CLINICAL ASPECTS OF DIABETIC NEUROPATHY

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Keywords: diabetic polyneuropathy; diabetic autonomic neuropathy; focal neuropathies; entrapment neuropathies; painful diabetic neuropathy Abstract: Approximately 30–50% of all diabetic patients are affected by neuropathy and it is the commonest form of neuropathy in the developed world. Diabetic neuropathies are among most common long-term complications of diabetes. Diabetic neuropathy (DN) is defined as the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes mellitus after the exclusion of other causes. There is now little doubt that glycaemic control and duration of diabetes are major determinants of distal symmetrical neuropathy. Distal symmetric polyneuropathy, the most common form of diabetic neuropathy, usually involves small and large nerve fibers. Small-nerve fiber neuropathy often presents with pain and loss of intraepidermal nerve fibers, but without objective signs or electrophysiologic evidence of nerve damage. The greatest risk from small-fiber neuropathy is foot ulceration and subsequent gangrene and amputation. Large-nerve fiber neuropathy affects profund sensitivity. Some patients may be completely asymptomatic, and signs may be only discovered by a detailed neurologic examination.

Cuvinte	cheie:
polineuropatia	
diabetică,	neuropatia
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neuropatii	focale,
neuropatii	de
încarcerare, neuropatia	
diabetică dureroasă	

Rezumat: Neuropatia diabetică afectează aproximativ 30–50% dintre pacienții cu diabet zaharat și este cea mai comună formă de neuropatie în țările dezvoltate. Cea mai frecventă complicație a diabetului zaharat este neuropatia. Neuropatia diabetică este definită ca prezența semnelor și/sau simptomelor de disfuncție a sistemului nervos periferic la un pacient cu diabet zaharat după ce se exclud alte cauze. Nu este nicio îndoială că determinanții majori ai neuropatiei simetrice distale sunt controlul glicemiei și durata diabetului. Polineuropatia simetrică distală, cea mai frecventă formă de neuropatie diabetică, afectează atât fibrele cu calibru mare cât și scăzut. Neuropatia de fibre cu diametru scăzut se prezintă cu durere și pierderea fibrelor nervoase intraepidermice, însă fără semne obiective sau electrofiziologice de afectare a nervilor. Cel mai mare risc al neuropatiei de fibre cu diametru scăzut este ulcerația piciorului care poate duce la gangrenă și amputație. Neuropatia de fibre cu diametru scăzut este ulcerația piciorului care neurole duce la gangrenă și amputație. Neuropatia de fibre cu diametru crescut afectează în primul rând sensibilitatea profundă. Unii pacienți pot fi complet asimptomatici dar pot să apară modificări la un examen neurologic detaliat.

SCIENTIFICAL ARTICLE OF BIBLIOGRAPHIC SYNTHESIS

DNs are among the most frequent complications of diabetes mellitus. The frequency of neurological complication in diabetes mellitus has been variably estimated in published reports. About 15% of patients with diabetes have both symptoms and signs of neuropathy, but nearly 50% have nerve conduction abnormalities. DN is the most common form of neuropathy in developed countries and is responsible for 50% to 75% of nontraumatic amputations. Foot ulceration can lead to gangrene and ultimately to limb loss. DN also has a tremendous impact on patients' quality of life predominantly by causing weakness, ataxia, and incoordination predisposing to falls and fractures (1,3,8).

Classification of Diabetic Neuropathy after Low and Suarez (7)

Symmetrical neuropathies

- Distal sensory and sensori-motor neuropathy
- Large-fiber type of diabetic neuropathy
- Small-fiber type of diabetic neuropathy
- Distal small-fiber neuropathy
- "Insulin neuropathy"

Asymmetrical neuropathies Mononeuropathy

polyradiculoneuropathy

- Mononeuropathy multiplex
- Radiculopathies
- Lumbar plexopathy or radiculoplexopathy
- Chronic inflammatory demyelinating polyradiculoneuropathy

A classification system by Thomas combines both anatomy and pathophysiology and is presented below with a few modifications: (10)

