Short Report

Fulminant type 1 diabetes in Caucasians: A report of three cases

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Abstract

Context. – Fulminant type 1 diabetes is a new clinical entity in which the process of β-cell destruction, and the subsequent progression of hyperglycaemia and ketoacidosis, are extremely rapid. Until now, this subtype of type 1 diabetes has only been reported in the Asian population, especially Japanese and Koreans.

Cases. – We report here on three cases of fulminant type 1 diabetes in Caucasian French women. Both the clinical and biological characteristics of these patients are similar to those reported in Japanese studies. Notably, all patients experienced severe ketoacidosis (pH < 7.1) that occurred abruptly after the onset of hyperglycaemic symptoms (<6 days), with near-normal HbA1c values at diagnosis (5.6, 6.4 and 6.8%). Patients were treated in the intensive care unit with basal-bolus insulin therapy with no remission of their diabetes; pancreatic islet-related autoantibodies were all negative. Fasting C-peptide levels were undetectable, suggesting complete destruction of pancreatic β-cells. HLA phenotyping of these Caucasian patients did not find the specific HLA haplotype (DRB1*0405-DQB1*0401) previously found to be linked to fulminant type 1 diabetes in Japanese patients.

Conclusion. – These are the first cases of fulminant type 1 diabetes reported in Caucasians. These cases reveal new perspectives as regards the worldwide distribution of this intriguing clinical entity.

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Keywords: Fulminant type 1 diabetes; Type 1B diabetes; Epidemiology; Caucasians

Résumé

Le diabète fulminant existe aussi chez les caucasiens : à propos de trois cas.

Le diabète fulminant est une entité clinique récemment décrite, qui est caractérisée par une destruction brutale et irréversible des cellules β pancréatiques d’origine non immunologique, qui conduit à une acidocétose sévère de survenue rapide. Jusqu’à présent, ce type particulier de diabète de type 1 avait été uniquement décrit dans des populations asiatiques, essentiellement japonaise et coréenne.

Cas cliniques. – Nous rapportons trois cas de diabète fulminant chez des patientes françaises d’origine caucasienne. Les caractéristiques cliniques et biologiques sont comparables à celles initialement décrites dans les cohortes japonaises. Notamment, toutes les patientes ont présenté une acidocétose sévère (pH < 7,1), survenue très rapidement après le début des premiers signes cliniques d’hyperglycémie (< 6 jours), avec des valeurs quasiment normales d’HbA1c au moment du diagnostic (5,6, 6,4 et 6,8 %). Les patientes ont été initialement hospitalisées en réanimation, puis traitées par un schéma d’insulinothérapie de type basal-bolus sans phase de « lune de miel ». Les anticorps (anti-GAD, -IA2 et ICA) étaient négatifs. Le peptide C à jeun était indétectable, témoignant d’une insulinopénie sévère. Les patientes n’avaient aucune origine asiatique. Le phénotype HLA na pas mis en évidence l’haplotype à risque de diabète fulminant décrit dans la population japonaise (DRB1*0405-DQB1*0401).

Conclusion. – Nous rapportons ici les premiers cas de diabète fulminant chez des caucasiens. Cela ouvre de nouvelles perspectives quant à la distribution géographique de ce sous-type de diabète.

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Mots clés : Diabète fulminant ; Diabète de type 1B ; Épidémiologie ; Caucasiens
1. Introduction

Fulminant type 1 diabetes is a recently discovered subtype of type 1 diabetes that was originally described in Japanese patients in 2000 [1]. The development of typical fulminant autoantibody-negative type 1 diabetes appeared to be strictly confined to Asia, with a high prevalence reported in Japan [2] and, more recently, in Korea [3]. It is defined as a form of diabetes in which the process of β-cell destruction—and therefore, the progression of hyperglycaemia and ketoacidosis—is extremely rapid. The main diagnostic criteria for fulminant type 1 diabetes, based on the results of a Japanese survey [2], are:

- the occurrence of diabetic ketoacidosis soon after the onset of hyperglycaemic symptoms (4.4 ± 3.1 days);
- highly elevated blood glucose levels (800 ± 300 mg/dL) associated with near-normal levels of HbA1c (6.4 ± 0.9%);
- fasting serum C-peptide < 0.3 ng/mL;
- virtually no detectable islet-related autoantibodies.

