Autonomic neuropathy and atypical myocardial infarction in a diabetic clinic population

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Summary

The incidence of autonomic neuropathy in 52 insulin-dependent and 87 non-insulin-dependent diabetic subjects was studied as well as the relationship between the type and duration of diabetes, metabolic control and the association of atypical infarctions with autonomic neuropathy. No statistically significant relationship was found between any parameter and the presence of autonomic neuropathy. Atypical infarctions were not confined to subjects with autonomic neuropathy, but the incidence was considerably higher than that in the general population. Position of the infarction did not determine whether it was silent or not. It is suggested that physicians should be alert to the occurrence of silent infarctions in all diabetics and not only those with clinical evidence of autonomic neuropathy.

Autonomic neuropathy is a complication of diabetes mellitus, and by objective bedside testing patients can be divided into three groups: (i) early parasympathetic autonomic neuropathy; (ii) definitive parasympathetic neuropathy; and (iii) sympathetic and parasympathetic neuropathy (combined autonomic neuropathy). Parasympathetic involvement usually precedes sympathetic neuropathy, but peripheral sympathetic neuropathy may present early in the form of neuropathic oedema and osteopenia.

The duration of diabetes and the adequacy of control may influence the development of autonomic neuropathy. The condition is likely to be irreversible, but it has been suggested that strict metabolic control could reverse the pathogenesis. The increased prevalence of atypical myocardial infarctions in diabetics may be related to the presence on histological examination of autonomic neuropathy.

The incidence of autonomic neuropathy among diabetic subjects is estimated to be in the region of 27%, while the incidence of atypical myocardial infarctions is between 25% and 30%, of which half are true silent infarctions.

The incidence of autonomic neuropathy among a group of 139 subjects with insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM) and the relationship between the occurrence of atypical myocardial infarction and autonomic neuropathy is described. An attempt was also made to assess the influence that the type of diabetes, the duration of the disorder, and metabolic control may have had or may not have had on the development of autonomic neuropathy.

Patients and methods

The study comprised 139 consecutive subjects attending the diabetes clinic at National Hospital — there were 52 IDDM and 87 NIDDM patients (according to WHO criteria). Of the IDDM subjects, 21 were male and 31 were female (mean age 45 years, range 11-80 years). There were 34 males and 53 females in the NIDDM group (mean age 64 years, range 32-82 years). The mean duration of diabetes in the IDDM group was 139 months (range 10-372 months), and in the NIDDM group 95 months (range 1-480 months).

The study period was 12 months, and patients were evaluated by the same 3 physicians at every visit. The subjects were questioned specifically about symptoms of autonomic neuropathy, peripheral neuropathy, and angina and previous myocardial infarction.

A parasympathetic autonomic neuropathy was considered present on the basis of an abnormal beat-to-beat variation during deep respiration (< 10 beats/min), and heart rate response to a Valsalva manoeuvre (R-R interval > 1.1). Sym pathetic autonomic neuropathy was considered to be present when the blood pressure response to standing was abnormal (a drop of systolic pressure > 30 mmHg). Abnormal vibration sense and loss or impairment of knee and ankle reflexes were considered objective indicators of peripheral neuropathy. ECG evidence of a transmural infarction (according to WHO criteria and as assessed by 2 cardiologists) of which the patient was unaware, was considered evidence of an atypical infarction.

Metabolic control was considered adequate when the fasting plasma glucose level (measured by a glucose oxidase method) during the previous 12 months had not exceeded 10 mmol/l, and the Hb A1 (measured using commercially available reagents, Behring Mannheim, West Germany) not more than 10%.

Data were statistically analysed by means of Student's t-test and the chi-square test of homogeneity tables.

Results

In 61 patients (20 IDDM and 41 NIDDM, 18 men and 43 women) beat-to-beat variation was abnormal; in 30 of these patients the response to the Valsalva manoeuvre was abnormal and in total there were 30 patients in whom the response to both tests of parasympathetic function was abnormal. Only 2 patients had combined autonomic neuropathy.

Subjects in whom at least two of the tests for autonomic neuropathy were abnormal were considered to have a definitive autonomic neuropathy (9 IDDM and 21 NIDDM, 12 men and 18 women). The remainder (109 subjects) were considered either to have no autonomic neuropathy or only early parasympathetic involvement (45 IDDM and 64 NIDDM, 44 men and 65 women).

