

Fractal Analysis of Peripapillary Vasculature in Eyes with Papilledema Using Optical Coherence Tomography Angiography

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Abstract

Background: Papilledema is swelling of the optic nerve secondary to increased intracranial pressure. Optical coherence tomography angiography (OCTA) is a technique that allows for fast and non-invasive imaging of the peripapillary microvasculature. Here, we evaluate a novel way of analyzing OCTA images of eyes with papilledema through the use of fractals to estimate vascular complexity through fractal dimension.

Methods: A retrospective clinical chart review of papilledema patients imaged with OCTA was performed. En face OCT angiograms identifying peripapillary vessels were obtained using a spectral-domain OCT system. Default automated peripapillary scans of 4.5 mm × 4.5 mm diameter were processed with ImageJ. Fractal analysis was performed with Fractalyse software.

Results: Fifty-six eyes with papilledema and 40 eyes from healthy controls were analyzed. The fractal dimension of eyes with papilledema (1.677, SD=0.075) was significantly higher than that of control eyes (1.630, SD=0.062; P=0.002). Subgroup analysis demonstrated significantly higher fractal dimension in Grade 0 papilledema (1.707, SD=0.047) as compared to controls.

Conclusion: Increases in fractal dimension of peripapillary vasculature for papilledema may reflect potential increases in microvasculature, particularly during early stages. OCTA fractal dimension analysis has potential to establish quantitative parameters for peripapillary microvascular pathology in papilledema.

Keywords: Fractal dimension; Papilledema; OCTA

Introduction

Papilledema, swelling of the optic nerves secondary to increased intracranial pressure, is associated with multiple disease entities including intracranial space occupying tumors, decreased cerebrospinal fluid (CSF) drainage from obstruction, and decreased absorption of CSF from infection, hemorrhage, venous sinus thrombosis, or idiopathic intracranial hypertension. Edema of the optic nerves occurs as increased intracranial pressure compresses the nerves and causes stasis of axoplasmic flow. Chronic papilledema can lead to optic nerve damage and permanent vision loss.

Diagnosis can be difficult in early papilledema given that fundoscopic changes may be subtle and often take time to develop. Diagnostic tools such as intravenous fluorescein angiography (IVFA), fundus photography, and ultrasonography are helpful, but often lack specificity and can be invasive and costly [1,2].

Optical coherence tomography (OCT) can be helpful in the evaluation of papilledema, by capturing structural information regarding the retina and the optic nerve, including retinal nerve fiber layer (RNFL) thickness. This is useful because among all mechanical and vascular signs commonly seen on funduscopy in papilledema,

peripapillary RNFL swelling is the most sensitive in diagnosing the disease [3]. Scott et al. demonstrated that in early stages of papilledema, both OCT RNFL thickness and OCT total retina thickness are correlated with clinical staging of optic nerve photographs [4]; with a higher grade of papilledema, OCT total retina thickness performs better than OCT RNFL thickness [4].

However, studies evaluating papilledema and optic nerve drusen using OCT RNFL have at times shown mixed results [5,6], and to the best of our knowledge, optical coherence tomography angiography (OCTA) has not been extensively studied in monitoring papilledema. OCTA is a technique that allows for noninvasive, fast imaging of the macular and peripapillary microvasculature [7]. Recent studies of OCTA imaging of the optic disc and peripapillary retina have demonstrated reduced perfusion in various disease processes including glaucoma [7-9] and diabetic retinopathy [10].

OCTA provides a detailed image of the microvasculature, which has a repeating pattern of self-similarity at each scale of measurement, or a fractal pattern [11,12]. "Boxcounting," a technique that involves dividing 2-dimensional images into increasingly smaller grids, has been utilized for fractal analysis [13]. In particular, fractal dimension (FD) can be calculated from the slope of the logarithmic relationship between grid number and grid size [13]. Fractal analysis has been used to investigate lung [14] and brain cancers [15]. Furthermore, this

technique has been applied to fundus photography [16,17] and fluorescein angiography [18,19] with limited resolution. A previous study by our group reported that the FD of diabetic eyes was lower than in normal eyes, which may reflect the microvascular burden of disease in diabetic retinopathy [8].

