CARDIOVASCULAR AUTONOMIC NEUROPATHY IN DIABETES MELLITUS

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Acknowledgement: Research supported from CNCSIS project number 1277 of Ministry of Education
Abstract

Diabetes mellitus (DM) is a disease of modern world, with a great impact on the life of the affected individual. Autonomic neuropathy (AN), also called visceral neuropathy is a disease of the autonomic nervous system affecting mostly the internal organs. The diagnosis of AN can be made in early stages, and is called sub-clinical neuropathy. Cardiovascular autonomic neuropathy (CAN) correlates with a lot of signs and symptoms, which are more or less specific. CAN is associated with poor prognosis and may result in severe symptomatic diseases, but is also associated with silent ischemia. In conclusion, CAN is a very important complication of both type 1 and type 2 diabetes which can be early diagnosed by some specific test and should be taken into account in all the cases, even the asymptomatic ones.

Rezumat

Diabetul zaharat este o boală a lumii moderne, cu un impact deosebit aprovieții individului afectat. Neuropatia vegetativă sau autonomă este o suferință a sistemului nervos vegetativ, afectând în special organele interne. Diagnosticul neuropatiei vegetative se poate face încă din stadiile precoce de boală, când vorbim de neuropatia sub-clinică. Neuropatia vegetativă cardiovasculară (NVC) se corelează cu o paletă largă de semne și simptome mai mult sau mai puțin specifice. Se asociază, de asemenea, cu un prognostic mai prost al diabetului zaharat și cu simptome cardiovasculare severe, dar și cu episoade de ischemie miocardică silențioasă. În concluzie, NVC este o complicație redutabilă a diabetului zaharat atât de tio 1 cât și de tip 2, ce poate fi diagnosticată precoce prin teste specifice care ar trebui considerate la toți pacienții, chiar și la cei asimptomatici.
Diabetes mellitus (DM) is a disease of modern world, with a great impact on the life of the affected individual, regarding the quality of life, work capacity, morbidity and mortality. On the other hand, DM is a chronic disease which requires treatment on a lifetime basis, the individual and global costs being also important. WHO showed that for one diabetic patient there were spent 13,000 dollars in 2002, comparing with a non-diabetic patient were the costs were around 2000 dollars (1). In 2006 there were 264 million diabetics all over the world (1, 2); in 2005 there were 20.8 million persons with DM in USA and 54 billions with pre-diabetes. In Europe, the number of the persons affected by DM differs from region to region but is continually growing (1, 2, 3).

The American Diabetes Association reported in 2009 that there are 23.6 million children and adults in the United States - 7.8% of the population, who have diabetes. While an estimated 17.9 million in the US alone have been diagnosed with diabetes, nearly one in four (5.7 million) diabetics are unaware that they have the disease (1).

Autonomic neuropathy (AN), also called visceral neuropathy is a disease of the autonomic nervous system affecting mostly the internal organs such as the bladder muscles, the cardiovascular system, the digestive tract, and the genital organs. These nerves are not under a conscious control and function automatically. Most commonly, autonomic neuropathy is seen in persons with long-standing diabetes mellitus type 1 and 2. AN develops slowly and without significant symptoms at the beginning, and the prevalence varies widely with the study methods and end-points, reaching 100% in hospitalized patients in some studies (2, 3).

It is very important to remember that the diagnosis of AN can be made in early stages, called sub-clinical neuropathy, which are after the first year from the diagnosis for DM type 2 and after the first 3 years for DM type 1. The most important etiopathogenetic factors involved are: the gender (females are more affected than the males), a higher body mass index, the age, and a poor glycemic control. From the diabetic patients with symptomatic AN, 25 to 50% are prone to die in the next 5 to 10 years, which represents another reason for the early diagnosis and treatment of those complications (2, 3).

