

# Discovery and Establishment of Fulminant type 1 Diabetes -From a patient to clinical entity

**Akihisa Imagawa, MD, FACP**

Osaka University, Japan

ACP Japan Chapter meeting

Tokyo, Japan

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# Type 1 diabetes

- Beta cell destruction, usually leading to absolute insulin deficiency
- A chronic autoimmune disease
  - =Autoantibody in patients' sera
    - Islet cell antibodies (ICA)
    - Anti-GAD antibody
    - Anti-IA-2 antibody

# 内科診療録

診察医 **佐間外澤** 18<sup>時35分</sup> 月 日  
**'9 8.11**

紹介者名

借用フィルム

[ 有 ・ 無 ]

返還済

## 【主訴】

## 【現病歴】

8.8 511 20時がけにて水10をとりて

10 511 水10の人でけり

11 3時 1時にて 水10けりの人でけり

尿も多し

ET 36.9℃

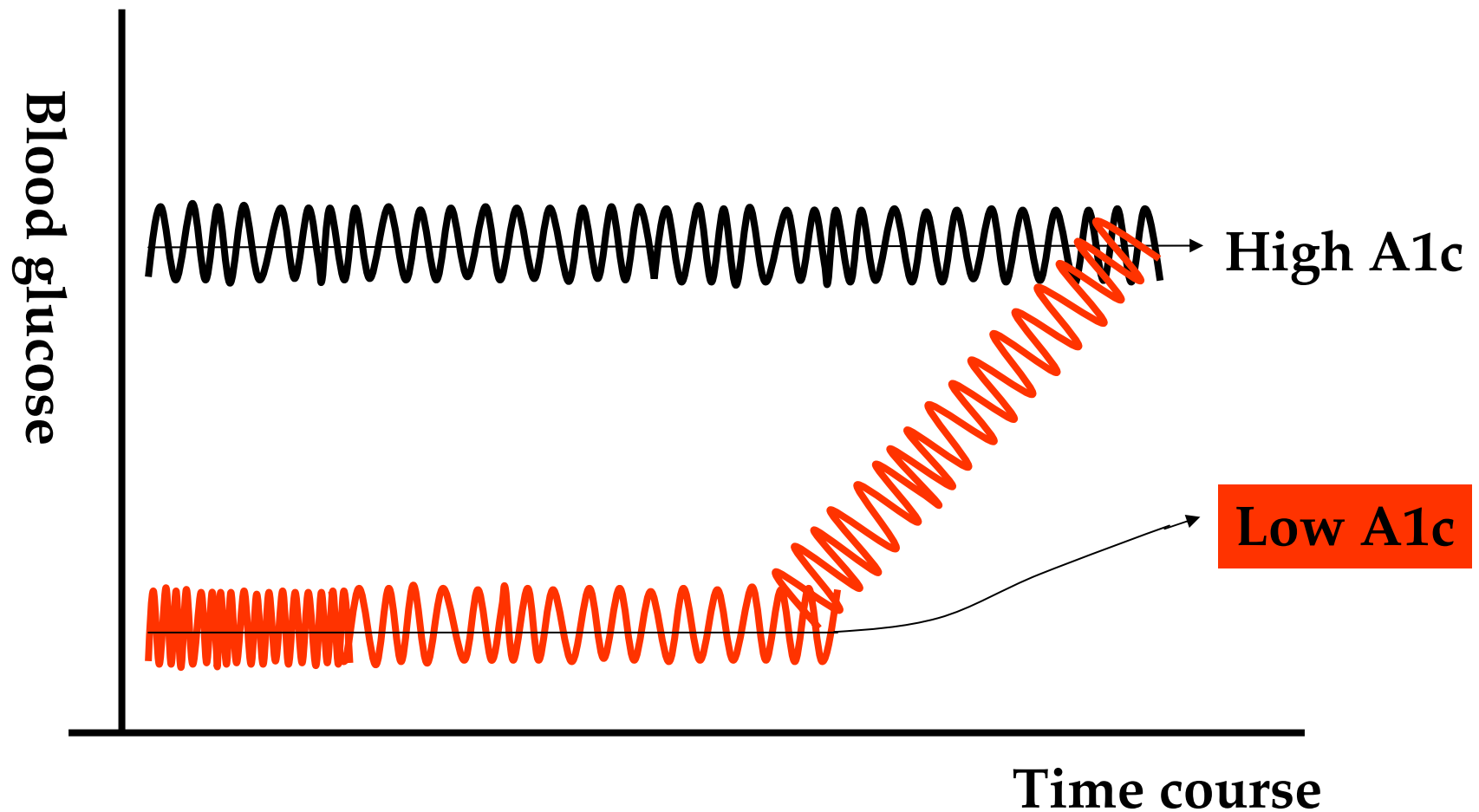
内  
精神  
神内  
小  
外  
整形  
脳外  
心外  
皮  
泌



