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Original Article

Relatively Small Birth Size and Accelerated Early Growth of Japanese Type 1 Diabetic Children with Younger Onset

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Abstract. We investigated the changes of anthropometrical parameters in Japanese children with type 1 diabetes (T1DM) from birth to the onset of diabetes. One-hundred ninety-nine children (79 males and 120 females) diagnosed between 0–16 yr of age during the period between 1990 and 2003 were the subjects of this study. The subjects were categorized into 3 groups according to onset age (0–5 yr; n=74, 5–10 yr; n=61, 10–16 yr; n=64). At birth, the younger onset (<5) group had significant lower height and weight standard deviation score (SDS) compared with the older onset (5≤) group (p=0.01 and p=0.02, respectively). When the changes in height SDS from birth to onset were compared, height SDS at onset were significantly greater than those at birth in the younger onset group (p<0.001). However, no significant difference was observed in the other groups (p=0.95 and p=0.39). These results suggest that relatively small size at birth and accelerated growth after birth until the onset of diabetes may be a characteristic of Japanese T1DM children with younger onset and may further support the hypothesis that emphasizes accelerated growth and subsequent insulin resistance as a cause of earlier onset of T1DM.

Key words: type 1 diabetes, onset age, anthropometrical parameters

Introduction

The onset of type 1 diabetes (T1DM) is influenced by both environmental and genetic factors (1). The difference of genetic background, especially human leukocyte antigen (HLA), is known to cause great differences in the incidence of T1DM between ethnic groups (2). On the other hand, the incidence of T1DM has increased in many Western countries over the past several decades (3). Such a remarkable increase in incidence seems too rapid to be explained by changes in genetic factors (4). Therefore, the increasing incidence is probably due to changes in environmental factors partially linked to changes in life-styles. Several environmental factors, such as viral infection or exposure to cow milk, have been thought to initiate and accelerate the progression of

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Table 1 Clinical characteristics of patients at the onset of diabetes

onset age	Total	M	F	symptom			pH			HbA1c			
yr	number			chanced	non DKA	DKA	mean	SD	n	<7.5	7.5≤<10	10≤	na
<1	3	2	1	0	1	2	7.171	0.296	2	1	0	1	1
1≤<2	17	6	11	1	3	13	7.141	0.140	10	2	3	5	7
2≤<3	17	10	7	0	11	6	7.311	0.154	9	0	4	6	7
3≤<4	21	6	15	1	13	7	7.265	0.137	10	1	1	12	7
4≤<5	16	6	10	0	12	4	7.267	0.141	9	0	3	9	4
<5	74	30	44	2	40	32	7.240	0.156	40	4	11	33	26
5≤<10	61	23	38	11	37	13	7.310	0.128	44	2	8	40	11
10≤	64	26	38	20	33	11	7.319	0.094	43	4	6	42	12

DKA: diabetic ketoacidosis.

autoimmune destruction of pancreatic β-cells and westernized modern life-styles increase the risk of early exposure to these factors (5, 6). In addition, a rapid rate of increase in children with younger onset has also been reported, especially in Europe (7, 8). Among several hypotheses that try to explain these phenomena, one argues insulin resistance has contributed to the increase and accelerated onset of T1DM as well as type 2 diabetes (T2DM), the so-called 'Accelerator Hypothesis' (9–11).

In Japan, the incidence of T1DM is very low, but it has been reported to have increased during last several decades, similar to the trend seen in other countries (3, 12). The physique of Japanese children has dramatically improved during the past half century, but conversely, birth weight has been reported to have decreased during the same period (13). The growth pattern of T1DM children before onset has been examined in Caucasians and several characteristics such as accelerated early growth have been reported (14–16). However, it has not been examined whether such characteristics are also evident in other ethnic groups with different genetic backgrounds and low disease incidence.

In the present study, we studied anthropometrical data of Japanese T1DM children at birth and at the onset of diabetes. We specially focused on the patients of younger onset (diagnosed before 5 yr old) and compared their data with patients with older onset (diagnosed at 5 yr and after).

