JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
CASE REPORT

Maturity-onset diabetes of the young type 5, presenting as diabetic ketoacidosis with alkalemia: A report of a case

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Keywords
Diabetic ketoacidosis with alkalemia, *HNF1B*, Maturity-onset diabetes of the young type 5

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J Diabetes Investig 2022; 13: 923–926

doi: 10.1111/jdi.13737

ABSTRACT

A 34-year-old man visited our Department of Gastroenterology and Metabolism, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan, because of dry mouth and weight loss. His plasma glucose level was 32.8 mmol/L and serum levels of ketone bodies were increased, but with metabolic alkalemia. He was also suffering from renal tubular hypomagnesemia and hypokalemia. Abdominal computed tomography showed bilateral renal cysts. These findings were suggestive of maturity-onset diabetes of the young type 5. Genetic testing showed heterozygous hepatocyte nuclear factor 1 beta gene deletion. In the present case, it seemed reasonable to view hepatocyte nuclear factor 1 beta gene deletion as the common cause of maturity-onset diabetes of the young type 5-associated diabetic ketoacidosis and tubular malfunction-induced hypokalemic alkalosis. This case exemplifies the importance of hepatocyte nuclear factor 1 beta gene abnormality as a potential cause of diabetic ketoacidosis with alkalemia.

INTRODUCTION

Maturity-onset diabetes of the young (MODY) is a group of monogenic forms of diabetes that are inherited in an autosomal dominant manner. Although the prevalence of MODY syndromes is estimated to be between 0.6 and 2% of all diabetes[1], hepatocyte nuclear factor 1 beta (*HNF1B*)-MODY type 5 (MODY5) is exceedingly rare, comprising less than 5% of all MODY subtypes[2]. More importantly, MODY5 is uniquely associated with a broad clinical spectrum from renal phenotypes to pancreatic β-cell dysfunction[3]. Clinical symptoms, such as polyuria and/or weight loss, are present in 47% of patients, but ketoacidosis is rare at the time of diabetes diagnosis in patients with MODY5[4].

Here, we report a patient newly diagnosed as MODY5, who presented with diabetic ketoacidosis with renal tubular alkalemia, and later was diagnosed genetically as *HNF1B* syndrome.

Received 1 July 2021; revised 10 December 2021; accepted 16 December 2021

CASE REPORT

A 34-year-old man visited Department of Gastroenterology and Metabolism, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan, because of dry mouth and weight loss of 10 kg within 1 year. He had no medical history, except for hyperglycemia identified in a health examination 1 year before that was left untreated. He had no family history of diabetes or kidney disease. His height was 170 cm and bodyweight was 47.0 kg. Laboratory examination showed that the casual plasma glucose level was 32.8 mmol/L, with the hemoglobin A1c level was 189 mmol/mol (Table 1). Although serum levels of ketone bodies were increased, blood gas analysis showed a pH of 7.48 and HCO_3^- of 36.7 mmol/L, suggesting an existence of metabolic alkalosis. Therefore, he was diagnosed with diabetic ketoacidosis with alkalemia and treated with linagliptin as a tentative pharmacotherapy. He was admitted to our hospital 1 week later for further examination and treatment.

After admission, linagliptin was stopped and multiple daily injections of insulin were initiated. Urinalysis showed a rather low level of urinary C-peptide secretion (9.8 nmol/day), suggesting a certain level of β-cell dysfunction. Anti-islet antibodies

Table 1 | Postprandial laboratory data on patient's first visit

Hematology		Glycometabolism tests	
White blood cells ($\times 10^9$/L)	9.3	Glucose (mmol/L)	32.8
Hemoglobin (g/L)	170	HbA1c (mmol/mol)	189
Platelets ($\times 10^9$/L)	236	Insulin (pmol/mL)	12.5
		C-peptide (nmol/L)	0.1
Biochemistry		Anti-GAD antibodies (IU/mL)	<5.0
Total protein (g/L)	78	Anti-IA2 antibodies (IU/mL)	<0.4
Albumin (mmol/L)	0.6	Anti-insulin antibodies (IU/mL)	<0.4
AST (μmol/s L)	0.47	Anti-ZnT8 antibodies (IU/mL)	<10.0
ALT (μmol/s L)	0.62		
LDH (μmol/s L)	4.22	Endocrinological tests	
γGTP (μmol/s L)	1.17	Plasma renin activity (μg/L/h)	22.0
ALP (μmol/s L)	6.8	Aldosterone (pmol/L)	1,144
Creatine kinase (μmol/s L)	2.85	ACTH (pmol/L)	4.17
Amylase (μmol/s L)	1.08	Cortisol (nmol/L)	303.5
Uric acid (μmol/L)	244	TSH (mIU/L)	3.68
Creatinine (μmol/L)	91.1	Free T4 (pmol/L)	19
BUN (mmol/L)	8.39	Free T3 (pmol/L)	3.01
eGFR (mL/min/1.73 m^2)	68.3		
Sodium (mmol/L)	133	Venous blood gas analysis	
Potassium (mmol/L)	3.7	pH	7.48
Chloride (mmol/L)	79	$PaCO_2$ (kPa)	6.66
Calcium (mmol/L)	2.6	PaO_2 (kPa)	8.53
Magnesium (mmol/L)	0.5	HCO_3^- (mmol/L)	36.7
Phosphate (mmol/L)	1.1	BE (mmol/L)	11.3
Triglyceride (mmol/L)	2.6		
HDL cholesterol (mmol/L)	1.8	Urinalysis	
LDL cholesterol (mmol/L)	2.1	Specific gravity	1.031
		pH	5.0
Ketone body fractions		Glucose	(4+)
Total ketone bodies (mmol/L)	1.016	Protein	(±)
Acetoacetic acid (mmol/L)	0.395	Ketone body	(–)
β-hydroxybutyric acid (mmol/L)	0.621		

