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ORIGINAL ARTICLE

Japanese cases of acute onset diabetic ketosis without acidosis in the absence of glutamic acid decarboxylase autoantibody

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Abstract We report consecutive Japanese patients presented with acute onset diabetic ketosis who had negative glutamic acid decarboxylase autoantibody (GADAb) to clarify the clinical characteristics of them. A total of consecutive 1,296 in-patients with newly diagnosed diabetes mellitus, who were admitted to our center from April 2003 to October 2008, were analyzed. Among them, 17 patients who presented with acute onset diabetic ketosis without acidosis, and found to be negative for GADAb, were included. They showed male preponderance ($n = 15$). Ten patients had history of excessive ingestion of sugar-containing soft drink. Patients who successfully withdrew insulin therapy by 6 months ($n = 7$) showed significantly higher insulin secretion capacity and higher body mass index at the time of diagnosis than those who continued insulin therapy at least for 6 months ($n = 10$). These findings suggest that some of Japanese patients who presented with acute onset diabetic ketosis and negative for GADAb share several clinical characteristics with atypical type 2 diabetes such as ketosis-prone diabetes and "soft-drink ketosis," but others do not.

Keywords Diabetic ketosis · Ketosis-prone diabetes · Soft-drink ketosis · GADAb

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Introduction

Acute onset hyperglycemia and ketosis with impaired insulin secretion are usually regarded as features of type 1 diabetes, which requires insulin therapy. However, it has been suggested that there is a subgroup of type 2 diabetes characterized by acute onset diabetic ketosis, and subsequent normoglycemic remission without insulin therapy [1]. Ketosis-prone type 2 diabetes (KPD) belongs to this subgroup, which has mainly been reported in African–Americans [1, 2]. "Soft-drink ketosis" is also included in this subgroup, which is characterized by acute onset ketosis induced by excessive ingestion of sugar-containing soft drink in obese type 2 diabetic patients. The latter has been reported exclusively in Japan [3, 5].

It is often difficult to classify the patients with acute onset diabetic ketosis at the time of diagnosis, especially those without glutamic acid decarboxylase autoantibody (GADAb), because they substantially overlap with type 1B and type 2 diabetes. In the present report, we describe retrospectively consecutive patients with acute onset diabetic ketosis, and found to be negative for GADAb, to clarify the clinical characteristics of them.

A representative case

A 35-year-old Japanese man presented to our center complaining of a three-week history of general fatigue, polydipsia and polyuria. He had consumed more than 3 l of sugar-containing soft drinks daily. His past medical history was unremarkable. He did not have any family history of diabetes. His blood glucose level was 588 mg/dl and plama keton bodies were elevated, although metabolic acidosis

Table 1 Data on admission: a representative case

	Value	Normal range
HbA1c	8.6%	4.3–5.8%
Acetoacetate	800 μmol/l	<55 μmol/l
3-hydroxy butyrate	1,980 μmol/l	<85 μmol/l
Fasting blood glucose	183 mg/dl	70–109 mg/dl
2 h postprandial blood glucose	305 mg/dl	70–169 mg/dl
Fasting CPR	0.19 ng/ml	0.74–3.48 ng/ml
2 h postprandial CPR	0.25 ng/ml	
24 h urinary CPR	7.1 μg/day	29.2–167 μg/day
GADAb	<0.3 U/ml	<0.3 U/ml
IA-2 antibody	<0.4 U/ml	<0.4 U/ml
Arterial blood gas		
pH	7.363	7.35–7.45
Bicarbonate ion	22.7 mmol/l	22–28 mmol/l
Base excess	−1.8 mmol/l	−2–2 mmol/l

was not documented (Table 1). He was emergently admitted for treatment of diabetic ketosis.

On admission, he was 167.2 cm tall and weighed 47 kg, body mass index (BMI) was 16.8 kg/m^2. His physical findings were normal. Endogenous insulin secretion was remarkably impaired (Table 1). GADAb and antibody to insulinoma-associated antigen (IA-2) were undetectable. Therefore, he was diagnosed as type 1B diabetes mellitus. Intensive insulin therapy with insulin aspart and NPH insulin was started, and his blood glucose level was normalized after 3 days. Furthermore, he was educated to correct dietary customs including soft-drink ingestion. After discharge, he continued intensive insulin therapy more than 2 years and his glycated hemoglobin (HbA1c) became within normal range. We tapered dose of insulin, although could not withdraw it since plasma C-peptide (CPR) level remained low (0.15–0.61 ng/ml).

Method

We included consecutive 1,296 adult Japanese patients who were admitted to our center from April 2003 to October 2008. Among them, 26 patients presented with acute onset diabetes with ketosis. Patients with autoimmune-associated type 1 diabetes were excluded, and 17 without GADAb were included for evaluation.

