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ORIGINAL COMMUNICATION

Optical coherence tomography for the diagnosis and monitoring of idiopathic intracranial hypertension

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Abstract The objectives of the study were to investigate the value of optical coherence tomography in detecting papilledema in patients with idiopathic intracranial hypertension (IIH), a disease which is difficult to monitor and which can lead to permanent visual deficits; to analyze retinal changes over time. In this non-interventional case–control study, spectral-domain optical coherence tomography (SD-OCT) was used to analyze the retinal and optic nerve head (ONH) morphology of 21 patients with IIH and 27 age- and sex-matched healthy controls over time. We analyzed the ONH volume using a custom-made algorithm and employed semi-automated segmentation of macular volume scans to assess the macular retinal nerve fiber layer (RNFL) and ganglion cell layer and inner plexiform layer complex as well as the total macular volume. In IIH patients, the ONH volume was increased and correlated with cerebrospinal fluid (CSF) pressure. The ONH volume decreased after the initiation of treatment with acetazolamide. The macular RNFL volume decreased by 5% in 3.5 months, and a stepwise multivariate regression analysis identified CSF pressure as the main influence on macular RNFL volume at diagnosis. The only factor predicting macular RNFL volume loss over time was ONH volume. SD-OCT can non-invasively monitor changes in retinal and ONH morphology in patients with IIH. Increased ONH volume leads to retinal atrophy in the form of macular RNFL volume loss, presumably due to mechanic jamming of the optic nerve at the disc and subsequent axonal loss.

Keywords Idiopathic intracranial hypertension · Optical coherence tomography

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Introduction

Idiopathic intracranial hypertension (IIH) is characterized by diffuse, chronic headache and visual disturbances. It mainly occurs in obese women of childbearing age (20–44 years) and reaches an annual incidence of 1–3 cases per 100,000 [1]. Diagnostic criteria [2] include papilledema, normal cerebral MRI and cerebrospinal fluid (CSF) composition, normal neurological examination except for sixth nerve abnormalities and increased CSF pressure (>25 cmH_2O) measured by lumbar puncture (LP). If the CSF pressure is below 25 cm, the diagnosis of IIH is considered probable if all the other parameters are fulfilled.

Imaging findings such as an empty sella, slit-like ventricles or 'tight' subarachnoid spaces may support the diagnosis. Additional characteristic features include an enlarged blind spot, a progressive daily headache, visual field defects, pulsating tinnitus and ocular or back pain [3]. Headache and visual deficits typically develop in the context of increased intracranial pressure and temporarily improve after CSF withdrawal [4].

Besides weight reduction, therapeutic options include the carbonic anhydrase inhibitor acetazolamide [5], repeated LPs, and CSF shunting or optic nerve sheath fenestration [6]. Transient obscurations of vision are found in 70% of patients and moderate to severe visual loss occurs in up to 20% [7], but tools to identify patients at risk and to monitor the efficacy of treatment have been limited to visual testing, visual field perimetry and funduscopy.

Optical coherence tomography (OCT) has been identified as a powerful tool to accurately monitor optic nerve head (ONH) volume [8–10] and neuro-axonal retinal damage [11–14]. Recently, a large multicenter trial demonstrated that acetazolamide treatment and weight loss effectively improved OCT-derived measures of ONH swelling in patients with IIH [15].

In this study, we employed a custom-developed and cross-sectionally validated algorithm to calculate the ONH volume for papilledema assessment [9, 16]. The exact methodology and the technical aspects of the algorithm are described elsewhere [16]. In brief, the algorithm computes the ONH volume comprised between the inner limiting membrane (ILM) and retinal pigment epithelium (RPE) using the information obtained from the RPE segmentation in the regions where this layer is present to create an extension of it through the ONH by means of an adaptive least square spline-fitting approach [16].

We conducted this prospective longitudinal study to evaluate whether this ONH volume measure is suitable to monitor the response to therapy in IIH. Furthermore, we aimed to investigate if the chronic disc edema in IIH causes degeneration of the retinal nerve fiber layer (RNFL) and the ganglion cell/inner plexiform layer complex (GCIP) at the macula.

Materials and methods

Ethics

The local ethics committee of Heinrich Heine University Düsseldorf approved this prospective observational study. Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

Patients

Patients were prospectively recruited at the Departments of Neurology and Ophthalmology, Heinrich Heine University Düsseldorf, Germany. However, the assessments and management of the patients were performed in line with standard clinical care rather than imposing a strict timing of follow-up visits. Inclusion criteria were age >18 years and probable or definite IIH with papilledema according to the modified Dandy criteria [2]. All IIH patients had papilledema with Frisen grades ranging from 1 to 5. Exclusion criteria were relevant ophthalmologic and systemic diseases with potential influence on retinal morphology as defined by the OSCAR-IB criteria [17].

Out of 55 patients recruited at the neurological inpatient clinic of the Heinrich Heine University Düsseldorf, 7 were excluded due to retinal or systemic diseases: 4 because of optic nerve head changes (2 because of the diagnosis of papillitis, 1 because of acute ischemic optic neuropathy (AION), 1 because of a disc abnormality of unknown origin and relevance but normal CSF pressure) and 3 because of systemic diseases (1 because of acute myeloid leukemia, 1 because of multiple sclerosis, 1 because of malignant hypertension). The remaining 48 patients consisted of 21 patients with IIH and 27 age- and sex-matched healthy controls (Fig. 1).

The diagnosis of definite or probable IIH was made or ruled out based on increased CSF pressure (>25 cmH_2O for definite and >20 cmH_2O for probable) assessed by LP, cerebral MRI and formal neurological and ophthalmological examination according to the modified Dandy criteria [5]. In all patients, the diagnosis of papilledema was made based on the ophthalmological examination. For the group of patients <25 cmH_2O CSF, all were obese, eight of nine were female, all had unremarkable neurological examinations, MRI was in line with the modified Dandy criteria (two with additional edema of the optic nerve sheath) and all had normal CSF composition. Therefore, they met the criteria for probable IIH. Five of 27 controls were patients who were examined with suspicion of IIH, but for whom the diagnosis could be refuted due to normal CSF pressure, regular ophthalmological and neurological examination and inconspicuous cerebral MRI; 22 of 27 controls were healthy volunteers without abnormalities in a short neuroophthalmology examination including tonometry, slit lamp examination and funduscopy. In all patients, formal ophthalmologic examination included funduscopy, tonometry, slit lamp examination and assessment of corrected visual acuity (Sloan charts). Furthermore, confocal scanning laser ophthalmoscopy (cSLO) was performed on all subjects. LP was performed after the ocular assessments when done within the same visit.

