Clinical characteristics of type 1 diabetes mellitus in Taiwanese children aged younger than 6 years: A single-center experience

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Background/purpose: Cases of type 1 diabetes mellitus in children aged younger than 6 years in Taiwan has increased in the past 10 years. This retrospective study aimed to review the management experience of such patients in a single center.

Methods: From January 2004 to June 2015, 52 newly diagnosed diabetic children younger than 6 years who had regular follow-up for > 1 year were enrolled, as well as 94 older diabetic children for comparison. Their medical records were thoroughly reviewed.

Results: The most common symptoms and signs were polyuria, polydipsia, dry lips, weight loss, and nocturia. Among the children younger than 6 years, 87% had ketoacidosis upon diagnosis—significantly higher than that of the older age group—and 88% had at least one islet cell autoantibody detected. Their serum C-peptide levels were significantly lower and the frequency of insulin autoantibodies detected was significantly higher compared with the older age group (37% vs. 10%). The remission rate of the young diabetic patients was significantly lower than that of the older age group (40% vs. 59%), but there was no difference in time of onset and duration of remission between the two groups.

Conclusion: Autoimmune destruction of pancreatic β-cells is an important cause of type 1 diabetes mellitus in Taiwanese children aged younger than 6 years. These patients usually have a low insulin reserve and severe ketoacidosis upon diagnosis. A high index of suspicion in the presence of classic symptoms of diabetes in young children is important to prevent complications.

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Introduction

The most common type of diabetes mellitus in children is type 1 diabetes mellitus (T1DM), which in most cases is caused by the autoimmune destruction of pancreatic β-cells. Although the incidence of T1DM in Taiwanese children is much lower than that among Caucasian children, the underlying mechanisms are the same. Some newly diagnosed T1DM patients experience a period of good blood glucose control, with a reduction of daily insulin dose after the start of insulin therapy. This period is known as the “honeymoon period.” The underlying mechanism of the honeymoon period remains unknown but a transient restoration of residual pancreatic β-cell function in an otherwise insulin-sensitive environment has been proposed. Few cases remain symptom-free without any insulin injection (complete remission) and most patients still require small amounts of insulin to maintain near normal blood glucose levels (partial remission) during the honeymoon period. This period has since become the potential target window for immunomodulation therapy to preserve residual pancreatic β-cell mass. However, there is a paucity of updated data in Taiwanese children with T1DM.

In the past few decades, the annual incidence of T1DM in children worldwide, including Taiwan, has been increasing. Cases of T1DM in younger children is increasing but few reports present clinical data. Thus, this retrospective study aimed to assess a single-center experience in the management of T1DM in Taiwanese children aged younger than 6 years.

Subjects and methods

From January 2004 to June 2015, the medical record of all children aged ≤18 years with new onset of T1DM diagnosed at the Department of Pediatrics of National Taiwan University Hospital were reviewed. Among them, 52 children aged younger than 6 years, who had detailed data for analysis, and who had been followed-up at the Pediatric Endocrine Clinic of National Taiwan University Hospital for longer than 1 year were enrolled in this study. In the same period, 94 children aged 6–18 years were enrolled for comparison. The diagnosis of T1DM was made according to the 1997 Criteria of the Expert Committee. Diabetic ketoacidosis (DKA) was diagnosed in the presence of pH < 7.3, hyperglycemia, ketonemia and/or ketonuria, and serum bicarbonate < 15mM.

Complete history, including family history, and physical examination were recorded for all patients with T1DM upon diagnosis. Laboratory tests, including blood glucose, glycated hemoglobin (HbA1c), ketone bodies, serum sodium, potassium, chloride, blood gas analysis, antiglutamic acid decarboxylase 65 autoantibodies (GADA), anti-insulinoma antigen-2 autoantibodies (IA-2A), insulin autoantibodies (IAA), and C-peptide levels were measured using commercially available kits. Islet-cell autoantibodies, including GADA, IA-2A, and IAA were measured as previously reported.

All of the patients were regularly followed up once every 3 months. The patients’ height, weight, daily insulin doses, blood sugar, and HbA1c levels were checked upon each visit. Remission was defined according to the criteria reported by Mortensen et al.

Statistical analysis

All data were presented as percentage or as mean ± standard deviation. Pearson’s χ² test was used to compare categorical data, whereas the Mann–Whitney U-test was used to compare numerical data. One-way analysis of variance was used for the analysis of the remission period in both age groups. Statistical significance was set at p < 0.05. All statistical analyses were performed using SPSS 20.0 Package for Windows (SPSS Inc, Chicago, IL, USA).

Results

The study enrolled 52 children aged younger than 6 years, including 26 boys and 26 girls. Their age upon diagnosis was 4.3 ± 1.6 years. One patient had a mother and two patients had siblings with T1DM. However, of the 94 children aged 6–18 years enrolled for comparison, there were 40 boys and 54 girls. Their age upon diagnosis was 10.8 ± 2.6 years.

