SUMMARY

Diabetic autonomic neuropathy is a common and serious complication of diabetes. In its course, it can affect any organ in the body and result in a variety of symptoms and signs. Unfortunately, it is often recognized too late and then it can have serious consequences for patient health and even life. With the help of simple cardiovascular autonomic tests, autonomic neuropathy can be diagnosed already in the asymptomatic phase. Strict blood glucose control is still the only causal therapy aimed at preventing, halting or slowing the progression of diabetic autonomic neuropathy. Symptomatic treatment consists of simple measures and lifestyle changes and, in severe cases, medication therapy may be needed.

INTRODUCTION

Diabetic autonomic neuropathy (DAN) is the most neglected, yet one of the most serious complications of diabetes. It is a form of peripheral neuropathy, i.e. damage to parasympathetic and/or sympathetic nerves in people with diabetes, and excluding other causes of neuropathy.

The prevalence of DAN varies from 1% to 90% in patients with type 1 diabetes and from 20% to 73% in patients with type 2 diabetes. The great diversity of data is a result of inconsistencies in the criteria used for the diagnosis of DAN, as well as major differences in the groups of patients included in the research, particularly in relation to risk factors (e.g., patient age, sex, duration of diabetes) (1). After extensive analysis of published papers, the Consensus Panel on Diabetic Neuropathy has concluded that the prevalence of confirmed cardiovascular autonomic neuropathy (CAN) in an unselected group of patients with type 1 and type 2 diabetes is about 20%, but can be up to 65% with increasing age and diabetes duration (2).

The importance of this diabetic complication is best illustrated by the fact that the mortality rate in patients with CAN is 5-6 times higher in the period of 5-6 years than the mortality in patients with diabetes but without CAN in the same period (3). DAN results in
significant morbidity and may lead to mortality in some patients with diabetes. Longitudinal studies have shown that the 5-year mortality rates of people with CAN are 16%-50% in patients with type 1 and type 2 diabetes, most often due to sudden cardiac death. A meta-analysis of 15 studies reports a relative risk of mortality of 3.45 in patients with CAN. It is known that CAN significantly increases the risk of life-threatening arrhythmias and sudden death with the contribution from other risk factors such as hypoglycemia, drug side effects, hypokalemia, hypotension, ischemia, etc. (4,5).

Risk factors for autonomic neuropathy are age, duration of diabetes, glycemic control, microvascular complications (polyneuropathy, retinopathy, nephropathy) and other factors such as hypertension, dyslipidemia, smoking, obesity and alcohol consumption. The main factor among the listed is glycemic control. The results of the Diabetes Control and Complication Trial (DCCT) showed that tight glycemic control resulted in 50% reduction of the incidence of CAN during 6.5-year follow up. This protective effect persisted for 14 years after the end of the study despite the disappearance of HbA1c differences that were reached between the groups during the randomized phase (6). Steno-2 study in patients with type 2 diabetes and microalbuminuria has shown that intensive pharmacological treatment of hypertension, hyperlipidemia and microalbuminuria together with lifestyle changes significantly diminishes not only the risk of DAN, but the risk of cardiovascular disease as well, and reduces overall diabetic patient mortality (7). Investigation results also indicate a significant correlation between DAN and microvascular disease. Diabetic nephropathy, retinopathy and polyneuropathy are considered clinical predictors for DAN, which is understandable because all diabetic microvascular complications share a common pathogenic mechanism and the same risk factors (8,9).

**PATHOGENESIS**

The etiology of diabetic neuropathy is complex and still completely unclear. Hyperglycemia leads to a number of metabolic, neurotrophic, vascular and immune changes that result in progressive damage and nerve fiber loss.

