Differentiating Optic Disc Edema From Optic Nerve Head Drusen on Optical Coherence Tomography

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Objective: To assess optical coherence tomography in differentiating optic disc edema (ODE) due to papilledema and other optic neuropathies from optic nerve head drusen (ONHD).

Methods: Optical coherence tomographic images from 60 subjects (20 with ODE, 20 with ONHD, and 20 control subjects) were assessed qualitatively and quantitatively. Qualitative criteria for ODE included an elevated optic nerve head with smooth internal contour and subretinal hyporeflective space (SHYPS) with recumbent “lazy V” pattern. Optic nerve head drusen displayed a “lumpy-bumpy” internal optic nerve contour and a rapid decline in SHYPS thickness. Quantitative comparisons included retinal nerve fiber layer and SHYPS thickness.

Results: Optical coherence tomography differentiated ODE from ONHD qualitatively (sensitivity, 63%; specificity, 63%) and quantitatively (sensitivity, 80%; specificity, 90%). Respective differences in mean retinal nerve fiber layer thickness between ODE and ONHD were significant (P < .002) superiorly (206.8 vs 121.7 µm), nasally (176.3 vs 78.6 µm), inferiorly (247.2 vs 153.8 µm), and temporally (180.0 vs 85.5 µm). Respective differences in mean SHYPS thickness between ODE and ONHD were significant (P < .001) at radii of 0.75 mm (512.1 vs 274.4 µm), 1.5 mm (291.4 vs 103.0 µm), and 2.0 mm (145.5 vs 60.7 µm).

Conclusion: Optical coherence tomography can differentiate ODE from ONHD, particularly when the nasal retinal nerve fiber layer and SHYPS thickness at the 2.0-mm radius are greater than 86 µm and 127 µm, respectively.

thelium and choriocapillaris complex (hereafter termed subretinal hyporeflective space [SHYPS]) in these ODE cases. We also noted the presence of the SHYPS on cross-sectional OCT images in both ODE and ONHD. In ODE, the optic nerve head generally had a smooth internal contour and the SHYPS was thickest near the optic nerve head followed by a gradual tapering away from the optic nerve to form a recumbent “lazy V” pattern (Figure). In comparison, in ONHD, the optic nerve head generally had a “lumpy-bumpy” internal contour with an abrupt decline in the SHYPS (Figure).

To our knowledge, a comparative study of the RNFL and SHYPS thickness in ONHD and ODE has not been reported. Consequently, we investigated the potential benefit of quantitative differences in RNFL and SHYPS thickness and of qualitative differences in optic nerve head contour and peripapillary SHYPS in differentiating ODE from ONHD on OCT.

METHODS

The study was approved by the institutional review board of the University of Missouri–Columbia. Stratus OCT images (software version 4.0.1; Carl Zeiss Meditec, Inc, Dublin, California) from 1 eye each of 60 subjects were assessed retrospectively, consisting of 20 normal eyes, 20 well-documented ONHD cases (11 with buried ONHD, 5 with visible ONHD, and 4 with buried and visible ONHD combined), and 20 well-documented ODE cases (10 with papilledema, 5 with nonarteritic anterior ischemic optic neuropathy, and 5 with optic neuritis) consisting of 6 mild, 6 moderate, and 8 marked ODE cases graded on the papilledema scale of Johnson et al. All OCT was performed by one of us (C.W.H.). All OCT in subjects with ODE or ONHD was performed after pupillary dilation, and approximately half of the control subjects underwent OCT after pupillary dilation.

Quantitative OCT measurements were obtained from high-resolution (10-µm) cross-sectional images on the fast RNFL thickness scan and the fast optic disc scan. The fast RNFL thickness scanning protocol consisted of an average of 256 A-scans along a circular scan path with a 3.4-mm diameter (radius, 1.73 mm) cen-
tered on the optic nerve. Accepted images were judged as being centered on the optic nerve head and had a signal strength score of at least 8. We evaluated the average RNFL thickness of the superior, nasal, inferior, and temporal quadrants in both ONHD and ODE. We did not obtain RNFL thickness in controls.

