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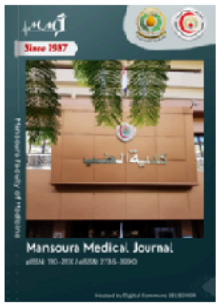

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SCREENING AND ASSESSMENT OF CARDIAC AUTONOMIC NEUROPATHY IN LONG STANDING TYPE 2 DIABETIC WOMEN

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ABSTRACT

Background : Patients with long standing DM undergoing surgical interventions are put under great challenge as they may have cardiovascular and/or cardiac autonomic neuropathy (CAN). CAN is serious, often overlooked and under diagnosed, with possible arrhythmias and silent ischemia that threaten life. *Objectives:* Screening for one of the under diagnosed high risk problem by assessment of CAN in long standing type 2 diabetic women undergoing stressful situations. S*tudy design:* Cross section study. *Patients and methods:* 100 type 2 diabetic women scheduled for major surgery were assessed by the autonomic function tests. CAN was assessed by analyzing HR variations during three standard tests (deep breathing, lying to standing and valsalva maneuver). Sympathetic functions were assessed by checking orthostatic hypotension. The CAN score of each patient was analyzed. Continuous 24 hours ECG monitoring (Holter) to evaluate arrhythmia, QTc and QTd. Transthoracic Doppler echocardiography, stressing on LVH, diastolic and systolic dysfunctions were carried out. Cases were classified as mild (with only one abnormal test) or severe CAN when 2 or more abnormal function tests were present. Exclusion criteria include any systemic illness that can affect the study results or the autonomic functions, smoking, hypertension and cases with evident ischemia. *Results:* CAN was detected in 70% of the studied cases, and 70% was severe CAN. Postural hypotension was detected

in 34% of the studied cases. QTc prolongation and QT dispersion were frequent. ECG and Doppler echocardiography changes of LVH were more prevalent among patients with CAN. Diabetics with CAN were significantly older had longer duration of DM and higher HbA1-c, higher pulse pressure, triglyceride, uric acid and urinary albumin execration rate. They also had significant increased LVM index and diastolic dysfunction. *Conclusion:* Middle aged women with long standing diabetes are vulnerable to CAN with postural hypotension and prolonged QTc intervals, QT dispersion, and increased LVMI. Identification of CAN is crucial to exercise prevention against hazards of CV insults during stressful situation and cases with severe CAN may be in need for CAD screening preoperatively.

Key word : cardiac autonomic neuropathy.

Abbreviations: CAN: Cardiac autonomic neuropathy, LVH: Left ventricular hypertrophy, DM: Diabetes mellitus, HTN: Hypertension.

INTRODUCTION

Autonomic neuropathy, although not rare, is one of the most insidious complications of diabetes mellitus (DM) especially if long standing and poorly controlled. Cardiac autonomic neuropathy (CAN) is often overlooked both in diagnosis and treatment simply because there is no widely accepted single approach to its diagnosis [1]. CAN embraces exercise intolerance, intraoperative cardiovascular liability, orthostatic syndromes and silent myocardial ischemia [2, 3, 4]. These clinical manifestations can result in life threatening outcome which unquestionably associate the presence of CAN with the increased risk of CV morbidity and mortality in DM.

In Eurodiab prospective study (2001) CAN was among the strongest risk markers of future total and CV mortality exceeding the effect of traditional risk factors as age, obesity, hypertension, dyslipidemia, inflammatory and prothrombotic emerging cardiac risk factor [4, 5]. In a Meta analysis of 12 published studies Vinik et al (2003) [6] reported a constant association between CAN and silent myocardial ischemia and in DIAD study, CAN was a stronger predictor of silent ischemia and subsequent cardiac events [7].

QTc interval and QTd have been

considered as a marker of cardiac autonomic dysfunction and have been demonstrated as an independent predictor of CV mortality and all cause mortality risk in type 2 DM patients [4]. Combined abnormality in HRV and QT index was a strong predictor of mortality independent of conventional risk factor [8, 9].

Action to Control Cardiovascular Risk in Diabetes (ACCORD trial 2010) in the presence of CAN at baseline was an independent contributor to the higher CV mortality risk in both the intensive and standard glycemic arm treatment. Individuals with baseline CAN were two times more likely to die compared with individuals without CAN [10, 11]. A lot of attention has been given to the CV aspect of autonomic dysfunction especially with the view regarding very tight glycemic control with increased mortality ACCORD trial [12] attributed increased mortality to hypoglycemia induced arrhythmias [1].

