Peripheral and Autonomic Nerve Function in Newly Diagnosed Diabetes Mellitus

D. M. Fraser, M.R.C.P., I. W. Campbell, M.R.C.P., D. J. Ewing, M.R.C.P., A. Murray, Ph.D., J. M. M. Neilson, Ph.D., and B. F. Clarke, F.R.C.P. Edinburgh, Scotland

SUMMARY

Peripheral and autonomic nerve function was assessed in 10 newly diagnosed male diabetics (six insulin-treated and four sulfonylurea-treated) with repeated observations over the subsequent six months. There was significant impairment of motor-conduction velocity in the common peroneal nerve at diagnosis in both treatment groups, with improvement following treatment in only the insulin-treated patients.

In contrast, although the blood glucose level fell in both groups, the mean level was significantly lower in the sulfonylurea-treated patients at two months and at each subsequent visit.

In the autonomic function tests significant abnormality was found in the electrocardiographic R-R-interval (beat-to-beat) variation in resting heart rate in two of the insulin-treated patients and all of the sulfonylurea-treated group, with improvement in only one of the latter. One patient in the sulfonylurea-treated group also showed an abnormal response to the Valsalva maneuver (expressed as the Valsalva ratio), and this remained abnormal throughout the period of study. All other patients had normal responses to the Valsalva maneuver and sustained handgrip test. None of the patients had postural hypotension. Abnormalities in autonomic nerve function in diabetics at diagnosis have not been previously reported. DIABETES *26*:546-50, June, 1977.

Delay in peripheral nerve motor-conduction velocity (MCV) in diabetic patients may be demonstrated before the development of symptoms of peripheral neuropathy.[1,2] Gregerson[3] and Ward et al.[4] showed that MCV could be abnormal even at the time of diagnosis of diabetes and that improvement may occur following effective treatment. Subclinical autonomic neuropathy may be detected in patients with established diabetes by such simple techniques as the Valsalva maneuver,[5] the blood pressure response to sustained handgrip,[6] and the electrocardiographic R-R-interval (beat-to-beat) variation in resting heart rate.[7,8] The aim of the present study was to determine whether abnormal autonomic nerve function was present in newly diagnosed diabetics and, if so, whether improvement occurred after treatment.

PATIENTS AND METHODS

Ten newly diagnosed male diabetics agreed to participate in the study. The patients were subdivided into two treatment groups for the purpose of analysis. Six patients aged 18 to 40 years (mean age 27 years) were treated with insulin and four patients aged 46 to 58 (mean age 50 years) with a sulfonylurea (chlorpropamide). The mean duration of symptoms in the insulin-treated group was eight weeks and in the sulfonylurea-treated group 12 weeks. None was known to be alcoholic and all had normal blood urea, serum electrolytes, creatinine, thyroxine, and vitamin B_{12} levels.

Each patient was assessed at diagnosis and at each subsequent visit for symptoms and signs of peripheral and autonomic neuropathy by a questionnaire and full physical examination, and no abnormalities were detected. Tests of peripheral and autonomic nerve function were carried out at the first clinic attendance, and treatment was commenced the same day. Peripheral nerve tests were repeated at intervals of one day, six days, three months, and six months after treatment was established. Autonomic nerve function tests were performed at these times and also at one month and two months.

Peripheral Nerve Function

MCV and terminal latency (TL) were estimated in the motor fibers of the right common peroneal, ulnar,

From the Diabetic and Dietetic Department and University Departments of Medicine and Medical Physics, the Royal Infirmary, Edinburgh, Scotland.

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and median nerves. All measurements were made by the same investigator in the same environment, with skin temperature maintained at or above 30° C. Surface electrodes were used for stimulating the nerve with 1-cm. silver discs placed 5 cm. apart. Standard DISA surface recording electrodes and a DISA two-channel electromyograph were used in all studies.

Autonomic Nerve Function

Autonomic nerve function was assessed with four simple noninvasive tests: the heart rate response to the Valsalva maneuver, the blood pressure response to sustained handgrip, the electrocardiographic R-R-interval (beat-to-beat) variation in resting heart rate, and the postural fall in blood pressure.

1. *Valsalva maneuver.* The Valsalva maneuver was carried out under a standardized technique as previously described.[9] The heart rate response was measured by a simultaneous electrocardiograph, and the results were expressed as the Valsalva ratio (the ratio of the longest R-R interval after the maneuver to the shortest R-R interval during the maneuver). A ratio of 1.10 or less was defined as an abnormal response, 1.11 to 1.20 as borderline, and 1.21 or more as a normal response.

