Fulminant type 1 diabetes, an underrecognized and unique subtype of type 1 diabetes: A case series from Singapore

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ABSTRACT

Fulminant type 1 diabetes (FT1D) is a unique subtype of type 1 diabetes, characterized by acute absolute insulin deficiency, severe ketosis, and increased risk of hypoglycemia, glycemic variability and microvascular complications. Seven people with FT1D were identified from two tertiary centers in Singapore. Six were Chinese, the mean age was 35 years and all were lean (mean body mass index 20.3 kg/m^2). All presented with diabetes ketosis or ketoacidosis and low C-peptide. All but one had low glutamic acid decarboxylase antibodies. Nearly half had a missed/delayed diagnosis of FT1D. Three had frequent hypoglycemia, which improved after transition to continuous subcutaneous insulin infusion therapy. Individuals with FT1D experience unique diagnostic and management challenges associated with rapid absolute insulin deficiency. Greater awareness about this clinical entity is required.

INTRODUCTION

Fulminant type 1 diabetes (FT1D) is a subtype of type 1 diabetes (T1D) that was recognized in 2000, largely described among East Asian populations[1,2]. It is characterized by rapid pancreatic β-cell destruction and the absence of autoantibodies[3]. Unlike classical autoimmune type 1 diabetes (AT1D), individuals with FT1D have a much shorter duration of hyperglycemic symptoms, present with a greater severity of ketoacidosis and hyperglycemia, yet have misleadingly normal glycated hemoglobin (HbA1c) at presentation[4].

We describe a case of FT1D that was missed at first presentation, followed by a series of FT1D from multi-ethnic Singapore, highlighting the importance of characterizing the correct diabetes subtype, as this informs optimal management from the outset.

METHODS

People diagnosed with FT1D between 2014 and 2022 at endocrinology units in two tertiary centers were identified using the 2012 diagnostic criteria for FT1D: (1) diabetes ketosis or ketoacidosis <7 days after onset of hyperglycemic symptoms, (2) plasma glucose ≥16 mmol/L and HbA1c <8.7% at presentation, and (3) serum C-peptide <0.3 µg/L (fasting) or <0.5 µg/L (post-meal)[1]. Clinical characteristics were collected. Statistical analysis was carried out using IBM SPSS Statistics 21.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics are expressed as the mean ± standard deviation (continuous variables), and frequency (percentage; categorical variables).

RESULTS

A 27-year-old man (case 1) with no medical history presented with 1 day of polyuria and polydipsia. He was lean (body mass index 19.7 kg/m^2). Investigations showed hyperglycemia (32.2 mmol/L), yet HbA1c was not raised (5.5%; normal hemoglobin level). The Emergency Department administered a single dose of subcutaneous aspart insulin (15 units), and discharged him with advice to see a general practitioner in a week. As his HbA1c was normal, he was not discharged with glucose-lowering medications or insulin.

Within 24 h, the patient returned with nausea, epigastric pain and lethargy, and was tachycardic and dehydrated. He now had diabetes ketosis (glucose 34.4 mmol/L, ketones 2.5 mmol/L), and was immediately started on intravenous hydration and insulin. Amylase and lipase levels were not raised. He was discharged on multiple daily insulin injections. One month later, C-peptide was undetectable (<0.01 µg/L, glucose 6.7 mmol/L). Anti-glutamic acid decarboxylase (GAD) levels were weakly positive (0.9 U/mL, reference 0–0.8 U/mL) and anti-islet cell antibodies were negative. A diagnosis of FT1D was made, and the patient was continued on multiple daily insulin injections.

CASE SERIES

Over 8 years, seven people with FT1D were identified. The mean age was 35.0 ± 6.4 years, 6/7 (85.7%) were Chinese, and three (42.9%) were female. None were overweight (body mass index 20.3 ± 1.6 kg/m^2). Symptom duration was very short (2.4 ± 1.2 days). Osmotic symptoms and abdominal pain were present in six (85.7%) people, whereas only one (16.7%) reported flu-like symptoms. Two had infective triggers, of whom one had COVID-19 infection.

