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Characterization of Peripapillary Hyperreflective Ovoid Mass-like Structures in a Broad Spectrum of Neurologic Disorders

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Purpose: Peripapillary hyperreflective ovoid mass-like structures (PHOMSs) have been identified in ophthalmic and neurologic diseases. Because PHOMSs were found more frequently in these cohorts compared with healthy control participants, it is assumed that the presence of PHOMSs reflects a secondary disease marker of unknown significance. The extent to which disease-specific differences are reflected in PHOMSs has not yet been investigated sufficiently.

Design: Monocentric, retrospective study.

Participants: We analyzed a large cohort of people with a broad spectrum of neurologic disorders, including neuroimmunologic diseases (NIDs; n = 237), epilepsy (n = 153), movement disorders (MDs; n = 44), intracranial hypertension (IH; n = 13), and inborn errors of metabolism (n = 90).

Methods: We analyzed the prevalence, location, volume, and intensity of PHOMSs. Peripapillary hyperreflective ovoid mass-like structure volumes were correlated with demographic and other OCT parameters.

Main Outcome Measures: Prevalence, location, volume, and intensity of PHOMSs.

Results: We identified PHOMSs in 7% of the analyzed eyes. Peripapillary hyperreflective ovoid mass-like structures were detected in all cohorts, and their location was predominantly nasal. The median volume of all PHOMSs was 0.06 mm^3. However, the median PHOMS volume was increased in those with IH compared with those with NID ($P = 0.009$), epilepsy ($P = 0.038$), or MDs ($P = 0.027$). The PHOMS volume correlated positively with the opening of the Bruch membrane and correlated negatively with the age of the cohort after the exclusion of patients with IH. Overall, PHOMS intensity was comparable with that of the optic nerve.

Conclusions: Because larger PHOMS volumes were found in individuals with IH, a mechanistic link to increased intracranial pressure can be assumed. It remains unclear whether this explanation also applies to individuals with other neurologic disorders with PHOMSs. Because PHOMSs have a relevant influence on OCT parameters, their presence also should be considered in nonophthalmic scientific studies in the future.

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Peripapillary hyperreflective ovoid mass-like structures (PHOMSs) are oval structures that can be visualized using OCT B-scans when evaluating the optic nerve head. The core features of PHOMSs were defined by a multirater validation study.[1] Since then, PHOMS occurrence has been reported in different pediatric[2–8] and adult[9] cohorts. Interestingly, PHOMSs have been described as a diagnostic or monitoring marker in ophthalmic, neuro-ophthalmic, and neurologic cohorts, including in those with intracranial hypertension (IH), multiple sclerosis, neuromyelitis optica spectrum disorders, and myelin oligodendrocyte glycoprotein-IgG-associated disease.[9–16] These relatively smaller cohorts have demonstrated that PHOMSs also can be detected in diseases with central nervous system involvement, which provides a basis for establishing PHOMSs as a potential marker in neurology.[13–16] Originally, PHOMSs were reported not to be observed in healthy individuals.[14] However, we and others recently reported that PHOMSs may be detectable in healthy individuals without systemic or ophthalmic diseases,[16,17] with a prevalence of 3% to 4% in a healthy control group.[16] In comparison, 12% of eyes in individuals with neuromyelitis optica spectrum disorders were affected.[16] Consequently, even if a disease-specific occurrence is unlikely based on the cohorts investigated to date, evidence suggests a disease-dependent occurrence with a higher prevalence of PHOMSs compared with healthy control participants. Based on histopathologic results, PHOMSs currently are

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considered an unspecific marker of axoplasmic stasis,[18] whereas other hypotheses suggest an impairment of glymphatic drainage or a translaminar pressure gradient.[14] Only limited data are available on the morphologic features and volume of PHOMSs. Yet, one study describes volumetric measurements of PHOMSs in a cohort of patients with optic disc drusen.[19]

In the present study, we (1) screened different cohorts of patients with a broad spectrum of neurologic disorders for the prevalence of PHOMSs (eyes with PHOMS vs. eyes without PHOMS) and (2) characterized the PHOMSs in terms of their disease-specific localization, volume, and intensity. The disease cohorts studied included patients with various inflammatory, degenerative, and metabolic disorders. We hypothesized that a more precise characterization of PHOMSs allows for a better understanding of possible disease-specific mechanisms of its presence.

