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High-Resolution Imaging of the Optic Nerve and Retina in Optic Nerve Hypoplasia

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Purpose: To investigate the optic nerve and macular morphology in patients with optic nerve hypoplasia (ONH) using spectral-domain optical coherence tomography (SD OCT).

Design: Prospective, cross-sectional, observational study.

Subjects: A total of 16 participants with ONH (10 female and 6 male; mean age, 17.2 years; 6 bilateral involvement) and 32 gender-, age-, ethnicity-, and refraction-matched healthy controls.

Methods: High-resolution SD OCT (Copernicus [Optopol Technology S.A., Zawiercie, Poland], 3 μm resolution) and handheld SD OCT (Bioptigen Inc [Research Triangle Park, NC], 2.6 μm resolution) devices were used to acquire horizontal scans through the center of the optic disc and macula.

Main Outcome Measures: Horizontal optic disc/cup and rim diameters, cup depth, peripapillary retinal nerve fiber layer (RNFL), and thickness of individual retinal layers in participants with ONH and in controls.

Results: Patients with ONH had significantly smaller discs ($P < 0.03$ and $P < 0.001$ compared with unaffected eye and healthy controls, respectively), horizontal cup diameter ($P < 0.02$ for both), and cup depth ($P < 0.02$ and $P < 0.01$, respectively). In the macula, significantly thinner RNFL (nasally), ganglion cell layer (GCL) (nasally and temporally), inner plexiform layer (IPL) (nasally), outer nuclear layer (ONL) (nasally), and inner segment (centrally and temporally) were found in patients with ONH compared with the control group ($P < 0.05$ for all comparisons). Continuation of significantly thicker GCL, IPL, and outer plexiform layer in the central retinal area (i.e., foveal hypoplasia) was found in more than 80% of patients with ONH. Clinically unaffected fellow eyes of patients with ONH showed mild features of underdevelopment. Visual acuity and presence of septo-optic dysplasia were associated with changes in GCL and IPL. Sensitivity and specificity for the detection of ONH based on disc and retinal optical coherence tomography (OCT) parameters were >80%.

Conclusions: Our study provides evidence of retinal changes in ONH. In addition to thinning of retina layers mainly involving the RNFL and GCL, signs reminiscent of foveal hypoplasia were observed in patients with ONH. Optic nerve and foveal parameters measured using OCT showed high sensitivity and specificity for detecting ONH, demonstrating their useful for clinical diagnosis. *Ophthalmology 2015;122:1330-1339 © 2015 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

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Optic nerve hypoplasia (ONH) is a nonprogressive congenital abnormality of the optic nerve characterized by up to a 90% reduction in the number of axons in histologic samples.[1] Optic nerve hypoplasia has a prevalence estimated between 7.1 and 10.9/100 000 children per year.[2,3] It can present as an isolated entity in 1 or both eyes, or can coexist with other central nervous system abnormalities. The most well-documented association is septo-optic-dysplasia (SOD). Septo-optic-dysplasia, also known as de Morsier syndrome, consists of the triad of ONH, midline brain abnormalities, including absent septum pellucidum, hypothalamic dysfunction, and endocrine abnormalities.

The cause of ONH is not fully understood, and multiple causative etiologies may produce clinically indistinguishable phenotypes. The majority of cases are sporadic. However, there have been familial cases of SOD with ONH described with mutations in HESX1[4] and SOX2.[5] Optic nerve hypoplasia has been associated with abnormal intrauterine development, for example, in maternal diabetes[6] or fetal alcohol syndrome.[7]

Optic nerve hypoplasia is a clinical diagnosis; visualization of the disc reveals an abnormally small optic nerve head, characteristically pale or grey in color. A "double-ring sign" is often described, consisting of a normal junction between the sclera and the lamina cribrosa (outer ring) and an abnormal extension of the retina and pigment epithelium over the outer portion of the lamina cribrosa (inner ring). Vascular abnormalities are described, frequently vascular tortuosity,[8] although abnormally straight vessels with reduced branching have been documented.[9]

Spectral-domain optical coherence tomography (OCT) is a noninvasive, noncontact imaging modality that produces in vivo images comparable to histologic samples[10] with good reproducibility.[11] Little is known about the morphologic changes of the optic disc in ONH. A histopathology study performed by Mosier et al[12] on 1 patient with ONH

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showed thinning of the retinal nerve fiber layer (RNFL) and ganglion cell reduction. These findings were confirmed by other researchers.[13,14] To date, there are only a few articles investigating the in vivo eye morphology in ONH using optical coherence tomography (OCT).[15,16] In 2013, Moon and Park[16] described RNFL thinning and thinning of the structures located between the posterior boundary of the RNFL and the posterior boundary of the outer plexiform layer (OPL) of the retina measured together in 1 patient with ONH compared with the healthy eye using SD OCT. There are no investigations about possible macular changes associated with ONH. A previous study using fundus photography has found no relationship between the size of the optic nerve and the visual acuity in patients with ONH.[13]

The aim of this study is to perform the first cross-sectional observational study to characterize the optic nerve and macular morphology in a series of patients with various degrees of ONH using high-resolution SD OCT. We also explore the clinical utility of SD OCT in detecting ONH and correlate associated changes with the visual outcome and presence of SOD.

