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Sasaki, Haruka
Institute of Health Science, Kyushu University | Fukuoka University Chikushi Hospital

Kaku, Yoshio
Fukuoka University Chikushi Hospital

Fukudome, Miho
Fukuoka University Chikushi Hospital

Tomita, Ken’ichi
Fukuoka University Chikushi Hospital

他

https://doi.org/10.15017/18346

出版情報：健康科学. 32, pp.103-107, 2010-03-30. Institute of Health Science, Kyushu University
バージョン：
権利関係：

健 康 科 学
Vol.32, 2010 年 3 月

— Report —

The Occurrence of Emotional/Mental Stress-Induced Atypical "Ketosis-prone Type 2 Diabetes" in Newly Diagnosed Japanese Subjects—Preliminary observations

Haruka SASAKI, MD, PhD [1, 2], Yoshio KAKU, MD [2], Miho FUKUDOME, MD [2],
Kenichi TOMITA, MD [2], Kenzou IINO, MD, PhD [2],
Keiko UEZONO, MD, PhD [1], Shuzo KUMAGAI, PhD [1]

1. Introduction

The onset of diabetes mellitus secondary to emotional stress has been cited frequently in the literature. Balasubramanyam et al.[1), 2)] and Umpierrez[3)] suggested a need for a more accurate classification (Aβ classification) of ketosis-prone diabetes (KPD) in recent articles, including their own aimed at guiding clinical practice and pathophysiological studies. KPD, an emerging form of diabetes defined by presentation with diabetic ketoacidois, is phenotypically heterogeneous. We have read their study with great interest and wondered whether there were any stressful life events before the actual "onset" of ketosis and/or ketoacidosis in their cases (specially, Type 2B A−β +)[1)-3)].

Psychological stress is widely recognized among the environmental factors playing a role the development of diabetes[5), 6)]. However, this concept is vague, and there are individual differences, so it is difficult to provide direct substantiation in humans with exacerbating factors other than hyperglycemia or stress stimulus. The authors have treated some cases, which have been tentatively referred to as emotional stress-induced Atypical "KPD".

2. Research design including Cases presentation and Methods

The index case involved a 63-year-old homemaker who had worries concerning serious problems with her inheritance. She became aware of polydipsia and polyuria in addition to systemic fatigue at the end of 1997. She began to lose weight (-13kg/3 months) and started drinking mineral water due to extreme thirst. In February 1998, she lost consciousness after urination and was hospitalized immediately because her blood glucose was 420 mg/dl and HbA_{1c} was 15.0 % (reference value; 4.8-5.8%). On admission, her weight was 67 kg (BMI: 24.6 kg/m^2), feeling exhausted, and a blood gas analysis showed pH 7.425 and 556 μM/l total ketone bodies. She was negative for anti islet cell (ICA) and glutamic acid decarboxylase (GAD-65) antibodies. The insulin treatment was intensified and the

1) 九州大学健康科学センター Institute of Health Science, Kyushu University
2) 福岡大学筑紫病院 Division pf Diabetic and Endocrine Medicine, Chikushi Hospital, Fukuoka University
*連絡先：佐々木 悠 〒614-0001 福岡県早良区百道浜 1-2-6-1202 Tel&Fax：092-822-1735
*Correspondence to: Haruka Sasaki 1-2-6-1202 Momochihama, Sawaraku, Fukuoka 614-0001, Japan
Tel&Fax: +81-92-822-1735 E-mail: haruka-s@mx3.canvas.ne.jp

required insulin dosage was decreased following continuous subcutaneous insulin infusion (CSII) after hospitalization. After the metabolic imbalance such as hyperglycemia was corrected, the fasting serum C-peptide concentration was 3.1 ng/ml. The insulin infusion was withdrawn on the 31st day of administration, she is currently under observation while maintaining glycemic control (HbA_{1c} 6.4 %) using 3mg/day glimepiride and 750mg/day metoformin (first line in table).

