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CAN THE AGE AT DIAGNOSIS OF TYPE 1 DIABETES MELLITUS AFFECT THE COURSE OF DIABETIC RETINOPATHY

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Key words: type 1 diabetes mellitus, onset of diabetes, diabetic retinopathy

SUMMARY

The aim of this study was to investigate whether poor control of type 1 diabetes mellitus at the time of onset increases the risk of developing diabetic retinopathy. Data from 566 diabetic persons were studied. Subjects were divided into two groups according to duration of diabetes: group 1 with diabetes duration of 10 to 15 years and group 2 with diabetes duration of 16 years and more. In addition, they were divided according to the onset of diabetes into three subgroups (prepuberty, puberty and after puberty). The results of the two groups were analyzed separately. The group with the puberty onset of diabetes (time of poor glycemic control) were expected to have a significant prevalence and most severe form of diabetic retinopathy. When the known risk factors for the development of diabetic retinopathy were excluded, group 1 revealed no statistically significant differences in the prevalence and severity of diabetic retinopathy between subgroups. In group 2, the subgroup with the puberty onset of diabetes had a statistically significant prevalence of diabetic retinopathy in comparison to the subgroups with pre- and after-puberty onset of diabetes ($p=0.05$). The subgroups with prepuberty and puberty onset of diabetes had a statistically significantly more severe form of diabetic retinopathy than the subgroup with after-puberty onset of diabetes ($p<0.01$). This could mean that diabetes control during the first years of the disease onset could, in the long run, determine whether and in which form diabetic complications on the eyes would develop. It also raises a question whether our children (the prepuberty onset of diabetes) have good glycemic control.

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INTRODUCTION

One of the first evidence that good glycemic control is beneficial concerning the development and progression of diabetic retinopathy came from the experiments on dogs (1). Later on, large studies like DCCT (2) and EURODIAB (3) have shown that the most important risk factors for the development and progression of diabetic retinopathy in type 1 patients are the duration of diabetes, metabolic control and diastolic blood pressure values. Although some of the studies showed a connection between the progression of diabetic retinopathy and renal diseases, anemia, hyperlipoproteinemia, pregnancy, decreased serum albumin and reduced carotid blood flow, no large multicenter studies were conducted. That is the reason why these parameters were not included in our study as risk factors for the development and progression of diabetic retinopathy.

There are still some unsolved problems regarding metabolic control. It is not clear why retinopathy develops in a certain percentage of patients with type 1 diabetes with good metabolic control, whereas a relatively high percentage of type 1 diabetics remain free from retinopathy despite poor metabolic control, or why in clinical trials type 1 diabetics with the same risk factors differ regarding diabetic retinopathy. In 1987, Engerman and Kern (4) concluded that when 30 months of good control in diabetic dogs were preceded by 30 months of poor control, retinopathy was almost as severe as in those with poor control throughout the 5-year period, even though retinopathy was not present when the switch from poor to good control occurred. To the extent that these results may apply to human diabetes, they suggest that good control may be effective only if instituted early in the course of diabetes or that, if improving control is of benefit, there may be a considerable delay before the beneficial effects become apparent. In addition, Zhang *et al.* (5) have suggested that previous glycemic exposure might provide a possible explanation to such paradoxical clinical situations.

EURODIAB suggested an additional risk factor, the onset of diabetes before puberty. According to the WISCONSIN study (6), prepubertal years might have a neutral effect on the progression to proliferative diabetic retinopathy. Several studies also suggest that retinopathy in pubertal-onset diabetes has worse prognosis than retinopathy in diabetes diagnosed before puberty (7,8). Puberty is the time of hormonal disturbances and rebellious behavior as well as the time of poor glycemic control (9-11).

The aim of this study was to investigate whether poor control of type 1 diabetes at the time of onset increased the risk of the development and progression of diabetic retinopathy.

