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DIABETIC GASTROINTESTINAL AUTONOMIC NEUROPATHY AND THE ROLE OF MICROCIRCULATORY DISORDER

Kizurina J.V., Kutikov D.A.
Scientific adviser: PhD, MD, Assoc. Prof. Shapoval E.V.

V. N. Karazin Kharkiv National University, Department of General and Clinical Pathology, Kharkov

Ключевые слова: сахарный диабет, качество жизни, диабетическая автономная нейропатия, диабетическая энтеропатия, микроангиопатия.

Резюме: *Статья посвящена аспектам патофизиологических механизмов развития диабетической автономной нейропатии (ДАН) гастроинтестинального тракта, как позднего осложнения диабета. Рассмотрены классификации ДАН, проявления гастроинтестинальной формы ДАН, а также оценка механизмов развития гастроинтестинальной формы ДАН.*

Keywords: diabetes mellitus, quality of life, diabetic autonomous neuropathy, diabetic enteropathy, microangiopathy.

Resume: *The article deals with aspects of pathophysiological mechanisms of formation of diabetic autonomic neuropathy (DAN) of gastrointestinal tract, as a late complication of diabetes mellitus. Classification of DAN, manifestations of DAN gastrointestinal form, as well as evaluation of mechanisms of development of DAN gastrointestinal form are reviewed.*

Relevance. According to data of the World Health Organization, the number of people with diabetes mellitus (DM) has risen from 108 million in 1980 to 422 million in 2014.

Diabetic neuropathy (DN) is one of the most common complications of diabetes mellitus. It finally lead to decline the quality of life (QoL) and disability in DM patients. Diabetic autonomic neuropathy (DAN) is particularly noteworthy. According to the definition, DAN is a combination of clinical symptoms and objectively identified and confirmed disorders of the functions of a corresponding organ or system. [5]. DAN is characterized with polysyndromal manifestations. One of the complications most troublesome for patients is DAN of the gastrointestinal tract (DGAN). Statistical data show that DGAN affects 10% to even 100% of patients with a long-standing disease [8]. Damages triggered by DAN are non-specific, therefore it is difficult to diagnose and treat them.

Purpose. To study the main characteristic of DAN and the mechanisms of microcirculation disorders in DGAN.

Tasks:

1. To perform an analysis of literature.
2. To study the classification of DAN.
3. To consider the manifestations of DGAN.
4. To analyze the mechanisms of development of microcirculation disorders.

Methods and materials. The study of microcirculation disorders in DGAN was carried out on the base of an analysis of data from literature.

Results. DN is a consequence of a widespread lesion of neurons and processes in the central (CNS) and peripheral (PNS) nervous system. The progress of neuronal death is often

Репозиторий БГМУ

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irreversible due to impairments of regeneration processes in DM. Regenerative failure likely exacerbates deficits from polyneuropathy or focal neuropathies in patients who might otherwise exhibit spontaneous improvement. The frequency of damage of the nervous system due to DM correlates with the duration and severity of illness, age of the patients, as well as the level of hyperglycemia [4, 8].

Data on the prevalence of DN vary. Numerous studies have pointed out the manifestation of DM in 3.5-6.1 % of patients whereas there have been already certain signs of DN. After 5 years, they are detected in 12.5-14.5 %, after 10 years - in 20-25 %, after 15 years - in 23-27 %, after 25 years - in 55-65 % of patients [1].

Classification. Depending on the predominant involvement of the spinal nerves in to the pathological process, DAN is classified into the peripheral neuropathy and the autonomic neuropathy [1]. V.M. Prikhozhan's classification (1973) is based on the topical principle.

Its advantages include the fact that it is taken into account the presence of the transient impairments of function or disorder of CNS and PNS. At the same time, this classification does not take into account forms of lesion that are detectable with additional paraclinical methods only. This classification distinguishes central, peripheral and visceral neuropathy [5].