Methods

Study Design

We performed a cross-sectional, retrospective study. The following cohorts were studied: (1) patients with neuroimmunologic diseases (NID; Institute of Clinical Neuroimmunology, LMU Hospital), (2) epilepsy (Epilepsy Center, LMU Hospital), (3) movement disorders (MDs) and intracranial hypertension (IH; both at Department of Neurology, LMU Hospital), and (4) inborn errors of metabolism (IEMs; Department of Inborn Errors of Metabolism, LMU Hospital). The cohorts were examined in separate cohort-specific studies in the NeuroVisionLab by the respective departments. Individuals with a refractive error of more than +5 diopters or less than −5 diopters, as well as those with reported ophthalmic comorbidities in their medical history, were excluded. OCT scans with insufficient image quality to assess PHOMS presence were not considered. In patients with eyes with PHOMSs, basic demographic data and OCT parameters were evaluated. The local ethics committee of the LMU, Munich, approved a retrospective analysis of OCT datasets 427-14 and 163-16 (NID), 21-0014 (epilepsy), 17-0710 (MD), 21-0705 (IIH), and 19-0453 (IEM). All procedures were performed according to the 2013 revised Declaration of Helsinki and national ethical standards for experiments on humans. Written informed consent was obtained from all participants, their legal representatives, or both.

OCT Imaging

OCT imaging was performed as described previously[15,16] using a Spectralis spectral-domain OCT device with automated eye tracking (OCT2-Module; Heidelberg Engineering GmbH). Peripapillary hyperreflective ovoid mass-like structure screening was conducted on circular star-shaped optic disc scans centered on the optic nerve head (radial scan, 15° angle, 27 B-scans). This scan also was used to acquire the peripapillary retinal nerve fiber layer (pRNFL) thickness (in micrometers), as well as the Bruch membrane opening (BMO; in square millimeters) and the BMO minimum rim width (MRW; in micrometers). Retinal layer segmentation was carried out by Heyex version 2.5.5 software (Heidelberg Engineering GmbH).

Peripapillary Hyperreflective Ovoid Mass-like Structure Rating

Two independent experts (T.C., J.A.G.), masked to clinical data, assessed the presence of PHOMSs on radial OCT scans according to the current guidelines.[1]

Peripapillary Hyperreflective Ovoid Mass-like Structure Characterization

Volume measurements of PHOMSs were performed according to the method proposed by Jørgensen et al.[19] The PHOMS surfaces were delineated manually on the radial scan, and the resulting parameters were used to calculate the PHOMS volume by simulating a torus volume.[19] Furthermore, the star scan generates 48 sectors, which were used to analyze the localization of PHOMSs. A sector was classified as PHOMS-positive if a PHOMS was detected on both limiting scans. Finally, by using the software ImageJ2 version 2.14.0/1.54f (National Institutes of Health),[20] the intensity of the PHOMS surface on all PHOMS-positive radial scans was compared with the intensity of the following regions of interests: (1) the internal to the external limiting membrane, (2) the outer nuclear layer, and (3) the optic nerve and corresponding ratios (Fig S1, available at www.aaojournal.org), which were reported as:

$$i1 = \frac{\text{Intensity PHOMS}}{\text{Intensity ILM to ELM}} \quad i2 = \frac{\text{Intensity PHOMS}}{\text{Intensity ONL}}$$

$$i3 = \frac{\text{Intensity PHOMS}}{\text{Intensity optic nerve}}.$$

Statistical Analysis

SPSS Statistics 29 (IBM Corp. Released 2023. IBM SPSS Statistics for Windows, Version 29.0.2.0 Armonk, NY: IBM Corp) and GraphPad Prism version 10.3.1 (GraphPad Prism version 10.3.1 for Windows, GraphPad Prism Software, Boston, MA, www.graphpad.com) were used for statistical analysis and creation of figures. Interrater agreement on the rating of PHOMSs was calculated using Cohen's κ. Patients with unilateral PHOMSs were classified as PHOMS-positive patients. The Kruskal-Wallis test was used to compare PHOMS volumes among the subgroups, and Pearson correlation was used to associate PHOMS volume to clinical and OCT parameters. Data are represented as the median with a corresponding interquartile range (IQR) or mean ± standard deviation. Statistical significance was set at $P < 0.05$.

