Is Pubertal Onset a Risk Factor for Blindness and Renal Replacement Therapy in Childhood-Onset Type 1 Diabetes in Japan?

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We previously reported that mortality is worse for pubertal-onset type 1 diabetes than for the prepubertal-onset variety (1). Other studies have disparately reported that the risk for incipient microangiopathy in type 1 diabetic patients is higher during puberty than before puberty (2–4) or that the risk is similar (5,6). However, evidence regarding the relationship between puberty and advanced microangiopathy is limited (7). We therefore investigated the incidence of blindness and renal replacement therapy (RRT) by pubertal status at diagnosis.

RESEARCH DESIGN AND METHODS

A total of 1,408 type 1 diabetic patients diagnosed at <18 years of age were placed on insulin therapy within 1 month of diagnosis. They were chosen from two nationwide type 1 diabetes surveys (1,8,9). The patients were either *1*) diagnosed between 1965 and 1969 and alive as of 1 January 1970 (the 1960s cohort) or 2) diagnosed between 1970 and 1979 and alive as of 1 January 1980 (the 1970s cohort). Follow-up for the 1960s and 1970s cohorts was initiated on 1 January in 1970 or 1980, respectively. Diagnosis in males aged ≥12 years and females aged ≥11 years was defined as pubertal onset, as earlier reported (1,2,5,9–11). The cohorts accounted for ~75% of all type 1 diabetic subjects in Japan (1,8,12).

Status of blindness and RRT as of 1 January 1995 was identified by questionnaires completed by attending physicians, with blindness defined as visual acuity of light perception or a worse state in at least one eye and RRT as either receiving dialysis or post–kidney transplantation status. Cumulative incidence rates of blindness and RRT were calculated using the Kaplan-Meier method and analyzed by log-rank tests. Logistic regression models were used to estimate the odds ratios (ORs) for these complications at 15 years of follow-up, with prepubertal/pubertal onset, sex, and 1960s/1970s (year of onset) included as predictor variables after adjusting for disease duration before follow-up. The study was approved by the institutional review board of Jikei University School of Medicine.

RESULTS

Subjects comprised 1,408 individuals (of whom 566 were male and 842 female) with 965 (417 male and 548 female) classified as prepubertal onset and 443 (149 male and 294 female) as pubertal onset. The age at diagnosis was 6.7 ± 3.0 and 13.5 ± 1.7 years for prepubertal and pubertal onset, respectively, and the follow-up was 16.1 ± 4.2 and 15.8 ± 5.2 years. Blindness developed in 52 prepubertal and 45 pubertal onset patients ($P = 0.0003$ by χ^2 test) and RRT in 64 and 78 patients ($P < 0.0001$). The last confirmed complication status was used for 124 deceased patients and for 62 patients whose status as of 1995 was missing. The presence or absence of blindness or RRT was confirmed in 90.7 and 95.8%, respectively.

The cumulative incidence of blindness and RRT during follow-up was significantly higher in the pubertal-onset group than that in the prepubertal-onset group (Fig. 1*A*). However, analysis by whether the subject attained 18 years of age demonstrated no significant difference in cumulative incidence between these complications, regardless of age at onset (Fig. 1*B*).

Logistic regression models revealed that the pubertal-onset group had a 2.15 times higher risk for blindness (95% CI 1.43–3.24, $P = 0.0002$) and a 4.00 times higher risk for RRT (2.74–5.84, $P < 0.0001$) than the prepubertal-onset group at 15 years of follow-up. Being in the 1960s cohort was a significant risk factor for blindness (OR 4.07 [95% CI 2.52–6.58], $P < 0.0001$) and RRT (3.13 [2.01–4.89], $P < 0.0001$). Sex was not a risk factor for either complication in these models.

CONCLUSIONS

Our main finding was that pubertal-onset type 1 diabetic patients had a higher risk for developing blindness and RRT than that for prepubertal-onset patients. A Swedish study reported similar results for end-stage renal disease (7). However, to date, there is no large-scale longitudinal prospective study investigating the influence of pubertal status at onset of disease on developing blindness. Furthermore, we demonstrated that attained age was a determinant of these advanced microangiopathies, regardless of age at onset.

Insulin resistance and abnormalities in the growth hormone/insulin-like growth factor-1 axis lead to poor metabolic control

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Abbreviations: RRT, renal replacement therapy.

