Parasympathetic denervation of the iris in diabetes mellitus¹

A clinical study

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SYNOPSIS Sixty-two patients with diabetes mellitus were tested for the presence of parasympathetic denervation hypersensitivity of the iris using a 2% solution of methacholine. Fifty patients (81%) had a measurable miotic response compared with three (8%) of a group of 36 control subjects. An abnormal response was obtained from 17 (74%) of 23 patients with a clinical course of less than two years and 33 (85%) of 39 patients with a clinical course of longer duration. These findings corroborate other evidence of a high incidence of peripheral neuropathy appearing early in the clinical course of diabetes mellitus and extend the observations to the parasympathetic innervation of the iris. The methacholine test is a simple bedside method which is of potential value for establishing parasympathetic iris denervation of diverse aetiologies.

Peripheral neuropathy is recognized as one of the major complications of diabetes mellitus. Somatic neuropathy occurs early in the course of diabetes mellitus in most patients (Downie and Newell, 1960; Lamontagne and Buchthal, 1970; Chochinov *et al.*, 1971) and at times precedes the manifestations of disordered carbohydrate metabolism (Rundles, 1945; Martin, 1953; Ellenberg, 1966). Autonomic neuropathy can also occur early, though it is usually a late complication. It is manifested by bladder and bowel dysfunction, impotence, sweating defects, and faulty temperature regulation (Rundles, 1945; Martin, 1953; Colby, 1965; Ellenberg, 1966; Goodman, 1966; Friedman and Simmons, 1967b). Abnormal innervation of the iris has also been reported as a late manifestation of diabetic neuropathy. This may present as irregular and unequal pupils, excessive miosis, a sluggish and delayed reaction to light, prolongation of the dilatation phase (Waite and Beetham, 1935; Jordan, 1936; Rundles, 1945; Martin,

1953; Friedman *et al.*, 1967a; Ohrt, 1968) and diminished response to mydriatic solutions (Ohrt, 1968).

We report a high incidence of parasympathetic denervation of the iris early in the clinical course of diabetes mellitus, demonstrated by constriction of the pupil in response to topical administration of dilute methacholine, a cholinergic drug.

METHODS

The subjects of the study were diabetic inpatients and outpatients of the Strong Memorial and Monroe Community Hospitals in Rochester, New York, and of the Dartmouth-Hitchcock Medical Center in Hanover, New Hampshire. The criteria for admission to the study were the presence of chemically confirmed diabetes mellitus and absence of other conditions known to be associated with neuropathy. Sixty-two patients were studied. Twenty-three with documented disease of two years or less were considered short-term diabetics. The remainder (39) were considered long term.

The short-term group included 15 females and eight males with a mean duration of known diabetes of 9.9 months (range 0.1 to 24 months). The mean age was 57.7 years (range 17 to 79 years). Sixteen

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were maintained on diet alone, three were on oral hypoglycaemic agents, and four were insulin dependent. Two had had one episode each of ketoacidosis. Two reported the presence of lower extremity paraesthesiae. There was no history suggestive of autonomic dysfunction.

The long-term group included 20 females and 19 males with a mean duration of known diabetes of 12.4 years (range 2.1 to 37 years). The mean age was 60.6 years (range 16 to 81 years). Six patients were being controlled solely by diet, 15 were receiving oral hypoglycaemic agents, and 16 were insulin dependent. Six patients reported one or more episodes of ketoacidosis. Lower extremity paraesthesiae were present in five patients. Autonomic dysfunction by history was present in 10 patients; nine complained of impotence, two of diarrhoea, and two of constipation.

Peripheral nervous system examination included evaluation of light touch, vibration sense (C_{128}), proprioception, pin perception, the presence of wasting or weakness, and major deep tendon reflexes. Autonomic function was evaluated by testing the pupillary light reflex, orthostatic blood pressure changes, and the blood pressure and pulse rate response to immersion of the hand in ice water for one minute (cold pressor test). The sweating response was observed after occluding the skin of the feet with a plastic bag and covering the patients with blankets for 30 minutes. It was compared with the response of control subjects. Some patients refused autonomic function testing. The total number of patients tested is indicated in the results (Figs 1 and 2). Additional eye examination included funduscopy, evaluation of extraocular muscle function, visual fields, and visual acuity.

