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Research article

Advances in diagnostics and outcome measures in peripheral neuropathies

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HIGHLIGHTS

- Pathologic and functional diagnostic tests in small fiber neuropathy.
- Peripheral nerve imaging: new diagnostic approaches.
- New genetic tests: next-generation sequencing techniques in hereditary neuropathies.
- Outcome measures in neuropathies: improving the quality of trials.

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ABSTRACT

Peripheral neuropathies are a group of acquired and hereditary disorders presenting with different distribution and nerve fiber class involvement. The overall prevalence is 2.4%, increasing to 8% in the elderly population. However, the frequency may vary depending on the underlying pathogenesis and association with systemic diseases. Distal symmetric polyneuropathy is the most common form, though multiple mononeuropathies, non-length dependent neuropathy and small fiber neuropathy can occur and may require specific diagnostic tools. The use of uniform outcome measures in peripheral neuropathies is important to improve the quality of randomized controlled trials, enabling comparison between studies. Recent developments in defining the optimal set of outcome measures in inflammatory neuropathies may serve as an example for other conditions. Diagnostic and outcome measure advances in peripheral neuropathies will be discussed.

1. Introduction

Peripheral nerves can be affected as a consequence of underlying systemic illnesses (e.g., diabetes mellitus, vitamin deficiencies, infectious diseases, malignancies), neurotoxic drugs (e.g., chemotherapy), primary disorders of the immune system (e.g., Guillain–Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy (MMN)), and hereditary disorders (e.g., Charcot–Marie-Tooth disease (CMT), amyloidosis, mitochondrial diseases). Among them, primarily axonal or demyelinating neuropathies, and in some cases mixed forms, can be recognized, and different classes of nerve fibers, namely motor, large sensory conveying touch and proprioceptive sensation, and small sensory conveying thermal and nociceptive sensation and autonomic functions, can be differently involved. The large spectrum of clinical presentations can make the diagnosis challenging. Specific laboratory and neurophysiologic investigations are required to achieve the correct diagnosis and to guide adequate disease-modifying and symptomatic therapies. Finally, the use of uniform outcome measures is determinant to improve the quality of randomized controlled trials, that are of major importance to advance the evidence-based knowledge in the field.

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The epidemiology of peripheral neuropathy varies from quite common (e.g., in diabetes) to rare (e.g., CIDP). The overall prevalence is approximately 2400 (2.4%) per 100,000 people, but in individuals older than 55 years, it rises to approximately 8000 (8%) per 100,000 [53,54]. Hereditary neuropathies have an estimated prevalence of 1 per 2500 people [170], but may be as high as 1 in 1214 persons [24]. The diagnosis of a peripheral neuropathy can be made by careful history, neurological examination and nerve conduction studies (NCS) that helps to distinguish between demyelinating and axonal neuropathies [109]. Features of demyelination are slowing of motor and/or sensory nerve conduction velocity, dispersion of compound motor action potentials (CMAP), prolongation of distal latencies, and increased latency of *F*-waves. Some forms are typically characterized by motor or sensorimotor conduction blocks outside the entrapment sites (e.g., MMN and Lewis–Sumner syndrome, respectively) or at the entrapment sites (e.g., hereditary neuropathy with liability to pressure palsies [HNPP]). In contrast, axonal neuropathies are characterized by reduced amplitude of compound motor action potentials (CMAP) and sensory nerve action potentials (SNAP) with relative preservation of conduction velocities, distal latencies, and *F*-waves [109].

NCS can only assess motor and sensory large nerve fibers. Therefore, it does not provide information on small nerve fibers (e.g., thinly myelinated Aδ and unmyelinated C fibers) that are selectively affected in small fiber neuropathies (SFN). The clinical picture of SFN includes neuropathic pain and autonomic complaints. Pathologically, it is characterized by the degeneration of the distal endings of small nerve fibers in the skin as demonstrated by reduced density of dermal and intraepidermal nerve fibers (IENF) [93,94]. In addition, various other tests may contribute to the diagnosis of SFN, including quantitative sensory testing (QST), corneal confocal microscopy (CCM) and nociceptive evoked potentials.

Several tests, including cardiovascular reflex recording, Laser doppler analysis of cutaneous blood flow (e.g., single-point laser-doppler flowmetry and 2-dimensional laser doppler imaging), and quantitative sudomotor axon reflex testing (QSART) may be useful as a diagnostic tool in autonomic neuropathies.

