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ORIGINAL ARTICLE

Corneal nerve fiber involvement in chronic inflammatory demyelinating polyneuropathy

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Abstract

Background Despite the primary myelin-related pathophysiology, small fiber neuropathy (SFN) and axonal degeneration are also considered to be involved and associated with disabling symptoms and impaired quality of life in chronic inflammatory demyelinating polyneuropathy (CIDP). Demonstration of SFN usually requires complex or invasive investigations.
Objects In vivo corneal confocal microscopy (IVCCM) has evolved as a non-invasive, easily applied method for quantification of small fiber involvement in peripheral nerve disorders. We aimed to investigate the potential role of IVCCM in CIDP.
Methods In this cross-sectional study, 15 patients with CIDP underwent assessment with clinical disability scales, neuropathic pain (NP) and autonomic symptom questionnaires, nerve conduction studies, and IVCCM. IVCCM parameters were analyzed and compared to those from 32 healthy controls.
Results Corneal nerve fiber density (CNFD) and corneal nerve fiber length (CNFL) were significantly decreased in the CIDP group, compared to those in controls ($p=0.03$ and $p=0.024$, respectively). Langerhans cells and fiber tortuosity were increased in CIDP patients ($p=0.005$ and $p=0.001$, respectively). IVCCM parameters were significantly lower in patients with NP compared to those in patients without NP.
Conclusion IVCCM shows promise as a non-invasive complementary biomarker in the assessment of demyelinating polyneuropathies, providing insights into the potential pathophysiology of these non-length-dependent neuropathies.

Keywords Corneal confocal microscopy · Inflammatory polyneuropathy · Small fiber · Neuropathic pain

Introduction

Chronic demyelinating polyneuropathies are a heterogeneous group of peripheral nerve disorders, including the acquired immune-mediated and the inherited forms [1]. Chronic inflammatory demyelinating polyneuropathy (CIDP), which presents as an acquired chronic progressive or relapsing sensorimotor polyneuropathy with symmetrical proximal and distal involvement, is the most common one. Patients with this polyneuropathy exhibit common pathophysiological and electrodiagnostic features, predominantly related to myelin sheath damage, thus representing distinct manifestations of large myelinated fiber dysfunction. However, there has been substantial clinical and histopathological evidence, indicating the accompanying small fiber involvement recently [2–4]. Importantly, symptoms related to secondary axonal degeneration and small fiber neuropathy (SFN) are considered to be primarily responsible for the impaired quality of life in CIDP patients [5, 6]. As well known, routine conventional nerve conduction studies (NCS) demonstrate large fiber dysfunction. SFN can only be detected by more complex and time-consuming tests, or invasive procedures such as skin biopsy.

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Recently, corneal confocal microscopy is being used as a surrogate in this area. It shows the corneal nerve fiber structure "in vivo." Therefore, it gives promise as a rapid non-invasive means of visualizing and quantifying the peripheral nerve fibers and also dendritic cells (presumably related with inflammation) in the cornea. The utility of in vivo corneal confocal microscopy (IVCCM) has been well-established in many axonal neuropathies, such as diabetic neuropathy [7–9]. However, relatively fewer data are available in myelin-related ones [10–13]. Given the non-length-dependent nature and immune etiopathogenesis of CIDP, the potential clinical implications of IVCCM may indeed warrant further investigation in this disorder.

The aim of this study was to investigate the utility of IVCCM parameters in assessing the potential involvement of small fibers and immune cells in CIDP, comparing them with clinical and electrophysiological features.

Materials and methods

Study participants

This cross-sectional controlled study was conducted at the Departments of Neurology and Ophthalmology in Marmara University Hospital, Istanbul, Turkey. Consecutive patients aged 18–65 years, with CIDP, were prospectively recruited from the outpatient clinic of Neuromuscular Diseases for 8 months. Control subjects without any neurological or ophthalmological disease were selected from the medical staff and other healthy volunteers. The study was approved by the Institutional Ethics Committee and conformed to the Declaration of Helsinki. Written informed consent was obtained from all participants.