# A Case of Type 1 Diabetes

- 57-y.o. Male
- Chief Complaints:  
Thirsty, Polyuria
- 3 days' history of the  
above symptoms
- Physical Exam. :  
Unremarkable
- U. glucose (++++)
- U. Ketone (+++)
- Glucose 811 mg/dl
- Arterial pH 7.22
- U.-CPR 6.5 µg/day  
(N:50-100)
- GAD Ab(-), IA-2Ab (-),  
ICA (-)
- HbA<sub>1c</sub> 6.5 %

# Blood glucose and HbA1c





# Research question

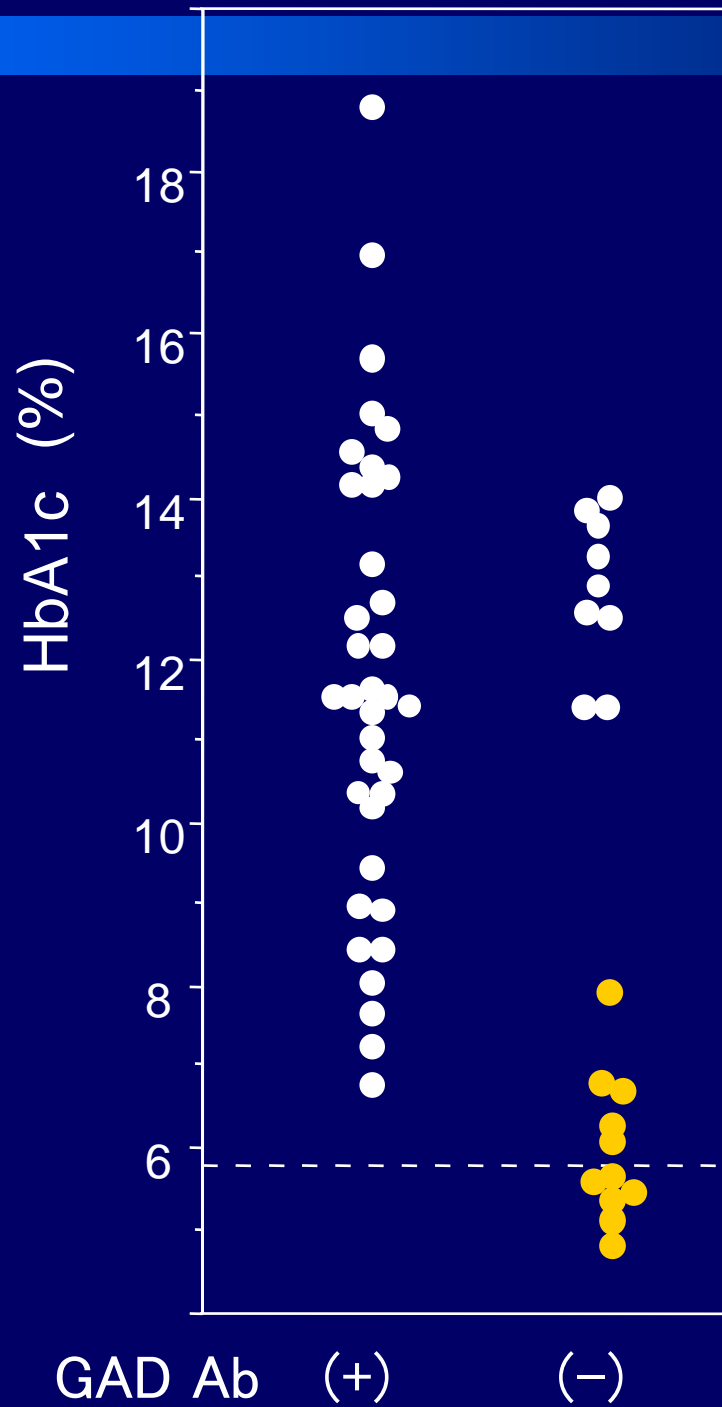
- Such atypical cases might be a new subgroup of diabetes and if so, can we prove it? And how can we do that?
  - Autoantibody negative
  - Low A1c despite high BG at onset