*A list of the Diabetes Epidemiology Research International Study Group members can be found in the APPENDIX.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

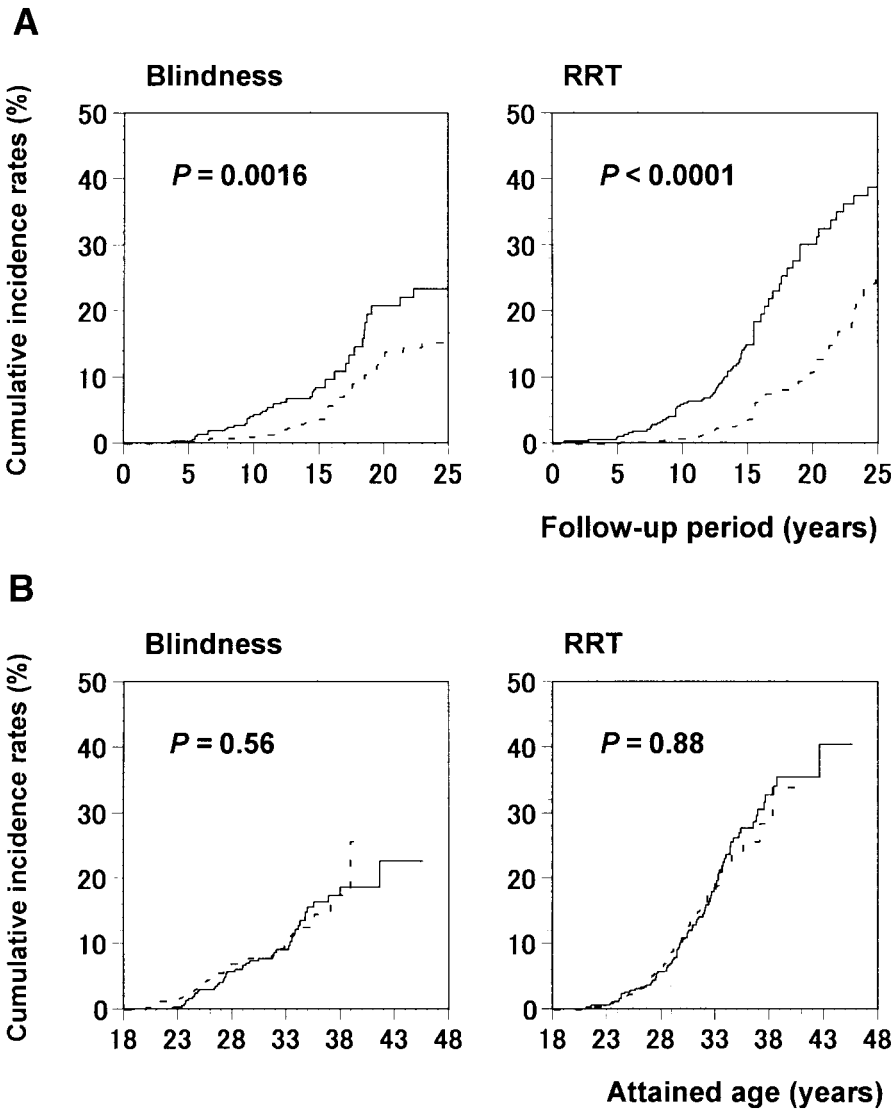

Figure 1—*Cumulative incidence rates of blindness and RRT throughout the follow-up period* (A) *and after the age of 18 years* (B). P *values were calculated by log-rank test.* —, *pubertal onset;* ----, *prepubertal onset.*

(13–15) and nephropathy (16–19) during puberty among type 1 diabetic patients. Glycemic control is poorer among pubertal-onset patients than among prepubertal-onset patients (13,20). These factors likely led to the development of blindness and RRT in later life.

There are some limitations in the current study. First, pubertal status was defined by age, not by Tanner stage, which was culturally difficult to determine in a population-based cohort in Japan. Because very few reliable reports had examined pubertal-onset age in Japan, as well as to compare our data with those previously published (1,2,5,9–11), we used the same definition of pubertal status by age. Second, glycemic status of the subjects was not addressed, as it was technically impossible to evaluate in a standardized manner in our questionnaire survey.

We conclude that special attention should be paid to those who develop type 1 diabetes during puberty, given their higher risk for late complications.

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APPENDIX

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