Instructions:

• Each speaker will prepare a syllabus that must be submitted through the online submission system.
• The length of the syllabus will be no shorter than 4 single spaced pages in essay (not point) format, plus references.
• Use single spaced, 11 point type and (if possible) Times New Roman font.
• When typing the text use word wrap, not hard returns to determine your lines.
• If headings and subheadings are used, these may be highlighted by using all caps and bold.
• Do not use the header or footer feature or endnotes in preparing the text.
• The submission must be submitted online.

Title:

OCT in Papilledema: What Am I Missing?

Learning Objectives:

1. The attendee will be able to describe the problems with subjective grading of papilledema by ophthalmoscopy or digital photography.
2. The attendee will be able to describe the OCT features that have been shown to vary continuously with the severity of papilledema.
3. The attendee will be able to describe OCT related features that can explain decrease in visual acuity in papilledema.

CME Questions:

1. Which of the following describe the main drawbacks of using a subjective grading scale for quantifying papilledema:
   a. Inter-observer disagreement in Frisen grading of papilledema
   b. Intra-observer repeat variability in Frisen grading of papilledema
   c. It does not provide a continuous scale assessment of papilledema
   d. All of the above

2. Which of the following OCT based features is the most robust and least subject to software segmentation artifact for quantifying the severity of papilledema:
   a. Displacement of Bruch’s membrane
   b. Disc volume
   c. Total retinal peripapillary thickness
   d. Retinal peripapillary nerve fiber layer thickness (RNFL)

3. Which of the following is not considered a typical cause of acute decrease in visual acuity in papilledema:
   a. Neurosensory retinal detachment encompassing the fovea
   b. Choroidal folds
   c. Loss of photoreceptors
   d. Loss of retinal ganglion cells

Keywords (Max 5):

1. papilledema
2. optical coherence tomography (OCT)
3. retinal nerve fiber layer (RNFL)

Introduction/Abstract (Please see instructions for formatting details):
To the experienced neuro-ophthalmologist, the most relevant question is: Do we really need an imaging modality such as optical coherence tomography (OCT) to evaluate papilledema? Most clinicians feel that careful ophthalmoscopy or digital fundus photography is more than adequate for diagnosing the presence of papilledema, determining its severity and deciding on whether it has changed over time. After all, this is what has been done for years, so why do we need something more? The need for “something more” derives from a number of studies, including the multicenter NIH-sponsored Idiopathic Intracranial Pressure Treatment Trial (IIHTT):

- Inter-observer agreement on grading the severity of papilledema is poor among expert observers, even using well-defined criteria such as the Frisen scale, whether this is done using ophthalmoscopy or by grading of digital fundus photographs (1-3).
- Non-expert clinicians often find it difficult to properly view the optic nerve using ophthalmoscopy and to accurately interpret digital fundus photographs when using non-mydriatic retinal cameras at the point of care. This can lead to failure to diagnose papilledema in non-ophthalmologic care settings such as emergency rooms, family practice offices, neurology clinics, or neurosurgery clinics and may delay treatment, which can result in vision loss.
- Distinguishing papilledema from pseudopapilledema is difficult when obvious surface drusen are not present. Buried drusen, when un-calcified, may not be readily apparent using funduscopy, ultrasound, optical coherence tomography, or Computed Tomographic (CT) scans.
- It is often difficult to determine whether a reduction in optic nerve edema is due solely to improvement in the status of the nerve or whether this represents concomitant loss of axons and viable retinal ganglion cells, leading to a poor visual outcome. More timely advancement of treatment would occur if loss of neurons could be diagnosed at an earlier stage of evaluation while optic disc edema is still present.

An important (and reachable) long-term goal is to provide a portable, low cost retinal imaging device with embedded software that would not require expertise for acquiring and making a diagnosis of papilledema or other optic nerve pathology. Ultimately, generation of an automated report providing diagnostic probability at the point of care and at the time of image acquisition is needed which would bypass the need for a telemedicine reading center. Use of such a device would be adopted in clinical settings lacking easy access to ophthalmologists and neuro-ophthalmologists, such as in emergency rooms, family practice offices, neurology and neurosurgery clinics and inpatient units.