There is no widely accepted single approach to the diagnosis of CAN, however during the 1970s Ewing et al (1980) [13], advised a number of simple bedside tests of short term RR difference to detect CAN including changes in RR with deep breathing, RR response to standing which induce reflex tachycardia followed by bradycardia and Valsalva ratio which evaluates cardiovagal function in response to standard increase in intrathorathic pressure.

Orthostatic hypotension with its many troublesome symptoms ranging from light headedness to near syncope that may be associated with poor quality of life with fall in systolic BP ≥ 20 mmHg and ≥10 mmHg in diastolic BP during 3 minutes of standing and resolving with sitting or lying down is characteristic of CAN [14, 15].

The clinical symptoms of CAN may be late, however subclinical CAN manifest as changes in HRV may be detected within one year of diagnosis of type 2 DM [16].

Pop Bussi (2010) [17], reported that screening for CAN revealed that it ranges from as low as 2.5% (DCCT) to as high as 90% in long standing DM and should be instituted at diagnosis of type 2 DM and after 5 years of diagnosis of type 1 [18]. Vinik and Ziegler (2007) [19], re-

ported that, detection of CAN is a must before exposing patients with long standing DM to stressful situation and also before planning exercise. Diabetics must be tested with a cardiac stress test before undergoing an exercise program. Patients with CAN need to rely on their perceived exertion and not heart rate to avoid the hazardous levels of exercise intensity [19].

Aims : Screening and assessment of cardiac autonomic dysfunction in middle aged women with long standing type 2 DM who are going to be exposed to stress in the form of major surgery.

Design : Cross- section study.

Subjects and Methods : The studied cases included one hundred and six women who are known to be diabetics and were under oral hypoglycemic agents (70 cases) and 36 cases were under combined insulin and sulphonylurea. All were receiving metfornin 1.7 gm/ day. Six cases did not complete the study for unknown reasons and only 100 cases completed the study. Their age ranged from 40 to 60 years (mean 52.4± 3.7 years). The studied cases had no polys symptoms. The mean duration of DM was 10± 2 years ranging from (6- 14 years). BMI ranging from 25.1 to 29.2 (mean 27.1± 1.1).

All medications that can affect the study results or the autonomic functions were withhold during and one week preceding the clinical assessment of autonomic functions.

Examinations were undertaken in the morning at least 2 hours after a light breakfast and no caffeine was allowed. The patients were asked about symptoms suggestive of autonomic neuropathy, postural hypotension and myocardial ischemia.

Diabetic complications as retinopathy were checked and peripheral neuropathy, sudomotor neuropathy was stressed upon. Peripheral neuropathy and sudomotor neuropathy were detected clinically by monofilament and dryness of the feet. Clinical examination, with stress on heart rate, SBP, DBP, pulse pressure was undertaken, Testing of autonomic parasympathetic dysfunction was assessed by HRV testing (heart rate ECG RR intervals on resting, standing, respiration and valsalva). Heart rate variability was calculated from

the RR interval using short continuous ECG recording. Continuous 24 hours ECG monitoring (Holter) was also used to evaluate ischemia, arrhythmia, QTc intervals and QTd. Cases with evident ischemia or arrhythmias were not included. The resting 12 lead ECG was also undertaken to show beside HRV evidences of LVH and/or ischemia. Prolongation of the QTc interval > 460 ms, and QTd > 10 ms were considered as evidences of HRV. Flattening of T wave and ST segment depression were considered as evidences of myocardial ischemia. Cases with angina ECG, Holter monitor evidences of ischemia were not included in the screening study.

Testing for sympathetic dysfunction by postural hypotension in supine and after standing for 3 minutes was undertaken with the standard mercury sphygmomanometer. The measurement in the supine position was taken after at least 15 minutes of rest and measurement in standing position was taken at the third minute of standing.

Transthoracic Doppler echocardiography was done stressing on LVMI, diastolic and systolic dysfunctions were carried out.

Biochemical studies were undertaken stressing on blood glucose, fasting and post 75 gm glucose challenge together with HbA1-c, serum creatinine, plasma cholesterol, triglyceride, serum uric acid and 24 hours urine albumin excretion.

The prevalence and the severity of CAN was assessed according to the number of autonomic function tests of Ewing's methodology, and the CAN score in each patient was analyzed.

Subclinical CAN cases or mild CAN with only one abnormal function test were compared to severe CAN cases (2 or 3 abnormal autonomic function).

The study protocol was approved by the scientific committee of Mansoura Faculty of Medicine and informed consents were obtained.