Subjects and Methods

Subjects and methods

In Japanese children registered to the first and second cohort of the Japanese Study Group of Insulin Therapy for Childhood and Adolescent Diabetes (17), seven-hundred-forty-three subjects (boys=283, girls=460) were diagnosed as having T1DM between 0–16 yr old during 1990–2003. The diagnosis of T1DM was determined according to the classification of the Japan Diabetes Society and the American Diabetes Association (18, 19). Among them, the 199 subjects (79 males and 120 females) for whom we were able to obtain anthropometrical parameters both at birth and at the onset of diabetes were the subjects of this study. Their clinical characteristics at the onset of diabetes are summarized in Table 1. The subjects were categorized into 3 groups according to onset age (<5 yr, 5≤<10 yr, 10≤yr). Each group included

Table 2 Anthropometrical parameters(mean ± SD) at birth and at the onset of diabetes

onset age	<5	5≤		
		total	5≤<10	10≤
height SD at birth	–0.28 ± 1.01	0.14 ± 1.07†	0.13 ± 1.28	0.15 ± 0.85†
at onset	0.18 ± 1.08*	0.17 ± 0.94	0.10 ± 1.00	0.24 ± 0.89
weight SD at birth	–0.01 ± 0.97	0.37 ± 1.08†	0.33 ± 1.21	0.40 ± 0.94†
at onset	–0.52 ± 1.07*	–0.25 ± 1.18*	–0.32 ± 1.23*	–0.20 ± 1.13*

*p<0.001 vs. at birth. †p<0.05 vs. <5 group.

74, 61 and 64 participants, respectively. For convenience, we named each group as group Y (young onset), group M (middle onset) or group O (old onset). Children diagnosed before 5 months old were excluded from this study, because the major part of this population is said to include monogenic diabetes (20).

All anthropometrical data were converted to standard deviation score (SDS) adjusted for age and sex. The birth weight and height SDS were calculated according to the Japanese population fetal growth curve published in 1994 by a study group of the Japanese Ministry of Health and Welfare. Height and weight SDS at diagnosis were calculated according to a cross-sectional growth chart published in 2000 by a study group of the Japanese Ministry of Health, Labour and Welfare. Age of diagnosis was documented to the nearest month by the referring physician and is the same as the time of the start of insulin treatment in most cases. The study protocol was approved by the ethics committee of The University of Tokushima School of Medicine.

Statistical analysis

Proportions of sex, HbA1c value and clinical symptoms at diagnosis were compared by the χ^2 test. The differences of anthropometrical parameters between each group were analyzed by the Mann-Whitney U-test. The changes in height SDS from birth to onset were analyzed by Wilcoxon's signed-rank test. Significance was considered to be p<0.05. The analysis was conducted with StatView software (version 5.0 for Windows, SAS Institute Inc., Cary, NC).

Results

Table 1 shows the clinical characteristics of patients divided according to the onset age of diabetes. There were no significant differences among the 3 groups concerning gender ratio and HbA1c value. Group Y suffered diabetic ketoacidosis at onset with significantly greater percentage and had lower pH value than the other groups.

At birth, group Y had significantly lower height SDS compared with Group O and the whole older onset group (Group M+O) (p=0.02 and p=0.01, respectively). On the other hand, no significant difference of height SDS among these 3 groups was observed at the onset of diabetes. With regard to weight SDS, group Y showed significantly lower birth weight compared with Group O and whole older onset group (Group M+O) (p=0.01 and p=0.02, respectively). At onset, all groups had significant declines in weight SDS compared to those at birth (Table 2).

Since weight SDS at onset is modulated by diabetic conditions, such as dehydration or DKA and does not always reflect an individual's nutritional condition, we examined the changes in height SDS from birth to diabetes onset. Height SDS at onset were significantly greater than those at birth in group Y (0.18 ± 1.08 versus