2. *Sustained handgrip test.* A standardized sustained handgrip test was also performed.[6] The maximum voluntary contraction was first determined, and then handgrip was maintained steadily at 30 per cent of that maximum voluntary contraction for as long as possible up to a maximum of five minutes. Blood pressure was measured with a sphygmomanometer on the nonexercising arm. Observations were made three times at rest, at one-minute intervals during handgrip, and twice more immediately after release. The changes in blood pressure were taken as the difference between the mean of the three resting readings and the last reading before release of handgrip. A rise in diastolic blood pressure of less than 10 mm. Hg was defined as abnormal, 11-15 mm. Hg as borderline, and 16 mm. Hg or more as normal.

3. *R-R-interval variation in resting heart rate.* The R-R-interval (beat-to-beat) variation in resting heart rate was measured with a sensitive electrocardiographic computer technique.[8] The patient stood quietly for five minutes before the resting heart rate was recorded onto magnetic tape for five minutes. Each subject's electrocardiogram was later fed at high speed (x 60) from the previously recorded tape into an arrhythmia computer for accurate timing of the R-R intervals. The mean R-R interval for the five-minute period was then calculated for each patient, and the variation in resting heart rate was expressed as the standard deviation of that mean R-R interval, our lower limit of normal being 35 milliseconds.

4. *Postural fall in blood pressure.* Postural hypotension was defined as a fall in systolic blood pressure of 30 mm. Hg or more immediately on the subject's standing up from the supine position.

Standard statistical methods were used in analyzing the results, which are expressed as mean ± standard deviation.

RESULTS

Blood Glucose Levels (Table 1)

There was no significant difference in the mean blood glucose levels at diagnosis between the two treatment groups. The blood glucose level fell satisfactorily in both groups after the introduction of therapy. At two months the mean blood glucose level in the sulfonylurea-treated group was significantly lower ($p < 0.05$) than in the insulin-treated group, and this difference was maintained throughout the remainder of the study.

Peripheral Nerve Function (Table 2)

1. *Common Peroneal Nerve*

(a) *Motor conduction velocity.* The mean MCV at diagnosis was delayed in both treatment groups. In the insulin-treated group there was an improvement over the period of study, reaching statistical significance by day 6 (day 1 vs. day 6, $p < 0.01$; day 1 vs. three months, $p < 0.02$; day 1 vs. six months, $p < 0.005$). In the sulfonylurea-treated group, however,

TABLE 1

Blood glucose levels (mg./100 ml.) in the two treatment groups at each attendance over a six-month period
Mean ± S.D.

	Day 1	Day 2	Day 6	1 month	2 months	3 months	6 months
Insulin-treated group	380 ± 72	194 ± 76	174 ± 85	159 ± 45	174 ± 51	187 ± 37	150 ± 34
Sulfonylurea-treated group	330 ± 57	250 ± 36	160 ± 36	105 ± 22	107 ± 10	114 ± 10	106 ± 14
	N.S.	N.S.	N.S.	N.S.	$p < 0.05$	$p < 0.05$	$p < 0.05$

TABLE 2
Motor-conduction velocity (MCV) and terminal latency (TL) in six diabetics treated with insulin (I) and four with sulfonylurea (SU)

Mean ± S.D.

	Common peroneal nerve				Ulnar nerve				Median nerve			
	MVC (m/s)		TL (ms)		MCV (m/s)		TL (ms)		MCV (m/s)		TL (ms)	
	I	SU	I	SU	I	SU	I	SU	I	SU	I	SU
Day 1	42.3 ± 7.5	42.5 ± 4.3	6.0 ± 2.2	4.8 ± 1.0	56.4 ± 3.3	55.3 ± 5.2	2.9 ± 0.4	2.9 ± 0.4	54.1 ± 3.7	55.3 ± 4.6	3.5 ± 0.5	3.8 ± 0.9
Day 2	45.0 ± 3.6	41.7 ± 2.3	5.5 ± 1.7	5.6 ± 1.9	55.1 ± 4.0	52.5 ± 8.1	2.7 ± 0.5	3.4 ± 1.0	52.7 ± 3.2	53.2 ± 5.3	3.6 ± 0.6	3.9 ± 1.1
Day 6	47.5 ± 4.5	43.6 ± 4.4	5.3 ± 1.7	4.4 ± 1.1	56.3 ± 4.6	52.5 ± 9.8	2.8 ± 0.3	3.0 ± 0.5	57.3 ± 3.9	53.8 ± 6.4	3.4 ± 0.4	4.0 ± 1.0
3 months	46.8 ± 2.4	39.9 ± 4.5	4.7 ± 1.2	4.3 ± 0.7	56.5 ± 2.2	54.8 ± 3.3	2.9 ± 0.2	3.0 ± 0.3	56.5 ± 2.1	55.6 ± 1.3	3.5 ± 0.4	3.8 ± 0.7
6 months	49.2 ± 3.2	44.3 ± 1.6	4.5 ± 0.5	4.3 ± 0.4	58.5 ± 2.7	54.6 ± 2.5	2.7 ± 0.3	2.9 ± 0.2	58.0 ± 3.4	54.6 ± 2.7	3.4 ± 0.2	3.7 ± 0.2
Normal values for this laboratory	47.2 ± 5.1		4.4 ± 1.3		58.4 ± 8.4		2.9 ± 0.5		54.1 ± 3.0		3.5 ± 0.4	

