

Evidence for a neuropathic aetiology in the small pupil of diabetes mellitus

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SUMMARY Infrared television pupillometry was performed on 34 insulin-treated diabetic patients and 55 healthy subjects. Sixteen of the diabetic patients had pupils that failed to dilate normally in darkness. The occurrence of a small pupil was associated with cardiac vagal dysfunction and somatic sensory loss. The small pupil was found to be supersensitive to the mydriatic effect of topical 2% phenylephrine but normally sensitive to 0.5% hydroxyamphetamine eyedrops. It is concluded that the failure of the pupil to dilate in darkness in some diabetic patients is due to neuropathy of the sympathetic innervation.

Diabetics with neuropathy often have abnormally small pupils that fail to dilate normally in darkness.¹ One possible cause is neuropathy of the sympathetic innervation of the dilator pupillae. This explanation is supported by the fact that the small pupil commonly occurs in association with autonomic dysfunction in other organs.¹ However, the iris of such patients is often damaged, with lesions of the smooth muscles, connective tissue, and blood vessels.^{2,3} This suggests an alternative explanation of the small pupil, namely, that local damage to the iris limits its mobility.

These alternative aetiologies have been investigated by studying the pupillary responses to topical sympathomimetic amines in diabetic patients with and without small pupils. Experience from studies on Horner's pupils has shown that denervation enhances the response to phenylephrine, a directly acting sympathomimetic amine, which dilates the pupil by activation of the α -adrenoceptors on the dilator pupillae.⁴ By contrast the response to hydroxyamphetamine, an indirectly acting sympathomimetic which works by releasing transmitter (noradrenaline) from the sympathetic nerve terminals, is variably affected according to the site of the lesion.^{5,6} Local iris damage on the other hand can be expected to reduce the response to any dilating agent. Healthy subjects were also studied to define the normal mydriatic response to phenylephrine and hydroxyamphetamine.

Subjects and methods

Thirty-four insulin-treated diabetic patients participated. None was taking drugs known to interfere with autonomic function. The neuropathic status of each was assessed by means of the following tests of peripheral somatic and autonomic nerve function.

Peripheral nerve function tests. Thresholds to vibration sense in both feet were measured at the tips of the great toe and over the medial malleoli with a Bio-Thesimeter (Bio-Medical Instruments Ltd). A raised threshold was identified by comparison with the age-related normal range obtained from a large data bank held in this laboratory. Patients were also examined for impairment of ankle and knee jerks and reduction of testicular sensation in males. They were classified as having peripheral neuropathy if any one of these tests was abnormal.

Cardiac vagal nerve function tests. Cardiac beat-to-beat interval variation was measured with an electrocardiograph coupled to a Commodore Pet micro-computer as described elsewhere.⁷ This technique was used to measure variations in rate due to sinus arrhythmia at rest and during deep breathing. In both states the amount of variation depends on both resting heart rate and the age of the subject. These factors have been defined in the normal ranges, and the results for each patient are calculated as a percentage of the normal accounting for age and rate. The 'sinus arrhythmia percentage' was averaged from

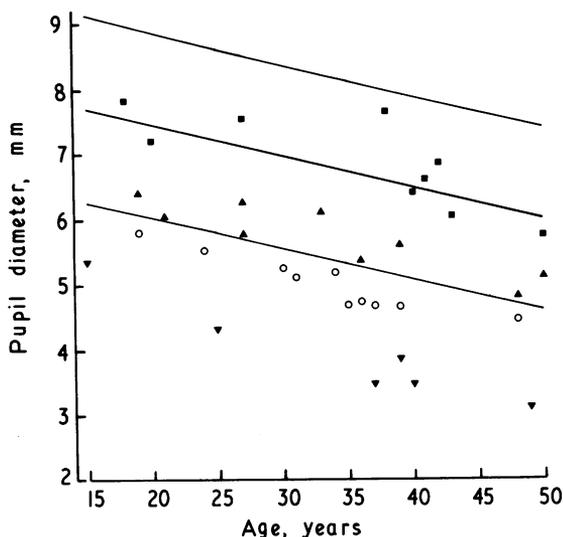


Fig. 1 Vertical pupil diameters in darkness in 34 diabetic subjects. The normal range and regression line on age for healthy subjects is shown. The diabetics were divided into 4 groups on the basis of the number of standard deviations (where 1 SD=0.71 mm) by which their diameter differed from the normal regression line. Group 1 (■) had diameters above or within 1 SD below the line; group 2 (▲) between 1 and 2 SD; group 3 (○) between 2 and 3 SD; group 4 (▼) between 3 and 4 SD.

