Original Article

Prevalence of cardiac autonomic neuropathy in Asian Indian patients with fibrocalculous pancreatic diabetes

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ABSTRACT

Background: It was formerly believed that since fibrocalculous pancreatic diabetes (FCPD) is a secondary form of diabetes, specific diabetic complications were uncommon. This is no longer considered to be true. Our objective was to study the prevalence and pattern of cardiac autonomic neuropathy (CAN) in patients with FCPD. **Materials and Methods:** A cross-sectional study on consecutive male patients with FCPD was performed. Using an automated CAN System Analyzer, heart rate response to deep breathing, Valsalva maneuver, standing and blood pressure response to standing were measured. The standard Ewing's criteria were used to define normal, borderline, and abnormal values. Prevalence rates were calculated and the patients were defined to have normal autonomic function, parasympathetic, sympathetic, and combined dysfunction. **Results:** The prevalence of CAN in this study population was 63.3%. Isolated parasympathetic dysfunction (42.3%) was the most common abnormality. Combined sympathetic and parasympathetic dysfunction was noted in 13.3% of patients. Isolated borderline dysfunction was noted among 13.3% of patients. CAN was detected in six patients with a duration of diabetes of less than 1 year after diagnosis. Patients with autonomic dysfunction were found to have a lower body mass index (BMI) and low density lipoprotein (LDL)-cholesterol when compared to those with normal autonomic functions, which was not statistically significant. **Conclusion:** The prevalence of abnormal cardiac autonomic function is as high as 63.3% in the present study population which warrants regular screening of patients with FCPD for autonomic dysfunction. Patients with FCPD and autonomic dysfunction were found to have a lower BMI and lower LDL-cholesterol, which may be indicators of malnutrition in the group with autonomic dysfunction. Whether this malnutrition contributes to autonomic dysfunction needs further exploration.

Key words: Asian Indians, cardiac autonomic neuropathy, fibrocalculous pancreatic diabetes, prevalence

Introduction

Chronic pancreatitis (CP) is characterized by chronic inflammatory fibrosis resulting in progressive loss of both exocrine and endocrine pancreatic functions. Alcoholic pancreatitis is the most common cause of chronic pancreatitis that is observed in the western world. A distinct type of non-alcoholic pancreatitis that is referred to as tropical calcific pancreatitis (TCP) is seen mostly in tropical countries such as India. When it manifests with diabetes, it is called as fibrocalculous pancreatic diabetes (FCPD).

Although diabetes secondary to pancreatitis accounts for only <1% of all diabetes in the western world, in many parts of the world (especially in tropical countries such as Nigeria and Indonesia, and in South India), pancreatitis associated with pancreatic calculi may account for 10–15% of all diabetics and up to 50% of young patients (<30 years) with diabetes.[1]

It was formerly believed that since FCPD is a secondary form of diabetes, specific diabetic complications were uncommon. This is no longer considered to be the case, as long-term follow-up studies have shown that patients

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.100668

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with FCPD develop microvascular complications along the course of the disease.[2-4] In contrast, macrovascular complications are less common,[5] perhaps owing to the relative youth of the patients, their leanness, and the low cholesterol levels. Other complications frequently seen in FCPD are tuberculosis, urinary tract infections, and cataract.[6]

Cardiac autonomic neuropathy (CAN) has recently become a subject of special interest in view of the associated high risk of mortality.[7,8] Cardiac dysfunction due to CAN has been demonstrated in diabetic patients without evidence of ischemic heart disease and this can increase the risk of sudden unexpected death. Mohan *et al*., in a study conducted on 40 subjects with FCPD,[9] reported the prevalence of autonomic neuropathy to be over 16.6% in patients with a disease duration ranging between 0 and 5 years and over 60% in patients having FCPD for more than 16 years. Govindan[10] has demonstrated that autonomic dysfunction can occur as early as 2 years after the onset of the disease, much before the patients have had any symptoms referable to autonomic dysfunction. Our objective was to study the prevalence and pattern of cardiac autonomic dysfunction in patients with FCPD.

Materials and Methods

The study was designed as a cross-sectional study and was undertaken in the Department of Endocrinology, Diabetes and Metabolism from February to August 2011.

Subjects

Patients were selected from the endocrine and diabetes outpatient clinic run by the department. Consecutive male patients with FCPD, attending the clinic during the study period, were included, with FCPD being defined by the criteria proposed by Mohan *et al*. as follows:

a. Occurrence in a "tropical" country.
b. Diabetes by the WHO study group criteria.
c. Evidence of chronic pancreatitis: Pancreatic calculi on X-ray or at least three of the following:
    i. Abnormal pancreatic morphology by sonography.
    ii. Chronic abdominal pain since childhood.
    iii. Steatorrhea.
    iv. Abnormal pancreatic function tests.
d. Absence of other causes of chronic pancreatitis, i.e. alcoholism, hepatobiliary disease, primary hyperparathyroidism, etc.

