SHORT COMMUNICATION

Association of peripapillary hyper-reflective ovoid masslike structures and disease duration in primary progressive multiple sclerosis

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Funding information
Benjamin Knier is funded by the Else Kröner-Fresenius-Stiftung (Else Kröner-Fresenius Exzellenzstipendium). Joachim Havla is (partially) funded by the German Federal Ministry of Education and Research (grant numbers 01ZZ1603[A-D] and 01ZZ1804[A-H] [DIFUTURE]). The project was associated with DIFUTURE (Data Integration for Future Medicine, BMBF 01ZZ1804[A-H]). Bernhard Hemmer received funding for the study by the European Union’s Horizon 2020 Research and Innovation Program (grant MultipleMS, EU RIA 733161) and the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under Germany’s Excellence Strategy within the framework of the Munich Cluster for Systems Neurology (EXC 2145 SyNergy—ID 390857198).

Abstract

Background and purpose: Peripapillary hyper-reflective ovoid masslike structures (PHOMS) are a novel finding during retinal optical coherence tomography in patients with multiple sclerosis (MS). To date, there are no data on the occurrence of PHOMS in early MS. The aim of this study was to investigate the frequency of PHOMS in patients with first diagnosed early relapsing–remitting MS (RRMS) and to search for associations of PHOMS with disease patterns in different MS subtypes.

Methods: This was a cross-sectional analysis in two different cohorts: cohort 1, consisting of early RRMS patients (n = 349); cohort 2, consisting of patients with primary progressive MS (PPMS) (n = 66) and RRMS (n = 65).

Results: Peripapillary hyper-reflective ovoid masslike structures were detected in 18.3% of patients with early RRMS. The occurrence of PHOMS was not associated with age, disease duration and disability. Investigating clinical patterns and the occurrence of PHOMS (cohort 2), an association of PHOMS with higher Expanded Disability Status Scale measures (PHOMS 4.9, 3.7–6.1; no PHOMS 3.5, 3.0–5.3; p = 0.03) and longer disease durations (PHOMS 6.5 years, 1.9–11.0; no PHOMS 1.0 years, 0.0–4.0, p = 0.0007) was found in patients with PPMS but not RRMS. After p value adjustment, the disease duration appeared to be more relevant (β = 0.16, p = 0.06).

Conclusion: Peripapillary hyper-reflective ovoid masslike structures were found in 18% of patients with early MS. The presence of PHOMS might be associated with disease progression only in PPMS but not RRMS, suggesting that PHOMS might be embedded in neurodegenerative processes.

Keywords
disability, optical coherence tomography, PHOMS, progressive multiple sclerosis, relapsing–remitting multiple sclerosis
INTRODUCTION

Peripapillary hyper-reflective ovoid masslike structures (PHOMS) can be observed in a variety of diseases during retinal optical coherence tomography (OCT) and have recently been described in about 16% of patients with later stage multiple sclerosis (MS) [1,2]. PHOMS are assumed to represent the bulging of distended axons into the peripapillary retina and are most probably caused by axoplasmic stasis or congestion in the prelaminar optic nerve head [3].

The aim of this cross-sectional study was to investigate the frequency of PHOMS in the so far underrepresented MS subtype of early relapsing–remitting MS (RRMS) and to search for associations of PHOMS with disease patterns in patients with primary progressive MS (PPMS) and RRMS.

MATERIALS AND METHODS

Study design

In this cross-sectional study, individuals with clinically isolated syndrome, RRMS and PPMS as defined by the 2017 McDonald criteria [4] aged 15–73 were retrospectively included from two prospective observational cohorts at the Department of Neurology, Technical University of Munich (TUM), and the Institute of Clinical Neuroimmunology, Ludwig-Maximilians Universität München (LMU), respectively (recruitment period 2013–2020). Patients underwent an assessment of disease history, disability as measured by the Expanded Disability Status Scale (EDSS) and retinal OCT. Patients with incomplete clinical data and eyes with substantial eye disease or poor OCT quality were excluded [5]. The study was approved by the ethics commissions of TUM and LMU and adhered to the Declaration of Helsinki.

Two different cross-sectional cohorts underwent analysis. Cohort 1 included patients with RRMS or clinically isolated syndrome with disease durations of less than 12 months to assess the occurrence of PHOMS during the early stages of MS. Cohort 2 consisted of PPMS patients of any disease duration and disease-duration-matched RRMS patients without a history of optic neuritis (ON) to analyse the association of PHOMS occurrence and clinical patterns.

