Original article

Incidence of cardiac autonomic neuropathy in type 2 Diabetes, & its relation to Silent Myocardial Ischemia

1Dr Rajeshwari Vhora , 2Dr Govind Shiddapur , 3Dr Mathews Jose , 4DR A L Kakrani

1Professor Emergency Medicine, Dr D Y Patil Medical college & Hospital, Pune
2Professor Medicine, Dr D Y Patil Medical college & Hospital, Pune
3DM in Medical Oncology, Specialist in Medical Oncology, Lake shore Hospital, Cochin.
4Professor & HOD, Dr D Y Patil Medical college & Hospital, Pune
Corresponding author: DR Rajeshwari S Vhora

Abstract

Introduction: Cardiac autonomic neuropathy (CAN) has been found in 30–70% of unselected diabetic patients. In asymptomatic diabetic patients, CAN appears to be a better predictor of major cardiac events and inducible ischemia. Our aim was to detect CAN in Type 2 Diabetes by simple bedside clinical test.

Material: The study sample consisted of 100 asymptomatic type 2 diabetic patients between 35 to 70 years. CAN was tested by simple bedside test. Results were analysed using SPSS 11.

Result: In our study, the prevalence of autonomic dysfunction was 45%. Autonomic dysfunction, as judged by bedside cardiovascular reflex tests was observed in 17 out of 24 patients of Silent myocardial Infarction (SMI) 70.1% which was highly significant.

Conclusion: CAN has been proposed to be the major contributing factor for development of “painless myocardial ischemia” in DM.

Key Words : Cardiac Autonomic Neuropathy (CAN), Silent Myocardial Ischemia (SMI), Type 2 Diabetes Mellitus (DM).

Introduction

Coronary artery disease (CAD), a major cause of mortality in type 2 diabetes is often diagnosed late because of silent myocardial infarction 1. Accordingly, early accurate diagnosis of coronary artery disease in patients with diabetes is needed, and reliable prognostication is mandatory. In asymptomatic diabetic patients, Cardiac autonomic Neuropathy (CAN) appears to be a better predictor of major cardiac events and inducible ischemia 2. Autonomic neuropathy has been proposed to be the major contributing factor for development of “painless myocardial ischemia” in DM.

Cardiovascular autonomic neuropathy is associated with a poor overall prognosis in patients with type 2 diabetes. Autonomic neuropathy might also be a parallel consequence of cardiac risk factors, including hyperglycemia, dyslipidemia, and renal disease.

Autonomic neuropathy was a major predictor of inducible ischemia in the DIAD (Detection of Ischemia in Asymptomatic Diabetics) study 3 and has been associated with abnormal cardiac test findings. The ADA has recently recommended screening for cardiac autonomic neuropathy, at least with a history and an examination for signs of autonomic dysfunction, beginning at diagnosis of type 2 diabetes or 5 years after the diagnosis of type 1 diabetes (33). The possibility of cardiac autonomic neuropathy should be considered in the presence of unexplained tachycardia, orthostatic hypertension and/or hypotension, and other autonomic or peripheral neuropathies. Our aim was to study the prevalence of autonomic dysfunction in Type
2 diabetic patients and to study the correlation between silent myocardial ischemia and autonomic dysfunction seen in Type 2 diabetic patients.

**Materials and methods**

The present study was conducted from August 2009 to August 2011 in tertiary care hospital &medical college. The study sample consisted of 100 asymptomatic type 2 diabetic patients (in relation to their coronary artery disease). The age group was between 35 to 70 years. Patients had normal resting ECG, but with two or more additional atherogenic risk factors.

**Atherogenic risk factors include**

1. Sedentary life style, age > 35 years.
2. Dyslipidemia.
3. Blood pressure >140/90 mm hg or history of antihypertensive medication.
4. Family history of premature coronary artery disease (CAD)
5. Positive micro or macroalbuminuria

**Exclusion criteria**

1. Abnormal ECG at rest.
2. Undetermined chest pain that might be attributed to myocardial ischemia.
3. Apparent angina pectoris.
4. Previous history of myocardial infarction
5. History of congenital and rheumatic heart disease.
6. Patients receiving digitalis glycoside and Beta blockers
7. Smoking

Written and informed consent was taken from all patient.

Detailed clinical history was taken including history of atherogenic risk factors. Detailed clinical examination was carried out.

