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Diabetic Autonomic Neuropathy

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Introduction

DIABETIC AUTONOMIC NEUROPATHY is not uncommon and produces a variety of effects. The importance of recognition of these manifestations is three-fold: firstly, to avoid diagnostic error; secondly, to alleviate patients from symptoms; and thirdly, as a guide to prognosis (Ewing et al, 1976).

The diagnosis of diabetic autonomic neuropathy is usually based on characteristic clinical features and is often unsubstantiated by objective testing of the autonomic nervous system. Tests to establish the presence of autonomic neuropathy are generally complex and not easily performed at the bedside, and are based on the integrity of the vascular reflexes.

The twin objectives of this paper are to review the pattern of diabetic autonomic neuropathy manifestation in the local population, and to present two simple tests of cardiac denervation, which may be performed by any practitioner without the use of any elaborate apparatus.

Patients and Methods

Twenty-seven patients were selected for the study, on the basis of the presence of one or more of the following known manifestations of diabetic autonomic neuropathy:

1. Postural hypotension

A postural drop of systolic blood pressure of 30 mm Hg and above on changing from lying to standing position, with or without symptoms of faintness, giddiness or vertigo. Patients who had been on hypotensive drugs were excluded.

2. Gastrointestinal disturbances
   (a) Diarrhoea: Intermittent or nocturnal, with watery stools but no blood or mucus;
   (b) Gastric fullness with or without nausea and vomiting;
   (c) Dysphagia.

3. Impotence

Defined as inability to achieve or sustain full penile erection, without loss of libido.

4. Bladder disturbances

Urinary retention, incontinence or decreased flow rate in the absence of prostatic enlargement.

5. Sweating abnormalities

Hyperhidrosis, anhidrosis, nocturnal or gustatory sweating, in the absence of thyroid disorders.

6. Hypoglycaemia unawareness in patients not known to be on beta blocker therapy.

Each case selected was subjected to:

1. A thorough physical examination for evidence of:
   (a) Peripheral vascular disease; Absent peripheral pulses with or without ischaemic changes of the limbs.
   (b) Peripheral neuropathy: Loss of ankle jerks with or without sensory impairment. In all male patients, testicular pain was elicited by the method of Campbell I.W. (1974).

(c) Retinopathy: Background, exudative or proliferative.
(d) Pupillary abnormalities.

2. Supine and erect pulse and blood pressure measurement.

3. Urine examination for proteinuria.

4. Intravenous atropine 1.8 mg test, recording the pulse rate every minute for ten minutes.

5. Measurement of heart rate variability.

In the absence of a heart rate monitor, heart rate variability was indirectly measured from an electrocardiograph tracing. The patient was taught to breath in and out as deeply as possible for 30 seconds to enhance sinus arrhythmia. Heart rate was measured by converting R-R interval from the ECG tracing, and heart rate variability was taken as the mean difference between the lowest and highest heart rates during deep breathing.

Results

There were 15 males and 12 females. Their mean age was 56 years (range 16-70 years) and the mean duration of diabetes was 12 years (range 1-30 years). The youngest patient was a 16 year old juvenile diabetic known to be suffering from the disease since the age of ten. Twelve patients were insulin dependent.

The complications of diabetes found in association with autonomic neuropathy in these patients were shown in Table 1.

Table 1

Associated Complications

Peripheral Neuropathy	16 (2 with trophic ulcers)
Peripheral Vascular Disease	4 (1 with below-knee amputation)
Retinopathy	13 (5 background, 6 exudative and 2 proliferative)
Nephropathy	6 (1 with uraemia)

Manifestations of Diabetic Autonomic Neuropathy. (Table 2)

The most common manifestation of diabetic autonomic neuropathy was impotence. All but one of the 15 male patients were impotent, and in six of them it was the sole manifestation of autonomic neuropathy. Only six patients were found to have impaired or absent testicular pain.

Table 2

Manifestations of Diabetic Autonomic Neuropathy

Impotence	14
Sweating Abnormalities	12
Diarrhoea	11
Postural Hypotension	7
Gastric Fullness	4
Bladder Disturbances	2
Hypoglycaemia Unawareness	1

Sweating abnormalities were common (12 patients). The usual complaint was profuse sweating involving face and upper part of body unrelated to exertion or heat. This occurred in eight patients, three of whom also had nocturnal sweating with similar distribution. Gustatory sweating involving face, head and neck occurred in seven patients. No particular food was incriminated in this form of sweating abnormality.

Diarrhoea was present in eleven patients, all of whom gave a history of passing watery stools intermittently, averaging two to three days for each episode. Only two patients had nocturnal diarrhoea.

Seven patients had a postural drop of systolic blood pressure of more than 30 mm Hg. One patient in fact was admitted as a case of idiopathic orthostatic hypotension, but glucose tolerance test showed a frankly diabetic pattern without glycosuria. Two patients, one with a postural drop of 50 mm Hg and the other 30 mm Hg, denied having any symptom of postural hypotension.