Patient eligibility criteria

Patients were included in the study if they fulfilled the electrophysiological and clinical diagnostic criteria for typical CIDP according to the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) guideline [14] [15]. Exclusion criteria were a history of any other potential cause of peripheral neuropathy (e.g., diabetes mellitus and other systemic diseases, exposure to toxic agents and medications), previous ocular surgery, ocular trauma, dry eye disease, or contact lens use.

Clinical assessment

All participants underwent a detailed neurological and ophthalmic examination. Patients were further assessed with specific clinical scales to quantify the impairment and disability. Thus, CIDP patients were evaluated with Inflammatory Neuropathy Cause and Treatment validated overall disability sum score (INCAT/ODSS) [16].

For assessment of clinical symptoms of small fiber impairment, all patients completed the Composite Autonomic Symptom Score-31 (COMPASS-31) [17] to evaluate autonomic dysfunction, and the painDETECT [18] screening questionnaire to identify neuropathic pain (NP).

Patients with a painDETECT score of 19 or more were accepted as having NP. Patients under NP treatment with effective dosage and over an effective time were also accepted to have NP whatever their current painDETECT score is. The remaining patients were considered to be in the "non-NP group."

Nerve conduction studies

Each patient underwent standard NCS using a Keypoint Net 4-channel electroneuromyography device (Natus Medical, İnc., San Carlos, CA). Bilateral posterior tibial, common peroneal motor nerves and bilateral sural, superficial peroneal, and medial plantar sensory nerves with left median, ulnar motor and sensory nerves, and left radial sensory nerves were studied, as described previously [19].

In vivo corneal confocal microscopy

All subjects were examined with the Heidelberg Retina Tomography III/Rostock Cornea Module device by two experienced ophthalmologists in a masked fashion in the Department of Ophthalmology, Marmara University Hospital, Istanbul. To perform the procedure, a right eye was topically anesthetized using 0.5% proparacaine hydrochloride (Alcaine, Novartis Ophthalmics). The cornea module was mounted with a disposable, sterile polymethylmethacrylate cap (Tomo-Cap, Heidelberg Engineering GmbH). Viscotears gel was applied to the inside and surface of the cap. Several scans of the sub-basal nerve plexus in the central corneas were captured.

The optimal (best focused, with single layer, minimum folds, and good contrast) 5 pictures that contain sub-basal nerve plexus from the right eyes of patients, were analyzed by the image processing software *ACC Metrics Corneal Nerve Fibre Analyser V.2* (M.A. Dabbah, Manchester, England) [20, 21]. The average score of 5 pictures was accepted. Corneal nerve fiber morphological parameters included corneal nerve fibre density (CNFD), a measure of the total number of main corneal nerves/mm^2; corneal nerve branch density (CNBD), the number of junctions between branches and main nerves/mm^2; corneal nerve fiber length (CNFL), the total length of all corneal nerve fibers (mm/mm^2); and corneal nerve fiber tortuosity (CNFT), as expressed by the tortuosity coefficient (TC).

Langerhans cell density (LCD) (number/mm^2) was calculated using the confocal microscope's original software and was analyzed manually in a blinded fashion in the same images used to analyze sub-basal nerve plexus parameters (Fig. 1).

Statistical analysis

SPSS for Mac (version 20.0, SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Arithmetic mean and standard deviation values were used for descriptive analysis of numerical variables, and percentages were used for analysis of categorical variables. The Shapiro–Wilk normality test was used to determine whether the data were from the normal distribution. The chi-square test was used to compare categorical variables, the Student *t* test was used as a parametric test, and the Mann–Whitney *U* test was used as a non-parametric test for comparison of continuous variables. Pearson and Spearman's rank correlation coefficients were used for correlation analyses. *p* value less than 0.05 was required for statistical significance.