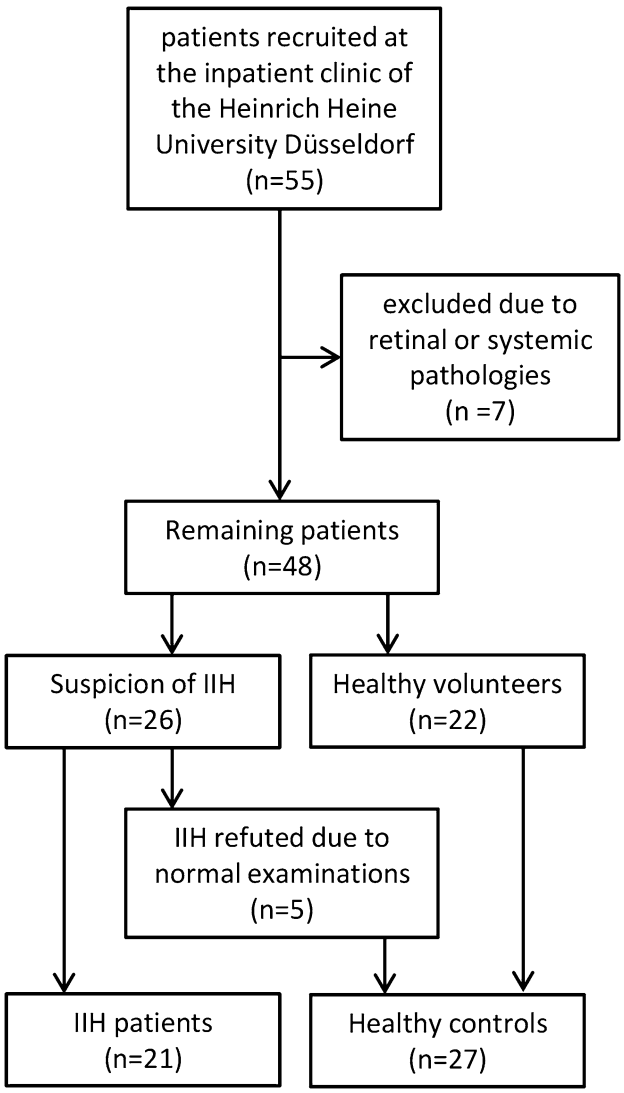


Fig. 1 Recruitment. Flowchart of patient recruitment at the Heinrich Heine University Düsseldorf. 7 of the 55 patients had retinal or systemic diseases and were excluded. 22 of the remaining 48 patients were healthy volunteers with unremarkable neuro-ophthalmologic examinations. We included five additional patients in our healthy control group who were first examined with suspicion of IIH but for whom the diagnosis could be refuted due to normal CSF pressure and unremarkable ophthalmological, neurological and MRI examinations, so that the healthy control group consisted of 27 patients

Optical coherence tomography

Optical coherence tomography methodology and results are reported in line with the APOSTEL reporting recommendations [18]. We obtained volumetric retinal scans consisting of 25 vertical scans centered on the ONH and on the fovea (both 20° × 20°, high speed scanning mode) as well as 12° peripapillary ring scans centered on the disc (high-resolution scanning mode) using a SPECTRALIS OCT device (Heidelberg Engineering, Germany) with image alignment eye-tracking software (TruTrack and Nsite analytics, Heidelberg Engineering). The ONH volume was determined using a custom-made MATLAB-based (Mathworks) fully automated segmentation algorithm [9]. All scans were performed with support of the eye-tracking system. The ONH and macular volume scans were averaged from 9 images, while the peripapillary ring scans were averaged from 100 scans (Automatic Real Time, ART). The image quality of all scans was above 20 dB.

Segmentation of retinal layers was performed semi-automatically with manual correction using the Heidelberg Eye Explorer software (version HEYEX 1.8.6.0, Viewing Module 5.8.3.0). All scans were checked for correct segmentation; segmentation errors were corrected manually by a blinded rater (CB) and scans not meeting the OSCAR-IB quality control criteria [17] were discarded. Therefore, not all scans of all patients were available for analysis. Due to the low contrast between the ganglion cell layer (GCL) and the inner plexiform layer (IPL), both layers were measured together as the ganglion cell/inner plexiform layer complex (GCIP). We indicate the layer volumes of the RNFL, GCIP as well as the total retinal volume (TRV), measured using the mean volume of all sectors of the standard 1, 3, 6 mm ETDRS (early treatment of diabetic retinopathy study) grid in macular volume scans.

Ultrasound measurements

In addition to OCT, we measured the ONH prominence as well as the optic nerve sheath diameter (ONSD) by ultrasound as previously described [19, 20], using a Toshiba Xario XG ultrasound device with a 7.5 MHz probe.

Statistical evaluation

Statistical analyses were performed using Prism 5.0 (GraphPad) and SPSS Statistics 20 (IBM). Generalized estimation equation models (GEE) accounting for within-subject inter-eye correlations using an exchangeable working correlation matrix and correcting for age and sex were applied to analyze associations between OCT parameters and clinical data and to test for differences of the OCT parameters between IIH patients and controls.

Each visit's time point was entered as a factor when comparing longitudinal data. For comparing rates of change over different time intervals, the mean change per month was calculated. Furthermore, we performed a stepwise multivariate linear regression analysis to analyze which clinical and/or ocular findings influence macular RNFL thinning. We used a one-sample *t* test to analyze if the rates of change for the different retinal parameters over time differed from zero. The stepwise regression analysis and the one-sample *t* test were performed using the left

eyes of patients only. Parametric and normally distributed parameters such as body mass index (BMI) were compared using an independent sample two-tailed t test. Subjects with missing data were excluded from the respective analysis. The means and standard deviations (SD) are reported; p values ≤ 0.05 were considered significant.