CAN was diagnosed clinically by five standard bedside cardio-vascular tests done in all study group patients. Those with two or more abnormal tests were defined as having autonomic neuropathy. The test were as follows

**1. Heart rate response to deep breathing.**

The maximum and minimum heart rates during each 10 seconds breathing cycle were calculated from RR intervals recorded by ECG. The difference between maximum and minimum heart rate was
taken abnormal if it was less than 10 beats per minute.

2. Heart rate response to valsalva manoeuvre.
   The valsalva ratio i.e. the ratio of longest RR interval after 20 beats of the end of manoeuvre to the shortest RR interval during the manoeuvre was calculated. The result was taken as mean of 3 successive readings, A ratio of 1.1 or lower was taken abnormal.
   The valsalva manoeuvre was done by asking the patient to blow into a sphygmomanometer, maintaining a pressure of 40 mmHg for 15 seconds.

3. Heart rate response to standing up from supine position.
   The ratio of longest RR interval (around 30th beat after standing) to the shortest RR interval, (around 15th beat after standing) was calculated. A ratio upto 1.0 was taken as abnormal.

4. Blood pressure response to sustained handgrip
   A less than 10 mmHg increase in diastolic pressure before and 3 minutes after sustained hand grip was taken as abnormal.

5. Blood pressure response to standing up from supine position.
   It was measured while the subject was lying supine and again one minute after standing up and the difference was noted. In normal subjects, the systolic blood pressure should not decrease by more than 10 mmHg. In patients with autonomic dysfunction, the systolic blood pressure falls more than 30 mm.
   Thus entire data collected from complete examination of all study patients were compiled and conclusions were drawn.
   Baseline Investigations were carried out including Blood sugar level, Lipid profile, Urine for Microalbuminuria, & ECG.
   Statistical analysis namely SPSS 11 were used for the analysis of the data. Microsoft word and Excel have been used to generate graphs, tables by using $X^2$-test, t-test. ‘P’ value less than 0.05 was considered as significant.

Result:
Age of patient ranged between 36-70 years. Maximum number of patients were between age group of 46-50 years. Number of male patients included in this study were more than female patients. Age was not statistically different in male and female groups.$[X^2=1.61, P>0.05$ not significant]
TABLE 1: AGE AND SEX WISE DISTRIBUTION OF CASES IN STUDY GROUP

<table>
<thead>
<tr>
<th>Age (Yrs)</th>
<th>Sex</th>
<th>No of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>36 - 40</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>41 - 45</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>46 - 50</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>51 - 55</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>56 - 60</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>61 - 65</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>66 - 70</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>56</td>
<td>44</td>
</tr>
</tbody>
</table>

In our study SMI was observed in 17 out of 56 male patients (30.3%) and 7 out of 44 female patients (15.9%). This is not statistically significant. Chi-Square = 2.820, P>0.05.

TABLE 2: ASSOCIATION BETWEEN SEX AND SILENT MYOCARDIAL ISCHEMIA IN STUDY GROUP

<table>
<thead>
<tr>
<th>Sex</th>
<th>SMI</th>
<th>No of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Male</td>
<td>17</td>
<td>39</td>
</tr>
<tr>
<td>Female</td>
<td>7</td>
<td>37</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>76</td>
</tr>
</tbody>
</table>

Chi-Square = 2.820, P>0.05

AUTONOMIC DYSFUNCTION:
Autonomic dysfunction was observed in 45% patients. Out of 24 SMI patients 17 had autonomic dysfunction. This is statistically significant. Out of 76 patients without SMI 28 had autonomic dysfunction.
TABLE 3: ASSOCIATION BETWEEN AUTONOMIC DYSFUNCTION AND SILENT MYOCARDIAL ISCHEMIA IN STUDY GROUP

<table>
<thead>
<tr>
<th>Autonomic dysfunction</th>
<th>SMI</th>
<th>No of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Positive</td>
<td>17</td>
<td>28</td>
</tr>
<tr>
<td>Negative</td>
<td>7</td>
<td>48</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>76</td>
</tr>
</tbody>
</table>

Chi-Square = 8.515, P<0.005

Discussion:
In accordance with ATP - III, 4 or JNC -VII 5 guidelines, high risk asymptomatic people should have all coronary heart disease risk factors treated to reduce the coronary heart disease and total cardiovascular disease risk.

The primary aim of this study was to screen type 2 diabetic patients with high risk Framingham category for the presence of coronary artery disease in asymptomatic phase so that preventive interventions such as lipid lowering agents, Aspirin or ACE (Angiotensin converting enzyme) inhibitors can be used to reduce the risk for future unfavorable coronary event. All these preventive measures are easily available, effective and relatively safe.