Subjects with the following problems were excluded: proliferative diabetic retinopathy; ingestion of drugs that can alter heart rate like β-blockers, anticholinergics, and antidepressants; ingestion of drugs that can alter the blood pressure (BP) like diuretics, β-blockers, and calcium channel blockers; ischemic heart disease; respiratory illnesses like asthma; neuromuscular weakness of the upper limb; alcoholism, smoking, and major psychiatric illnesses. Patients who met the above criteria were requested to participate in the study. Those who gave a written informed consent were studied.

Methods

Subjects were selected as per the inclusion and exclusion criteria. A brief medical history was taken from all subjects, and anthropometric measures like height, weight, and waist circumference were measured. Body mass index (BMI) was calculated. A thorough general and physical examination including the vital data was done for all the subjects. Blood was collected in a fasting state for plasma glucose, glycated hemoglobin (HbA1C), serum creatinine, and lipid profile. Blood glucose in the postprandial state was measured using a glucose meter. 24-hour urine was collected for protein estimation. Patients were asked to restrain from smoking, consumption of coffee and tea for 2 hours prior to this assessment.

Assessment of CAN was done using an automated CAN System Analyzer (CANS 504), a personal computer-based analyzer which analyzes both the sympathetic and parasympathetic nervous systems (SNS and PNS, respectively). The system uses an ECG cardiotocogram (R–R interval) and an advanced automatic non-invasive blood pressure module to conduct a battery of tests. The following variables were measured.

Tests of the PNS:

a. Heart rate response to deep breathing expressed as E:I ratio
b. Heart rate response to Valsalva maneuver expressed as Valsalva ratio
c. Heart rate response to standing expressed as 30:15 ratio

Tests of the SNS:

a. Blood pressure response to standing
b. Blood pressure response to sustained hand grip

The criteria proposed by Ewing *et al*.[11] were used to define normal, borderline, and abnormal values in the above tests.

Definitions

1. Parasympathetic abnormality: Patient is defined to have PNS abnormality if ≥1 of the three tests (E:I ratio, Valsalva ratio, 30:15 ratio) were found to be abnormal.
2. Sympathetic abnormality: Patient is defined to have SNS abnormality if BP response to standing and/or sustained hand grip was found to be abnormal.

3. Patients were defined as having combined dysfunction of both system (PNS and SNS) if:
   i. Valsalva ratio was abnormal;
   ii. any test of PNS was abnormal and any test of SNS was borderline;
   iii. any test of PNS was borderline and any test of SNS was abnormal; or
   iv. any test of PNS was abnormal and any test of SNS was abnormal.

Statistical methods

No intricate sample size calculation was performed since there are no large studies looking into the prevalence of CAN in patients with FCPD and FCPD constitutes less than 10% of all young diabetics (age below 50 years). A total number of 30 patients was considered the appropriate sample size.

The data were expressed as means ± SD or median (range). The prevalence rates were calculated. Analysis of variance (ANOVA) was used to compare the continuous variables between different groups. Statistical analyses were performed with Microsoft Excel and the commercially available software package (SPSS for Windows, version 17.0, SPSS, Inc., Chicago, IL, USA). $P < 0.05$ was considered statistically significant. The study protocol was approved by the institute's ethics committee (IRB Min. No. 7378 dated 27.01.2011) and all the participants gave written informed consent.

Results

Table 1 shows the clinical and biochemical profile of patients. The age of patients ranged from 25 to 63 years, with a mean age of 40.4 ± 8.75 years. Nine patients (30%) had duration of diabetes ≤1 year. Three patients had renal dysfunction with a creatinine of ≥1.4 mg/dl. Glycemic control was moderate in this study population with a median HbA1C of 8%. One-third (33.3%) had an HbA1C of 10%. Hypertension (BP > 140/90 mm of Hg) was found in 33.3% of the patients.

A resting tachycardia was noted in 3.3%, deep breathing E:I ratio was abnormal in 10%, and 30:15 beat ratio was abnormal in 18% of the patients. Among the 26 patients who performed the Valsalva maneuver successfully, all had a normal Valsalva ratio. Four patients were unable to perform the test. BP change during sustained handgrip was abnormal in 93.3%, but as none of our patients were able to sustain their hand grip for the stipulated duration of 3 minutes, only the postural drop in BP which was abnormal in 3.3% was taken into account as an indicator of SNS dysfunction during the final analysis. Table 2 summarizes the abnormalities detected in each of the individual tests.