A simplified pathogenesis of diabetic neuropathy includes the following:
- increased activity of aldose reductase, resulting in the accumulation of sorbitol and fructose, and imbalance in the ratio of nicotinamide adenine dinucleotide phosphate and nicotinamide adenine dinucleotide
- increase in vascular oxidative stress with the formation of reactive oxygen species (ROS)
- creating products of glycoxygenation through hexosamine pathway, glycation of intracellular and extracellular proteins with the formation of advanced glycation end (AGE) products
- inadequate activation of protein kinase C pathway
- increased cytokine release; and
- deficit of neurotrophic factors (10,11).

Results of recent studies indicate a possible protective role of residual β-cell function in the development and incidence of microvascular complications in patients with type 1 diabetes. It is assumed that C-peptide activates Na/K channels, reduces inflammation and improves endothelial function (12). The latest researches seek to identify genes associated with a higher prevalence of DAN, but unfortunately, the results are still contradictory (13,14).

All these pathogenic mechanisms may act independently or interdependently and thus lead to the development of diabetic neuropathy by direct damage to nerve cells or indirectly through damage to vasa nervorum.

The pathophysiological changes result in degeneration of neurons, axonal degeneration with the loss of nerve fibers, demyelination and impairment of the nerve fiber regenerability. This creates an imbalance between degeneration and regeneration of nerve fibers at the expense of the degenerate ones.
Most sensitive are neurons with the longest axons. This may explain earlier affection of parasympathetic than sympathetic nerves in the course of DAN.

COURSE OF THE DISEASE

Diabetic neuropathy is a ‘length dependence’ disease resulting in affection of the neurons with the longest axons at the beginning. Vagus, the tenth cerebral nerve that is responsible for 75% of the parasympathetic activity of the body, is the longest nerve of the autonomic nervous system and because of that it is damaged early in the course of the disease. Therefore, in an early phase of DAN, we can find decreased parasympathetic activity resulting in sympathetic predominance. The sympathetic dominance lasts until the late stages of the disease when sympathetic denervation takes place. During DAN, asymptomatic (subclinical) and symptomatic phases can be recognized. Using simple cardiovascular tests, DAN can be detected already during the asymptomatic phase of the disease.

Symptomatic autonomic neuropathy can affect any organ in the body and therefore varies considerably in symptoms and signs. The famous phrase “who knows DAN knows the whole medicine” best illustrates the diversity of clinical presentations. It should be kept in mind that the symptoms of DAN occur late in the course of the disease, i.e. when significant impairment of the autonomic nervous system has already occurred.

CLINICAL PRESENTATION (SYMPTOMS AND SIGNS)

The symptoms and signs of DAN vary widely and depend on the affected organ (1,2,15,16).

Cardiovascular system (CAN)
1. loss of circadian rhythm of blood pressure (‘nondipping’)
2. resting tachycardia
3. exercise intolerance
4. intraoperative cardiovascular lability
5. ‘silent ischemia’ and ‘painless’ myocardial infarction
6. diabetic cardiomyopathy
7. arrhythmias, cardiac arrest
8. orthostatic hypotension

Gastrointestinal system
1. dysfunction of the esophagus
2. gastroparesis
3. change in gut motility (constipation, diarrhea)
4. anorectal dysfunction (fecal incontinence)

Genitourinary system
1. bladder dysfunction
2. sexual dysfunction in both sexes

Respiratory system
1. central dysregulation of breathing
2. reduced bronchial reactivity

Neurovascular system
1. sweating abnormalities (anhidrosis, hyperhidrosis, gustatory sweating)
2. changes in skin blood flow (warm skin, varicose veins, peripheral edema)

Neuroendocrine system
1. decrease or loss of signs of hypoglycemia
2. impaired counter-regulation mechanism in hypoglycemia
3. change in the formation of renin

