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COMMENTARY

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Painful diabetic neuropathy

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Abbreviations MRI: magnetic resonance imaging · DSP: distal symmetrical sensory polyneuropathy

Polyneuropathy affects approximately 30–50% of all diabetic patients and is the most common form of neuropathy in the developed world [1]. Diabetic polyneuropathy encompasses several neuropathic syndromes, by far the most common of which is distal symmetrical sensory polyneuropathy (DSP). The two main clinical consequences of DSP—foot ulceration sometimes leading to amputation and painful neuropathy—are associated with high rates of patient morbidity and mortality [2]. There is now little doubt that glycaemic control and duration of diabetes are major determinants of DSP. A major European prospective study has recently shown that potentially modifiable, traditional markers of macrovascular disease, such as hypertension, hyperlipidaemia and smoking, are also independent risk factors [3].

Pain is the most distressing symptom and is the main factor that prompts the patient to seek medical advice [4]. Focal and multifocal diabetic neuropathies, such as isolated cranial nerve palsies and proximal lower limb motor neuropathy, may also be associated with pain. Few studies have investigated the prevalence of painful diabetic neuropathy, and these have reported a prevalence rate of 7–20%; the variation reflecting the different criteria used to define neuropathic pain [4]. Nearly 25% of the type 1 diabetic patients enrolled in the European Diabetes (EURODIAB) prospective study developed neuropathic symptoms over a 7-year period [3]. Thus, a high proportion of diabetic patients suffer from neuropathic pain and, unfortunately, current drug treatments are largely symptomatic and frequently ineffective [5].

The features of pain in DSP were documented in the latter part of the 19th century: Pavy observed that it was of burning and unremitting quality, often with a nocturnal exacerbation [6]. Patients describe their pain in various terms as burning, prickling ("pins and needles"), lancinating, shooting ("like an electric shock"), cramping, aching, and report also contact hypersensitivity (allodynia) and "dead feeling" (numbness) in their legs [4]. Walking is experienced by some patients as the sensation of walking barefoot on 'pebbles' or 'scalding sand'. Others describe odd sensations of swelling in their feet. The spectrum of severity is wide. Some patients may have mild symptoms in a toe or two, others may have continuous painful symptoms involving both legs and extending to the upper limbs. In the latter case sleep is usually disturbed. It is therefore not surprising that such patients may be so disabled by the pain that they experience a reduction in their daily activities, or may even lose their employment, become profoundly depressed and have a poor quality of life [4].

Neuropathic pain may present acutely within the context of very poor glycaemic control, typically in type 1 subjects (acute painful neuropathy of poor glycaemic control) or after the initiation of treatment (acute painful neuropathy of rapid glycaemic control) [7]. These acute syndromes are relatively rare compared with the chronic painful neuropathy associated with DSP, and are associated with a rapid build-up of unpleasant sensory symptoms within weeks. This leads to persistent burning pain in the lower limbs, paraesthesiae and allodynia, with a nocturnal exacerbation of symptoms [7]. Depression and precipitous weight loss may also feature. Sensory loss is often mild or absent, and there are no motor signs. Thankfully, in acute painful neuropathies, symptoms may resolve within a year [7].

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Mechanisms of neuropathic pain

Pain is an unpleasant, subjective sensory and emotional experience. Psychological and cultural factors play an important role in its perception and expression. Unlike nociceptive pain, neuropathic pain is caused by dysfunction of the peripheral or central nervous system, and does not require any receptor stimulation [8]. Painful symptoms are relayed via small myelinated A–δ fibres, and unmyelinated C fibres. Unmyelinated C fibres are thought to transmit the slower component of pain, whereas myelinated A–δ fibres relay the faster component. Although the exact pathophysiological mechanisms of neuropathic pain in diabetes remain unknown, several mechanisms have been postulated [8]. During the 1970s and 1980s, researchers tried to identify a neurostructural correlate for painful neuropathy [9]. Asbury and Fields suggested that spontaneous ectopic impulse generation in small-diameter regenerative sprouts could be the cause of neuropathic pain [10]. Experimental evidence for this postulate was provided by Wall and Gutnick [11]. Later studies on sural nerve biopsies were, however, unable to detect a correlation between painful neuropathy and morphological indicators of regeneration [12, 13].

