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Current perspectives in the diagnosis of diabetes-associated peripheral neuropathies

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Abstract

Objective: To review the current diagnostic modalities for diabetic neuropathy, common long-term complications of diabetes mellitus.

Methods: We performed a MEDLINE using a combination of words (diabetic neuropathy, diagnosis, and treatment) to identify original studies, consensus statements, and reviews published in the last thirty years. Emphasis was on the diagnosis of diabetic distal symmetrical polyneuropathy (the most common form), especially newer modalities.

Results: A plethora of tests are available for the diagnosis of diabetic neuropathy. Some of these are simple and easy to perform in clinical settings while others require sophisticated equipment and expertise to be carried out.

Conclusion: Early screening and diagnosis of diabetic neuropathy, preventive modalities, patient, and physician education remain cardinal factors in reducing this complication and mortality.

Keywords: diabetes, peripheral, neuropathy, diagnosis, distal, symmetrical

Introduction

Diabetic neuropathy is the presence of symptoms and or signs of peripheral nerve dysfunction in people with diabetes mellitus after excluding other causes [1]. The San Antonio consensus criteria recommend at least one measurement in five different categories (symptoms, signs, nerve conduction abnormalities, quantitative sensory testing and quantitative autonomic testing) [2]. To diagnose clinical neuropathy, the guidelines the guidelines require symptoms and signs, or one of these with abnormal electrophysiologic findings or quantitative sensory test results. Subclinical neuropathy is identified by an abnormal result only.

Peripheral neuropathy is the most disabling long-term complications of diabetes mellitus [3]. It is more common in type 2 diabetes, and its prevalence increases as the duration and severity of DM increases. The risk of neuropathic dysfunction increases progressively over time so that >50% of people with diabetes are affected after ten years [4]. It is a major reason for hospital admission, accounting for more hospitalizations than all other diabetic complications combined [5]. It should be considered in all persons with type 2 diabetes and those with type I that have had it for more than five years [6].

Clinicians should be well equipped with the various methods for its diagnosis as it is commonly encountered in clinical practice. This article highlights the various modalities for the diagnosis of diabetic neuropathy with emphasis on DSPN since it is the commonest form [7].

Diagnostic Modalities

Some of the instruments used to screen for the presence of diabetic peripheral neuropathy are cheap, practically applicable, non-invasive, and highly predictive of clinical end points with good sensitivities and specificities [8]. Some of these modalities preferentially assess small or large fiber damage in diabetic neuropathy. Other diagnostic modalities are complex requiring sophisticated equipment and technical expertise. These may not be readily available in resource-poor settings.

Table 1: Diagnostic modalities for diabetic peripheral neuropathy

Nerve conduction studies
Quantitative sensory tests
Skin biopsy
Sural nerve biopsy
Sudomotor function tests
Confocal corneal microscopy
Peripheral nerve imaging
Clinical scoring systems

Nerve Conduction Studies (NCS)

These measure the ability of peripheral nerves to conduct electrical impulses and are abnormal when pathological changes are present in myelinated nodes of Ranvier and axons. Routine nerve conduction studies (NCS) includes evaluation of the motor function of the median, ulnar, peroneal and tibial nerves, and sensory function of sural, ulnar, median and radial nerves [9]. Motor nerve conduction velocities is reported in meters per second (m/s), motor amplitudes in millivolts (mV) and sensory amplitude in microvolts (μV).

NCS are usually considered an extension of the clinical neurological examination and correlates well with clinical endpoints. Nerve potential amplitudes reflect the degree of nerve fiber loss. The prevalence of abnormal NCS increases with the duration of diabetes, disease severity, and correlates with glycaemic control. NCS have also helped in our understanding of the natural history of diabetic sensory neuropathy regarding long-term changes in conduction parameters [10].

The most distal sensory nerves (plantar and sural) are the first evidence of distal sensory neuropathy. As DSP progresses, NCS show loss of distal sensory and motor amplitudes and

then changes in more proximal and upper limbs. Its disadvantages are availability especially in resource-poor settings; technical expertise; standardization issues; and discomfort of the procedure, and an inability to detect small fiber neuropathy. Also, it does not directly reflect symptoms or neuropathological deficit. This test has considerable appeal because it is objective, repeatable, sensitive, and specific. Inferences have to be made about a meaningful degree of nerve conduction abnormality related to clinical symptoms and deficits. Studies have shown a strong correlation between VPT, NCS results and subjective symptoms of neuropathy [11].

Quantitative Sensory Tests (QST)

These tests are qualitative measures of sensation. They have been demonstrated to provide a valuable quantitative sensory function in subjects with polyneuropathy. Several QST technologies are now in clinical use for measuring vibration, thermal and current perception thresholds [12]. The primary drawback of these tests is the psychosocial nature of the examination since they relies on subjective responses by the patient.