The main clinical signs and symptoms of autonomic neuropathy in DM are: abnormal changes in pupillary diameter, Argyll-Robertson pupil; hypoglycemic episodes without symptoms; cardiovascular signs and symptoms of AN include: orthostatic
hypotension, abnormal heart rate variability (HRV), abnormal control of heart rate (expressed by impaired effort adaptation and nocturnal tachycardia), cardiac denervation syndrome; gastrointestinal signs and symptoms are: dysphagia, abdominal pain, nausea, vomiting, malabsorption, fecal incontinence, diarrhea and/or constipation (2,3,4); neurological signs: symmetrical anhidrotic areas, hyperhidrosis; genitourinary signs: erectile dysfunction, retrograde ejaculation, neurogenic bladder. Differential diagnosis involves a lot of diseases and syndromes like: idiopathic orthostatic hypotension, Shy-Drager syndrome, hypopituitarism, pheochromocytoma, Chagas disease, amyloidosis, hypovolemia of different causes, insulin adverse effects, other drugs adverse effects, alcoholic neuropathy, heart failure, diarrhea and constipation of various causes, erectile dysfunction of other causes (organic or psychological)(4, 5, 6).

Diabetes has a great influence on the prevalence of atherosclerosis and coronary heart disease, and also increases the risk of heart failure. Patients with diabetes are two to five times more likely to develop heart failure than those without diabetes. Diabetic cardiomyopathy means that in diabetic patients there is a direct alteration in myocardial function, but the exact prevalence, nature and cause of cardiac dysfunction is still unclear because there are other factors common in diabetes, such as hypertension, coronary atherosclerosis and microvascular dysfunction, which can independently impair myocardial performance (5, 7, 8, 9). Possible contributors to diabetic cardiomyopathy are: collagen accumulation leading to decreased myocardial compliance, diastolic dysfunction due to the accumulation of advanced glycosylation end product-modified extracellular matrix proteins, direct effect of altered energy substrate supply and utilization, abnormal myocardial calcium handling, endothelial dysfunction, deposition of intramyocardial fat, cardiac autonomic neuropathy and genetic abnormalities (8, 9, 10).

Cardiovascular autonomic neuropathy (CAN) correlates with a lot of signs and symptoms, as we already stated above, which are more or less specific, like:

- Orthostatic hypotension, defined as fall of systolic BP over 30 mmHg and diastolic BP over 10 mmHg in response to a postural change from supine to standing. Orthostatic hypotension may be completely asymptomatic, or symptomatic, when it can be confused with hypoglycemia (6, 7, 11, 12).
- Imbalanced effort adaptation occurs by reducing the response in heart rate and blood pressure with incomplete increasing in cardiac output during exercise.
- Increased cardiovascular instability intra and post surgery. Perioperative cardiovascular morbidity and mortality are increased 2 to 3 fold in patients with diabetes (6).
- Tachycardia / bradycardia. Resting tachycardia and a fixed heart rate are characteristic late findings in DM patients with vagal impairment, as opposed to HRV which occurs earlier but is asymptomatic. There is also a syndrome called postural tachycardia syndrome with obscure pathogenesis. Some patients have paradoxical bradycardia on standing.
- Silent myocardial ischemia; more frequent than in non-diabetic patients, myocardial infarction, lower survival rates post myocardial infarction (5, 6). This problem is reported in 17% for type 1 DM and 22% for type 2 DM, but in fact the percents are influenced by the study methodology (4). The impact on mortality is important: a five years meta-analysis showed a significant lower mortality in patients with DM and normal HRV compared with DM patients with abnormal HRV (4).
- Cardiac denervation syndrome;

The most analyzed signs to asses CAN are the following:
- abnormal circadian pattern of the blood pressure (BP), with increased BP at night;
- the lack of beat to beat RR variability in deep inspiration, with the prevalence increasing with disease duration (from 1.6% at 5 years to 12% at 9 years) (5);
- resting tachycardia; postural or orthostatic tachycardia (postural tachycardia syndrome);
- long corrected QT with increased risk for sudden death and cardiac arrhythmias;
- standardized stress testing for silent ischemia (12, 13, 14);
A large number of studies (6, 15, 16, 17, 18) compared the prevalence of silent ischemia in diabetic patients with CAN compared with diabetic patients without CAN. The presence of silent ischemia was assessed mainly with standardized stress testing. In some studies (6, 19) there is a significant amount of silent ischemic episodes in diabetic subjects with CAN.