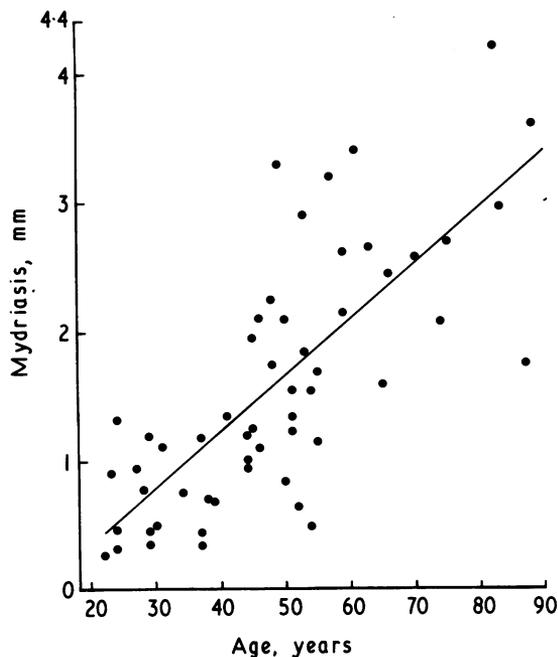


Fig. 2 The age-dependent mydriatic response to 2% phenylephrine in 55 healthy subjects. The correlation with age was highly significant ($r=0.76$, $p<0.001$).

the values obtained at rest and during deep breathing. Reduced sinus arrhythmia indicates cardiac vagal dysfunction.

Pupillary measurements. These were performed in darkness with an infrared television system. Patients were dark-adapted by wearing red goggles for a 30 min rest period. Vertical diameter was recorded in one eye with the subject focusing on infinity. Five 0.5 s light flashes were given, and the resting diameter was measured at the foot of the reflex response, averaged from the last 4 responses as previously described.⁸ Studies on healthy subjects have shown that pupil diameter in darkness declines with age by

0.48 mm per decade.⁹ The normal range is described by the 95 percentiles, which enclose diameters of 1.42 mm (or 2 standard deviations) on either side of the regression line on age as shown in Fig. 1.

Glycosylated haemoglobin. An estimate of diabetic control was obtained by recording the percentage of glycosylated haemoglobin (HbA_{1c}%) by a microcolumn method in which the normal range is 6.0–8.5%.¹⁰

Drug studies. These were performed in the 34 diabetics and in 55 healthy subjects, none of whom had a history of eye disease or took contraindicating drugs. Pupil diameters were measured in both eyes

Table 1 Clinical characteristics of diabetic subjects divided into 4 groups on the basis of their darkness pupil diameter

Group	Mean pupil diameter in darkness, mm (observed-expected)*	n	Age (yr): mean, range	Duration of diabetes (yr): mean, range	HbA _{1c} %, mean, range	No. with peripheral neuropathy	Sinus arrhythmia % of normal: mean ± SE
1	0.18	9	35.4 (18–50)	10.6 (2–23)	10.2 (5.5–18.7)	3	94 ± 12
2	-1.10	9	33.3 (19–50)	18.0 (6–40)	10.9 (7.8–14.6)	3	100 ± 12
3	-1.80	10	33.3 (19–48)	15.3 (4–26)	12.2 (9.2–18.4)	9	67 ± 13 [†]
4	-2.85	6	34.2 (15–49)	23.0 (11–36)	13.5 (9.5–18.9)	5	40 ± 9 [†]

*The expected value for pupil diameter (E) for the individual's age (x) where $E=8.415-0.048x$.

[†]Significantly different from normal (=100%), i.e., $p<0.05$.

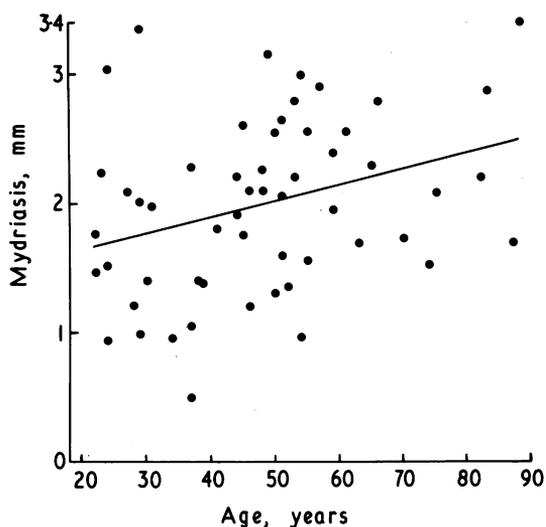


Fig. 3 The mydriatic response to 0.5% hydroxyamphetamine in healthy subjects. There was a significant correlation on age ($r=0.32$, $p<0.05$) but the age influence was less marked than with phenylephrine.

with the television system described but with constant background illumination. Control measurements were taken prior to instillation of drops to one eye. Each subject was treated with 2 drops of 2% phenylephrine hydrochloride (Boots Co.) and 2 drops of 0.5% hydroxyamphetamine hydrobromide (Smith Kline and French Ltd) at 2 visits at least one week apart. Drug solutions were freshly prepared each day in 0.15 M phosphate buffer pH 6.5, and warmed to 34°C before instillation with a Pasteur pipette with 1 min between drops. Pupillary measurements were made again at one hour after treatment, at which time the response is maximal. The drug effect was recorded as the difference between the anisocoria before and after the eye drops.

