CNS Involvement in Chronic Inflammatory Demyelinating Polyneuropathy
Subtle Retinal Changes in Optical Coherence Tomography

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Abstract

Background and Objectives
Chronic inflammatory demyelinating polyneuropathy (CIDP) is an autoimmune disease primarily affecting the peripheral nervous system. However, several noncontrolled studies have suggested concomitant inflammatory CNS demyelination similar to multiple sclerosis. The aim of this study was to investigate an involvement of the visual pathway in patients with CIDP.

Methods
In this prospective cross-sectional study, we used high-resolution spectral-domain optical coherence tomography to compare the thickness of the peripapillary retinal nerve fiber layer and the deeper macular retinal layers as well as the total macular volume (TMV) in 22 patients with CIDP and 22 age-matched and sex-matched healthy control (HC) individuals. Retinal layers were semiautomatically segmented by the provided software and were correlated with clinical measures and nerve conduction studies.

Results
In patients with CIDP compared with healthy age-matched and sex-matched controls, we found slight but significant volume reductions of the ganglion cell/inner plexiform layer complex (CIDP 1.86 vs HC 1.95 mm³, \( p = 0.015 \)), the retinal pigment epithelium (CIDP 0.38 vs HC 0.40 mm³, \( p = 0.02 \)), and the TMV (CIDP 8.48 vs HC 8.75 mm³, \( p = 0.018 \)). The ganglion cell layer volume and motor nerve conduction velocity were positively associated (\( B = 0.002, p = 0.02 \)).

Discussion
Our data reveal subtle retinal neurodegeneration in patients with CIDP, providing evidence for visual pathway involvement, detectable by OCT. The results need corroboration in independent, larger cohorts.
Chronic inflammatory demyelinating polyneuropathy (CIDP) is an autoimmune disease of the peripheral nervous system (PNS) characterized by primary myelin sheath destruction and secondary axonal damage, leading to sensory and autonomic deficits, flaccid paresis, and muscle atrophy. The disease usually follows a chronic progressive course with or without superimposed relapses or is relapsing, thus resembling multiple sclerosis (MS), the most common primary demyelinating autoimmune disease of the CNS. Forrester and Lascelles were the first to describe 2 cases of coincident MS and inflammatory polyneuropathy in 1979. In 1987, 6 additional cases of CIDP with CNS demyelination evidenced by MRI were reported. Several subsequent studies suggested CNS involvement in CIDP. Further investigations associated CIDP specifically with visual pathway disturbance. Holtkamp et al. showed histologically optic nerve inflammation in a patient with CIDP. Japanese and Chinese groups have recently suggested the existence of a condition termed combined central and peripheral demyelination that resembles both MS and CIDP in the same patient.

All these investigations, however, were noncontrolled studies, mainly case reports and case series. In a previous effort, investigating conductivity changes of the visual pathway in patients with CIDP using multifocal visual evoked potentials (mfVEP), we were not able to detect relevant changes compared with age-matched and sex-matched healthy individuals. This finding was recently corroborated by another controlled study using full-field VEPs.

Here, we investigated structural retinal changes as a marker of CNS degeneration in patients with CIDP compared with age-matched and sex-matched healthy individuals using spectral-domain optical coherence tomography (SD-OCT). OCT uses near-infrared light to generate cross-sectional and 3-dimensional images of the retina as part of the CNS. In recent years, OCT has emerged as a reliable and accurate, easy-to-access, and noninvasive technique to assess microscopic retinal pathologies, for example, in MS and other inflammatory and degenerative CNS diseases. In MS, spectral-domain OCT has been documented to predict long-term worsening.

Methods

Patients
We performed a prospective study at the Department of Neurology, Heinrich-Heine-University Düsseldorf. Subjects were included as previously described. Inclusion criteria were of age >18 years, probable or definite CIDP according to the European Federation of Neurological Societies/Peripheral Nerve Society CIDP guidelines and response to immunomodulatory treatment. The flowchart in Figure 1 gives an overview of the subject recruitment. Of 66 subjects (44 patients with probable or definite CIDP and 22 healthy subjects), 22 patients had to be excluded because of diabetes mellitus (n = 13) or concomitant ophthalmologic diseases (n = 9), such as bilateral drusen (4), cataract (2), glaucoma (1), papilledema (1), and choroidal neovascularization (1), which could confound the OCT measurements. Furthermore, 7 single eyes were excluded because of drusen (6) and macular edema (1). All subjects received neuropsychological examinations, including tonometry, slit-lamp examination, and fundoscopy. In addition, 16 of 22 patients with CIDP (73%) were tested for corrected low contrast letter recognition using 2.5% contrast early treatment of diabetic retinopathy study (ETDRS) charts. Because nerve conduction studies of the lower limbs showed a high rate of signal loss, the right ulnar nerve was used to investigate associations with OCT parameters. Figures 2A–C exemplify the measurement of the macular volumes by consecutive vertical scans (Figure 2A) and the peripapillary retinal nerve fiber layer (pRNFL) thickness (Figure 2B), and illustrate a cross-section through the deeper retinal layers (Figure 2C). The Strengthening the Reporting of Observational Studies in Epidemiology cross-sectional reporting guidelines were used.