Among those with definitive autonomic neuropathy (30 patients) the mean duration of diabetes was 131.2 ± 20.7 months (range 12-372 months). The mean duration of diabetes among the

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subjects with early or no parasympathetic involvement (109 patients) was 105.5 ± 9.3 months (range 1-480 months). By means of Student's t-test, it was determined that the mean duration of illness in those with autonomic neuropathy did not differ significantly from those without autonomic neuropathy (P > 0.05).

Among the patients with definitive autonomic neuropathy, 9 had IDDM and 21 NIDDM; 20 subjects were well controlled and 10 were considered to be poorly controlled. In the remaining 109 cases, who were considered not to have autonomic neuropathy, there were 45 patients with IDDM and 64 with NIDDM; 54 subjects were well controlled and 55 were poorly controlled.

The distribution of control (good or poor) among patients with autonomic neuropathy did not differ from those without autonomic neuropathy. The chi-square value was 2.913 (with significance > 0.05). Thus there was no significant homogeneity between patient group and control of diabetes. There was also no statistically important relationship between the presence of autonomic neuropathy and type of diabetes (chi-square test, 1.26; P = 0.2615).

There was evidence of peripheral neuropathy in 25% of the patients and evidence of myocardial infarction in 19 subjects of whom 14 were considered to be atypical (4 subjects with and 10 subjects without definitive autonomic neuropathy). Two patients with typical infarctions had autonomic neuropathy and in 3 there was no evidence of autonomic neuropathy. Of the atypical infarctions 5 were anteroseptal, 7 were inferior and 2 were lateral. There was no significant relation between the type of infarction and the presence of autonomic neuropathy (chi-square test 1.58; P = 0.4530).

Discussion

In a group of 139 diabetics 21% had parasympathetic autonomic neuropathy, which is in accord with the literature (incidence of 20-40%). The 2 subjects in whom sympathetic involvement was evident had a combined autonomic neuropathy, which emphasises the fact that a parasympathetic neuropathy usually precedes development of sympathetic involvement.

Both vascular and metabolic factors are most probably important in the pathogenesis of an autonomic neuropathy. There are two pathways for degrading glucose. The most common pathway is via the formation of glucose-6-phosphate and is controlled by insulin. The other pathway is insulin-independent and leads to accumulation of sorbitol and fructose which cause damage mainly to the peripheral nervous system. Diminished myoinositol concentration in the nerves or reduced myelin synthesis may also be of importance. Despite the suggestion that strict metabolic control could reverse the process we were unable to correlate metabolic control with the development of autonomic neuropahties.

The duration of diabetes may be important in the development of autonomic neuropathy but possibly relates only to patients with early autonomic neuropathy. We found no relationship with the duration of diabetes. The presence of autonomic neuropathy also was not influenced by the type of diabetes. In the total study population, there was a higher prevalence of diabetes in women (84 women and 33 men). This was also reflected in the subgroup analysis. Thus we conclude that there was no sexual preponderance for the development of autonomic neuropathy.

Since data on platelet counts and lipid profiles were inadequate, we did not attempt to study the possible effect of vascular factors on the development of autonomic neuropathy. In respect of peripheral neuropathy 25% of these patients also had parasympathetic autonomic neuropathy.

The incidence of atypical myocardial infarction among the general population is about 25%, and is possibly due to a defective 'anginal warning system'. Among diabetic subjects, the incidence is twice that of the general population, and carries a higher mortality rate. The latter is possibly due to the nature of their infarctions as well as defective respiratory reflexes.

There is one report on a small series of patients with atypical myocardial infarction, all of whom had histological evidence of an autonomic neuropathy. Within this series, 14 of 19 patients had atypical infarction, but we could not prove that the incidence was related to the presence of a clinically evident autonomic neuropathy. The position of the infarction did not determine whether it was silent or not. We do not think that the presence of hypercholesterolaemia influenced our impression as there is no evidence of abnormal cholesterol relating to any specific type of infarction.

In conclusion, the diagnosis of autonomic neuropathy can be confirmed by using relatively simple bedside procedures. We could find no evidence that gender, metabolic control, type or duration of diabetes influenced its development nor could we prove an association between the presence of autonomic neuropathy and the occurrence of atypical infarction, so that physicians need to be alerted to the possibility of myocardial infarction in any diabetic patient who presents with symptoms such as dyspnoea, abdominal pain, fatigue, coughing, nausea, vomiting or syncope.

REFERENCES