RESEARCH ARTICLE

Corneal Confocal Microscopy Identifies Parkinson's Disease with More Rapid Motor Progression

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ABSTRACT: Background: Corneal confocal microscopy (CCM) is a noninvasive, reproducible ophthalmic technique to quantify corneal small nerve fiber degeneration. CCM demonstrates small nerve fiber damage in Parkinson's disease (PD), but its role as a longitudinal biomarker of PD progression has not been explored.
Objective: The aim of this study was to assess corneal nerve morphology using CCM in relation to disease progression in PD.
Methods: Sixty-four participants with PD were assessed at baseline and at 12-month follow-up. Participants underwent CCM with automated corneal nerve quantification and assessment of Movement Disorder Society Unified Parkinson's Disease Rating Scale, Hoehn and Yahr stage, and Montreal Cognitive Assessment.
Results: Corneal nerve fiber density (CNFD), corneal nerve branch density, corneal nerve fiber length, corneal total branch density, and corneal nerve fiber area were significantly lower in participants with PD compared with healthy control subjects. Worsening of Movement Disorder Society Unified Parkinson's Disease Rating Scale part III score over 12 months was significantly greater in participants with a CNFD in the lowest compared with the highest quartile at baseline (mean difference: 6.0; 95% CI: 1.0–10.9; $P = 0.019$). There were no significant changes in CNFD, corneal nerve branch density, corneal nerve fiber length, corneal total branch density, corneal nerve fiber area, or corneal nerve fiber width between baseline and 12-month follow-up.
Conclusions: CCM identifies neurodegeneration in patients with PD, especially those who show the greatest progression in neurological disability. CCM may be a useful tool to help enrich clinical trials with those likely to exhibit more rapid progression and reduce required sample size and cost of studies.

Key Words: Parkinson's disease; biomarkers; corneal confocal microscopy; small fiber; disease subtype

Parkinson's disease (PD) is a heterogenous clinical syndrome in relation to both movement disorder and associated nonmotor manifestations. Indeed, nonmotor features, such as autonomic dysfunction,[1] sleep disorders,[2] and peripheral neuropathy,[3] have prognostic value and may indicate distinct subtypes of PD.[4]

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Peripheral nerves are a target for α-synuclein deposition,[5-7] and peripheral neuropathy[3] and autonomic dysfunction[1] have been associated with more severe disease phenotypes. Subtyping PD may enable a better understanding of disease mechanisms and prediction of disease progression.

Skin biopsies in people with PD demonstrate α-synuclein deposition and small fiber neurodegeneration.[7-9] Higher α-synuclein ratios have been correlated with more advanced disease in PD,[9] and cutaneous small fiber degeneration has been correlated with motor severity.[8]

Corneal confocal microscopy (CCM) is a novel noninvasive ophthalmic method that enables in vivo quantification of small nerve fiber damage. It was initially developed to overcome the limitations of light microscopy, which can only study corneal nerve architecture in vitro and produces poor-resolution images.[10] The cornea has the densest small fiber innervation in the body and has a central corneal nerve density of approximately 7000 nociceptors per square millimeter, resulting in the cornea being 300 to 600 times more sensitive than skin.[11] CCM has been used to detect small fiber degeneration in a range of peripheral neuropathies, including diabetic neuropathy,[12] idiopathic small fiber neuropathy,[13] chronic inflammatory demyelinating polyneuropathy,[14] and Charcot–Marie–Tooth disease.[15] The key parameters to quantify corneal nerve morphology are corneal nerve fiber density (CNFD); a measure of the number of main nerves, corneal nerve branch density (CNBD); a measure of the number of branch points and corneal nerve fiber length (CNFL); and a measure of the total length of main nerves and branches (see Fig. 2). More recently, fully automated analysis has enabled the quantification of corneal nerve fiber area (CNFA), corneal nerve fiber width (CNFW), and corneal total branch density (CTBD).[16] CNFD has been shown to have a better sensitivity and specificity compared with intraepidermal nerve fiber density from skin biopsies in the diagnosis of diabetic polyneuropathy.[17,18] CCM can also identify early nerve regeneration evidenced by an increase in CNFD and CNFL after simultaneous kidney and pancreas transplantation in patients with type 1 diabetes[19] and CNFD, CNBD, and CNFL after bariatric surgery in patients with obesity.[20] CCM has undergone multiple validation studies and has been shown to be a reliable and highly reproducible corneal nerve imaging technique.[21,22]