Vibration perception is defined as the subjective appreciation of an oscillating and frequently repeated stimulation on the body surface in the form of an intermittent quivering or trembling motion [13]. VPT is measured using a hand-held device called a biothesiometer which quantifies vibration threshold in the big toe [14]. The intensity of vibration is increased progressively by increasing voltage to the stimulator. The vibration threshold is determined by the method of limits. The subject exposed to a stimulus of changing intensity is asked to indicate the first onset of sensation. This is noted on the scale of the device in volts [15].

The point at which the subject perceives vibration sensation delivered from the probe of the biothesiometer on the plantar pulp of the hallux is the vibration perception threshold. Three readings are taken at the test sites. The average of the three consecutive readings to gain more precision [16]. The vibration perception is abnormal when the mean voltage of three readings exceeds 25 mV [17].

The biothesiometer is quick to use and reliable, giving objective measures [18]. It is also more accurate than the tuning fork but more expensive and cumbersome [19]. However, it cannot give readings more than 50mV. This ceiling effect limits its use in detecting the actual extent of vibratory sensory loss. To overcome this, a device called a maxivibrometer was designed to give the maximal reading of vibratory sensory loss in mV [20]. The sensitivity of VPT relative to NCS for diagnosing diabetic neuropathy ranges from 77.3 to 100.0% with its specificity ranging from 72.8 to 81.0% 133, [21].

Vibration perception threshold measurements have certain limitations. Age increases VPT especially in the lower limbs [22, 23]. This is due to degenerative transformations of the Pacinian corpuscles, demyelinisation and fiber loss in the peripheral nerves that occur with aging [24]. Arterial insufficiency is also associated with loss of vibratory perception [25]. Age-related degenerative changes in the arteries may lead to reduction in blood flow to the peripheral nerves of the lower limb. This could be responsible for the impairment of vibration [26]. The pressure applied to the vibrator also influences VPT readings. Lowenthal *et al.* [27] found out that increasing tractor pressure artificially lowered the vibration threshold as more vibration receptors are activated in response to greater pressure.

Temperature perception threshold (TPT) is measured with an automatically heated or cooled probe on the dorsum of each foot. Six consecutive methods for cold and six consecutive methods for hot are performed and the TPT is calculated as a mean value [28]. The reduction of thermal sensation may be the only abnormality in painful neuropathy [29].

Current perception threshold (CPT) is assessed with a neurometer, a neuro-selective diagnostic stimulator which measures the sensitivity to electric current or CPT. It is said to be able to discriminate between neuropathic and non-neuropathic patients and is also able to test different types of nerve fibers by using different frequencies of electric stimulus: high frequencies for large fibers and low frequencies for small unmyelinated nerve fiber [30].

Touch-pressure perception is assessed using the Semmes-Weinstein monofilament (SWMF) 10g monofilament [31]. In one of suggested several approaches, it is applied perpendicular to the plantar surface of the foot on three sites (first and fifth metatarsal heads and heel), with enough force to cause it to buckle. The test is deemed abnormal if the SWMF is not perceived at any one site on either foot [32].

Pain perception is assessed using the neurotip which is attached to the neuropen device. The blunt and sharp edges of the neurotip are randomly pressed against the plantar surface of the hallux and patients are required to distinguish between painful and painless stimuli. The test is considered abnormal if two out of three responses are wrong [33].

Temperature perception is assessed using the tiptherm, a pen-like device with a plastic cylinder on one end and a metal cylinder on the other which is applied to the dorsum of each foot. It is portable, easy to handle and gives reproducible results in ambient temperatures of 23 degrees Celsius. Temperature perception is impaired if there are at least two incorrect responses out of three readings on the dorsum of the foot [34].

Sudomotor function tests

Sweat gland function is controlled by sympathetic C fibers which might be affected early in the process of the pathogenesis of diabetes. Hence it could be used to screen sympathetic system dysfunction which is common in subjects with impaired glucose tolerance (IGT) and diabetes.

Sudomotor function tests include the quantitative sudomotor axon reflex test (QSART), the sweat imprint test, the thermoregulatory test, and the sympathetic skin response. Such tests are very expensive and require expensive equipment and trained personnel [35].

Sudoscan is a new, cutting-edge, non-invasive device for easy, quick, and quantitative assessment of sudomotor function associated with small nerve fiber neuropathy commonly found in persons with prediabetes and diabetes [36]. By combining direct current stimulation and reverse iontophoresis, it measures electrochemical conductance-local conductance derived from electrochemical reaction between sweat chloride and nickel electrodes. Lower ESC is indicative of sudomotor dysfunction [37].

