The Occurrence of Emotional/Mental Stress-Induced Atypical “Ketodid-prone” Type 2 Diabetes” in Newly Diagnosed Japanese Subjects: Preliminary observations

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

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1. Introduction
The onset of diabetes mellitus secondary to emotional stress has been cited frequently in the literature. Balasubramanyam et al.1, 2) and Umpierrez3) 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 ketoacidosis, 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 Aβ1)-3).

Psychological stress is widely recognized among the environmental factors playing a role the development of diabetes5, 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 HbA1c was 15.0% (reference value; 4.8-5.8%). On admission, her weight was 67 kg (BMI: 24.6 kg/m²), feeling exhausted, and a blood gas analysis showed pH 7.425 and 556 μ M/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
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 (HbA₁c 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 drinks7) 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 differences8). 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 unknown9). Psychological stress is an
important trigger for both an insufficiency of insulin
secretion and insulin resistance6). 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
variation9-11), a correlation with metabolic syndrome10) or
human herpes-virus 8 infection11) and Björtorp’s theory12).
Can an episode of extreme stress be a potential trigger of
these atypical diabetes manifestation (KPD Type 2B A-
2)) ? Preserved β-cell function is also a feature of KPD even
in Japanese subjects9, 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>
<thead>
<tr>
<th>No.</th>
<th>Age / Sex</th>
<th>Family history of diabetes / Flu-like symptoms / MVC*</th>
<th>Episodes of stressful events **</th>
<th>Performance at diagnosis</th>
<th>Blood total Ketone (μ M/I) / Ketonuria</th>
<th>Pancreatic islet autoantibody (GAD-65 / ICA)</th>
<th>Glucagon test at glycemic control, CPR ng/ml (before/6 min.)</th>
<th>Observation period (years) / Final HbA(_1c)(%)</th>
<th>Recent treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1)</td>
<td>63 / F</td>
<td>(+) / (–)/(–) Troubles with inheritance</td>
<td>24.5 / 30.1</td>
<td>420 / 15.0</td>
<td>7.42 / 24.4</td>
<td>556 / (1+)</td>
<td>(-) / (–)</td>
<td>3.1 / 5.8</td>
<td>4.5 / 6.4</td>
</tr>
<tr>
<td>2)</td>
<td>61 / F</td>
<td>(–) / (–)/(–) Business bankruptcy &amp; suicide of a brother</td>
<td>23.1 / 36.5</td>
<td>324 / 10.8</td>
<td>7.419 / 25.7</td>
<td>596 / (1+)</td>
<td>(-) / ND</td>
<td>1.5 / 3.2</td>
<td>4.1 / 5.7</td>
</tr>
<tr>
<td>3)</td>
<td>60 / M</td>
<td>(–) / (–)/(–) Gamma knife treatment due to acoustic neuroma</td>
<td>24.1 / 25.8</td>
<td>806 / 12.6</td>
<td>7.38 / 24.9</td>
<td>383 / (1+)</td>
<td>(-) / (–)</td>
<td>2.7 / 6.3</td>
<td>2.9 / 5.8</td>
</tr>
<tr>
<td>4)</td>
<td>55 / F</td>
<td>(–) / (–)/(–) Death of husband &amp; moving from a house</td>
<td>29.6 / 31.3</td>
<td>368 / 8.9</td>
<td>7.38 / 22.6</td>
<td>1,821 / (2+)</td>
<td>(-) / (–)</td>
<td>1.2 / 6.0</td>
<td>Diet</td>
</tr>
<tr>
<td>5)</td>
<td>46 / M</td>
<td>(+) / (–)/(–) Forced job change &amp; disability for work</td>
<td>22.9 / 25.6</td>
<td>575 / 11.3</td>
<td>7.39 / 20.6</td>
<td>2,381 / (3+)</td>
<td>(-) / (–)</td>
<td>0.5 / 1.9</td>
<td>4.2 / 11.2</td>
</tr>
<tr>
<td>6)</td>
<td>55 / M</td>
<td>(+) / (–)/(–) Serious work problems</td>
<td>17.9 / 23.1</td>
<td>549 / 16.5</td>
<td>7.46 / 25.2</td>
<td>1,551 / (2+)</td>
<td>(-) / (–)</td>
<td>1.4 / 3.9</td>
<td>8.5 / 5.8</td>
</tr>
</tbody>
</table>

Table 1: Clinical characteristics of the cases

### 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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References