Results

Study Cohort and Peripapillary Hyperreflective Ovoid Mass-like Structure Frequency

We investigated these cohorts as part of our routine clinical practice and studies: NID (n = 237), epilepsy (n = 153), MD (n = 44), IH (n = 13), and IEM (n = 90). A detailed list of the diagnoses included is presented in Table S1 (available at www.aaojournal.org). From these cohorts, a total of 537 people (n = 1032 eyes; average age, 36 years [IQR, 26−51 years] and 58% women) were examined for PHOMS prevalence. The agreement of the two experts evaluating PHOMSs was 0.95 (κ = 0.69) per eye and 0.94 (κ = 0.71) per patient. In total, PHOMSs were found in 56 patients (10%) and 74 eyes (7%). Peripapillary

Table 2. Demographic Data and Peripapillary Hyperreflective Ovoid Mass-like Structure Frequency

Variable	Total	Neuroimmunologic Disease	Epilepsy	Movement Disorders	Intracranial Hypertension	Inborn Errors of Metabolism
All screened patients						
No. of patients	537	237	153	44	13	90
No. of eyes	1032	457	294	83	25	171
Age (yrs)	36 (26–51)	44 (32–54)	32 (24–41)	66 (56–73)	32 (30–44)	22 (13–29)
Female sex	314 (58)	145 (61)	82 (54)	19 (43)	12 (92)	56 (62)
All patients with PHOMS						
Patients	56 (10)	17 (7)	17 (11)	4 (9)	7 (54)	11 (11)
Eyes	74 (7)	20 (4)	22 (7)	5 (6)	11 (44)	16 (9)
Age (yrs)	32 (23–48)	42 (22–54)	30 (22–42)	60 (55–74)	34 (29–39)	22 (9–26)
Female sex	34 (61)	11 (65)	8 (47)	0 (0)	7 (100)	8 (73)
BMI (kg/m^2)*	26 (22–34)	23 (21–32)	26 (23–30)	25 (25–26)	35 (35–38)	22 (20–38)

BMI = body mass index; PHOMS = peripapillary hyperreflective ovoid mass-like structure.
Data are presented as no. (%) or median (interquartile range) unless otherwise indicated.
*Information available for 47 of 56 patients (all > 18 years of age).

hyperreflective ovoid mass-like structures were detected in patients from all cohorts, with frequencies ranging from 7% (NID) to 54% (IH; Table 2). Patients with PHOMSs had a median age of 32 years (IQR, 23–48 years), 34 of whom were women (61%), and the median body mass index (BMI) was 26 kg/m^2 (IQR, 22–34 kg/m^2; Table S1).

Peripapillary Hyperreflective Ovoid Mass-like Structure Localization

A classification of the localization of all PHOMSs showed that more than 65% were found in the nasal sector and only 5% to 10% were found in the temporal sector (Fig 2). A comparison of the PHOMS localization between the eyes with PHOMSs of the different subgroups revealed a nasal preponderance among all cohorts. In the MD cohort, PHOMSs were present in more than 90% in the nasal sector, but not within the temporal sectors. In patients with IH, PHOMSs were located in the nasal sector in more than 40% and in more than 10% in the temporal, temporal-superior, nasal-superior, and nasal-inferior sectors (Fig 2).