Several cross-sectional studies using CCM have demonstrated corneal nerve fiber degeneration in participants with PD compared with control subjects.[23-25] Our initial pilot study of CCM in 26 participants with PD demonstrated a decrease in CNFD and an increase in CNBD and CNFL compared with control subjects, indicative of proximal nerve degeneration with more distal nerve regeneration.[23] Several skin biopsy studies have reported cutaneous denervation in PD compensated by nerve regeneration (suggested by the presence of increased nerve branching), which declines over time.[26,27] Our more recent study of 98 participants with PD demonstrated a reduction in all CCM parameters compared with control subjects.[28] Nerve regeneration may result in an increase in branches and total length of nerves; thus, CNBD and CNFL may vary according to the stage of disease. All PD studies using CCM to date have been cross sectional, which does not allow an assessment of the utility of quantifying CCM parameters to predict disease progression. In this study, we have assessed corneal nerve morphology at baseline and over 12 months in relation to change in disease severity in patients with PD.

Subjects and Methods

National Research Ethics Service (NRES) Committee/North West approved the study (Reference no. 17/NW/0144). Written informed consent was obtained from each participant. This research adhered to the tenets of the Declaration of Helsinki for clinical research involving human subjects.

Subjects

Patients with PD who fulfilled Queen Square Brain bank criteria[29] were recruited from clinics across Greater Manchester and via Fox Trial Finder and Parkinson's UK websites between September 2017 and September 2018. Eighty-four participants were screened based on their clinical history and blood tests (full blood count, urea and electrolytes, glycated hemoglobin, immunofluorescence antinuclear antibodies, B12, folate, immunoglobulins, serum electrophoresis, and thyroid function tests). Exclusion criteria were concurrent diagnosis of diabetes, active malignancy, hepatic disease, any known cause of neuropathy, chronic corneal pathologies, history of refractive surgery, and any systemic disease known to affect the cornea, such as Fabry's disease, chronic kidney disease, and Sjogren's disease. Seventy-five participants with PD were enrolled into the study, and 64 were followed up after 12 months (Supporting Information Fig. S1).

Twenty-five healthy volunteers were recruited as control subjects and compared with the baseline CCM parameters of the 64 participants with PD.

Medical History and Neurological Assessment

Participants' age, sex, medical history, and medications, including dopaminergic therapy, were documented. Levodopa-equivalent daily dose was calculated according to validated conversion tables.[30-32] Disease duration was calculated from the date of diagnosis to the date of assessment. All participants underwent a neurological examination to exclude participants with clinically manifest peripheral neuropathy. All parts of the Movement Disorder Society Unified Parkinson's Rating Scale (MDS UPDRS)[33] were performed on participants

in the ON state, the Hoehn Yahr scale was used to assess disease stage, and cognitive function was assessed using the Montreal Cognitive Assessment (MoCA)[34] scale.

Ophthalmic Assessment

All ophthalmic assessments were performed by trained optometrists. Both eyes were first assessed with a slit-lamp biomicroscope (Slit Lamp BD 900; Haag-Streit, Koeniz, Switzerland) to exclude anterior eye pathology. Laser scanning CCM (Rostock Cornea Module/Heidelberg Retina Tomograph lll; Heidelberg Engineering GmbH, Heidelberg, Germany) was performed at baseline and after 12 months of follow-up. CCM was performed with patients in the ON state to minimize interference from motor symptoms. A drop of 0.4% benoxinate hydrochloride (Oxybuprocaine Hydro 0.4%; Bausch & Lomb, Surrey, UK) was used to anesthetize each eye. Viscotears (Carbomer 980, 0.2%; Novartis, London, UK) was also applied to the participants' eyes to reduce any discomfort. Head/chin frames were used to stabilize the position of the participant's head. The participants were asked to fixate on an outer fixation target with the contralateral eye and a charge-coupled device was used to identify the exact location of the camera on the corneal surface during the examination.

The full thickness of the central cornea was scanned using the section mode, and 2D images measuring 384 × 384 μm with optical resolution of 10 μm/pixel were obtained. Multiple images of the subbasal plexus were taken and stored in a database. The total time taken to acquire CCM images for each patient was ~10 min.