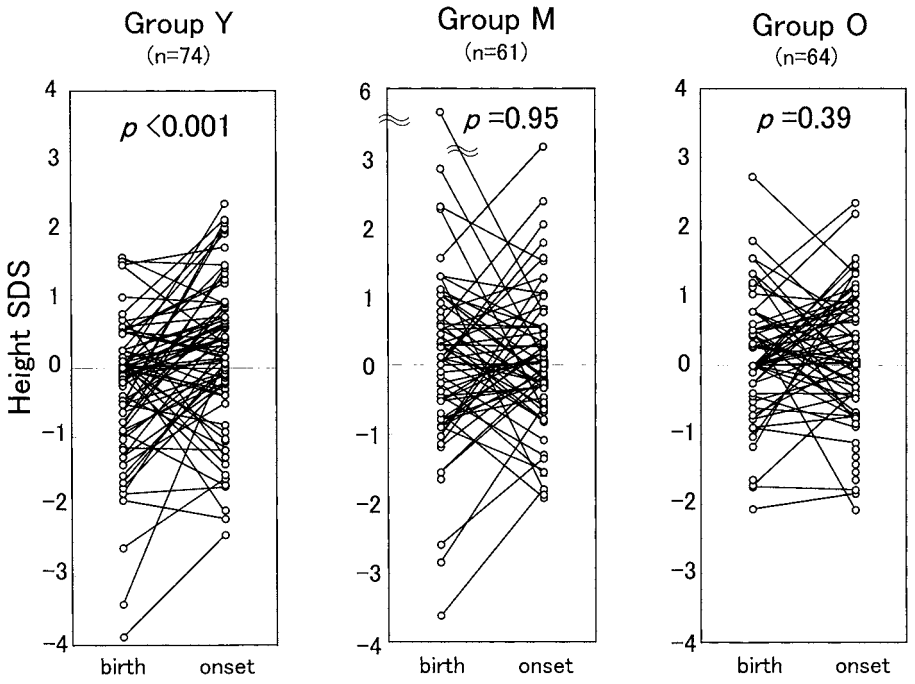

Fig. 1 Height SDS changes in T1DM from birth to the onset of diabetes. Each bar represents the change in each patient. Height SDS at onset was significantly greater than that at birth in the younger onset (group Y, <5 yr) group (0.18 ± 1.08 vs. –0.28 ± 1.01, $p<0.001$). No significant difference was observed in the other groups (group M, 5≤<10 yr and group O, 10≤yr); ($p=0.95$ and $p=0.39$, respectively).

–0.28 ± 1.01, $p<0.001$). However, no significant difference was observed in group M and group O ($p=0.95$ and $p=0.39$, respectively) (Fig. 1).

Discussion

Our results show several anthropometrical features of Japanese type 1 diabetic children from birth to onset. First, patients were taller than non-diabetic subjects at onset unrelated to onset age. Second, patients with younger onset had lower height and weight SDS at birth. Third, the younger onset group had accelerated height gain during their growth, a consequence of the low weight SDS at birth.

Accelerated growth before onset of T1DM has been observed in Caucasians and early weight gain during infancy has been reported to be associated with an increased risk of T1DM (14, 15). A cross-sectional study showed that the increase in risk of T1DM for 1 SDS increment in relative height was 20–30% in Finnish children (16). These epidemiological observations of accelerated growth, probably due to a predominant nutritional condition, were cited as a cause of the increase and accelerated onset age of T1DM during past several decades in most industrial countries (3, 7, 8).

In our study, we did not use weight SDS as a parameter of nutritional condition, because weight SDS at onset is modulated by the diabetic condition around the time of diagnosis and does not always reflect the nutritional condition until the onset of diabetes. Although it might be controversial whether the height SDS itself well represents the nutritional condition during

growth, the nutritional condition is one of the most important factors that determine height gain, especially during infancy. For this reason, a significant positive change of height SDS in patients with younger onset suggests that accelerated growth might be a risk factor in the acceleration of T1DM onset even in Japanese.

Younger onset patients had significantly lower birth height and weight SDS in this study. With regard to birth weight, low birth weight infants have been reported to show earlier onset of T1DM (21). Pancreatic β-cell mass increases rapidly between the 12^{th} intrauterine week and the 5^{th} postnatal month (22). In the field of T2DM, infants born small for gestational age are considered to have an increased risk of glucose intolerance in adulthood due to low β-cell mass which is determined early in life (23). It is considered that a relatively poor nutritional condition *in utero* might be reflected lower in birth height and weight and be a cause of lower β-cell mass, which would accelerate the progression of β-cell damage in children who have a genetic disposition to T1DM. Thus, lower birth size might be an independent characteristic of the younger onset group.

In summary, this study demonstrated the accelerated early growth of Japanese children with T1DM with younger onset and suggested the universality of this phenomenon unrelated to ethnic origin and incidence of T1DM. This may further support the Accelerator Hypothesis, one of the theories explaining the increase and accelerated onset of T1DM during the past several decades. However, further basic studies are needed. For example, a non-obese-diabetic (NOD) mouse study that examines the acceleration of diabetes onset in overnutrient groups may be necessary to provide empirical evidence in support of these epidemiology-based observations.

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