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COMMENTARY

Diagnostic strategy for diabetic polyneuropathy: Focus on nerve fiber type and magnetic resonance neurography

Diabetic neuropathies are a group of heterogeneous peripheral neuropathies, and are roughly classified into polyneuropathy and focal neuropathy. Diabetes-specific neuropathy is polyneuropathy, which is pathophysiologically associated with metabolic disorders as a result of hyperglycemia and microangiopathy. Recently, classification[1,2] of the spectrum of diabetic polyneuropathy (DPN) based on the different types of nerve fiber involved has grown (e.g., myelinated, unmyelinated, autonomic, somatic). DPN is divided into diabetic distal sensory neuropathy (DSN), diabetic small-fiber neuropathy (DSFN) and diabetic autonomic neuropathy[2]. The most common type is DSN, which mainly affects the large myelinated fibers, more often sensory than motor. DSN shows a length-dependent, primarily sensory neuropathy of large nerve fibers, while often being asymptomatic. DSFN mainly affects the unmyelinated small nerve fibers, not the large fibers, and occasionally carries the phenotype of burning feet syndrome. DSFN occurs early in metabolic disorders associated with hyperglycemia. Subsequent neurodegeneration through uncontrolled diabetes might promote DSFN to DSN, but it is not clear whether DSFN consistently progresses to DSN. Diabetic autonomic neuropathy occurs when the widespread involvement of autonomic unmyelinated fibers occurs, and patients can suffer from unpleasant autonomic dysfunction. We will not describe diabetic autonomic neuropathy here due to a limited word count. As severe DSN or DSFN causes severe neuropathic pain, or foot ulcer, and morbidity might significantly deteriorate, early diagnosis is important.

This commentary describes the diagnostic strategy for DSN and DSFN based on recent advances in neurodiagnostic technology. Table 1 shows the classification, manifestations, validated examinations of each nerve fiber types and their implication for the phenotypes of DPN. Nerve fiber types involved in DSN and DSFN consist of sensory small fiber (c-, Aδ-fiber) to large fiber (Aβ-, Aα-fiber), and motor large fiber (Aα-fiber). As the intra-epidermal terminal end of c- and Aδ-fibers is unmyelinated small fibers, disorder of these two fibers is called small-fiber neuropathy. DSN is actually considered to be a mixed small- and large-fiber neuropathy, as an obvious loss of intra-epidermal nerve fibers has been reported in DSN or advanced DSN. In advanced DSN, small muscle atrophies in the distal legs are caused by large motor fiber impairment.

In daily practice, DSN is diagnosed by the presence of voluntary sensory symptoms and/or neuropathic signs, including decreased Achilles tendon reflex and symmetric decreased distal sensation in both legs. All of these clinical symptoms/signs other than neuropathic pain, such as burning, electric shock-like, stabbing and tingling, are due predominantly to large myelinated fiber disorders. Therefore, definitive diagnosis of DSFN was difficult until effective diagnostic methods for small nerve fiber damage had been established. Even for DSN, it was not easy to make a definitive diagnosis, because symptoms are not objective, and the accuracy of evaluating these signs depends on the skill of the examiner. Therefore, an objective, quantitative and reliable neurological examination is required to accurately diagnose DPN. Neurological examinations that satisfy these requirements include quantitative sensory testing (QST), nerve conduction study (NCS), pathological/morphological examination and magnetic resonance (MR) neurography.

As sensory impairment significantly harms the patients' quality of life, various QSTs have been developed to evaluate each sensory dysfunction. In small nerve fibers, unmyelinated C- and Aδ-fibers transmit dull pain and warm sensations, and sharp pain and cold/hot sensations, respectively. Sensory thresholds are determined by various computer-based thermal testers and pinprick testing. In large nerve fibers, Aβ-fibers transmit vibratory and pressure sensation, and Aα-fibers transmit proprioception and modulate tendon reflex. Perception thresholds are evaluated by various tuning forks, monofilaments or quantitative vibration meters. Decreased Achilles tendon reflex also indicates large-fiber neuropathy. The results of QST are not completely objective, as they depend on the patient's response. However, QST appears to be the most sensitive method for individually assessing different types of sensory nerve fibers.