# Study design and methods

- Consecutive 56 patients with new-onset type 1 diabetes in 8 hospitals
  - Age, sex, etc.
  - Signs and symptoms
  - **Blood glucose and HbA1c levels**
  - Blood biochemistry
  - **C-peptide**
  - Blood gas analysis
  - **Islet-related autoantibodies**

# GAD Ab /HbA1c







# Clinical characteristics of the 3 groups

	<b>GAD(-)- low A1c N=11</b>	<b>GAD(-)- high A1c N=9</b>	<b>GAD(+) N=36</b>
HbA1c (%)	<b>6.4*</b>	12.9	11.7
BS (mg/dl)	<b>773*</b>	439	398
Duration(days)	<b>4*</b>	46	53
U-C peptide (µg/day)	<b>3*</b>	20	21
ICA (%)	<b>0*</b>	43	68
IA-2 Ab (%)	<b>0*</b>	43	84

\*P<0.05



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**=Fulminant type 1 diabetes**

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# Fulminant Type 1 Diabetes

A nationwide survey in Japan

AKIHISA IMAGAWA, MD<sup>1</sup>  
TOSHIAKI HANAFUSA, MD<sup>2</sup>  
YASUKO UCHIGATA, MD<sup>3</sup>  
AZUMA KANATSUKA, MD<sup>4</sup>  
EJI KAWASAKI, MD<sup>5</sup>  
TETSURO KOBAYASHI, MD<sup>6</sup>

AKIRA SHIMADA, MD<sup>7</sup>  
IKKI SHIMIZU, MD<sup>8</sup>  
TETSUYA TOYODA, MD<sup>9</sup>  
TARO MARUYAMA, MD<sup>10</sup>  
HIDEICHI MAKINO, MD<sup>11</sup>

**T**ype 1 (insulin-dependent) diabetes is characterized by insulin deficiency from the destruction of pancreatic  $\beta$ -cells. According to the recently proposed classification of diabetes by the American Diabetes Association (ADA)

**-161 patients with Fulminant T1D**  
**- Cons in 45%**  
**- 1 patient died**

**RESULTS** — In our hospitals, of the 222 patients studied, 43 (19.4%) were diagnosed with fulminant type 1 diabetes, 137 (61.7%) were classified as having autoimmune type 1 diabetes, and 42 were type 1 diabetic subjects who were not fulminant and did not have anti-islet antibodies. An additional 118 fulminant patients outside our hospitals were enrolled, making a total of 161 fulminant type 1 diabetic subjects (83 male and 78 female subjects; 14 children/adolescents and 147 adults) identified from all over Japan. (In 2000, the average incidence was three cases per month.) Flu-like symptoms and pregnancy were more frequently observed in the fulminant than in the autoimmune group ( $P < 0.001$ ). In the fulminant patients, 4.8% were positive for anti-GAD antibodies and none were positive for anti-islet antigen 2 antibodies.