γGTP, gamma-glutamyl transpeptidase; ACTH, adrenocorticotropic hormone; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BE, base excess; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; GAD, glutamate decarboxylase; HDL, high-density lipoprotein; IA2, islet antigen 2; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; TSH, thyroid-stimulating hormone; ZnT8, zinc transporter 8.

in the serum were negative. The patient's hyperglycemia improved a few days later. During the course, however, he developed profound hypomagnesemia and hypokalemia. Additional urine electrolyte analysis showed an inappropriately high fractional excretion of magnesium (FeMg: 22.7%) and increased urinary potassium excretion (38 mmol/day), suggesting renal magnesium and potassium wasting. A challenge with hydrochlorothiazide showed a blunted response. We then initially suspected that along with diabetes, the patient was complicated with Gitelman syndrome.

Abdominal computed tomography showed bilateral multiple renal cysts and pyelectasis (Figure 1). Based on these clinical observations, MODY5 was suspected. Furthermore, the *HNF1B* score, a pivotal tool for rational genetic testing[5], was 19, confirming a high level of clinical suspicion for *HNF1B*-related disease. We carried out multiplex ligation probe amplification using patient-derived lymphocyte, and identified heterozygous entire deletion of the *HNF1B* gene (Figure 2).

After the diagnosis, we continued multiple daily injections of insulin, taking into consideration a decline of insulin secretion in the future. We also started supplementation of potassium and magnesium with high confidence in the prevention of muscle weakness, convulsion or arrhythmia.

DISCUSSION

We herein report a case of MODY5 presenting diabetic ketoacidosis with alkalemia as an initial manifestation, possibly due to the coexistence of *HNF1B*-associated renal tubular dysfunction.

Genetic mutations of *HNF1B*, located on chromosome 17q12, cause multiple organ disorders, collectively known as the *HNF1B* syndrome. Among 33 Japanese patients with *HNF1B*-related disorders, including the present case,

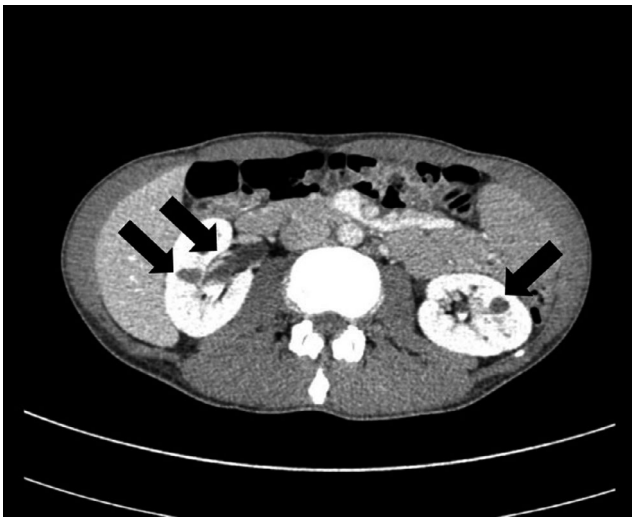

Figure 1 | Contrast agent-enhanced computed tomography scan of the abdominal plane. Bilateral multiple renal cysts and pyelectasis were visualized. Pancreatic and genital tract were spared.

whole-gene deletion and heterozygous variants account for up to 14 and 19 cases, respectively[6]. Although the genotype–phenotype relationship has not yet been conclusive, a report suggests that patients with *HNF1B* deletion less often show end-stage chronic kidney disease than those with point mutations[4], consistent with an absence of kidney dysfunction in the present case.

It is well known that manifestations of *HNF1B* syndrome vary among patients[3]. For example, diabetes or renal morphological abnormalities, such as renal cystic disease, was present in 38.7 and 77.4% of patients, respectively[6]. The co-existence of renal cysts in diabetes-complicating cases is known as renal cysts and diabetes syndrome, as found in the current case. Clinical features observed in the present case are summarized in Figure 3.

It has been reported that *HNF1B* mutations can also affect Na-Cl cotransporter function in the distal convoluted tube, leading to hypokalemia, hypomagnesemia and metabolic alkalosis[7,8]. In the present case, hypokalemic alkalosis potentially caused by Na-Cl cotransporter dysfunction seems to predominate over a mild diabetic ketoacidosis caused by insulin deficiency in MODY5 (Figure 3).