The following summary will outline and define the critical need for new imaging modalities such as OCT and image analysis aimed at providing tools for improved diagnosis of papilledema, differentiating papilledema from pseudopapilledema and other causes of optic nerve edema, and for identifying early signs of retinal nerve loss in order to optimize treatment and prevent vision loss.

**Body (Please see instructions for formatting details):**

**1. Diagnosis and grading of severity of papilledema based on fundus features: are we good enough?**

Many clinicians are confident in their ability to accurately diagnose and grade the severity of papilledema and most use the accepted standard of the Frisen grading scale (1). However, even in the original report by Frisen, there was intra-observer variability in grading of photographs on repeat testing, whether the grading was done by a medical student, resident or expert (Figure 1). Significant variability among experts in grading papilledema from digital fundus photographs has also been established in our own studies (2), as shown in Figure 2 and in the study by Sinclair et al (3), shown in Figure 3.

![Figure 1: Reproducibility for three difference observers, who staged the same fundus photographs for disc swelling on two separate occasions. Each dot represents one photograph. The diagnosis represent identity of stage numbers on test and](image-url)
Frisen Grade Variability Between Experts

Figure 2: Four neuro-ophthalmology experts (3 from Iowa and the 4th was Lars Frisen) independently graded papilledema based on criteria outlined in the Frisen scale. Disagreement within one grade scale was common (43% of cases) and there were even cases where there were 2 or more grade scale difference between experts (3.6% of cases) at the higher grades. Modified after Scott CJ, Kardon RH, Lee AG, Frisen L, Wall M. Diagnosis and grading of papilledema in patients with raised intracranial pressure using optical coherence tomography vs clinical expert assessment using a clinical staging scale. Arch Ophthalmol. 2010 Jun;128(6):705-11.

Concordance In Assigning Frisen Grades Amongst Pairs Of Reviewers

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These studies give us pause in relying upon humans (including experts) to accurately and reliably diagnose and grade papilledema. Efforts to refine and provide even more specific criteria for each Frisen scale may help to improve reliability between observers. Since the Frisen scale consists of 6 grades (0-5) that are non-continuous, a further improvement would be to devise a continuous grading scale, based on structural features, that could be objectively quantified by computerized...
image analysis of fundus images. We have shown that quantitative analysis of digital fundus images is a promising approach (4) and features that incorporate sharpness of the disc border, texture of the retinal nerve fiber layer and discontinuity of blood vessels can be used by a machine classifier to assign a Frisen grade to a disc photograph (4). The next step would be to map features from digital fundus photography to a continuous scale based upon OCT measurements of papilledema such as disc volume or thickness of the peripapillary retina (5,6). This would associate fundus photo features with OCT based features, so that quantification of papilledema on a continuous scale could be made (superseding the non-continuous Frisen scale) using either of these two imaging modalities. The imaging modality to be used could be flexible and selected for a given patient based on availability and cost in a telemedicine setting where the patient enters the medical system.

2. Towards a continuous scale quantification of papilledema severity (Retinal Nerve Fiber Layer, Total Retinal Thickness, and Disc Volume)

When time domain OCT first came on the scene around 2001, there had already been attempts at quantifying papilledema using confocal microscopy with Heidelberg Retinal Tomography (HRT) and scanning laser polarimetry. HRT appeared promising (7), but was limited by the difficulty in defining an appropriate “reference plane” in the peripapillary retina for quantifying elevation of the nerve head above that plane, especially in higher grades of papilledema. Even in glaucomatous optic neuropathy, there was disagreement as to what portion of the retina was best suited for a reference plane that was not affected by the pathology under evaluation. Also, the availability of HRT was not widespread; only some academic institutions had the resources and interest to acquire the instrumentation for evaluating the optic nerve and retina using confocal laser microscopy. Scanning laser polarimetry (SLP), which also predated OCT, was gaining use for glaucoma evaluation and was based on changes in the retardation of reflected polarized light from the retinal nerve fiber layer that contained regularly oriented microtubules and microfilaments which could modify polarized light passing through it. Reports of its use for showing thickening of the retinal nerve fiber layer in papilledema were initially negative or only showed mild thickening (8,9); there was very little change in retardation of polarized light by axoplasmic flow stasis, since in most cases the organization of the microfilament substructure was unaffected. However, SLP did reveal axon loss, similar to its use in glaucoma (8-10).

