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DIAGNOSES OF CARDIAC AUTONOMIC NEUROPATHY IN PATIENTS WITH DIABETES MELLITUS TYPE II

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Background

Diabetes Mellitus type II (DM) is an important metabolic disorder that can affect nearly every organ system in the body. Prevalence of diabetes in adults worldwide was estimated to be 4.0% in 1995 and to rise to 5.4% by the year 2025 [14]. As a developing country, Ukraine is also a vulnerable country for DM Type II, day by day this disease is increasing in this country [14]. Cardiovascular disease is one of its most common complications that increase mortality in these patients. The cardiovascular complications of Diabetes Mellitus type II can be classified into three groups: atherosclerotic coronary artery disease, diabetic cardiomyopathy, and cardiac autonomic neuropathy (CAN) [3, 4, 5]. Perhaps one of the most overlooked of all serious complications of diabetes is CAN [2, 11, 15]. CAN results from damage to the autonomic nerve fibers that innervate the heart and blood vessels and results in abnormalities in heart rate control and vascular dynamics [8, 18, 19]. CAN is a common form of diabetic autonomic neuropathy and causes abnormalities in heart rate control as well as central and peripheral vascular dynamics, the clinical manifestations of which include exercise intolerance, intraoperative cardiovascular liability, orthostatic hypotension and painless myocardial ischemia, and contributes to morbidity, mortality, and reduced quality of life for persons with diabetes mellitus [13, 16]. The incidence of silent myocardial ischemia in diabetics is very high and CAN seems to be the most

probable reason for the absence of pain [10, 15]. The risk of sudden death is also high in patients with CAN [13, 17, 20]. In our daily practice, sometimes we also overlook the sign-symptoms of CAN. Though, there are very easy bedside tests to evaluate the CAN even at primary medical examination without difficult and long methods of investigations.

Goal of the study: to establish the presence of CAN among the Diabetes Mellitus type II patients, who usually admit to the hospital for conventional.

Materials and methods

We examined 45 patients with Diabetes Mellitus Type II (DM-II) who were hospitalized in the endocrinology department for regular treatment (table 1). All patients were investigated routinely - complains, anamnestic data, objective examination, additional examination (blood test, sugar test, GTT, HbA1, urine test, other standard tests).

Table 1

Characteristic of patients

Points	DM type 1
No of patients	40
Mean age, years	50,17 ± 8,84
Mean age of onset of DM, years	43,18 ± 9,21
Male: Female ratio	16:24 (1:1,5)
Duration of the DM, years	8,33 ± 3,7
Mean BMI, kg/m^2	29,24± 6,18
Positive family history	15 (37,5%)
History of the pancreatitis	12 (30%)

Other tests done - each participant will be also examined for the presence or absence of peripheral neuropathy by testing for abnormal pin-prick sensations in the limbs, abnormality of position sense in the big toes, and the absence of Achilles' tendon reflex. Hypertensive and those with nephropathy were excluded from the study cohort because of their likelihood of having baseline ECG abnormalities and also because these diseases may interfere with the autonomic function tests. For defining of CAN next 5 classical tests were done.

Assessing cardiovascular parasympathetic function:

Resting tachycardia. If heart rate is >100/ minute at resting condition, it will be resting tachycardia and one of the sign of CAN.

Heart rate response to deep breathing. Beat-to-beat variation in heart rate with respiration depends on parasympathetic innervation. Several different techniques have been described in clinical literature, but measurement during paced deep breathing is considered the most reliable.

Procedure: Lie the patient flat. When the pulse has steadied, record the pulse rate during six slow maximal deep breaths. In normal subjects the pulse rate should slow by >15 beats/min; with autonomic disturbances the pulse rate slows <10 beats/min.

Heart rate response to standing. This test evaluates the cardiovascular response elicited by a change from a horizontal to a vertical position. In healthy subjects, there is a characteristic and rapid increase in heart rate in response to standing that is maximal at approximately the 15th beat after standing. This is followed by a relative bradycardia that is maximal at approximately the 30th beat after standing. In patients with diabetes and autonomic neuropathy, there is only a gradual increase in heart rate.

Procedure: Pulse. Record the R-R interval on the ECG and use it to determine the instantaneous heart rate, at rest and then on the 15th and 30th beats after standing. The heart rate should normally rise after about 30 seconds as part of the response to return the blood pressure to normal. The normal 30th:15th pulse heart rate ratio is >1,03 in normal subjects, and <1,0 when there is autonomic disturbance.