Six high-quality (three per eye) images of the subbasal nerve plexus were selected for each patient, following an established protocol to eliminate any variability in image selection.[21] Automated CCMetrics software, version 2.0 (University of Manchester, Manchester, UK) was used to quantify the nerve fibers. This fully automated analysis ensures blinded quantification of six corneal nerve parameters: CNFD, the number of main nerves per frame (number [no.]/mm^2); CNBD, the number of branches arising from major nerves (no./mm^2); CNFL, the total length of all nerve fibers and branches (mm/mm^2); CTBD, the total number of branches per frame (no./mm^2); CNFA, the total area of nerve fibers per frame (μm^2/mm^2); and CNFW, the average axial diameter of nerve fibers per frame (μm). A mean was derived for each parameter.

Statistical Analysis

IBM SPSS version 25 was used to analyze the results. Normality of distribution was assessed by the Shapiro-Wilk test. Means of continuous data for participants with PD and control subjects at baseline were compared using an independent *t* test for normally distributed data and Mann-Whitney *U* test for nonparametric data. Cohen's d was calculated to measure effect size: d = 0.2 (small), d = 0.5 (medium), d = 0.8 (large).[35] χ^2 test was used to compare categorical data. Paired samples *t* test was used to compare means of normally distributed data at baseline and 12-month follow-up. The McNemar-Bowker test was used to compare proportions of paired categorical outcomes.

To compare rate of disease progression in participants with the most and least corneal nerve damage at baseline, we divided participants into four quartiles based on their baseline CCM parameter values. An independent *t*-test was used to compare the means of change in MDS

TABLE 1. Clinical characteristics and corneal confocal microscopy parameters of participants with PD at baseline and 12-month follow-up

	Baseline	12-Month Follow-up	*P*
Clinical scores/LEDD			
MDS UPDRS II	10.5 ± 6.7	11.1 ± 6.8	0.203
MDS UPDRS III	27.4 ± 10.3	31.5 ± 12.3	<0.001*
Full MDS UPDRS	52.0 ± 19.4	58.1 ± 20.0	<0.001*
Hoehn & Yahr stage	I:9, II:45, III: 10 2 (2, 2)	I:7, II:49, III:7, IV:1 2 (2, 2)	0.593
MoCA	26.5 ± 2.8	26.1 ± 3.4	0.297
LEDD	483.5 ± 260.7	578.5 ± 312.8	<0.001*
CCM parameters			
CNFD (no./mm^2)	24.47 ± 7.28	24.75 ± 7.80	0.707
CNBD (no./mm^2)	25.24 ± 13.32	27.12 ± 15.86	0.191
CNFL (mm/mm^2)	14.06 ± 3.48	14.17 ± 3.63	0.703
CTBD (no./mm^2)	36.22 ± 18.53	38.95 ± 20.16	0.170
CNFA (μm^2/mm^2)	5234 ± 1419	5200 ± 1611	0.812
CNFW (μm)	20.67 ± 0.98	20.5 ± 1.00	0.273

Data are shown as mean ± SD apart from Hoehn & Yahr score (median with interquartile range).
LEDD, levodopa-equivalent daily dose; MDS UPDRS II, Movement Disorder Society Unified Parkinson's Disease Rating Scale part II; CCM, corneal confocal microscopy; MoCA, Montreal Cognitive Assessment; CNFD, corneal nerve fiber density; CNBD, corneal nerve branch density; CNFL, corneal nerve fiber length; CTBD, corneal total branch density; CNFA, corneal nerve fiber area; CNFW, corneal nerve fiber width.
*$P < 0.05$ was considered statistically significant.

UPDRS part III (MDS UPDRS III) scores after 12 months between participants in quartiles 1 and 4.

Linear regression was used to measure the variation in change in MDS UPDRS III scores after 12 months in participants with the lowest number of nerves (CNFD quartile 1) compared with the highest number of nerves (CNFD quartile 4) after adjusting for the effects of age, sex, and disease duration. The first linear regression model consisted of "CNFD quartile 1 versus CNFD quartile 4" as the independent variable. The second linear regression model studied the effects of "CNFD quartile 1 versus CNFD quartile 4" on change in MDS UPDRS III after 12 months, after adjusting for the effects of age, disease duration, and sex by entering all four factors as independent variables. Tests for linearity, homoscedasticity, multicollinearity, influential data points, and normality showed that the assumptions of the regression analysis were met.

