Pupillary Abnormalities in Type I Diabetes Occurring During Adolescence

Comparisons with cardiovascular reflexes

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OBJECTIVE — To evaluate computerized infrared pupillometry for the assessment of autonomic neuropathy in adolescents with type I diabetes.

RESEARCH DESIGN AND METHODS — We measured resting pupil diameters and pupillary light reflexes in 142 adolescents with type I diabetes (72 boys and 70 girls, 10.4–19.8 yr of age, duration of diabetes 0.7–18.3 yr) and in 75 nondiabetic control subjects (29 boys, 46 girls, 11.3–19.8 yr of age). All study participants were assessed using four standard cardiovascular tests: maximum − minimum heart rate during deep breathing (mean of three cycles); heart-rate change during a Valsalva maneuver (Valsalva ratio, mean of three maneuvers); lying-to-standing heart-rate change (30:15 ratio); and lying-to-standing BP change.

RESULTS — Mean resting pupil diameters were significantly smaller in the diabetic group: 6.28 ± 0.06 vs. 6.77 ± 0.11 mm, $P < 0.0001$); and significantly smaller with greater duration of diabetes ($r = -0.29$, $P = 0.0006$) and higher levels of GHb ($r = -0.24$, $P = 0.004$). Patients with retinopathy grade 30 or more (Wisconsin 191 grading) had significantly smaller resting pupil diameters: 5.9 ± 0.16 vs. 6.4 ± 0.12 mm, $P = 0.008$). The phasic light reflex as determined by reflex amplitude and maximum constriction velocity was significantly reduced in the diabetic group: 2.27 ± 0.03 vs. 2.44 ± 0.04 mm, $P = 0.0009$; and 6.68 ± 0.12 vs. 7.24 ± 0.16 mm/s, $P = 0.007$). Reduced reflex amplitude was related to a longer postpubertal duration of diabetes ($r = -0.18$, $P = 0.04$). We found no association between pupillary and cardiovascular tests.

CONCLUSIONS — Infrared computerized pupillometry demonstrates subclinical diabetic autonomic neuropathy as early as adolescence. Its presence seems to be related to longer duration of diabetes and unfavorable metabolic control.

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TYPE I DIABETES, INSULIN-DEPENDENT DIABETES MELLITUS; BP, BLOOD PRESSURE; HMF, HYDROXYMETHYLFURFURAL; TG, TRIGLYCERIDE; CV, COEFFICIENT OF VARIATION; CI, CONFIDENCE INTERVAL.

Little information is available about autonomic neuropathy in children and adolescents with type I diabetes. The prevalence of abnormalities in this age-group as defined by at least one abnormal cardiovascular test was reported as 31 and 39% in two different studies (1,2). These studies found no convincing relationship with duration or metabolic control. The autonomic nervous system also can be assessed by measuring pupil size (pupillometry). Pupil size at rest reflects mainly sympathetic activity, whereas the change in pupil size in response to a single brief light stimulus (phasic light reflex) is predominantly mediated by the parasympathetic system (3).

RESEARCH DESIGN AND METHODS

We studied 142 adolescents with type I diabetes, 72 boys and 70 girls with a mean age of 15.5 yr (range of 10.4–19.8 yr), mean diabetes duration of 7.7 yr (range of 0.7–18.3 yr), and mean GHb 1475 (range of 800-2110) pmol HMF/mg Hb). The control group comprised 75 nondiabetic adolescents, 29 boys and 46 girls with a mean age of 15.5 yr (range of 11.3–19.8 yr). The hospital's Ethics Committee approved the study, and participants gave informed written consent.

Pupillometry was performed in the left eye after 5 min of dark adaptation with an infrared computerized pupillometer (Pupilscan, Fairville Medical Optics, Amersham, UK). Phasic light reflex was induced by a light stimulus of 0.5 s, with a wave-length of 560 nm, and an intensity of 25-ft candles. Pupil size was recorded over the next 3 s at a rate of 20 scans/s. After averaging three pupillograms, we defined the following variables: resting pupil diameter (mm); reflex amplitude (resting − minimum pupil diameter [mm]); and maximum constriction velocity (mm/s).

