Publication News 94 - 30 October 2023

Cutaneous Schwann cell abnormalities in diabetic peripheral neuropathy

Aims: To investigate the structural changes of cutaneous Schwann cells on skin biopsy in people with type 1 diabetes (T1D) and diabetic peripheral neuropathy (DPN) and determine the relationship between these changes and neuropathic symptoms.

Methods: Participants enrolled in a larger cross-sectional study were selected from four groups [healthy controls, n=25; T1D without DPN (T1D), n=25; with Painless DPN (T1DPN) n=30; and with Painful DPN (P-T1DPN), n=27]. Participants underwent neurological assessments, including: DPN-Check (measuring sural nerve amplitude and velocity); skin biopsy with intra-epidermal nerve fibre density (IENFD); Biothesiometer; Toronto Clinical Neuropathy Score (TCNS); Michigan Neuropathy Screening Instrument (MNSI); and neurological examination. Confirmed DPN was diagnosed using the Toronto criteria, and symptoms of Painful-DPN defined as participants who 'reported pain in both feet/legs' in combination with confirmed DPN. Skin biopsy samples were immunostained with antibodies to visualise Schwann cells and nerve fibres.

Results: There was a group difference in the number density of nociceptive Schwann cells not abutting nerve fibres (thus considered structurally damaged Schwann cells) after adjusting for age, sex and HbA1c (p=0.004), with a greater number in the two DPN groups compared with healthy controls. Dermal Schwann cell area fraction and subepidermal Schwann cell process density were also lower in DPN compared to non-DPN groups. No measures differentiated painful- and painless-DPN, however. IENFD correlated with measures of Schwann cells; and there were weak correlations with Schwann cell measures and symptom scores, e.g. between dermal Schwann cell area fraction and MNSI/TCNS.

Conclusions: Thus, the authors conclude that the expression of cutaneous Schwann cells is reduced (processes and not somata) and interdependent (with cutaneous nerve fibres) in this cohort of DPN and correlates weakly with neuropathy severity, but not neuropathic pain.

Comments. Skin biopsy with IENFD is a minimally invasive technique, which has clinical applications including the diagnosis of diabetic peripheral neuropathy (DPN). However, IENFD does not differentiate between painful- and painless-DPN and does not correlate with neuropathic symptoms. Thus, studies, such as this one, have performed skin biopsies, and examined other markers to investigate whether they might explain neuropathic symptoms.

This study shows that cutaneous Schwann cells are damaged/reduced in DPN, this is consistent with other studies showing that Scwhann cells are involved in the pathophysiology of the condition. However, the results appear to indicate that cutaneous Schwannopathy is unrelated to Painful-DPN.

The great strength of this study is the multi-modal analysis of Schwann cells/neuronal markers, particularly important as there is no consensus as to how to quantify cutaneous Schwann cells. Moreover, the participant numbers were good for a skin biopsy study. Limitations include the definition of painful-DPN used, and that the included participants had mild symptoms, thus the painful-DPN group may not be entirely representative.

This novel study opens new avenues for research, as subtyping cutaneous Schwann cells may help us to better understand the mechanisms of DPN and may represent a target for new treatments.

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Reference. Hu X, Buhl CS, Sjogaard MB, Schousboe K, Mizrak HI, Kufaishi H, Jensen TS, Hansen CS, Yderstræde KB, Zhang MD, Ernfors P, Nyengaard JR, Karlsson P. Structural changes in Schwann cells and nerve fibres in type 1 diabetes: relationship with diabetic polyneuropathy. Diabetologia. 2023 Sep 20. doi: 10.1007/s00125-023-06009-z. Epub ahead of print. PMID: 37728731.
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