When all tests were considered together, regarding PNS, 23.3% had normal, 13.3% had borderline, and 63.3% had abnormal results. In SNS, 76.7% had normal, 20% had borderline, and 3.3% had abnormal results. In 23.3% patients, all tests of autonomic function were normal [Table 3]. The most common abnormal test in parasympathetic system was the 30:15 RR ratio on standing among 53.3% patients. Normal cardiac autonomic function was found in 23.3% patients. Both SNS and PNS involvement were found in one patient.

Table 1: Clinical and biochemical characteristics of patients

Variable	Mean ± SD/median (range)
Age (years)	40.4 ± 8.75
Duration of diabetes (months)	29 (0-108)
BMI (kg/m^2)	19.6 ± 3.10
Fasting plasma glucose (mg/dl)	152 (81 – 457)
Postprandial glucose (mg/dl)	263 (106–820)
HbA1c (%)	8 (6–16.8)
Serum creatinine (mg/dl)	1 (0.6–3.9)
Total cholesterol (mg/dl)	166.9 ± 43.5
Triglycerides (mg/dl)	129.5 (61–708)
HDL-cholesterol (mg/dl)	37 ± 15.04
LDL -cholesterol (mg/dl)	97 ± 33.5
Systolic BP (mm of Hg)	129.4 ± 23.9
Diastolic BP (mm of Hg)	83.8 ± 12.3

Table 2: Abnormalities found in individual tests of autonomic function

Characteristics	Normal n (%)	Borderline n (%)	Abnormal n (%)	Total n (%)
E:I ratio	27 (90)	0	3 (10)	30 (100)
30:15 RR ratio on standing	8 (26.7)	4 (13.3)	18 (60)	30 (100)
Heart rate	29 (96.7)	0	1 (3.3)	30 (100)
Systolic BP drop on standing	23 (76.7)	6 (20)	1 (3.3)	30 (100)
Diastolic BP change with hand grip*	0	2 (67)	28 (93.3)	30 (100)
Valsalva ratio†	26 (100)			

*None of the patients were able to sustain the hand grip for the required period of 3 minutes, †Four patients were unable to perform the Valsalva maneuver adequately

Table 3: Pattern of cardiac autonomic dysfunction among the study patients

		Parasympathetic nervous system functions			
		Abnormal	Borderline	Normal	Total
Sympathetic nervous system functions	Abnormal	1	0	0	1
	Borderline	4	2	0	6
	Normal	14	2	7	23
	Total	19	4	7	30

We compared various clinical and biochemical parameters between different groups – patients with normal autonomic function, with parasympathetic dysfunction, sympathetic dysfunction, and with combined dysfunction [Table 4]. There was a trend for patients with cardiac autonomic dysfunction to have a lower BMI; however, this was not statistically significant. Low density lipoprotein (LDL)-cholesterol was found to be lower in patients with cardiac autonomic dysfunction when compared to patients with normal cardiac autonomic functions, which was found to be statistically significant.

Discussion

The present study performed to assess the prevalence and pattern of autonomic dysfunction in patients with FCPD has shown a high prevalence of 63.3%. In the whole group of study patients, parasympathetic system dysfunction alone was found in 11 out of 26 patients (42.3%); none of the patients was found to have isolated sympathetic dysfunction. Combined sympathetic and parasympathetic dysfunction was noted in 13.3% patients, isolated borderline dysfunction among 13.3% patients, and 23.3% had normal cardiac autonomic functions.

In the present study, we did not find any significant association of fasting plasma glucose (FPG), postprandial plasma glucose (PPPG), HbA1c, and duration of diabetes with autonomic neuropathy. BMI among patients with cardiac autonomic dysfunction was lower compared to those with cardiac autonomic functions; this difference was not statistically significant. The LDL-cholesterol was found to be lower in patients with CAN compared to patients with normal cardiac autonomic functions, which was found to be statistically significant. The BP of patients with parasympathetic dysfunction was found to be higher when compared to the patients in the other groups, but the difference was not statistically significant.

In their study on 23 patients with FCPD, Govindan *et al*. had demonstrated the occurrence of autonomic dysfunction as early as 2 years from disease onset,[10] but in our study we found one patient to have autonomic dysfunction at the diagnosis of diabetes and five patients to have cardiac autonomic dysfunction with duration of known diabetes less than 1 year. In all, 20% of subjects had cardiac autonomic dysfunction within a year after the diagnosis of diabetes.

Mohan *et al*., in a study conducted on 40 subjects with FCPD,[9] reported the prevalence of autonomic neuropathy to be over 16.6% in patients with a disease duration between 0 and 5 years and over 60% of patients having FCPD for more than 16 years; however, in our study, we found 63.3% of our patients to have an abnormal autonomic function and 13.3% of them to have borderline autonomic dysfunction with a median duration of diabetes of barely 2.4 years. Govindan *et al*. and Mohan *et al*. had used different methodologies and criteria for diagnosing CAN.

Whether this indicates end-organ damage or reversible dysfunction due to severe hyperglycemia needs further interpretation.

