Scoping Review Protocol Summary: Corneal Confocal Microscopy in Neurodegenerative Diseases

Introduction

This scoping review explores the application of corneal confocal microscopy (CCM) as an emerging paraclinical tool for detecting and quantifying small fibre pathology in neurodegenerative diseases (NDDs). CCM, first introduced by Lemp and colleagues in 1985, revolutionised anterior segment imaging by allowing high-resolution, non-invasive, in vivo visualisation of the cornea at the cellular level. Although originally developed to evaluate corneal pathology such as infectious keratitis, dystrophies, and wound healing after refractive procedures, its role has expanded significantly over the past decade to include systemic neurological disease assessment.

The corneal sub-basal nerve plexus (SNP)—a dense network of unmyelinated sensory fibres situated between the epithelium and Bowman's layer—can be imaged with CCM to assess small nerve fibre structure and function. These corneal fibres originate from the ophthalmic branch of the trigeminal nerve and share many structural and physiological characteristics with peripheral and central small fibres implicated in neurodegenerative processes. Given this anatomical and pathophysiological overlap, the corneal SNP has been proposed as a surrogate biomarker for early neurodegenerative change.

Quantitative analysis of corneal nerve morphology using CCM has become increasingly sophisticated. Commonly reported parameters include corneal nerve fibre density (CNFD), corneal nerve fibre length (CNFL), corneal nerve branch density (CNBD), and corneal nerve fibre tortuosity (CNFT). Alterations in these metrics have been consistently demonstrated in various systemic neuropathies and, more recently, across a growing spectrum of NDDSs. The advent of automated image analysis and artificial intelligence (AI) has enhanced the reproducibility and scalability of these measurements, reducing inter-observer variability and enabling standardised, large-scale analysis.

Compared with conventional neurodiagnostic modalities such as magnetic resonance imaging (MRI) or cerebrospinal fluid (CSF) biomarkers, CCM provides a rapid, minimally invasive, and reproducible method for visualising small fibre pathology. Moreover, its ability to simultaneously assess corneal immune cell morphology and dendritic cell activation extends its potential application to neuroinflammatory conditions, broadening its relevance beyond classical NDDs.

Significant barriers to the clinical adoption of CCM include methodological heterogeneity, variability in imaging and analysis protocols, lack of consensus on

diagnostic thresholds, and limited availability of validated automated tools. Furthermore, differences in study design, disease stage, and patient demographics have contributed to inconsistent findings across the literature.

This scoping review aims to analyse and summarise the existing evidence on the use of CCM in a range of NDDs It also provides a quantitative overview through forest plots, which visually summarise trends in key corneal nerve parameters (CNFD, CNFL, and CNBD) across different NDD entities. These plots are not intended for meta-analytic inference but to enhance clarity and facilitate visual comparison between studies.

Research Questions and Rationale for Scoping Review Design

This scoping review aims to map the breadth and methodological diversity of research using corneal confocal microscopy (CCM) to assess small-fibre pathology in neurodegenerative diseases. The primary research questions are:

1. Which neurodegenerative diseases have been investigated using in vivo corneal confocal microscopy as a potential biomarker of neurodegeneration?
2. What CCM parameters (CNFD, CNFL, CNBD, CNFT, and immune cell metrics) and image analysis techniques have been used across studies?
3. How consistent are the reported findings across diseases and study designs, and what sources of methodological heterogeneity are evident?
4. What knowledge gaps and limitations exist in the current evidence base, and what directions are most suitable for future systematic reviews or meta-analyses?

A scoping review design was selected to capture the wide variability in study designs, disease entities, imaging methodologies, and analysis techniques. This approach allows inclusion of heterogeneous data while maintaining transparency and reproducibility, which is essential in emerging and methodologically diverse research fields such as CCM.

Methods

This project is a scoping review, conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR).

Search Strategy

A comprehensive search was carried out in PubMed and Scopus databases, assessing all

peer-reviewed studies using CCM in the assessment of neurodegenerative diseases. The search combined terms such as “corneal confocal microscopy” AND “neurodegenerative disease,” and was adapted for individual disease entities (e.g., Parkinson’s disease, Alzheimer’s disease, multiple sclerosis, amyotrophic lateral sclerosis, and others). Reference lists of included studies were manually screened to identify additional eligible articles, and forward citation tracking was used to ensure completeness. The last search was conducted on 30 November 2024.

Eligibility Criteria

Studies were included if they met the following criteria:

1. Studies published in English within the past ten years.
2. Investigated human participants with a clinically confirmed neurodegenerative disease.
3. Used CCM to visualise or quantify the corneal sub-basal nerve plexus (SNP).
4. Reported at least one quantitative corneal nerve fibre parameter (CNFD, CNFL, CNBD, CNFT).
5. Explored the diagnostic, monitoring, or prognostic utility of CCM in neurodegenerative disease.

Exclusion criteria included: animal or ex vivo studies, publications unrelated to neurodegeneration (e.g., purely ocular or inflammatory diseases without neurological involvement), case reports, reviews, editorials, preprints, and non-peer-reviewed articles.

Study Selection

Search results were imported into EndNote (version 2021) for reference management and duplicate removal. Two reviewers (E.O. and A.P.) independently screened titles and abstracts according to predefined eligibility criteria. Any disagreements were resolved by discussion and adjudication by a third reviewer (S.H.). Full-text screening followed the same procedure. The overall selection process was documented in a PRISMA flow diagram, providing transparency in inclusion and exclusion decisions.

Data Extraction

Data were charted using a standardised extraction form tailored for this scoping review. Extracted variables included:

1. Study characteristics (authors, year, country, and setting).
2. Participant demographics and disease type.
3. Study design and sample size.
4. CCM imaging methods and analysis software used.
5. Reported corneal nerve fibre parameters (CNFD, CNFL, CNBD, CNFT).
6. Key outcomes, correlations with disease severity, and limitations.

Data Synthesis and Presentation
Quantitative data from included studies will be summarised using descriptive statistics and visually represented in forest plots that display individual study findings for key parameters (CNFD, CNFL, CNBD). These plots are intended solely for descriptive visualisation, not for statistical pooling or meta-analytic inference. The aim is to enhance clarity and enable visual comparison of trends across studies while acknowledging that a formal quantitative synthesis lies beyond the scope of a scoping review. Results will also be tabulated to facilitate comparison of imaging methodologies, analysis software, and study designs.

Summary

This scoping review systematically maps all available evidence on the use of corneal confocal microscopy in neurodegenerative diseases, synthesising both qualitative and quantitative findings through narrative review and descriptive forest plot visualisation. The study aims to clarify the diagnostic potential of corneal nerve fibre parameters (CNFD, CNFL, CNBD) as biomarkers of systemic neurodegeneration and to guide future standardisation of imaging and analysis protocols.

Metadata

Keywords: Corneal confocal microscopy, Neurodegenerative diseases, Corneal nerves, Small fibre neuropathy, Scoping review, Forest plots, Biomarkers
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