Results

Patients and controls

Idiopathic intracranial hypertension patients and controls were predominantly female (90.5 vs. 92.6%, $p > 0.99$ Chi squared test) and age-matched (35.8 ± 10.8 vs. 36.9 ± 14.2 years, $p = 0.92$ Mann–Whitney U test). The mean interval between the first clinical manifestation (e.g., headaches or mild visual symptoms assessed via patient interviews) and OCT (in the following referred to as 'disease duration') was 20.2 ± 37.6 months for IIH patients (Fig. 2). At baseline, the CSF pressure was increased in IIH patients (32.6 ± 11.8 cmH_2O) in line with the diagnostic criteria; 9 patients had a CSF pressure between 20 and 25 cmH_2O and 12 had a CSF pressure above 25 cmH_2O, meeting the diagnostic criteria for probable and definite IIH, respectively. The Frisen grades were 1–5 in both groups with a mean of 3.06 ± 1.5 for the group with probable and 1.9 ± 1.4 for the group with definite IIH. The mean corrected visual acuity of our IIH patients was

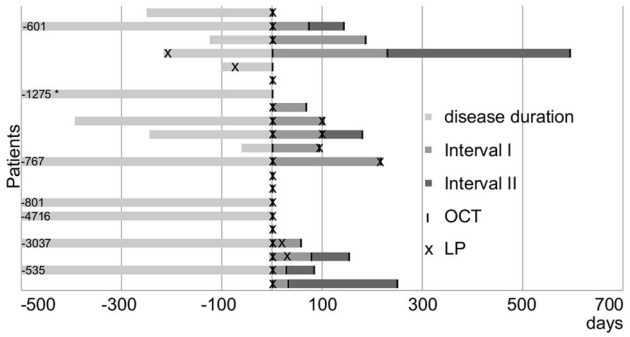


Fig. 2 Time course of assessments of OCT and LP. The mean interval between the first clinical manifestation and the first OCT at time point 0 (in the following referred to as disease duration) was 20.17 ± 37.56 months for IIH patients. The first OCT follow-up was performed between 1 and 7.45 months after baseline (Interval I: 3.47 ± 2.19 months; $n_{eyes} = 10$ for ONH volume, $n_{eyes} = 19$ for macular volume scans) and the second OCT follow-up occurred between 2.77 and 19.23 months (Interval II: 4.63 ± 4.00 months; $n_{eyes} = 11$ for ONH volume, $n_{eyes} = 8$ for macular volume scans). One LP was performed on day -625 from baseline which is outside the range of the x-axis and therefore not displayed, but instead marked with an *asterisk*. *OCT* optical coherence tomography, *LP* lumbar puncture

0.81 ± 1.65 (decimal). The BMI of IIH patients was 30.5 ± 7.3 kg/m^2 at baseline, which was significantly higher than in controls (25.7 ± 5.4 kg/m^2; $p = 0.025$, t test; Table 1). All patients diagnosed with probable or definite IIH were treated with 250–500 mg of acetazolamide twice daily and scheduled for follow-up visits. At follow-up, the BMI was unchanged from baseline ($p = 0.55$, two-tailed t test). Five patients received two LPs within the study period (94.6 ± 79.38 days) and the CSF pressure was unchanged between the first and second measurement ($p = 0.961$, two-tailed t test).

The mean visual acuity was lower at follow-up, although this difference failed to reach significance (0.75 ± 0.43 follow-up, $p = 0.227$, GEE analysis).

ONH and macular volume at baseline

Complete OCT scans were obtained from all patients and revealed no structural anomalies in any of the retinal layers or in the pigment epithelium in any of the subjects meeting the inclusion criteria. As the pathological changes in IIH are driven by the increased intracranial pressure, we first analyzed which retinal parameters were associated with the CSF pressure of our patients measured at baseline. A GEE-based regression analysis revealed that CSF pressure was significantly associated with ONH volume, but not with any other retinal parameter ($p = 0.025$, GEE analysis, Fig. 3a). Analysis of only the subgroup of IIH patients with a CSF pressure >25 cmH_2O, thus meeting the criteria for definite IIH, revealed an even more significant association between CSF pressure and ONH volume ($p < 0.001$, GEE analysis, Fig. 3b).

ONH volume was increased ($p < 0.001$, GEE analysis) in IIH patients compared to controls, indicating an increased excavation of the optic disc (Table 1; Fig. 4). The mean total macular volume, the macular RNFL volume and the GCIP volume ($p = 0.614$, $p = 0.557$, $p = 0.152$, respectively, GEE analysis), in contrast, did not differ between IIH and control patients, both for the group with >25 cmH_2O and for all IIH patients (Table 1; Fig. 4).

The visual acuity at baseline was lower for IIH patients compared to controls ($p = 0.05$, GEE analysis, Fig. 5). We observed a wide range of visual acuity among our patients with values ranging from 0.1 to 1.2 decimals and visual acuity was significantly associated with the ONH volume at baseline ($p = 0.033$, GEE regression analysis, Fig. 5).

To analyze if the ONH edema extended into the macular area of measurement, we compared the macular RNFL volume between patients and controls separately for the different sectors, but did not observe significant differences for the temporal or any other macular quadrant (data not shown).

