Diabetic autonomic neuropathy of the gastrointestinal tract – etiopathogenesis, diagnosis, treatment and complications

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▌Abstract

Introduction. Late complications of diabetes mellitus are a serious challenge for physicians treating diabetic patients. Micro- and macro-angiopathic changes are of the most severe sequels. However, it should be remembered that the effects of long-term diabetes are also associated with changes in the peripheral nervous system. One of the complications most troublesome for patients is diabetic autonomic neuropathy of the gastrointestinal (GI) tract.

Objective. The review article presents the pathogenesis of diabetic neuropathy of the autonomous gastrointestinal tract, and advances in the diagnosis and treatment of this disease. The study used materials in the database which demonstrate current standards of conduct, based on the principles of EBM.

Brief description of the state of knowledge. Diabetic neuropathy is one of the most common complications of diabetes mellitus. According to epidemiologists, it affects 10% to even 100% of patients with long-standing disease. Damage to the nervous fibres mainly results from hyperglycaemia, which leads to the typical symptoms of dysfunction of GI tract segments. The main additional examinations include abdominal ultrasound (US) and abdominal X-ray. In cases with oesophageal disorders accompanied by dysphagia, gastroscopy is found useful for excluding possible neoplastic lesions. The gold standard for evaluation of gastric emptying is radioisotopic scintigraphy, however it is available only in some specialistic departments. Other recommended methods include: manometry, EGG, insulin tests, NMR and expiratory tests. To date, the problem has been managed symptomatically; in special cases, surgical interventions have been required.

Conclusions. At present, a wide array of treatment options is available, including new forms of drugs and less radical surgical procedures carried out in numerous centres worldwide.

▌Key words

diabetic neuropathies, diabetes complications, diabetes mellitus, gastrointestinal autonomic neuropathy

INTRODUCTION

Diabetic neuropathy is one of the most common complications of diabetes mellitus. According to epidemiologists, GI tract diabetic neuropathy affects 10% to even 100% of patients with long-standing disease. Other statistical data reveal that the incidence of neuropathic complications of the GI tract in the diabetic population ranges from 11 – 18% of cases [1–4]. The statistical differences result predominantly from inconsistencies in the definition of such complications, and consequently underestimated data reported by diabetologists. Other causes include the lack of explicit criteria for patient`s evaluation and various degrees of diabetes control on examination [5, 6].

OBJECTIVE

This review article presents the pathogenesis of diabetic neuropathy of the autonomous gastrointestinal tract, and advances in the diagnosis and treatment of this disease. The study used the materials contained in the database demonstrsting current standards of conduct, based on the principles of EBM.

DESCRIPTION OF THE STATE OF KNOWLEDGE

Damage to the nervous fibres mainly results from hyperglycaemia that activates the polyol pathway leading to sorbitol accumulation in the neurones. The cellular fluid molality increases, so does the inflow of water, which induces oedema of and damage to the Schwann cells leading to demyelination. The excessive amounts of glucose accumulated inside the neurons are utilized by autoxidation, becoming the source of free reactive oxygen and nitrogen radicals, which to cell DNA damage. Degeneration of neurons and impaired processes of regeneration contribute to the progression of changes proportional to the disease duration. It is noteworthy that the changes mentioned above develop already during prediabetes [6]. Moreover, as far as vascularisation of nerves is concerned, enhanced glycaemia results in micro- and macro-angiopathy, which leads to impaired nutrition of nerves. Oxidative stress also triggers the immune response. In type 2 diabetes, insulin-resistance develops in association with the presence of pro-inflammatory cytokines. In type 1 diabetes, increased numbers of antibodies directed against B-cells of the islets of Langerhans are observed [7]. The most recent findings regarding diabetes-related complications, including

Journal of Pre-Clinical and Clinical Research, 2017, Vol 11, No 1
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GI neuropathy, have demonstrated a correlation between the episodes of normoglycaemic diabetic ketoacidosis (DKA) and hypertriglyceridaemia versus the severity of gastroparesis symptoms [8].

Moreover, it has also been demonstrated that colonisation with Helicobacter pylori is involved in the pathogenesis of diabetic gastroparesis. The available data reveal that the symptoms of delayed gastric emptying are likely to exacerbate after infections with EBV, CMV, VZV [9, 10]. Initially, autonomic neuropathy is asymptomatic, with time (after one year for type 2 diabetes and 2 years for type 1 diabetes, respectively) the symptoms start to develop gradually [6].