Results

Demographics

Nineteen patients with CIDP were initially recruited. However, 1 patient withdrew from the study, and 3 patients with CIDP variants and paraproteinemia were excluded because they did not meet the diagnostic criteria of "typical" CIDP. Finally, 15 patients (7 women, 8 men) and 32 healthy control subjects (19 women, 13 men) were included in the study.

Clinical and electrophysiological features

No significant differences between the patients and healthy controls were noted for age, sex, and body mass index ($p > 0.05$ for each demographic parameter). Clinical impairment was assessed by the INCAT/ODSS disability scale ranged from mild to moderate. Nine patients were determined to have NP based on the criteria mentioned in the "Materials and methods" section. Demographic and clinical data of the study participants are provided in Table 1.

NCS demonstrated demyelinating findings in all patients as expected, with slowing of the nerve conduction velocities and prolongation of distal latencies, and accompanying conduction blocks and temporal dispersion pattern. As most nerve action potentials were inelicitable in lower extremities in some patients, and median nerves were affected due to carpal tunnel syndrome, only ulnar motor and radial sensory nerve conduction parameters were included for further analysis.

In vivo corneal confocal microscopy

IVCCM showed a significant reduction of both CNFD and CNFL in patients with CIDP, compared to that in healthy controls ($p = 0.03$ and $p = 0.006$, respectively). CNFT was also significantly increased in CIDP patients ($p = 0.001$) (Table 2). Moreover, the average number of the Langerhans cells per square millimeter was significantly higher in CIDP patients compared to that in the control group ($p = 0.005$) (Fig. 2).

Association of in vivo corneal confocal microscopy parameters with clinical and electrophysiological findings

IVCCM parameters did not correlate with INCAT/ODSS in patients with CIDP. However, it was notable that CNFD and CNFL had a significant positive correlation with ulnar motor and radial sensory nerve action potentials. In contrary, there was no relationship between IVCCM parameters and nerve conduction velocities (Table 3).

Regarding clinical scales related to SFN, IVCCM parameters did not correlate with painDETECT and COMPASS-31 in patients. On the other hand, patients with NP had significantly lower CNFD and CNFL, compared to patients without NP

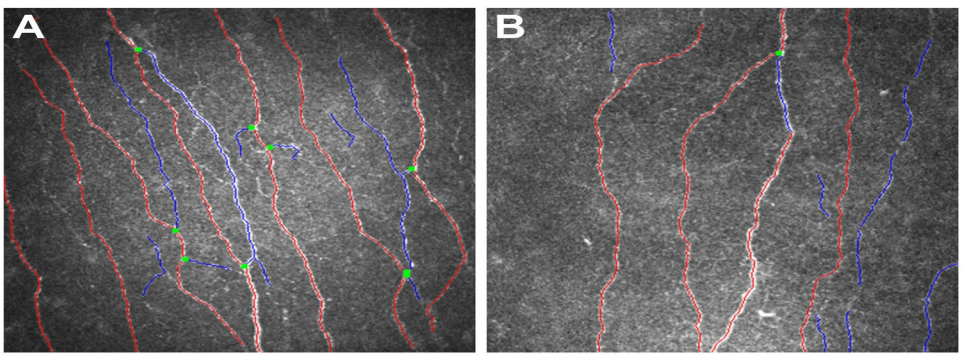

Fig. 1 Analyzed corneal confocal microscopic images of sub-basal nerve plexus. **A** Healthy control subject with normal corneal nerve fibers. **B** Decrease of sub-basal nerves in a patient with CIDP. Red lines: main nerve fibers, blue lines: nerve fiber branches, green dots: branching areas