Four patients had symptoms ascribed to delayed gastric emptying. One patient, a 55 year old Indian male, developed acute gastric dilatation with aspirate exceeding 1,500 ml per 24 hours four days after cataract surgery under local anaesthesia. He recovered with conservative treatment and potassium replacement.

There were two patients with bladder disturbances. A 53 year old Chinese male who had impotence for seven years and intermittent diarrhoea complained of decreased urine flow rate for last six months, and developed acute retention of urine following intravenous atropine test. The other patient was an elderly female who had to be catheterised repeatedly for a distended bladder.

Hypoglycaemia unawareness was seen in one patient. He was a 59 year old Indian male on chloropropamide 500 mg daily who presented as a case of cerebrovascular accident with slurred speech and right hemiparesis. He was conscious but restless and noisy. Random blood sugar done on admission was 30 mg%. His neurologucal deficit disappeared completely the following day after intravenous dextrose.

Pupillary abnormalities were not seen in this study.

Tests for Cardiac Denervation

All but one patient had intravenous atropine given for cardiac acceleration and ECG done for sinus arrhythmia, the exception being a case with atrial fibrillation. Two patients developed retention of urine after atropine.

The results of intravenous atropine test are shown in Fig. 1. The normal response to intravenous atropine is an increase of heart rate of at least 20 beats per minute (Wheeler and Watkins, 1973). Almost all the patients with subnormal response had a high resting heart rate.

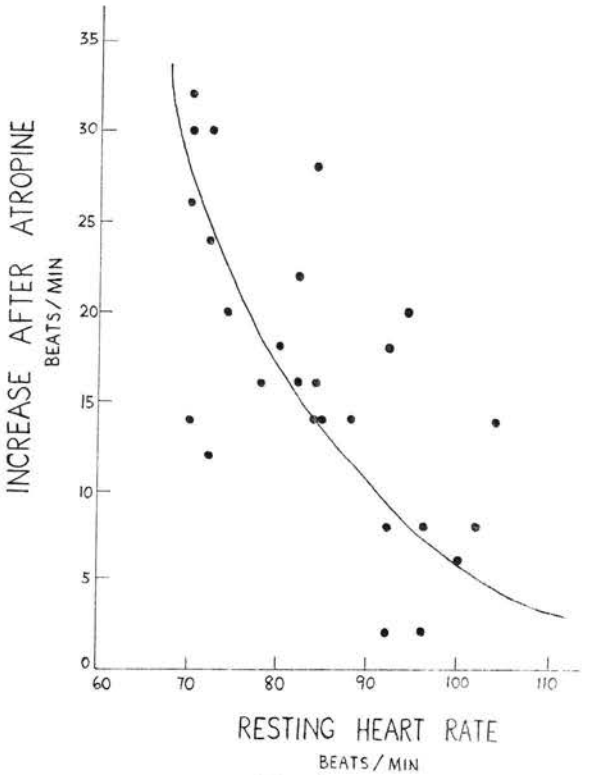

Fig. 1
The response of heart rate to intravenous atropine. The maximum rise in beats/min. is shown in relation to the resting heart rate.

The results of heart rate variability measurements are expressed in Fig. 2 which shows the relationship between heart rate variability and cardio-acceleration by atropine. Subnormal increase in beats per min after intravenous atropine was associated with low heart rate variability.

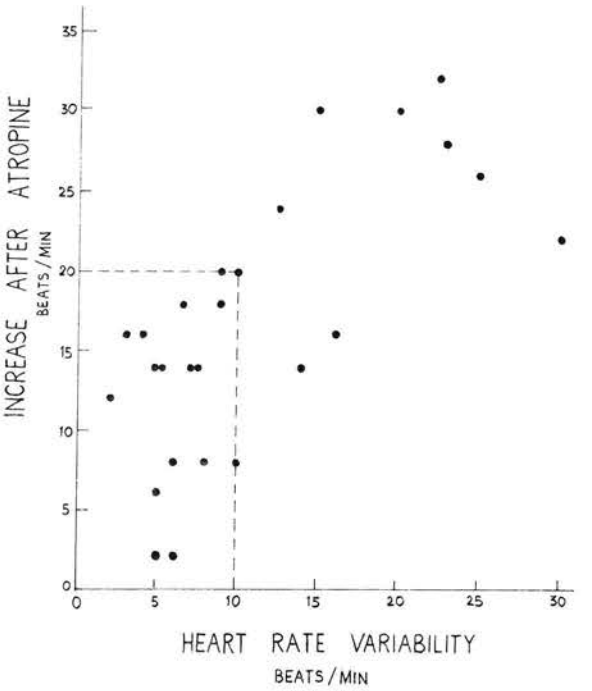

Fig. 2
Heart rate variability. Low heart rate variability is correlated with abnormal response to intravenous atropine, as shown by the dotted lines within which both tests are abnormal.

Discussion

Diabetic patients with autonomic neuropathy are more often associated with the complications of diabetes, particularly peripheral neuropathy, and with insulin dependence.