Retinal imaging

Optical coherence tomography images were acquired using spectral domain OCT (Spectralis OCT 2, Heidelberg Engineering) as previously described [6] with evaluation and segmentation of the macular area (30° × 25°) using a software-inbuilt algorithm (TUM, Heyex v2.5.4; LMU, Heidelberg Eye Explorer 1.10.4.0). The occurrence of PHOMS as defined by the Optic Disc Drusen Consortium [1] was evaluated by two experienced raters blinded to clinical information using a circular star-shaped optic disc scan centred on the optic nerve head (wheelscan, 15° angle, 27 B-scans; Figure 1a,b). The peripapillary retinal nerve fibre layer was also assessed by wheelscan (Figure 1a).

Statistical analysis

GraphPad Prism (v9.1.1) was used for statistical analysis. To account for inter-eye correlations of OCT measurements within each patient, a paired-eye statistical approach was used [6]. Mean values of both eyes were used as one data point when both eyes were available and allocated to the same group (PHOMS, no PHOMS). For demographic analyses, patients with at least one eye with PHOMS were characterized as PHOMS patients. Fisher’s exact test was used for contingency analysis concerning gender, occurrence of ON and PHOMS. Quantitative differences were calculated using the unpaired t test if values were normally distributed and the nonparametric Mann–Whitney U test if not. Values are given as mean ± standard deviation or median with 25%–75% interquartile range depending on the distribution. The correlation of EDSS and disease duration in PHOMS patients was assessed by Spearman nonparametric correlation. A multiple logistic regression model was used for p value adjustment and curve fitting was performed by simple logistic regression. Statistical significance was established at p < 0.05.

FIGURE 1 Peripapillary hyper-reflective ovoid masslike structures (PHOMS) in a patient with early relapsing–remitting multiple sclerosis (RRMS). (a) Representative wheelscan image of the right eye of a patient with RRMS. (b) Respective B-scan (see green arrow in (a)) showing a typical large PHOMS in the nasal quadrant (white arrows) [Colour figure can be viewed at wileyonlinelibrary.com]
RESULTS

Study cohorts

In all, 1536 patients (TUM 1437, LMU 99) were screened, of whom 461 were included in the study. Forty-six patients and 25 eyes were excluded due to exclusion criteria. A total of 349 early RRMS patients were included in cohort 1 (all TUM, 684 eyes), and 66 PPMS (all LMU, 127 eyes) and 65 RRMS patients (all TUM, 120 eyes) were included in cohort 2.

Occurrence of PHOMS during early RRMS

First, PHOMS occurrence was searched for in individuals with early RRMS (cohort 1). Here, patients revealed a median age of 31 years (26–40) and were predominantly female (240/349, 68.8%). Patients had a median disease duration of 1.0 month (0–2.0), an EDSS of 1.0 (1.0–2.0) and 127 patients (36.4%, 131 eyes) revealed a history of ON. PHOMS were detected in 18.3% (64/349) of patients with early RRMS of which 10.3% were found unilaterally and 8.0% bilaterally (Figure 1). There were no differences concerning age, sex, or EDSS in patients with or without PHOMS (Table 1). PHOMS were found in 16.8% of eyes (22/131) with a history of ON and in 12.7% of eyes (70/553) without a former ON history.

Focusing on eyes without a history of ON, PHOMS eyes of patients with early RRMS revealed discrete thinning of the total macular volume and the inner nuclear layer (INL) compared to eyes without PHOMS (Table 1).

Association of PHOMS occurrence and clinical patterns during RRMS and PPMS

In the next step, associations of clinical patterns, disease subtypes, retinal architecture, and PHOMS were searched for using cohort 2. Here, RRMS patients were younger (RRMS 43 years [36–51], PPMS 52 years [43–60], p < 0.0001) but revealed a comparable gender distribution (females RRMS 55.4%, PPMS 51.5%, p = 0.73) to individuals with PPMS. As defined by the inclusion criteria, disease durations were similar (RRMS 3.0 years [0–5.0], PPMS 2.0 years [0–5.5]; p = 0.98) but patients with PPMS revealed higher EDSS measures (RRMS 1.8 [1.0–2.0], PPMS 3.8 [3.0–5.5]; p < 0.0001). No patient suffered from a history of ON. PHOMS occurrence was similar in patients with RRMS (12/65; 18.5%) and PPMS (13/66; 19.7%); Table 1). In PPMS but not RRMS, PHOMS were associated with higher EDSS values and longer disease durations (Table 1). A correlation of EDSS values and the disease duration was seen (Spearman r = 0.46, 95% confidence interval [CI] 0.23–0.64, p = 0.0002). When applying multiple logistic regression models to adjust for disease duration, EDSS, age, and sex, the disease duration was shown to be more relevant for PHOMS occurrence (EDSS, β = 0.28, p = 0.28, odds ratio [OR] 1.17, 95% CI 1.00–1.40). In this cohort, no alterations of the retinal architecture in eyes with or without PHOMS in either MS subtype were detected (data not shown).

