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Review Article

Diabetic neuropathy

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ARTICLE INFO

Article history:
Received 4 April 2013
Received in revised form
10 September 2013
Accepted 7 October 2013
Available online 11 October 2013

Keywords:
Diabetes
Neuropathy
Risk factors
Treatment
Microvascular complication
Polyneuropathy

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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http://dx.doi.org/10.1016/j.poamed.2013.10.001

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

is based upon the severity of the symptoms: 0 – no neuropathy, 1 – subclinical neuropathy (asymptomatic), 2 – symptomatic neuropathy, 3 – disabling neuropathy.[8]

During the 8th International Symposium on Diabetic Neuropathy in Toronto (Canada) in 2009 another classification of diabetic polyneuropathy into typical and atypical form was adopted. Typical form of diabetic polyneuropathy is a diabetic sensorimotor polyneuropathy (DSPN). Atypical form is less well-known, with suspected inflammatory cause, intercurrent painful and autonomic symptoms, and may develop at any stage of the disease. In patients with atypical form usually other chronic complications of diabetes are absent.[31]

Besides the presented classifications of diabetic polyneuropathy, in Polish literature anatomical classification of neuropathy by Taton is used, which includes detailed division in relation to central, peripheral and autonomic nervous system.[30]

In the annually updated recommendations of Polish Diabetes Association, the following classification of diabetic polyneuropathy is provided:

I) generalized (diffuse), symmetrical polyneuropathies:
   - chronic sensimotor neuropathy,
   - autonomic neuropathy,
   - acute sensory neuropathy;

II) focal and multifocal, non-symmetrical neuropathies:
   - cranial nerve neuropathy (involves cranial nerves III, IV, VI, less frequently VII),
   - spinal nerve neuropathy (thoracic and lumbar),
   - focal limb neuropathies, including nerve compression syndromes,
   - proximal motor neuropathy (amiotrophy),
   - concomitant chronic neuropathy.[42]

The presented review of classifications of DN demonstrates that, despite the existence of numerous classifications, none refers to the disease pathophysiology. Results of the Rochester Diabetic Neuropathy Study should be considered, which demonstrated that in 10% of the diabetic patients with neuropathic complications, diabetes is not the underlying cause.[9] It should be also noted that neuropathic pain occurs in approximately 6%–7% of the healthy population.[2] Thus, the final diagnosis of DN must include differentiation with other conditions, such as hypothyroidism, uremia, vitamin B12 deficiency, chronic inflammatory demyelinating polyneuropathy, carpal tunnel syndrome, and many others.[17]

4.4. *Symptoms, diagnosis and treatment*

The variation in symptoms reported by patients is closely related to the size of the damaged nerve fibers. In case of pathology of thin nerve fibers, which seem to be affected first, sensory disturbances (sense of touch, pain, temperature, sometimes allodynia), paresthesia and autonomic symptoms are the most commonly occurring. Yet, tendon reflexes and muscle strength remain normal. On the other hand, the impairment of thick nerve function is accompanied by loss of proprioception, loss of vibration sense and reduced tendon reflexes.[39]

In accordance with recommendations developed by Tesfaye, screening for neuropathy in patients with type 1 diabetes in the absence of symptoms suggesting central nervous system damage, should be conducted five years after diagnosis, while in case of type 2 diabetes, given its insidious mildly symptomatic course, immediately starting at diagnosis and annually thereafter.[31] Similar guidelines for DN screening are provided by the Polish Diabetes Association.[8]

The most common form of DN is symmetrical diabetic peripheral neuropathy (DPN), which develops as a result of long-term hyperglycemia. Frequently, in patients with DN, other diabetes related organ damages coexist, such as nephropathy and retinopathy. In more than 50% of persons with DPN, predominant symptom is pain (painful diabetic peripheral neuropathy – PDPN).[29]

The genesis of neuropathic pain is multifactorial. It has been proven that fear and anticipation of painful stimulus can serve to increase the actual experience.[19] Patients with PDPN often suffer from weight loss, erectile dysfunction, depression, anxiety and insomnia.[38]