Impotence occurs in nearly 50% of patients who have had diabetes for over five years. It may be the sole manifestation of diabetes in a previously undiagnosed patient (Mahler and Hayes, 1972). Hence it is important to exclude diabetes in any patient complaining of impotence. Impotence resulting from diabetes may be distinguished from that caused by psychological problems by the presence of other features of autonomic neuropathy, the absence of spontaneous erection and the maintenance of libido.

Absent or diminished testicular sensation is said to correlate well with clinical features of autonomic neuropathy except where impotence occurs alone. Most patients with impotence alone have normal testicular sensation (Campbell et al, 1974). Only six of the 14 patients in this study had impaired or absent testicular sensation. The author has found this test to be of little practical use because of the wide variation in patients' pain threshold and the difficulty of exerting constant pressure in squeezing the testis.

Abnormalities in sweating are common. Spontaneous profuse sweating, worse at night, appears to affect only upper part of the body. Watkin (1973) described gustatory sweating as a new sign of diabetic autonomic neuropathy and found that cheese was the most powerful stimulus. The distribution of sweating is in the territory of superior cervical ganglion, similar to the pattern following cervical sympathectomy. The cause is aberrant nerve regeneration after degeneration from trauma or disease, between fibres of vagus nerve and sympathetic cholinergic sweat fibres at the level of superior cervical ganglion. Anti-cholinergic drugs are effective in abolishing gustatory sweating.

Persistent or episodic watery diarrhoea in diabetic patients represents a now well defined functional disorder best referred to as diabetic diarrhoea (Cecil Lobe, 1971). It is said to be particularly troublesome at night. The diabetes is not always clinically apparent or previously recognised. Its importance lies in the social disability and in the availability of striking benefits from therapy with tetracycline. Recently, Condon et al (1973) described the use of oral cholestyramine in diabetic diarrhoea, a point of similarity to post vagotomy diarrhoea. The other respects where the two conditions resemble are:

1. watery stools, sometimes steatorrhoea
2. disordered small intestine transit
3. gallbladder dysfunction and increased gallstone formation.

Postural hypotension is a prominent and disabling symptom of diabetic autonomic neuropathy. It usually results from a disturbance of the complex vascular reflex control of blood pressure, possibly with a decreased or absent renin secretion in response to the erect posture, and fludrocortisone is said to be of value in controlling this symptom, as found by Campbell et al (1976). In its mildest form, although there is an excessive postural fall in blood pressure, the patient has no symptoms, as in two cases in this study. In its severest form syncope may be sufficiently prolonged to produce convulsions and death from brain-stem anoxia.

Delayed gastric emptying, due to diminished gastric motility may cause bouts of otherwise inexplicable nausea and vomiting. Acute retention of urine results from an atonic bladder, but less severe disturbances such as increased bladder capacity, decreased bladder sensation and urine fow rate may only be shown by cystometry. Lack of warning symptoms of hypoglycaemia, presumably due to sympathetic denervation, is uncommon and was seen in only one patient in this study.

The most widely used test of autonomic function, the response to the valsalva manouvre, has several disadvantages. It is difficult to perform accurately unless arterial catheterisation is undertaken, and may be abnormal in some diabetics without autonomic neuropathy. The response of the heart rate to mental arithmetic, to unexpected noises, and to carotid sinus pressure are easy to measure but erratic even in normal subjects (Brit. Med. J. 1974).

Recently the blood pressure response to sustained hand grip has been proposed as another simple test of autonomic function (Ewing 1973). The test is easy to perform and correlates to some extent with the abnormal valsalva responses, but requires a specialised equipment, a hand grip dynanometer.

Impaired vagal innervation of the heart is evidenced by (Wheeler and Watkins 1973):

1. Persistent resting tachycardia
2. Failure to elicit a tachycardia after intravenous atropine
3. Loss of heart rate variability during deep breathing.

All three observations had been confirmed by this study which also shows that there was good correlation between these tests of cardiac denervation. Thus, patients with high resting heart rate were associated with poor response to atropine and almost all patients with subnormal response to atropine had low heart rate variability. Admittedly, this study had been done without a control group for heart rate response is known to decline with age due to decreased vagal tone. Nevertheless, the results are conclusive of the value of these tests providing simple, quantitative and objective evidence for the presence of autonomic neuropathy.

Summary

Recognition of diabetic autonomic neuropathy is important because the symptoms may cause

diagnostic confusion to the unwary, effective therapeutic measures are available for some of its manifestations and prognostic significance has been attached to it. In order of frequency, the manifestations of diabetic autonomic neuropathy seen in twenty-seven patients in this study were impotence, sweating abnormalities, diarrhoea, postural hypotension, gastric fullness, bladder disturbances and hypoglycaemia unawareness. The response of heart rate to intravenous atropine and heart rate variability as measured from ECG tracings are two simple quantitative tests for cardiac denervation providing objective evidence for the presence of autonomic neuropathy.

Acknowledgement

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