Valsalva maneuver. In healthy subjects, the reflex response to the Valsalva maneuver includes tachycardia and peripheral vasoconstriction during strain, followed by an overshoot in blood pressure and bradycardia after release of strain. The response is mediated through alternating activation of parasympathetic and sympathetic nerve fibers. In patients with autonomic damage from diabetes, the reflex pathways are damaged. This is seen as a blunted heart rate response and sometimes as a lower-than-normal decline in blood pressure during strain, followed by a slow recovery after release.

Procedure: The patient closes the glottis and attempts maximal expiratory effort for 15 seconds. The resultant reduced venous return should reflexly lower the pulse rate via the vagal parasympathetic.

The ratio of the highest pulse rate in a preliminary rest period to the lowest pulse rate during the test is >1,2 in normal subjects and <1,1 in patients with autonomic disturbances. The test may be repeated up to three times if the initial result is equivocal.

Assessing cardiovascular adrenergic (sympathetic) function

Systolic blood pressure response to standing. Blood pressure normally changes only slightly on standing from a sitting or supine position. The response to standing is mediated by sympathetic nerve fibers. In healthy subjects, there is an immediate pooling of blood in the dependent circulation resulting in a fall in blood pressure that is rapidly corrected by baroreflex-mediated peripheral vasoconstriction and tachycardia.

Procedure: Record the supine blood pressure after the patient has been resting quietly on a couch for 15 minutes. Then ask the patient to stand. This will reduce the recorded blood pressure, but sympathetic mechanisms should correct this over the next minute or so. Thus, measure the blood pressure 1 and 3 minutes after standing. A fall of over 20mmHg systolic compared to the supine pressure suggests autonomic failure.

Diastolic blood pressure response to sustained handgrip. In this test, sustained muscle contraction a rise in systolic and diastolic blood pressure and heart rate. This rise is caused by a reflex arc from the exercising muscle to central command and back along efferent fibers. The efferent fibers innervate the heart and muscle, resulting in increased cardiac output, blood pressure, and heart rate.

Procedure: With the patient lying flat, measure the maximal handgrip force by having the patient grip a semi-inflated sphygmomanometer cuff as hard as possible. Then, with a second sphygmomanometer, measure the rise in diastolic blood pressure after a 30% handgrip sustained for 5 minutes. The diastolic pressure should rise >16 mmHg; in autonomic disorders it will rise <10 mmHg.

Response to tilting. The hemodynamic response to standing is a commonly performed measure of autonomic function. Passive head-up tilting provides a more precise level of standardization to the orthostatic stimulus and reduces the muscular contraction of the legs, which can reduce lower-leg pooling of blood. A tilt angle of 60° is commonly used for this test.

Procedure: The Passive head-up tilting may be maintained for 10-60 min or until the patient's orthostatic symptoms can be reproduced. The orthostatic stress of tilting evokes a sequence of compensatory cardiovascular responses to maintain homeostasis. As for the stand response, the normal tilted reflex consists of an elevation in heart rate and vasoconstriction. If reflex pathways are defective, blood pressure falls markedly with hemodynamic pooling. An abnormal response is defined similarly to that associated with standing.

Table 2

The five autonomic function tests to detect cardiac autonomic

Autonomic function test	Points
1. Resting heart rate	
<100 beats/min	0
100–110 beats/min	0,5
>110 beats/min	1
2. Postural hypotension (fall in systolic blood pressure)	
<20 mm Hg	0
20–30 mm Hg	0,5
>30 mm Hg	1
3. Valsalva ratio	
>1.2	0
1.2–1.10	0,5
<1.10	1
4. Heart rate variability on deep breathing	
>15 beats/min	0
15–10 beats/min	0,5
<10 beats/min	1
5. Increase in diastolic blood pressure during sustained handgrip	
>15 mm Hg	0
15–10 mm Hg	0,5
<10 mm Hg	1

Determination of the CAN. The total points from each of these five tests will be added together and the cardiac autonomic neuropathy score [9, 22] (CAN score) will be categorized as follows: CAN score 0 (total points 0), CAN score 1 (points 0,5 - 1,5), CAN score 2 (points 2-3), and CAN score 3 (points 3,5). CAN would be considered absent, early, definite or severe if the CAN scores were 0, 1, 2 or 3, respectively [9]. Results from earlier research suggested that using

a battery of cardiovascular tests (some indicating parasympathetic involvement and others indicating possible sympathetic involvement) would make it possible to follow the progression of autonomic function over time. The San Antonio consensus panel further extended the utility of tests of cardiovascular autonomic function by suggesting that a battery of tests could be used to stage patients with autonomic neuropathy [1, 7, 21]. A three-stage model was proposed as follows:

- Early stage: abnormality of heart rate response during deep breathing alone.
- Intermediate stage: an abnormality of Valsalva response.
- Severe stage: the presence of postural hypotension.