Peripapillary Hyperreflective Ovoid Mass-like Structure Volumes

The median volume of all PHOMSs was 0.06 mm^3 (IQR, 0.02–0.12 mm^3). Peripapillary hyperreflective ovoid mass-like structure volumes were significantly larger in individuals with IH (median, 0.23 mm^3; IQR, 0.07–0.58 mm^3) compared with individuals with epilepsy (median, 0.05 mm^3; IQR, 0.02–0.09 mm^3), MD (median, 0.02 mm^3; IQR, 0.01–0.06 mm^3; $P < 0.05$ for both), and NID (median, 0.03 mm^3; IQR, 0.01–0.09 mm^3; $P < 0.001$; Fig 3A). The median PHOMS volume in the IEM cohort was 0.06 mm^3 (IQR, 0.02–0.11 mm^3; $P = 0.250$ vs. the IH cohort). All pairwise analyses were Bonferroni adjusted. After excluding patients with IH (n = 7), a significant negative correlation between PHOMS volumes and age was shown (for n = 49; $r = -0.377$; $P = 0.003$; Fig 3B). In the same cohort and after also excluding those younger than 18 years, PHOMS volumes were not associated with BMI (n = 40; $r = -0.147$; $P = 0.179$; Fig 3C). In patients with IH, no correlation was found between PHOMS volume and age or BMI (no data shown because the cohort was small). The PHOMS volumes were associated positively with global pRNFL ($r = 0.349$; $P = 0.002$), nasal-inferior pRNFL thickness ($r = 0.335$; $P = 0.003$), temporal-inferior pRNFL thickness ($r = 0.397$; $P < 0.001$), and temporal pRNFL thickness ($r = 0.283$; $P = 0.013$) segments (Fig 4A). The correlation between PHOMS volumes and all BMO MRW segments was $r > 0.05$ and $P < 0.001$ (Fig 4B). The correlation between PHOMS volumes and BMO (surface in square millimeters) did not correlate significantly (for n = 74; $r = 0.015$, $P = 0.900$).

Peripapillary Hyperreflective Ovoid Mass-like Structure Intensity

The intensity of all PHOMSs was measured in relationship to (1) the retinal volume (internal to external limiting membrane; mean ± standard deviation, 0.73 ± 0.14), (2) the outer nuclear layer (1.49 ± 0.32), and (3) the optic nerve (0.99 ± 0.19; Fig 3D). All pairwise comparisons among the 3 intensity ratios resulted in P values of less than 0.001 (Bonferroni adjustment). No significant differences were found when comparing the PHOMS intensities between the individual disease cohorts (data not shown).

Discussion

In summary, we were able to detect PHOMSs in 7% of eyes in a large cohort with a broad spectrum of neurologic diseases. Peripapillary hyperreflective ovoid mass-like structures were found in all investigated cohorts (NID, epilepsy, MD, IH, and IEM). The frequency of eyes with PHOMSs within the cohorts varied in our analysis, but the overall frequency of 7% seems lower compared with previously published cohorts. For example, a frequency of 12% to 18% eyes with PHOMSs was published for those with NIDs, including multiple sclerosis, neuromyelitis optica

