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Review Article

Diabetic neuropathy

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ABSTRACT

Introduction: Diabetes mellitus is gradually rising in global ranks of mortality and according to the World Health Organization it is estimated to occupy the seventh place by the year 2030. Diabetic neuropathy (DN) is the most common complication of diabetes and the symmetric distal polyneuropathy is its predominant form. Currently there are several clinical classifications of DN. Etiopathogenesis is presently the object of intense research and is yet to be fully comprehended.

Aim: The purpose of this paper is to present and systematize the current state of knowledge on DN, in particular distal symmetric polyneuropathy. We hope that this would be helpful in the prevention, diagnosis and treatment of DN.

Material and methods: It was based upon the available literature, publications and materials available in the online medical databases.

Discussion: Prolonged exposure to hyperglycemia is recognized as the major mechanism and the risk factors include, among others, the degree of metabolic control of diabetes mellitus. Neuropathic symptoms result from the severity of nerve fiber damage. Nevertheless, in more than 50% of cases pain is the predominant symptom, which should encourage popularization of the use of quality of life questionnaires in diabetics. The primary and most important elements of causal treatment include the proper level of metabolic equalization, blood pressure normalization and cessation of stimulant use. Apparently the only drug influencing pathogenetic mechanisms is alpha-lipoic acid, efficiency of which has been confirmed in the ALLADYN and the SYDNEY trials.

Conclusions: In light of the current state of knowledge, recommended first line medication in the treatment of pain associated with DN includes: tricyclic antidepressant, serotonin-norepinephrine reuptake inhibitor or antiepileptic drug. If monotherapy proves ineffective, adding a second drug may be considered, then adjuvant opioid and alternatively non-pharmacological treatment. In case of lack of response to treatment, stimulation of the spinal cord can be the final intervention.

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1. Introduction

Diabetic neuropathy (DN) is the most common chronic complication of diabetes mellitus.[28] It is associated with increased morbidity, mortality and reduction of overall quality of life, and accounts for more than one quarter of treatment costs of diabetes.[10,39,42] Although in 1864 Marchal de Calvi had already proposed that peripheral nerve disorders may result from diabetes, many aspects of this disease still remain unresolved.[16] According to the World Health Organization (WHO) more than 346 million people worldwide have diabetes and it is estimated that by the year 2030 diabetes will be the seventh leading cause of death worldwide. In Poland, according to International Diabetes Federation (IDF), the prevalence estimates for diabetes in the population of 20–79 years is 9.1%, out of which 90%–95% of the cases are type 2 diabetes.[41] Alarming WHO estimates show that by the year 2025 the number of persons with diabetes is expected to increase in developing countries, including Poland, by 170%. Polish epidemiological data presented in Natpol Plus study declare the prevalence of diabetes in 5.6% of adults (1.70 million people), 0.90% of which are newly diagnosed. In this study, impaired fasting glycemia (IFG) was identified in 1.5% of the subjects, while impaired glucose tolerance (IGT) occurred in 0.6% of the subjects.[43] The incidence of diabetes is constantly increasing and has already reached epidemic proportions; thus, the prevalence of DN is escalating at an alarming rate. In the absence of a clear diagnostic criteria for DN, determination of its prevalence is extremely difficult. According to various reports, in the diabetic population, incidence of DN is in the range from 10% to 90%.[39] It is believed, that DN affects approximately 110 million people worldwide. In view of this data, it is crucial to actively diagnose symptoms of DN in populations of both type 1 and type 2 diabetic patients.[11,12]

Diabetes mellitus as a systemic disease was first described by Thomas Willis in the London journal "Medical Observations and Inquiries" in 1776. First satisfactory definition of DN was adopted in 1988 at the San Antonio conference. It was characterized as a disorder of the peripheral nervous system (somatic and/or autonomic parts), confirmed by the presence of symptoms and/or signs and/or electrophysiological changes, that occurs in the setting of diabetes mellitus, without other possible causes.[6] From a neurological perspective, peripheral neuropathy and polyneuropathy are determined by syndromes resulting from extensive damage of peripheral nerves, manifested by palsies, loss of sensation and autonomic dysfunction.[21]

2. Aim

The aim of this work is to present DN as one of the most common chronic complications of diabetes.

3. Material and methods

It was based on the available literature, publications and materials available in the online medical databases.

4. Discussion

4.1. *Etiopathogenesis*

At the forefront of most publications there is a heterogenous theory that encompasses main causative factors: metabolic and microangiopathic changes. While the primary and proven cause of DN includes a prolonged hyperglycemia, among other causative factors the role of deficiency of neuronal growth factor (NGF), neurotrophins and insulin-like growth factor (IGF-1), impaired nerve fiber regeneration, inflammation in response to autoimmune processes, and genetic background are also emphasized.[23,25,27,28,30]

Chronic hyperglycemia, that accompanies uncontrolled diabetes, which positively correlates with concentrations of glucose in peripheral nerves and lack of insulin (or its ineffective use – insulin resistance), results in excess insulin-independent glucose transport into the nerve cells.[14,30] Together with neurons, endothelial cells also belong to insulin-independent cells, in which transport of glucose into the cell takes place through facilitated diffusion. As a consequence, other insulin-independent glucose metabolic pathways are triggered (polyol, hexosamine), leading to the production of advanced glycation end products, which in turn disturbs normal metabolic processes, impairs homeostasis and in consequence, leads to abnormal oxidation-reduction potential of the nerve cell (neuron).[4] Increased concentrations of glucose, fructose and sorbitol in peripheral nerves have been demonstrated in human models, while the expected decrease in myo-inositol content has not been observed.[28,30] In summary, glucose overload in neurons activates glycolysis and induces oxidative stress, which results in damage of intracellular structures of the neuron and impairs its proper functioning.

4.2. *Risk factors*

Risk factors for DN may be divided into modifiable and non-modifiable.

Modifiable risk factors include: degree of metabolic control (hyperglycemia, hypoglycemia, episodes of ketoacidosis), presence of microalbuminuria and retinopathy, arterial hypertension, atherosclerosis, dyslipidemia, smoking habit, and alcohol overuse.[1,2,24,32,]

Whereas non-modifiable factors include male gender, advanced age, duration of diabetes, height, genetic factors.[30]

4.3. *Classification*

There are numerous categorizations and classifications of DN. In 1988 during the San Antonio conference (organized by the American Diabetes Association and American Academy of Neurology) a classification of DN as latent, diffuse and focal was adopted.[5]

Subsequently, Watkins in his work in 1993 presented an interesting classification of DN based upon its natural course. The author distinguished between gradually progressive group (sensory and autonomic neuropathies) and remissive group (mononeuropathies, radiculopathies and acute painful neuropathies).[40] Another DN classification according to Dyck