Cardiovascular reflex tests included the maximum − minimum heart rate during deep breathing (mean of

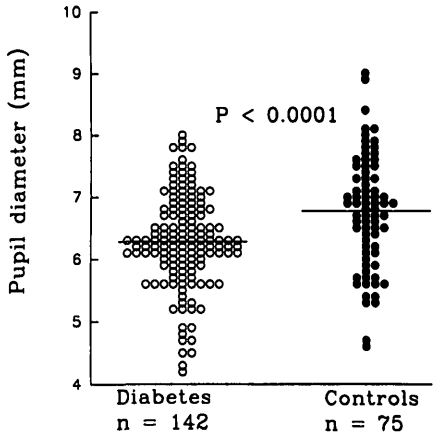

Figure 1—*Resting pupil diameters in diabetic and nondiabetic subjects. The horizontal lines indicate the mean of each group.*

three cycles), heart-rate change during a Valsalva maneuver (Valsalva ratio, mean of three maneuvers), lying-to-standing heart-rate change (30:15 ratio), and lying-to-standing BP change. We used Autocaft software for the tests (UnivEd Technologies, Edinburgh, UK)(4).

GHb was measured with a colorimetric method and expressed as pmol HMF/mg Hb (nondiabetic range 640-1040). Blood glucose was measured with a glucose oxidase method. Total cholesterol and TG levels were measured with standard laboratory techniques.

Retinopathy was assessed with stereofundal photography and graded according to the Wisconsin 191 System (5). All diabetic patients had an ophthalmological assessment to exclude other factors affecting pupil reaction. Postpubertal duration of diabetes was determined by arbitrarily defining onset of puberty as 11 yr for girls and 12 yr for boys (6).

We performed statistical analysis with the software package SAS and included Student's *t* test, Wilcoxon's rank-sum test, Pearson and Spearman correlation coefficients, and multiple linear regression analysis. The Shapiro-Wilk test was used to test for normal distribution of residuals, and $P < 0.05$ was considered significant. Results are given as means ± SE.

The 5% point of the control group was defined as the lower limit of the reference range. The maximum − minimum heart-rate change during deep breathing showed an age dependency in the control group, so the lower limit of the reference range was defined as the predicted value from the regression of age − the root mean square error × 1.645. We used χ^2 tests to study the association between pupillary and cardiovascular abnormalities.

RESULTS— Reference ranges for pupillary variables and cardiovascular tests as derived from the 75 control subjects are shown in Table 1. Of the 142 diabetic patients, 14 had a resting pupil diameter below the reference range. This group had a significantly longer duration of diabetes (9.2 vs. 7.5 yr, $P = 0.05$), higher GHb (1655 vs. 1455 pmol HMF/mg Hb, $P = 0.01$), higher serum cholesterol (5.0 vs. 4.4 mM, $P = 0.02$), and higher serum TG (2.1 vs. 1.5 mM, $P = 0.003$). Ten patients had a reflex amplitude, and 14 had a maximum constriction velocity lower than the reference range. The 30 diabetic patients who had at least one variable outside the reference range had a significantly higher mean GHb (1590 vs. 1440 pmol HMF/mg Hb, $P = 0.008$) and a longer postpubertal duration of diabetes (4.5 vs. 3.6 yr, $P = 0.02$).

We found significant differences between the diabetic and normal groups (Figs. 1–3). The diabetic group had a smaller mean resting pupil diameter (6.28 ± 0.06 vs. 6.77 ± 0.11 mm), $P < 0.0001$), a lower mean reflex amplitude (2.27 ± 0.03 vs. 2.44 ± 0.04 mm, $P = 0.0009$), and a lower mean maximum constriction velocity (6.68 ± 0.12 vs. 7.24 ± 0.16 mm/s, $P = 0.007$). Age had no effect on the resting pupil diameter.

Resting pupil diameters were significantly smaller with longer duration of diabetes ($r = -0.29$, $P = 0.0006$), higher levels of GHb ($r = -0.24$, $P = 0.004$), and higher blood glucose values ($r = -0.19$, $P = 0.03$). Duration was the best predictor of resting pupil diameter. After controlling for duration by multiple linear regression, we still found a significant negative effect of GHb ($P = 0.05$), but no effect of blood glucose ($P = 0.3$). Reflex amplitude was inversely correlated with postpubertal duration of diabetes ($r = -0.18$, $P = 0.04$).

Patients with retinopathy grade 30 or more on the Wisconsin Grading System ($n = 23$) had significantly smaller resting pupil diameters when compared with the group without retinopathy ($n = 37$, 5.9 ± 0.16 vs. 6.4 ± 0.12 mm, $P = 0.008$). When pupillometry was repeated 1–8 mo after the first measurement, the intrapatient CVs for averaged pupillograms were 5.8% for resting pupil diameter, 7.5% for reflex amplitude, and 11.4% for maximum constriction velocity.