Nerve conduction study has been considered the gold standard for DSN diagnosis because of its high objectivity. However, most of the results obtained

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Table 1 | Characteristics, manifestations and examinations of each class of nerve fiber, and phenotypes of diabetic polyneuropathy

Classification		Manifestations		Validated examinations			Possible clinical course of DPN	
							Pre-DM ⇒ DM ⇛ longstanding DM	
Fiber type Diameter (μm)	Functions	Symptoms	Signs (Simple test)	QST NCS	Pathology morphology	Magnetic resonance neurography	Diabetic small-fiber neuropathy (DSFN)	Diabetic sensory neuropathy (DSN)
C-fiber Unmyelinated 0.2–1.5	Nociceptor Warmth receptor	Burning pain		Warmth detection	IENFD CCM		Small fibers are affected, but large fibers are not.	Some painful cases, but also cases with raised pain thresholds Morphological fiber loss does not relate to pain
Aδ-fiber Myelinated 1–5	Nociceptor Cold/hot receptor	Electric Stabbing Tingling pains	Pinprick	Hot/cold detection Pinprick	IENFD CCM	T2w-high lesion	Burning pain in some cases, but may be asymptomatic.	
Aβ-fiber Myelinated 6–12	Mechanoreceptor Vibration Pressure	Numbness Tingling (painless)	Tuning fork MF (10-g)	QVT MF SNCS	Sural nerve biopsy	T2w-high lesion T2w-low lesion		Numbness in some cases Reduced ATR, impaired vibration or tactile sense, abnormal SNCS, loss of protective sense can exist
Aα-fiber Myelinated 13–20	Proprioception Golgi tendon organ	Instability	ATR	ATR SNCS	Sural nerve biopsy	T2w-high lesion		
Aα-fiber Myelinated 13–20	Motor function	Muscle weakness	Manual muscle testing	MNCS		T2w-high lesion T2w-low lesion		Abnormal MNCS Muscle atrophy⇛ foot ulcer

Nerve fibers are classified by the Erlanger–Gasser classification. High or low lesion means hyperintense or hypointense lesion, respectively. ATR, Achilles tendon reflex; CCM, corneal confocal microscopy; DM, diabetes mellitus; DPN, diabetic polyneuropathy; IENFD, intra-epidermal nerve fiber density; MF, monofilament; MNCS, motor nerve conduction study; MRN, magnetic resonance neurography; NCS, nerve conduction study; QST, quantitative sensory testings; QVT, quantitative vibration threshold; SNCS, sensory nerve conduction study; T2w, T2 weighted.

with NCS reflect the function of large nerve fibers, so small nerve fibers cannot be evaluated.

Pathological/morphological examinations are the most reliable and accurate way to diagnose peripheral neuropathy. A sural nerve biopsy is the most reliable method for diagnosing small- and large-fiber neuropathy, but it is not recommended for usual diagnosis of DSN because of its high invasiveness. When other non-invasive tests are exhausted, sural nerve biopsy becomes a valuable option for the potential diagnosis and treatment of undiagnosed neuropathy. In contrast, the measurement of intra-epineural nerve fiber density by skin biopsy can be used to confirm the diagnosis of DSFN because of its lower invasiveness. Quantification of intra-epineural nerve fiber density by immunostaining of skin biopsy samples with protein gene product 9.5 has been established as a reliable method for diagnosing DSFN. Furthermore, corneal confocal microscopy is a recently developed non-invasive method that can provide images of corneal unmyelinated small nerve fibers *in vivo*. Corneal nerve fiber length and density are reported as a reliable marker of DSFN. At present, intra-epineural nerve fiber density, corneal confocal microscopy or warm and/or cold detection thresholds of QST are considered valid methods to confirm DSFN, but abnormalities in these tests are also observed in DSN. In addition, abnormalities in these tests seem to be independent of a painful or painless phenotype.