Excluding case 1 who had been pretreated with insulin, the others presented with moderate to severe diabetes ketosis (mean glucose 40.9 ± 16.3 mmol/L, ketone level 5.3 ± 2.0 mmol/L, pH 7.18 ± 0.13). The mean HbA1c was not in the diabetes range (6.0 ± 0.5%). All but case 1 had negative GAD and ICA. C-peptide levels were low (0.05 ± 0.08 µg/L). Four people had abdominal imaging: one had diffuse pancreatic enlargement, another had peri-pancreatic fluid (Tables 1 and 2).

All patients were discharged with multiple daily insulin injections; four were later transitioned to continuous subcutaneous insulin infusion therapy (CSII), of whom three were on advanced hybrid closed loop systems (Table 3). They had experienced frequent symptomatic hypoglycemia episodes, which improved after structured education and transition to CSII. During the mean follow-up duration of 4.9 ± 2.9 years, one patient developed mild non-proliferative retinopathy 5 years after FT1D onset.

DISCUSSION

We describe the first case series of seven people with FT1D from Singapore. FT1D is not limited to East Asian populations, and presents unique diagnostic and management challenges.

Diabetes subtyping can be challenging among ethnic groups in Asia, where type 2 diabetes is more common, and develops at a younger age and lower body mass index than in people of white European ancestry[5]. Conversely, type 1 diabetes is rare (<1%), and the prevalence of positive GAD and ICA is low (maximum 41.5%) compared with white populations[6]. These overlapping phenotypes make it difficult to accurately subtype Asians with diabetes at presentation; the choice between insulin replacement versus sensitizing therapy becomes challenging.

Table 1 | Baseline characteristics

Characteristics	Results (Singapore cohort)	Results (Japanese cohort)[9]
Sex		
Female (%)	3 (42.9%)	–
Male (%)	4 (57.1%)	
Age at diagnosis (years)	35.0 ± 6.4	39.1 ± 15.7
BMI (kg/m^2)	20.3 ± 1.6	20.7 ± 3.9
Symptoms at presentation		
Flu-like symptoms (%)	1 (14.3%)	71.7%
Abdominal pain (%)	6 (85.7%)	72.5%
Osmotic symptoms (%)	6 (85.7%)	93.7%
Duration of symptoms (days)	2.4 ± 1.2	4.4 ± 3.1
Diabetic ketosis or ketoacidosis at presentation (%)	7 (100%)	100%
HbA1c at presentation (%)	6.0 ± 0.5	6.4 ± 0.9
Glucose level at presentation (mmol/L)	40.9 ± 16.3	44.4 ± 20.0
Ketone level at presentation (mmol/L)	5.3 ± 2.0	–
pH at presentation	7.18 ± 0.13	7.13 ± 0.13
Glutamic acid decarboxylase antibody-positive (%)	1 (14.3%)	5.07%
Islet cell antibody-positive (%)	0 (0%)	–
C-peptide level (ug/L), All paired glucose >5.5 mmol/L	0.05 ± 0.08	0.10 ± 0.10
Amylase levels (U/L; reference range 38–149 U/L)	221.6 ± 164.1	–
Lipase levels (U/L; reference range: 8–55 U/L)	290.8 ± 239.7	–
Total daily dose of insulin/ weight (u/kg)	0.62 ± 0.14	–

Data are presented as mean ± standard deviation, or total number (%). BMI, body mass index; HbA1c, glycated hemoglobin.

FT1D is an even rarer and more recently identified subtype of type 2 diabetes. Data are scarce, and limited to case reports outside of East Asia. FT1D differs from AT1D in its rapid onset of β-cell destruction, with our cohort presenting after a very short duration of osmotic symptoms, absence of weight loss and non-diabetes range HbA1c levels. Individuals with FT1D tended to be older than adult AT1D patients[2], and GAD and ICA were mostly negative. Given the lack of typical features associated with AT1D, the diagnosis was initially missed or delayed in three people. One was discharged without insulin, and two were initially diagnosed with acute pancreatitis, the latter being a common misdiagnosis in people with FT1D, as they often have elevated pancreatic enzymes (up to 98%)[1] and pancreatic swelling on imaging (36%)[7].

