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Tesfaye, S. and Sloan, G. (2021) Involvement of the central nervous system in diabetic distal symmetrical polyneuropathy. *Journal of Xiangya Medicine*, 6. 27.

<https://doi.org/10.21037/jxym.2020.02.03>

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Involvement of the central nervous system in diabetic distal symmetrical polyneuropathy

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Comment on: Zhang Y, Qu M, Yi X, *et al.* Sensorimotor and pain-related alterations of the gray matter and white matter in Type 2 diabetic patients with peripheral neuropathy. *Hum Brain Mapp* 2020;41:710-25.

Received: 15 January 2020; Accepted: 17 February 2020; Published: 30 September 2021.

doi: [10.21037/jxym.2020.02.03](https://doi.org/10.21037/jxym.2020.02.03)

View this article at: <http://dx.doi.org/10.21037/jxym.2020.02.03>

Diabetic peripheral neuropathy (DPN) is a serious and common chronic complication of diabetes mellitus, with up to half of the sufferers' developing chronic neuropathic pain (painful-DPN). Unfortunately, our understanding of the pathophysiology of both painless- and painful-DPN remains inadequate. Consequently, we currently have no efficacious disease modifying therapies for either condition, apart from robust evidence for good glycaemic control in preventing DPN in patients with type 1 diabetes. Neuronal injury in DPN has been well recognised within the peripheral nervous system for over a century. Studies in the 1960's identified pathological alterations in spinal cord and brain structures in patients with diabetes and advanced microvascular complications (1,2). However, for many years after these findings, the involvement of central nervous system (CNS) in DPN was largely overlooked until the advent of advanced neuroimaging techniques in the latter part of the 20th century.

Magnetic resonance imaging (MRI) is able to non-invasively investigate not only the gross structure, but the micro-structure, function and vascular supply of the brain. MRI studies have demonstrated a number of structural abnormalities, including spinal cord atrophy (3) and grey matter volume reduction (4) as well as functional abnormalities, including thalamic neuronal dysfunction (5), increased thalamic vascularity (6), altered thalamo-cortical connectivity (7) and functional reorganization of the somatosensory cortex (8), associated with DPN.

In a recent publication Zhang *et al.* studied 44 patients with type 2 diabetes and painless-DPN, 23 patients with

painful-DPN and 88 healthy control subjects without diabetes (9). Compared to healthy controls, patients with DPN had abnormalities in the pre- and post-central gyrus and a number of deep grey matter nuclei. They also demonstrated altered white matter tracts including corticospinal, spinothalamic and thalamo-cortical projecting fibres. They concluded that these findings suggest impaired motor and somatosensory pathways in DPN. In this study the presence of peripheral neuropathy was confirmed using detailed upper and lower limb neurological examination, nerve conduction testing and a battery of quantitative sensory testing measures, as well as symptoms and clinical signs. According to Toronto consensus (10) "confirmed" neuropathy is diagnosed in the presence of abnormal nerve conduction and the group appear to have adhered to this recommendation; however, both the painless- and painful-DPN groups had at best very mild peripheral neuropathy with almost normal peroneal and sural nerve amplitudes and nerve conduction velocities. Moreover, the neuropathy disability score was less than 3 in both the painful- and painless-DPN groups, again indicating almost subclinical-DPN. Thus, given the early neuropathy features of these DPN groups the demonstration of significant structural abnormalities in the brain does raise the possibility that the insult of hyperglycaemia/vascular risk factors associated with diabetes may concomitantly affect both the PNS and CNS. When the discovery of spinal cord atrophy in DPN was first demonstrated the assumption was that this was secondary to distal axonopathy ('dying back phenomenon') (11). However, a further larger study including subjects with

subclinical-DPN demonstrated involvement of the spinal cord, indicating that this process is very early or possibly concomitant to peripheral nerve injury (3). We know that diabetes affects the autonomic nervous system, corneal nerve fibres and cranial nerves. The impact of diabetes on the nervous system could therefore be more generalized, affecting both the periphery and CNS at the same time.

Although the study by Zhang *et al.* does point to significant CNS abnormalities in both painless- and painful-DPN, the natural history of these needs further examination in the context of a longitudinal study (9). This will give us insight into the direction of causality and pathological processes underlying cerebral involvement. The addition of a diabetes group without neuropathy as well as a disease control group of subjects with a non-DPN may be useful in identifying the diabetes effect and a generic neuropathy effect on the brain. Moreover, although there may be technical difficulties in conducting multiple MR techniques at the same time in the same subject, there is clearly a need to study both structure and function components at the same time. For example, we need to understand why there is a reduction in somatosensory peripheral grey matter volume (4). What are the potential mechanisms for this? It might be possible that these patients may have abnormal regional blood perfusion or a reduction in neuronal activity because of altered peripheral and long-tract neuronal function. Considerable insight could be gained from MR perfusion imaging, including dynamic susceptibility contrast and arterial spin labelling (12). MR proton spectroscopy could provide information into neuronal function (5) and changes in neurotransmitter (e.g., GABA) levels (13) within regions of interest in the brain. Furthermore, functional MR imaging, either in the resting state of task-based - such as blood oxygen dependent (BOLD) (7,8) could be used to inform areas of altered activity in carefully characterised and phenotyped patients with or without DPN. Although technically challenging, with the use of higher field strength MR scanners functional spinal cord imaging may become feasible to characterise involvement of spinal involvement in DPN. In addition, MR imaging has been largely used for the study of peripheral rather than autonomic neuropathy in diabetes; however, cardiac MR could be used to investigate the effect of diabetic cardiac autonomic neuropathy on cardiac haemodynamics. Other imaging modalities have been favoured for the investigation of autonomic neuropathy, e.g., PET/MIBG. Future studies need to be designed to be adequately powered, randomised, controlled and if possible in a multicentre setting, using standardised

imaging parameters. This is likely to make the findings generalizable. Moreover, there is recent evidence that DPN may have different underlying disease mechanisms in type 1 compared with type 2 diabetes. Therefore, studies must control for the type of diabetes. Investigation into the CNS alterations between type 1 and type 2 diabetes is important too, as it is unknown as to whether structural and functional alterations differ between types of diabetes. The involvement of CNS in DPN, hitherto considered a “purely peripheral neuropathy” (14), has opened a whole new area for further research and has a great potential for the development of new treatments for DPN.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This is an invited article commissioned by the Editorial Office, *Journal of Xiangya Medicine*.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at <https://dx.doi.org/10.21037/jxym.2020.02.03>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/jxym.2020.02.03

Cite this article as: Tesfaye S, Sloan G. Involvement of the central nervous system in diabetic distal symmetrical polyneuropathy. *J Xiangya Med* 2021;6:27.