Given that fractal geometry mirrors the branching in the peripapillary microvasculature, utilizing OCTA images with FD analysis of peripapillary vessels may provide further insight into the pathogenesis of papilledema as well as offer noninvasive opportunities for monitoring and diagnosing papilledema. In addition, given that vascular changes are considered to be involved in papilledema [20], we aim to quantify the FD of peripapillary microvasculature in eyes with varying stages of papilledema compared with control eyes using OCTA.

Methods

Patient Selection

This study was a retrospective clinical chart review approved by the Institutional Review Board of New York Eye and Ear Infirmary of Mount Sinai. This research study adhered to the tenets of the Declaration of Helsinki and complied with the Health Insurance Portability and Accountability Act of 1996. Patients and controls were recruited from The New York Eye and Ear Infirmary of Mount Sinai. A total of 56 eyes with papilledema and 40 eyes from healthy subjects were selected, one eye from each patient to minimize the effect of high interocular correlation. All patients with papilledema were those diagnosed with IIH by the modified Dandy criteria [21]. Patients were excluded if there was any ocular, neurologic, or vascular comorbidity with the exception of cataracts or if image quality was insufficient. All patients underwent a comprehensive ophthalmic examination including best-corrected visual acuity, slit lamp biomicroscopy, dilated fundus exam, disc photos, OCT RNFLs, and OCTA at the time of initial presentation. Diagnosis and grading of papilledema was performed using the Frisén grading scale [22]. Clinical data included basic demographic information and grade of papilledema.

OCTA image acquisition and processing

OCTA images were obtained using a commercial spectral-domain OCT system (Avanti RTVue-XR; Optovue, Fremont, CA, USA) as previously described [21]. Images with artifacts, such as lines and gaps indicating insufficient information for image reconstruction or motion artifacts, were excluded. OCTA image processing for fractal analysis has been previously described [13, 14]. Briefly, default automated peripapillary scans of 4.5mm × 4.5mm diameter were obtained for each eye without any manual manipulation of segmentation. Grayscale OCTA images were binarized with standard automatic threshold levels using ImageJ (National Institutes of Health, Bethesda, Maryland, USA). Representative binarized OCTA images of control and eyes with varying grades of papilledema are shown in Figures 1 and 2.

Fractal dimensional analysis

Fractal dimensional analysis and calculation was similar to that used by Zahid et al. [13]. In short, the box counting method was used to calculate fractal dimension (FD) for each image. In this method, the number of boxes needed to cover an image is calculated and repeated for different box sizes approaching an eventual size of zero. This FD is given by the following formula:

$$D = (\log N_r) / (\log r^{-1})$$

Where D is the fractal dimension, N_r is the number of boxes and r is the representative size of the boxes.

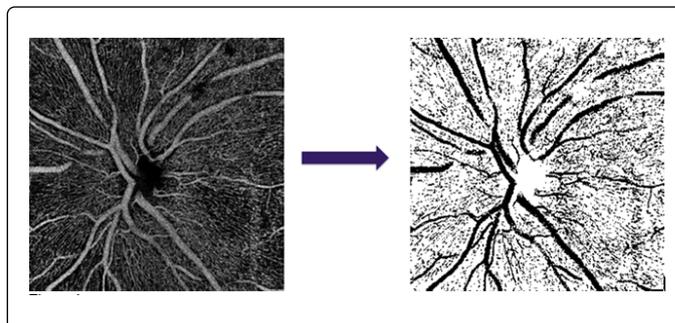


Figure 1: Representative binarized OCTA images of control.