Thirty-six subjects from the staff and inpatients of the above hospitals were used as controls. The presence of known diabetes, alcohol abuse, thyroid dysfunction, use of neurotoxic drugs, or other presumed causes of neuropathy was reason for exclusion from the control group. Subjects with a family history of diabetes were not excluded. The group was composed of 18 females and 18 males with a mean age of 55.6 years (range 29 to 87 years). There were no significant differences in age or sex composition between the control and diabetic populations. Only pupillary testing was carried out on the controls.

Both diabetics and controls were placed in a room in which the ambient lighting could be carefully controlled and were asked to look at a blank wall. The pupillary diameter was measured to the nearest 0.5 mm in the horizontal plane using a transparent plastic ruler. One drop of 2% methacholine in normal saline was instilled in each conjunctival sac. The lacrimal duct was occluded by pressure for one

minute. At the end of 20 minutes the pupillary diameter was again measured for the presence or absence of constriction.

Statistical analysis of data was performed using Student's *t* test and the Pearson product moment correlation coefficient.

RESULTS

PERIPHERAL NERVE EXAMINATION Eighteen (78%) of the 23 patients in the short-term group had some evidence of neuropathy. Thirty-eight (97%) of the 39 subjects in the long-term group had some evidence of neuropathy. When standard sensory, deep tendon reflex, and eye examination results are considered alone (excluding the autonomic function tests), 14 patients (23%) showed no abnormalities, including 11 (49%) in the short-term group.

FIG. 1. Percentage of patients with abnormalities found on peripheral somatic nervous system examination. The total numbers tested and those with abnormalities are shown at the top of each column. Diabetics compared with controls $P < 0.001$. □ Short-term diabetics. ▨ Long-term diabetics.

The most frequent abnormal finding was a diminished or absent Achilles tendon reflex, being observed in 10 patients (44%) in the short-term group and 30 patients (77%) in the long-term group. In the short-term group, eight patients had abnormal distal extremity responses to vibration, seven to pin, and seven to proprioception. In the long-term group, distal extremity

FIG. 2. Percentage of patients and controls with abnormalities found on peripheral autonomic nervous system examination and the results of methacholine testing. Not all examinations could be completed on all patients. Total number tested and those with abnormalities are shown at the top of each column. □ Short-term diabetics. ▨ Long-term diabetics. ■ Controls.

vibration perception was altered in 23 patients, pin perception in 18, and proprioception in 16 (Fig. 1).

Orthostatic hypotension of greater than $-30/-20$ mmHg was present in 21% (3 of 14) of the short-term group and 30% (nine of 30) of the long-term group. Decreased sweating was present in 25% (two of eight) of the short-term group and in 59% (20 of 34) of the long-term group. An excessive blood pressure response to the cold pressor test (rise greater than 50 mmHg diastolic or systolic) was present in 31% (eight of 24) of that same group. Only one of the 11 tested in the short-term group had an abnormal (excessive) response. Sluggish or asymmetrical responses to light were judged to be present in 17 patients (43%) in the long-term group and four patients (17%) in the short-term group (Fig. 2).

No abnormalities of the extraocular muscles were found. Fundal changes characteristic of diabetes mellitus (capillary aneurysms and/or neovascularization) were present in four patients (17%) in the short-term group and 14 patients (36%) in the long-term group.

