

Diabetic polyneuropathy: Progress in diagnostic strategy and novel target discovery, but stagnation in drug development

Diabetic polyneuropathy (DPN), one of the most prevalent diabetic complications, asymptotically progresses in the early stages of the disease. Although early diagnosis is critical, as therapeutic intervention is often delayed, no consensus has been established for early diagnosis. However, fortunately, the recent development of objective quantitative tests that contribute to the diagnosis of DPN has been remarkable. The nerve conduction study (NCS) has long been known as the gold standard test for DPN diagnosis. In an attempt to further develop the possibilities of NCS, Baba *et al.*¹ proposed an NCS-based diagnosis and severity classification of DPN (Figure 1). Using this classification, it was reported that the cardiovascular prognosis deteriorated significantly after 5 years in the moderate-to-severe DPN groups². Given this result, the reliability of this classification was validated; at the same time, the severity of DPN was recognized as an important factor to define the prognosis of diabetes patients. As NCS requires expensive equipment and well-trained examiners, it is difficult to clinically popularize the use of NCS. However, the usefulness of the simple NCS device, NC-stat/DPNCheck™ (Neurometrix, Inc., Waltham, MA, USA), which can reproduce a part of NCS, has been proven. Among studies considering the Asian population, Hirayasu *et al.*³ evaluated the difference in normal thresholds of the device between

people of Japanese and Caucasian descent. Furthermore, the authors showed the reproducibility of the device for the Japanese population and the strong correlation with conventional NCS⁴. In the future, researchers should establish further effectiveness of this device in the diagnosis and severity assessment of DPN. Another aspect that can be used for diagnosis and evaluation of DPN is autonomic nervous dysfunction. R-R interval variability in the electrocardiogram has mainly been used for the diagnosis of cardiovascular autonomic neuropathy, which is a major diabetic autonomic neuropathy⁵. However, a recent study reported that orthostatic hypotension, one of the symptoms of cardiovascular autonomic neuropathy, was found in the so-called non-dippers whose blood pressure does not show a normal fall during sleep, in which the cardiovascular prognosis was poor⁶. It would be necessary to verify the usefulness of the night-time blood pressure variability as a new parameter of diabetic autonomic neuropathy.

The relationship of DPN to newly-highlighted diabetic complications has been illuminated by recent findings. Among musculoskeletal complications of diabetes, Charcot neuroarthropathy, also called diabetic neuropathic arthropathy, which is one of the conditions contributing to diabetic foot, has been identified for a long time, although its pathology has not been fully elucidated. One of the most popularly supported hypotheses is that the disease develops in patients with DPN and abnormal bone metabolism, when their condition is compounded by trauma or vascular disorders. It has been

suggested that local inflammation, rather than DPN, is a critical factor in its pathogenesis^{7,8}. However, using a corneal confocal microscope, Khan *et al.*⁹ showed that severe impairment of small nerve fibers was associated with the disease. Although it is still difficult to explain the overall pathology of the disease, it was reconfirmed that the coexistence of DPN is an important factor in the underlying pathology.

Sarcopenia has recently attracted attention in older adults with diabetes. Especially in advanced countries with an aging population, sarcopenia and subsequent frailty are becoming a major social issue that needs to be addressed^{10,11}. It has been reported that the prevalence of sarcopenia increases in diabetes patients¹², and the prevalence further increases in patients with DPN¹³. Furthermore, it has been reported that the same functional deterioration of the musculoskeletal system is remarkable not only in the lower limbs, but also in the upper limbs¹⁴. We professionals should attend to the importance of DPN in upper limb dysfunction. Considering these new findings, in addition to the prevention and treatment of diabetic foot associated with severe DPN, countermeasure strategies against sarcopenia and frailty associated with mild DPN should be fully considered. In other words, the importance of early diagnosis and treatment of DPN must be recognized.

However, there is no well-established worldwide treatment protocol for DPN, although preferred regional treatments exist. For example, an aldose reductase inhibitor, epalrestat, is widely used in Japan. Epalrestat is highly effective in

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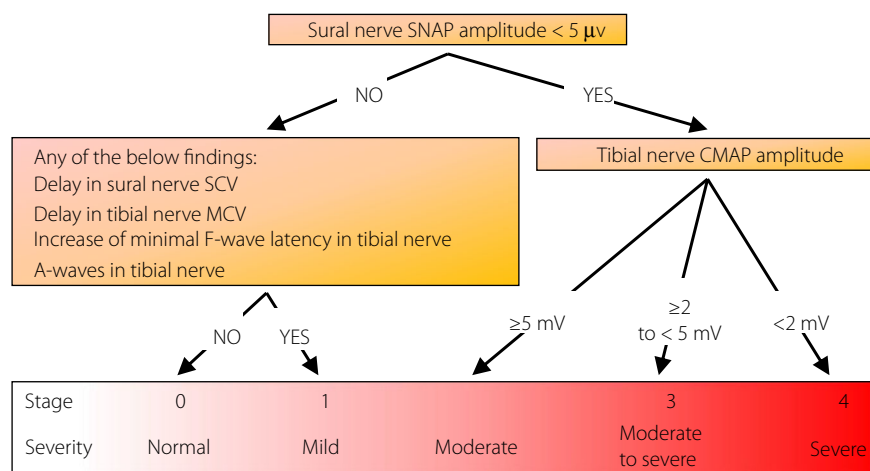


Figure 1 | Baba's classification: a diagnostic and staging algorithm for diabetic polyneuropathy based on nerve conduction study. CMAP, compound muscle action potential; MCV, motor nerve conduction velocity; SCV, sensory nerve conduction velocity; SNAP, sensory nerve action potential. Adapted/translated from Baba *et al.*,² *Japanese Journal of Clinical Neurophysiology*, 2018, by permission of Japanese Society of Clinical Neurophysiology. This image/content is not covered by the terms of the Creative Commons license of this publication. For permission to reuse, please contact the rights holder.


mild DPN, but has limited effectiveness in advanced DPN¹⁵. Although it is important to diagnose DPN at the early stage when epalrestat can be effective, early diagnosis and intervention are rarely achieved due to the limited availability of medical resources. Fortunately, a more effective aldose reductase inhibitor, ranirestat, has been developed in recent years. As ranirestat has been shown to ameliorate the parameters of NCS^{16,17}, it might improve the treatment of advanced DPN. In addition, preclinical studies are actively developing new treatments for DPN. Based on the reports that chronic inflammation associated with metabolic abnormalities also partially comprise the pathology in DPN¹⁸, the effect of omega-3 polyunsaturated fatty acids that have anti-inflammatory/anti-oxidative effects was investigated¹⁹. The report showed that omega-3 polyunsaturated fatty acids exerted neuroprotective effects through Nrf-2 signaling¹⁹.

Furthermore, it should be noted that attempts to elucidate new pathologies of DPN are steadily underway. As male sex has been shown as a risk factor for DPN in humans²⁰, male rodents have

been conventionally used as animal models for DPN. Paradoxically focusing on the current convention, one preclinical study attending to the insusceptibility of females to DPN has reported that DPN was less frequently induced in female rats, similarly to human females²¹. It is expected that the detailed mechanisms of their insusceptibility to DPN will be elucidated in the future. Additionally, there are prospective attempts to elucidate the pathophysiology of DPN; for example studies focusing on microribonucleic acids²², studies using metabolomics²³ and studies focusing on sphingolipids²⁴. We should carefully observe the future developments of DPN research.

DISCLOSURE

The authors declare no conflict of interest.

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