Spearman's correlation was used to assess for correlation between change in levodopa-equivalent daily dose, change in CCM parameters, change in MDS UPDRS scores, and change in MoCA over 12 months.

Data were reported as mean ± SD, and $P < 0.05$ was considered statistically significant. The study was an

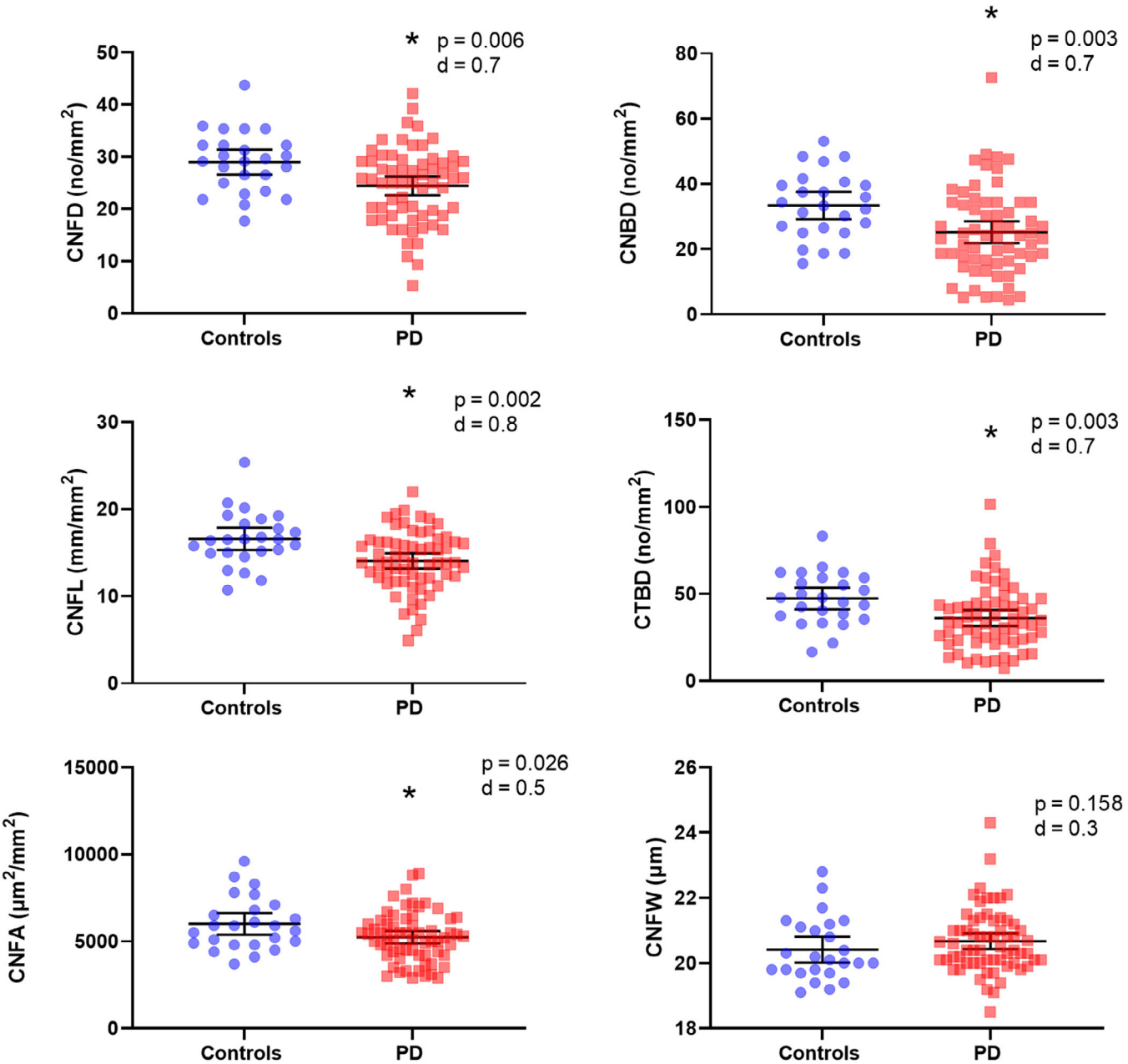

FIG. 1. Corneal confocal microscopy parameters in participants with Parkinson's disease (PD) compared with control subjects. Mean ± 95% CI of corneal nerve fiber density (CNFD), corneal nerve branch density (CNBD), corneal nerve fiber length (CNFL), corneal nerve total branch density (CTBD), corneal nerve fiber area (CNFA), and corneal nerve fiber width (CNFW) in patients with PD compared with controls with significance levels and Cohen's d effect size. no, number. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2. Change in MDS UPDRS III over 12 months between participants corneal nerve parameters in quartile 1 (most severe corneal nerve degeneration) compared with quartile 4 (least severe corneal nerve degeneration) at baseline

	No. of Participants	Change in MDS UPDRS III After 12 Months	*P*
CNFD quartile 1	17	6.9 ± 8.0	0.019*
CNFD quartile 4	18	0.9 ± 6.3	
CNBD quartile 1	16	5.4 ± 7.8	0.406
CNBD quartile 4	17	3.1 ± 7.5	
CNFL quartile 1	16	5.6 ± 8.1	0.367
CNFL quartile 4	16	3.0 ± 7.7	
CTBD quartile 1	16	3.5 ± 9.7	0.658
CTBD quartile 4	16	2.3 ± 5.7	
CNFA quartile 1	17	4.9 ± 9.3	0.796
CNFA quartile 4	16	4.1 ± 8.6	
CNFW quartile 1	16	5.9 ± 7.7	0.228
CNFW quartile 4	16	1.9 ± 10.5	

Data are reported as mean ± SD.
MDS UPDRS III, Movement Disorder Society Unified Parkinson's Disease Rating Scale part III; CNFD, corneal nerve fiber density; CNBD, corneal nerve branch density; CNFL, corneal nerve fiber length; CTBD, corneal total branch density; CNFA, corneal nerve fiber area; CNFW, corneal nerve fiber width.