Unlike HRT, OCT provided information on retinal thickening, and in particular, peripapillary thickening of the retinal nerve fiber layer (RNFL) in papilledema without the need for a reference plane (11-21). Also, since OCT was based on actual thickness of the retinal layers, it complimented SLP, which primarily demonstrated loss of microtubule and microfilament organization within the axon bundles. However, it was soon noticed that in the presence of moderate to severe papilledema (Frisen Grade 3 or above), substantial thickening of the peripapillary retinal nerve fiber layer would often cause the software algorithm that was used for determining the RNFL borders to fail in over a third of the cases (2), causing inaccurate reporting of RNFL thickness. A significant improvement in the quantification of papilledema was realized by segmenting the total retinal thickness (TRT) in the same peripapillary scan, since the inner and outer borders of the retina can be more readily defined by automated software in the presence of moderate to severe papilledema. The total retinal thickness was found to highly correlate with the RNFL thickness in eyes where the algorithm did not fail. Automated software segmentation of the retinal layers using a 3D graph-based approach has significantly improved upon the accuracy of defining the thickness of the retinal layers in papilledema (6), resulting in much fewer algorithm failures. In this approach, the entire surface of each retinal layer is determined within the scan volume using all of the surrounding 3D features in the OCT scan and not just the features in each individual B scan. We have further utilized this approach to segment the volume of the optic disc, which highly correlates with the RNFL, total retinal thickness and Frisen grade of papilledema (Figure 4) in patients with raised intracranial pressure (6).

3. Advanced feature analysis of the disc using digital fundus photography and OCT
The ability to accurately derive an OCT-based, continuous measurement of papilledema (for example, total disc volume, as explained in the previous section) provides an objective means of quantifying the severity of papilledema. The next step forward is to map other OCT and fundus-based features to a continuous scale of disc volume, such as shape of the disc volume, deformation of Bruch’s membrane at the neural canal along and texture, along with fundus based features to further enhance the ability to differentiate papilledema from other forms of optic disc edema and pseudopapilledema. This will also allow the quantification of features of digital fundus photographs (e.g. obscuration of the disc margin, discontinuity of disc vessels and texture of the peripapillary nerve fiber layer) to be mapped to OCT disc volume, and will provide the possibility of a continuous scale software measure of papilledema that can be derived and embedded in teleretinal imaging devices at the site of image capture for immediate diagnosis (4,6,22).

Figure 5: Computerized image analysis features of fundus photos that are specific for papilledema and its degree of severity include, from left to right, texture (“entropy”) of the peripapillary retina (with insert), degree of definition of the disc border, vessel discontinuity index (VDI) due to obscuration of retinal vessels by edematous overlying retinal nerve fiber layer, 3D disc volume derived from stereo pairs of disc photographs. From, Echegaray S, Zamora G, Yu H, Luo W, Soliz P, Kardon R. Automated Analysis of Optic Nerve Images for Detection and Staging of Papilledema. Invest Ophthalmol Vis Sci. 2011 Aug 23

Another OCT-based feature, which provides additional information about the direction of force vectors at the optic disc in papilledema, is the deformation of Bruch’s membrane surrounding the neural canal due to a pressure differential between the retrobulbar optic nerve and vitreous cavity (Figure 6). The shape characteristics of Bruch’s membrane in this area, in terms of the degree of angling towards the vitreous, can help in the monitoring of the force differential over time as the intracranial pressure changes and may also help to differentiate papilledema from other causes of optic disc edema or pseudopapilledema (23,24). This angle can vary to some degree within normal eyes without papilledema. The angle may be slightly positive angling toward the vitreous, neutral and horizontal, or negative, angling toward the retrobulbar compartment. Therefore, a very positive angle in an eye suspected of having papilledema may be very helpful, but slightly positive or neutral angle does not rule out papilledema. A change in the angle from positive to less positive following treatment or after lumbar puncture would also enforce a suspicion of papilledema and would verify a treatment effect (Dr. Pat Sibony, personal communication). Newer generation OCT instruments with enhanced depth penetration and longer wavelength light (exceeding 1 micron) provide even greater resolution of deeper structures, such as Bruch’s membrane, even in the presence of optic disc edema.

