Diabetic Cardiovascular Autonomic Neuropathy

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Abstract

Introduction: Diabetic neuropathies are thought to result from diabetic microvascular injury involving small blood vessels that supply nerves. Cardiac autonomic neuropathy (CAN) represents a serious complication associated with Diabetic neuropathies.

Objectives: The aim of the study is to investigate the presence of cardiovascular diabetic autonomic neuropathy in a group of adult diabetic Sudanese patients with ischemic heart disease.

Methodology: This is a descriptive prospective cross sectional hospital based study. The study population included type 1 and type 2 diabetic patients admitted to the cardiac care unit in ELshaab Teaching Hospital with acute coronary syndrome over a period of two years, from April 2017 to April 2019.

Results: A total of 49 males (65.33%) and 26 females (34.67%) were included in the study. CAN was detected in 94.67% of the studied group

Conclusion: An incidence of 94.67% cardiovascular autonomic neuropathy in our sample indicates a high occurrence of this syndrome among our diabetic patients. Poor glycemic control is a common feature among our studied group. Sub-clinical autonomic neuropathy can be detected early using autonomic function tests.

Introduction

Diabetic neuropathies are disorders associated with diabetes mellitus.¹⁻²⁻³ These conditions are thought to result from diabetic microvascular injury involving small blood vessels that supply nerves (vasa nervosum) in addition to macrovascular conditions that can culminate in diabetic neuropathy.⁴⁻⁵⁻⁶ The reported prevalence of DAN varies widely depending on the cohort studied and the methods of assessment. In randomly selected cohorts of asymptomatic individuals with diabetes, 20% had abnormal cardiovascular autonomic function.⁷⁻⁸⁻⁹⁻¹⁰

Cardiac autonomic neuropathy (CAN) is a serious complication because the risk of death in patients with diabetes is about five times that of patients with chronic liver disease, and the mortality rate is high may be related to silent myocardial infarction, cardiac arrhythmias, cardiovascular, cardiorespiratory instability and to other causes not yet explained.¹¹⁻¹²⁻¹³⁻¹⁴ Resting tachycardia due to parasympathetic damage may represent one of the earliest signs. Typical manifestations associated with autonomic dysfunction include exercise intolerance, orthostatic hypotension, and cardiac dysfunction during resting or exercise. After using a simple non-invasive test of cardiovascular reflex, a better understanding of the predictive value of autonomic neuropathy.¹⁵⁻¹⁶⁻¹⁷ These most commonly include heart rate variation in response to deep breathing, standing, the valsalva maneuver and blood pressure response to standing and sustained handgrip. At present, near normal blood sugar is considered to be the main method to prevent diabetic neuropathy, but it cannot be achieved in most patients. Cardiology experience shows that only the use of lipophilic drugs that easily cross the blood-brain/blood-brain barrier can prove the long-term increase in

heart rate variability and the reduction in sudden cardiac death.¹⁸⁻¹⁹⁻²⁰ In accordance with these observations experimental data indicate a preventive effect of benfotiamine on the development of CAN. Alpha-lipoic acid (thioctic acid), a powerful free radical scavenger improves nerve blood flow, reduces endoneurial hypoxia lipid peroxidation and oxidative stress.²¹⁻²²⁻²³⁻²⁴⁻²⁵

OBJECTIVES

The aim of the study is to investigate the presence of cardiovascular diabetic autonomic neuropathy in a group of adult diabetic Sudanese patients with ischemic heart disease.

Methodology

This is a descriptive prospective cross-sectional study conducted in a hospital. It was conducted at ELshaab Teaching Hospital in Khartoum, Sudan. The study population included type 1 and type 2 diabetic patients admitted to the cardiac care unit in ELshaab Teaching Hospital with acute coronary syndrome over a period of two years, from April 2017 to April 2019. All the patients were adult diabetic Sudanese and all of them gave their consent to participate in the study. A structured and standardized interviewer administered questionnaire, consisted of detailed history including personal data, type and duration of diabetes and questions concerning diabetic autonomic neuropathy, in addition to past medical history, family history, drug and social history was administered to type 1 and type 2 diabetes mellitus patients, diagnosed according to WHO diagnostic criteria.

Clinical examination was done for all patients including general examination temperature, pupil, mouth and skin), measurement of blood pressure and pulse rate in supine and standing position looking for postural hypotension, resting tachycardia and fixed heart rate in response to sitting and standing position. Also examination of the central nervous system was done for all patients looking for evidence of peripheral neuropathy and autonomic nervous system involvement. The following investigations were done for all patients: CBC, FBS, RBS, HbA1c, urine analysis, estimated GFR calculated according to modification of diet in renal disease (MDRD), lipid profile, Echo, Serum Troponin.

Cardiovascular autonomic neuropathy then assessed by the following cardiovascular autonomic tests (CATs):

Parasympathetic integrity assessment: all of the patients were connected to ECG machine; rhythm strip lead 2 was done looking for:

1. Beat to beat heart rate variation during inspiration and expiration with the patient at rest and supine, breathing 6 breaths/min, a difference in heart rate of > 15 beat/min is normal and < 10 beat/min is abnormal, R-R inspiration/R-R expiration > 1.17 is normal and abnormal if less.
2. Heart rate response to standing during continuous ECG monitoring. The RR interval is measured at 15 and 30 heartbeats after standing; usually tachycardia is replaced by reflex bradycardia. The 30:15 ratio is normally > 1.03 and abnormal if less.

3. Heart rate response to Valsalva maneuver during which the patient forcibly exhales into the mouthpiece of a manometer to 40 mmHg for 15 s during ECG monitoring. Healthy subjects develop tachycardia and peripheral vasoconstriction during strain and an overshoot bradycardia and rise in blood pressure with resale. The ratio of longest R-R to shortest R-R should be > 1.2 and abnormal if less.

- Sympathetic integrity assessment:

1. Measurements of blood pressure response to standing.
2. Blood pressure response to sustained handgrip.

Data was introduced into the computer from a master sheet recording using software program. It was entered and analyzed and then the results were expressed in form of figures and graphs using Statistical Package for Social Science.

Results

A total of 49 males (65.33%) and 26 females (34.67%) with diabetes and ischaemic heart disease were interviewed and studied, male to female ratio of (1.88 : 1). CAN was detected in 94.67% of the studied patients. Forty five male patients had CAN. All female patients had CAN. All patients their age above 50 years had CAN, while among 16 patients their age between 41–50 years, CAN was detected in 15. It did appear that 3 patients their age between 31–40 years, only one of them had CAN. Only one patient between 20–31 years, and he had no CAN. The study showed that all the Laborers, Professional, Housewives, and those with no job, had CAN, while 21.33% of Employee had CAN.. Among 17 patients who had duration of less than 5 years, 15 had CAN. It was found that all patients had DM duration between 6–10 years, had CAN (20). Out of 15 patients who had duration between 11–25 years, 13 had retinopathy. All patients had duration of DM more than 16 years, had CAN.

Regarding the incidence of CAN in relation to type of DM, it was found that out of 72 patients with type 2 DM, 71 had CAN while in all patients with type 1 DM (3patients), had no evidence of CAN. CAN was detected in all patients with systemic hypertension .Out of patients who used to smoke,() (21.33%) had CAN, while out of nonsmoker, (1.33%) had CAN. All patients with history of alcohol consumption, had CAN.

Chest pain is the main presenting complaint in diabetic patients with ischaemic heart disease, as 76% of those presented with chest pain had CAN. All patients presented with palpitations (46.7%), dyspnea(45.3%), light headiness (37.3%) and cough (32%) had CAN.

Regarding the relation between CAN and GIT symptoms. All those with abnormal GIT symptoms (53.33%) had CAN, while in those with normal symptoms 41.33% had CAN.

All patients with abnormal genitourinary symptoms (85.33%) had CAN, while among patients with no genitourinary (GU) symptoms 9.33% had CAN.

On fundal examination, 24% of those with normal fundus had CAN, while 5.33% had not. All the patients with dot and blot hemorrhages and hard exudates (45.33%), cotton wool spot (13.33%) and diabetic proliferative retinopathy(12%) had CAN.

Of those who had no sweating disturbances, 33.33% had CAN and 4% had not, and all those with reduced sweating(21.33%) and those with excessive sweating(30.67%) had CAN, while those with gustatory sweating, 9.33% had CAN. Regarding the relationship between CAN and temperature regulation, out of those who had normal temperature regulation(44), 40 had CAN. All those with hotness sensation (26) and coldness sensation (5) had CAN. All patients with abnormal feet sensation (73.33%) had CAN and those with normal feet sensation, 21.33% had CAN.

Diastolic B.P response to sustained handgrip test is positive in 84. %, while the postural hypotension is positive in 44% of the patients.

Valsalva test is positive in 58.7% of patients, the E: I Ratio is positive in 46.7%, and the Standing 30:15 ratio is positive in 30.7%of patients.

74.67% of those with abnormal HbA1C () had CAN, 20% of those with normal HbA_{1C} () had CAN.

Of those who had abnormal lipid profile, 25.34%had CAN, and 1.33% had not. Those with normal lipid profile, 69.33% had CAN, and 4% had not. Of those who had positive Troponin, 36%had CAN, and 2.67% had not. Those with negative Troponin, 58.67% had CAN, and 2.66% had not.

Discussion

Our study included 75 patients with diabetes and ischemic heart disease assessed for evidence of cardiovascular autonomic dysfunction, using tests described by Ewing.²⁶

The study showed that most of our patients had type 2 DM. The mean age affected was found to be 50 years. Most of our patients showed an evidence of cardiovascular autonomic neuropathy (CAN) (94.67%). This is combatable with the results from a large prospective observational study that suggest the incidence of Diabetic cardiovascular autonomic neuropathy is declining in type 1 diabetes, potentially reflecting improvements in the management of risk factors and is also combatable to the study done by Pappachan JM and his colleagues, which showed a significant association between cardiovascular autonomic neuropathy and higher age.²⁷⁻²⁸

Worldwide studies showed neither age nor type of diabetes are limiting factors in its emergence; it has been found both in young people with newly diagnosed type 1 diabetes and in older people newly diagnosed with type 2 diabetes.²⁹⁻³⁰

The study showed that patients with age group over 50 years had cardiovascular autonomic neuropathy more than other age groups, definitely this can be explained by the fact that with progressing of age and

duration of diabetes patients are more prone to develop cardiovascular autonomic neuropathy, this is similar to what was mentioned by researches worldwide.^{31–32}

The study revealed higher frequency of cardiovascular autonomic neuropathy in patients living in Khartoum, possibly related to easy access to medical services and because the study was conducted in Elshaab teaching hospital so most of the patients were from Khartoum, this is similar to what was reported by Awad M and his colleagues.³³

Interestingly, the duration of diabetes was not significantly associated with the development of cardiovascular autonomic neuropathy, this is consistent with the findings of Ellenberg, and to what was mentioned by S.-H. Ko, S.-A. Park and his colleagues. Although diabetes duration has been reported to play an important role in patients with type 1 diabetes, the influence of diabetes duration seems to play a less important role in type 2 diabetes.³⁴

The majority of our patients with systemic hypertension were found to have cardiovascular autonomic neuropathy, this similar to study conducted in Punjab, and the study done by Awad M. and his colleagues.³³

Cardiovascular autonomic neuropathy was observed to occur with high frequency in patients with no smoking or alcohol consumption history. This is in contrast to what was observed in EURODIAB study and this may be attributed to the low use of smoking and alcohol consumption in our culture.³⁵

Regarding the relation between cardiovascular autonomic neuropathy and cardiopulmonary symptoms, most patients presented with chest pain followed by palpitations, dyspnoea, light headiness and cough. This is in contrast to what was observed In the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study, where the main features of an MI in patients with cardiovascular autonomic neuropathy are: silence, cough, nausea and vomiting, dyspnea, tiredness, and ECG changes. The increase incidence of symptomatology in favor of cardiovascular autonomic neuropathy may due to co existence of other diseases like hypertension, ischemic heart disease and cardiomyopathy.³⁶

Regarding the incidence of cardiovascular autonomic neuropathy in relation to systemic involvement, higher incidence of cardiovascular autonomic neuropathy was found in patients with symptoms in favor of gastrointestinal involvement. Also it did appear that the prevalence of symptoms in favor of genitourinary system involvement is similar to what was mentioned in the literature and what was mentioned by Awad M. and his colleagues.³³

Cardiovascular autonomic neuropathy was detected in all patients who had fundal changes combatable with retinopathy, indicating higher frequency of diabetic retinopathy, this higher frequency of cardiovascular autonomic neuropathy in patients with retinopathy is consistent with previous studies, which found an association between cardiovascular autonomic neuropathy and microvascular complications (Pittenger GL, and his colleagues). Cardiovascular autonomic neuropathy progression is correlated with diabetic retinopathy, diabetic nephropathy, and an increased urinary microalbumin

excretion rate, this finding suggests that clinicians should pay more attention to patients with diabetic retinopathy or nephropathy, over and above the strict glycemic control required for the prevention of cardiovascular autonomic neuropathy.³⁷

The study showed that most of the patients had no sweating disturbances, but excessive sweating and reduction of sweating was detected in small number of patients. Localized bouts of sweating on the face during eating (gustatory sweating) are reported to be diagnostic of diabetic autonomic neuropathy although they were not seen in this study.³⁸

Symptoms of feet involvement were detected in a large number of patients (73.33%), most of them had poor glycemic control and they share features of both cardiovascular autonomic neuropathy and peripheral neuropathy, this is in accordance with the other works worldwide.³⁶⁻³⁷⁻³⁸

The high prevalence of cardiovascular autonomic neuropathy among patients with sensory peripheral neuropathy has lead some authors to recommend screening such patients with bedside tests to pick early signs of cardiovascular autonomic neuropathy and then might benefit from improving their glycaemic Control.³⁸

Cardiovascular autonomic neuropathy was detected in approximately most patients with sympathetic involvement (abnormal response of diastolic blood pressure to sustained hand grip and postural hypotension) and in most patients with parasympathetic involvement (abnormal valsalva, E/I ratio and 30:15 ratio),but with less frequency, this is contrast to what was mentioned in the literature, this may be due to that most our patients had type 2DM, with poor glycaemic control and long duration of undiscovered DM, indicating that presence of autonomic symptoms indicate necessarily a severe form of cardiovascular autonomic neuropathy,this is consistent with Smith's findings. We think that the rigid division of cardiovascular autonomic neuropathy into sympathetic and parasympathetic is not appropriate as both nerves are involved to differing degrees in most patients. Being rarely life threatening (as many doctors believe), the symptoms of cardiovascular autonomic neuropathy received little attention by researchers compared to other diabetic complications.³⁹⁻⁴⁰⁻⁴¹⁻⁴²⁻⁴³

It did appear that patients with cardiovascular autonomic neuropathy had significantly higher levels of glycosylated haemoglobin, this in agree with a study done by Pacher P. and his colleagues, this observation is supported by the results found in Ziegler D study, which found that the incidence of autonomic neuropathy was associated with poor glucose control.⁴⁴⁻⁴⁵

Conclusion

1. An incidence of 94.67% cardiovascular autonomic neuropathy in our sample indicates a high occurrence of this syndrome in our diabetic population.
2. Poor glycemic control is a common feature among our diabetic patients, this is due to poor diabetic care, shortage of anti-diabetic drugs, diet and treatment non-compliance.

3. The diabetes mellitus among our sample is typically longstanding.
4. Sub-clinical autonomic neuropathy can be detected early using autonomic function tests.

RECOMMENDATION

As the majority of the cardiovascular autonomic neuropathy cases are asymptomatic, we should encourage the workers in diabetes care to test the autonomic functions as they find a chance especially before surgery or even in an annual routine checkup.

Declarations

Consent for publication

Not applicable.

Availability of data and materials

The materials datasets used and/or analyzed during this study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors participated in planning the study, data collection, results and discussion sections.

Ethical Considerations

Ethical approval was obtained from the State Ministry of Health, Khartoum, Sudan

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