DISCUSSION

In this study, data on the prevalence of PHOMS during early stage RRMS are reported for the first time and provide novel aspects on PHOMS occurrence in different MS subtypes. Our data suggest PHOMS as an ON-independent feature that occurs in all MS subtypes in a similar frequency. During PPMS but not RRMS, PHOMS might be predominantly found in patients with longer disease duration and higher EDSS values.

Peripapillary hyper-reflective ovoid masslike structures were identified in 18% of patients with very early stage RRMS, which is comparable to data from Petzold et al. [2] who found PHOMS in 16% of individuals with advanced stage MS (mean disease duration 20 years). As shown there [2] no association of PHOMS appearance with age, sex, disease duration or disability was found in patients with RRMS.

Peripapillary hyper-reflective ovoid masslike structures have been discussed to be associated with an impaired glymphatic system of the retina [2,7]. Similarly, it has been hypothesized that frequently occurring dynamic changes and thickening of the INL, as a sign of inflammatory disease activity in RRMS, are also linked to an impaired glymphatic system [8–10]. In this study, PHOMS were associated with a discrete INL thinning in patients with early RRMS. Here, the clinical significance of this finding is unclear. It was not possible to reproduce these findings in patients with longer disease durations of RRMS or PPMS (cohort 2). This might be due, however, to imbalance in the sample size of the two cohorts and a reduced statistical power of cohort 2. Nevertheless, our data do not support the hypothesis of an inflammatory disruption of the glymphatic system with INL thickening as the underlying cause of PHOMS.

In our study, the occurrence of PHOMS was associated with longer disease durations in PPMS as a unique feature. Mitochondrial dysfunction and an impaired axonal transport are considered as hallmarks of PPMS pathophysiology [11]. Since PHOMS have been linked to an impaired axoplasmic flow within the visual pathway [12] their occurrence in PPMS could be a sign of later PPMS disease stages or disease progression and might occur especially after several years of disease.

Our study has several limitations. First, only cross-sectional data on PHOMS occurrence and its association with clinical patterns in RRMS and PPMS patients are provided. Secondly, the impact of inflammatory disease activity as measured by magnetic resonance imaging on PHOMS occurrence was not assessed and could possibly provide additional insights into the underlying mechanisms of their evolvement. Considering these aspects, further and longitudinal studies are needed to evaluate intra-individual dynamics of PHOMS evolvement in association with clinical patterns, inflammatory disease activity parameters, and disease progression in RRMS and PPMS in particular.
In conclusion, confirmatory evidence of PHOMS shows up in approximately 18% of eyes in early RRMS. An association of PHOMS development with disease duration seems conceivable during PPMS whereas underlying causes remain unclear.

**ACKNOWLEDGEMENTS**

Andrea Hennemann and Mira Radic (both TUM) and Christopher Hemingway and Angelika Bamberger (both LMU) are thanked for expert assistance during the OCT analysis. Dr Gildas Lepennetier is thanked for helping with the binomial regression model. Open Access funding enabled and organized by Projekt DEAL. WOA Institution: Technische Universität Münchener Blended DEAL: Projekt DEAL

**CONFLICT OF INTERESTS**

Rebecca Wicklein, Josephine Wauschkuhn and Katrin Giglhuber report no disclosures. Tania Kümpfel has received speaker honoraria and/or personal fees for advisory boards from Bayer Healthcare, Teva Pharma, Merck, Novartis Pharma, Sanofi-Aventis/Genzyme, Roche Pharma and Biogen as well as grant support from Novartis and Chugai Pharma in the past. Bernhard Hemmer has served on scientific advisory boards for Novartis; he has served as DMSC member for AllergyCare, Polpharma and TG therapeutics; he or his institution have received speaker honoraria from Desitin; his institution received research grants from Regeneron for MS research. He holds part of two patents, one for the detection of antibodies against KIR4.1 in a subpopulation of patients with MS and one for genetic determinants of neutralizing antibodies to interferon. All conflicts are not relevant to the topic of the study. Joachim Havla reports personal fees, research grants and non-financial support from Merck, Novartis, Roche, Santhera, Biogen, Alexion, Celgene, Sanofi Genzyme; and non-financial support of the Guthy-Jackson Charitable Foundation, all outside the submitted work. Benjamin Knier received travel support and a research grant from Novartis which are both outside the submitted work.