Table 1 Demographic and clinical characteristics of study participants

Characteristic	CIDP ($n=15$)	Healthy controls ($n=32$)	p value
Age* (years)	50.5 ± 7.2	44.2 ± 12.4	0.414
Sex*, female/male, n (% female)	7/8 (46.6%)	19/13 (59.4%)	0.074
Height* (cm)	168.7 ± 9.1	165.6 ± 8.8	0.275
Weight* (kg)	79.5 ± 10.9	74.7 ± 12.1	0.199
Body mass index* (kg/m^2)	27.86 ± 2.73	27.37 ± 4.82	0.719
INCAT/ODSS (range)	1.8 ± 1.2 (0–4)	NA	
PainDETECT score (range)	12.3 ± 7.1 (0–25)	NA	
COMPASS-31 (range)	15.7 ± 9.1 (3–32)	NA	
CSF protein (mg/dl)	58.2 ± 31.2	NA	
Patients with NP, n (%)	9 (60%)	NA	

Data are expressed as mean ± standard deviation (range), or as numbers (%)

*$p > 0.05$ compared to controls for each group

CIDP, chronic inflammatory demyelinating polyneuropathy; *CSF*, cerebrospinal fluid; *COMPASS-31*, Composite Autonomic Symptom Score-31; *INCAT/ODSS*, Inflammatory Neuropathy Cause and Treatment validated overall disability sum score; *NA*, not applicable; *NP*, neuropathic pain

Table 2 IVCCM parameters in CIDP patients and healthy control subjects

IVCCM parameter	CIDP ($n=15$)	Controls ($n=32$)	p value
CNFD (number/mm^2)	21.4 ± 9.1	26.1 ± 5.3	0.03*
CNFL (mm/mm^2)	12.8 ± 4.4	16 ± 3.1	0.006*
CNBD (number/mm^2)	26.3 ± 17.5	35.2 ± 15.3	0.063
CNFT, TC	3.1 ± 0.9	1.4 ± 1.2	0.001*
LCD (number/mm^2)	24.1 ± 11.5	13.3 ± 9.9	0.005*

Data are expressed as mean ± standard deviation

*$p < 0.05$

CIDP, chronic inflammatory demyelinating polyneuropathy; *CNFD*, corneal nerve fiber density; *CNFL*, corneal nerve fiber length; *CNBD*, corneal nerve branch density; *CNFT*, corneal nerve fiber tortuosity; *LCD*, Langerhans cell density; *IVCCM*, in vivo corneal confocal microscopy; *TC*, tortuosity coefficient

and healthy controls. IVCCM parameters in the CIDP patients are demonstrated in Fig. 3.

Discussion

This study demonstrates a remarkable corneal nerve fiber loss in patients with CIDP, with accompanying significant immune cell infiltration. Given that IVCCM has recently emerged as a useful, non-invasive tool in the assessment of peripheral, particularly axonal, polyneuropathies, our results contribute to the literature, highlighting the potential role of this novel technique also in this type of demyelinating polyneuropathies.

In the current study, a significant loss of corneal subbasal nerve fibers and increased tortuosity and Langerhans cells were found in the immune-mediated acquired demyelinating polyneuropathy patients, compared to healthy controls. CNFD reduction was associated with decreased ulnar motor nerve action potential amplitude in patients. Notably, patients with NP were found to have significantly reduced CNFD and CNFL, compared to patients without NP.

IVCCM presents a unique opportunity to non-invasively assess the living cornea, which is densely innervated by small-diameter fibers. It is a novel, highly reproducible ophthalmic imaging technique, enabling quantification of small fiber damage and axonal degeneration, similar to quantification of nerve fibers with the intraepidermal nerve fiber (IENF) analysis via skin biopsy [22, 23]. Therefore, in addition to its use in ophthalmology clinical practice, it has widely been studied in various systemic and neurological disorders [24–28]. The clinical utility of IVCCM in many axonal polyneuropathies has nearly been established, and it has even been proposed as a biomarker in diabetic neuropathy recently [8, 9]. On the other hand, IVCCM has relatively rarely been explored in demyelinating neuropathies [10–13].