From the available data from a limited number of studies on the prevalence of CAN in patients with FCPD, it appears that the prevalence of cardiac autonomic dysfunction is much higher among patients with FCPD than in patients with type 1 diabetes. Studies have shown that the prevalence

Table 4: Clinical and biochemical characteristics among the four groups of autonomic dysfunction among patients

Characteristics	Normal cardiac autonomic functions (n=7)	Parasympathetic abnormality alone (n=11)	Combined PNS and SNS abnormality (n=4)	Borderline cardiac autonomic dysfunction (n=4)	*P* value
Age (years)	38 (25-50)	37 (25-63)	38 (29-63)	37.5 (32-46)	0.867
BMI (kg/m^2)	20.9 ± 1.46	18.8 ± 2.2	18.17 ± 3.89	18.57 ± 0.71	0.430
Duration of diabetes (months)	34 (1-72)	17 (0-60)	8.5 (0-48)	13.5 (0-36)	0.145
Fasting plasma glucose (mg/dl)	130 (118-457)	150 (101-375)	142 (87-198)	116 (101-299)	0.554
Postprandial plasma glucose (mg/dl)	229 (116-567)	340 (138-590)	247.5 (138-820)	327 (106-366)	0.798
Systolic BP (mm of Hg)	126.5 ± 22.4	136.7 ± 28.2	110.5 ± 8.6	110.75 ± 11.61	0.858
Diastolic BP (mm of Hg)	78.57 ± 12.34	97.55 ± 13.2	75.5 ± 13.5	72 ± 4.5	0.683
HbA1c (%)	8.1 (6.8-16.8)	11.5 (6.8-16.8)	10.5 (6.6-14.9)	6.4 (6-10.4)	0.359
Serum creatinine (mg/dl)	1.0 (1-1.3)	1.05 (0.8-3.9)	0.9 (0.6-1.5)	1.05 (0.9-1.2)	0.907
Total cholesterol (mg/dl)	191±44.7	161±50.5	154.75±31.7	156.2±19.2	0-133
Triglycerides (mg/dl)	144 (65-581)	134 (72-708)	200.5 (61-708)	137 (117-195)	0.367
HDL-C (mg/dl)	31 ± 9.6	37.18 ± 15.6	26 ± 4.24	31.2 ± 5.6	0.096
LDL-C (mg/dl)	114 ± 21.2	85.36 ± 37	82.25 ± 18.4	100 ± 14.8	0.011

None of the patients were found to have isolated sympathetic nervous system dysfunction

of CAN in patients with type 1 diabetes may vary from 16.6[12] to 60%,[13] with just one study by Guyen Thi *et al*.[14] reporting autonomic dysfunction of 80%. It is worthwhile noting that this study that was done amongst the Vietnamese subjects also showed an abnormally high prevalence (68.3%) of autonomic dysfunction among the non-diabetic controls. The author attributed this to the effect of poor nutritional status on the cardiac autonomic functions.

Studies have also shown an increased prevalence of CAN in patients with nutritional deficiencies.[15,16] Malnutrition is well documented in patients with FCPD and could be a significant factor that contributes to the occurrence of autonomic neuropathy in these patients. Our study has also shown that the BMI of patients with CAN was lower when compared to their normal counterparts. This could be a reflection of their underlying poor nutritional status; however, further evaluation may be needed to confirm the presence of such a problem.

The major strength of our study is that we used the CAN 504 analyzer which is a fully automated computerized device to assess the autonomic functions in all our patients to minimize the intra-observer errors in manual recordings of various parameters. The major limitation is that controlling the factors which can influence the results of cardiac autonomic function test is difficult. Although precautions were taken to eliminate some of the well-known factors like smoking, coffee and tea consumption, and drugs like β-blockers, which can stimulate the autonomic nervous system, other possible extrinsic factors which may influence the autonomic functions could not be totally excluded.

The prevalence of abnormal cardiac autonomic function is as high as 63.3% in the present study population, which warrants regular screening of patients with FCPD for autonomic dysfunction. Isolated parasympathetic dysfunction was the most common abnormality with a prevalence of 42.3%. Among patients who had duration of diabetes less than a year, 66.7% had cardiac autonomic dysfunction. FCPD patients with autonomic dysfunction were found to have a lower BMI and lower LDL-cholesterol when compared to their counterparts with normal autonomic functions, which may be indicators of malnutrition in the group with autonomic dysfunction. Whether this malnutrition is responsible for the autonomic dysfunction needs further exploration.

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Cite this article as: Nanaiah A, Chowdhury SD, Jeyaraman K, Thomas N. Prevalence of cardiac autonomic neuropathy in Asian Indian patients with fibrocalculous pancreatic diabetes. Indian J Endocr Metab 2012;16:749-53.

Source of Support: Nil, **Conflict of Interest:** None declared.