DIABETIC NEUROPATHY. DIAGNOSIS

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[Neuropatia diabetica. Diagnosi]

ABSTRACT

Diabetic neuropathy occurs in the course of the diabetic disease in the absence of other causes of peripheral neuropathy. It is the most common complication of diabetes mellitus. Due to the great diversity of the clinical presentation, a thorough medical history, neurological examination and, of course, the neurophysiological confirmation are necessary for diagnostic purposes. In this review, the criteria and diagnostic methods of the disease are presented and discussed.

Key words: Diabetic neuropathy, neuropathy, diabetes, neurophysiology, diagnosis.

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Introduction

By definition, diabetic neuropathy, either clinically manifest or even subclinical, occurs in the course of the diabetic disease in the absence of other causes of peripheral neuropathy.

Diabetic neuropathy is the most frequent complication of both type 1 and type 2 diabetes mellitus. Although in different clinical and electrophysiological varieties, this complication can be observed clinically in about 30% of patients, with neurophysiological evaluation even in more than half of cases. Due to the great diversity of the clinical presentations, a thorough medical history, neurological examination and, of course, neurophysiological confirmation are necessary for diagnostic purposes. Nerve involvement may affect both the large sensory fibers and thin ones, and the autonomic nervous system, with its important consequences in terms of morbidity, quality of life, and at times mortality, whence the need for targeted screening of the population at risk, in order to take, as appropriate, all therapeutic measures available for primary or secondary prevention.

Diagnosis

The diagnosis is not always easy, unique and exclusive, as even diabetics may at times present other types of neuropathy besides diabetic neuropathy, as in any other patient that is referred to our attention. It should be borne in mind that the occurrence of other neuropathies having a different pathogenesis, i.e., non-diabetic, is possible, as in the case of ethylic, paraneoplastic, toxic, infectious, iatrogenic, dysimmune, compressive, traumatic, hereditary, acute or chronic neuropathies.

The diagnostic algorithm is aimed at distinguishing the signs and symptoms of autonomic neuropathy with the use of QAFT (Quantitative Autonomic Function Tests) or those of small fiber neuropathy through QST (quantitative sensory testing)[1]. In clinical cases indicating conditions affecting the large nerve fibers, it is essential to assess sensory and motor conduction velocity and perform electromyography.

According to the diagnostic protocol proposed at the 1988 *San Antonio Consensus Conference*, one of the following aspects is recommended to

fully classify diabetic neuropathy:

- Symptoms (S)
- Physical examination (PE)
- Electrophysiology (EP)
- Quantitative sensory tests (QST)
- Cardiovascular tests (CT)

An early diagnosis is extremely important for early treatment and the prevention of further damage. In clinical practice, the first step is a thorough clinical history and evaluation of sensory and motor symptoms, with the assessment of disability due to neuropathy and exclusion of other conditions, besides diabetes, which can cause neuropathy.

The clinical evaluation should include a careful examination of the feet, patellar and Achilles reflexes, measurement of pallesthetic sensitivity (with tuning fork and/or biothesiometer), tactile sensitivity (10-g monofilament test) and thermal sensitivity. It is also very important to consider the type of shoe, because if inappropriate it is the most common cause of trauma to the diabetic foot.

Some authors advocate the additional use of a clinical scoring system that classifies the degree of neuropathy based on the symptoms, reflexes, and sensitivity like the "Toronto Score" that is mainly based on changes in sensitivity and reflexes[2]. The control system has been validated and correlates well with electrophysiological studies and glycemic control (table 1).

The 10-g monofilament test is now a standard for the evaluation of the diabetic foot; it is very easy to perform and it gives fast and reliable results[3]. The test also predicts the possible occurrence of foot ulceration: patients who cannot feel the monofilament are 15 times more likely to develop ulcers in three years as opposed to those who still retain the plantar sensitivity[4].

Another important test is the sensory threshold of the vibration that identifies a possible subclinical neuropathy. It too is easy to use and predicts the plantar ulcerations. It is based on a score that between 0 and 5 volts indicates a low risk, 16 to 25 indicates an intermediate risk, and over 25 a high risk[5-6]. In addition, the assessment of vibration sensitivity also predicts mortality with a mortality rate higher in patients with alteration of the latter than in those without neuropathy[7].

In any case, for a good and more accurate typing of neuropathy, the study of nerve conduction velocity is essential.

The electrophysiological abnormalities observed are the result of the association at the level of the nerve fibers in diabetic patients of a predominant axonal degeneration on the distal portion of the nerves and a more proximal segmental demyelination that slows down nerve conduction. In the absence of any clinical manifestation, a slight reduction of the conduction velocity from 2 to 3 m/s is common and should not be systematically searched.