Pupillomotor
1. pupil dysfunction

AUTONOMIC NERVOUS SYSTEM TESTING

To confirm the diagnosis of DAN, a series of tests (depending on the organic system to be tested) can be used. Because of noninvasiveness, sensitivity, specificity and standardization, a standard ‘battery’ of cardiovascular tests is used as a gold standard.
Testing is conducted using a computerized system based on heart rate variation (RR interval) measurements, during resting, deep breathing, Valsalva maneuvering and active orthostatic test. Blood pressure is measured three times in supine position and in the same way after standing up. Testing should be conducted in a quiet room, without interruption, the patient being informed about the tests that are to be performed. Test conditions should be standardized, i.e. testing should be done in the morning, fasting or at least 2 hours after a light breakfast, and the patient is specifically asked to avoid smoking, coffee and black tea consumption for at least 3 h prior to testing. Three disposable, self-adhesive ECG electrodes are applied to the chest and a breathing sensor is placed using adhesive tape. Testing begins after checking the signal on the screen of the device. Statistical data are processed by standard, vector and spectral analysis and the following parameters are obtained: coefficient of variation of RR intervals at rest; spectrum of very low frequency, low frequency and high frequency in spectral analysis; coefficient of variation of RR intervals during deep breathing; E/I ratio; 30:15 ratio; and Valsalva ratio. The results obtained are then compared with normal values adjusted for age.

The data obtained indicate mainly the function of the parasympathetic nerves, while a drop in the systolic blood pressure in orthostasis by more than 30 mm Hg provides indications of sympathetic dysfunction (17,18).

CAN could be graded regarding the results of the testing as follows:
- the presence of one abnormal finding indicates a possible CAN
- at least two abnormal findings are required to confirm the diagnosis of CAN
- the presence of orthostatic hypotension in addition to other abnormal findings indicates advanced CAN (3).

Other methods
Among other methods used to confirm the diagnosis of DAN are baroreflex sensitivity measures, quantitative sudomotor axon reflex test (known as QSART), muscle sympathetic nerve activity, dynamic pupillometry and, more rarely, direct scintigraphic analysis of cardiac sympathetic fibers using SPECT or PET scans (2,15,19,20). As the mentioned tests are often very demanding, a standard battery of cardiovascular autonomic tests is considered a surrogate for confirmation of DAN in general.

Recommendations
All patients with the symptoms and/or signs of DAN should be evaluated. As the symptoms of DAN occur in the late stages of the disease, it is even more important to make the diagnosis in asymptomatic patients. According to the American Neurological Society guidelines, screening for autonomic dysfunction should be carried out immediately after the diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes. Patients at a greater risk because of poor glycemic control, cardiovascular risk factors and with the presence of other micro- and macrovascular complications of diabetes should be tested in particular. Each patient that is about to begin any kind of intense physical activity except for vigorous walk and any patient that is going to have a surgery in general anesthesia should be tested as well (3,19,21-23).

If the patient has symptomatic DAN, after confirming the diagnosis by autonomic testing, it is necessary to do further examinations to rule out other causes of the patient’s symptoms, since DAN symptoms are not specific. It should also be borne in mind that about 10% of the patients with diabetic neuropathy in general have another cause of neuropathy other than diabetes.

DIFFERENTIAL DIAGNOSIS OF DAN
* hereditary neuropathies (with affection of the autonomic nervous system)
* metabolic diseases (amyloidosis, chronic liver
and kidney disease
* endocrine diseases (panhypopituitarism, pheochromocytoma)
* inflammatory diseases (Chagas’ disease, HIV, botulism, leprosy, Guillain-Barré syndrome)
* cardiovascular disease (syncope, idiopathic orthostatic hypotension, POTS)
* chronic dysautonomies (PAF, Shy-Dräger syndrome, autonomic dysfunction in Parkinson’s disease)
* toxic neuropathy (heavy metals, chemotherapeutic drugs – vincristine, cisplatin, paclitaxel, alcohol)
* paraneoplastic neuropathy (24).

**TREATMENT**

**Basic measures**

A long-term strict glycemic control has the most important role in preventing the appearance and progression of DAN. Intensive pharmacological treatment of other risk factors (hypertension, dyslipidemia), as well as lifestyle modifications (healthy diet, physical activity, smoking cessation) also have a favorable effect.