PATIENTS AND METHODS

The study was carried out at the Vuk Vrhovac University Clinic for Diabetes, Endocrinology and Metabolic Diseases in Zagreb. Data were collected from CroDiab Net (12) and patient medical records. A total of 566 persons with type 1 diabetes and diabetes duration of 10 or more years were included in the study. The patients were divided according to diabetes duration into two groups: group 1 consisted of patients with diabetes duration of 10 to 15 years, and group 2 of those with diabetes duration of 16 years or more. According to the age at diagnosis of type 1 diabetes, the subjects were divided into three subgroups: subgroup A with the onset of diabetes before the beginning of puberty (male <11 years, female <10 years); subgroup B with the onset of diabetes at the beginning of puberty (male 11-13 years, female 10-12 years); and subgroup C with the onset of diabetes after the beginning of puberty (male >13 years, female >12 years).

The following parameters were assessed: HbA_{1c}, duration of diabetes, systolic and diastolic blood pressure, and presence and severity of diabetic retinopathy. HbA_{1c} was determined by an automated immunoturbidimetric assay (13). Blood pressure was measured at outpatient visits using an ambulatory sphygmomanometer. The best-corrected visual acuity was tested using Snellen chart. The presence and severity of diabetic retinopathy and maculopathy were determined ophthalmoscopically after pupil dilatation by experienced ophthalmologists. Retinopathy was classified as nonproliferative, preproliferative or proliferative, as recommended by the Working Group on Diabetes-Related Blindness (14).

Data were analyzed using Statistica for Windows software version 6.0. Relations between the level of HbA_{1c}, duration of diabetes and blood pressure were analyzed using t-test, independent by groups. Between-subgroup comparisons were made using χ^2-test.

RESULTS

The study included 566 persons with type 1 diabetes divided according to the duration of diabetes into two groups (group 1 with 187 persons and group 2 with 379 persons). Each group was further divided into three subgroups according to the time of type 1 diabetes onset.

Group 1 results

The three subgroups did not differ according to HbA_{1c} values or duration of type 1 diabetes mellitus, but they did differ according to systolic and diastolic blood pressure (the subgroup with puberty onset of

diabetes had a statistically lower blood pressure than the subgroup with after-puberty onset of diabetes) (Table 1).

Comparison of the frequency and severity of diabetic retinopathy revealed no statistically significant differences between the subgroups (Table 2).

Group 2 results

The three subgroups with diabetes duration of 16 years and more did not differ according to HbA_{1c} values, duration of type 1 diabetes mellitus and diastolic blood pressure. The subgroup with after-puberty onset of diabetes had a statistically higher systolic blood pressure than the subgroup with prepuberty onset of diabetes (Table 3).

We documented a statistically significant prevalence of diabetic retinopathy in the subgroup with puberty onset of diabetes as compared with both the prepuberty and after-puberty diabetes onset subgroups. Furthermore, the subgroup with prepuberty and the subgroup with puberty onset of diabetes had a statistically significantly more severe form of diabetic retinopathy compared to the subgroup with after-puberty onset of diabetes (Table 4).

DISCUSSION

The results obtained in the group of patients with diabetes duration of 10-15 years showed no statistically significant differences in retinopathy status, maculopathy, laser treatment or visual acuity. This

Table 1. **Basic characteristics of and known risk factors for diabetic retinopathy in patients with type 1 diabetes mellitus (type 1 DM) duration 10-15 years**

	Subgroup A	Subgroup B	Subgroup C	*p*
Onset of type 1 DM (yrs)	M 0-10 F 0-9	M 11-13 F 10-12	M 14> F 13>	–
n (%)	15 (8.02)	22 (11.76)	150 (80.21)	–
Duration of type 1 DM (yrs)	13±1.6	12.8±1.63	12.2±1.62	NS
Last value of HbA_{1c} (%)	8.62±1.75	8.23±1.08	8.02±1.59	NS
Systolic blood pressure (mm Hg)	125.8±18.14	116.1±11.25	129.7±17.11	<0.01
Diastolic blood pressure (mm Hg)	81.7±17.32	75.0±6.87	81.5±10.14	<0.01

Table 2. **Prevalence and severity of diabetic retinopathy (DR) in patients with diabetes duration 10-15 years, divided into three subgroups according to onset of type 1 diabetes mellitus**