Although large myelinated fibers are expected to be primarily involved in these disorders, it has become increasingly evident that small fiber damage and axonal degeneration have a substantial impact on the clinical impairment and disability in these patients [2–4, 6, 29]. However, the demonstration of SFN usually requires invasive or time-consuming techniques such as skin biopsy. IVCCM has emerged as a promising non-invasive tool in the assessment of SFN with a sensitivity comparable to skin biopsy [22, 23].

There is emerging evidence showing corneal nerve alterations in chronic immune-mediated demyelinating polyneuropathies in recent studies [10–12]. Schneider et al. showed a significant reduction in CNFD and CNFL and an increase in CNFT in 16 patients with CIDP, compatible with our

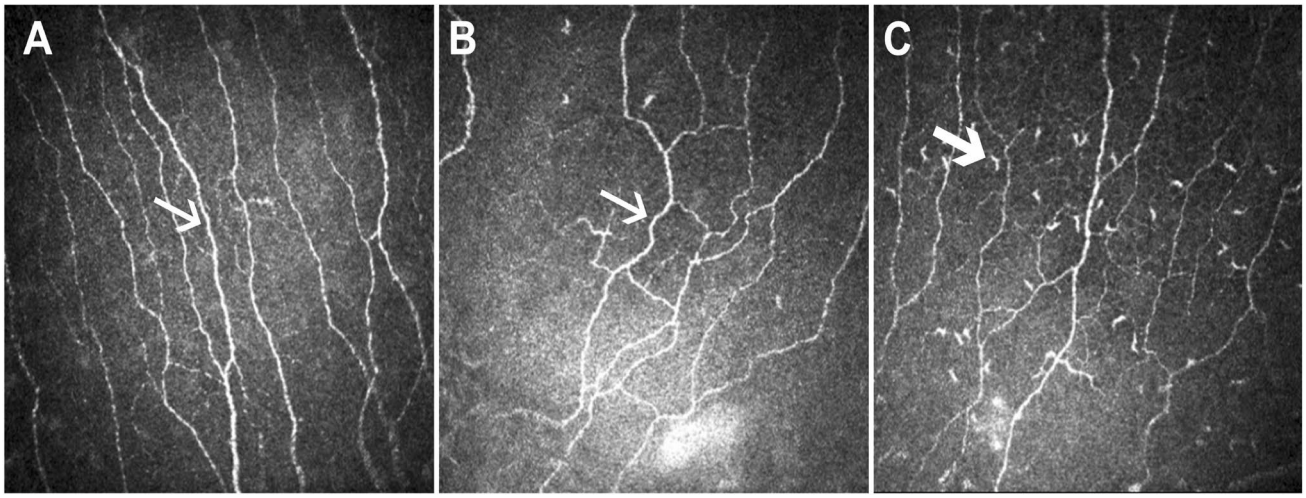

Fig. 2 Corneal confocal microscopic images of sub-basal nerve plexus. **A** Corneal nerve fibers demonstrate normal tortuosity in a healthy control subject (arrow). **B** Corneal nerve fibers shows increased tortuosity in a patient with chronic inflammatory demyelinating polyneuropathy (CIDP) (arrow). **C** Increase of Langerhans cells in another patient with CIDP (bold arrow)

Table 3 Correlations between IVCCM parameters and clinical scales and electrophysiological findings in CIDP patients

IVCCM		INCAT/ODSS	painDETECT	C31	Ulnar CMAP amplitude	Ulnar motor NCV	Radial SNAP amplitude	Radial sensory NCV
CNFD	*r*	−0.328	−0.368	0.215	0.702	0.014	0.613	0.475
	p	0.232	0.177	0.441	0.004*	0.960	0.015*	0.073
CNFL	*r*	−0.170	−0.360	0.151	0.757	−0.118	0.573	0.314
	p	0.544	0.188	0.592	0.001*	0.676	0.025*	0.225
CNBD	*r*	−0.141	−0.036	0.160	0.422	−0.218	0.204	−0.075
	p	0.616	0.898	0.569	0.117	0.435	0.465	0.790