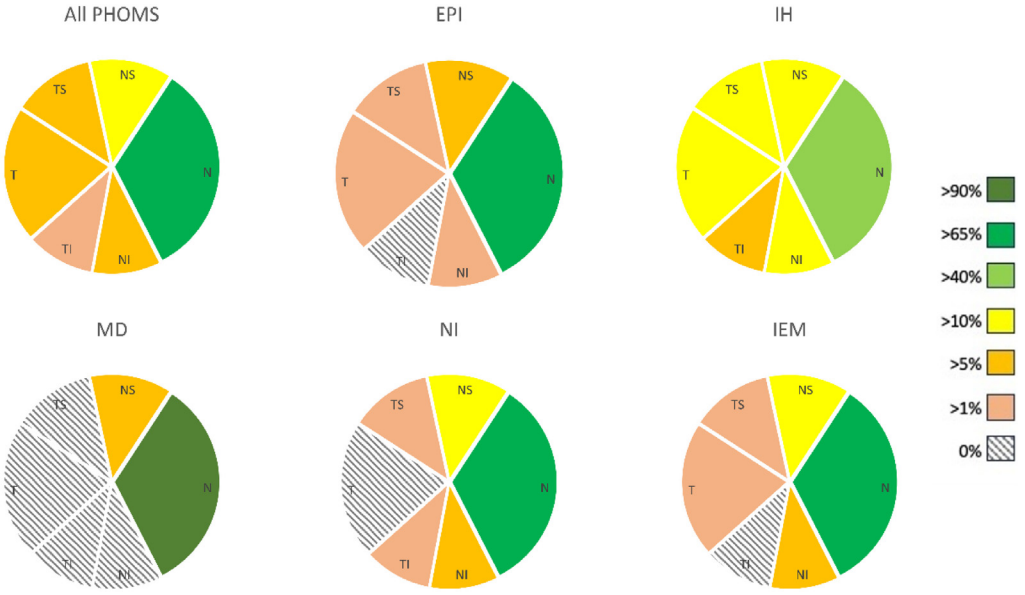

Figure 2. Pie graphs showing PHOMS location in eyes with PHOMSs. The number of B-scans showing PHOMSs in the different anatomic regions was set in relationship to the B-scans not showing PHOMSs. The ratios of PHOMS localization for the different sectors are represented by a color code. EPI = epileptic disorders; IEM = inborn error of metabolism; IH = intracranial hypertension; MD = movement disorder; N = nasal; NI = nasal-inferior; NID = neuroimmunologic disease; NS = nasal-superior; PHOMS = peripapillary hyperreflective ovoid mass-like structure; T = temporal; TI = temporal-inferior; TS = temporal-superior.

spectrum disorders, or myelin oligodendrocyte glycoprotein-IgG-associated disease,[14–16] and 62% to 81% of eyes with PHOMSs for patients with IH.[13,14] We speculate that the lower number of PHOMSs in this cohort (NID, 7%; IH, 54%) is most likely the result of the following methodologic reasons. First, we performed a strict screening procedure and scored eyes as having PHOMSs only if a PHOMS was detectable on at least 2 consecutive B-scans. Second, the total number of patients examined and the individual timing of the OCT examination during the disease course probably influences PHOMS frequency. Third, data on the prevalence of eyes with PHOMSs was not yet available for some of the individuals in our study.