Neuropathic pain in diabetic patients is defined as pain arising as a direct consequence of abnormalities affecting the somatosensory system.[37] In clinical practice, it is a severe, burning pain, frequently combined with allodynia, located in the distal parts of the limbs, escalating at night. Diagnosis of PDPN is made based upon medical interview and physical examination. Intensity of neuropathic pain is assessed on the Likert scale. In addition, widespread pain assessment questionnaires are used: Neuropatic Pain Symptoms Inventory, Brief Pain Inventor, Neuropathic Pain Questionnaire, or those including quality of life assessment (QoL), e.g. NeuroQol or Norfolq Quality of Life Scale.[31]

For clinical purposes, DPN was divided according to the incidence probability:

- possible – typical symptoms may be present (impaired sensation, numbness while sleeping, exquisite, severe, burning pain, particularly of the toes, feet or entire lower limbs) and/or distal symmetrical impairment of sensation; and/or loss or diminution of ankle reflex,
- probable – at least two of the following symptoms: signs of neuropathy, distal impairment of sensation, or loss or diminution of ankle reflex.
- confirmed – nerve conduction abnormalities and at least one of signs and symptoms of neuropathy,
- subclinical – nerve conduction abnormalities with no signs or symptoms of neuropathy.[31]

Slightly different diagnostic criteria for somatic polyneuropathy, based on semi-quantitative scale of the largest (++++) and smallest (−) risk, were proposed by the Polish Diabetes Association.[42]

The highest risk of diabetic polyneuropathy is in the case of abnormal neurophysiological tests (nerve conduction studies) and at least three out of four of the following elements in clinical examination:

- signs: sensory disturbances, numbness, burning, tingling, tearing, spontaneous pain, muscle cramps (particularly in

the feet and lower limbs) persistent for several months (appearing or worsening particularly at night; physical activity does not induce or exacerbate symptoms),
– symptoms: weakness, absence or asymmetry of deep tendon reflexes (knee and ankle); limitation or loss of the sense of touch (determined by the Semmes–Weinstein 10 gram monofilament), sense of vibration (assessed with a calibrated tuning fork by the Rydel–Seiffer 128 Hz, so-called tuning fork, or a biotensionmeter or a neurotensiometer), sense of pain (with the use of sterile needle, neuro-tips) and sense of temperature (with tip-therm).

Recently, in the diagnosis of DPN new diagnostic tools are used. These include biopsy of the nerve and skin, since it has been proven that there are differences in the microscopic image of the skin of a healthy and diabetic subject. These differences include reduction of the number of cutaneous nerve fibers shown by staining for the neuronal antigen PGP 9.5, in small nerve fiber neuropathy.[26] Confocal microscopy and new immunohistochemical methods were used to test non-myelinated nerves of the skin and internal organs.[15]

Confoscan, which is a variation of light microscopy and is characterized by increased contrast and resolution, was used to examine cornea, as a non-invasive and safe method. Significant thinning (reduction of density) of corneal nerve fibers was defined as the early marker of DPN.[22] Furthermore, an increase in tortuosity of corneal nerve fibers was observed in patients with diabetes, as compared with control group. Rosenberg's research team at the University of Helsinki has demonstrated a correlation between structural changes of corneal nerves, reduced corneal sensitivity and the intensity of DPN in patients with type 1 diabetes.[7] New research techniques have also shown that one of the mechanisms of acute neuropathic pain is a disorder of blood circulation in small blood vessels that supply the nerves.[20] On the basis of magnetic resonance imaging, researchers from Chicago have demonstrated the presence of structural changes in the brain of diabetic patients with chronic (present for more than a year) back pain. In 26 subjects a 5%–11% reduction in prefrontal and thalamic gray matter was found, while in the normal brain ageing processes such reduction may be up to 0.5%. Demonstrated differences are the equivalent of 10–20 years of physiological ageing processes.[3]

