Publication News 92 - 16 October 2023

Corneal sub-epithelial microneuromas and axonal swelling are more common in people with painful compared with painless diabetic neuropathy

***Aims*:** To further investigate corneal nerve pathology in distal symmetrical polyneuropathy (DSPN) using corneal confocal microscopy (CCM).
***Methods*:** In this cross-sectional study, 27 non-diabetic controls, 33 individuals with diabetes and without DSPN (DM), 25 individuals with non-painful DSPN, and 18 individuals with painful DSPN were included. Participants underwent clinical laboratory tests, questionnaires, neurological examination, nerve conduction studies (NCS), and CCM. DSPN diagnosis was made using presence of signs and symptoms of DSPN and abnormal peroneal nerve conduction velocity (<42 m/s). Painful DSPN was defined according to the presence of pain with intensity of ≥4/10. Corneal nerve fibre morphology was compared using ANCOVA. The presence of corneal sub-epithelial microneuromas (CSEMN) and axonal swellings between groups was tested with Fisher's exact test.
***Results*:** No significant differences were found in central corneal, inferior whorl, or combined metric parameters between painful and non-painful DSPN participants (p=0.58). CCM parameters were reduced in painful and non-painful DSPN compared to non-diabetic controls (both p≤0.009) and those with DM (both p=0.032). Corneal nerve fibre length (CNFL) (p=0.025) and density (CNFD) (p=0.031) were reduced in DM participants versus non-diabetic controls. Inferior whorl length was lower in painful DSPN compared to non-diabetic controls (p=0.036), and a greater loss was found in non-painful DSPN compared to those with DM (p=0.005) and non-diabetic controls (p=0.002). Axonal swellings were more prevalent in individuals with painful DSPN compared to those with non-painful DSPN (p=0.018), DM, and non-diabetic controls (both: p<0.001). Axonal swellings were more frequently observed in non-painful DSPN compared to non-diabetic controls (p=0.014). CSEMNs were more prevalent in painful DSPN compared to DM (p=0.008) and non-diabetic controls (p=0.001), and in individuals with non-painful DSPN compared to DM (p=0.042) and non-diabetic controls (p=0.007). The presence of axonal swelling and all CSEMN combined was increased in individuals with painful DSPN compared to all other groups (p=0.026). There was a noticeable trend towards an increased presence of these features in more severe DSPN presentations (p=0.022).
***Conclusions*:** CSEMN and axonal swelling in the cornea are more prevalent in individuals with DSPN, suggestive of an escalation from DM which may be related to the presence of pain in DSPN.

Comments. Painful DSPN is challenging to treat due to the limited efficacy and safety concerns of current treatments. Distinguishing painful from painless presentations could offer crucial insights into the underlying pathophysiology. Studies exploring markers of dermal innervation have yielded conflicting results. CCM serves as a diagnostic tool, detecting nerve fibre loss and early axonal damage in the cornea. The study highlights the potential for novel morphological features of CCM images. Limitations include the exploratory nature of this study, the absence of a validated screening tool for neuropathic pain, and reliance on pain intensity to delineate painful and painless presentations. The non-painful DSPN group included 6/25 (24%) participants reporting pain intensity <4 while undergoing analgesic treatment possibly affecting their pain scores and leading to possible misclassification. However, the study is of interest for the differences found in CCM between painful and painless DSPN, with potential to serve as biomarkers for understanding the pathogenic mechanisms associated with neuropathic pain. Prospective longitudinal studies in people with incipient DSPN using CCM could provide insight into a causative link between neuropathic pain and corneal axonal swellings. This may offer the opportunity for skin biopsies as a comparator to determine whether the manifestation of these morphological small fibre pathologies is heterogeneous between the skin and cornea in people with DSPN.

Jamie Burgess

Reference. Sierra-Silvestre E, Andrade RJ, Holguín-Colorado L, Edwards K, Coppieters MW. Occurrence of corneal sub-epithelial microneuromas and axonal swelling in people with diabetes with and without (painful) diabetic neuropathy. Diabetologia. 2023 Sep;66(9):1719-1734. doi: 10.1007/s00125-023-05945-0. Epub 2023 Jun 10. PMID: 37301795; PMCID: PMC10257488.
https://link.springer.com/article/10.1007/s00125-023-05945-0