The fast optic disc scanning protocol consisted of 6 line scans centered on the optic disc, with each line scan having a 4.0-mm diameter (radius, 2.0 mm) and with each line scan spaced circumferentially 30° apart from the preceding line scan. Each 4.0-mm line scan was constructed by averaging 128 A-scans. The thickness of the peripapillary SHYPS, located between the sensory retina and the retinal pigment epithelium and choriocapillaris complex, was measured at radii of 0.75 mm (corresponding to near the optic disc margin), 1.5 mm (doubled distance from 0.75 mm), and 2.0 mm (corresponding to each end of the 4.0-mm line scan), providing 36 measurements for each eye (Figure). We used a manual caliper to measure the SHYPS thickness directly on the computer screen (1 mm = 21.1 µm).

Intraexaminer reliability documented that 95% of the SHYPS measurements were within 106 µm at the 0.75-mm radius, and 42 µm at the 2.0-mm radius (absolute test-retest difference).

While viewing an overhead projection of the 6 cross-sectional OCT images of the fast optic disc scans for each eye, three of us (L.N.J., C.W.H., and D.N.S.), unaware of the true diagnosis, assigned the diagnosis of ONHD, ODE, or normal based on the following qualitative criteria: (1) the presence of an elevated optic nerve head with a smooth internal optic nerve contour and a rapid and abrupt decline in SHYPS thickness directly on the computer screen (1 mm = 21.1 µm). Intraexaminer reliability documented that 95% of the SHYPS measurements were within 106 µm at the 0.75-mm radius, 84 µm at the 1.5-mm radius, and 42 µm at the 2.0-mm radius (absolute test-retest difference).

Using the qualitative criteria, we found that OCT had a mean sensitivity (true-positive rate) of 63% and a mean specificity (true-negative rate) of 63% in discriminating ODE from ONHD. Most errors occurred in incorrectly classifying eyes with mild ODE as having ONHD or, conversely, incorrectly classifying eyes with ONHD as having mild ODE.

The Table provides the quantitative measurements of the RNFL and SHYPS data. Differences in RNFL and SHYPS thickness on OCT were helpful in distinguishing ODE from ONHD. The mean RNFL thickness was significantly greater for ODE than for ONHD in all quadrants (P < .002). The respective mean RNFL thicknesses for ODE and ONHD were 206.8 µm and 121.7 µm superiorly (P < .001), 176.3 µm and 78.6 µm nasally (P < .001), 247.2 µm and 153.8 µm inferiorly (P = .001), and 180.0 µm and 85.5 µm temporally (P < .001).

The ROC curve areas for discriminating ODE from ONHD were calculated for each quadrant for RNFL thickness, and a single optimal cutoff for diagnosis was identified. The ROC curve areas for RNFL were nearly similar for the 4 quadrants, being 0.86 nasally (for RNFL thickness > 86 µm: sensitivity, 80%; specificity, 70%), 0.83 superiorly (for RNFL thickness > 149 µm: sensitivity, 75%; specificity, 80%), 0.83 temporally (for RNFL thickness > 97 µm: sensitivity, 80%; specificity, 70%), and 0.80 inferiorly (for RNFL thickness > 165 µm: sensitivity, 65%; specificity, 75%).

The mean SHYPS thickness was larger for ODE than for ONHD and was larger for ONHD than for controls. The mean SHYPS thickness for ODE was 512.1 µm at the

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Table. Subretinal Hyporeflective Space and Retinal Nerve Fiber Layer Thickness

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>SHYPS Thickness, µm</th>
<th>RNFL Thickness, µm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.75-mm Radius</td>
<td>1.5-mm Radius</td>
</tr>
<tr>
<td>ODE</td>
<td>Mean (SD)</td>
<td>Median</td>
</tr>
<tr>
<td></td>
<td>512.1 (224.2)</td>
<td>291.4 (195.5)</td>
</tr>
<tr>
<td></td>
<td>527.5</td>
<td>253.2</td>
</tr>
<tr>
<td></td>
<td>21.1-1055.0</td>
<td>21.1-844.0</td>
</tr>
<tr>
<td>ONHD</td>
<td>Mean (SD)</td>
<td>Median</td>
</tr>
<tr>
<td></td>
<td>274.4 (178.1)</td>
<td>103.0 (102.5)</td>
</tr>
<tr>
<td></td>
<td>306.5</td>
<td>63.3</td>
</tr>
<tr>
<td></td>
<td>21.1-801.8</td>
<td>21.1-633.0</td>
</tr>
<tr>
<td>Control</td>
<td>Mean (SD)</td>
<td>Median</td>
</tr>
<tr>
<td></td>
<td>80.2 (75.1)</td>
<td>70.2 (35.3)</td>
</tr>
<tr>
<td></td>
<td>42.2</td>
<td>63.3</td>
</tr>
<tr>
<td></td>
<td>21.1-422.0</td>
<td>21.1-211.0</td>
</tr>
</tbody>
</table>