Exclusion criteria : Systemic illness that can affect the study results or the autonomic functions as CHF, CAD, arrhythmia, renal, hepatic impairment, HCV infection, severe anemia, thyroid dysfunction, smoking,

concomitant treatment with anticholinergic agents, adrenergic antagonists, vasoconstrictive agents and patients with BP≥ 140/90 mmHg on two occasions 2 weeks apart were not included.

Statistical analysis : was performed by using the statistical package for social science program (SPSS) version "16". The qualitative data were presented as frequency and percentages. The quantitative data were examined by using Kalmogrov-Smirnov test to test for normal distribution of the data and when parametric, expressed as mean and standard deviation. Student t test was used, to test for difference in normally distributed quantitative data between the two groups. Mann-Whitney-μ test was used for comparison between two groups when data are not normally distributed. Significance was considered when P value less than 0.05.

RESULTS

The prevalence of CAN as assessed by signs of autonomic neuropathy including HRV tests E/I ratio (expiration to inspiration) standing to lying flat, valsalva maneuver, were 70% (20 cases with single HRV testing, 26 cases with 3 HRV testing, and 24 cases with moderate CAN where two HRV tests were present).

Postural hypotension was detected in 34% of the studied cases and mean pulse pressure were significantly elevated in diabetic with CAN when compared to those without CAN ($P < 0.01$).

Prolonged QTc (> 460 ms) in 42% of the whole studied cases and 60% of the CAN cases and significantly increased QTd (> 10 ms) in the CAN group when compared to the non CAN group as evident by the continuous 24 hrs ECG Holter monitoring.

Women with DM and CAN were significantly older with significant longer duration of uncontrolled DM with insignificant differences in BMI.

There was no significant difference in the prevalence of CAN in relation to the method of controlling hyperglycemia (oral versus combined

oral hypoglycemic and insulin).

Symptoms suggestive of CAN in other systems, mainly urogenital were evident in the CAN group (P<0.04). Peripheral neuritis detected by monofilament with dryness of their feet (P<0.01). SBP, DBP and the mean pulse pressure were significantly higher in the CAN group (P < 0.001).

Transthoracic echo Doppler revealed presence of mild LVH (LV wall mass index ≥ 126 gm/ m2 in 70.01% of CAN versus 33.3% in the non CAN group P < 0.001) and significant abnormal relaxation pattern (E/A < 1) with preserved LV systolic functions.

Significantly higher BG level and HbA1-c in the CAN group was observed, with significant hypertriglyceridemia and elevation in uric acid in the CAN group. The urinary albumin excretion in the CAN was significantly elevated than in non CAN group (P< 0.01).Comparing the studied parameters in relation to the severity of CAN showed insignificant changes apart from significant older age, more postural hypotension, HbA1-c, serum creatinine, urine albumin excretion and QTc. Signs of LVH and QTd revealed borderline significant increase in severe CAN cases.

Table (1): Clinical findings in diabetes with CAN versus diabetics without CAN

	Present CAN No. 70 cases	%	Absent CAN No. 30 cases	%	P
Age (years)	54.4±6.1		48.6±4.1		<0.001
BMI(Kg/ m2)	26.3±1.2		26±1.1		0.226
Duration Of DM	9.9±3.1		7.3± 1.1		<0.001
Resting Heart Rate	94±8		92±6		0.172
Postural hypotension	34cases	48.57%	2 cases	6.66%	<0.001
Symptoms suggestive of CAN in other systems					
- gastrointestinal	4 cases	7.1%	1 case	3.3%	0.88
- Urogenital	20 cases	28.6%	3 cases	10%	0.044
- Sudomotor (dry feet)	8 cases	11.4%	3 cases	10%	0.84
Peripheral neuritis	56 cases	80%	6 cases	20%	<0.001
Dry skin	42 cases	60%	3 cases	10%	<0.001
SBP	130± 5		120± 5		<0.001
DBP	80±4		75±5		<0.001
Mean pulse pressure	50.5±3		45.5± 2		<0.001
Treatment of DM					
- Oral	21 cases	30%	9 cases	30%	1
- Combined oral and insulin	49 cases	70%	21 cases	70%	1

Table (2): Biochemical findings in Diabetes with CAN versus diabetics without CAN

	Present CAN No. 70 cases	Absent CAN No. 30 cases	P
FBG mgm/dl	180±10	138.6±4.1	<0.001
Post 75 gm glucose challenge mgm/dl	310±9	260±1.1	<0.001
HbA1-c%	10.2±1.1	9.2± 1.1	<0.001
S. cholesterol mgm/dl	198±16	193±30	0.39
S. Triglyceride mgm/dl	189±11	180±8.0	<0.001
S. Uric acid mgm%	6.9±1.2	6.1±1.9	0.035
S. Creatinine mgm	1±0.35	1.1 ±0.2	0.074
Urine 24 hr alb excretion mg/24h	130±1.2	105±1.1	<0.001
HB gm%	10.9±0.2	10.8±0.3	0.097
S. TSH	1.8±0.4	1.7±0.5	0.334

Table (3): Prevalence of CAN by the different assessment tests.

