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ORIGINAL ARTICLE

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.

Conflicts of interest: The authors have no conflicts of interest relevant to this article.

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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.[1] Although the incidence of T1DM in Taiwanese children is much lower than that among Caucasian children,[2] the underlying mechanisms are the same.[3] 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.[4,5] 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.[4,6] This period has since become the potential target window for immunomodulation therapy to preserve residual pancreatic β-cell mass.[7] 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.[2,8–11] Cases of T1DM in younger children is increasing but few reports present clinical data.[12] 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 $\leq$ 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 with new onset of T1DM were also enrolled for comparison.

The diagnosis of T1DM was made according to the 1997 Criteria of the Expert Committee.[13] 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 at glucagon test were also determined upon diagnosis. A 6-minute glucagon test was performed according to the protocol in literature,[14] whereas C-peptide levels were measured using commercially available kits. Islet-cell autoantibodies, including GADA, IA-2A, and IAA were measured as previously reported.[3]

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.[15]

Statistical analysis

All data were presented as percentage or as mean $\pm$ standard deviation. Pearson's χ^2 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 the 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 $\pm$ 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 $\pm$ 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, pCO_2, 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.