In this study, the authors used Bellavere et al. [9] methods for scoring of CAN as well as the "San Antonio consensus panel's suggestions to score the CAN" [21].

Results and discussions

Some patients of DM-II (17,5%) came to hospital for regular check up. Other 82,5% patients came to hospital with the complaints of general weakness, for the problem of their high blood glucose level & decreased sensation at both legs and hands, 45% patients came for polyurea, polydipsia and dryness of mouth and rest of the patients came for other complaints like pain at both legs or pain during walking, palpitation, headache, dizziness, general discomfort (bad feelings), decreased eye vision etc.

Standard diabetic tests showed bad compensation of DM-II in all patients (table 3).

Table 3

Results of routine diabetic tests

Tests	Results
Mean HbA1c level, %	12,1 ± 2,7
Mean fasting blood glucose, mmol/L	10,4 ± 3,1
Glucose level in urine, g/L	22,7± 5,1

Clinically 20% of patients had palpitation, resting tachycardia, 62,5% of patients felt dyspnea in physical exertions, 35% of patients had weakness, dizziness, visual impairment from a lying to a standing posture (orthostatic hypotension). After providing 5 examination tests for diagnosis of CAN we analyzed next results (see table 4).

Scoring of CAN in examined patients made next results (see table 5). In 15 patients CAN was absent, there were persons without clinical features of cardiovascular problems. 7 patients had early and the same amount had definite CAN, it was mainly correspondent with clinical picture, but not always. Definite and Severe CAN had 18 patients (45%).

Table 4

Positive results of the 5 tests for determination of CAN

CAN tests	DM-II patients
1) Resting tachycardia	8 (20%)
2) Standing tests for orthostatic hypotension	12 (30%)
3) Valsalva maneuver	13 (32,5%)
4) Heart rate response to deep breathing	7 (17,5%)
5) Diastolic blood pressure response to sustained handgrip	14 (35%)

Table 5

Stages of CAN in DM-II patients

Stages of CAN with score	DM-II patients
1) No CAN (score-0)	15 (37,5)
2) Early CAN (score-1). Points 0,5 – 1,5	7 (17,5)
3) Definite CAN (score-2). Points 2 - 3	11 (27,5)
4) Severe CAN (score-3). Points ≥ 3,5	7 (17,5%)

It was compare how duration of DM-II can correlate with presenting of CAN (see table 6).

Table 6

Relation between duration of disease and CAN in DM-II patients

Duration of DM-1	CAN present	CAN absent	Total
< 10 years	14 (48 %)	15 (52%)	29 (100%)
> 10 years	11 (100 %)	0 (0%)	11 (100%)
Total	25	15	40

The mean duration of the study population's Diabetes mellitus was 6 years. The range was 0 years to 23 years. 29 patients had duration of DM-II less than 10 years. Among them 48% of persons had Cardiovascular autonomic neuropathy. 15 patients had duration of DM-II more than 10 years. All these persons had Cardiovascular autonomic neuropathy. Duration of the disease over 10 years significantly increased the risk CAN in diabetic patients.

It was compare how the age of DM-II patients can correlate with presenting of CAN (see table 7).

Higher age of the patient also is a risk factor for developing the CAN. Especially higher age with long duration of DM is a significant risk factor for the CAN according to our study. The high prevalence of CAN (60%) among the patients with diabetes in our study was similar to previous observations [12, 18].

Table 7

Relation between the age and CAN in DM-1 patients

Age	CAN present	CAN absent	Total
< 50 years	17 (77.3%)	5 (22.7%)	22 (100%)
> 50 years	8 (44.4%)	10 (55.6%)	18 (100%)
Total	25	15	40

It was compare how the HbA1c level of DM-II patients can correlate with development of CAN (see table 8).

Table 8

CAN and HbA1c level in DM-II patients

Type	Mean HbA1c of non CAN patients, %	Mean HbA1c of CAN patients, %
DM-II patients	8,23 ± 2,21	14,87 ± 4,34

We can see that bad glycemic control increase risk of CAN development and also stimulate its progression.