Spectral-Domain Optical Coherence Tomography

APostel reporting recommendations were applied for the SD-OCT methodology and results. The methods are well established and have also been used and described elsewhere.22,23,28 The RNFL assessment, using a high-resolution scanning mode, we obtained 12° peripapillary, disk-centered ring scans. For macular volume evaluation, we captured 61 fovea-centered vertical scans (30° × 25°, high-speed scanning mode). The total retinal volume and the volumes of the different retinal layers were measured by applying the
standard 1-, 3-, and 6-mm ETDRS grid in macular volume scans and using the mean volume of all sectors. For SD-OCT imaging of both eyes, the SPECTRALIS OCT device (Heidelberg Engineering, Germany) with the image alignment eye-tracking software system (TruTrack and Nsite analytics, Heidelberg Engineering) was used. Averaging of macular volume scans was performed from 14 images and of peripapillary ring scans from 100 scans (automatic real time). The threshold for the image quality was beyond 20 dB. Semi-automatic segmentation of all retinal layers using the Heidelberg Eye Explorer software (version HEYEX 1.8.6.0, Viewing Module 5.8.3.0) was manually corrected by a blinded rater. For analysis, we used only scans meeting the OSCAR-IB quality control criteria.29

Statistical Evaluation
SPSS Statistics 24 (IBM) was used for statistical analyses. Generalized estimation equation (GEE) models correcting for sex and age and accounting for within-subject, intersegment, or intereye correlations using an exchangeable working correlation matrix were applied to analyze associations between clinical data and SD-OCT parameters and to test for differences of SD-OCT parameters between controls and patients with CIDP.

Patient Consent and Standard Protocol Approvals
This study was approved by the local ethics committee of Heinrich-Heine-University Düsseldorf (registry number 4389). In accordance with the Declaration of Helsinki, written informed consent was obtained from all study participants.

On reasonable consent from any qualified investigator, anonymized data not published within this article will be made available.

Results
The mean total macular volume (TMV) was significantly reduced in patients with CIDP (8.48 mm³ ± 0.38) compared with HCs (8.75, ± 0.37 mm³; p = 0.018, GEE, Figure 2D). Further analyses of the different macular layers revealed a significant thinning of the ganglion cell layer (GCL) in patients with CIDP (1.03 ± 0.10 mm³) compared with HCs (1.07 ± 0.11 mm³, p = 0.037) and of the inner plexiform layer (IPL) in patients with CIDP (0.83 ± 0.08 mm³) vs healthy individuals (0.88 ± 0.06 mm³, p = 0.015). Consequently, the often-used combined ganglion cell IPL (GCIIPL) volume also showed a significant difference (CIDP 1.86 ± 0.17 vs HCs 1.95 ± 0.13 mm³, p = 0.018). Furthermore, the pigment epithelium was significantly reduced in patients with CIDP compared with HCs (0.38 ± 0.04 vs 0.40 ± 0.03 mm³, p = 0.02). No changes were observed for the macular retinal nerve fiber layer (0.93 ± 0.15 vs 0.96 ± 0.11 mm³; p = 0.415), the inner nuclear layer (0.99 ± 0.08 vs 0.98 ± 0.06 mm³; p = 0.715), the outer plexiform layer (0.77 ± 0.08 vs 0.80 ± 0.07 mm³, p = 0.067), and the outer nuclear layer (1.72 ± 0.16 vs 1.78 ± 0.23 mm³; p = 0.758). Moreover, the peripapillary retinal nerve fiber layer (pRNFL) thickness did not differ between patients with CIDP (96.58 ± 9.55 μm) and HCs (97.37 ± 8.39 μm; p = 0.635) (Table).