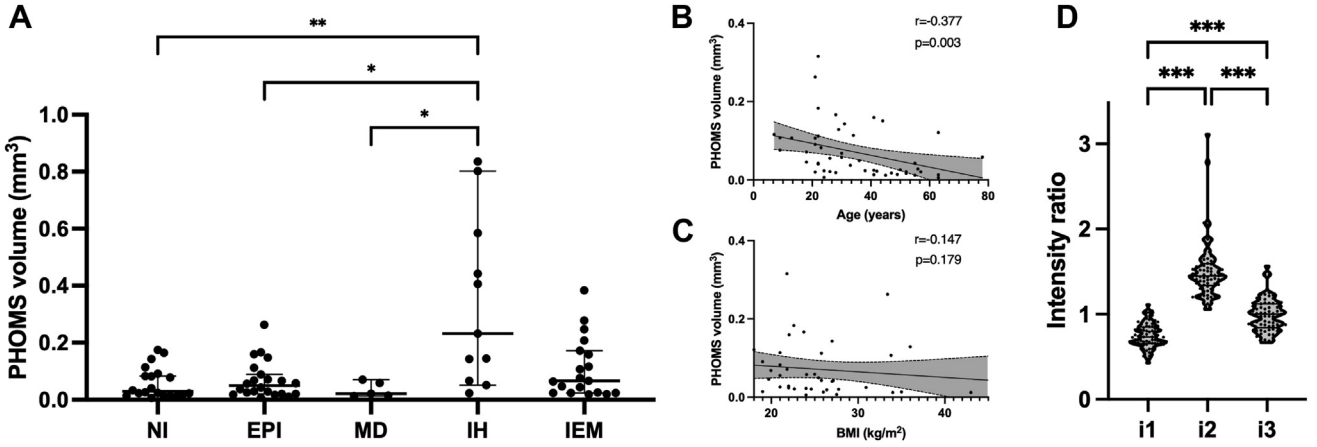

Figure 3. Graphs showing peripapillary hyperreflective ovoid mass-like structure (PHOMS) volume and intensity. **A**, Kruskal-Wallis test comparing PHOMS volume (in cubic millimeters) among the different cohorts. Median with interquartile range is displayed. Only significant (Bonferroni-adjusted) effects are marked. Significance was set at $P < 0.05$. **B**, Correlation between PHOMS volume (in patients with epilepsy [EPI], inborn errors of metabolism [IEMs], movement disorders [MDs], and neuroimmunologic disease [NID]) and age. **C**, Correlation between PHOMS volume (in patients with epilepsy, IEMs, MDs, and NID older than 18 years) and body mass index (BMI). **D**, Intensity of all eyes with PHOMS compared with different reference regions on B-scans for the total retinal layers from the internal to the external limiting membrane (*i*1), the outer nuclear layers (*i*2), and the optic nerve (*i*3). The 3 different ratios differed in the pairwise comparison ($P < 0.001$), but within 1 ratio, no differences were found between the disease cohorts. *$P < 0.05$. **$P < 0.01$. ***$P < 0.001$. IH = intracranial hypertension.