Table 1 shows the clinical characteristics of six adults, including the case described above, who do not have a history of consuming large amounts of soft drinks[7] and obvious changes of inhibited food-intake and/or an over-consumption of alcohol, but do include episodes within the past three or eight months from the point when the patients noticed typical symptoms of diabetic ketosis and/or mild ketoacidosis which were determined to be the "onset". No history of any obvious infections (abscesses, sepsis, urinary tract and upper respiratory infections) was found, such as cerebro-cardiovascular disease. All of the cases indicate a novel presentation of diabetes and insulin was temporarily used along with CSII and intensified insulin treatment. They presented diabetic ketosis as the initial manifestation of the disease. Such patients are usually relatively obese, upper middle-aged adults without any immunologic evidence of type 1 diabetes (JDS/WHO 1998 and ADA 2005 classification: Type 1A [autoimmune]). We did not find any severe acidosis in these cases, because the relative high insulin levels may have mitigated the development of lypolysis and ketogenesis. Problems of internal conflict and coping and/or the allostatic response of the patients were involved, in addition to aging and events including individual differences[8]. The clinical characteristics and clinical course of these patients are shown in Figure 1 and Table 2. One limitation of this retrospective investigation is that we did not measure the level of stress. However, it was not easy to measure the emotional or mental stress directly at that time.

3. Results and discussions

The definite pathophysiology of ketosis-prone type 2 diabetes remains unknown[4]. Psychological stress is an important trigger for both an insufficiency of insulin secretion and insulin resistance[6]. These conditions can be associated with an absolute indication of insulin, an involvement of slowly progressive "glucose toxicity"[9], a correlation between idiopathic type 1 (Type 1B) of the honeymoon remission or genetic/ethnic minority variation[2)-4)], a correlation with metabolic syndrome[10] or human herpes-virus 8 infection[11] and Björtorp's theory[12]. Can an episode of extreme stress be a potential trigger of these atypical diabetes manifestation (KPD Type 2B A-β + [2)]) ? Preserved β -cell function is also a feature of KPD even in Japanese subjects[9), 10)]. The establishment of the clinical condition of type 2 diabetes includes a heterogeneous spectrum of symptoms and it is believed that such cases may be due to the influence of our modern "stressful society". The mechanisms of this phasic course might be still speculative, so this hypothesis necessitate a thorough investigation. However, the recognition of this type of patient is important and has implications for adequate long-term management strategies for counseling and emotionally-focused therapy in the follow-up.

Table 1: Clinical characteristics of the cases

No.	Age / Sex (years)	Family history of diabetes / Flu-like symptoms/ MVC*	Episodes of stressful events **	Performance at diagnosis			Blood total Ketone (μ M/l) / Ketonuria	Pancreatic islet autoantibody (GAD-65 / ICA)	Glucagon test at glycemic control, CPR ng/ml (before/6 min.)	Observation period (years) / Final HbA_{1c}(%)	Recent treatment
				BMI / Maximum BMI (Kg/m^2)	Plasma glucose (mg/dl) / HbA_{1c}(%)***	pH / HCO_3 (mEq/l)					
1)	63 / F	(+) / (–)/(–)	Troubles with inheritance	24.5 / 30.1	420 / 15.0	7.42 / 24.4	556 / (1+)	(–) / (–)	3.1 / 5.8	4.5 / 6.4	Diet + BG, SU
2)	61 / F	(–) / (–)/(–)	Business bankruptcy & suicide of a brother	23.1 / 26.5	324 / 10.8	7.419 /25.7	596 / (1+)	(–) / ND	1.5 / 3.2	4.1 / 5.7	Diet + SU
3)	60 / M	(–) / (–)/(–)	Gamma knife treatment due to acoustic neuroma	24.1 / 25.8	806 / 12.6	7.38 / 24.9	383 / (1+)	(–) / (–)	2.7 / 6.3	2.9 / 5.8	Diet + SU, α GI
4)	55 / F	(–) / (–)/(–)	Death of husband & moving from a house	29.6 / 31.3	368 / 8.9	7.38 / 22.6	1,821 / (2+)	(–) / (–)	Urine CPR 42 μ g/day	1.2 / 6.0	Diet
5)	46 / M	(+) / (–)/(–)	Forced job change & disability for work	22.9 / 25.6	575 / 11.3	7.39 / 20.6	2,381 / (3+)	(–) / (–)	0.5 / 1.9	4.2 / 11.2	SU & Recurrence of KPD with brain abscess, Death
6)	55 / M	(+) / (–)/(–)	Serious work problems	17.9 / 23.1	549 / 16.5	7.46 / 25.2	1,551 / (2+)	(–) / (–)	1.4 / 3.9	8.5 / 5.8	Diet + SU

M: Male, F: Female, *MVC: Micro-vascular complications, **: Within 3 or 8 months prior to "onset", BMI: body mass index, ***: HbA_{1c}; HPLC method,
GAD-65: Anti glutamic acid decarboxylase antibody (Cosmic corporation, Tokyo),
ICA: Islet cell antibody (Indirect immunofluorescence method: Scripps Research Institute, San Diego, CA), KPD: Ketosis-prone diabetes, SU:sulfonylureas, BG:biguanide, α -GI: α -glucosidase inhibitor, ND:not determined.