there was no significant change, even at six months.

(b) *Terminal latency.* The mean TL was slightly prolonged at diagnosis in the insulin-treated group and showed some improvement following the initiation of treatment, the change being significant by three months (day 1 vs. three months, $p < 0.05$; day 1 vs. six months, $p < 0.05$). In the sulfonylurea-treated group the mean TL was within the normal range at diagnosis and showed no significant change thereafter.

2. *Ulnar Nerve*

(a) *Motor-conduction velocity.* All values were within the normal range for nondiabetic subjects. However, there was significant improvement within this range in the insulin-treated group (day 1 vs. six months, $p < 0.05$), although no change occurred in the sulfonylurea-treated group.

(b) *Terminal latency.* All values were again within the normal range for nondiabetic subjects and showed no significant change throughout the period of study.

3. *Median Nerve*

All values for MCV and TL were within the normal range for nondiabetic subjects in all patients and no significant changes occurred in these values.

Autonomic Nerve Function

(a) *Valsalva maneuver.* In the insulin-treated group the pretreatment values were all within the normal range and no significant change occurred thereafter. Three out of four patients in the sulfonylurea-treated group also showed normal responses throughout the period of study. The fourth patient, however, had an abnormal response to the Valsalva maneuver at onset, and this remained abnormal even at six months. The mean value for Valsalva ratio in the sulfonylurea-treated group at onset (1.41 ± 0.29) was significantly lower ($p < 0.05$) than the mean value in the insulin-treated group (1.98 ± 0.36). This difference was maintained throughout the study and persisted at six months (insulin-treated group, 1.78 ± 0.49; sulfonylurea-treated group, 1.23 ± 0.22; $p < 0.05$).

(b) *Sustained handgrip and postural hypotension.* All patients had normal responses to sustained handgrip and no postural hypotension, with no change after starting treatment. There were no significant differences in the results between the two treatment groups.

(c) *R-R-interval variation (figure 1).* In the insulin-treated group, two out of the six patients had abnormal results at diagnosis, and these were still abnormal at the end of the study. All results in the sulfonylurea-treated group were abnormal at diagnosis and in three of the patients remained so throughout the study,

whereas in one there was improvement to within the normal range. The mean value in the sulfonylurea-treated group at onset (19 ± 8 msec.) was significantly less ($p < 0.05$) than in the insulin-treated group (38 ± 13 msec.), and this difference persisted at six months (insulin-treated group, 41 ± 13 msec.; sulfonylurea-treated group, 20 ± 6 msec.; $p < 0.02$).

DISCUSSION

The present study has investigated both peripheral and autonomic nerve function in newly diagnosed diabetic patients. We have confirmed the previous findings of impaired peripheral nerve function at diagnosis, which may improve when treatment is established.[3,4] In addition, we have shown that autonomic nerve dysfunction may be present in these patients at diagnosis.

The peripheral nerve studies in our patients have demonstrated delay in MCV and prolongation of TL of the common peroneal nerve at diagnosis, whereas ulnar and median nerve function remained normal throughout the study. Although significant improvement to within the normal range occurred in both MCV and TL in the insulin-treated group, patients in the sulfonylurea-treated group failed to show similar improvement despite satisfactory diabetic control. This is in contrast to Ward et al.,[4] who did not find return of MCV to normal, and, further, the major contribution to improvement in nerve function in their patients occurred in those treated with sulfonylureas, with no significant change in those treated with insulin. It is known that hyperglycemia without obvious symptoms may be present for years before diabetes is diagnosed,[10] and our findings in the maturity-onset diabetics may reflect a longer period of asymptomatic metabolic upset. It would appear that even the lower blood glucose levels achieved in the sulfonylurea-treated patients over the period of study did not compensate for this difference. However, the changes may also be a function of age, since Gregerson[11] has shown that MCV in diabetics falls with increasing age. We have shown no abnormalities in MCV and TL of both the ulnar and median nerves, which is consistent with the fact that peripheral neuropathy in diabetics is common in the lower limbs but unusual in the upper limbs[12,13] and in keeping with our previous similar findings in diabetic patients with established autonomic neuropathy.[14]

