CHAPTER

175

Prevention and Management of Diabetic Autonomic Neuropathy

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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 due to damage to parasympathetic and/or sympathetic nerves in people with diabetes,excluding other causes of neuropathy. It is manifested by dysfunction of one or more organ systems (e.g., cardiovascular, gastrointestinal [GI], genitourinary, sudomotor, or ocular).

The importance of this diabetic complication is best illustrated by the fact that the mortality rate in patients with Cardiac autonomic neuropathy (CAN) is 5-6 times higher in the period of 5-6years than the mortality in patients with diabetes but without CAN in the same period.[1] 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 lifethreatening arrhythmias and sudden death with the contribution from other risk factors such as hypoglycemia, drug side effects, hypokalemia,hypotension,ischemia etc.[2,3]

EPIDEMIOLOGY

Prevalence rates of DAN from several different studies exhibit a dramatic variability from as low as 7.7% for newly diagnosed patients with type 1 diabetes, when strict criteria to define CAN were used[4], to as high as 90% in potential recipients of pancreas transplant.[5] The prevalence varies 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 differencesin the groups of patients selected in research, particularly with respect to risk factors (e.g. patient age,sex, duration of diabetes).[6]

After extensive analysis of published reports, the Consensus Panel on Diabetic Neuropathy has concluded that the prevalence of confirmed cardiovascular autonomic neuropathy(CAN) in an unselected group of patients with both type 1and type 2 diabetes is about 20%, but can be up to 65%with increasing age and diabetes duration.[7]

CLINICAL MANIFESTATIONS

During the course of DAN, asymptomatic (subclinical) and symptomatic phases can be recognized. Using simple cardiovascular tests, DAN can be detected early during the asymptomatic phase of the disease.Vagus nerve (the longest of the autonomic nerves) accounts for 75% of all parasympathetic activity[8] and DAN, being a length dependent disease, manifests first in longer nerves. That's why even early effects of DAN are widespread in the form of decreased parasympathetic activity and sympathetic predominance. The sympathetic dominance lasts until the late stage of the disease when sympathetic denervation takes place. It is this phase when symptoms of DAN are apparent.

The symptoms and signs of DAN vary widely and depend on the affected organ[6,7,9]

Metabolic

1. Hypoglycemia unawareness
2. Hypoglycemia associated autonomic failure

Cardiovascular system (CAN)

1. Loss of circadian rhythm of blood pressure ('non-dipping')
2. Resting tachycardia
3. Exercise intolerance
4. Intra-operative cardiovascular lability
5. 'Silent ischemia' and 'painless' myocardial infarction
6. Diabetic cardiomyopathy
7. Arrhythmias, sudden 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. Neurogenic bladder (diabetic cystopathy)
2. Erectile dysfunction
3. Retrograde ejaculation
4. Female sexual dysfunction (e.g. loss of vaginal lubrication)

Respiratory system

1. Central dysregulation of breathing
2. Reduced bronchial reactivity

Table 1: Differential Diagnosis: Diabetic autonomic neuropathy
Hereditary neuropathies
Metabolic diseases (amyloidosis, chronic liver and kidney disease)
Endocrine diseases (panhypopituitarism, pheochromocytoma)
Inflammatory diseases (Chagas' disease, HIV, botulism, leprosy, Guillain-Barre syndrome)
Cardiovascular disease (syncope, idiopathic orthostatic hypotension, POTS)
Chronic dysautonomies (Shy-Drager syndrome, autonomic dysfunction in Parkinson disease)
Toxic(heavy metals, alcohol, chemotherapy-vincristine, cisplatin, paclitaxel)
Paraneoplastic neuropathy
Drugs (Vasodilators, sympathetic blockers, diuretic induced hypovolemia, insulin therapy)

Sudomotor

1. Hyperhydrosis of upper limbs
2. Gustatory sweating
3. Anhidrosis of lower limbs, dry skin
4. Heat intolerance
5. Changes in skin blood flow (warm skin, varicose veins, peripheral edema)

Pupillomotor

1. Pupil dysfunction (decreased diameter of dark adapted pupil)
2. Argyll-Robertson pupil

DIAGNOSIS

The diagnosis of diabetic autonomic neuropathy is one of exclusion, and many other causes of autonomic dysfunction should first be ruled out (Table 1). It should also be borne in mind that even about 10% of symptomatic DAN patients in general have another cause of neuropathy other than diabetes.