The mechanisms described above damage the nervous fibres in the region of the tract innervation, cause atrophy of the interstitial cells of Cajal and changes in the population of non-specific immune response cells [11, 12]. The disorders are accompanied by impaired secretion of motilin and ghrelin, which leads to the typical symptoms of dysfunction of the individuals GI tract segments.

Dysfunction of the oesophagus is rare, and occurs predominantly in the form of gastroesophageal reflux. Oesophageal disorders are more common in patients with accompanying retinopathy [13]. Neuropathy of the lower oesophageal sphincter increases the incidence of episodes of its reduced tone, which results in dyspeptic disorders. In single cases, patients are likely to develop dysphagia [6,14].

The common symptoms that patients present with, such as nausea, flatulence, feeling of fullness, particularly after meals, are evidence of advanced neuropathy [15,16]. Diabetic gastroparesis is associated with delayed gastric emptying, which induces troublesome symptoms and has serious ramifications. For physicians, the changeability of glycaemia is of extreme importance as it hinders the optimal therapy and prevents appropriate control of diabetes. It becomes a vicious circle – poor control of glycaemia, especially chronic hyperglycaemia, increases neuropathy [6], which is accompanied by pseudodyslipidaemia, i.e. increased serum levels of lipids resulting from delayed gastric emptying and not from actual metabolic disorders. Due to the above process, hypolipemizing treatment applied can be inadequate in some cases [17].

Furthermore, epigastric pain sensations are relatively common, but it should be remembered that they could not be dominant. When accompanied by peritoneal symptoms, their cause should be identified as such in patients and can be related to ketoacidosis (except for organic disorders), and therefore require metabolic correction rather than surgical interventions.

Every 5th patient develops periodically diabetic diarrhoea (in extreme cases, several defecations a day), which results from impaired vegetative innervation of the intestines. In patients with type 1 diabetes, it should be noted that diarrhoeal episodes can be induced by celiac disease. Dysfunction of the colon manifests as constipations, excessive mucous secretion, or faecal incontinence (albeit only in the most severe cases) [18, 19].

Biliary tract disorders are extremely rare and predominantly asymptomatic. Occasionally, bile retention in the gall bladder with possible formation of gallstones can be observed.

The diagnosis of diabetic autonomic neuropathy should be started with accurate history taking (including past glycaemias determined during home measurements), physical examination and basic laboratory tests, i.e. blood tests, levels of electrolytes, urea, creatinine, uric acid, hepatic enzymes, inflammatory parameters, and urine analysis. In patients with hyperglycaemia > 300 mg/dl and suspected ketoacidosis, arterial blood gasometry, should be performed.

Since the symptoms accompanying impaired innervation of the GI tract are non-specific, a differential diagnosis is required. The main additional examinations include abdominal ultrasound (US) and abdominal X-ray. In cases with oesophageal disorders accompanied by dysphagia, gastroscopy is found to be useful for excluding possible neoplastic lesions.

Diabetic gastroparesis should be suspected when patients with dyspeptic symptoms additionally report episodes of severe hypoglycaemia between the administration of short-acting insulin and meals [20]. According to the available study findings regarding the 24-hour monitoring of glycaemia, the time of reaching maximum concentration of glucose in blood in this group of patients is 20-fold longer, which is the cause of hypoglycaemia [21, 22].

The gold standard for evaluation of gastric emptying is radioisotopic scintigraphy. During the preparation of patients, it is essential to maintain normoglycaemia for 3–4 hours before and during the examination, and to discontinue prokinetic drugs for 72 hours. On examination, patients receive a radioisotope meal, whose activity is assessed using a gamma camera. The ongoing studies focus on a standardized meal, which should enable even more accurate evaluation of motor activity. Somasundaram et al. have suggested a gluten-free vegan meal for patients with dietary restrictions. Their findings are promising [23, 24, 25]. Despite its accuracy and conditions similar to the physiological findings, their diagnostic examination is not commonly used due to considerable costs. The other recommended methods include: manometry, EGG, insulin tests, NMR and expiratory tests assessing the content of labelled CO_2 in the expired air, which corresponds to the rate of gastric emptying[26]. The majority of procedures evaluating gastroparesis are not widely available, which results in diagnostic difficulties and delayed institution of effective therapy.

The major issue in the treatment of diabetic autonomic neuropathy is dietary management. The diet should be based on low-fat meals with the dietary fibre in its dissolved form. Moreover, supplementation with vitamins, micro- and macro-elements and hydration of patients are essential. Spicy, fatty foods, raw fruits and vegetables and carbonated beverages should be excluded. If the symptoms are mild, foods are administered orally without any changes in their consistency. If, however, the symptoms do not allow the ingestion of solid foods, mixed pulps should be prepared.