Statistical analysis. This was by standard techniques of linear regression by the method of least squares and by Student's *t* tests. Results were taken as significant if the probability values were less than 5%. Repeatability was assessed by calculation of the coefficient of variation (standard deviation of the within-subject variance divided by the mean) between 2 repeat measures in 20 individuals.

Results

Pupil size in the diabetic patients is shown in Fig. 1. Eighteen had diameters within and 16 had diameters below the normal range. They were further subdivided into 4 groups on the basis of the number of standard deviations below the normal regression as shown.

Table 1 summarises the neuropathic status of the 4 groups of diabetics in relation to their age, duration of diabetes, and degree of diabetic control as indicated by the HbA_{1c}%. The 4 groups were of a similar age. Long duration of disease and poor control of blood sugar were significantly related to the degree of pupillary abnormality as shown by the correlation coefficients: for duration, $r=0.41$, $p<0.05$; for HbA_{1c}%, $r=0.38$, $p<0.05$. More of the diabetics with small pupils had peripheral neuropathy than those with normal pupils. In groups 3 and 4 with small pupils there was a significant reduction in sinus arrhythmia to 67 and 40% of normal respectively.

The response to both sympathomimetic amines in the healthy subjects was dependent on their age. The response to 2% phenylephrine, shown in Fig. 2, varied widely from 0.28 to 4.40 mm, and 57.4% of this variance was age-dependent. The response to 0.5% hydroxyamphetamine, shown in Fig. 3, varied from 0.50 to 3.40 mm, but with this mydriatic only 10.3% of the variance was due to age. The equations for the 2 regressions are:

$$\begin{aligned} \text{phenylephrine: } & y=0.04x-0.52 \\ \text{hydroxyamphetamine: } & y=0.01x+1.38 \end{aligned}$$

where y =mydriatic response in mm and x =age in years.

The age dependence of the response to these drugs was taken into account in assessing the results in the diabetic patients, illustrated in Figs. 4 and 5. These show that the small pupil in patients with diabetic neuropathy was associated with an exaggerated response to phenylephrine and a normal response to hydroxyamphetamine. The mean mydriatic response for the 4 groups is shown in Table 2. Only in the 2 groups with significantly reduced pupil diameters was the response to phenylephrine significantly greater than normal.

Twenty of the diabetic patients, from all 4 groups, had repeat pupillary measurements performed to assess their reliability. The darkness pupil diameter was remarkably constant, with a coefficient of

Table 2 Mydriasis to 2% phenylephrine and 0.5% hydroxyamphetamine in diabetic patients, mean \pm SE

Group	Phenylephrine mydriasis, mm (observed-expected)*	Hydroxyamphetamine mydriasis, mm (observed-expected)*
1	0.04 \pm 0.18	-0.26 \pm 0.14
2	0.36 \pm 0.26	-0.19 \pm 0.16
3	0.95 \pm 0.29†	0.04 \pm 0.20
4	1.35 \pm 0.36†	0.14 \pm 0.19

*Expected values for age calculated from the equations given in the text.

†Significantly different from normal (=0), i.e., $p<0.05$.

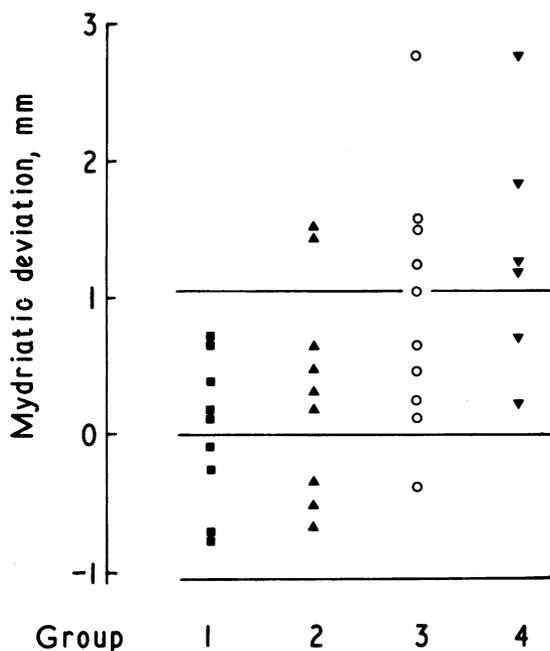


Fig. 4 The mydriatic response to phenylephrine in diabetic subjects. The responses are expressed as deviations from the normal for age, as in Table 1. The normal range is indicated by the horizontal bars. Clearly the response to phenylephrine was enhanced in diabetics with small pupils.

variation of only 6%. The coefficients for the mydriatic responses were higher: 23% for phenylephrine and 13% for hydroxyamphetamine.