Six of seven individuals were of Chinese ethnicity, consistent with the high prevalence of FT1D (7–20% of type 1 diabetes) previously described amongst East Asians[8]. This is postulated to be related to genetic susceptibility unique to the Asian

Table 2 | Case details

Case	Age (years)	Sex	Ethnicity	BMI (kg/m²)	Precipitant	HbA1c (%)	C-peptide (ug/L)	Pancreatic imaging	Treatment	Total daily dose of insulin (units/kg)	Complications Macrovascular	Microvascular	Frequent hypoglycemia
1	27	M	Malay	19.7	NA	5.5	0.01	NA	MDI	0.604	No	Yes (mild non-proliferative retinopathy)	No
2	40	F	Chinese	20.1	NA	7.1	0.2	NA	MDI	0.828	No	No	No
3	32	M	Chinese	21.7	NA	6.2	NA	NA	MDI	0.679	No	No	No
4	44	F	Chinese	19	NA	5.5	0.01	Diffuse pancreatic enlargement with mild fat stranding	CSII	0.556	No	No	Yes
5	39	M	Chinese	19.9	Infection	6.2	0.02	Normal pancreas	CSII	0.444	No	No	Yes
6	35	F	Chinese	26.7	NA	6	0.01	Mild fluid around pancreatic tail	CSII	0.434	No	No	No
7	28	M	Chinese	18.7	COVID-19 infection	5.6	0.06	Normal pancreas	CSII	0.787	No	No	Yes

BMI, body mass index; CSII, continuous subcutaneous insulin infusion; F, female; HbA1c, glycated hemoglobin; M, male; MDI, multiple daily insulin injections; NA, not available.

Table 3 | Changes to glycemic parameters among people with fulminant type 1 diabetes initiated on advanced hybrid closed loop therapy

Glycemic variables	Pre-AHCL	Post-AHCL
Case 4		
HbA1c	5.5%	5.6%
Time in range	50%	92%
Time below range	37%	5%
Coefficient of variation	37.3%	29.4%
Case 5		
HbA1c	6.9%	6.2%
Time in range	56%	84%
Time below range	5%	3%
Coefficient of variation	46%	36.1%
Case 7		
HbA1c	6.6%	6.6%
Time in range	61%	81%
Time below range	15%	1%
Coefficient of variation	–	34.1%

ACHL, advanced hybrid closed loop; HbA1c, glycated hemoglobin.

population, due to class II human leukocyte antigen haplotypes (*DRB1*04:05-DQ1B*04:01* and *DRB1*09:01-DQB1*0303*)[8]. Baseline characteristics and clinical features were similar between the present cohort and that of Imagawa *et al.*[9], suggesting particular attention should be paid to individuals of East Asian descent presenting with features of FT1D, regardless of the country of diagnosis.

The failure to diagnose FT1D can be fatal. Unlike individuals with AT1D who experience a gradual decline in pancreatic β-cell function, individuals with FT1D develop absolute insulin deficiency from the onset, resulting in greater severity of hyperglycemia and acidosis at presentation. Prompt recognition and full insulin replacement from the onset is critical[1].

Even after diagnosis, long-term management is complex. Individuals with FT1D experience high glycemic variability (GV), a higher frequency of severe hypoglycemia, higher total daily insulin doses and higher incidence of microvascular complications within the first 5 years of diagnosis compared with AT1D[10]. In the present study, nearly half of the patients experienced high GV and frequent symptomatic hypoglycemia, and underwent early transition to CSII (<1 year from diagnosis), with demonstrable improvements in GV, TIR and hypoglycemia rates. Although the role of CSII in FT1D is limited to case reports[11], CSII clearly improves TIR and hypoglycemia rates in people with type 1 diabetes[12]; people with FT1D would be anticipated to similarly benefit from CSII and advanced hybrid closed loop systems.

This first case series of FT1D from Singapore highlights the need to promote awareness of this underrecognized subtype of type 1 diabetes. Normal HbA1c levels or negative GAD should not negate the diagnosis. Rapid β-cell destruction in these

individuals necessitates immediate insulin therapy. Early use of CSII could help address the higher GV and hypoglycemia.

DISCLOSURE

The authors declare no conflict of interest.

Approval of the research protocol: SingHealth Centralized Institutional Review Board (CIRB Reference Number 2022/2671).

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