Meals should be consumed 4–5 times a day at regular intervals and in small amounts. The intake of additional amounts of liquids is recommended during each meal [27, 28, 29, 30].

Another crucial element of the symptomatic treatment of autonomic neuropathy is the effective control of glycaemia, because persistent levels of glucose above 200 mg/dl lead to the progression of changes. Moreover, hyperglycaemia weakens the efficacy of the prokinetics drugs used symptomatically in this disease [31].

While choosing the therapy, unfavourable effects of GLP1 agonists should be considered as they delay gastric emptying.

Whenever diet modifications and optimisation of diabetes treatment are found ineffective, symptomatic pharmacotherapy

should be initiated, although the most recent data suggest more cautious use of prokinetics due to their side-effects. However, they are still considered important as they are widely available and inexpensive [32].

The first group described in the presented study consists of dopamine receptor antagonists: metoclopramide, domperidone, itopride. The oldest drug is metoclopramide, which is administered orally, or intravenously in severe cases. The test dose is 2mg SC followed by 5-0 mg PO, twice a day [33]. Nasal sprays have also become available, the which efficacy of which is mainly demonstrated in women; in male patients, no significant effects were observed [34, 35].

Once metoclopramide is ineffective, domperidone can be applied, which is a newer and more effective drug. Nevertheless, due to its severe cardiac side-effects in the form of arrhythmias, the use of domperidone is limited. Its oral dose is 10 mg 3x/day and max 20 mg 3x/day in resistant cases [36].

Itopride is a drug acting selectively on the upper GI tract. Its combination with proton pump inhibitors was found to result in excellent effects [37].

The applications of another drug, cisapride, which is a 5HT4 receptor agonist, are limited due to cardiac complications and interactions with the drugs metabolised by P450–3A4 isoenzyme [38].

Among antibiotics, macrolides exhibit the properties of motilin receptor agonists. Two of them are used, i.e. erythromycin, effective intravenously at a dose of 40 mg-250 mg 3×/day, and azithromycin at a dose of 250 mg 3×/day; the latter is considered to be safer.

In cases of intensified nausea and vomiting, antiemetics are temporarily used, e.g. ondansetron.

The findings reported by Chen et al. are of interest; they administered ID autological serum to patients with the symptoms of diabetic gastroparesis and observed decreased levels of motilin and gastrin in serum, as well as relief from symptoms, which gives hope for wider applications of their management in future [39].

In cases of gastroparesis resistant to standard non-invasive methods, endoscopic botulinum toxin injections were found useful. Initially, it was hoped that the procedure would permanently relieve the symptoms. At present, it is well known that such injections provide only short-term improvement of symptoms, and are particularly recommended for patients awaiting surgical procedures [40].

The majority of patients respond to non-invasive treatment. Invasive methods involve only several percent of patients.

The most popular and effective endoscopic procedure applied is gastric electrostimulation using electrodes placed on the vagus nerve branches located in the lower oesophagus. Thanks to electrical impulses, the gastric contractility can be modulated, thus decrease discomfort associated with its impaired emptying [41, 42, 43]. Moreover, positive effects were demonstrated for the therapy with stents inserted into the pyloric canal. In the population studied, nausea and vomiting were alleviated [44]. Pyloroplasty was also found to be highly effective. According to the retrospective study by Mancini et al., patients suffered less severe symptoms, their quality of life improved, and gastric emptying was accelerated.

When dietetic management, pharmacotherapy and interventional procedures fail and patients cannot be nourished due to the symptoms experienced, gastrojejunostomy is required.

Parenteral nutrition should be tailored individually for each patient and can be of long duration.

As a last resort, patients with resistant diabetic gastroparesis undergo palliative gastrectomy [45].

Alternative medicine is offered by acupuncture, which has been demonstrated to reduce flatulence, limit the symptoms of post-meal fullness and early satiety in some patients; however, acupuncture is not specific and should be considered as a form of complementary therapy [46].

Causal therapy involves the prevention of oxidative stress by the use of alpha-lipoic acid, supplementation of benfotiamine, ACEI-induced improvement of microcirculation and administration of statins [47].

CONCLUSIONS

The management of gastrointestinal disorders caused by diabetic autonomic neuropathy still presents a challenge for clinicians; therefore, many methods are being tested to verify their safety and efficacy. Further studies should determine whether the consequences of such disorders could be limited.

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