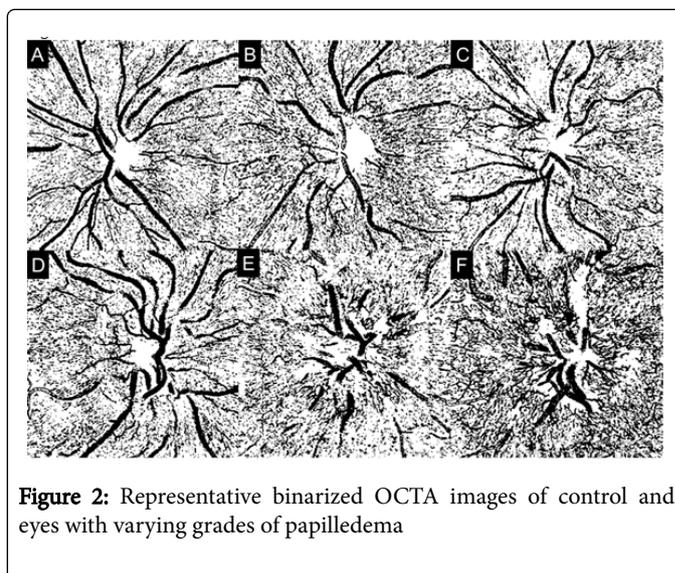


Figure 2: Representative binarized OCTA images of control and eyes with varying grades of papilledema

Fractal box-counting analysis was done using Fractalyse (ThéMA, Besançon Cedex, France) as described in previously published studies [8,13]. FD was used as a measure of complexity to allow for comparisons between the level of complexity of vascular patterns in eyes with papilledema and control eyes.

Statistical analysis

Statistical analysis was performed using one-way analysis of variance (ANOVA) with post-hoc Tukey's multiple comparisons test using GraphPad Prism Versions 6.0 for Macintosh (GraphPad Software, La Jolla, California, USA). Statistical significance was set at 0.05. Comparisons were made between normal eyes and all eyes with papilledema and further analysis was done on papilledema subgroups based on severity (Grade 0, n=12; Grade 1, n=15; Grade 2, n=13; Grade 3, n=5; Grade 4/5, n=4).

Results

Fractal dimension analysis in control eyes

Forty eyes of normal patients were evaluated. The mean age was 52. None of these eyes exhibited any papilledema or retinal pathology. The mean FD in control eyes was 1.630 (SD=0.062).

Fractal dimension analysis in all eyes with papilledema

Fifty-six eyes of 56 patients with papilledema were evaluated. The mean age of papilledema patients was 35 years. Of these patients, there were 47 females and 9 males. The mean FD of all eyes with papilledema (1.677, SD=0.075) was significantly higher ($P=0.002$) than control eyes (1.630, SD=0.062).

Comparison of fractal dimension between papilledema subgroups and control eyes

Based on the Frisen grading scale, papilledema patients were classified based on severity into Grade 0, Grade 1, Grade 2, Grade 3, Grade 4/5 (Figure 3). The FD in papilledema subgroups based on severity were 1.707 (SD=0.047) for Grade 0, 1.675 (SD=0.046) for Grade 1, 1.674 (SD=0.090) for Grade 2, 1.610 (SD=0.139) for Grade 3, and 1.694 (SD=0.060) for Grade 4/5. Analyses between papilledema subgroups demonstrated a significant increase ($P<0.001$) in FD in Grade 0 papilledema compared to control eyes. There were no significant differences in pairwise comparisons between other subgroups. Figure 3 illustrates the data as scatterplots for control, and eyes with papilledema based on grade (Figure 3).