- Hyperglycemic neuropathy (acute)
- Generalized symmetric polyneuropathies
- Sensory
- Sensorimotor (chronic, symmetric)
- Autonomic
- Focal and multifocal neuropathies
- Cranial
- Proximal motor (amyotrophy)
- Thoracic or lumbar radiculopathies
- Focal limb (entrapment neuropathies)
- Superimposed chronic inflammatory demyelinating

⁻ Chronic inflammatory demyelinating

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polyneuropathy

Chronic Distal Symmetrical Neuropathy is probably the most common variety of diabetic neuropathy. Is an exclusion diagnosis. It can only be made after careful clinical investigation and after the exclusion of other causes, chronic inflammatory demyelinating polyneuropathy, vitamin B12 deficiency, monoclonal gammapathy, hypothyroidism, uremia. In type 1 diabetes mellitus, distal polyneuropathy becomes symptomatic after many years of chronic prolonged hyperglycemia. Conversely, in type 2, it may present after only a few years of known poor glycemic control. Patients with type 2 diabetes mellitus may sometimes already have neuropathy at the time of diagnosis (6,9).

Most frequently, DPN is a mixed sensorimotor neuropathy. Sensory symptoms are more prominent than motor symptoms and usually involve the lower limbs. When sensory symptoms reach the knees, hands develop similar symptoms, progressing proximally. Anterior aspect of the trunk and vertex of the head may be affected at a very late stage. Sensory symptoms include pain, paresthesiae, hyperesthesia, and allodynia wherein patients report pain with nonpainful stimuli such as touch, contact with bedclothes. Patients may experience negative symptoms such as hypo/analgesia, hypo/anestesia, reduction of thermal, vibration and pressure sensation, reduction of peripheral reflexes. Diabetic neuropathic pain is characteristically more severe at night, and often prevents sleep. A curious feature of the neuropathic foot is that both numbness and pain may occur, the so called "painful, painless" leg (1, 9, 13, 14).

Muscle strength is usually normal during the early course of the disease, although mild weakness may be found in toe extensors. With progressive disease there is significant generalized muscular wasting, particularly in the small muscles of the hand and feet. Trophic changes in the form of deep ulcerations and neuropathic degeneration of the joints (Charcot joints) are seen in the most severe cases, due to sensory lost and repetitive injury (1,8,13)

The American Diabetes Association recommends that all patients with type 2 diabetes mellitus be screened for DN at diagnosis, and all patients with type 1 diabetes mellitus be screened 5 years after diagnosis. Screening should be repeated annually and must include sensory examination of the feet and ankle reflexes (6).

Small-fiber neuropathy is a distinct entity usually within the context of young type 1 patients. A prominent feature of this syndrome is neuropathic pain. Paraesthesae is also often experienced and allodinia may be present. The pinprick and temperature sensation are reduced in a "stocking" and "glove" distribution. There is relative sparing of vibration and position sense (because of relative sparing of the large diameter $A\beta$ fibers). Muscle strength and reflexes are usually normal. Autonomic function tests are frequently abnormal and affected male patients usually have erectile dysfunction. Sural sensory conduction velocity may be normal, although the amplitude may be reduced. It is unclear, whether this syndrome is in fact distinct or it represents the early stages of distal symmetrical neuropathy (9,13).

Pure Diabetic autonomic neuropathy is rare. Some degree of autonomic involvement is present in most patients with diabetic polyneuropathy. Signs may include orthostatic hypotension, resting tachycardia, anhydrosis, pupillary and lacrimal dysfunction, nocturnal diarrhea, bladder disfunction, sexual impotence and necrobiosis lipoidica (polycyclic cutaneous atrophy in women) (1,8,11).

Acute Painful Neuropathy of Poor Glycemic Control may occur in the context of type 1 or type 2 diabetic subjects.

There is no relationship to the presence of other chronic diabetic complications. There is often an associated severe weight loss. Ellenberg coined the description of this condition as "neuropathic cachexia". Patients typically develop persistent burning pain associated with allodynia. The pain is most marked in the feet, but often affects the whole of the lower extremities. The pain is typically worse at night although persistent pain during day time is also common. These symptoms often lead to depression. There are usually no motor signs, although ankle jerks may be absent. Nerve conduction studies are also usually normal or mildly abnormal. Symptoms usually improve with prolonged glycemia control. Symptoms are often refractory to other pharmacologic treatment. Recovery may be incomplete and prolonged over many months (9,13).

