient did not demonstrate acidosis as evidenced by his venous blood pH, 7.42; pCO2, 42.5 mmHg; and $HCO3^{-}$, 26.5 mmol/L. The relatively hypoketotic state of patients with FAODs, as observed in our patient, probably masks the underlying insulin resistance and/or deficiency. While the absence of excessive ketone production may appear fortunate, the development of hyperosmolar, hyperglycemic syndrome is inevitable if the masked metabolic status is left untreated. Thus, it is crucial to recognize it at an early stage. This case underscores the difficulty of detecting diabetic ketosis in patients with FAODs like MADD given their limited capacity for ketone body production. Healthcare providers, patients, and caregivers should remain vigilant regarding the potential progression of diabetes in patients with FAODs such as those with MADD.

This report also emphasizes the effect of a long-term, high-carbohydrate diet which may contribute to insulin resistance. Patients with FAODs treated with frequent meals and a high-carbohydrate diet might not necessarily develop insulin resistance and subsequently T2DM. While previous research has noted the link between high-carbohydrate diets and the potential for inducing obesity and other lifestyle diseases such as T2DM [14], only one case of an individual with concurrent MADD and T2DM has been previously reported [15]. In that case, the patient was initially diagnosed with T2DM and was subsequently found to have MADD in adulthood. The findings of animal studies seem to align with the observations in humans. *Vlcad* knockout mice exhibited resistance to obesity and sensitivity to insulin compared to wild type mice possibly due to activation of *Ampk* or *Pparα* [16]. A similar phenomenon was observed in knockout mice of *Cpt2* which is responsible for converting long-chain acylcarnitine to long-chain acyl-CoA in mitochondria for β-oxidation [17]. However, *Lcad* knockout mice, which are phenotypically more similar to patients with VLCAD deficiency than *Vlcad* knockout mice, displayed hepatic insulin resistance [18]. Further research is required to clarify the relationship of insulin resistance development between patients with FAODs and healthy controls consuming the same long-term carbohydrate intake.

In addition, this patient exhibited certain risk factors that could be attributed to the MADD-specific diet and are associated with the development of T2DM. First, obesity is a well-established risk factor for T2DM [19]. The patient had a long-standing history of obesity with a BMI of 31 kg/m^2 two months before presentation. Second, the presence of non-alcoholic fatty liver disease (NAFLD) is also a known risk factor for T2DM [20,21]. NAFLD is observed in a smaller proportion of patients with MADD [22], while our patient had this finding, as confirmed by both ultrasound and CT scan. Finally, excessive consumption of sugar-containing soft drinks is a recognized risk factor for the onset of diabetic ketosis which may present as an initial manifestation of non-insulin dependent diabetes mellitus [12]. Our patient had a long-standing habit of consuming 500–1000 mL of soft drinks daily to prevent hypoglycemia and had increased his intake to 1500–2000 mL/day to compensate for his thirst around the time of this episode. Managing both obesity and NAFLD in patients with MADD can be challenging given the nature of the disease and the dietary interventions required. Nevertheless, the presence of obesity, NAFLD, and excessive sugar-containing soft drink intake may have increased his risk for developing T2DM. To the best of our knowledge, a discussion on the relationship between phenotypes, including hepatic involvement, and the genetic background is limited due to the absence of reports detailing patients with *ETFA* pathogenic variants along with comprehensive clinical and laboratory data. Therefore, future large cohort studies focusing on adult patients with MADD are crucial to gain a thorough understanding of the genetic and phenotypic characteristics.

Interestingly, his AST, ALT, and GGT values had decreased significantly at the time of presentation. Two months prior to the diagnosis of T2DM, his AST, ALT, and GGT levels were 121 U/L, 224 U/L, and 74 U/L, respectively. These values align with the characteristics of NAFLD which is typically associated with elevated levels of AST, ALT, and GGT, with ALT levels being significantly higher than AST [23]. Intriguingly, coinciding with the worsening of T2DM, the patient's AST, ALT, and GGT levels decreased to 26 U/L, 52 U/L, and 41 U/L, respectively, suggesting an improvement in NAFLD [24]. His cholinesterase level, which inversely correlates with the severity of NAFLD [25], also supports the suggestion of an improvement in NAFLD as it decreased from 371 U/L two months prior to presentation to 293 U/L. Furthermore, a comparison of his CT scan with one taken 12 years previously revealed a reduction in liver steatosis (Fig. 2). Notably, no significant changes were observed in the patient's blood acylcarnitine profile which is consistent with the observed level of improvement in liver steatosis [26]. Collectively, these findings suggest the hypothesis that untreated T2DM resulted in cellular energy insufficiency which enhanced fatty acid catabolism in the liver through partially active flavoprotein, ultimately leading to the improvement of NAFLD as fasting [27].

In conclusion, this case highlights not only the potential association between long-term adherence to carbohydrate-rich dietary therapy and the development of T2DM in patients with MADD, but also the difficulty in detecting signs of T2DM, especially ketosis or DKA, due to the innate inability to produce ketones in FAODs. These findings warrant further research into the long-term complications of treatment and a better understanding of the clinical presentations of the complications in patients with FAODs. Healthcare providers, patients, and caregivers are encouraged to recognize the possibility of T2DM silently advancing in individuals with MADD. As such, regular medical check-ups and patient education are essential for vigilant monitoring.

Ethics approval

This study was approved by the Ethics Committee of Tohoku University School of Medicine (approval number: 31844).

Patient consent statement

Written informed consent was obtained from the patient described in this manuscript.

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CRediT authorship contribution statement

Nodoka Ikeda: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. **Yoichi Wada:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Tomohito Izumi:** Conceptualization, Investigation, Resources, Validation, Writing – review & editing. **Yuichiro Munakata:** Conceptualization, Investigation, Resources, Validation, Writing – review & editing. **Hideki Katagiri:** Conceptualization, Resources, Validation, Writing – review & editing. **Shigeo Kure:** Conceptualization, Resources, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

None.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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