Table 1—*Limits of reference ranges for pupillary variables and cardiovascular tests*

	5% POINT	90% CI FOR 5% POINT
RESTING PUPIL DIAMETER (MM)	5.3	5.0–5.5
REFLEX AMPLITUDE (MM)	1.7	1.5–1.9
MAXIMUM CONSTRICTION VELOCITY (MM/S)	5.0	4.7–5.4
INSPIRATORY/EXPIRATORY-RATIO (BEATS/MIN)	48.4–1.817 × AGE (YR)	
VALSALVA (RATIO OF LENGTHENING)	1.48	1.44–1.53
30:15 (RATIO OF LENGTHENING)	1.07	1.03–1.10
BP RESPONSE (MMHG)	−13	−17 TO −9

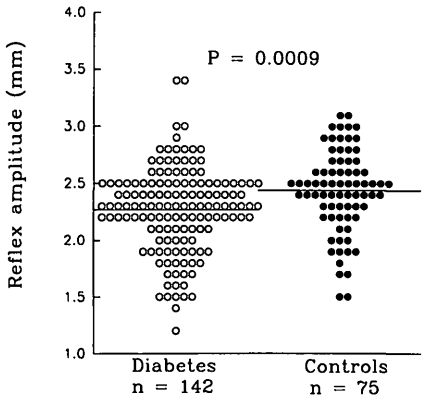

Figure 2—*Reflex amplitudes in diabetic and nondiabetic subjects. The horizontal lines indicate the mean of each group.*

In the cardiovascular tests of the 142 diabetic patients, 12 had abnormal results for the maximum − minimum heart-rate change during deep breathing, 13 for the Valsalva ratio, 11 for the 30:15 ratio, and 13 for postural BP change. The 12 patients with a maximum − minimum heart rate below the reference range had a significantly higher mean serum TG level (2.2 vs. 1.5 mM, $P = 0.007$). The 13 patients with an abnormal postural BP change were significantly older (17.3 vs. 15.3 yr, $P = 0.0025$) and had a longer postpubertal duration of diabetes (5.2 vs. 3.7 yr, $P = 0.01$). Of the 142 diabetic patients, 44 had at least one abnormal cardiovascular test, and 5 had two abnormal tests. The mean results for the cardiovascular tests were not significantly different between the diabetic and the control groups. We found no associations between pupillary abnormalities and abnormal cardiovascular reflexes, either when considered as a group, or when separated into single tests (data not shown).

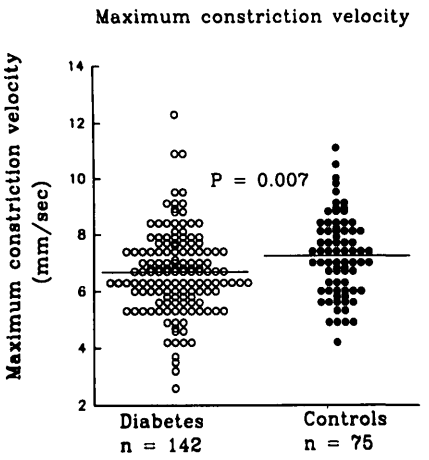

Figure 3—*Maximum constriction velocities in diabetic and nondiabetic subjects. The horizontal lines indicate the mean in each group.*

CONCLUSIONS— Our study found resting pupil diameters significantly smaller in the diabetic group and related to longer duration of diabetes, higher GHb values, and higher grades of background retinopathy. These results expand the findings in adults (7–9), demonstrating a possible role of duration of diabetes and metabolic control in the course of diabetic autonomic neuropathy as early as adolescence. One previous study investigated dark-adapted resting pupil diameters of children and found it significantly reduced in the diabetic group (10). No relationship to duration of diabetes or metabolic control was found, however.

Previous studies have reported parasympathetic damage as indicated by a decreased change in pupil size in response to light (7,9,11). In our study, reflex amplitude and maximum constriction velocity were significantly lower in the diabetic group, suggesting early parasympathetic disturbances. We found the reflex amplitude was reduced with longer postpubertal duration of diabetes.

Relationships between pupillary variables and cardiovascular tests for autonomic neuropathy have been found in adu s (7,12), but not in children (10). In our study, prevalence of pupil variables and cardiovascular tests outside the reference range were similar. No association occurred between pupillary abnormalities and abnormal cardiovascular tests, however. This may be attributable to the complex involvement of sympathetic and parasympathetic pathways in the different tests. Assessment of the resting pupil size and phasic light reflex by infrared pupillometry extends our understanding of the pathophysiological process of diabetic autonomic neuropathy evolving during adolescence.

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