According to classification of P.K. Thomas et al., sensorimotor (symmetric, focal and multifocal neuropathies) and autonomic neuropathy are detected [3].

The modern classification of DN (San-Antonio, 1998) is based on the ability of modern methods to define impaired functions of the nervous system in the absence of complaints and clinical manifestations.

P. Kemple's classification divides DAN into subclinical and clinical stages. Among others, gastrointestinal form of DAN is distinguished, DGAN is characterized with corresponding pathogenetically stipulated manifestations [7].

Manifestations. DGAN has a wide range of manifestations and occurs quite often. Neuropathic lesions can occur along the entire length of the gastrointestinal tract (GIT) and their manifestations are clinically various depending on the localization of the lesion [2].

Impairments of the microcirculation are caused by DAN, and these impairments are etiological for the manifestations of DAN. This is often associated with impaired acidity of the GIT, glucose tolerance, an imbalance of the ionic composition, as well as neurological disorders.

Mechanisms of development of microcirculation disorders. Diabetic enteropathy is a trigger for intestinal malabsorption developing itself through a progressive ionic imbalance. Subsequently, a sufficient number of different ions are not entered into the blood, that in turn leads to impaired gastric acid production (lack of Cl^-) and GIT motility (disturbance of the Na^+ / K^+ ratio). The impaired gastric acid production is the etiological component of the development of a hypoacidic condition.

The next etiological component of the development of the hypoacidic condition is hyperkalemia, that is characteristic of DM. Hyperkalemia causes an excess of extracellular K^+, that complicates the activity of the proton pump and, as a result, enhances adenosine triphosphate (ATP) deficit, which leads to local depletion and impairment of microcirculation and secretion of hydrochloric acid in the cardial part.

Репозиторий БГМУ

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Ф94

It should be noted, that there is impairment of the perception of taste (taste hypersalivation) at whole, and sweet taste in particular. The mechanism is based on a change in the taste threshold due to abovementioned problems with assimilation of nutrients and minerals. In general, functional hypoacidosis leads to digestive disorders and dysbacteriosis ("diabetic enteropathy").

A special attention should be given to microangiopathy and small vessel disease (SVD). Hyperglycemia is a trigger mechanism of SVD and microangiopathy. Hyperactivation the enzyme protein kinase-C (PK-C), which normally regulates vascular permeability, cell proliferation, synthesis of substances by the vascular basal membrane, activity of tissue growth factors (TGF), raising of TNF-Alpha, metal proteinase and C-reactive protein levels, causes damages of glycocalyx of vessel endothelium and leads to aggregation of low density lipoproteins in intima media complex, that ensures the development of SVD and microangiopathy. A further progress of neuronal impairments is connected with an increasing of amount of intra- and extravessel tissues. The increasing of amount of intravessel tissue is realized through a platelet aggregation activated by von Willebrandt factor represented on the damaged endothelium. The extravessel process is realized through oedema and polymorphic nuclear infiltration.

Impairments of the microcirculation in all organs, including GIT and the thalamus, have the same pathogenesis mentioned above. Involvement of the thalamus in the process is manifested in particular as the decreased tonus of the vagus nerve. The consequence of this is an impairment of the secretion of gastric acid and bile, as well as impaired motility of the esophagus (dysphagia), stomach (gastroparesis), intestines (diarrhea or constipation), gall bladder (atony), biliary tract (dyskinesia with a tendency to cholelithiasis).

Conclusions. For progressing DAN, the prognosis is poor. DAN is not only dramatically reduces the QoL. Being a serious risk factor for the development of late complications of DM, it leads to disability, increases the mortality, and in some cases becomes the direct cause of death.

The microcirculatory disorder has a multietiological character, including decreased gastric acidity and glucose tolerance, ionic imbalance, as well as neurological disorders. In the case of DGAN, microcirculation disorder leads to an impaired functioning of the body's systems due to the development of ischemization, metabolic disorders, dysbacteriosis, and digestive disorders in general.

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