Discussion

These results have shown that the small pupil in diabetic patients is supersensitive to phenylephrine. Enhanced pressor responses to intravenous phenylephrine have also been reported.¹¹ This supersensitivity, which is also found in Horner's pupils,^{5,6} is evidence in favour of a neuropathic rather than a myopathic aetiology in the miotic pupil of diabetes.

Supersensitivity to agents which mimic the action of the normal transmitter occurs with pre- and post-ganglionic lesions in sympathetic pupillary denervation.^{5,6,12} It is likely to be due to an increased activity of receptors on the muscle cell surface, although the precise nature of this increase has not been established in smooth muscle.¹³ It is unlikely to be due to a failure of the neuronal uptake mechanism, as suggested by Korczyn,¹⁴ since phenylephrine has a negligible affinity for this process—5% that of noradrenaline.¹⁵

In contrast to the phenylephrine results the

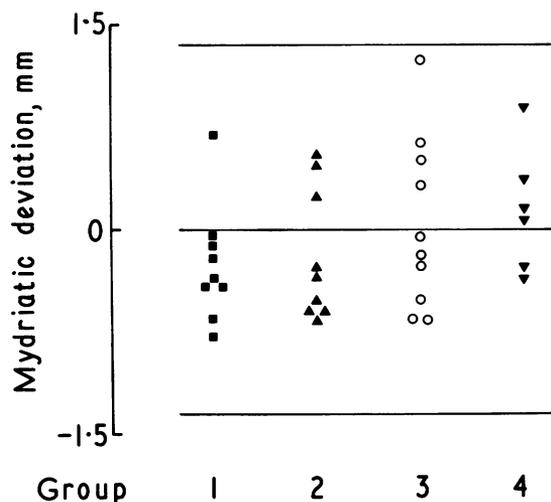


Fig. 5 The mydriatic response to hydroxyamphetamine in diabetic subjects, age-corrected as in Fig. 4. Comparison with the normal range shows that the responses in diabetics are normal.

mydriatic response to hydroxyamphetamine was found to be normal. This argues against a nonspecific cause of the phenylephrine supersensitivity, such as increased corneal penetration in diabetic patients. Similar results with these 2 amines have been found in Horner's syndrome in which the lesion is situated proximally to the superior cervical ganglion.⁵ While it is unwise to extrapolate to the complex pathology in diabetes mellitus, it can be concluded that the site of the damage is not confined to the postganglionic sympathetic fibres.

Diagnostic drug tests of pupillary denervation have been gaining in popularity.^{16,17} This study has emphasised the need for an accurate assessment of the normal response to such drugs before they can be used reliably in diagnosis. The marked influence of age on the response to the 2 agents used here may well be found with other drugs used in diagnostic tests.

There are a number of similarities between senile miosis and diabetic miosis. In comparison with that of healthy young people the pupil in both groups fails to dilate in darkness and is differentially more sensitive to phenylephrine than to hydroxyamphetamine. The action of cocaine is reduced in the elderly pupil,¹⁸ which suggests that a reduction of sympathetic activity occurs with age due to a degenerative process that is accelerated in diabetes.

It is a common clinical impression that the pupil in patients with diabetic neuropathy is difficult to dilate for fundal inspection. The agents used are most commonly atropinic agents such as homatropine, cyclopentolate, and tropicamide. These normally

work by paralysing the parasympathetic constrictor drive, allowing the sympathetic input to the dilator to dominate. The loss of sympathetic tone in patients with diabetic neuropathy would thus limit the usefulness of the anticholinergic mydriatics. Addition of a directly acting sympathomimetic, to which the pupil is supersensitive, may well improve the mydriasis.

The purpose of the present investigation was to differentiate between neuropathy and myopathy as causes of the small pupil, since disorders of both types occur in diabetes.² The same problem of interpretation occurs with all the conventional autonomic function tests, usually cardiovascular, that depend on measuring the activity of the end organ rather than the activity of the nerve. The present finding that abnormal pupillary dilatation in darkness is indeed due to neuropathy validates the measurement of resting pupil size as a diagnostic test of diabetic autonomic neuropathy.

Sympathetic neuropathy of the pupillary innervation was associated with cardiac vagal and somatic sensory dysfunction. These neuropathic signs were more common in patients with long duration and poor control of their disease. This confirms the findings of Pirart¹⁹ and others that the degree and duration of chronic hyperglycaemia are important risk factors in the development of diabetic complications.

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