Overall, the intensity of the neurological disorders is correlated with that of the lowering of the sensory and motor action potentials, and not with that of the conduction velocity[8]. Patients with sensorimotor distal symmetric polyneuropathy have reduced or no sensory action potentials, especially in the lower limbs. With the progression of the disease, the amplitudes of the motor action potentials may be reduced and anomalies may also be evident in the hands.

These changes reflect the length-dependent degeneration of large myelinated fibers.

As previously mentioned, the conduction velocity are generally normal or only slightly slowed down in distal symmetric polyneuropathy.

If the conduction velocities are 70% below normal, or if there is a conduction block, an overlapping peripheral demyelination in addition to axonal loss is to be suspected..

If there is a focal slowdown in conduction velocity in common compression sites, this may indicate a mononeuropathy.

Alterations of nerve conduction can be found in diabetic patients even in the absence of clinical symptoms of polyneuropathy.

The electromyographic examination of the distal muscles of the lower limbs may reveal acute and ongoing denervation in the form of net positive waves and fibrillation potentials. Modifications due to reinnervation such as polyphasic motor unit action potentials of large amplitude and long duration reflect the chronicity of the pathology.

Some alterations of the paraspinal muscles, such as spontaneous discharges, reflect the disease in the roots of the spinal nerves[9].

Although electrophysiological studies are the most sensitive and reliable measures of nerve function, these cannot distinguish though a diabetic neuropathy from other types of neuropathy. Therefore, in order to reach a correct diagnosis, it is essential to integrate electrophysiological studies, clinical measurements, composite scores (which can be matched with observations on a possible reduction of heart rate variability with deep breathing or the

TORONTO CLINICAL SCORE		
SYMPTOM SCORES (0-6)	**REFLEX SCORES (0-8)**	**SENSORY TEST SCORES (0-5)**
Foot pain	Knee	Pinprick
Numbness	Ankle	Temperature
Tingling	(both)	Light touch
Weakness		Vibration
Ataxic		Position
Upper-limb symptoms		

Maximum score = 19
0-6 = no neuropathy; 6-8 = mild neuropathy, 9-11 = moderate neuropathy; ≥ 12 = severe neuropathy.

Table 1

Valsalva maneuver) and, if necessary, correlate them with morphological changes detectable in nerve biopsy[10-11].

The latter, while being an excellent diagnostic method, is now only rarely indicated for the diagnosis and assessment of diabetic neuropathy because of the invasive nature of the procedure with its attendant risks, the discomfort of the patient, the costs, the possible sampling errors, and the availability of other methods to obtain similar information[12]. In the majority of cases, nerve biopsy is conducted on the sural nerve at the level of the lateral malleolus. In humans, it is a purely sensory nerve whose removal, in most cases, does not cause any damage and/or after-effect for patients.

The biopsy is processed with histochemical and immunohistochemical methods and then analyzed under light and electron microscopy.

The histopathological study of the sural nerve allows us to define: 1) axonal or myelin damage, and 2) the involvement of the vasa nervorum, connective coating and support structures, and 3) the presence of extraneous infiltrates (13-14).

Back in 1994, the Michigan Neuropathy Program (*Feldman et al., 1994*) proposed the DIABETIC NEUROPATHY SCORE (DNS) based on:

• Quantitative sensory testing:

• Vibratory perception threshold - biothesiometer

• Tactile perception threshold - 10 g monofilament.

• Pain perception threshold - pinprick

• District muscle strength in all 4 limbs

• ROT in all 4 limbs

• ENG

The subsequent diagnostic processing of neuropathy was, as quoted above, the one proposed by the San Antonio Conference (1988) that, by implementing the contribution of neurodegenerative disorders, was based on the following elements:

Neuropathy if 2 alterations present from among:

• Symptoms (S) (Neuropathy Symptom Score, Dick, 1988)

• Signs - clinical examination (CE)

• Quantitative sensory tests (QST)

• Cardiovascular tests (CT)

• ENG

Dyck (1988) crossed the diagnostic mode of neuropathy with its staging and proposed the following scoring table 2:

Today it is common practice to distinguish between positive and negative symptoms in three areas of possible involvement of the peripheral ner-

STAGE		
0	No neuropathy	< 2 abnormalities from among S, CE, CT and QST, ENG
1	Asymptomatic neuropathy	≥ 2 abnormalities from among CE, CT and QST, ENG, but not S
2	Symptomatic neuropathy	S mild to moderate and ≥ 1 abnormality from among CE, CT or QST, ENG
3	Disabling neuropathy	S severe and ≥ 1 abnormality from among CE, CT or QST, ENG

Table 2: DIAGNOSIS & STAGING - Dyck, 1988

vous system (Diabete.net). The positive symptoms include tingling, numbness, burning, pain, cramps and watery eyes, hyperhidrosis. While the negative symptoms comprise tactile, pain, or thermal anesthesia, sensory ataxia, weakness and bowel disorders including intestinal hypomotility and lacrimal hyposecretion.