Table 1 Retinal parameters

Parameter	Healthy controls		IIH		Significance
	$N = 54$ eyes		$N = 42$ eyes		
	N	Mean ± std. deviation	N	Mean ± std. deviation	p (GEE)
CSF pressure				32.56 ± 11.82	
ONH vol.	32	2.26 ± 0.58	33	5.82 ± 3.71	<0.001
RNFL vol.	54	1.01 ± 0.10	40	1.03 ± 0.13	0.557
GCIP vol.	54	2.97 ± 0.27	40	2.83 ± 0.52	0.152
TMV vol.	54	8.80 ± 0.32	40	8.86 ± 0.45	0.614
PPR − RNFL th.	52	99.63 ± 7.76	41	161.80 ± 85.70	<0.001
PPR th. − TRT	52	321.83 ± 12.84	41	450.32 ± 186.44	<0.001
BMI	44	25.71 ± 5.408	38	30.47 ± 7.275	0.025 (*t* test)

Means and standard deviations of the acquired parameters are provided for IIH patients and healthy controls at baseline. Volume is indicated in mm^3, thickness in µm. All comparisons were performed using GEE analysis except for the comparison of BMI which was done by a two-tailed *t* test

Vol. volume, *th* thickness, *RNFL* retinal nerve fiber layer, *GCIP* ganglion cell/inner plexiform layer complex, *TMV* total macular volume, *GEE* generalized estimation equation, *PPR* measured in peripapillary ring scans, *TRT* total retinal thickness, *BMI* body mass index

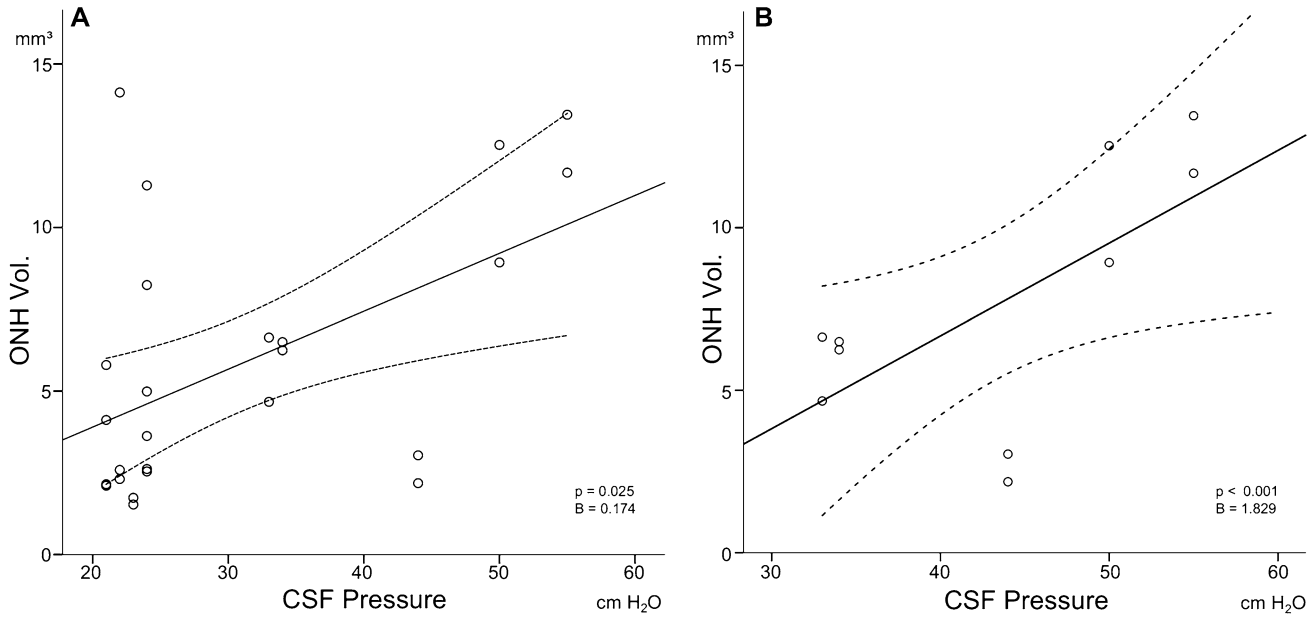


Fig. 3 Regression analyses between ONH volume and CSF pressure. The association between ONH volume and CSF pressure of the patients' eyes are displayed, **a** analysis for all IIH patients' eyes, **b** analysis for the eyes of IIH patients with CSF pressure >25 cmH_2O only. Each *circle* represents one eye of an IIH patient; the linear regression line including the 95% confidence interval is provided. The *p* value and regression coefficient are indicated (GEE regression analysis)

Retinal changes over time

The first OCT follow-up was performed between 1 and 7.5 months after baseline (3.5 ± 2.2 months; $n_{eyes} = 10$ for ONH volume, $n_{eyes} = 19$ for macular volume scans) and the second follow-up OCT occurred between 2.8 and 19.2 months (4.6 ± 4.0 months; $n_{eyes} = 11$ for ONH volume, $n_{eyes} = 8$ for macular volume scans). In the analyzed scans, the ONH volume decreased after initiation of therapy by acetazolamide and advice of weight reduction (baseline 5.83 ± 3.71, follow-up 4.55 ± 3.1, $p = 0.033$, GEE analysis, Fig. 6). Retinal layer investigation in macular volume scans over time revealed lower values for the total macular volume (baseline 8.85 ± 0.45, follow-up 8.8 ± 0.5), macular RNFL (baseline 1.03 ± 0.13, follow-up 0.96 ± 0.12) and macular GCIP (baseline 2.83 ± 0.52, follow-up 2.93 ± 0.28) at follow-up compared to baseline, suggesting retinal degeneration as a consequence of the