The most common initial clinical manifestations in children aged < 6 years were polyuria (96%), polydipsia (92%), dry lips (81%), body weight loss (79%), nocturia (77%), previous history of respiratory tract infection (48%), dyspnea (46%), sunken eyeballs (24%), and polyphagia (21%). There were no significant differences in most of the clinical findings between children aged < 6 years (younger age group) and those aged 6–18 years (older age group). However, there were significant differences in dry lips (81% vs. 63%, p < 0.05), frequency of previous respiratory tract infections (48% vs. 22%, p < 0.005), and dyspnea (46% vs. 29%, p < 0.05). In the younger age group, 45 (87%) had DKA as the initial manifestation. This was significantly higher than the 55% in the older age group (p < 0.001).

Plasma glucose level was significantly higher and plasma HbA1c, pCO₂, bicarbonate, and sodium levels were significantly lower in the younger age group than in the older age group (Table 1). In terms of C-peptide levels during the glucagon test, both C-peptide levels at baseline and at 6 minutes after glucagon stimulation were significantly lower in the younger age group than in the older age group.

Only 12% in the younger age group and 7% in the older age group did not have any detectable islet cell autoantibodies (Table 1). The frequency of islet cell autoantibodies detected in the younger age group was 62% in GADA and 69% in IA-2A. These were not significantly different from those detected in the older age group. However, 37% of patients in the younger age group had IAA detected. This was significantly higher than the 10% of the older age group.

In the younger age group, remission occurred in 21 patients (40%), being complete in two (4%). However, 55 children (59%) in the older age group achieved remission, being completed in 11 (12%; Table 2). The remission rate of the younger age group was significantly lower.

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In the younger age group, the proportion of boys (57% vs. 46%) and girls (43% vs. 54%) were comparable between the remitter and the nonremitter (p = 0.397). Most patients, 90% in the younger age group and 89% in the older age group, had an onset of remission during the 1st 3 months (Table 2), which was not statistically significant. Twelve (57%) in the younger age group achieved remission < 9 months, whereas 59% in the older age group achieved remission < 6 months. However, six out of 21 (19%) in the younger age group and 13 out of 55 (24%) in older age group achieved remission longer than 1 year. The difference was not statistically significant.

Among patients in the younger age group, different clinical and laboratory variables were compared between patients with and without remission to determine the associated factors. However, there were no associations among DKA at diagnosis, HbA1c levels at diagnosis, C-peptide levels, and rate of remission.

### Discussion

In literature, 9% of young Caucasian children with T1DM have had a first degree family member with T1DM, with a predominance of fathers over mothers. However, in this study, only one patient had a mother with T1DM. This may be partially due to ethnic differences.

In both the younger and older age groups, the most common symptoms noted upon diagnosis were polyuria, polydipsia, body weight loss, and nocturia. However, ketoacidosis, dry lips, and dyspnea are more common initial clinical manifestations in the younger age group compared with the older age group. Such findings may suggest that patients aged < 6 years experience a more unstable metabolic situation upon diagnosis than older patients.

In this study, serum C-peptide levels, both basal and glucagon-stimulated, of patients younger than 6 years were lower than those of older patients, implying that the younger age group had less insulin reserve than older age group. This is consistent with findings of our previous report and other studies. The present study also showed that the frequency of previous respiratory tract infection in children younger than 6 years was higher than that of the older age group, which is similar to the results of another study.

In this study, ~87% of patients younger than 6 years had ketoacidosis upon diagnosis. They also had higher blood glucose levels, lower pCO₂ levels, and lower bicarbonate levels upon diagnosis than the older patients. Taken together, these suggest that patients younger than 6 years not only have a higher frequency, but also more severe degrees of ketoacidosis than older patients. Thus, less insulin reserve with stress related to viral infection may play an important role in unstable situations of patients aged < 6 years upon diagnosis.

The frequency of islet cell autoantibodies has been reported to be significantly less in early-onset diabetes. However, in this study, 88% of diabetic patients aged younger than 6 years had at least one autoantibody detected. Their frequency of GADA and IA-2A positivity was similar to those of the older age group, but their frequency of IAA positivity was significantly higher, similar to findings of our previous report and other studies. This may be explained by the fact that IAA is the first detectable β-cell autoantibody among high-risk prediabetic children and that it disappears more rapidly than other autoantibodies.

The present study confirms that autoimmune destruction of pancreatic β-cell is an important cause of T1DM in Taiwanese children younger than 6 years old.

This study also demonstrates a higher rate and severity of DKA with lower HbA1c levels upon diagnosis of diabetic children aged < 6 years. The results may suggest more rapid and extensive pancreatic β-cell damage by an autoimmune process, resulting in a more severe metabolic decompensation at diagnosis, consistent with results of previous reports.

In newly-diagnosed type 1 diabetic children, there is often a period of remission during the natural course of the disease.

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**Table 1** Laboratory data in children with type 1 diabetes mellitus.