*$P < 0.05$ was considered statistically significant.

exploratory study, and therefore corrections for multiple comparisons were not performed.

Results

Demographics and Clinical Characteristics of Participants

Sixty-four participants with PD (16 female, 48 male), with a mean age of 64.1 ± 7.8 years, and 25 control participants (11 female, 14 male), with a mean age of 63.1 ± 6.8 years, were recruited to the study. There was no significant difference in age ($P = 0.56$) or sex ($P = 0.08$) between the PD cohort and the control cohort. The participants with PD were followed up after a mean duration of 12.0 ± 1.0 month. The mean duration of PD was 56.9 ± 42.6 months at visit 1 (baseline). Clinical characteristics at visits 1 and 2 (12-month follow-up) are summarized in Table 1.

Corneal Nerve Morphology in Participants with PD at Baseline and in Control Subjects

CNFD, CNBD, CNFL, CTBD, and CNFA were significantly lower in participants with PD at baseline compared with control subjects (CNFD mean difference: 4.55 no./mm^2, 95% CI: 1.31–7.79, d = 0.7, $P = 0.006$; CNBD mean difference: 8.18 no./mm^2, 95% CI: 2.31–14.05, d = 0.7, $P = 0.003$; CNFL mean difference: 2.53 mm/mm^2, 95% CI: 0.94–4.11, d = 0.8, $P = 0.002$; CTBD mean difference: 11.19 no./mm^2, 95% CI: 2.92–19.45, d = 0.7, $P = 0.003$; and CNFA mean difference: 773.9 μm^2/mm^2, 95% CI: 97.0–1450.8, d = 0.5, $P = 0.026$). CNFW did not differ significantly between participants with PD and control subjects (CNFW mean difference: −0.257 μm, 95% CI: 0.23–0.20, d = 0.3, $P = 0.158$) (Figs 1 and 2).

Corneal Nerve Morphology in Participants With PD at Baseline and 12-Month Follow-up

Across the whole PD cohort, there were no significant changes in CCM parameters between baseline and follow-up at 12 months (Table 1).