METHACHOLINE RESPONSE A total of 50 (81%) out of the 62 patients with diabetes mellitus responded by pupillary constriction to the dilute solution of methacholine. In contrast, only three (8%) of 36 controls responded (Fig. 2). Of the 50 responding diabetics, six (12%) had an observable change in one eye only. Seventeen (74%) of the 23 short-term diabetics reacted; whereas a measurable response was present in 33 (85%) of the 39 long-term diabetics. The differ-

ence between the long-term diabetics and the short-term diabetics was not statistically significant but appeared to indicate a trend. Weak correlations were found between the known duration of diabetes and both the degree of peripheral neuropathy and the magnitude of the response of the iris to methacholine. No correlation was found between the presence of peripheral neuropathy or autonomic neuropathy alone and the iris response. Nine of 12 (75%) of the patients who had no response to methacholine had evidence of a peripheral neuropathy on examination, and eight out of 50 (16%) of the patients who responded had no evidence of an autonomic peripheral neuropathy, though all had evidence of a somatic peripheral neuropathy. No correlation was found between age or sex and the iris response or the presence of neuropathy.

DISCUSSION

Observation of adrenergic and cholinergic hypersensitivity in sympathetic and parasympathetic denervated irides (Meltzer and Auer, 1904; Shen and Cannon, 1936) led Cannon and Rosenbluth (1949) to propose the principle of denervation hypersensitivity. This is considered the mechanism of the 'Mecholyl test', which uses dilute methacholine as a diagnostic test for pupillotonia (Scheie and Adler, 1940). The validity of using this test for detecting parasympathetic denervation hypersensitivity in the iris has been confirmed by several authors (Francheschetti and Bischler, 1946; de Haas,

1959; Smith *et al.*, 1965; Harriman and Garland, 1968).

The present study demonstrates early and frequent involvement of the peripheral autonomic nervous system in diabetes mellitus. The irides of 85% of the long-term diabetes and 74% of the short-term diabetics responded to 2% methacholine. Only 8% of the controls responded. This is in agreement with Brunnschweiler (1954) who, using a stronger solution, 2.5% methacholine, tested 100 unselected controls and found pupillary constriction in 14%. He found, as we did, no correlation with sex and only minimal increase in sensitivity with patient age.

Previous studies have not reported such frequent involvement of the iris. Pupillary abnormalities associated with diabetes were first mentioned by Pryce (1887). Depending upon the diagnostic criteria and testing techniques, subsequent reports associated pupillary abnormalities with diabetes in 1.9% to 36% of subjects (Waite and Beethman, 1935; Rundles, 1945; Martin, 1953; Friedman *et al.*, 1967a; Ohrt, 1968). Thirty-six per cent of the diabetic patients reported by Friedman *et al.* (1967a) and 'almost one-third' of the patients of Ohrt (1968) had pupillary abnormalities consisting of sluggish light reflexes, and asymmetries and prolongation of the dilatation phase of the light reflex in combination or isolation as compared with controls. We observed abnormal light reflexes in 21 patients (33%); 17% of the short-term group and 43% of the long-term group.

The clinical presentation of the autonomic neuropathy associated with diabetes is similar to that of the somatic neuropathy in time course and severity. As with the somatic nervous system, there is some evidence that abnormalities of the peripheral autonomic nervous system can precede other manifestations of diabetes (Ellenberg, 1966). However, clinically evident autonomic dysfunction is most often a late manifestation (Martin, 1953; Goodman, 1966; Zitomer *et al.*, 1968). In those patients examined in our series, 59% (20 of 34) of the long-term diabetics had hypohydrosis of the feet in contrast with 25% (two of eight) of the short-term diabetics. Orthostatic hypotension was observed in 30% (nine of 30) of the long-term diabetics and in 21% (three of 14) of the short-term diabetics. The small number of patients tested for auto-

nomic neuropathy may be the reason for lack of a statistically significant correlation with the presence of iridic denervation. It is also possible that separate pathogenetic factors underlie the iridic and other peripheral autonomic defects.

Our findings on evaluation of both the peripheral autonomic and somatic nervous systems are in agreement with previous studies.

The autonomic nervous system has been difficult to evaluate quantitatively for minor changes. We consider the methacholine test a simple and sensitive method for demonstrating autonomic neuropathy and specifically for demonstrating parasympathetic denervation of the iris in diabetics. Previously, its use has been mainly for diagnosing pupillotonia. We have extended this use to diabetes mellitus and consider the test to be of potential value for the demonstration of denervation of the parasympathetic iris mechanism in neuropathies of various aetiologies.

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