Method	No of cases	percentage
HRV: E/I ratio	20	20%
HRV: Standing to lying flat	20	20%
HRV:Valsalva maneuver	30	30%
Postural hypotension	34	34%
QTc prolongation> 460 mm	42	42%
QTd >10ms	42	42%

Table (4): ECG findings and transthoracic Doppler Echocardiography in Diabetes with CAN versus diabetics without CAN

	Present CAN No. 70 cases	%	Absent CAN No. 30 cases	%	P
QTc interval≥ 460 ms	42 cases	60%	10cases	33.3%	0.01
QTd≥ 10 ms	42 cases	60%	10cases	33.3%	0.01
Evidence of LVH	28 cases	40%	3 cases	10 %	0.003
LVM index ≥ 126 gm/ m2	50cases	70.1%	10 cases	33.3%	<0.001
E/A ratio < 1	40cases	57.1%	10 cases	33.3%	0.029
EF> 60%	60 cases	85.7%	26 cases	86.6%	0.599

Table (5): Clinical, biochemical and ECG findings of cases with subclinical mild CAN versus severe CAN cases

	Mild CAN 18 cases	Severe CAN 52 cases	P
Age (years)	56.9±2.1	55.1±2.5	0.003
BMI(Kg/ m2)	26.6±1.2	27.2±1.1	0.066
WC	95±3.5	96±4.1	0.321
Duration Of DM	9.8±3.1	9.9± 1.1	0.893
SBP	138± 5	140± 5	0.148
DBP	88±4	90±5	0.091
Mean pulse pressure	74.5±4	75.5±3	0.335
Resting Heart Rate	96±8	99±6	0.149
Postural hypotension	2cases 11.1%	32 cases 64%	<0.001
HbA1-c	8.9± 1.1	10.3±1.1	<0.001
S. cholesterol mgm/dl	205±10.2	210±8.9	0.068
S. Triglyceride mgm/dl	199±8.1	201±7.1	0.355
S. Uric acid mgm%	6.6±1.2	7.1±2.2	0.233
S. Creatinine mgm	1.0±0.2	1.2±0.1	<0.001
Urine 24 hr alb excretion	190±1.2	200±1.2	<0.001
QTc interval	448.1±9.9	460.1±10.1	<0.001
QTd > 10 ms	6 cases 33.3%	30 cases 57.7%	0.076

DISCUSSION

It was aimed in the present screening study to evaluate the CAN in middle aged women with long standing diabetes scheduled for stressful situation in the form of major surgery. Detection of CAN preoperatively is necessary as such patients are vulnerable to perioperatve cardiovascular instability with a greater decline in heart rate and BP during induction of anesthesia and more severe hypothermia [19, 3].

In the present study, the prevalence of CAN as detected by Ewings et al 1970s proposals of heart rate variability tests (Ewings et al 1980) was high (70%). As the determination of CAN is usually based on a battery of autonomic function test and as the proceeding from a consensus conference (1992) (20), recommended three tests. In the present study, the golden standard clinical autonomic testing ([21]) was followed (Expiration/inspiration ratio, standing to lying flat and valsalva maneuver and postural hypotension)

The prevalence of CAN ranged from 20% to 42% according to the way of detecting HRV state being highest (30%) by the valsalva maneuver procedure and lowest (20%) by the diminished expiration to inspiration ratio (E/I ratio) and by standing to laying flat. The scoring of CAN was calculated, where more than one fourth (26%) had ≥ 3 positive tests and 24% had ≥ 2 positive. This is in accordance with Katsilamborus et al (2011) [1], who found that autonomic neuropathy and CAN are not at all rare, but are often overlooked.