Abbreviations: ODE, optic disc edema; ONHD, optic nerve head drusen; RNFL, retinal nerve fiber layer; SHYPS, subretinal hyporeflective space; ellipses, not available.

a Data are from the article by Savini et al.16
b Data are from the article by Park et al.17

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0.75-mm radius, 291.4 µm at the 1.5-mm radius, and 145.5 µm at the 2.0-mm radius. In contrast, the mean SHYPS thickness for ONHD was 274.4 µm at the 0.75-mm radius, 103.0 µm at the 1.5-mm radius, and 60.7 µm at the 2.0-mm radius. The mean SHYPS thickness for controls was 80.2 µm at the 0.75-mm radius, 70.2 µm at the 1.5-mm radius, and 66.6 µm at the 2.0-mm radius. Significant differences (P < .001) of SHYPS thickness were present in pairwise comparisons at all 3 radii (0.75 mm, 1.5 mm, and 2.0 mm) between ODE and ONHD and between ODE and controls. The mean SHYPS thickness was significantly larger for ONHD than for controls at the 0.75-mm radius (P < .001) but no different between ONHD and controls at the 1.5-mm radius (P = .03) and the 2.0-mm radius (P = .53).

Because visual inspection of the SHYPS at the 2.0-mm radius appeared to be able to distinguish ODE from ONHD, we computed ROC curve areas using the largest and second largest SHYPS thicknesses at the 2.0-mm radius for each of the 60 study eyes. An optimal cutoff for discriminating ODE from ONHD was identified. The ROC curve area for the largest SHYPS thickness at the 2.0-mm radius was 0.87 (for SHYPS thickness > 169 µm: sensitivity, 70%; specificity, 90%). When the second highest value of the SHYPS thickness at the 2.0-mm radius was assessed for sensitivity and specificity in discriminating ODE from ONHD, the ROC curve area was 0.90 (for SHYPS thickness > 127 µm: sensitivity, 75%; specificity, 90%).

The ratio of the median SHYPS thickness at the 0.75-mm radius to the median SHYPS thickness at the 1.5-mm radius was 5.0 for ONHD, 2.1 for ODE, and 0.8 for controls. This thickness disparity between the 0.75-mm and 1.5-mm SHYPS corresponded to the rapid decline in SHYPS noted qualitatively for ONHD. In contrast, the ratio of the median SHYPS thickness at the 1.5-mm radius to the median SHYPS thickness at the 2.0-mm radius was greater for ODE at 2.4 as compared with 1.5 for ONHD and 1.0 for controls. The difference in SHYPS thickness between the 1.5-mm and 2.0-mm radii corresponded to the gradual tapering of the SHYPS observed with ODE.

**COMMENT**

Our study documented that qualitative and quantitative OCT criteria can be established to differentiate ODE due to papilledema and other optic neuropathies from ONHD. In general, ODE displayed the following qualitative and quantitative characteristics on OCT: (1) an elevated optic nerve head with a smooth internal contour; (2) a recumbent lazy V pattern of the SHYPS due to the SHYPS thickness at the 1.5-mm radius being greater than twice that at the 2.0-mm radius; (3) an increased RNFL thickness, particularly a nasal RNFL greater than 86 µm; and (4) a normal SHYPS thickness at the 2.0-mm radius with a mean value of 60.7 µm. The ability to discriminate ODE from ONHD on OCT ranged in sensitivity from 63% for qualitative criteria alone to 80% for nasal RNFL thickness greater than 86 µm. The ability to discriminate ODE from ONHD on OCT ranged in specificity from 63% for qualitative criteria alone to 90% for a SHYPS thickness greater than 169 µm at the 2.0-mm radius (or > 127 µm for the second largest SHYPS measurement at the 2.0-mm radius).

Differentiating ODE or ONHD from a normal optic nerve is generally not difficult on clinical examination of the fundus, particularly with the use of direct and indirect ophthalmoscopy and 90-diopter stereoscopic examination. However, difficulty will sometimes arise in differentiating ODE from ONHD on clinical examination. Although both sensitivity and specificity are important, it is arguable that in differentiating ODE from ONHD, specificity (or the true-negative rate) is more important than sensitivity (or the true-positive rate). We have documented that nasal RNFL thickness and SHYPS thickness at the 2.0-mm radius provide excellent discrimination between ODE and ONHD. A nasal RNFL thickness greater than 86 µm has 80% specificity, and a SHYPS thickness greater than 169 µm at the 2.0-mm radius (or > 127 µm for the second largest SHYPS measurement at the 2.0-mm radius) has 90% specificity.