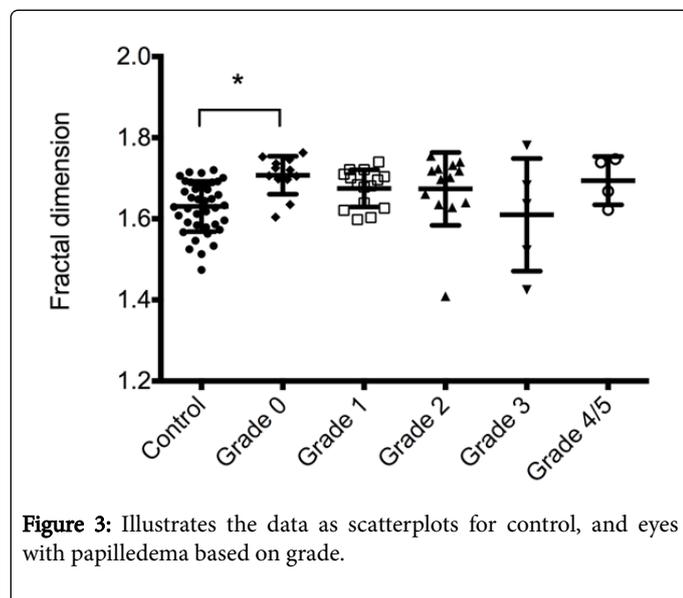


Figure 3: Illustrates the data as scatterplots for control, and eyes with papilledema based on grade.

Discussion and Conclusion

This study utilized OCTA imaging and FD analysis in normal eyes and eyes with papilledema. Prior novel studies have evaluated vascular patterns of fluorescein angiography images utilizing fractal analysis [23]. To the best of our knowledge, our study is the first to utilize fractal analysis of the peripapillary microvasculature in OCTA images to analyze papilledema. Our finding that FD is higher in eyes with Grade 0 papilledema than in normal eyes may indicate a potential

increase in microvasculature or perfusion in the peripapillary region. This may reflect increased flow to thresholds sufficient for detection with OCTA in small peripapillary vessels that otherwise remain subthreshold in physiologic states. Eyes with Grade 0 papilledema are defined as being clinically normal with no risk to the optic disc. Our study demonstrates that these eyes, which are normal on clinical fundoscopic exam, are judged as abnormal by computerized fractal dimension analysis. This is a statistically significant, yet subclinical, effect. As such, OCTA may provide means of detecting early, subclinical changes that may progress to higher grades of papilledema.

Fractal geometry models branching in peripapillary microvasculature. Although other studies have evaluated microvasculature using different techniques such as vessel density [24,25], we believe that FD analysis provides a more naturally physiologic analysis. In particular, a larger blood vessel with few branches would represent a large area of vessel density; however, it is less physiologic than a smaller blood vessel with many more branches that may subtend less total vessel density but have a higher FD, highlighting the significance of physiologic fractal geometry in biology.

Thus, it is reasonable to note that an increase in FD in eyes with papilledema may correlate with increased vasculature. Given the statistically significant difference between Grade 0 papilledema and control eyes, this may suggest an early increase in perfusion of peripapillary microvasculature. Over the course of papilledema severity, the statistical difference in FD is not maintained. The mean FD of eyes with Grades 1, 2, 3, and 4/5 papilledema are not statistically different from that of normal eyes. It is possible that this lack of statistical difference from normal is due to the relatively small number of subjects included at higher levels of papilledema severity.

There are several limitations to our study and to the use of OCTA for evaluation of papilledema. Given the pathophysiologic state of nerve head edema, the penetration power of the imaging beam can be reduced. Similarly, the accuracy of OCT layer segmentation, and thus accuracy of OCTA vascular layer visualization, may also be affected by the swollen nerve head. There is also potential for motion artifact during acquisition. Ideally these technical challenges will be minimized as the software and technology improve. In addition, this study utilized a retrospective cross-sectional design with limited sample size, particularly for higher grade papilledema, which limited the power of the study. It is possible that a more significant change in FD over the course of papilledema severity may be mapped out with more subjects. Thus, this study serves as a starting point for future investigations into fractal analysis of microvasculature in papilledema, which should employ larger samples with prospective design to evaluate FD analysis in providing longitudinal grading of papilledema.

Utilizing fractal analysis in OCTA imaging has the potential to establish quantitative parameters for peripapillary microvascular pathology in papilledema. The combination of FD and current imaging modalities in papilledema may one day provide additional parameters for disease diagnosis and monitoring.

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