	Subgroup A	Subgroup B	Subgroup C	*p*
Diabetic retinopathy (%)	50.0	59.1	50.0	NS
Nonproliferative DR (%)	41.0	50.0	39.6	NS
Preproliferative/proliferative DR (%)	6.7	9.1	9.4	NS
Maculopathy (%)	13.3	4.6	11.3	NS
Argon laser photocoagulation (%)	13.3	13.6	10.7	NS
Decreased vision accuracy * (%)	0.0	4.6	1.3	NS

* Decreased vision accuracy=visus ≤0.1

Table 3. **Basic characteristics of and known risk factors for diabetic retinopathy in patients with type 1 diabetes mellitus (DM type 1) duration >15 years**

	Subgroup A	Subgroup B	Subgroup C	*p*
Onset of type 1 DM (yrs)	M 0-10 F 0-9	M 11-13 F 10-12	M 14> F 13>	–
n (%)	88 (23.2)	51 (13.5)	240 (63.3)	–
Duration of type 1 DM (yrs)	25.3±7.61	24.4±7.24	24.48±7.79	NS
Last value of HbA_{1c} (%)	7.74±1.24	7.62±1.45	7.66±1.32	NS
Systolic blood pressure (mm Hg)	127.8±19.81	131.7±24.73	134.9±20.55	<0.05
Diastolic blood pressure (mm Hg)	79.7±11.62	81.6±14.03	81.1±10.49	NS

Table 4. **Prevalence and severity of diabetic retinopathy (DR) in patients with diabetes duration >15 years, divided into three subgroups according to onset of type 1 diabetes mellitus**

	Subgroup A	Subgroup B	Subgroup C	*p*
Diabetic retinopathy (%)	82.1	96.0	83.1	=0.05
Nonproliferative DR (%)	42.1	58.8	61.0	<0.01
Preproliferative/proliferative DR (%)	48.9	39.2	24.2	<0.01
Maculopathy (%)	42.1	41.2	30.8	NS
Argon laser photocoagulation (%)	54.6	45.1	35.4	<0.01
Decreased vision accuracy* (%)	14.8	9.8	9.7	NS

* Decreased vision accuracy=visus ≤0.1

could be explained by the fact that more severe forms of retinopathy and maculopathy, and the need of laser treatment are not as frequent in type 1 diabetes with shorter duration as in long-standing diabetes (15).

In the group of patients with diabetes duration of 16 years or more there was a statistically significantly highest percentage of patients with retinopathy in the subgroup with the onset of diabetes at the beginning of puberty, as expected. Our expectation was based on the hypothesis that the first years of diabetes control might have a great impact on later complications (4,5), and on the fact that puberty is the time of probably the worst glycemic control (9-11). This is consistent with the results from some studies on incipient and nonproliferative retinopathy (7,8,16). An interesting experimental work has also shown that blood-retinal barrier remains stable until puberty, achieving a maximum of efficiency and protection (17). A progressive decline then begins, suggesting that this period of growth is associated with factors that, under the influence of diabetes, contribute to the progressive damage of the blood-retinal barrier. This could probably explain our findings of more severe forms of diabetic retinopathy and the need of laser treatment in patients with puberty onset diabetes. Preproliferative and proliferative retinopathy was statistically significantly more frequent in the subgroup with prepuberty onset of diabetes as well as in the subgroup with the onset of diabetes at the beginning of puberty, compared to the group with the onset of diabetes after the beginning of puberty. The first two subgroups underwent puberty relatively early in the course of diabetes, and the first few years of a probably better control were not sufficient to prevent later, more severe complications triggered by puberty.

The fact that, despite the higher percentage of severe forms of diabetic retinopathy in the first two subgroups, the three subgroups did not differ statistically significantly according to impaired visual acuity, probably due to adequate laser treatment, gives grounds for optimism (18).

CONCLUSION

The onset of diabetes before or at the beginning of puberty could be a risk factor for the development and progression of diabetic retinopathy. It is still not quite clear whether this is due to poor glycemic control, or to some additional factors related to puberty. Continuous education of children and their parents as well as insisting on strict glycemic control from the very beginning of diabetes seem to be extremely important. According to our results, the majority of serious visual impairments due to proliferative retinopathy were prevented by laser treatment. To be effective, laser treatment has to be performed on time. As diabetic retinopathy is asymptomatic unless it is too advanced, the need of regular fundus examinations should once again be emphasized.

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