2. Case reports

2.1. Patient 1

A 42-year-old French woman complained of nausea, vomiting and severe upper abdominal pain, which began the day of her admission to hospital. Flu-like symptoms had developed five days earlier but without excessive thirst (polydipsia) or weight loss (BMI: 26.7 kg/m²). Upon admission, her blood glucose levels were highly elevated (536 mg/dL) and associated with near-normal levels of HbA1c (6.4 ± 0.9%);

- fasting serum C-peptide < 0.3 ng/mL;
- virtually no detectable islet-related autoantibodies.

2.2. Patient 2

An 18-year-old French woman complained of abdominal pain and nausea, which had begun six days before coming to hospital. She was admitted into the ICU because of uncontrolled vomiting and loss of awareness (Glasgow score: 9/15). She had not lost any significant weight (BMI: 19.5 kg/m²) but exhibited hypothermia at 35 °C. Physical examination revealed only a diffuse abdominal swelling without haemodynamic instability. Her plasma glucose levels were highly elevated (1200 mg/dL) and associated with severe ketoacidosis (urine ketone 3+; arterial blood pH: 7.05; arterial blood HCO3: 3.1 mEq/L). HbA1c was normal at 5.6%, without haemoglobinopathy on haemoglobin (Hb) electrophoresis. Her fasting serum C-peptide levels were below the detection limit (<0.1 ng/mL) after metabolic decompensation. Anti-GAD, anti-IA2, anti-islet cell and antithyroperoxidase antibodies were all negative. Serum pancreatic enzyme levels were within normal limits at the time of admission (lipase: 0.72 μkat/L, normal range: 0.00–1.00) but were transiently and moderately increased seven days later (lipase: 7.06 μkat/L; amylase: 3.48 μkat/L, normal range: 0.00–1.37). Abdominal CT was normal, excluding an acute pancreatitis. No diabetic complications were present.

The patient was Caucasian, and heterozygous for HLA-DRB1*07/04 and DQB1*02/DQB1*03 haplotypes. She rapidly recovered two days later after intravenous insulin infusion and rehydration. She was subsequently treated with a basal-bolus insulinotherapy regimen and did not experience any remission of her diabetes. However, due to glycaemic instability, insulin pump therapy was begun 16 months later. Three years after the diabetes diagnosis, her HbA1c had risen to 7.5% with 52 IU/day of insulin.

2.3. Patient 3

A 66-year-old French woman was hospitalized with a confusion syndrome that had begun the day before her admission to hospital. Neither flu-like nor abdominal symptoms were reported. The patient had been treated for nine months with corticosteroids (20 mg/day of prednisone) for severe leg arthralgia of unknown origin, with valpromide for bipolar disorder and spironolactone for hypertension. There was no weight loss, and her BMI was 22.3 kg/m² at the time of admission. Except for the disturbance in consciousness, physical examination was normal. Plasma glucose levels were drastically elevated (1213 mg/dL), and associated with severe ketoacidosis (capillary ketonaemia: 5 mmol/L; arterial blood pH: 6.98; arterial blood HCO3: 3.0 mEq/L). HbA1c was moderately increased at 6.8%. Fasting and glucagon-stimulated serum C-peptide levels were below the detection limit (<0.1 ng/mL) after metabolic decompensation. Anti-GAD and anti-IA2 antibodies were negative. However, serum pancreatic enzyme levels were elevated at the time of admission (lipase: 118 IU/L, normal range: 0–60; amylase: 1847 IU/L, normal range: 0–100). No pancreatic abnormality was observed on abdominal CT, and no diabetic complications were present.

As with the two other cases, the patient was Caucasian. She was heterozygous for HLA-DRB1*01/DRB1*04 and DQB1*03/DQB1*05 haplotypes. The patient was initially treated in the ICU with intravenous insulin and a large volume of intravenous normal saline for diabetic ketoacidosis. Her consciousness rapidly improved, and she was subsequently...
treated with a basal-bolus insulino therapy regimen. Her diabetes remained unstable, however, with HbA1c at 8.5% two months after diagnosis with 24 IU/day of insulin.