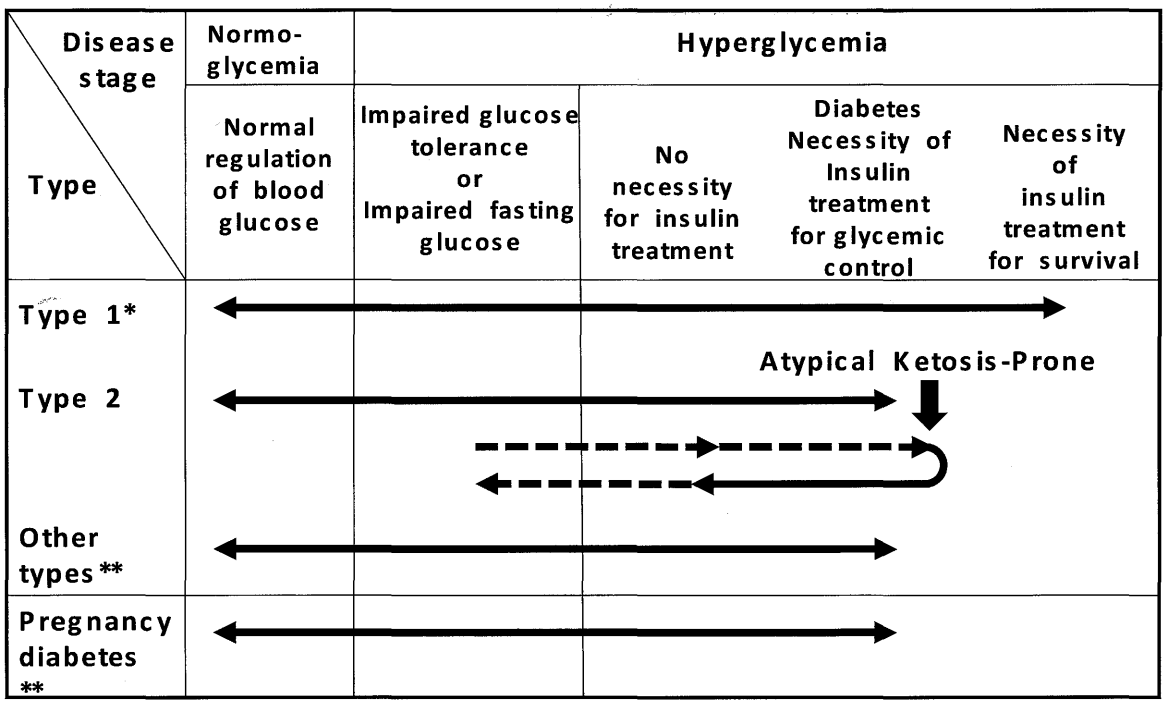

Figure 1: Correlation between the etiological classification of glucose metabolic disorder and disease stages (revised version of ADA, 1997)

*Including type 1 diabetes in the "honeymoon" regression period.
**Cases in which insulin treatment is necessary to sustain life are observed on rare occasions.

Table 2: Clinical characteristics of Atypical "Ketosis-prone Type 2 diabetes mellitus"

1) Acute onset (hyperglycemia, thirst and weight loss, etc)
2) There were stressful life-events in most cases, but there is not obvious causes such as infection and/or CVD, and onset occurs with the expression of ketosis(acidosis does not always occur)
3) There are many cases with a history of moderate obesity in relatively upper middled aged adults.(No history of excessive intake of soft drinks)
4) Insulin secretory property is maintained to some degree (Urine CPR and glucagon load indices)
5) Negative ICA, Anti-GAD-65 antibody and IA-2 antibody
6) There is not always a family history of diabetes
7) Insulin can be withdrawn with temporary implementation of CSII and intensified insulin therapy, and subsequently be remitted
8) After withdrawal of insulin, it can be controlled only by diet or oral diabetic drugs for a certain period of time

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