Diabetic ketosis typically manifests with acidemia due to an accumulation of acidic ketone bodies. However, it can present as alkalemia under certain, but limited, conditions, including vomiting and the use of diuretics, for which it was not relevant in the present case.

The absence of clinical manifestation in the patient's parents shows that the deletion of the gene might be a spontaneous de novo mutation, although we could not obtain agreement from his parents for their genetic analysis. De novo mutations reportedly occur relatively frequently, as seen in 50–60% of patients with *HNF1B* gene abnormality[9]. This is believed to be the case, because chromosome 17q12 contains a sequence with high homogeny, and meiotic cross-over might sometimes lead to mistakes during gene replication[10].

Collectively, when a young diabetes patient presents with diabetic ketoacidosis with alkalemia or electrolyte abnormalities, genetic testing for MODY5 is recommended. Conversely, when a patient is genetically diagnosed as MODY5, clinical screening tests for *HNF1B* mutation-related multi-organ complications need to be carried out.

COMPLIANCE WITH ETHICAL STANDARDS

Genetic testing was carried out in accordance with the ethical standards of Nagoya City University and Kobe University,

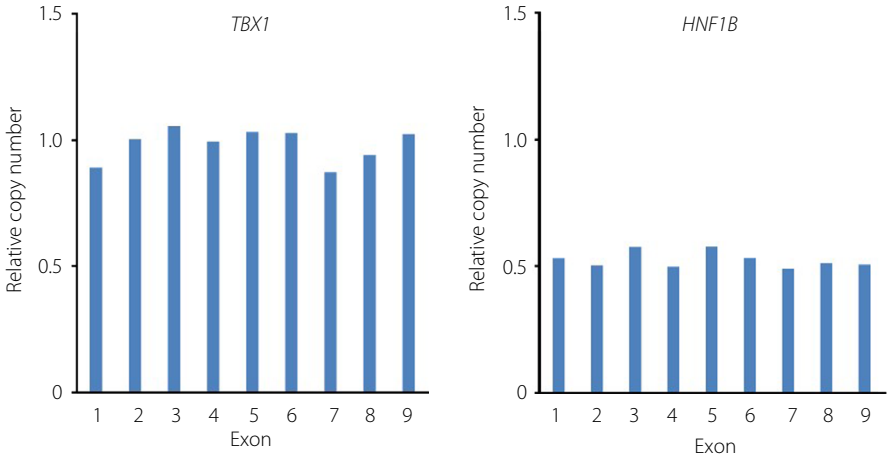

Figure 2 | Multiplex ligation probe amplification analysis. Briefly, genomic deoxyribonucleic acid was denatured and hybridized with the probe to detect the deletion of *HNF1B*. Ligation and polymerase chain reaction amplification were carried out with the SALSA P357 MPLA kit and analyzed by capillary electrophoresis using Gene Mapper v.3.7 (Thermo Fisher, Waltham, MA, USA). Heterozygous deletion in the *HNF1B* gene was identified, whereas no copy number alterations in the *TBX1* gene, located in chromosome 22q11.2 region, was detected.

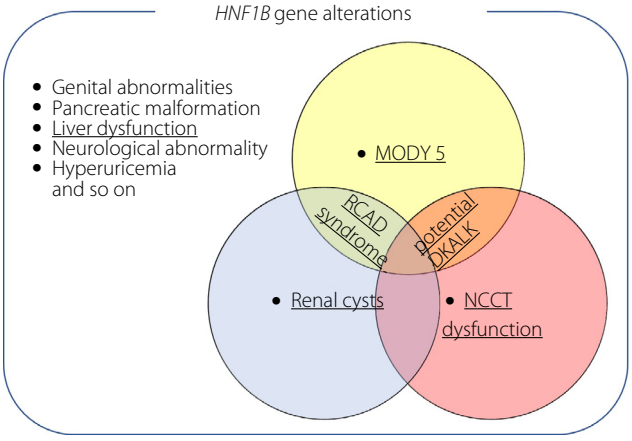

Figure 3 | Schematic diagram of the clinical manifestations in the present case within the broad spectrum of *HNF1B*-related multi-organ disorders. Underlines indicate disorders found in the patient. When maturity-onset diabetes of the young type 5 (MODY5) and Na-Cl cotransporter (NCCT) dysfunction overlaps in a single patient, potential occurrence of diabetic ketoacidosis with alkalemia (DKALK) is suggested, as in the present case. RCAD, renal cysts and diabetes.

related laws, and the Declaration of Helsinki, and under the permission of the institutional review board of Kobe University (no. 301). Patient's written informed consent was obtained.

DISCLOSURE

The authors declare no conflict of interest.

Approval of the research protocol: Research protocol was approved by the institutional review board of Kobe University.

Informed consent: Written informed consent was obtained from the patient.

Approval date of registry and the registration no. of study/trial: Approval date of the registry was 25 January 2021. The registration number of the study is 301.

Animal studies: N/A.

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