The clinician should take a careful history, asking about diabetes, cancer,drug use, alcohol use, HIV exposure, and familyhistory of familial amyloidosis.

Patients should be asked whether they have traveled to South America, where they might have been exposed to Trypanosoma cruzi, the cause of Chagas disease. Serologic testing for antibodies to this organism may be valuable.

Testing the norepinephrine response to standing may help identify the cause of idiopathic orthostatic hypotension. Basal valuesand the response to standing are normal in diabetic autonomic neuropathy; whereas are severelyreduced in multiple system atrophy or idiopathic orthostatic hypotension and impaired in Shy-Drager syndrome.

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. Cardiovascular autonomic neuropathy (CAN) is the most clinically important and well-studied form of DAN due to its association with a variety of adverse outcomes including cardiovascular deaths. Also because of noninvasiveness, sensitivity, specificity and standardization, a standard 'battery' of cardiovascular tests (Table 2) is used as gold standard.[10]

CAN could be graded regarding the results of the testing as follows:

- Presence of one abnormal finding indicates a possible CAN
- Atleast two abnormal findings are required to confirm the diagnosis of CAN
- Presence of orthostatic hypotension in addition to other abnormal findings indicates Advanced CAN[1]

Other Methods

Among other methods used to confirm the diagnosisof DAN are Baroreflex sensitivity measures, Quantitative sudomotor axon reflex test (QSART), Muscle sympathetic nerve activity, Dynamic pupillometry and more rarely, direct scintigraphic analysis of cardiac sympathetic fibers using SPECT or PET scans.[7,11,12] As the mentioned tests are often very demanding, the standard battery of CAN tests is considered a surrogate for confirmation of DAN in general.

SPECIFIC INVESTIGATIONS

If CAN testing is abnormal, specific investigations (Table 3)depending on symptoms and organ involvement can be carried out.[10]

PREVENTION

Successful prevention of diabetic autonomic neuropathy lies in the strategy of intensive glycemic control and treating risk factors mainly. Risk factors 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 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.[13]

There has been a number of agents designed to improve the underlying pathophysiology of the the disorder rather than for symptomatic relief. Of the proposed mechanisms that underlie the diabetes induced damage to peripheral nerve, two are linked to 'oxidative stress'. These include advanced glycosylation end product(AGEs) and the accumulation of sorbitol. There have been no clinical

Table 2: Diagnostic tests for cardiovascular autonomic neuropathy [10]

Resting heart rate > 100 beats/minute is abnormal
Beat-to-beat heart rate variation The patient should abstain from drinking coffee overnight Test should not be performed after overnight hypoglycemic episodes When the patient lies supine and breathes 6 times per minute, a difference in heart rate less than 10 beats/minute is abnormal An expiration:inspiration R-R ratio > 1.17 is abnormal (age dependent index)*
Heart rate response to standing The R-R interval is measured at beats 15 and 30 after the patient stands A 30:15 ratio of less than 1.03 is abnormal
Heart rate response to Valsalva maneuver The patient forcibly exhales into the mouthpiece of a manometer, exerting a pressure of 40 mm Hgfor 15 seconds A ratio of longest to shortest R-R interval of less than 1.2 is abnormal
Systolic blood pressure response to standing Systolic blood pressure is measured when the patient is lying down and 2 minutes after the patient stands A fall of more than 30 mm Hg is abnormal A fall of 10 to 29 mm Hg is borderline
Diastolic blood pressure response to isometric exercise The patient squeezes a handgrip dynamometer to establish his or her maximum The patient then squeezes the grip at 30% maximum for 5 minutes A rise of less than 16 mm Hg in the contralateral arm is abnormal
Electrocardiography A QTcinterval of more than 440 ms is abnormal Depressed very-low frequency peak or low-frequency peak indicate sympathetic dysfunction Depressed high-frequency peak indicates parasympathetic dysfunction Lowered low-frequency/high-frequency ratio indicates sympathetic imbalance
Neurovascular flow Noninvasive laser Doppler measures of peripheral sympathetic responses to nociception