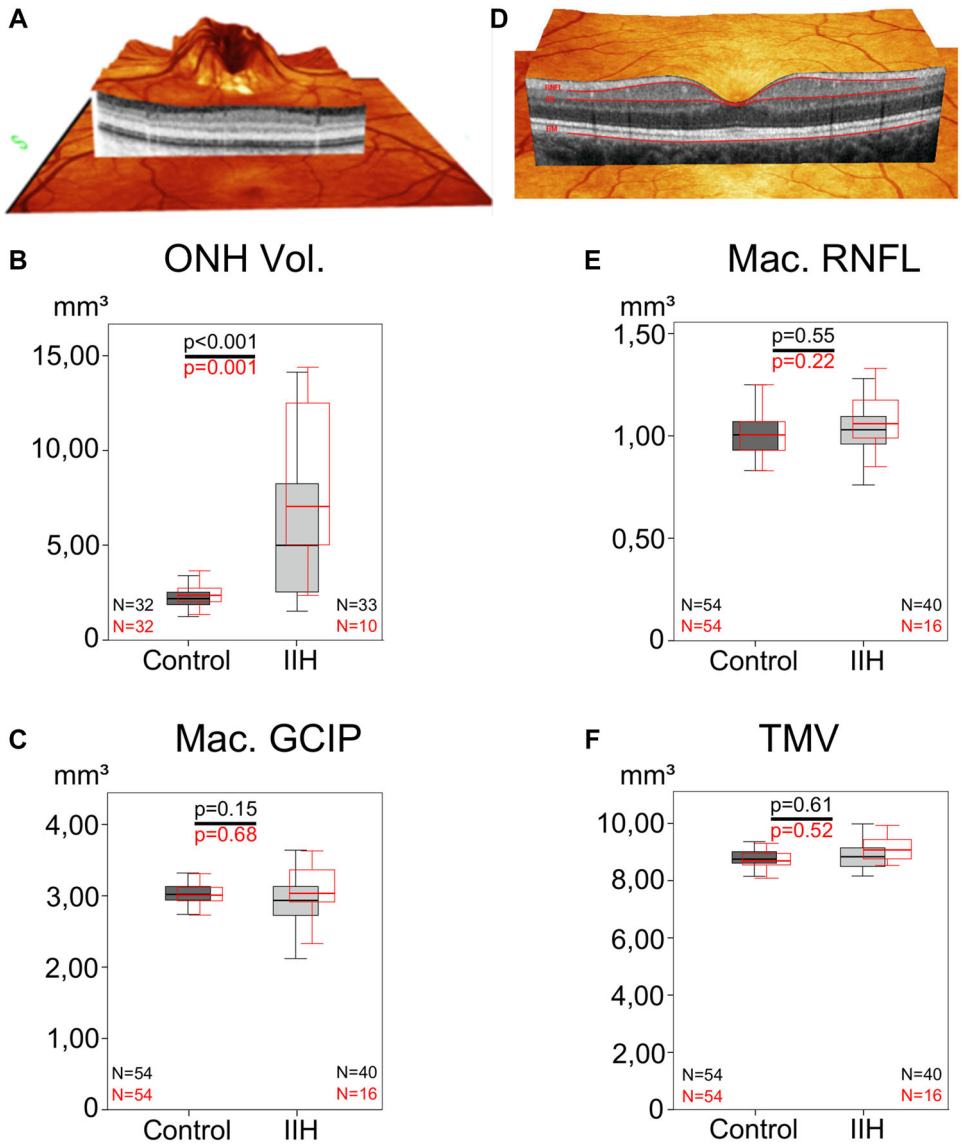


Fig. 4 Optic nerve head volume and macular volume scans at baseline. The optic nerve head (ONH) volume and the macular area were measured in volume scans centered on the optic disc (**a**, **b**) or the foveolar (**d**–**f**). **a**, **d** Representative images from an IIH patient. The volumetric analysis revealed a highly significant reduction of the ONH volume in IIH patients compared with healthy controls. The volume of the macular RNFL (retinal nerve fiber layer) and GCIP (ganglion cell/inner plexiform layer complex) as well as the total macular volume (TMV) were measured after semi-automated segmentation (*colored lines*) in volume scans centered on the fovea. *Box*-and-*whiskers plots* of the mean baseline values for the different retinal parameters are presented (**b**, **c**, **e**, **f**). Results of the analysis of all IIH patients' eyes are depicted in *black*, while results of the analysis of eyes of IIH patients with CSF pressure >25 cmH_2O only are shown in *red*. Compared to control subjects, the ONH volume (**b**) was increased in patients with IIH, while the volume of the RNFL (**e**), GCIP (**c**) and the TMV (**f**) did not differ. *Bars* in the *boxes* mark the median, *boxes* the interquartile range and *whiskers* the minimum and maximum. Numbers of eyes as well as *p* values for differences for comparison between the IIH patients and healthy controls are indicated (GEE analysis)

increased CSF pressure and ONH volume (Fig. 6). However, these differences only reached statistical significance for the RNFL of the patients with definite IIH ($p = 0.02$, GEE analysis, Fig. 6), while the RNFL change of all IIH patients only reached borderline significance for the RNFL when analyzing all IIH patients ($p = 0.05$, GEE analysis, Fig. 6) and the results for the GCIP were not significant even when analyzing only definite IIH ($p > 0.05$, GEE analysis, Fig. 6). One patient already presented very low RNFL values at baseline. However, this outlier did not differ from the other IIH patients in disease duration or severity and we detected no other pathology explaining the low RNFL volume.

To analyze if this RNFL thinning had a significant impact on visual acuity, we investigated the association of macular RNFL volume with visual acuity and, indeed,