**CONCLUSIONS** — Fulminant type 1 diabetes is a distinct subtype and accounts for ~20% of the ketosis-onset type 1 diabetes cases in Japan. Flu-like symptoms are characteristic of disease onset. Metabolic derangement is more severe in this subtype than in autoimmune type 1 diabetes.


a marker of type 1 diabetes. These islet-related autoantibodies are anti-GAD antibodies (GADAb), insulin autoantibodies (IAA), and anti-islet antigen 2 (IA-2)/IA-2 $\beta$  antibodies (4,5).

However, type 1 diabetic patients are not always positive for these autoantibodies, even at the onset of overt diabetes (6,7). Patients with type 1 diabetes who do not have islet autoantibodies at the time of diagnosis are classified as having idiopathic or type 1B diabetes. In Japan, several cases have been reported in which islet-related autoantibodies were negative and the onset of diabetes was acute (8–12). Imagawa and colleagues (13,14)



# Criteria of Fulminant type 1 diabetes

- For screening
  - Ketosis within a week after the onset of hyperglycemic symptoms
  - Plasma glucose level  $\geq 288\text{mg/dl}$  at first visit
  
- For definite diagnosis



# Lessons from the clinical research of fulminant type 1 diabetes

- See a patient carefully
- Proceed step by step
  - Case report (n=1)
  - Hospital based study (n=11)
  - Nationwide survey (n=161)



# Has “fulminant type 1 diabetes” changed the clinical scene?

- Yes.
- Pick up the patients with life-threatening diabetes at first visit.



# 劇症1型糖尿病の発見と確立



# A Case of Type 1 Diabetes

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# -161 patients with Fulminant T1D

**OBJECTIVE** — To describe the clinical and immunologic characteristics of fulminant type 1 diabetes, a novel subtype of type 1 diabetes, we conducted a nationwide survey.

**RESEARCH DESIGN AND METHODS** — History and laboratory data, including islet-related autoantibodies, were examined in 222 patients with fulminant and nonfulminant type 1 diabetes in our hospitals in addition to another 118 patients with fulminant type 1 diabetes located outside our hospitals in Japan.

**RESULTS** — In our hospitals, of the 222 patients studied, 43 (19.4%) were diagnosed with fulminant type 1 diabetes, 137 (61.7%) were classified as having autoimmune type 1 diabetes, and 42 were type 1 diabetic subjects who were not fulminant and did not have anti-islet antibodies. An additional 118 fulminant patients outside our hospitals were enrolled, making a total of 161 fulminant type 1 diabetic subjects (83 male and 78 female subjects; 14 children/adolescents and 147 adults) identified from all over Japan. (In 2000, the average incidence was three cases per month.) Flu-like symptoms and pregnancy were more frequently observed in the fulminant than in the autoimmune group ( $P < 0.001$ ). In the fulminant patients, 4.8% were positive for anti-GAD antibodies and none were positive for anti-islet antigen 2 antibodies.


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into idiopathic (type 1B) diabetes (1,2).

Since 1974, when Bottazzo et al. (3) reported the presence of islet cell antibodies (ICAs) in the sera of type 1 diabetic patients, several autoantibodies to pancreatic islet cells have been recognized as a marker of type 1 diabetes. These islet-related autoantibodies are anti-GAD antibodies (GADAb), insulin autoantibodies (IAA), and anti-islet antigen 2 (IA-2)/IA-2 $\beta$  antibodies (4,5).

However, type 1 diabetic patients are not always positive for these autoantibodies, even at the onset of overt diabetes (6,7). Patients with type 1 diabetes who do not have islet autoantibodies at the time of diagnosis are classified as having idiopathic or type 1B diabetes. In Japan, several cases have been reported in which islet-related autoantibodies were negative and the onset of diabetes was acute (8–12). Imagawa and colleagues (13,14)



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