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

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Running Title: Puberty, blindness and ESRD in type 1 diabetes

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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 diabetics 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 patients were chosen from two nationwide type 1 diabetes surveys (1,8,9): those diagnosed at age < 18 years between 1965-69 and alive as of January 1, 1970 (1960s cohort) or between 1970-1979 and alive as of January 1, 1980 (1970s cohort) and placed on insulin therapy within 1 month of diagnosis. Follow-up for 1960s/1970s cohorts was initiated in January 1, 1970/1980. Diagnosis in males at ≥ 12 years and females at ≥ 11 years was defined as pubertal-onset, as reported earlier (1,2,5,9-11). The cohorts accounted for approximately 75% of the entire type 1 diabetics in Japan (1,8,12).

Status of blindness and RRT as of January 1, 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. The last confirmed complication status was used for 124 deceased patients and 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 the follow-up was significantly higher in the pubertal-onset group than in the prepubertal-onset group (Figure 1A). However, analysis by attained age ≥ 18 years demonstrated no significant difference in cumulative incidence between these complications, regardless of age at onset (Figure 1B).

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 (odds ratio, 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 diabetes patients had a higher risk for developing blindness and RRT than 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 (13-15) and nephropathy (16-19) during puberty among type 1 diabetics. Glycemic control is poorer among pubertal-onset patients than 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. Firstly, puberty 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, and to compare our data with those previously published (1,2,5,9-11), we used the same definition of puberty status by age. Secondly, 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 developed type 1 diabetes during puberty, given their higher risk for late complications.

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APPENDIX

References