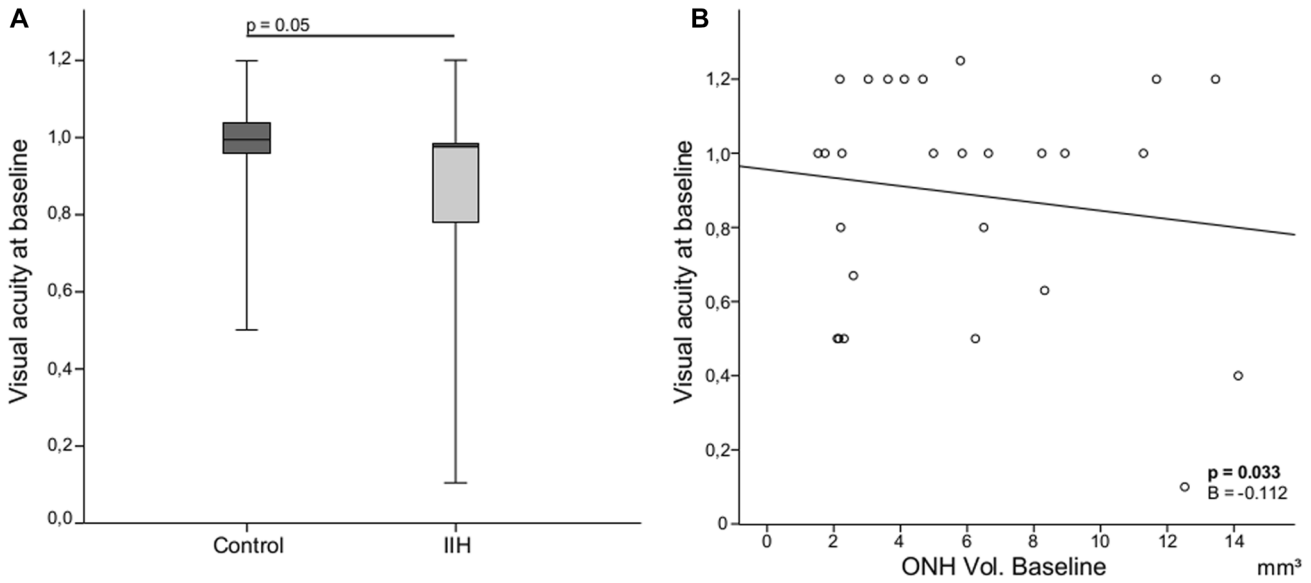


Fig. 5 Visual acuity at baseline is associated with ONH volume. **a** IIH patients presented a lower visual acuity at baseline compared to controls ($p = 0.05$, GEE analysis) and **b** was significantly associated with ONH volume in our IIH patients ($p = 0.033$, GEE regression analysis). *Boxes* in **a** indicate the standard error of the mean, the *horizontal line* the median and *whiskers* the minimum and maximum

observed a significant association ($p < 0.001$, GEE regression analysis). At the same time, macular RNFL volume change was significantly associated with ONH volume at baseline, suggesting a pathogenic role of ONH volume and CSF pressure.

To analyze the dynamics of the retinal changes during longer periods of follow-up, we calculated the mean volume changes of the different layers and structures per month for consecutive visits. In patients with IIH, the rate of decrease (Δmm^3/month) in ONH volume was more pronounced within the first few months after initiation of therapy (Interval I, baseline to visit 1, 1–7.5 months) as compared to the rate observed during long-term follow-up (Interval II, visit 1 to visit 2, 2.8–19.2 months after visit 1). We observed a thinning rate of -1.99 mm^3/month for Interval I and -0.35 mm^3/month for Interval II, albeit this difference in change rate did not reach significance ($p = 0.079$, GEE analysis, Fig. 7). The rates of change did not significantly differ from zero for ONH volume, RNFL, GCIP and total macular volume (TMV) (Interval I: $p = 0.24$, $p = 0.21$, $p = 0.28$, $p = 0.42$, respectively, t test; Interval II: $p = 0.49$, $p = 0.10$, $p = 0.18$, $p = 0.22$, respectively, t test, Fig. 7).

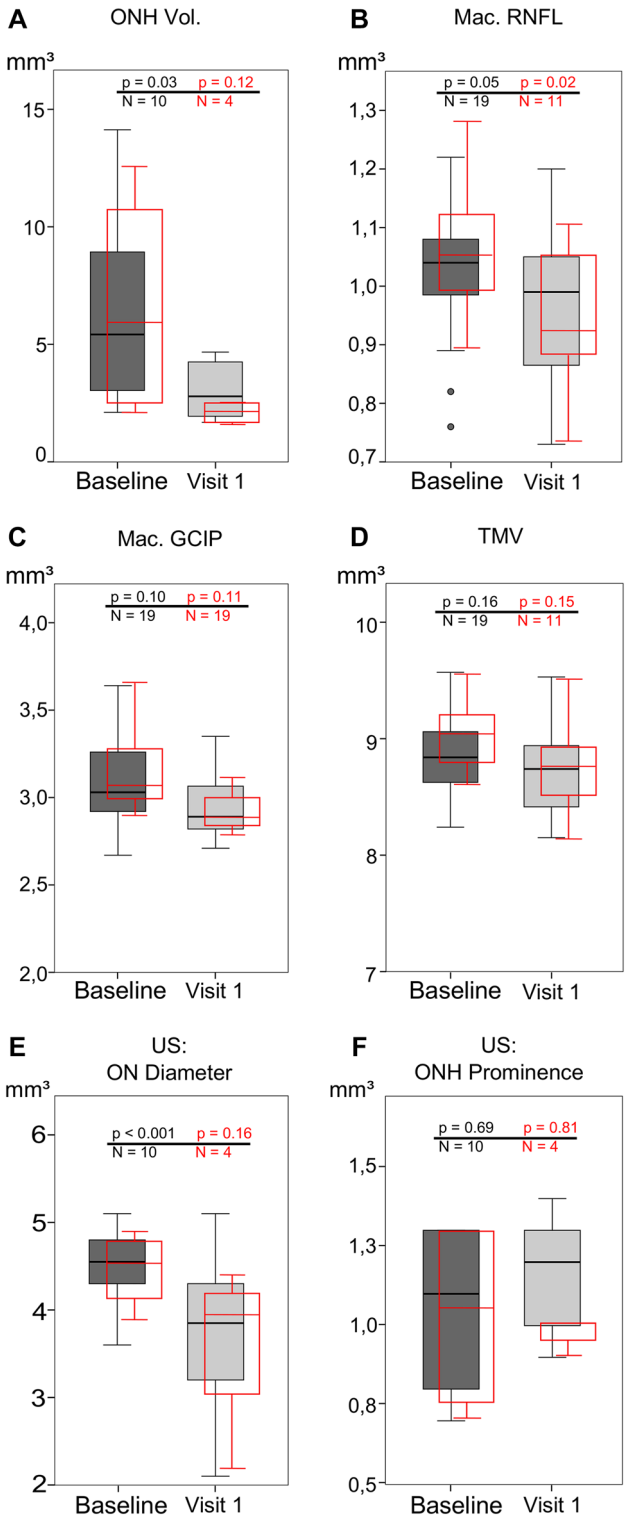
To analyze whether macular RNFL thinning was due to axonal degeneration or a reduction of edema extending from the disc into the nasal macular area, we compared the difference in mean volume changes per month within the different quadrants of the macular RNFL. We observed no significant difference between the different quadrants in macular RNFL volume at baseline or in rates of change in macular RNFL volume ($p > 0.05$, GEE analysis). This suggests that the disc edema did not extend into the macular area of measurement and thus macular RNFL thinning represents neuro-axonal damage.