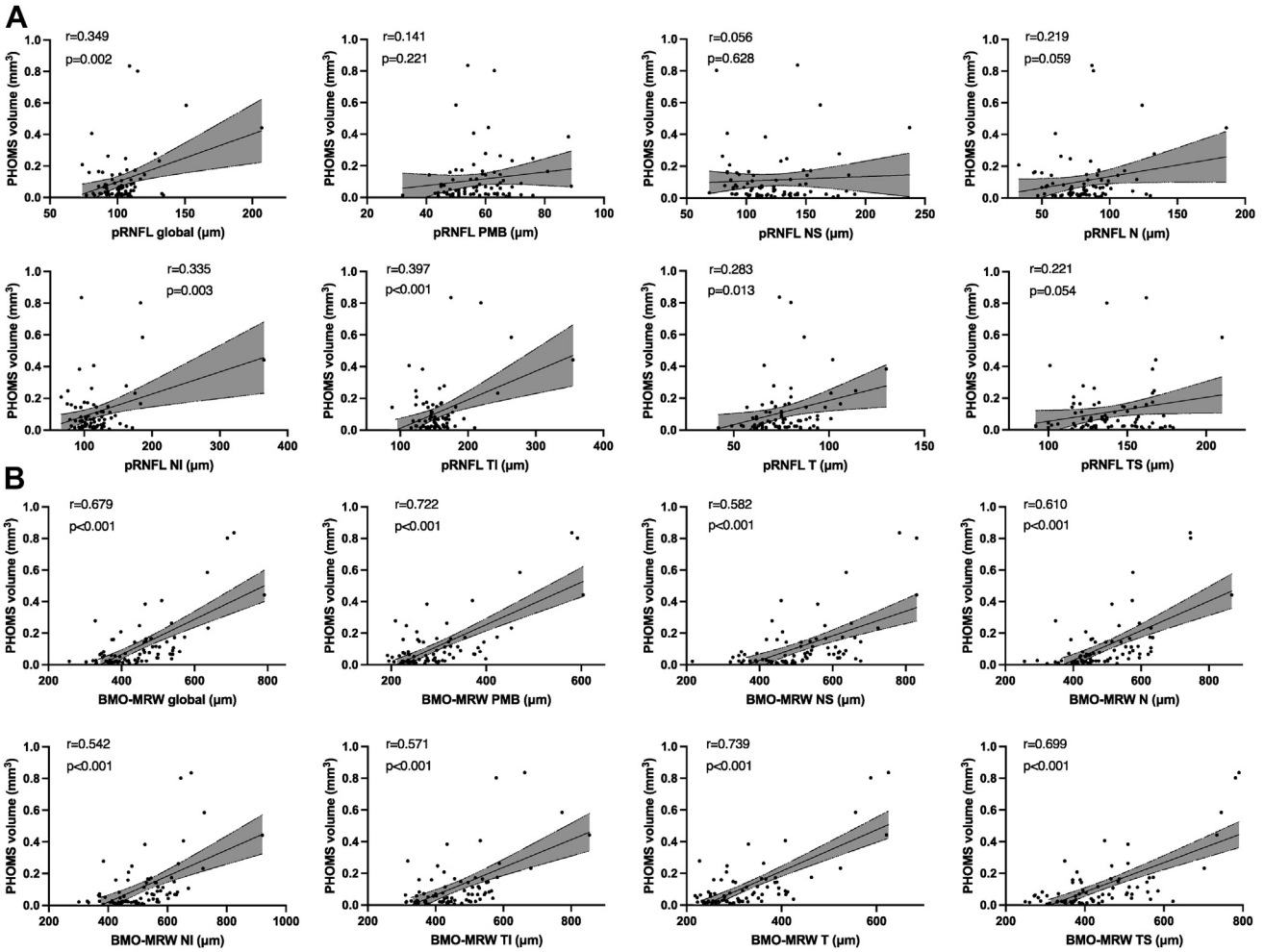

Figure 4. Graphs showing peripapillary hyperreflective ovoid mass-like structure (PHOMS) volume and correlation with peripapillary retinal nerve fiber layer (pRNFL) and Bruch membrane opening (BMO) minimum rim width (MRW). **A**, Correlation graphs for PHOMS volume and the pRNFL (global pRNFL as well as different segments). **B**, Correlation graphs for PHOMS volume and BMO MRW (global BMO MRW as well as different segments). N = nasal; NI = nasal-inferior; NS = nasal-superior; PMB = papillomacular bundle; T = temporal; TI = temporal-inferior; TS = temporal-superior.

We present data on PHOMS prevalence in patients with epilepsy (7%), MDs (6%), and IEMs (11%). This could enable future studies to analyze specific disease entities systematically within the cohorts regarding PHOMS occurrence. In addition to contributing to the understanding of PHOMS pathologic features and enhancing their diagnostic value, we further characterized PHOMS in terms of morphologic and intensity characteristics. The main findings of this analysis are as follows. In line with current literature, we found PHOMSs to be present predominantly in the nasal area.[19,21] Notably, an exclusively temporal location of PHOMSs has been described only in individuals with Leber's hereditary optic neuropathy.[10] Peripapillary hyperreflective ovoid mass-like structure volumes were significantly larger in patients with IH compared with patients with NIDs, MDs, or epilepsy. This supports recent findings that patients with IH tend to have larger PHOMS volumes.[21] The absolute PHOMS volumes in the IH cohort are comparable with the volumes of PHOMSs in patients with optic disc drusen published previously.[19] In summary, larger PHOMS volume in IH is associated with the broader distribution of PHOMSs across several sectors, probably because of an increase in intracranial pressure (ICP).[19] Therefore, the disease-specific difference in PHOMS volume could be the result of higher chronic and global ICP. Neuroimmunologic diseases, MDs, epilepsy, and IEM disorders typically are not known to be associated with increased ICP. However, the opening pressure has not been studied in larger cohorts and contrasting results have been reported, for example, in people with multiple sclerosis.[22,23] In future, the measurement of intraocular and retrolaminar pressure to determine the translamina cribrosa pressure difference in association with PHOMSs would be an interesting target to address this issue. Furthermore, age and body weight also have been discussed as additional factors that could influence PHOMSs.[2,19] A significant negative correlation between PHOMS volume and the individual's age was found in a cohort excluding the patients with IH. However, the different age distributions across the cohorts, reflecting the known age peaks of the different diseases, limits this result. We found no association between PHOMS volumes and patients' BMI.