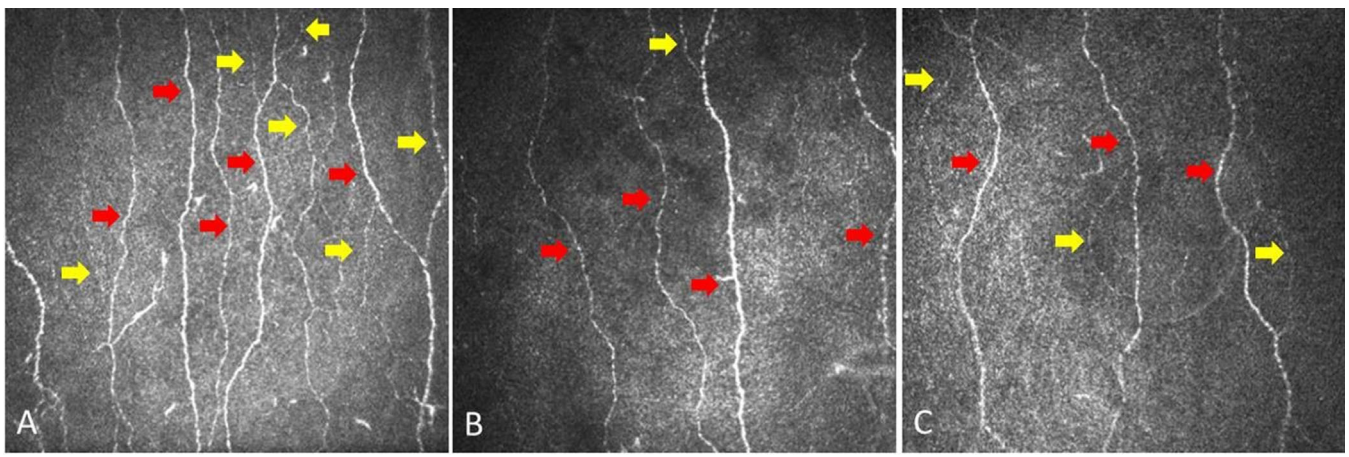

FIG. 2. Corneal confocal microscopy images. Corneal confocal microscopy image of a healthy control (**A**), an age-matched participant with Parkinson's disease (PD) (**B**), and the participant with PD after 12 months (**C**). Corneal nerve fiber density is the total number of main nerves (indicated by red arrows) per square millimeter (no./mm^2), corneal nerve branch density is the total number of junctions between branches (indicated by yellow arrows) and main nerves (red arrows) per square millimeter (no./mm^2), corneal nerve fiber length is the total length of main nerves and nerve branches per square millimeter (mm/mm^2). [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3. Regression analysis

CNFD (quartile 1 vs quartile 4)	Mean difference in change in MDS UPDRS III over 12 months (B)	Standard Error	*P*	R^2
Unadjusted	5.99	2.4	0.019*	15.6%
Adjusted for age, sex, and disease duration	5.55	2.5	0.036*	22.4%

CNFD, corneal nerve fiber density; MDS UPDRS III, Movement Disease Society Unified Parkinson's Disease Rating Scale part III.
*$P < 0.05$ was considered statistically significant.

Disease Progression Between Patients Based on Severity of Baseline Impairment of Corneal Nerve Parameters

The change in MDS UPDRS III over 12 months was significantly different between patients in quartile 1 (most severe corneal nerve degeneration) compared with quartile 4 (least severe corneal nerve degeneration) for CNFD and did not differ for CNFL, CNBD, CTBD, CNFW, and CNFA (Table 2).

Regression Analysis

Compared with patients in quartile 4, those in quartile 1 of CNFD had a significantly greater increase in MDS UPDRS III after 12 months (mean difference = 5.99, $P = 0.019$). This difference remained significant even after adjusting for age, sex, and duration of the disease of the participants (adjusted mean difference = 5.55, $P = 0.036$) (Table 3).

Correlations Between Change in Levodopa-Equivalent Daily Dosage, MDS UPDRS Scores, and Change in CCM Parameters

There were no correlations between change in levodopa-equivalent daily dose and change in CNFD (Rho = −0.143, $P = 0.260$), MDS UPDRS II (Rho = −0.155, $P = 0.221$), MDS UPDRS III (Rho = −0.047, $P = 0.715$), full MDS UPDRS (Rho = −0.168, $P = 0.185$), and MoCA (Rho = −0.047, $P = 0.715$) over 12 months.