Peripapillary ring scans

In addition to the direct assessment of papilledema by measuring the ONH volume, we also assessed RNFL thickness in 12° peripapillary ring scans, as the disc edema typically extends into this layer and can be measured at this distance from the ONH. Similarly to the observations made for ONH volume, the peripapillary RNFL and total retinal thickness were increased at baseline, decreased after the initiation of therapy and showed lower degrees of change during longer follow-up (supplemental figure).

Ultrasound measurements

In addition to the OCT assessments, we used ultrasound to assess the ONH prominence and diameter of the optic nerve in our IIH patients at baseline and visit 1. At baseline, the patients presented with an ONH prominence of 0.88 ± 0.64 mm and an optic nerve sheath diameter (ONSD) of 4.8 ± 0.76 mm, which was in line with the values for IIH patients in previous reports [21, 22]. Comparison of the ultrasound-derived outcomes between baseline and the first follow-up revealed a significantly reduced value for the ONSD ($p < 0.001$, GEE analysis), while the prominence of the optic head measured by ultrasound did not change significantly over time ($p = 0.699$, GEE analysis).



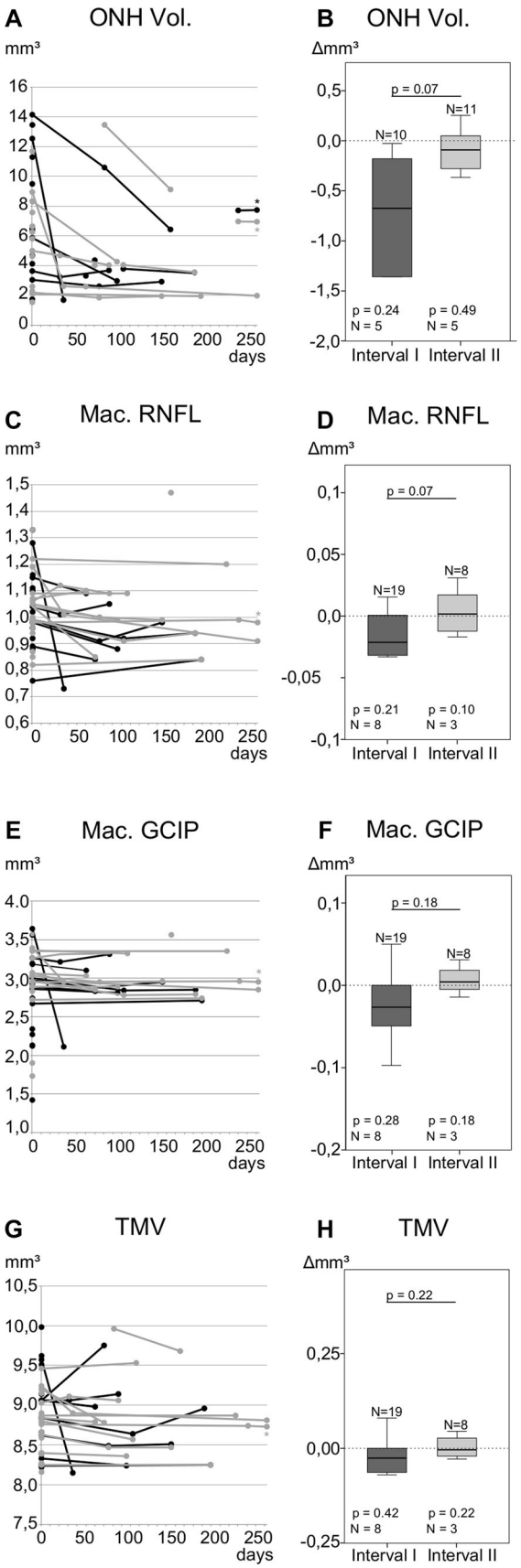
◀**Fig. 6** Retinal changes over time. *Box-and-whisker plots* of the baseline values and the first follow-up visit (visit 1) as well as *p* values for their comparison (GEE analysis) are provided for the different retinal parameters. *Horizontal lines* in the *boxes* mark the median and the interquartile range; *whiskers* mark the minimum and maximum. Results of the analysis of all IIH patients' eyes are depicted in *black*, while results of the analysis of eyes of IIH patients with CSF pressure >25 cmH_2O only are shown in *red*. The investigation only includes those IIH patients who performed a follow-up measurement which was of sufficient quality for analysis. The optic nerve head (ONH) volume and the macular RNFL were significantly reduced in IIH patients at follow-up compared to baseline (**a**, **b**), while the GCIP and the total macular volume (TMV) revealed lower but not significant ($p < 0.05$) values (**b–d**). The diameter of the optic nerve (ON) measured by ultrasound (US) was significantly reduced in IIH patients at follow-up compared to baseline, while the prominence of the ONH measured by ultrasound did not differ significantly. Numbers of eyes are indicated

Regression analyses

To analyze which parameter had a significant influence on the change in macular RNFL volume, we performed a multivariate stepwise regression analysis. This revealed a significant influence on the macular RNFL volume at baseline only for CSF pressure ($p = 0.001$), while the ONH volume or prior duration of symptoms had no influence. A similar stepwise regression analysis on the factors influencing the change of macular RNFL volume (baseline to visit 1) revealed an influence only of the ONH volume ($p = 0.001$), while the CSF pressure and prior duration of symptoms had no significant effect.

Discussion

We investigated the value of OCT for detecting papilledema in patients with IIH and analyzed the retinal changes after LP and initiation of treatment with acetazolamide. The greatest strength of our study was its longitudinal design, which allowed us to investigate the retinal sequelae of the increased CSF pressure in IIH. While similar investigations of the optic disc region have been performed in the context of a controlled study on a larger collective [15], to our knowledge we provide the first study to focus on the longitudinal changes of macular RNFL volume in patients with IIH. At baseline, we observed an increased ONH volume in our IIH patients compared to controls as expected and previously demonstrated in several studies (reviewed in [23, 24]). The increased ONH volume was associated with lower visual acuity in IIH patients, which points out to the potential clinical relevance of the parameter. The longitudinal analyses revealed that ONH volume measured by OCT decreased after the initial LP and initiation of therapy with acetazolamide, which is in line with the results of a recent large multicenter study [15]. However, it is important to point out that our study, in contrast to the aforementioned, was not a controlled trial. In our study, all patients were initiated on treatment for ethical reasons, so we cannot prove that the observed decrease in papilledema is really the consequence of