The ECGs of diabetic patients with chest pain and diabetes mellitus there is a delay in pain perception, from the moment of significant ST depression, over 1 mm, to the moment in which the patient feel the pain; this phenomenon is present in subjects with associated CAN. They are exposed to an increased risk because they will perform effort despite the presence of myocardial ischemia, as they don’t feel any pain, so the risk of complications is more important. The explanation for the silent ischemia is the presence of CAN secondary to DM, the presence of CAN secondary to coronary heart disease, or both (4, 6).

In Framingham study, unrecognized myocardial infarction rate was 39% in DM patients and 22% in non-diabetic patients, but the difference wasn’t statistical significant. The mechanisms of silent myocardial ischemia depend on many factors and are only partially explained even today (6, 20).

The alterations in pain perception, insufficient ischemia to induce pain, afferent fibers dysfunction, may be possible explanations (6). A large study entitled Detection of Ischemia in Asymptomatic Diabetics (DIAD) (21), realized in a group of more than 1000 patients with type 2 diabetes mellitus, showed that the presence of autonomic dysfunction was an significant predictor for ischemic episodes. All the studies performed on this matter underline the importance of closer surveillance of DM patients with cardiac autonomic dysfunction, and on the other hand the importance of investigating the presence of CAN, as an major factor in cardiovascular risk stratification (4, 8, 21, 22).

Some particular clinical aspects in DM patients with CAN are: lack of symptoms, cough, nausea, dyspnea, and asthenia. Those symptoms, if there are sudden, in a DM patient should lead to ECG registration which may or may not confirm the diagnosis of acute coronary syndrome (5, 23).

Effort intolerance is a frequent finding in DM patients with CAN via reduction in cardiac response to physical exercise (insufficient increasing of heart rate and blood
pressure, with concomitant decrease in cardiac output). Diabetic patients with CAN should be tested for cardiac stress before undertaking an rehabilitation program with physical exercise. Patients with CAN should rely on their perceived exertion not on heart rate, to avoid hazardous and dangerous levels of exercise intensity. Exercise test is not routinely used but may be useful in DM with longer disease duration, with associated cardiovascular risk factors and known CAN. (6, 8)

In cardiac denervation syndrome, there is a reduced appreciation for ischemic pain, which may delay the treatment both in chronic cases with silent ischemia and in acute coronary syndromes without pain.

The evaluation of CAN includes: spectral analysis of heart rate variation during 24 hours and during deep breath, resting heart rate, heart rate ratio with standing and Valsalva, blood pressure in standing, 24 hours blood pressure monitoring, diastolic blood pressure during physical exercise; on 24 hours ECG registration and heart rate variability analysis there are some parameters which are more frequently used: LF (low frequency) which reflects sympathetic activity and is lower than normal in CAN, HF (high frequency), which reflects parasympathetic activity and LF/HF rate which reflects sympathetic / vagal. Therapeutic options are: a good glycemic control in all DM patients, and medications such as beta blockers (24, 25, 26).

The last decades have witnessed the recognition of a significant relationship between the autonomic nervous system and cardiovascular mortality, including sudden cardiac death. Evidence for an association between lethal arrhythmias and signs of either increased sympathetic or reduced vagal activity has encouraged the development of quantitative markers of autonomic activity. Heart rate variability (HRV) represents one of them. Recognition of these problems led the European Society of Cardiology and the North American Society of Pacing and Electrophysiology to constitute a Task Force charged with the responsibility of developing appropriate standards (24). There are time-domain and frequency-domain items to be measured for assessing HRV in general. In neuropathy associated with diabetes mellitus, characterized by alteration of small nerve fibres, a reduction in time-domain parameters of HRV seems not only to carry negative prognostic value but also to precede the clinical expression of autonomic neuropathy. In diabetic patients without evidence of autonomic neuropathy, reduction of the absolute
power of LF and HF during controlled conditions was also reported. However, when the LF/HF ratio was considered or when LF and HF were analyzed in normalized units, no significant difference was present. Thus, the initial manifestation of this neuropathy is likely to involve both efferent limbs of the autonomic nervous system (24, 25, 27).

In conclusion, CAN is a very important complication of both type 1 and type 2 diabetes which can be early diagnosed by some specific test and should be taken into account in all the cases, even the asymptomatic ones.
References

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