

Diabetic Neuropathy: Perception Beyond the Seam of the Periphery

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Diabetic peripheral neuropathy (DPN) is a common, debilitating and distressing complication of diabetes. Most patients develop painless, insensate distal nerve damage which increases the risk of foot ulceration and subsequent amputation. Amputation is not only devastating in its impact on the person with diabetes and their family, leading to loss of independence and livelihood; it is also very expensive in material terms and results in only 50% surviving for two years. Around a quarter of all diabetic patients also develop a chronic painful condition mainly affecting the legs which can result in considerable disability and suffering. Many such patients with painful DPN have depression, anxiety, fear and stress, and do not sleep well. There is thus an urgent need to detect DPN early by using objective, validated point-of-care devices as clinical exam or the use of the 10 gram monofilament is not reliable. Early detection will lead to an earlier intervention to reduce risk factors for the development of DPN.

There has also been emerging evidence that DPN may not be as its name suggest, and may involve the central nervous system. Recent studies examining the pathophysiology of painful-DSPN have identified maladaptive alterations at the level of both the peripheral and central nervous systems. We have reported the involvement of the spinal cord in DPN on MRI. More recently we have reported the involvement of the brain in DPN by demonstrating: 1) thalamic neuronal dysfunction using MR Spectroscopy, 2) increased thalamic vascularity in painful DPN on MR perfusion imaging and disruption of the resting state network connectivity on functional MRI. If we are able to develop non-invasive, objective biomarkers of painful DPN this would be a great advance as it would serve as a target for the development of new drugs for this distressing condition.

Additionally, genetic studies have suggested that patients with variants of voltage gated sodium channels may be more at risk of developing neuropathic pain in the presence of a disease trigger such as diabetes. The lecture will review the recent advances in genetics, skin biopsy immunohistochemistry and neuro-imaging, which have the potential to further our understanding of the condition, and identify targets for new mechanism based therapies.

The symptomatic management of painful DPN continues to pose considerable challenge to clinicians as less than 50% of patients respond to current drugs. Innovative, head-to-head and combination trials of new and existing drugs are required.

We have obtained \$4.8 m funding from the UK NIHR to conduct such a trial. Finally, there is early evidence that a patient's pain phenotype may determine response to treatment although further studies are required.