Although abnormal autonomic nerve function has been frequently reported in established diabetic patients, there have been no previous studies at the time of diagnosis. We and others have shown abnormalities in simple noninvasive autonomic function tests (Valsalva maneuver, sustained handgrip test, R-R-interval variation in resting heart rate, and postural hypotension) in diabetics with symptomatic autonomic neuropathy,[9,15] in those without clinical features of autonomic neuropathy,[5,6,8] and following ketoacidosis.[16] Probably the most sensitive test of autonomic dysfunction is the R-R-interval variation in resting heart rate, and this has been shown to be dependent on intact vagal innervation of the heart.[7] We have previously studied 42 young, long-standing male diabetics without symptoms of autonomic neuropathy, 22 of whom had R-R-interval variations less than any of the 25 control subjects had.[8] The present study now shows that autonomic nervous system damage may be present even at diagnosis, as the R-R-interval variation in resting heart rate was abnormal in more than half of our patients. There were significant differences between the two treatment groups, the more abnormal results being in those on

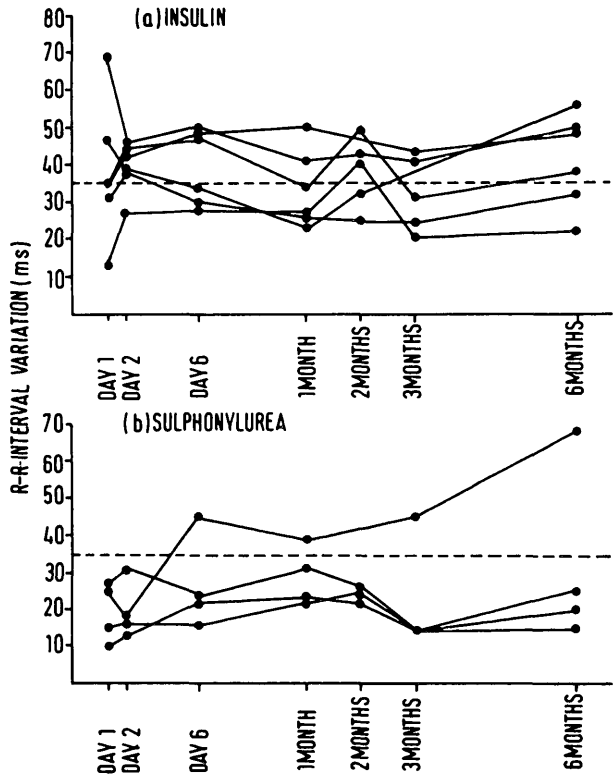

FIG. 1. Individual R-R-interval (beat-to-beat) variations in resting heart rate in six insulin-treated and four sulfonylurea-treated patients over a six-month period following diagnosis.

sulfonylureas. This may be a reflection of the more prolonged metabolic upset or the difference in age. There were also similar differences in the mean Valsalva ratios of the two groups, but only one patient (in the sulfonylurea-treated group) had an abnormal Valsalva ratio. There were no abnormal responses to the sustained handgrip test and no postural hypotension was demonstrated during the study. This is in keeping with our previous experience, in which abnormalities of these two tests are more usually associated with clinically overt autonomic neuropathy.[17]

Fibers mediating the autonomic responses are both myelinated and unmyelinated, while the MCV is measured in large myelinated fibers. The most constant underlying lesion in the peripheral neuropathy of diabetes has been shown to be segmental demyelination.[18,19] This is usually thought to be due to disturbance of the Schwann cells, but it has been suggested that segmental demyelination may result from axonal disturbance.[20,21] Axonal loss has been demonstrated in more severe cases.[22] Histologic studies of autonomic nerves in diabetics are limited, but Low et al.[23] have shown significant reduction in fiber density in the greater splanchnic nerve of diabetics, with the predominant pathology on tease-fiber preparations being that of demyelination. These authors have also studied the pathologic changes in the sural nerve of diabetic subjects with autonomic dysfunction and shown active axonal degeneration affecting mainly unmyelinated and small myelinated fibers.

We have thus demonstrated previously unreported abnormalities of autonomic nerve function at the time of diagnosis of diabetes mellitus. Not all tests were abnormal, however, and this might be due to selective damage to certain pathways in the early stages. Our findings show that improvement in autonomic function cannot necessarily be expected, even if satisfactory diabetic control is achieved. Although symptomatic autonomic neuropathy is a late manifestation of diabetes,[17] cumulative damage may be occurring from the time of diagnosis.

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