Excessive ingestion of sugar-containing drink was defined by more than 2 l of daily consumption. All patients were educated to modify their life style, including excessive soft-drink ingestion, during first hospitalization. After discharge, patients were followed up in our outpatient clinic every 2 months. Doses of insulin were decreased and withdrawn when the blood glucose can be controlled without it.

Next, we compared retrospectively clinical characteristics of the patients who successfully withdrew insulin therapy by 6 months of diagnosis (group A) and those who continued it (group B). Differences in variables were examined for statistical significance using Mann–Whitney test. Statistical significance was determined as $P < 0.05$. Statistical analysis was performed using SPSS 11.0 J (SPSS Inc., Chicago, IL, USA) on a personal computer.

Results

Baseline characteristics of 17 patients are shown in Table 2. All data were obtained at the time of first hospitalization. Ten patients (58.8%) had history of excessive ingestion of sugar-containing drink. They showed significantly higher BMI on admission compared to patients without such histories (26.7 ± 5.22 kg/m^2 versus 20.4 ± 4.25 kg/m^2, $P < 0.05$). All patients were compliant with

Table 2 Comparison of the patients who successfully withdrew insulin therapy by 6 months of diagnosis (group A) and those who continued it (group B)

	All cases	Group A	Group B	*P* value*
Number of cases	17	7	10	NA
Age (year)	46.1 ± 17.3	41.9 ± 13.8	49.0 ± 19.5	0.6
Soft-drink ingestion	10	5 (71.4%)	5 (50.0%)	0.37
HbA1c (%)	10.8 ± 2.35	11.4 ± 1.81	10.3 ± 2.67	0.32
Fasting CPR (ng/ml)	0.95 ± 0.59	1.26 ± 0.57	0.74 ± 0.52	0.04
2 h postprandial plasma CPR (ng/ml)	1.51 ± 1.14	1.62 ± 0.48	1.44 ± 1.47	0.19
ΔCPR (ng/ml)	0.56 ± 0.88	0.36 ± 0.73	0.70 ± 0.98	0.96
24 h urinary CPR (μg/day)	47.7 ± 31.8	69.4 ± 26.5	32.6 ± 26.6	0.03
BMI (kg/m^2)	24.1 ± 5.84	28.6 ± 2.66	21.0 ± 5.41	0.01

Data are presented as mean ± SD

NA not applicable

* Mann–Whitney test

insulin treatment even after discharge, which was confirmed by our outpatient clinic every 2 months.

Patients in group A showed that significantly higher fasting plasma CPR, 24 h urinary CPR excretion, and BMI compared to those in group B. In contrast, there were no significant differences in the age of onset, HbA1c, and 2 h postprandial plasma CPR between two groups.

Discussion

Acute onset ketosis is usually regarded as a typical feature of type 1 diabetes. However, there are "atypical" forms of type 2 diabetes, which present with acute onset ketosis such as KPD [1] and "soft-drink ketosis" [5]. Although, it is clinically important to distinguish this "atypical" type 2 diabetes from autoantibody-negative type 1 (type 1B) diabetes, the exact differentiation of these two forms is often difficult at the time of diagnosis [13].

Ketosis-prone type 2 diabetes (KPD) is a heterogeneous subgroup of type 2 diabetes which is characterized by an initial episode of acute diabetic ketosis with beta-cell dysfunction and subsequent improvement of glycemic control [2]. Several cases have been reported in African–American population [12], although it has been also reported in other ethnicities such as Native-American [9], Chinese [10], Hispanic [11], White [11], and Japanese [6] populations. In this report, some of clinical characteristics, such as male predominance and middle-age-onset, were similar to KPD [2].

On the other hand, "soft-drink ketosis" is another form of type 2 diabetes reported exclusively from Japan [3, 5]. It is characterized with negative GADAb, excessive sugar-containing soft-drink ingestion, male preponderance, and obesity [4]. In our cases of acute onset ketosis without GADAb, however, only 58.8% of the patients had history of excessive soft-drink intake, and only 64.7% were obese. Since patients with history of excessive soft-drink intake had significantly higher BMI, sugar-containing soft drink may aggravate insulin secretion transiently even in patients with higher capacity of insulin secretion.

One of the most prominent clinical features of the patients with acute onset diabetic ketosis is that a substantial proportion of the patients can achieve normoglycemic remission [2, 7], which is associated with better beta-cell function [11] and higher BMI [8]. In accordance with this, 7 of 17 patients with higher fasting plasma CPR, higher 24 h urinary CPR excretion and higher BMI on admission achieved insulin discontinuation in this report. However, 10 patients continued insulin therapy.

In summary, some of Japanese patients who presented with acute onset diabetic ketosis and negative for GADAb share several clinical characteristics with KPD and "soft-drink ketosis," but others do not.

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