In an exploratory approach, we correlated the significantly altered retinal layers (TMV, GCIPL, and pigment epithelium) with neurographical and clinical parameters in the CIDP group. We found a positive association of the motor nerve conduction velocity of the right ulnar nerve with the GCL (p = 0.02, B = 0.002, Figure 3A) and negative associations of the compound muscle action potential with the retinal pigment epithelium (RPE, p = 0.009, B = −0.003, Figure 3B) and of the sensory nerve conduction velocity with the TMV (p = 0.009, B = −0.01, Figure 3C). Regarding clinical parameters, positive
associations were detected regarding the time since clinical disease manifestation and the TMV (p = 0.005, B = 0.003, Figure 3D) and the IPL (p = 0.015, B = 0.001, Figure 3E). No associations were observed between retinal layers that were found to be changed in CIDP and low-contrast visual acuity, clinical severity of the disease as assessed by ODSS, time since diagnosis, therapy duration, and CSF protein levels.

**Discussion**

We herein present data demonstrating subtle retinal degeneration in patients with CIDP detected by optical coherence tomography. Our observations provide further evidence for a CNS involvement in CIDP. A number of case reports or small series have implicated some connection between autoimmune peripheral demyelination and specific CNS pathologies. Two case-control studies have recently been published. We looked at mfVEPs in CIDP and found no clear-cut evidence of CIDP-dependent alterations. Dziadkowski et al. compared multi-modal evoked potentials in patients with CIDP and HCs and detected prolonged latencies in VEP, brainstem acoustic evoked potentials, and somatosensory-evoked potentials.

Because CIDP is an autoimmune and primary demyelinating PNS disease, its most obvious CNS counterpart is MS. Classic OCT alteration in MS occurs in the pRNFL, which is decreased in thickness especially after optic neuritis, but also independent of optic neuritis. Here, we did not observe any alterations in pRNFL thickness in CIDP. GCIPL, which contains the neurons forming nonmyelinated axons of the RNFL and their dendritic arbors, has been shown to be also affected in patients with MS and displayed robust differences between patient and control eyes. It has been suggested to be equivalent to the pRNFL, concerning its utility in diagnosis, monitoring, and research in MS. In the GCIPL, as well as the GCL and the IPL separately, we observed a significant volume reduction in CIDP compared with HC eyes. The GCL is believed to be a sensitive biomarker of neurodegeneration and may even have advantages compared with the RNFL because it is not affected by edema in optic neuritis in MS, and therefore, atrophy becomes detectable earlier. Whether these findings are applicable in the context of CIDP, however, is unclear because we have previously found that mfVEP was not markedly altered in patients with CIDP. Because mfVEP is quite sensitive in detecting optic nerve damage, the significant changes in the GCL may therefore point toward a retinal, rather than optic nerve pathology. Another explanation may be a degenerative process in the posterior visual pathway, which could lead to...
retrograde transsynaptic degeneration in the retina. However, the lack of MRI brain imaging limits this study in assessing for that possibility.

We also noted a decrease in RPE layer volumes in patients with CIDP. Concerning embryology, the RPE stems from neuroectodermal cells, and thus, these epithelial cells can be considered as CNS cells.40 The biological context of this finding seems unclear. The TMV was significantly decreased in patients with CIDP, which rather reflects a thinning of single retinal layers.

At this point, it can only be speculated how retinal degeneration and immune mediated peripheral nerve damage are linked biologically. Retinal atrophy can result from retrograde degeneration after an insult to the optic nerve, activation of apoptotic pathways, and glial activation.41-44 Because CIDP is an autoimmune disease, one possibility would be the presence of a common antigen in peripheral nerves and the optic nerve or the retina, but to date, none has been identified.

A direct immune attack on the retina remains a theoretical possibility, but likewise, nothing is known about antigens shared with peripheral nerves. To learn more about possible clinical implications, we investigated relations between the retinal layer volumes and nerve conduction and clinical parameters. In an exploratory approach, we found a number of associations. The most remarkable was a positive association between the macular GCL volume and the motor nerve conduction velocity of the right ulnar nerve.

The study has obvious limitations. The cohort size of 22 individuals per group does allow for statistical evaluation, but it does not withstand corrections for multiple testing. Because the study is explicitly of exploratory nature, we deem this to be acceptable. Furthermore, our findings suggest that an in-depth investigation of the visual pathway is warranted in CIDP by, for example, applying OCT side-by-side with MRI covering the optic radiation. Although this was not part of the current investigation, it would be important and of interest to correlate subclinical MRI involvement with OCT alterations in CIDP.