Recently, a potential association between BMI and the presence of PHOMSs in children was investigated but was not found to be significant.[2] No analysis regarding BMI and PHOMS frequency or volumes has been reported for patients with IH. Additionally, we investigated the relationship between PHOMS volumes and other OCT parameters. The significance of the correlation between PHOMS volume and pRNFL thickness shown in our study remains unclear. A decrease in pRNFL recently was reported in 3 children with bilateral PHOMSs.[24] However, previous studies observed no difference in pRNLF thickness when comparing eyes with and without PHOMSs.[14,15] A potential limitation in the interpretation of these results could be the heterogeneity of the analyzed diseases themselves, because they may be associated with different pRNFL atrophy patterns independent of the presence of PHOMSs.[25] However, the thickness of all BMO MRW segments was associated significantly with PHOMS volume. This might be explained by the mass-like structure characteristic of PHOMSs, which is known to lead to a peripapillary deflection of retinal layers and thus to an increased MRW.[18] Like Jørgensen et al,[19] we found no association between PHOMS volume and BMO surface. In summary, the presence of PHOMSs should be investigated not only in ophthalmic diseases, but also in (rare) neurologic diseases, in the future. We hypothesize that intensity measurement of PHOMSs might reveal a better understanding of their pathomechanism. Our OCT B-scan analysis, which compared the structural hyperreflective intensity of PHOMSs with that of reference structures, revealed that PHOMSs exhibit an intensity comparable with that of the optic nerve, lower than the total retinal layers, but higher than the outer nuclear layer. No differences in the distribution of intensity ratios between the different cohorts were discovered. Our findings align with histopathologic observations in papilledema, suggesting that PHOMSs most likely involve bulging optic nerve fibers.[18] However, histopathologic analyses in different disease cohorts are necessary to understand better the development and evolution of PHOMSs. Although our methodologic approach to measuring the intensity of PHOMSs is easily reproducible, it has yet to be validated in an external cohort. Additionally, our study is limited by its cross-sectional nature, and the inherent heterogeneity across the cohorts—such as differences in age, disease pathologic features, phenotype, disease duration, and treatment—limits the ability to draw meaningful conclusions regarding these factors. Therefore, the different frequencies of eyes with PHOMSs shown in the present cohort do not allow any meaningful conclusions to be drawn about these factors. This requires additional large, multicenter cohort studies.

In conclusion, in this large cohort representing a broad spectrum of neurologic disorders, a significantly larger PHOMS volume in individuals with IH compared with those with other disorders was detected, which may be related to an elevated global ICP. Peripapillary hyperreflective ovoid mass-like structures were localized predominantly nasally and exhibited an intensity comparable with that of the optic nerve in all cohorts. In addition, the PHOMS volumes correlated with segments of the pRNFL and with the BMO MRW. Our approach represents an interdisciplinary attempt to study different cohorts of rare diseases regarding eyes with PHOMSs. Moving forward, further multimodal characterizations of PHOMSs across different disease groups are needed specifically to understand the role and presence of PHOMSs in each disease.

Footnotes and Disclosures

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The data presented in this study are available on reasoned request from the corresponding author if the data exchange is possible with respect to valid data protection laws.

HUMAN SUBJECTS: Human subjects were included in this study. The local ethics committee of the LMU Munich approved a retrospective analysis of OCT datasets. All procedures were performed according to the Declaration of Helsinki and national ethical standards for experiments on humans. Written informed consent was obtained from all participants and/or their legal representatives.

No animal subjects were included in this study.

Author Contributions:

Conception and design: Gernert, Christmann, Lotz-Havla, Havla

Analysis and interpretation: Gernert, Christmann, Lotz-Havla, Havla

Data collection: Gernert, Christmann, Kaufmann, Delazer, Kirsch, Levin, Schönecker, Fietzek, zu Eulenburg, Velten, Gripshi, Parhofer, Maier, Kümpfel, Lotz-Havla, Havla

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Abbreviations and Acronyms:
BMI = body mass index; **BMO** = Bruch membrane opening; **ICP** = intracranial pressure; **IEM** = inborn error of metabolism; **IH** = intracranial hypertension; **IQR** = interquartile range; **MD** = movement disorder; **MRW** = minimum rim width; **NID** = neuroimmunologic disease; **PHOMS** = peripapillary hyperreflective ovoid mass-like structure; **pRNFL** = peripapillary retinal nerve fiber layer.

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