The prevalence of CAN ranged from as low as 2.5% (DCCT) ([17]) to as high as 90% in long standing DM and in 69% of treatment induced neuropathy [22]. In the present study the valsalva ratio was 30% and E/I ratio was 20%. Our results are not in accordance with England and coworkers (2009) [23], who found that HRV with deep breathing is the most widely used test of cardiovagal parasympathetic dysfunction. Cardiovascular sympathetic function was assessed by measuring the BP response to orthostatic changes [24, 25] and was detected in 34% of the studied cases.

The prevalence of CAN in the present study is higher than that of Zeigler et al 1992 [26], who by using HRV tests found that 34.3% of type

2 DM patients had abnormal functions. Similar to Cabezas- Cerrato et al 2009 ([27]), the HR response to deep breathing in the present study was the least evident among the studied cases.

In the present study, the studied cases were all females this could avoid gender related difference in biochemical and hematological values [28, 29]. CAN was more prevalent in diabetic of longer duration, older age those with more pulse pressure, higher serum triglycerides and with more elevated HbA1-c. Kodama et al (2012) [30], in a Meta analysis study described the association of pulse pressure as a cardiovascular risk in DM. Makimattila et al (2000) [31], found that poor glycemic control was the most important independent predictor of decrease in all measures of absolute power of HRV.

Our findings are also in agreement with those of Voulgari et al 2011[21] who mentioned that in type 2 DM patients, CAN has been independently associated with elevated BP, hyperglycemia, longer diabetes duration, dyslipidemia and the presence of microvascular complications [32, 21]. Katsilambors et al (2011) (1) reported the association of high serum uric acid level and sundomotor dysfunction in patient with type 2 DM and CAN. In the present study similarly serum uric acid showed significant differences.

Symptoms of orthostatic intolerance and gastrointestinal function, urinary frequency, nocturia and anhydrosis were reported more frequently in diabetics with CAN. This is in line with Gibons and Freeman (2011) [33], although in the present study only the urogenital symptoms were significantly more frequent in CAN group.

Peripheral neuropathy was present in 80% of the examined cases. This is in agreement with Vinik and Ziegler (2007) [34], Gandhi et al (2010) [35] who found that combined indices of autonomic and peripheral neurological dysfunction is associated with earlier CAN detection [36, 37]. In the EURODIAB [24] prospective complication study peripheral and autonomic neuropathy was among the strongest risk markers exceeding the effects of the traditional risk factors.

Orthostatic hypotension was dem-

onstrated in 34% of the whole studied cases and in 60% of the CAN group. Orthostatic symptomatology as light headedness, dizziness, fatigability, faintness on standing was very frequent (60%). However no reported cases of clear or near syncope were reported. Orthostatic hypotension in CAN is secondary to efferent sympathetic vasomotor denervation causing reduced vasoconstriction of the splanchinic and other peripheral bed [20].

In the present study the resting heart rate in the CAN group was around 100 bpm but was insignificantly rapid than in the non CAN group. This is in line with Pop-Bussi (2010) [17] who stated that increased resting heart rate is not a reliable diagnostic criterion for CAN in the absence of other signs.

In the present study QTc prolongation and the more prevalent QT dispersion, are in agreement with Voulgari et al (2011) (4). QTc interval was considered as a marker of cardiac autonomic dysfunction and is significantly associated with LVH [4]. The increase in the number of the abnormal CAN function tests increase the risk more [38]. Pappachen et al (2008) ([39]) concluded that QTc interval can be used to diagnose CAN and the combined abnormality of HRV, QTc and QTd were strong predictors of mortality independent of conventional risk factors [40, 41].

Prolongation of QTc interval was detected in 60% of the CAN cases. This coincides with the finding of Lombardi (2002) [42]. LVH was significantly manifest in the CAN group in comparison to the non CAN group.

In the present study QTc interval prolongation (> 440 ms) has been associated with increased age and duration of DM, SBP, DBP, mean pulse pressure and severity of autonomic neuropathy. This is in accordance with the finding of Ewing et al (1991) [43] and Veglio et al 2000 [44].

Comparing mild CAN cases and severe CAN cases revealed some clinical, biochemical, electrocardiographic and echocardiographic significant differences including; older age, more postural hypotension, elevated HbA1-c, serum creatinine, urine 24 albumin excretion and more frequent QTc prolongation which

may impose more cardiovascular risk.

CONCLUSION

CAN in women with type 2 DM are common. Detection of CAN irrespective of its scoring in patient with DM is of importance and can help to exercise more precautions during their diabetic management. As patients with prolonged QT intervals are at higher risk of sudden cardiac death, cases with sever CAN have to be screened for CAD preoperatively and special clinic for cardiac autonomic neuropathy may be warranted.

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