*$p < 0.05$

C31, Composite Autonomic Symptom Score-31 (COMPASS-31); *CMAP*, compound muscle action potential; *CNFD*, corneal nerve fiber density; *CNFL*, corneal nerve fiber length; *CNBD*, corneal nerve branch density; *INCAT/ODSS*, Inflammatory Neuropathy Cause and Treatment validated overall disability sum score; *IVCCM*, in vivo corneal confocal microscopy; *NCV*, nerve conduction velocity; *SNAP*, sensory nerve action potential; *r*, Spearman's rho; *IVCCM*, in vivo corneal confocal microscopy

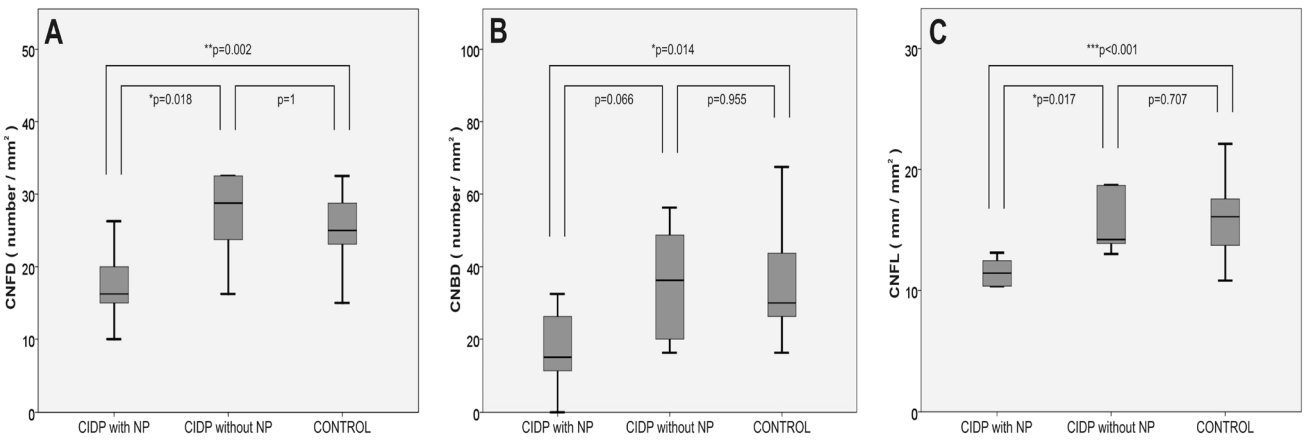

Fig. 3 Corneal nerve fiber parameters (mean ± standard deviation): **A** corneal nerve fiber density (CNFD), **B** corneal nerve branch density (CNBD), and **C** corneal nerve fiber length (CNFL) in chronic inflammatory demyelinating polyneuropathy (CIDP) patients with and without neuropathic pain (NP) and healthy controls. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

results. Stettner et al. confirmed and extended these findings in a more heterogeneous group of patients with CIDP and multifocal motor neuropathy, also emphasizing corneal immune cell infiltrates, in concordance with our findings. These cells were notably found to be related with clinical progression in further studies [10].

Remarkably, our study showed a significant increase in the number of Langerhans cells in patients with CIDP. As known, Langerhans cells are important in antigen presentation in the cornea. They have a role in modulating immunity and immune tolerance. A study showed that the presence of these cells and their contact with the sub-basal nerve plexus may trigger nerve fiber damage [30]. In support of this finding, a recent study demonstrated that IVCCM was useful in differentiating inflammatory from non-inflammatory diabetic neuropathy [31]. These data have important clinical implications in the future role of IVCCM in the differential diagnosis of polyneuropathies based on pathophysiological features.