4.5. *Causal treatment*

The basis for the treatment of diabetic polyneuropathy is good metabolic control of diabetes, arterial hypertension, as well as smoking cessation and avoiding alcohol abuse.[42] Validity of these recommendations has been demonstrated in the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS). In patients treated with intensive functional insulin therapy (FIT) lower incidence of neuropathy has been demonstrated and in patients with clinical demonstration of neuropathy relief of symptoms was observed. In addition, in DCCT after five years of observation of two groups: the first treated with FIT (with a mean HbA1c – 7.2%) and the second treated with conventional insulin therapy (with a mean HbA1c – 9.1%), in the first group approximately 50% less cases of DN were observed.[35,36] In 1997 results of the annual observation of patients after pancreas transplantation were published, which showed that in 50% of subjects with type 1 diabetes one year after pancreatic islet cell transplantation stabilization or improvement of DPN symptoms was observed.[18] Due to the fact that a 1% increase in the HbA1c increases the risk of DPN by 10%–15%,[12] any form of achieving improved glycemic control helps to alleviate neuropathic symptoms. On the other hand however, caution is advised in excessive attempt to achieve normoglycemia, which may lead to reduced blood flow and nerve ischemia, thus enhancing pain and other symptoms associated with neuropathy. Therefore, an indicated desired blood glucose range is 90–180 mg/dL (5.0–10.0 mmol/L).

In addition to glycemic control, α-lipoic acid (ALA) appears to be the only effective drug in the treatment for DPN. This is a mitochondrially synthesized octanoic acid derivative with a potent antioxidant effect. ALA shows a hypoglycemic effect, reduces insulin degradation and insulin resistance, increases glucose metabolism and its uptake in the liver and muscles. Effectiveness of the drug was demonstrated in the ALLADYN and the SYDNEY trial, in which significant reduction of total symptom score (TSS; pain, burning, sensory disturbances) was observed already after 3 weeks of therapy vs. placebo. The optimal dose was 600 mg/day. More pronounced therapeutic effects were observed in patients who received the drug intravenously. However, the ALLADYN II trial (consisting of 24-month oral therapy of ALA) and the ALLADYN III trial did not demonstrate a significant superiority of ALA over placebo.[29]

4.6. *Symptomatic treatment*

In June 2012 latest reports on the treatment of PDPN, including algorithms for the treatment of patients with PDNP, were published. The following were recommended as a first line medication:

– tricyclic antidepressant (amitriptyline at a dose of 25–75 mg/day, imipramine at a dose of 25–75 mg/day, recommended initial dose, particularly in the elderly is 10 mg/day),
– serotonin-noradrepinephrine reuptake inhibitor (duloxetine at a dose of 60–120 mg/day),
– anticolvunsants (antiepileptics) (pregabalin 300–600 mg/day; gabapentin 900–2600 mg/day), which are ligands of $\alpha 2\sigma$ subunit of voltage-dependent calcium channels present in the central nervous system.[13]

Worth mentioning is the fact that only duloxetine and pregabalin are Food and Drug Administration of US and European Medicines Agency approved treatments of PDPN.

The choice of medication depends on comorbidities, contraindications and the economic status of the patient. When no desirable results are obtained with the use of one of the above mentioned first line medication, combination therapy with two drugs is preferred. If the pain persists, adjuvant

opioid should be added (tramadol 200–400 mg/day, oxycodone 20–80 mg/day; morphine 20–80 mg/day). The guidelines also outline topical medication – capsaicin cream (0.075%, 3–4 times per day). Non-pharmacological therapies include above all: acupuncture, infrared radiation, laser therapy, transcutaneous electrical nerve stimulation, and external muscle stimulation.[29,33,34] When all of the above mentioned treatment methods have been used, spinal cord stimulation may be indicated. The effectiveness of this method was demonstrated in a study, in which 10 patients had stimulating electrodes implanted in the epidural space. Significant improvement was reported by 8 patients, which was reflected in the visual analog scale of pain, and after completion of a 12-month study, 6 patients decided on continuation of this mode of pain management.[34]

Worth noting is the fact that the presented recommendations lack any indications for use of conventional analgesics, such as paracetamol or non-steroid anti-inflammatory drugs.

5. Conclusions

Diabetic polyneuropathy is one of the most common chronic complications of diabetes. It is a subject of ongoing clinical researches, but still no firm recommendations for the treatment of this complication have been established.

Conflict of interest

None declared.

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