Recently, studies on the MR neurography (MRN) of DPN (DSN and DSFN) have been accumulating. MRN has been developed as an imaging method to capture the morphological changes of peripheral nerve bundles using MR imaging.

In 2015, Pham *et al.*[3] imaged MRN from the proximal sciatic nerve to distal tibial nerve using 3-D T2-weighted (T2w) sequences in DSN patients, non-DSN diabetes patients and controls participants without diabetes. DPN was diagnosed and assessed by symptoms/signs, and a load of nerve lesions was quantitatively evaluated by the voxel

number of T2w high-intensity signals. As a result, the load of nerve lesions increased in parallel with DPN severity, highest in the mid sciatic nerve at thigh level and lower in the distal tibial nerve with a strong proximal-to-distal gradient. The authors speculated that the accumulation of microstructural nerve alterations at the thigh level, which might represent a vulnerable region for ischemic and/or metabolic injury, could precede and possibly trigger distal fiber loss in a length-dependent manner.

In 2018, Jende *et al.*[4] evaluated T2w-hyperintense and T2w-hypointense lesions of the sciatic nerve by MRN in type 1 and type 2 diabetes patients, and the association between MRN findings, and clinical, serological and electrophysiological data. The results showed, in both type 1 and type 2 diabetes patients, T2w-hyperintense and T2w-hypointense lesions increased with DPN, but T2w-hypointense lesions were more prevalent in type 2 diabetes patients than in type 1 diabetes patients. T2w-hyperintense lesions were associated with nerve conduction function and glycated hemoglobin, and T2w-hypointense lesions correlated positively with triglyceride and negatively with high-density lipoprotein cholesterol. Therefore, the etiology of DPN in type 1 diabetes patients might be mainly due to poor glycemic control, and that of type 2 patients diabetes might be related to dyslipidemia.

In 2020, Groener *et al.*[5] reported the association of T2w-hyperintense or hypointense lesions in MRN of the sciatic nerve, and impairments of various types of nerve fiber in type 2 diabetes patients and healthy controls. The function of each type of nerve fiber was evaluated using NCS and QST. In large nerve fibers, Aα- and Aβ-fibers were evaluated by NCS and the mechanical detection threshold. Aδ fibers were evaluated by the mechanical pain threshold, and the unmyelinated C-fibers were evaluated by the warmth detection or pain threshold. The results showed the T2w-hyperintense lesion load was significantly associated with decreased Aα-, Aβ- and Aδ-fiber function, but not C-fiber function. T2w-hypointense lesions were negatively correlated only with mechanical detection, peroneal conduction velocity and amplitude. The authors concluded that T2w MRN lesions in the sciatic nerve might be pathophysiologically associated with a decline in middle and large-fiber nerve function of DPN.

A summary of MRN studies is as follows: (i) the MRN lesion load in peripheral nerves and severity of the DPN correlate positively, and the most affected site is the sciatic nerve in the proximal thigh; (ii) the MRN lesion load reflects middle-to-large-fiber dysfunction, but not small C-fiber dysfunction; and (iii) differences in MRN lesions between type 1 and type 2 diabetes might reflect etiological differences in DPN. However, several problems exist as follows: (i) the pathophysiological condition of MRN lesions is unknown; (ii) the optimal MRN imaging method and cut-off value for evaluating lesions have not been established; and (iii) overlap with healthy controls is large, and it is difficult to distinguish normal from abnormal. MRN has the great advantage of being able to evaluate morphology, which is the most objective index, non-invasively, and might be extremely useful as a tool for evaluating DPN. Further studies including device innovation and longitudinal studies are desired.

DISCLOSURE

The authors declare no conflict of interest.

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