3. Discussion

The pathogenesis of type 1 diabetes mellitus involves the physical destruction of pancreatic β-cells, leading to absolute insulin deficiency and, in severe cases, to life-threatening ketoacidosis. Type 1 diabetes can be divided into two subgroups:

- autoimmune type 1 diabetes (1A);
- idiopathic diabetes (1B) [4].

Type 1B diabetes includes ketosis-prone diabetes that is mainly observed in patients of African origin. However, more recently, fulminant type 1 diabetes has also been identified in Asian populations. This diabetes subtype, which is also included in type 1B diabetes, accounts for approximately 20% of acute-onset type 1 diabetes in Japanese patients [1] and 30% in Korean patients with adult-onset type 1 diabetes [3]. In addition, cases have been reported among Filipino [5] and Chinese patients [6].

Type 1B diabetes includes ketosis-prone diabetes that is mainly observed in patients of African origin. However, more recently, fulminant type 1 diabetes has also been identified in Asian populations. This diabetes subtype, which is also included in type 1B diabetes, accounts for approximately 20% of acute-onset type 1 diabetes in Japanese patients [1] and 30% in Korean patients with adult-onset type 1 diabetes [3]. In addition, cases have been reported among Filipino [5] and Chinese patients [6].

As for Caucasians, no fulminant type 1 diabetes was reported among 82 cases of newly diagnosed type 1 diabetes in Italy [7]. However, it should be mentioned that a case of type 1 diabetes with rapid onset was described during a severe systemic echovirus-9 infection in a six-week-old girl in the Netherlands [8], but the clinical context in that case was very different from that reported here.

In the present report, we describe—for the first time—three cases of fulminant type 1 diabetes in adult Caucasian patients. As summarized in Table 1, the clinical course of the disease, as well as its biological parameters, is similar to those reported in Japan [9]. Notably, all of our patients fulfilled the main diagnostic criteria for fulminant type 1 diabetes:

- abrupt onset of disease with a brief duration of diabetic symptoms (<6 days) and near-normal HbA1c levels at diagnosis;
- the presence of severe acidosis requiring ICU hospitalization at diagnosis;
- negative findings for islet-related autoantibodies;
- no detectable C-peptide secretion, suggestive of complete destruction of pancreatic β-cells.

Also as usually reported, serum pancreatic enzyme levels were transiently elevated in two out of our three patients, with no pancreatic swelling on CT scans. Surprisingly, pancreatic enzyme HbA1c levels did not rise in Patient 1, although a similar observation has been reported among Japanese patients [10]. However, it should be pointed out that elastase-1 was not measured in our study.

As initial clinical features, two of our patients experienced abdominal symptoms (vomiting and abdominal pain, respectively). Disturbance of consciousness was also seen in two patients. The flu-like symptoms that often preceded the disease onset in the Japanese survey [2] were only observed in Patient 1.

The pathogenesis of this disease remains unclear. Pancreatic biopsies performed in patients with fulminant type 1 diabetes reveal a severe reduction in the number in both β- and α-cells [11]. While insulitis is not a common feature in the pancreas of such patients, lymphocytic infiltration of exocrine pancreatic tissue is often observed [1,10]. The involvement of viruses has also been suggested in the pathogenesis of the disorder, as coxsackieviruses and human herpesvirus 6 have both been associated with fulminant type 1 diabetes [9].

In the nationwide survey in Japan, a specific HLA haplotype (DRB1*0405-DQB1*0401) was found to be linked to fulminant type 1 diabetes, having been retrieved in 41.8% of cases [12]. However, the HLA haplotypes in our patients were different from those found to confer susceptibility to the disorder in the Japanese population. This is not surprising as HLA-associated susceptibility to autoimmune type 1 diabetes differs between Caucasians and Asians. Moreover, it has been previously reported that, in the case of fulminant type 1 diabetes, there is no common HLA DR-DQ haplotype among the Japanese, Koreans, Chinese or Filipinos. This suggests that a genetic factor other than HLA class II apparently confers susceptibility to the development of fulminant type 1 diabetes [13].

Until now, fulminant type 1 diabetes was thought to be restricted to Asian ethnicity. Our clinical findings in Caucasians uncover new perspectives in terms of the worldwide distribution of this intriguing clinical entity.

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References