Methods

Subjects

Sixteen patients with ONH (10 female and 6 male; mean age, 17.2 years; standard deviation ±16.22) and 32 gender-, age-, ethnicity-, and refraction-matched healthy controls were included in this prospective observational study. Six patients demonstrated clinically bilateral involvement. Eyes were divided into 2 subgroups: eyes with (affected, n = 22) and without (unaffected, n = 10) clinically detected ONH.

All participants underwent a standard ophthalmologic examination, including best-corrected visual acuity, refraction, orthoptic examination, slit-lamp examination, and dilated fundoscopy (Table 1, available at www.aaojournal.org). When nystagmus was present, eye movements were recorded (EyeLink 1000, SR Research Ltd, Osgoode, Canada) under binocular conditions and either eye occluded. Nystagmus waveforms were observed for infantile nystagmus (i.e., accelerating or sinusoidal slow phases) and manifest latent nystagmus (decelerating waveforms with the slow phase directed toward the occluded eye). Two participants (aged 12 and 16 years) were too young to cooperate with eye movement recordings, and nystagmus type was determined clinically (manifest latent nystagmus if change in direction on covering).

The diagnosis of ONH was established on the basis of clinical examination. Patients with ONH had no other known ophthalmic pathology. Magnetic resonance imaging of the brain and orbits was performed in 10 of 16 patients (6 adult patients preferred not to undergo magnetic resonance imaging as part of the examination) to determine the presence of SOD. Five of 16 patients did not have nystagmus. All 5 patients had unilateral ONH.

A total of 32 gender-, age-, ethnicity-, and refraction-matched healthy controls with best-corrected visual acuity of 0.2 logarithm of the minimum angle of resolution (logMAR) or better, normal visual fields, and intraocular pressure (when possible to assess, because some participants were too young to cooperate) were included. The control group had no known eye pathology, systemic disease, or previous intraocular surgery. The study adhered to the tenets of the Declaration of Helsinki and was approved by the local ethics committee. Informed consent was obtained from all participants or their parents or guardians.

Optical Coherence Tomography

Ultra–high-resolution spectral-domain OCT (Copernicus; Optopol Technology S.A., Zawiercie, Poland) was used to acquire tomograms with a wavelength of 850 nm and a theoretic axial resolution of 3.0 μm (7×7×2 mm, 75 B-scans, 743 A-scans per B-scan, fixation target set to image the optic disc) in 9 older participants in whom we could achieve a stable head position to obtain good-quality scans. In 7 participants (aged 1–7 years), SD OCT images were obtained using a handheld device (HH-OCT, Envisu, Bioptigen Inc, Research Triangle Park, NC) with a wavelength of 840 nm and theoretic axial resolution of 2.4 μm (10×10×2.46 mm, 100 B-scans and 500 A-scans per B-scan). Individual horizontal B-scans were analyzed as opposed to automated volumetric analysis because of the presence of nystagmus in 10 patients. Because of the rapid acquisition time for individual B-scans (14.3 ms for Copernicus and 15.6 ms for Bioptigen Inc), distortion of individuals' B-scans due to nystagmus was minimal.

The consistency of measurements between the 2 devices was checked by comparing measurements from 15 adults with both devices. Interclass correlation coefficients for key parameters were all >0.8 (rim diameter = 0.91; cup diameter = 0.93; retinal thickness = 0.94, 0.93, and 0.95 for nasal, central, and temporal, respectively; GCL, central = 0.83).

Optic Nerve Head Analysis

A flattened B-scan through the deepest point of the optic nerve cup was used for ONH analysis. Quantitative OCT analysis was conducted in a semiautomated manner using an ImageJ macro (National Institutes of Health, Bethesda, MD, available at: http://rsbweb.nih.gov/ij/) by the same investigator (AP) for all scans.

On the horizontal tomograms, the edges of the retinal pigment epithelium (RPE) (optic disc margins), the position of the internal limiting membrane, and the RNFL position were marked manually (Fig 1A). The cup diameter (using a cup offset 150 μm anteriorly to the disc axis), cup maximal depth, and horizontal rim size (distance between horizontal disc and cup diameters) and temporal and nasal height (between the horizontal cup diameter level and the RNFL, limited on the periphery by the disc margins) were measured automatically by the macro. Peripapillary RNFL thickness was measured in a region from 1200 to 1600 μm on both sides of the center of the cup (same as the default setting in the Optopol automated analysis).

Foveal Analysis

A central horizontal flattened B-scan was selected at the deepest point of the foveal pit where the outer segment (OS) of photoreceptors was thickest, indicating specialization (i.e., elongation) of photoreceptors at the pit. If there was no clear foveal pit, the center of the macula was identified as the point with greatest extent of thinning of the inner retinal layers and doming of the outer nuclear layer (ONL).

Detailed SD OCT analysis was conducted in a semiautomated manner using an ImageJ macro with the retinal layer borders positioned manually by locating points that were fitted with a spline fit. The borders were used to calculate thickness measurements of the RNFL, ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL), OPL, ONL, inner segment (IS), OS, contact cylinder, and RPE layers (Fig 1B). The position of the retinal layers was measured across the whole scan. For statistics, the thickness measurements in the central point, paracentral area (averaged thickness of each layers from 250 μm nasally to 250 μm temporarily from the center), and nasal/temporal areas (averaged thickness of each layers from 500 to