To our knowledge, Savini et al. were the first to report the presence of a prominent peripapillary SHYPS in ODE. We are now reporting the increased peripapillary SHYPS in ONHD. However, Hoye et al. had alluded to the presence of an expanded SHYPS by their documentation of subretinal fluid in the macular region on OCT in 7 subjects with increased intracranial pressure and papilledema. In 4 of the 7 subjects, the submacular fluid was continuous with the peripapillary subretinal fluid. Because fluorescein accumulation in the macular region was not documented in the 2 subjects who underwent intravenous fluorescein angiography, Hoye and colleagues concluded that the submacular fluid on OCT did not emanate from the retinal or choroidal vasculature. Rather, they speculated that the subretinal fluid arose from the optic nerve head.

Given the absence of retinal or choroidal fluorescein leakage and the presence of late hyperfluorescence staining of the optic disc on fluorescein angiography in ODE and ONHD, the most plausible cause for the increased SHYPS thickness in both ODE and ONHD is extravasated fluid from the optic nerve head percolating into and elevating the subretinal space.

Fluid expansion of the subretinal space is dependent on retinal adhesive forces between the sensory retina and the retinal pigment epithelium. Retinal adhesive forces are complex, but the principal components include capillary and interstitial tissue hydrostatic pressure, capillary and tissue osmotic or oncotic pressure, and the rate of active transport across the retinal pigment epithelium. Of these forces, active transport across the retinal pigment epithelium may be the major factor for retinal adhesion and for preventing thickening of the subretinal hyoreflective space.
We have documented that in ONHD, the SHYPS is thicker than normal at the 0.75-mm radius but not at the 1.5-mm and 2.0-mm radii. Because ONHD is generally a longstanding condition when it is first evaluated, this rather parochial expansion of the SHYPS in ONHD would suggest that a homeostatic balance had been achieved between the capillary hydrostatic pressure and the combined interstitial tissue hydrostatic pressure and active transport of the retinal hydrostatic pressure to the optic nerve head. However, we documented that the SHYPS is significantly thicker in ODE at all of the 3 radii (0.75 mm, 1.5 mm, and 2.0 mm from the optic disc center) as compared with ONHD and controls. Additionally, Hoye et al\(^\text{18}\) have documented expansion of the SHYPS in the macular region in some cases of ODE. These findings suggest that in ODE from recent-onset papilledema and acute optic neuropathies, the relatively sudden increase in capillary hydrostatic pressure exceeds the interstitial tissue hydrostatic pressure and the rate of active transport across the retinal pigment epithelium. With the capillary hydrostatic pressure from the optic nerve head exceeding the retinal adhesive forces in ODE, there is wider dispersion of fluid and greater thickening of the SHYPS as compared with that occurring in ONHD.

There are several limitations of our study. Our measurements of the SHYPS were obtained with a manual caliper directly from the computer screen. Despite fairly good reproducibility for test-retest differences, such a method of measurement is prone to errors in variability. This potential for error would be reduced if OCT manufacturers made an internal caliper for SHYPS measurement that was easily accessible. A second limitation is the relatively small sample size. Additional studies are needed to validate the proposed cutoff values that we have established.

The frequency of ONHD is estimated to be 0.3% to 2.4% of the population, and ONHD is bilateral in approximately 75% of cases.\(^\text{23}\) The annual incidence of optic neuropathy with ODE is estimated to be at least 19.4 persons per 1 million in the US population.\(^\text{23}\) According, there are individuals who have both ODE from papilledema or other optic neuropathies and ONHD simultaneously. Our study did not include such individuals. However, it would be important to know whether the OCT characteristics are different in eyes with combined ODE and ONHD as compared with ODE or ONHD alone.

In summary, we have documented that qualitative and quantitative parameters on OCT can aid in differentiating ODE due to papilledema or other optic neuropathies from ONHD. A prospective comparative study of the accuracy of OCT, intravenous fluorescein angiography, B-scan ultrasonography, and computed tomography in differentiating ODE from ONHD would be valuable.

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