A number of peripheral and central mechanisms have recently been proposed based on the results of experiments in animal models of neuropathic pain (Table 1) [14]. It is increasingly apparent that the insult of diabetes affects all levels of the nervous system, from the peripheral nerve to the brain [15]. Magnetic resonance imaging (MRI) has provided evidence for the involvement of the spinal cord at an early stage of DSP [16, 17]. Lesions in the spinal cord may result in pain syndromes similar to those seen after spinal cord injury or demyelination [18]. In some patients with painful neuropathy there may be few abnormalities on clinical examination or in terms of electrophysiological parameters, but there may be evidence of marked abnormalities in somatosensory-evoked potentials within the spinal cord [19]. A study using magnetic resonance spectroscopy has also recently indicated the presence of thalamic neuronal dysfunction in DSP [20]. Thus, the impact of diabetes on the nervous system appears to be far more generalised than was previously thought, and is in keeping with the recent finding that vascular abnormalities are independent risk factors for DSP [3]. Future research will need to address the full extent of involvement of the central nervous system in both DSP and painful neuropathy.

Table 1 Mechanisms of neuropathic pain [8, 14, 15, 21]

Peripheral mechanisms	Central mechanisms
Changes in sodium channel distribution and expression	Central sensitisation
Altered neuropeptide expression	A–β fibre sprouting into lamina II of the dorsal horn
Sympathetic sprouting	Reduced inhibition of descending pathways
Peripheral sensitisation	
Altered peripheral blood flow	
Axonal atrophy, degeneration or regeneration	
Damage to small fibres	
Glycaemic flux	

Managing neuropathic pain

The assessment and management of neuropathic pain continues to pose a considerable challenge to clinicians [4, 5]. A careful history and peripheral neurological/vascular examination of the patient is essential to exclude other possible causes of leg pain, such as peripheral vascular disease, prolapsed intervertebral discs, spinal canal stenosis and corda equina lesions. Unilateral leg pain should arouse suspicion of lumbar–sacral nerve root compression, and these patients may need to be investigated with a lumbar–sacral MRI. The quality and severity of pain should be assessed using a suitable scale, so that response to treatment may be evaluated [4, 5]. An empathic approach with multidisciplinary support is crucial, since psychological dysfunction is an important factor in the suffering associated with all aspects of the condition [4].

Although there is a strong case for the prevention/delay of the onset of DSP by good blood sugar control, no controlled studies have evaluated the extent to which glucose control reduces pain perception [21]. Despite the lack of well-designed studies in this area, there is, however, general consensus that intensive blood glucose control should be the first step in the treatment of any form of diabetic polyneuropathy. Traditional markers of large vessel disease, including hypertension, obesity, hyperlipidaemia and smoking, also appear to be independent risk factors for DSP and need to be managed effectively [3].

The pharmacological treatment of painful DSP is not entirely satisfactory; available drugs are often ineffective and their use is complicated by side effects [5]. Tricyclic compounds have been used as first-line agents for many years, but many patients fail to respond to them and side effects are frequent [5]. The anticonvulsants gabapentin [5] and pregabalin [21] appear to be better tolerated. Other agents include anticonvulsants such as carbamazepine; opiates such as tramadol and oxycodone; membrane stabilisers including mexiletine and intravenous lignocaine; the antioxidant α-lipoic acid; and topical capsaicin, a substance P depleter [5, 21]. Despite these therapies, the treatment scenario remains less than satisfactory, and many sufferers experience sub-optimal pain relief [21].

Side effects and lack of response to conventional treatment have forced many patients to try alternative therapies such as acupuncture [5], near-infrared phototherapy [22], low-intensity laser therapy [23], magnetic field therapies [24] and transcutaneous electrical nerve stimulation (TENS) [5] and, as a last resort, implantation of an electrical spinal cord stimulator [25]. In this issue of *Diabetologia*, Bosi et al. investigate the efficacy of frequency-modulated electromagnetic neural stimulation (FREMS) therapy and report a significant improvement in pain scores and in some measures of nerve function [26]. Reichstein et al. demonstrate the

effectiveness of high-frequency external muscle stimulation in relieving neuropathic pain [27]. Although both studies report encouraging results, the findings of these two studies need to be confirmed in larger, multicentre, randomized, controlled, long-term trials. The suitability of the 'placebo' devices employed also needs to be addressed. In the study conducted by Bosi et al., small and, hence, less significant amounts of current may be applied as placebo in future studies. Nevertheless, both studies offer novel approaches for the management of neuropathic pain, perhaps with fewer side effects than conventional drug therapy.

Ultimately, targeted studies comparing patients with and without painful symptoms are required to elucidate the underlying mechanisms of pain in DSP, particularly the extent of the pathology in the central nervous system, in order to develop more effective treatments.

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