*E/I ratio lowest normal value: 1.17 (age 20-24 y), 1.15 (25-29 y), 1.13 (30-34 y), 1.12 (35-39 y), 1.10 (40-44 y), 1.08 (45-49 y), 1.07 (50-54 y), 1.06 (55-59 y), 1.04 (60-64 y), 1.03 (65-69 y), 1.02 (70-75 y)

Table 3: Specific Investigations in DAN

Organ involved	Specific Tests
Orthostatic hypotension	Measure blood pressure standing and supine Measure catecholamines*
Cardiac	Multigated angiography (MUGA), Thallium scan 123I metaiodobenzylguanidine (MIBG) scan
Gastrointestinal	Emptying study , Barium study, Endoscopy, Manometry Fasting serum Vaso-intestinal peptide, urinary 5HIAA(5-hydroxyindoleacetic acid)* Foregut carcinoid markers: substance P and CGRP(calcitonin gene-related peptide)*
Sexual Dysfunction	Penile-brachial pressure index(less than 0.7 indicates vascular cause) Penile Doppler Sonography (evaluates a venous leak manifested as vasodilator unresponisveness) Nocturnal penile tumescence (Normal study & intact morning erection: psychogenic) Testosterone, Prolactin assay*, Thyroid function test
Bladder	Cystometrogram Postvoiding sonography (Post-void Residual volume>150 ml indicates cystopathy)
Sudomotor	Quantitative sudomotor axon reflex, Sweat test,Skin blood flow

*consider on clinical suspicion only

trial of AGE in patients with diabetic neuropathy. Aldose reductase inhibitor(ARI) have been used in a number of trials over the past 30 years, which demonstrated an improvement in sensory and motor conduction velocity(CV) compare to placebo in some RCT.[25]

Subsequent large, multicenter studies of others ARI, including tolrestat, ponalrestat, epalrestat, zenarestat and ranirestat did not demonstrate a convincing clinical efficacy.

Recombinant human nerve growth factor (rhNGF) has been the subject of several trials. A phase II trial of rhNGF over six months showed preliminary evidence of efficacy in patient with diabetic neuropathy.[26]

C-peptide replacement therapy in patients with type 1 diabetes with short term use had early beneficial effects on sensory nerve conduction studies and some measure of sensory function.[27]

Dietary supplementation with myoinositol over 6 months

improve NCSs in rats, but no definitive clinical or electrophysiologic benefits were seen in human trials.[28]

Others vitamine like thiamine, B12, and pantothenic acid, were ineffective when performed as controlled clinical trials.[29]

As all diabetic microvascular complications share a common pathogenic mechanism and same risk factors; diabetic nephropathy, retinopathy and polyneuropathy are considered clinical predictors for DAN. Screening and management aimed at these complications play a pivotal role in DAN prevention as well.[15,16]

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.[14]

Use of antioxidants [20]and ACE inhibitors [21] along with management of risk factors, hyperglycemia reduce the odds ratio for autonomic neuropathy to 0.32.

It has been shown in DIGAMI study that mortality is a function of loss of beat-to-beat variability with myocardial infarction which can be reduced by 33% with acute administration of insulin.[22]

Kendall and coworkers[23] reported that successful pancreatic transplantation improves epinephrine response and normalizes hypoglycemia symptom recognition in patients with longstanding diabetes and established autonomic neuropathy.

Buerger's group[24] showed a reversible metabolic component in patients with early cardiac autonomic neuropathy in diabetes.