|                  | Early RRMS | PHOMS | No PHOMS | p value |
|------------------|------------|-------|----------|---------|
| **Cohort 1**     |            |       |          |         |
| **Demographics** | n = 64     | n = 285 |          |         |
| Sex female, no. (%) | 44 (68.8) | 196 (68.8) | >0.99   |         |
| Age, years       | 31 (23–42) | 32 (27–39) | 0.42    |         |
| Disease duration, months | 1.0 (0–2.0) | 1.0 (0–2.0) | 0.39    |         |
| EDSS             | 1.3 (0.2–2.3) | 1.0 (1.0–2.0) | 0.47    |         |
| History of optic neuritis, no. (%) | 22 (34.4) | 105 (36.8) | 0.77    |         |
| **OCT measurements** | n = 69 eyes | n = 480 eyes |          |         |
| pRNFL, µm        | 98 (86–109) | 101 (95–108) | 0.07    |         |
| TMV, mm³         | 8.6 (8.2–8.9) | 8.7 (8.3–9.1) | 0.04    |         |
| GCIPL, mm³       | 2.0 (1.8–2.1) | 2.0 (1.8–2.2) | 0.70    |         |
| INL, mm³         | 0.96 (0.90–1.02) | 0.98 (0.94–1.04) | **0.005** |         |
| **Cohort 2**     |            |       |          |         |
| **RRMS**         | n = 12     | n = 53 |          |         |
| Sex female, no. (%) | 8 (66.7) | 28 (52.8) | 0.74    |         |
| Age, years       | 41 (32–50) | 44 (37–51) | 0.34    |         |
| Disease duration, years | 1.5 (0.3–5.0) | 3.0 (0–5.0) | 0.78    |         |
| EDSS             | 1.8 (0.7–3.0) | 1.8 (0.3–2.0) | 0.69    |         |
| **PPMS**         | n = 13     | n = 53 |          |         |
| Sex female, no. (%) | 7 (53.8) | 27 (50.9) | >0.99   |         |
| Age, years       | 53 (44–62) | 51 (43–60) | 0.55    |         |
| Disease duration, years | 6.5 (1.9–11.0) | 1.0 (0–4.0) | **0.0007** |         |
| EDSS             | 4.9 (3.7–6.1) | 3.5 (3.0–5.3) | **0.03** |         |

**Notes:** For demographic analysis, patients with at least one eye with PHOMS were characterized as PHOMS patients. For OCT analysis of cohort 1, 135 eyes of 684 eyes were excluded due to a history of optic neuritis (131 eyes) or an incomplete macular OCT dataset (four eyes). Mean ± standard deviation or median (25%–75% interquartile range) depending on normality distribution; unpaired t test, Mann–Whitney U test, Fisher’s exact test; in bold p < 0.05.

**Abbreviations:** EDSS, Expanded Disability Status Scale; GCIPL, ganglion cell–inner plexiform layer; INL, inner nuclear layer; OCT, optical coherence tomography; PHOMS, peripapillary hyper-reflective ovoid masslike structures; PPMS, primary progressive multiple sclerosis; pRNFL, peripapillary retinal nerve fibre layer; RRMS, relapsing–remitting multiple sclerosis; TMV, total macular volume.

**TABLE 1** Demographics and OCT characteristics in patients with MS and PHOMS

In conclusion, confirmatory evidence of PHOMS shows up in approximately 18% of eyes in early RRMS. An association of PHOMS development with disease duration seems conceivable during PPMS whereas underlying causes remain unclear.
AUTHOR CONTRIBUTIONS
Rebecca Wicklein: Conceptualization (supporting); data curation (equal); formal analysis (lead); investigation (equal); methodology (equal); visualization (lead); writing—original draft (lead). Josephine Wauschkuhn: Data curation (equal); validation (equal); writing—review and editing (supporting). Katrin Laura Veronika Giglhuber: Resources (equal); writing—review and editing (supporting). Tania Kümpfel: Writing—review and editing (equal). Bernhard Hemmer: Funding acquisition (supporting); resources (supporting); writing—review and editing (equal). Joachim Havla: Conceptualization (equal); data curation (equal); funding acquisition (equal); resources (equal); supervision (equal); validation (equal); writing—review and editing (equal). Benjamin Knier: Conceptualization (equal); data curation (equal); formal analysis (supporting); funding acquisition (equal); investigation (equal); project administration (equal); resources (equal); supervision (equal); validation (supporting); writing—review and editing (equal).

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on request from the corresponding author and after subscription of a data transfer agreement. The data are not publicly available due to privacy or ethical restrictions. We will share data not shown or raw data for analysis in an anonymized and numerical way by request from any qualified investigator. OCT images are unique in each person and might allow identification of the respective participant. We are not allowed to share original OCT images or OCT files outside approved studies due to legal requirements of our departments (TUM, LMU).

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How to cite this article: Wicklein R, Wauschkuhn J, Giglhuber K, et al. Association of peripapillary hyper-reflective ovoid mass-like structures and disease duration in primary progressive multiple sclerosis. Eur J Neurol. 2021;28:4214–4218. https://doi.org/10.1111/ene.15056