Neuropad is an adhesive indicator test able to detect sweating through a color change. It is a patch that assesses plantar sweat production by using a chemical reaction that is

manifested as a color change from blue to pink [38]. The indicator test contains the blue complex salt anhydrous cobalt II chloride. In the presence of water, each molecule of this salt absorbs six water molecules, and the color changes to pink. The time needed to produce a complete change in color is inversely related to skin humidity [39]. It is an easy, practical and cheap test for the assessment of sudomotor function in the feet. A few studies demonstrated high sensitivity and limited specificity of neuropad in detecting DPN [40].

Sural Nerve Biopsy

It is used to assess large nerve involvement in diabetic neuropathy. This nerve is an ideal anatomical site for biopsy since it is a distal lower limb nerve involved early in the course of DSP [41]. Its main limitation is its invasiveness, risks of infection, pain and sensory deficits. Also, it provides information only from one site in a single nerve at only one time point in a process that is generalized.

Skin Biopsy

Small nerve affectation can be accomplished by assessment of cutaneous nerve fibers obtained from skin punch biopsy. Epidermal innervations can be studied successfully using immuno-histochemical methods that target the neuronal marker protein gene product 9.5, a pan-axonal marker. It has been shown in several studies that there is a direct relationship between the clinical severity of distal sensory neuropathy and severity of intraepidermal nerve fiber density [42].

Confocal Corneal Microscopy

Confocal corneal microscopy is a relatively new method for assessing nerve involvement in diabetic polyneuropathy. In confocal microscopy, the cornea is scanned and the images of Bowman's layer, which contains a rich nerve plexus are examined for nerve fiber, length and branch densities. These parameters are significantly reduced in DN and correlated with the severity of neuropathy. Because of its noninvasive nature, confocal microscopy may have great potential in assessing nerve structure in vivo without need for nerve biopsy [43].

Peripheral Nerve Imaging

Imaging techniques appear to offer promise for evaluating the status of peripheral nerves in patients with diabetes. A decade ago, Eaton *et al.* [44] used magnetic resonance imaging (MRI) to demonstrate that the water content of the sural nerve was increased in diabetic subjects with symptomatic neuropathy as well as some diabetics who were not yet symptomatic. They suggested that the endoneurial edema reflected by these measurements may initiate the deterioration that is later detected in electrophysiologic testing and neurologic examination.

Subsequent studies in patients and experimental animals confirmed the MRI-detected increase in nerve hydration in diabetes [45]. The strengths of MRI include the ability to target specific areas, the lack of invasiveness, and the feasibility of repeat procedures. Limitations are the costs and as-yet unproven diagnostic sensitivity.

Peripheral nerve ultrasound is becoming more common for the diagnosis of peripheral neuropathies [46, 47]. Sural nerve ultrasound has been shown to visualize the inner portions of the sural nerve allowing for morphological changes of diabetic neuropathy to be seen [48]. The crossectional area of the posterior tibial nerve using ultrasound was found to be larger in diabetics with distal symmetrical polyneuropathy when compared with those without [49].

Symptom Scores

Several symptom scoring systems have been developed to assess symptoms of DN. Some of these have the advantage of being practically applicable and reproducible in clinical practice. Others are difficult to perform, time-consuming and incorporate electrodiagnostic parameters [50]. Before use in clinical practice, they should have been validated and standardized using an independent reference standard with an adequate spectrum and number of patients using a sound item-based selection [51].

The diabetic neuropathy symptom score (DNSS) is a four-item validated symptom score with high predictive value to screen for peripheral neuropathy in DM. The symptoms asked for are unsteadiness in walking, neuropathic pain, paraesthesias and numbness. The presence of one symptom is scored as 1 point. The maximum score is 4 points. A score of 1 or higher is defined as positive for neuropathy. It has been validated against biothesiometry (VPT) with sensitivity and specificity of 81% and 58%, respectively [52]. It has also been validated against NCS and found to have 64% sensitivity and 81% specificity with positive predictive value of 86% and negative predictive value of 55% [53].

Michigan neuropathy disability score (MNDS) is based on 4 parameters for each foot. Each parameter of this system is scored as 0, 0.5 or 1 depending on the results of the examination. Therefore total score for each patient could range from 0-8. If the sum of the scores was 2.5 or less, the patient does not have neuropathy, but a total score of 3 or more is diagnostic. It is used with the Michigan Neuropathy Screening Instrument (MNSI) patient version to determine the neuropathic symptoms patients may have [54]. It has been validated against nerve conduction studies with sensitivity, specificity, positive predictive value, negative predictive value of 80%, 95%, 97%, and 74% respectively [55]. Other symptoms scores include clinical neuropathy examination score of Valk [56, 57], Toronto score [58], the University of Texas subjective peripheral neuropathy verbal questionnaire [59].

Conclusion

Diabetic neuropathies are commonly encountered in clinical practice. It is important for clinicians to familiarize themselves with these of diagnostic modalities. Possibility of underlying neuropathic complication should be kept in mind for all T2DM at presentation and T1DM after five years of disease duration.

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