<table>
<thead>
<tr>
<th></th>
<th>&lt; 6 y (n = 52)</th>
<th>6–18 y (n = 94)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mg/dL)</td>
<td>521 ± 156</td>
<td>451 ± 210</td>
<td>0.006</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>12.3 ± 2.1</td>
<td>13.9 ± 2.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ketone (mM)</td>
<td>4.1 ± 1.4</td>
<td>3.8 ± 2.0</td>
<td>0.552</td>
</tr>
<tr>
<td>pH</td>
<td>7.23 ± 0.16</td>
<td>7.27 ± 0.14</td>
<td>0.314</td>
</tr>
<tr>
<td>pCO₂ (mmHg)</td>
<td>20.5 ± 8.8</td>
<td>29.7 ± 13.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HCO₃⁻ (mM)</td>
<td>10.3 ± 7.5</td>
<td>15.1 ± 8.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Na (mM)</td>
<td>131.1 ± 5.6</td>
<td>133.5 ± 4.4</td>
<td>0.002</td>
</tr>
<tr>
<td>K (mM)</td>
<td>4.3 ± 0.7</td>
<td>4.4 ± 0.7</td>
<td>0.923</td>
</tr>
<tr>
<td>Cl (mM)</td>
<td>101.9 ± 8.0</td>
<td>101.2 ± 5.5</td>
<td>0.431</td>
</tr>
</tbody>
</table>

**Table 2** Natural course of remission in children with type 1 diabetes mellitus.

<table>
<thead>
<tr>
<th></th>
<th>&lt; 6 y</th>
<th>6–18 y</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients (N)</td>
<td>52</td>
<td>94</td>
<td>0.036</td>
</tr>
<tr>
<td>Patients with remission (N)</td>
<td>21</td>
<td>55</td>
<td>0.637</td>
</tr>
<tr>
<td>Onset of remission, n (%)</td>
<td></td>
<td></td>
<td>0.094</td>
</tr>
<tr>
<td>&lt;3 mo</td>
<td>19 (90)</td>
<td>49 (89)</td>
<td></td>
</tr>
<tr>
<td>3–6 mo</td>
<td>2 (10)</td>
<td>4 (7)</td>
<td></td>
</tr>
<tr>
<td>6–9 mo</td>
<td>0</td>
<td>2 (4)</td>
<td></td>
</tr>
<tr>
<td>Duration of remission, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3 mo</td>
<td>4 (19)</td>
<td>26 (47)</td>
<td></td>
</tr>
<tr>
<td>3–6 mo</td>
<td>2 (9)</td>
<td>7 (12)</td>
<td></td>
</tr>
<tr>
<td>6–9 mo</td>
<td>6 (29)</td>
<td>8 (15)</td>
<td></td>
</tr>
<tr>
<td>&gt;12 mo</td>
<td>5 (24)</td>
<td>1 (2)</td>
<td></td>
</tr>
</tbody>
</table>

GADA = antilgutamic acid decarboxylase autoantibodies; HbA1c = glycated hemoglobin; IA-2A = anti-insulinoma antigen-2 autoantibodies; IAA = anti-insulin autoantibodies.
disease, characterized by a striking fall in insulin doses to maintain good metabolic control. Different criteria have been used to define remission. Daily insulin requirement alone or HbA1c alone has been used to define remission in some studies, whereas other studies include daily insulin requirements and HbA1c in defining remission. As remission defined by daily insulin requirement alone or HbA1c tends to overestimate remission rates, insulin dose-adjusted A1c, proposed by Mortensen et al. to define remission, was used in the present study. The reported remission rates vary between 25% and 100%, which partially reflects the different definitions used and the difference in patients’ ages.

In this study, the frequency of remission is 40% in the younger age group, which is similar to a previous study using the same definition for remission. The result is also similar to other studies with different definitions for remission. Although complete remission is rare in children with T1DM, this study shows that complete remission has occurred in 4% of patients younger than 6 years, as previously reported. Pecheur et al. reported that children younger than 4 years had similar remission rates to older children. However, this study demonstrates that children younger than 6 years have remission rates lower than older children, confirming results of other reports. This study also reveals that children younger than 6 years were similar to the older age group with regards to time of onset and duration of remission. The result is consistent with the study reported by Pecheur et al.

In addition, DKA at diagnosis has been associated with a lower remission rate and shorter duration of remission. However, there has been no association between DKA and remission rate. In this study, most patients younger than 6 years had DKA at diagnosis, which might disguise a potential influence of DKA on remission. Lower HbA1c levels at diagnosis have also been associated with higher remission rate and C-peptide levels have been correlated with remission rate. However, in this study, there is no such association. Thus, further study is warranted to clarify the discrepancy.

In conclusion, most Taiwanese children younger than 6 years old have T1DM due to autoimmunne destruction of pancreatic β-cells. Most of them have severe ketoacidosis as the initial manifestation. Primary care physicians should have a high index of suspicion when managing young children with classic symptoms and signs of diabetes mellitus in the presence of a respiratory tract infection for proper timely intervention.

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