Taken together, the data suggest degenerative processes in the retina and thus the CNS in CIDP. Particularly, the changes in the GCIPL could point to underlying processes that may be

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**Table** Demographical, Clinical, and OCT Parameters of Patients With CIDP and HCs

| Characteristics                           | Patients with CIDP n = 22 | HCs n = 22 | p Value |
|------------------------------------------|---------------------------|------------|---------|
| Age (y, mean ± SD)                       | 58.27 ± 12.91             | 57.68 ± 12.21 | —       |
| Male                                     | 14 of 22 (63.6%)          | 13 of 22 (59.1%) | —       |
| White ethnicity                          | 22 of 22 (100%)           | 21 of 22 (95.5%) | —       |
| Disease duration at OCT (mo, mean ± SD)  | 102.5 ± 81.9              | n.a.       | —       |
| Duration of IVIG treatment at OCT (mo, mean ± SD) | 41.40 ± 36.48             | n.a.       | —       |
| ODSS at OCT (mean ± SD)                  | 3.11 ± 1.69               | n.a.       | —       |

**OCT parameters**

| TMV (mm³, mean ± SD)                      | 8.48 ± 0.38 (~3.1%)       | 8.75 ± 0.37 | 0.018   |
| mRNFL volume (mm³, mean ± SD)            | 0.93 ± 0.15               | 0.96 ± 0.11 | 0.415   |
| GCIP volume (mm³, mean ± SD)             | 1.86 ± 0.17 (~4.6%)       | 1.95 ± 0.13 | 0.018   |
| GCL volume (mm³, mean ± SD)              | 1.03 ± 0.10 (~3.7%)       | 1.07 ± 0.11 | 0.037   |
| IPL volume (mm³, mean ± SD)              | 0.83 ± 0.08 (~5.6%)       | 0.88 ± 0.06 | 0.015   |
| INL volume (mm³, mean ± SD)              | 0.99 ± 0.08               | 0.98 ± 0.06 | 0.715   |
| OPL volume (mm³, mean ± SD)              | 0.77 ± 0.08               | 0.80 ± 0.07 | 0.067   |
| ONL volume (mm³, mean ± SD)              | 1.72 ± 0.16               | 1.78 ± 0.23 | 0.758   |
| Pigment epithelium volume (mm³, mean ± SD)| 0.38 ± 0.04 (~5.0%)     | 0.40 ± 0.03 | 0.020   |
| pRNFL thickness (μm, mean ± SD)          | 96.58 ± 9.55              | 97.37 ± 8.39 | 0.635   |

Abbreviations: CIDP = chronic inflammatory demyelinating polyneuropathy; IVIG = IV immunoglobulins; mGCIPL = macular ganglion cell/inner plexiform layer; mGCL = macular ganglion cell layer; mINL = macular inner nuclear layer; mIPL = macular inner plexiform layer; mRNFL = macular retinal nerve fiber layer; mONL = macular outer nuclear layer; mOPL = macular outer plexiform layer; n.a. = not available; OCT = optical coherence tomography; ODSS = overall disability sum score; pRNFL = peripapillary retinal nerve fiber layer. Indicated are the demographical, clinical, and optical coherence tomography parameters as means and SD.
functionally and biologically relevant. To consolidate these intriguing findings, an independent longitudinal study of a larger patient cohort should be conducted.

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**Appendix**

| Name         | Location                                      | Contribution                                                                 |
|--------------|-----------------------------------------------|-----------------------------------------------------------------------------|
| Jens Ingwersen, MD  | Department of Neurology, Medical Faculty, Heinrich-Heine-University Düsseldorf, Germany | Drafting/revision of the article for content, including medical writing for content; Analysis or interpretation of data |
| Jonas Graf, MD           | Department of Neurology, Medical Faculty, Heinrich-Heine-University Düsseldorf, Germany | Drafting/revision of the article for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data |
| Julia Kluge            | Department of Neurology, Medical Faculty, Heinrich-Heine-University Düsseldorf, Germany | Major role in the acquisition of data; Analysis or interpretation of data |
| Margit Weise, PhD      | Department of Neurology, Medical Faculty, Heinrich-Heine-University Düsseldorf, Germany | Major role in the acquisition of data; Analysis or interpretation of data |
| Michael Dietrich, PhD  | Department of Neurology, Medical Faculty, Heinrich-Heine-University Düsseldorf, Germany | Analysis or interpretation of data                                           |
| John-Ih Lee, MD        | Department of Neurology, Medical Faculty, Heinrich-Heine-University Düsseldorf, Germany | Major role in the acquisition of data                                        |
| Jens Harmel, MD        | Department of Neurology, Medical Faculty, Heinrich-Heine-University Düsseldorf, Germany | Analysis or interpretation of data                                           |

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