◀**Fig. 7** Early vs. late retinal volume changes over time after diagnosis. Time course/overview of the raw data of the baseline values and the first and second follow-up visits (visit 1 and visit 2) are provided for the different retinal parameters (**a**, **c**, **e**, **g**). Each point represents one examination of one eye, connected with lines when follow-ups were available. *Black* and *gray lines* indicate patients' left and right eyes, respectively. Eyes that were examined on day 596 are marked by *asterisk* (measured values on day 596: $ONH_{left\ eye}$, 8.33; $ONH_{right\ eye}$, 6.56; RNFL, 0.87; GCIP, 2.8; TMV, 8.65). *Box-and-whisker plots* of the mean rates of change per month (Δmm^3/month) for the different retinal intervals and retinal parameters (**b**, **d**, **f**, **h**). *Horizontal lines* in the *boxes* mark the median and the interquartile range and *whiskers* the minimum and maximum. Numbers of eyes are indicated. *p* values for differences to zero (below the *boxes*; one-sample *t* test of left eyes) and for comparison between the intervals (*bar*, GEE analysis) are indicated

acetazolamide treatment and/or LP as we cannot rule out a spontaneous reduction of edema. Even though all patients were advised to reduce weight, no significant weight reductions were observed at follow-up ($p = 0.96$, *t* test), so we can rule out an effect of weight reduction on the disease course in our patients.

The longitudinal analysis of the macular region revealed thinner values for macular RNFL and GCIP volumes at the first follow-up, although only the RNFL volume changes reached significance. Overall, the macular RNFL volume loss was 0.05 mm^3, corresponding to 5% of the macular RNFL volume, which is about 1.4 µm change in thickness within the 6 mm ETDRS ring. The fact that only macular RNFL volume showed a significant decrease during the short-term follow-up is not surprising. The macular RNFL has been identified as the retinal parameter with the best effect strength in a recent phase II study on neurodegeneration and neuroprotection in optic neuritis [25]. As the macular RNFL and GCIP volumes were not increased at baseline and the volume loss of the nasal macular quadrant was not higher than the other quadrants, we assume that this loss of volume reflects axonal and neuronal degeneration resulting from the disc pathology rather than a decrease of edema extending into the area of measurement (6 mm around the foveola). The fact that stronger thinning of the macular RNFL volume was associated with lower visual acuity of our patients further supports the point that thinning of the RNFL does indeed reflect axonal damage and degeneration rather than decrease of edema. The probable causes for this degeneration could be a mechanic jamming of the optic nerve at the disc and/or pathology resulting from impaired circulation, i.e., due to venous stasis.

We have to acknowledge that the decrease in macular RNFL volume was rather small and mainly observed in patients with >25 cmH_2O CSF pressure. However, the fact that the macular GCIP, which contains the neurons and the dendritic arbor of the RNFL's axons, showed a similar

(albeit not significant) volume decrease and that RNFL thinning was associated with decreased visual acuity argue for a real change and against a false-positive result. In this context, it has to be emphasized that our study was of an exploratory nature addressing several end points, which is why no power calculation was performed a priori. Further, sufficiently powered studies on larger cohorts over longer observational periods are warranted and already underway to investigate if these findings can be corroborated.

A strength of our study was that the majority of the patients (15 of 21) were enrolled when the clinical diagnosis of IIH was first posed and before any therapy was initiated. Furthermore, CSF pressure was measured during the same hospitalization as the OCT assessments. This allowed us to analyze the retinal sequelae of elevated CSF pressure and papilledema early in the course of disease and the effect of treatment. In line with this, the RNFL and the total retinal volume measured in macular volume scans did not differ between patients and controls, suggesting that the ONH edema did not extend to the macula and that no significant macular atrophy had occurred.

A limitation of our study is that it was a non-interventional observation and not a randomized, controlled trial, thus characterized by heterogeneous times to follow-up and lack of a placebo group. However, our findings of a decrease in papilledema after initiation of therapy are in line with the positive effects of acetazolamide reported in a recent controlled trial [15].

Besides OCT, we used optic nerve ultrasound measuring the ONSD and optic disc elevation, as a well established approach to diagnose and monitor papilledema [20]. We were able to detect a decrease in ONSD after initiation of therapy while disc elevation assessed by ultrasound did not change, suggesting that ONSD assessments were more sensitive to change. However, in contrast to our findings, others found no reduction in ONSD and optic disc elevation after therapeutic LP [20]. Using OCT for quantifying disc edema has the advantage that the retinal pathology, papilledema, and its detrimental long-term consequences, axonal degeneration, can be measured at the same time with the same modality.

Our data corroborate and extend the results of previous studies that OCT is highly suitable for the monitoring of ONH swelling in IIH and that papilledema decreases after initiation of treatment with acetazolamide [15]. Furthermore, our findings suggest that macular OCT measurements are suitable to monitor the chronic structural damage to the macular RNFL resulting from the disc edema in IIH. This is novel and of particular interest, as macular measurements can be used not only for monitoring of neuroaxonal damage but possibly also for the evaluation of novel therapeutic or neuroprotective strategies.

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Author contributions PA conceived the study, performed data acquisition and analysis and drafted the manuscript. CB performed data acquisition and analysis, revised the manuscript for intellectual content and created the artwork. MR performed data acquisition and analysis and revised the manuscript for intellectual content. A-KM performed data acquisition and analysis and revised the manuscript. E-MK performed data analysis and revised the manuscript. DF performed data acquisition and revised the manuscript for intellectual content. RG revised the manuscript for intellectual content. OA revised the manuscript for intellectual content and helped with the interpretation of the data. H-PH revised the manuscript for intellectual content and helped with the interpretation of the data. FP revised the manuscript for intellectual content and helped with the interpretation of the data. AB performed data analysis, revised the manuscript for intellectual content and helped with the interpretation of the data. AM drafted and revised the manuscript for intellectual content and interpreted the data.

Compliance with ethical standards

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Ethical standards The local ethics committee of Heinrich Heine University Düsseldorf approved this prospective observational study.

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