In our study, CNFD and CNFL correlated positively with ulnar motor and radial nerve action potential amplitudes. Lower extremity nerve conduction studies were not included in the correlation analysis, because they were also mostly inelicitable. Median motor and sensory NCS were neither included in the analysis, due to possible carpal tunnel syndrome, commonly seen in this population. This correlation between IVCCM parameters and upper extremity nerve action potential amplitudes, not the velocities, suggests that IVCCM may demonstrate objective findings of axonal degeneration in demyelinating polyneuropathies.

IVCCM parameters did not correlate with clinical scales and questionnaires. This might be explained by the finding that our patients had mild-to-moderate disability and mild symptoms related to small fiber dysfunction. Similar results were also reported in the literature [10, 11]. Schneider et al. explained this lack of correlation between IVCCM and some clinical parameters with the hypothesis of multifocal nerve fiber involvement [11]. Further studies including patients with a diverse range of clinical impairment and with more detailed clinical scales may give insights to these associations.

Importantly, IVCCM showed a greater corneal nerve fiber damage in patients with NP; however, it did not correlate with the severity of NP. CNFD and CNFL were found to be significantly decreased in patients with NP compared to those in patients without NP. Of note, CIDP patients without NP had similar IVCCM parameters with those of healthy controls. This finding is in consistent with the literature, and it highlights the clinical utility of IVCCM in the assessment of NP and related quality of life in polyneuropathy patients, by providing objective demonstration and quantification of small fiber involvement [12, 32].

Lack of correlation between IVCCM and painDETECT scale, however, is considered to be related to the inherently non-homogeneous clinical and therapeutic status of the patient groups. Due to the cross-sectional nature of our study, most of the patients were already on NP and/or immunomodulatory treatment, and their symptoms were mostly under control, as discussed before. Lack of correlation of IVCCM and COMPASS-31 is also well-appreciated, given the fact that autonomic involvement in CIDP has been reported to be mild, limited, and predominantly distal [2]. Autonomic tests, which are usually time-consuming and complex procedures with relatively low sensitivity, were indeed not applied to our patients.

We acknowledge that lack of IENF analysis in the investigation of SFN in our patients is a limitation of our study. However, recent studies have reported that the diagnostic utility of IVCCM is comparable with the IENF analysis, making IVCCM a potential non-invasive surrogate in the assessment of small fiber involvement in polyneuropathies [22, 23]. Our findings contribute to this information and should be further investigated and replicated in future studies.

Relatively small sample size is another limitation of our study. Nonetheless, it was a selected specific patient group. Patients with acute inflammatory demyelinating polyneuropathy, such as Guillain–Barre syndrome (GBS), were not included in our cross-sectional study so as not to involve the potential dynamic pathophysiological processes in GBS. Prospective multicenter studies evaluating IVCCM findings longitudinally in a range of immune-mediated polyneuropathies may elucidate the pathophysiological processes and hopefully aid in therapeutic options.

In conclusion, this study extends information about the clinical utility of IVCCM gained from previous studies. Implementation of IVCCM into the clinical assessment of demyelinating neuropathies and thereby quantification of corneal small fibers and immune cells provides useful information about the presence of accompanying axonal degeneration and small fiber involvement in primarily myelin-related pathologies.

Author contribution K.U., E.T., and P.K.K. contributed to the conception and design of the study; E.K.O., S.A.T., H.A., and P.K.K. contributed to the acquisition and analysis of the data; E.K.O., S.A.T., E.T., K.U., H.A., T.T., and P.K.K. contributed to drafting the text or preparing the figures.

Data Availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Consent to participate Written informed consent was obtained from all participants.

Ethical approval The study was approved by the Institutional Ethics Committee and conformed to the Declaration of Helsinki.

Conflict of interest The authors declare no competing interests.

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