Capturing changes in peripheral neuropathies using uniform outcome measures is important to improve the quality of randomized controlled trials in neuropathies that enables comparison between studies, but also for clinical practice. Recent developments in defining and getting international consensus regarding the optimal set of outcome measures in inflammatory neuropathies may serve as an example for other conditions [200].

2. Advances in diagnostics

NCS still represent the most important tool in the diagnostic work-up of patients with clinically suspected peripheral neuropathy [130]. Recent advances include recommendations for the interpretation of the neurophysiologic findings useful for the diagnosis of the different forms of neuropathy, among which we emphasize diabetic neuropathy [186], CIDP [1,2], MMN [2], paraproteinemic neuropathies [3], and CMT [134].

3. Skin biopsy

The availability of skin biopsy with quantification of IENF has enabled the recognition of SFN as a distinct clinical entity. IENF are unmyelinated sensory endings with exclusive somatic function that arise from nerve bundles of the subpapillary dermis. They lose the Schwann cell ensheathment as they cross the dermal–epidermal junction [23,92,98] and widely express the capsaicin receptor, making them the most distal nociceptors. Their quantification is possible by means of a 3-mm skin biopsy performed using a disposable circular punch that can include the epidermis and the dermis, allowing also the analysis of sweat glands, hair follicles, and arterovenous anastomosis [96]. A less invasive sampling method is the removal of the epidermis alone by applying a suction capsule to the skin [86,133].

The number of IENF is counted under the optical microscope and is divided by the length of the epidermal surface to obtain a linear density per millimetre (IENF/mm). Normative reference values adjusted for gender and age decade (using the bright-field method) are available [91]. The density of IENF declines with aging and differs between genders. The quantification of epidermal nerve fibers is highly reproducible. However, sensitivity is moderate to good, as in about 12% of patients with complaints of SFN IENF density was normal [45]. The diagnostic value of skin biopsy in patients with SFN neuropathy has been established [95]. The combination between IENF density and dermal nerve quantification may increase the diagnostic yield of skin biopsy in SFN [205]. The morphometric analysis of dermal nerves is more complex than that of IENF. A new method for determination of dermal nerves by measuring the overall length of the fibers was reliable in terms of diagnostic yield in patients with pure SFN [93], but the diagnostic value of this test needs to be established. New methods were recently proposed to obtain a reliable morphometry of sweat gland and pilomotor muscle innervation, which appeared to be concordant with sweating impairment in diabetic neuropathy [64,125].

Skin biopsy correlated with the loss of pinprick sensation in idiopathic SFN [207], with the number of symptoms of SFN assessed by a specific inventory questionnaire [17], and, inversely, with the pain score in patients with sarcoid neuropathy [14]. The relationship between IENF density and neuropathic pain has been investigated in several studies. Although SFN patients may have a higher probably to suffer from neuropathic pain, no correlation was found with pain features [45]. On the other hand, profound loss of IENF has been reported in several painless conditions, like hereditary sensory and autonomic neuropathy type IV with insensitivity to pain [124], Friedreich's ataxia [126], and Ross syndrome characterized by altered sweating but no pain complaints [127]. However, regeneration of IENF has been associated with the recovery from neuropathic pain [172], as observed in hypothyroidism related neuropathy after hormonal therapy [137], steroid responsive neuropathy [123], and impaired glucose tolerance after metabolic improvement [171]. Therefore, our current understanding is that IENF loss may increase the risk to develop neuropathic pain in neuropathy patients, but likely it is not the only cause. Indeed, IENF density can be normal even in some patients harbouring mutations in genes encoding for pain-related sodium channel subunits [56,79].

In patients with Guillain–Barré syndrome, the loss of IENF was found to occur early in the course of the disease and to correlate with severity of neuropathic pain [157]. In CIDP, skin biopsy also revealed a correlation between loss of IENF and autonomic symptoms, but not with pain [33]. Specific IgM deposits have been found on skin nerves in anti-myelin-associated glycoprotein neuropathy [103,173] and a correlation between with IgM blood levels was also described [173]. Skin biopsy is not useful in the diagnosis of vasculitic neuropathy because dermal nerves bundles do not include vessels. However, mononuclear cell infiltration has been observed in unspecific vasculitic neuropathy, systemic lupus erythematosus or eosinophilia [31,192]. The quantification of inflammatory cells in skin biopsies has been proposed as an additional diagnostic tool in diagnosing non-systemic vasculitic neuropathy [194], but this finding needs further studies. Skin biopsy may deserve interest in immune-mediated and inflammatory neuropathies for research purposes, but currently it does not have a role in the diagnosis and no biomarkers have been established yet.