It was compare how presenting of sensory peripheral neuropathy in DM-II patients can correlate with development of CAN (see table 9).

Table 9

Sensory peripheral neuropathy among CAN patients

Type	CAN present	Peripheral neuropathy present	Peripheral neuropathy absent
DM-II patients	25 (100%)	19 (76%)	6 (24%)

76% of CAN patients had peripheral neuropathy (sensory) but only 24% of persons without periferal neuropathy had CAN. There were no patients with periferal neuropathy and without CAN.

It was compare how presenting of Diabetic retinopathy in DM-II patients can correlate with development of CAN (see table 10).

69% of patients with Diabetic retinopathy had CAN but only 31% of persons without CAN had Diabetic retinopathy. 40% of patients

with CAN had not Diabetic retinopathy. So, Diabetic retinopathy or CAN can develop primarily, but with time they always present together.

Table 10

Diabetic retinopathy and CAN

Type	Diabetic retinopathy present	Diabetic retinopathy with CAN	Diabetic retinopathy without CAN
DM-II patients	16 (100%)	11 (69%)	5 (31%)

Conclusions

1. 85% of patients with Diabetes Mellitus type II were suffering from Cardiovascular Autonomic Neuropathy. So, CAN is a common complication of DM-II.

2. Longer duration and increasing age of Diabetes Mellitus type II are risk factors for the CAN.

3. Peripheral neuropathy is associated with higher prevalence of CAN in DM-II and CAN often develops primarily then Peripheral neuropathy manifests.

4. Strong correlation is shown between presenting of CAN and Diabetic retinopathy (69% of cases). Diabetic retinopathy or CAN can develop primarily, but with time they always present together.

5. Endocrinologist, cardiologist as well as general practitioner for easy management, economical treatment and to prevent sudden death, silent MI and cerebrovascular diseases should use these easy five tests to diagnosis of CAN in Diabetes Mellitus type II patients during their daily practice.

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Summary

Shuper V.A., Abdullah - Al - Mamun, Shuper S.V., Tedeeva M.K.
Diagnoses of cardiac autonomic neuropathy in patients with diabetes mellitus type II.

Cardiac autonomic neuropathy is one of the most often, early, serious, but overlooked complication of Diabetes Mellitus Type II. Routine investigations of diabetic patients must include easy complex tests for initial diagnosis of CAN. Prevalence of CAN in patients with DM-II shows importance of careful examination, adequate compensation of glycemic disorders for prevention of severe fatal cardiac diabetic complications.

Key words: Diabetes mellitus type II, cardiac autonomic neuropathy, diagnosis.

Резюме

Шупер В.А., Abdullah - Al - Mamun, Шупер С.В., Тедеева М.К.
Диагностика кардиальной автономной нейропатии у больных сахарным диабетом II типа.

Кардиальная автономная нейропатия является наиболее частым, ранним, тяжелым, но вовремя не диагностируемым осложнением сахарного диабета II типа. Протокол обследования больных СД II типа должен включать простые в применении, диагностически достоверные и недорогие тесты для своевременной диагностики кардиальной автономной нейропатии. Высокая частота выявления кардиальной автономной нейропатии у больных СД II типа демонстрирует необходимость проведения качественной своевременной диагностики, адекватной компенсации гликемических нарушений в целях профилактики возникновения тяжелых кардиальных осложнений сахарного диабета.

Ключевые слова: сахарный диабет II типа, кардиальная автономная нейропатия, диагностика.

Резюме

Шупер В.О., Abdullah - Al - Mamun, Шупер С.В., Тедєєва М.К.
Діагностика кардиальної автономної нейропатії у хворих на цукровий діабет II типу.

Кардиальна автономна нейропатія є найбільш частим, раннім, важким, але вчасно не діагностованим ускладненням цукрового діабету II типу. Протокол обстеження хворих на ЦД II типу повинен включати прості у використанні, діагностично достовірні та недорогі тести для своєчасної діагностики кардіальної автономної нейропатії. Висока частота виявлення кардіальної автономної нейропатії у хворих на ЦД II типу демонструє необхідність проведення якісної своєчасної діагностики, адекватної компенсації глікемічних порушень з метою профілактики виникнення важких, фатальних кардіальних ускладнень цукрового діабету.

Ключові слова: цукровий діабет II типу, кардіальна автономна нейропатія, діагностика.

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