Cardiovascular autonomic tests that assess the responses with predominant involvement of the parasympathetic or sympathetic system are shown in table 3.

predominant parasympathetic	Forced respiration
	Change of posture
	Valsalva maneuver
	Coughing test
predominant sympathetic	Isometric muscle contraction

Table 3

Recently, in an attempt to simplify the diagnostic procedures and to allow them to be done by the highest possible number of operators, the European Diabetic Nephropathy Study Group has recommended very simple methods for the assessment of Diabetic Neuropathy.

Clinical approach to diabetic neuropathy:

- Always examine both feet
- For sensitivity to pain: use a pin and ask when it is painful
- For tactile sensitivity: use a cotton swab
- For vibration sensitivity: use a 128-Hz tuning fork
- For the perception of pressure: use a 10g monofilament
- Detect Achilles reflexes bilaterally

An extensive diagnostic protocol will also include nerve biopsy and cerebrospinal fluid examination. Sural nerve biopsy shows the coexistence of axonal degeneration and segmental demyelination associated with more or less relevant aspects of microangiopathy of the vasa nervorum. Since the CSF glucose level reflects the blood glucose level, glycorrhachia is high in all diabetics, with or without neuropathy.

Differential diagnosis

In a diabetic patient the possibility of another cause of neuropathy must always be taken into consideration. In a retrospective study of 100 diabetic patients with debilitating neuropathy, it was found that 30% of the neuropathies could be attributed to another cause, especially focal and multifocal neuropathies: nine patients had chronic polyradiculoneuritis possibly superimposed on a diabetic neuropathy[15].

Focal and multifocal neuropathies are far rarer neuropathies than classic diabetic polyneuropathy. Though somewhat rare, it is necessary to exclude other causes of neuropathy before attributing them a metabolic origin. In particular, mononeuropathies of limbs are extremely rare[16].

A differential diagnosis is to be made with compression syndromes that are much more common in diabetics than in the general population, probably due to an increased sensitivity of the diabetic nerve to compression. The carpal tunnel syndrome is reported in 12% of diabetic patients compared to 4-5% of the general population[17].

The lumbosacral radiculoplexopathy or proximal neuropathy of the lower limbs, better known as diabetic amyotrophy, accounts for about 1% of diabetic neuropathies. Differential diagnosis with classic diabetic polyneuropathy is easy and exquisitely clinic: lumbosacral radiculoplexopathy is proximal, asymmetric, predominantly motor and has a spontaneous recovery.

With regard to neuropathies of different origin, these are relatively common in diabetic patients

with distal symmetric polyneuropathy, such as cranial neuropathies due to demyelinating disease (18).

The chronic inflammatory demyelinating polyneuropathy (CIDP) is the most common non-diabetic neuropathy in this population. CIDP is an immune-mediated inflammatory disorder of the PNS responsive to anti-inflammatory and immunomodulatory therapies. Restrictive diagnostic criteria for the diagnosis of CIDP based on clinical and electrophysiological evidence of demyelination have been developed by the European Federation of Neurological Societies (EFNS). CIDP should be suspected in a patient with diabetes when motor symptoms are prevalent and more severe than those expected in a diabetic polyneuropathy. Nerve conduction studies are needed to confirm the suspected diagnosis[19,20].

The following laboratory data are useful to exclude common causes of non-diabetic neuropathy: complete blood count, electrolytes, liver, thyroid and kidney function tests, B12 and folate levels, erythrocyte sedimentation rate, and blood protein electrophoresis.

Other tests that are useful are those that allow us to exclude a possible autoimmune disease: ANA, ANCA, anti-SSA and SSB, rheumatoid factor.

In addition, for the diagnosis of visceral disorders that include intestinal hypomotility, esophageal manometry is used. It allows for a study of the amplitude and motor coordination of the esophagus[21].

Particular attention should be focused on axonal neuropathies to exclude a concurrent involvement of the first motor neuron, which constitutes a very different disease, namely amyotrophic lateral sclerosis[22-23].

In addition, in certain clinical settings, MRI of the cervical, thoracic, and/or lumbar regions can help to exclude other causes in case of symptoms similar to those of diabetic neuropathy. For all patients in whom it is not possible to perform MRI, the alternative is a CT myelogram to exclude compressive lesions and other pathologies of the spinal canal.

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