In case of Acute Painful Neuropathy of Rapid Glycemic Control ("Insulin neuropathy") the patient presents with burning pain, paraesthesiae, allodynia, often with a nocturnal exacerbation of symptoms; and depression may be a feature. There is no associated weight loss. Sensory loss is often mild or absent, and there are no motor signs. There is usually complete resolution of symptoms within 12 months. A recent study looking into the epineurial vessels of sural nerves in patients with acute painful neuropathy of rapid glycemic control demonstrated marked arterio/venous abnormality including the presence of proliferating new vessels, similar to those found in the retina (12).

Proximal Motor Neuropathy may occur in the cervical or lumbosacral distributions. Is referred to in the literature by various designations including diabetic amyotrophy, Bruns-Garland syndrome, and diabetic plexopathy. This condition often occurs in patients older than 50 years, in conjunction with weight loss and is associated with mildly elevated serum glucose levels. The patient presents with severe pain, which is felt deep in the thigh, but can sometimes extend lower than the knee and to the opposite side. The pain is usually continuous and often causes insomnia and depression. On examination there is profound wasting of the quadriceps with marked weakness. Hip flexors and hip abductors can also be affected. The knee jerk is usually reduced or absent. Sensory loss is unusual, and if present indicates a coexistent distal sensory neuropathy. Electrophysiological studies may demonstrate increased nerve latency and active denervation of affected muscles. (1,5,8,13).

Chronic Inflammatory Demyelinating Polyradiculopathy (CIDP) occurs more commonly among patients with diabetes. One should particularly be alerted when an unusually severe, rapid, and progressive polyneuropathy develops in a diabetic patient. Nerve conduction studies show features of demyelination. The presence of 3 of the following criteria for demyelination is required: partial motor nerve conduction block, reduced motor nerve conduction velocity, prolonged distal motor latencies, and prolonged F-wave latencies. CSF demonstrate increased protein and a normal or only slightly elevated cell count (11,13).

The most common cranial mononeuropathy is the third cranial nerve palsy. The patient presents with pain in the orbit, headache, followed by diplopia. There is typically ptosis and ophthalmoplegia. The pupil is usually spared. Recovery occurs usually over three months. Fourth, sixth and seven cranial nerve palsies (taste is not normally involved) have also been described in diabetic subjects. Most recover spontaneously in 3-6 months. Anterior ischemic optic neuropathy manifests as acute visual loss or visual field defects (usually inferior altitudinal). The optic disk appears pale and swollen. Flame-shaped hemorrhages may be present. Pupillary motility is disturbed in 10-20% of diabetics. Anisocoria and an anormally slow light response are the most common abnormalities (4,8,9,13).

Multiple nerves may be affected simultaneously and in different teritories (mononeuritis multiplex) (1,13).

Truncal radiculopathy is well recognized to occur in diabetes. It is characterized by an acute onset pain in a dermatomal distribution over the thorax or the abdomen. The pain usually begins unilaterally; then may become bilateral There may be patchy sensory loss detected by pin prick and light touch examination. Single or multiple spinal roots are involved. Recovery is usually the rule within several months, although symptoms can sometimes persist for a few years (1,13)

Pressure Neuropathies (entrapment neuropathies). In the Rochester Diabetic Neuropathy Study, Dyck et al. (5), found electrophysiological evidence of median nerve lesions at the wrist in about 30% of diabetic subjects, although the typical symptoms of carpel tunnel syndrome occurred in less than 10%. Focal neuropathies in the extremities caused by entrapment or compression at common pressure points or by ischemia and subsequent infarction. Entrapment and compression tend to occur in the same nerves and at the same sites as in individuals without diabetes. Median nerve entrapment at the wrist (carpal tunnel syndrome) is more common in patients with diabetes and can be treated in the same manner as in patients without diabetes. Symptoms are often bilateral. The susceptibility to ulnar nerve entrapment at the elbow or common peroneal nerve entrapment at the fibular head is not definitely increased among patients with diabetes (4,9,13).

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