Figure 4: Top section shows examples of how disc volume, derived from OCT increases with increasing Frisen grade of papilledema (lower left section of figure). B scan sagittal sections are shown in the upper row and corresponding 3D disc volumes are shown in lower row. Bottom section shows a highly linear correlation between Frisen grade and the disc volume (lower left) or disc volume and the retinal nerve fiber layer (RNFL determined by either the Iowa 3D graph-based segmentation algorithm or the Zeiss Cirrus software algorithm) and total retinal thickness (TR). From, Wang JK, Kardon RH, Kupersmith MJ, Garvin MK. Automated quantification of volumetric optic disc swelling in papilledema using spectral-domain optical coherence tomography. Invest Ophthalmol Vis Sci. 2012 Jun 29;53(7):4069-75.
Differentiating papilledema from pseudopapilledema using OCT

The ability to differentiate true papilledema due to raised intracranial pressure from other forms of optic disc edema or from pseudopapilledema can be challenging, particularly when the degree of edema is not severe (i.e. Frisen grade 1 or 2). When calcified optic disc drusen are located superficially, the diagnosis is relatively easy and can be made with careful ophthalmoscopic observation. When calcified drusen are deep and buried under the surface, then clinical observation may be equivocal and the use of autofluorescence (a modality offered on OCT instruments that use a blue scanning laser), ultrasound, or observation of CT scans of the optic nerve have been useful. Features on OCT have been used to differentiate papilledema from pseudopapilledema (25-33), including calcified drusen, which have been visualized on OCT scans through the nerve head as shown in Figure 7. Sometimes calcified drusen and their shadows, visualized on OCT, are not easy to distinguish from larger, superficial blood vessels. Non-calcified drusen are not usually visualized, as they are presumed not to exhibit a significant difference in reflectivity from surrounding disc tissue. Often a patient with pseudopapilledema (with or without calcified drusen), may show visual field loss. In these eyes, the retinal nerve fiber layer may appear thickened in some areas, presumably due to axoplasmic flow stasis, and thin in other areas, corresponding to locations of visual field loss. Another OCT approach to differentiating papilledema from pseudopapilledema is based on defining topographical shape characteristics of the elevated nerve head. In this approach, a machine classifier is used to define shape characteristics that are more likely to be associated with true papilledema and those characteristics that are more likely to be associated with pseudopapilledema. As outlined in the previous section, shape characteristics of Bruch’s membrane may also help in differentiating papilledema from pseudopapilledema and other forms of optic disc edema not due to raised intracranial pressure.

Figure 7: A very large, coalescing druse imaged in several SD-OCT modalities. a, Fundus photo with two vertical markers placed on either side of the druse, obtained with 3D Disc scan on Topcon 3D-OCT 2000. b, Low-resolution SD-OCT image, obtained on same 3D Disc scan. c, High-resolution image, obtained with 7-Line Raster on Topcon 3D-OCT 2000. d, High-resolution (5-Line Raster) image, obtained with Zeiss Cirrus. HD-OCT. From Slotnick S, Sherman J. Buried disc drusen have hypo-reflective
5. Why is my patient with papilledema losing vision? Differentiation of visual loss due to optic neuropathy vs maculopathy (fluid and surface wrinkling)

When a patient with papilledema has best corrected vision of 20/25 or worse, then there is a concern for whether this may be caused by optic neuropathy, requiring more aggressive treatment that may have an urgency associated with it or whether it may be due to a more benign, reversible macular abnormality such as subfoveal fluid or choroidal folds. The more benign outer retinal causes are relatively easy to diagnose with OCT and can help resolve the uncertainty rather quickly. The most obvious sign that can be easily discerned with OCT is a neurosensory retinal detachment from peripapillary fluid between the retina pigmented epithelium and photoreceptors that tracks into the fovea (34,35). On OCT B scans, the fluid appears dark and low reflective. The macular thickness is greater than surrounding areas without fluid on the color OCT thickness plot and the probability plot shows the area with fluid to be significantly thicker than age matched normative data (Figure 8). Decrease in vision due to fluid under the fovea is largely reversible and should not be considered a cause of vision loss requiring urgent management and may be treated with weight loss and acetazolamide. However, rarely, with chronic papilledema, a subretinal neovascular membrane in the peripapillary retina may form and cause fluid that will not go away unless treated more definitively with either intravitreal anti-VEGF agents or laser treatment to the peripapillary area in the location of the membrane. Another outer retinal cause of decreased visual acuity is choroidal folds caused by distortion of the posterior globe by abnormal amounts of fluid under pressure in the subarachnoid space surrounding the optic nerve as it exits the globe. Choroidal folds can be recognized in OCT B scans, in the infrared fundus image, or on digital photography and fundus exam. The folds may contribute to metamorphopsia and are often reversible with successful resolution of papilledema, but not always.