Discussion

This study confirms previous findings by our group[23,28] and others[24,25] of corneal nerve damage in patients with PD compared with healthy control subjects. Although there was no significant decline in corneal nerve parameters over 12 months, intriguingly, participants with a baseline CNFD in the lowest quartile (most severe corneal nerve degeneration) compared with the highest quartile (least severe corneal nerve degeneration) showed the most rapid clinical deterioration based on an increase in MDS UPDRS III. Studies in patients with diabetic neuropathy have shown that it may take 2 to 4 years for a significant reduction in corneal nerve parameters.[36,37] A recent study in 590 patients with diabetes followed over ~5 years demonstrated more rapid corneal nerve loss in a subgroup of participants who showed more rapid worsening of neuropathy and were referred to as progressors.[38]

In this study, there was overlap in CCM parameters between the control cohort and the PD cohort, suggesting that there are subgroups of patients with PD with different degrees of corneal denervation. Indeed, we show that the severity of small nerve fiber degeneration at baseline may confer a poorer prognostic outcome in relation to greater worsening of motor disability over 12 months after adjusting for age, sex, and disease duration. The six-point increase in MDS UPDRS III after 12 months between patients with the least and most corneal nerves at baseline exceeds the margin of 4.6, which is considered to be a clinically important worsening of the MDS UPDRS III score.[39]

Extranigral involvement and nonmotor features have been increasingly used to subtype PD and assess rates of disease progression. A recent cluster analysis study identified that three nonmotor features (rapid eye movement sleep behavior disorder, mild cognitive impairment, and orthostatic hypotension) at baseline predict the most rapidly progressive subtype termed the "diffuse malignant subtype."[40] The authors have suggested that the diffuse malignant subtype may represent diffuse neurodegenerative pathology because the features involve the simultaneous dysfunction of different anatomical regions.[41] Other studies have also demonstrated that autonomic dysfunction is associated with a more severe PD phenotype with a greater risk for falls, wheelchair dependence, and cognitive impairment.[42] Neuropathy is associated with worse motor and cognitive scores and nonmotor disability.[3] Interestingly, a recent study has shown that the reduction in the ganglion cell-inner plexiform layer and peripapillary retinal nerve fiber layer thickness over 3 years was related to cognitive decline, but not motor deterioration, in patients with PD.[43] In this study, CNFD had prognostic value for motor deterioration because it is a more stable measure of proximal nerve degeneration, whereas CNFL, CNBD, and CTBD are more variable due to ongoing distal nerve regeneration.[8] Indeed, our previous study showed a decrease in CNFD but an increase in CNBD and CNFL in PD.[15]

PD-related peripheral neuropathy may be caused by the iatrogenic effects of dopaminergic therapies and intrinsic neurodegeneration. Studies have demonstrated an association between therapy with levodopa and large fiber neuropathy,[44] but not small fiber neuropathy.[45] Many studies have suggested that small fiber neuropathy is an intrinsic part of the disease process in PD.[23,45-47] Nolano and colleagues[45] found large and

small fiber neuropathy in drug-naive patients and showed that large, but not small, fiber pathology worsened with levodopa use. Doppler and colleagues[46] found no correlation between intraepidermal nerve fiber density and the cumulative levodopa intake. Our previous study demonstrated no correlation between corneal nerve parameters and cumulative levodopa dose.[23] This study also demonstrates no correlation between change in levodopa daily dose and change in corneal nerve parameters after 12 months.

Some limitations should be noted. It was not possible to establish a robust link between peripheral and central neurodegeneration because we have not directly compared CCM parameters with imaging markers of central dopaminergic neuronal integrity. The number of patients in the highest and lowest quartiles of CNFD was relatively small, and the findings require validation in other PD cohorts. A longer follow-up period will also be required to fully assess progression of corneal nerve degeneration in PD.

This study confirms corneal nerve loss in patients with PD and further suggests that CCM may be a useful marker of neurodegeneration to identify patients with PD with a more progressive and severe disease phenotype, termed "fast progressors." Identification of slow and fast progressors may allow the identification and recruitment of patients with PD who are more or less responsive to disease-modifying therapies[48] to enable the design of shorter, more cost-effective clinical trials and to eliminate heterogeneity in the PD cohort. ■

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.