If the symptoms of DAN are already present, patients need to be advised about simple behavioral measures and lifestyle changes that can alleviate the symptoms (18,25):

* Orthostatic hypotension
  - getting up in gradual stages; perform physical counter-maneuvers (leg crossing, stooping, squatting); wearing elastic stockings reaching to the waist; increasing fluid and salt intake; reducing the dosage or excluding medications that may precipitate orthostatic hypotension; raising the head of the bed by 10-20° (stimulation of renin-angiotensin-aldosterone system)

* Gastroparesis
  - multiple, small meals; staying upright for half an hour after each meal; if necessary semi-liquid or liquid food; low fat/fiber diet; omission of drugs that slow gastric emptying (e.g., calcium channel blockers, GLP-1 analogs, tricyclic antidepressants)

* Constipation
  - increasing fluid intake; regular exercise; increasing intake of foods rich in fiber

* Diarrhea
  - restriction of gluten and lactose in the diet

* Loss of hypoglycemic signs
  - often self-control; recognition of some unusual symptoms (e.g., tingling in the hands or feet).

**Symptomatic treatment**

In cases of advanced, symptomatic DAN, it is sometimes necessary to use drugs. Medicines are prescribed by specialists depending on the affected organ. Unfortunately, there are currently no generally accepted guidelines for the treatment of DAN (18,25).

* Orthostatic hypotension
  - α-receptor agonist – midodrine; mineralocorticoid – 9-α-fluorohydrocortizone; somatostatin and its analogs; erythropoietin; sympathomimetic – ephedrine

* Gastroparesis
  - antiemetics – metoclopramide, domperidone; antibiotics – erythromycin; gastric electrical stimulation

* Constipation
  - osmotic laxatives – lactulose; motility or secretion stimulating laxatives – magnesium sulfate, sodium sulfate; prokinetics (dopamine antagonists) – metoclopramide

* Diarrhea
  - broad-spectrum antibiotics – erythromycin, tetracycline, ampicillin; synthetic opioids – loperamide; agonists of α-2 receptors – clonidine; somatostatin analog – octreotide

* Bladder dysfunction
  - mechanical methods (suprapubic pressure, intermittent self-catheterization); anticholinergics (detrusor hyperreflexia); parasympathomimetics (reduced contractility of the detrusor)

* Sexual dysfunction
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- 5-phosphodiesterase inhibitors; intracavernous injection; transurethral application of prostaglandins; penile implants; vaginal lubricants
* Hyperhidrosis and gustatory sweating
- anticholinergics; agonist of α-2 receptors – clonidine.

CONCLUSION

Diabetic autonomic neuropathy is a common and serious complication of diabetes. It is present in a quarter of patients with type 1 and one-third of patients with type 2 diabetes. In its course, it can affect any organ in the body and therefore result in a variety of symptoms and signs. The most common symptoms and signs are exercise intolerance, silent myocardial ischemia, orthostatic hypotension, impaired intestinal motility, bladder and erectile dysfunction, sweating disturbances and hypoglycemia unawareness. The consequences of DAN significantly affect the survival of diabetic patients and are associated with increased mortality from malignant arrhythmias and sudden cardiac death. DAN is unfortunately often recognized too late. Thanks to a standard battery of cardiovascular autonomic tests, which is the gold standard for confirming the diagnosis of CAN today, damage can be diagnosed in the asymptomatic phase. Screening testing is necessary in patients with type 1 and type 2 diabetes, especially those who have additional risk factors such as poorly controlled glycemia, other vascular disease factors, as well as other micro- and macrovascular diabetic complications.

Strict blood glucose control is still the only causal therapy that allows delaying, halting or slowing the progression of DAN. Symptomatic treatment consists of simple measures and lifestyle modifications and, in severe cases, pharmacological treatment.

REFERENCES