In our study age of patients ranged between 36 to 70 years, mean age was 51.3 years. Maximum number of patients were between age group of 46-50 years.

Number of male patients included in this study were more than female patients.

This age group was similar to the age group found in other studies e.g.

In Anatoly Langer et al 6 study; age of diabetic subjects ranged from 35 to 75 years and mean age in patients with silent ischemia in this study was 50 while it was 57 in patients without silent ischemia.

In M.J. Koistinen et al. 7 the mean age was 49.3 years.

Fleg et al 8 reported a progressive increase in the prevalence of exercise induced silent myocardial ischemia in apparently healthy individuals from 1 decade to the next in the Baltimore Longitudinal Aging Study. The prevalence was 2.5% for those under age of 60 years and more than 10% for those above the age 70 years.

In our study prevalence of silent ischemia was 16% in age group less than 45 years and 26.5% in age group more than 45 years.

The mean age of patients with silent ischemia was 48.8 years, while it was 62 years in 41 patients of type 2 diabetes in Motoji Naka et al study. The mean age of patients without silent ischemia was 47.1 years in our study while it was 60 year in Motoji Naka et al study.

Thus with increase in age there is increase prevalence of silent ischemia.

The percentage of female patients in different studies range between 29.68% to 60.66%. Anatoly Langer 6 et al, Koistinen et al 7, ACIP study 9, Motoji Naka 10 et al. There were no female patients in Anatoly Langer et al 6 study. In our study the percentage of female was 44.

sex

In our study SMI was observed in 17 out of 56 male patients (30.3%) and 7 out of 44 female
patients (15.9%). This is not statistically significant. Chi-Square = 2.820, P > 0.05.

Autonomic dysfunction was observed in 45% patients. Out of 24 SMI patients 17 had autonomic dysfunction. Out of 76 patients without SMI 28 had autonomic dysfunction. This is statistically significant.

In our study, the prevalence of autonomic dysfunction was 45%, out of 24 patients with SMI autonomic dysfunction as judged by bedside cardiovascular reflex tests was observed in 17 patients (70.1%).

In Sukhija et al., 11 50% of diabetic patients had evidence of autonomic dysfunction. O’ Brien et al., 12 found autonomic dysfunction in 17% of 500 IDDM patients. A study in Pondicherry by Balachander J. et al reported 38% prevalence of autonomic neuropathy.

The prevalence found by Langer et al and O’Sullivan et al were 36% and 41.5% respectively.

In our study, out of 45 patients with autonomic dysfunction 17 had SMI (37.7%). Out of 55 patients without autonomic dysfunction 7 had SMI (12.7%).

In our study, among patient with silent ischemia, 70.1% had autonomic dysfunction as compared to 36.7% of autonomic dysfunction patients without silent ischemia. This difference was statistically highly significant.

Thus a strong correlation was found between silent ischemia and autonomic dysfunction.

This was supported by Sukhija et al study.

DIAD (Detection of Ischemia in Asymptomatic Diabetics) study 14 shows that Autonomic neuropathy was a major predictor of inducible ischemia and has been associated with abnormal cardiac test findings.

Mantel-Haenszel estimates for the pooled prevalence rate risk for silent myocardial ischemia in meta-analysis was 1.96, with a 95% confidence interval of 1.53 to 2.51 (P<0.001; n=1468 total subjects), demonstrating a consistent association between CAN and the presence of silent myocardial ischemia.

Hume et al 15 found silent ischemia in 23.3% patients without any difference from those who had neuropathy from those who did not. Murray et al 16 find that silent ischemia was much more common in patients with severe autonomic neuropathy. (92% Vs 39%). Langer et al 6 and O’Sullivan 17 also found silent ischemia more common in patients with autonomic neuropathy.

Our findings which demonstrate a correlation between autonomic dysfunction and silent myocardial ischemia were supported by autopsy study of Faerman et al 18 who found, evidence of typical diabetic neuropathic changes involving afferent sympathetic and parasympathetic tracts in patients dying with silent but not symptomatic myocardial infarctions.

Conclusion

- Coronary artery disease is a major cause of mortality in patients with type 2 diabetes.
- It is often diagnosed late because of silent myocardial ischemia.
- Silent ischemia in type 2 diabetes is due to defective anginal warning system caused by autonomic dysfunction.
- Autonomic dysfunction in Type 2 diabetes can be judged by simple bedside test.

References: