DIABETIC CARDIOVASCULAR AUTONOMIC NEUROPATHY - CLINICAL IMPACT -

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Abstract: Cardiovascular autonomic neuropathy (CAN) is one of the most overlooked of all complications of diabetes, which encompasses damage to the autonomic nerve fibres that innervate the heart and blood vessels, resulting in abnormalities in heart rate control and vascular dynamics. CAN represents a prevalent and serious complication as it carries an approximately fivefold risk of mortality in the patients with diabetes, but it is one of the least frequently diagnosed. The high mortality rate may be related to silent myocardial infarction, cardiac arrhythmia, cardiovascular and cardiorespiratory instability. Patient's history and physical examination are not effective for the early detection of the autonomic nerve dysfunction, therefore it is important to identify the early stages of CAN with an easily available tool, such as the non-invasive cardiovascular reflex test. Tight glycemic control is the tool for preventing the development and the progression of CAN.

Cuvinte cheie: *diabetul zaharat, sistemul nervos autonom, neuropatia autonomă cardiovasculară, variabilitatea ritmului cardiac*

Rezumat: *Neuropatia autonomă cardiovasculară (NAC) este una dintre cele mai ignorate complicaţii ale diabetului zaharat (DZ), care apare din cauza lezării fibrelor nervoase autonome care inervează inima şi vasele de sânge, determinând dereglări în controlul ritmului cardiac şi al dinamicii vasculare. NAC reprezintă o complicaţie prevalentă şi importantă a DZ deoarece reprezintă o cauză importantă de morbiditate şi mortalitate la pacienţii diabetici. Rata crescută a mortalităţii se datorează aritmiilor cardiace, infarctului miocardic nedureros, instabilităţii cardiovasculare şi cardiorespiratorii. Examenul fizic şi anamneza nu sunt utile pentru detectarea precoce a disfuncţiei nervoase autonome, de aceea, pentru identificarea NAC în stadiu precoce, avem la dispoziţie mijloace utile, non-invazive reprezentate de testele reflexe cardiovasculare. Controlul glicemic strict reprezintă mijlocul prin care se poate preveni dezvoltarea şi progresia NAC.*

Diabetes mellitus is a growing problem of public health across the world. Cardiovascular autonomic neuropathy (CAN) is a serious chronic complication of diabetes, which results from the damage to the autonomic nerve fibres that innervate the heart and blood vessels and results in abnormalities in heart rate control and vascular dynamics. CAN is associated with poor prognosis and poor quality of life. CAN represents a significant cause of morbidity and mortality in diabetic patients because it is associated with high risk of cardiac arrhythmias and sudden death, possibly related to silent myocardial ischemia. A better understanding of clinical and prognostic importance of autonomic neuropathy was closely related to the widespread use of the simple non-invasive cardiovascular reflex tests.(1)

The aim of this report was to review the importance of the clinical identification of patients with early stage of CAN.

Epidemiology

The reported prevalence of CAN varies greatly depending on the criteria used to identify CAN and the population studied. In a large cohort of patients with type 1 and 2 diabetes, Ziegler et al., using predefined heart rate variability tests and spectral analysis of R-R intervals, found that 25.3% of the patients with type 1 diabetes and 34.3% of the patients with type 2 diabetes had abnormal findings. In a review of several epidemiological studies among individuals diagnosed with diabetes, it was shown that the 5-year mortality rate regarding this serious complication is five times higher in the individuals with CAN than for individuals without cardiovascular autonomic involvement.(2,3)

CAN is significantly associated with overall mortality and in some studies with morbidity, such as silent myocardial ischemia, coronary artery disease, stroke, diabetic nephropathy progression and perioperative morbidity. Some pathogenic mechanism may link CAN to cardiovascular dysfunction and diabetic complication. Thus, CAN assessment may be used for cardiovascular risk stratification in the patients with and without cardiovascular disease, as a marker for the patients requiring more intensive monitoring during the perioperative period and other physiological stressors, and as an indicator for more intensive pharmacotherapeutic and life-style management of the comorbid conditions.(4,5)

Clinical Presentation

The decrease in heart rate variability and resting tachycardia are one of the earliest indicators of cardiac autonomic dysfunction, and appear due to parasympathetic damage. Large epidemiological studies indicated that tachycardia of any origin is a major risk factor for cardiovascular and non-cardiovascular death, because of vascular damage and the development of atherosclerosis.(6) Autonomic dysfunction can affect exercise tolerance, reduces

response in heart rate and blood pressure during exercise. In the patients with CAN, there is a decreased cardiac output in response to exercise. Decreased ejection fraction, systolic dysfunction and diastolic filling limit the exercise tolerance.

The presence of autonomic dysfunction may limit the capacity of individual's exercise and increases the risk of a cardiovascular event during exercise. Because diabetic patients with CAN have a potential for impaired exercise tolerance, they should have cardiac stress testing before undertaking any exercise programme.(7,8,9) Patients with CAN have an intraoperative and perioperative cardiovascular instability, and this may lead to a perioperative cardiovascular morbidity and mortality which are much higher in the patients with diabetes. Any diabetic with CAN is at a considerable anaesthetic risk.(9) Orthostatic hypotension (OH) may cause dizziness, faintness, weakness, blackouts or visual impairment, even syncope after the change from lying to the standing posture. Sometimes, these symptoms are mistakenly assigned to hypoglycemia. In the patients with diabetes, OH is usually due to the damage to efferent sympathetic vasomotor fibres, causing reduced vasoconstriction in the splanchnic and other peripheral vascular beds.(10)

Diagnosis

Symptoms that are possibly reflecting the autonomic dysfunction should not, by themselves be considered markers for its presence, because the correlation between symptoms and deficits is weak in mild CAN. A better understanding of clinical and prognostic importance of CAN was related to the widespread use of cardiovascular reflex tests, which are the gold standard in clinical autonomic testing. The most commonly used battery of cardiovascular reflex tests are those proposed by Ewing and Clark, which have a good sensitivity, specificity, reproducibility, are non-invasive, safe and well-standardized. The Ewing tests include heart rate variation in response to deep breathing, standing and Valsalva manoeuvre, as well as blood pressure response to standing and sustained handgrip. These validated tests are recommended for CAN diagnosis and can be performed in general practice. Heart rate tests that evaluate the parasympathetic function appear to be abnormal more frequently and earlier in cardiac autonomic involvement, and blood pressure tests that evaluate sympathetic damage are abnormal in advanced stage. The presence of one abnormal cardio-vagal test indicates early CAN, at least two abnormal heart rate tests are necessary for diagnosis if definite CAN and abnormal blood pressure response in addition to heart rate abnormalities identify a severe or advanced CAN.(11)

Other methods that are currently used mostly in research settings are: spectral analysis of HRV, evaluation of baroreflex sensitivity, scintigraphic assessment using I-metaiodobenzylguanidine (123 I-MIBG) and single photon-emission computed tomography, microneurography. It should be noted that these methods are more sensitive in detecting cardiovascular autonomic neuropathy than the conventional autonomic function tests, but there are special needs for using these methods, so they cannot be used for the widespread detection of CAN. Evaluation of QTc interval may provide a simple additional diagnostic aid to identify patients with an increased cardiovascular risk.(12,13)

Clinical implication

Increased mortality risk - CAN is associated with a high risk of cardiac arrhythmias and sudden death. In the EURODIAB Prospective Cohort Study of 2787 type 1 patients, the strongest predictor for mortality during 7 years of follow-up was CAN, exceeding the effect of traditional cardiovascular risk factors. Another cohort of type 2 diabetic patients showed that a combined abnormality in HRV and QT index was a strong

predictor of mortality independent of the conventional risk factors. The mechanism responsible for increased mortality remains obscure, because it is difficult to determine the independent effects of CAN on mortality because of the coexistence of the cardiovascular disease. There were reported the results of a study designed to assess the risk of mortality due to CAN but without clinical manifestation of severe complications (proteinuria, proliferative retinopathy, coronary artery disease or stroke) 8 years after their first clinical examination. The mortality of diabetic patients with CAN increased steadily over the 8-year period compared with an age, gender and duration of diabetes matched group. Autonomic cardiac dysfunction was found to be an independent risk factor with poor prognosis.(14,15,16,17)

Silent myocardial ischemia - Patients with CAN have an inability to detect ischemic pain that can impair timely the recognition of myocardial ischemia or myocardial infarction and thereby delay appropriate treatment. Vinik et al. reported in a meta-analysis of 12 published studies that there is a statistically significant increased frequency of silent myocardial ischemia (measured by exercise stress testing) in individuals with CAN compared with individuals without CAN. In the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study of 1123 patients with type 2 diabetes, CAN was a strong predictor of silent ischemia and subsequent cardiovascular events. Therefore, the patients with diabetes need to be more carefully investigated, the cardiovascular autonomic function testing should be an important component in the risk assessment of diabetic patients with coronary artery disease.(9,18,19)

Sudden death - Sudden, unexpected deaths have been reported among the subjects with CAN. Potential causes of sudden death may be severe, but asymptomatic cardiac ischemia, which can induce lethal arrhythmias, or by QT interval prolongation that may also predispose individuals to life-threatening cardiac arrhythmias and sudden death. In the Rochester Diabetic Neuropathy Study, the investigators found that all cases of sudden death in individuals with and without diabetes had severe coronary artery disease or left ventricular dysfunction. Therefore, they demonstrated that CAN was not a significant independent cause of sudden death, but it could be a contributing factor.(17,20,21)

Stroke - The frequency of ischemic cerebrovascular events is higher in type 2 diabetic patients, especially in those with CAN. In a study reported by Toyry et al. about the impact of CAN on the risk of developing brain strokes, abnormalities of parasympathetic and sympathetic autonomic function were found to be independent predictors for stroke. There is another study in type 2 diabetic patients which reported that the presence of CAN was one of the strongest predictors of ischemic stroke together with age and hypertension.(22,23)

Progression of CAN

In subclinical stage, functional and reversible alterations are predominant and autonomic dysfunction can be detected by early using the autonomic function tests. In this stage, typically abnormal are the results of cardiovascular autonomic function tests that are mediated by the parasympathetic nervous system. Clinical stage is symptomatic and is associated with sympathetic nervous system dysfunction, and blood pressure variability tests are abnormal.(3,24) It is well known that the onset of type 2 diabetes occurs at least 4-7 years before the clinical diagnosis. As a consequence, neuropathy is a common complication even in the patients with newly diagnosed type 2 diabetes. Subclinical autonomic dysfunction can be detected at the time of diagnosis or within a year after the diagnosis in type 2 diabetic patients and within 5 years in type 1 diabetic patients. Measurement of HRV at the time of diagnosis

of type 2 diabetes and within 5 years after the diagnosis of type 1 diabetes are important for establishing a baseline, with which 1-year interval tests can be compared.(9,24,25,26)

The natural evolution of CAN is overlooked by the degree of glycemic control. Poor glycemic control plays an important part in the development and progression of CAN. The importance of long-term glycemic control in the development and progression of CAN is now generally accepted. The DCCT and UKPDS studies demonstrated that strict glycemic control is a priority in primary and secondary prevention of neuropathy. Data resulting from these studies demonstrated that intensive diabetes therapy resulting in long term HbA1c levels of approximately 7% prevents the onset and slows the progression of neuropathy in type 1 and 2 diabetic patients, and in the DCCT study, intensive diabetes therapy was able to slow the progression and the development of abnormal autonomic function tests, as well. The favourable effect of strict glycemic control on myocardial sympathetic innervation assessed by MIBG scintigraphy was shown in a 4-year prospective study in patients with type 1 diabetes.(24,27,28,29)

Conclusions

CAN is a serious common complication of diabetes and despite its relation to an increased risk of cardiovascular mortality is among the least recognized and understood complication of diabetes. The assessment of cardiovascular reflex tests represents an easily available tool to document the presence of CAN. Because the natural progression of CAN is insidious and the symptoms are miscellaneous and manifest at a relatively late stage, the early detection is important to prevent irreversible damage. Conclusive clinical evidence from randomized prospective trials supports an important role for tight glycemic control in preventing the development and progression of CAN, with the aim of preventing these complications, the diabetic patients should receive a precocious diagnosis and be instructed to have a good metabolic control.

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