**Figure 8:** OCT example of a papilledema associated with a neurosensory retinal detachment between the left optic nerve and the fovea. Top is the macula total retinal thickness plot showing the elevation in the area of the fluid (arrows). Bottom left is one B scan through the detachment area showing the fluid (dark reflective layer) between the pigmented epithelium and the photoreceptors (arrow). At right is the 3D macula thickness plot showing the elevation in the area of the detachment with fluid (arrow).

Most neuro-ophthalmologists would agree that perhaps the most important cause of reduced visual acuity in papilledema is from optic neuropathy, which can progress to profound visual loss. Once diagnosed, progressive optic neuropathy requires more aggressive, urgent treatment to attempt to minimize the degree functional and structural deficit and restore any reversible component of vision. A decline of visual acuity in the absence of macular fluid or folds is usually the most obvious sign of progressive optic neuropathy in this setting. Since the retinal nerve fiber layer is thickened in papilledema, a reduction in its thickness, assessed by OCT, may be difficult to interpret and could represent either a reduction in disc edema due to improvement or due to axon loss (36-38). We have shown that imaging early signs of axon loss in the presence of papilledema can be revealed by using scanning laser polarimetry (10). Since scanning laser polarimetry is sensitive to disorganization of axon microtubules and microfilaments, which may be one of the earliest signs of axon disruption. However, this technology has become somewhat obsolete and was superseded by OCT for
glaucoma diagnosis and monitoring. One next generation prototype OCT was developed with the capability of polarization assessment, but is not presently commercially available.

As an alternative, assessment of ganglion cell loss by OCT in the setting of papilledema may be suitable for early detection of neuron loss in order to identify patients in need of more aggressive treatment. Since optic disc edema and axon swelling does not appear to directly affect the retinal ganglion cell layer thickness, allowing it to be an effective tool for the early diagnosis of progressive optic neuropathy. However, commercial algorithms for segmenting the ganglion cell-inner plexiform layer complex (GCL-IPL layer) were designed for normal and glaucoma eyes and often fail in the presence of optic disc edema. OCT algorithms that take advantage of 3D information instead of just 2D information from single B scans are better suited to overcome this problem (ref). The working assumption is that thinning of the GCL-IPL will reveal early signs of progressive optic neuropathy in the presence of papilledema. This will undoubtedly be the focus of studies in the near future to understand the usefulness of GCL-IPL thickness in the evaluation and monitoring of papilledema.

Another recent development in OCT which has possible relevance to understanding the pathogenesis of visual loss in papilledema due to ischemia relates to the visualization of optic nerve capillaries and capillary blood flow. Using phase contrast OCT it is now possible to visualize capillaries and quantify flow within a capillary bed without the use of contrast agents (39). An example of OCT derived capillary flow in the normal and glaucomatous optic nerve head is shown in Figure 9.

**Figure 9**: Disc photographs (A, C) and en face OCT angiograms (B, D) of the ONH in representative normal (A, B) and preperimetric glaucoma (PPG) subjects (C, D). Both examples are from left eyes. In (B) and (D) the solid circles indicate the whole discs, and the dash circles indicate the temporal ellipses. A dense microvascular network was visible on the OCT angiography of the normal disc (B). This network was greatly attenuated in the glaucomatous disc (D). From Jia Y, Morrison JC, Tokayer J, Tan O, Lombardi L, Baumann B, Lu CD, Choi W, Fujimoto JG, Huang D. Quantitative OCT angiography of optic nerve head blood flow. Biomed Opt Express. 2012 Dec 1;3(12):3127-37.

**CME Answers** (Use lowercase letters if it's an a/b/c option; feel free to include a description next to the correct answer):

1. D
2. B
3. C


30) Slotnick S, Sherman J. Buried disc drusen have hypo-reflective appearance on SD-OCT. Optom Vis Sci. 2012 May;89(5):E704-8.