SCREENING

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. Clinician should repeat testing yearly if CAN testing comes normal.[1,11,17]

Every patient who 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 also be tested as well.[18]

TREATMENT

Basic measures

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[19]:

*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 e.g. thiazides, beta blockers, phenothiazines, tricyclic antidepressants etc;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)

  Modify insulin dosage & timing (Even when mild, gastroparesis interferes with nutrient delivery to the small bowel, disrupting the relationship between glucose absorption and exogenous insulin administration. This may result in wide swings of glucose levels, unexpected episodes of postprandial hypoglycemia, and apparent "brittle diabetes.").

- Constipation

  Rule out other causes such as hypothyroidism,drug effects e.g. amitriptyline or calcium channel blockers and colonic carcinoma by fecal occult blood test.

  Increased fluid intake; regular exercise;increased 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); higher target plasma glucose level

- Bladder dysfunction

  Patients are instructed to palpate their bladder and to try to urinate when it is full. If they are unable to start urination, they should massage or press the abdomen just above the pubic bone (Credé maneuver) to start the flow.

- Sexual dysfunction

  Avoidance of alcohol and smoking, cease taking medications known to cause erectile dysfunction e.g. beta-blockers, thiazides, phenothiazines, tricyclic antidepressants, spironolactone, fibrates, marijuana etc.

- Anhidrosis of lower limbs & gustatory sweating

  Foot care, Avoid particular inciting food if present in case of gustatory sweating.

Symptomatic treatment: Pharmacological therapy

In cases of advanced, symptomatic DAN, it is sometimes

necessary to use drugs which should be prescribed by specialists depending on the affected organ. Unfortunately, there are currently no generally accepted guidelines for the treatment of DAN.[19]

- Orthostatic hypotension

  Central α-2 agonist- clonidine (0.1-0.5 mg bedtime); mineralocorticoid – 9 alpha-fludrocortisone (0.5-2 mg/day); somatostatin analog-octreotide.

- Gastroparesis

  Antiemetics – metoclopramide, domperidone(10 mg 30-60 mins before meals and bedtime); levosulpiride(25 mg thrice daily); gastric electrical stimulation

- Constipation

  Osmotic laxatives – lactulose; motility or secretion stimulating laxatives – magnesiumsulfate, sodium sulfate

  Prokinetics (dopamine antagonists) – metoclopramide

- Diarrhea

  Broad-spectrum antibiotics –ampicillin; Metronidazole (250 mg thrice a day for atleast 3 weeks); synthetic opioids –loperamide (2 mg 4 times a day); α-2 agonist-clonidine (0.1 mg twice or thrice a day); somatostatin analog–octreotide (50 microgm thrice a day)

- Bladder dysfunction

  Mechanical methods (intermittent self-catheterization);

  Anticholinergics (in detrusor hyperreflexia); parasympathomimetics (in reduced contractility of the detrusor)-Bethanechol 10 mg four times a day

  α-1blocker- Doxazosin(1-2 mg 2-3 times a day) relaxes sphincter

- Sexual dysfunction

  5-phosphodiesterase inhibitors- Sildenafil (50 mg 1 hr before sexual activity,once only per day); intracavernous injection of vasodilator; transurethral application of prostaglandins

  Penile implants; vacuum devices (in vascular cause of erectile dysfunction)

  Vaginal lubricants in females

- Hyperhidrosis and gustatory sweating

  Anticholinergics; agonist of α-2 receptors – clonidine.

CONCLUSION

Diabetic autonomic neuropathy is a common and serious complication of diabetes, presenting most commonly as 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 used as gold standard screening tests in diabetic patients,especially in those who have additional riskfactors such as poorly controlled glycemia, vascular risk factors,other microvascular complications; DAN can be detected early. Strict blood glucose control is still the only major therapy that allows delaying, halting or slowing theprogression of DAN. Symptomatic treatment consistsof simple measures and lifestyle modifications and insevere cases, pharmacological treatment.

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