The macula in pediatric glaucoma: quantifying the inner and outer layers via optical coherence tomography automatic segmentation

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BACKGROUND Recent Spectralis (Heidelberg, Germany) spectral domain optical coherence tomography (SD-OCT) research software can automatically quantify the thickness of each individual retinal layer. The macular ganglion cell layer (GCL) and ganglion cell complex may be more sensitive for detecting glaucoma than the peripapillary retinal nerve fiber layer (pRNFL). The aim of this study was to characterize and compare the volume of each macular layer in the eyes of children with glaucoma versus those of normal controls.

METHODS The medical records of children with primary glaucoma and physiologic cupping who had undergone Spectralis SD-OCT imaging of the macula and pRNFL were reviewed retrospectively. Controls were recruited from a separate prospective study. Children with refractive error of $<\pm 5$ or retinal or neurologic abnormalities were excluded. The average volume of each of the 8 retinal layers in the macula (central 6 mm) and pRNFL were compared among diagnostic groups.

RESULTS A total of 80 eyes of 80 children were included: 37 glaucoma eyes (25 with primary congenital and 12 with juvenile open-angle glaucoma) and 43 nonglaucoma eyes (28 with physiologic cupping). Eyes with glaucoma had significantly thinner mean macular nerve fiber layers, ganglion cell layers, inner plexiform layers, and pRNFLs than nonglaucomatous eyes: 0.82 ± 0.24 μm versus 1.00 ± 0.12 μm; 0.93 ± 0.22 μm versus 1.13 ± 0.10 μm; 0.80 ± 0.14 μm versus 0.91 ± 0.07 μm; 81.6 ± 26.5 μm versus 102.7 ± 10.0 μm, respectively ($P < 0.00556$ for all). Eyes without cupping and those with physiologic cupping were equivalent for all variables tested.

CONCLUSIONS Children with glaucoma have thinning of the three innermost retinal macular layers. (J AAPOS 2016;20:332-336)

Spectral domain optical coherence tomography (SD-OCT) provides an objective measurement of the thickness of the retina in the macula and the peripapillary retinal nerve fiber layer (pRNFL) around the optic nerve. In adults, pRNFL thickness is used to diagnose and monitor the progression of glaucoma.[1] This measure has been shown to be reproducible over time[2-4] and to correlate well with glaucoma severity.[5-7] This quantitative measurement supports the subjective evaluation of the optic nerve head and cup:disk ratio and subjective visual fields.[7,8]

Over the past 20 years, OCT has evolved tremendously, and time-domain OCT has been largely replaced by SD-OCT. The latter provides increased resolution and faster image acquisition, making it ideal for children (most of whom have short attention spans during testing). The increased resolution and advancing image processing provides the ability for automatic computer discrimination and quantification of the macular layers from an SD-OCT image.[8]

OCT in glaucoma has focused primarily on the pRNFL, because the axons from entire retina coalesce at the optic nerve head. Recent studies have investigated macular parameters, such as the ganglion cell complex (GCC = macular nerve fiber layer [mNFL] + ganglion cell layer [GCL] + inner plexiform layer [IPL]) and found that the

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GCC protocol improved the diagnostic power of OCT for glaucoma.[8-11] This technique has not been explored extensively in children, although there is evidence that the ganglion cell complex in children is thinner in eyes with primary congenital glaucoma (PCG) compared to similarly aged children who presented for general examination or refractive error correction (up to ±6.00 D sphere and ±3.00 D of cylinder).[11]

The mainstay of treatment for childhood glaucoma involves surgery and/or medication to reduce intraocular pressure (IOP). While optic nerve head cupping may reverse in children with successful and sustained IOP reduction, glaucomatous pRNFL thinning and optic nerve damage usually do not.[12] Therefore, it is important to develop other methods of monitoring children with glaucoma, because many cannot complete a reliable and reproducible visual field.[13]

Recent Spectralis (Heidelberg, Germany) SD-OCT research software (beta version) can quantify the thickness and total macular volume of each individual retinal layer in an automated fashion. Macular thickness in children has been evaluated previously, but segmentation required manual input and could be performed only on one linear scan (2 individuals independently marked the retinal layer boundaries and a custom-designed program calculated the thickness of retinal layers, which is a time-intensive task) or combined the thickness of multiple layers.[10,11,14] The purpose of the present study was to characterize and compare the thickness and total volume of each macular layer in children with PCG, juvenile open-angle glaucoma (JOAG), physiologic cupping, and normal eyes.

Subjects and Methods

This study was approved by the Duke University Medical Center Institutional Review Board and conducted in accordance with the standards of the US Health Insurance Portability and Accountability Act of 1996. The medical records of children (<18 years of age) with ophthalmic diagnoses of PCG, JOAG, and physiologic cupping who had undergone Spectralis (Heidelberg; Heidelberg, Germany) SD-OCT were reviewed retrospectively. Normal pediatric control eyes were enrolled prospectively as part of a pediatric OCT normative database study.[15] Children presenting for scheduled clinic visits at Duke Eye Center and who had (or were scheduled to have) Spectralis SD-OCT scans of the macula and pRNFL were identified both retrospectively and prospectively. Spectralis SD-OCT imaging was part of standard of care for children with PCG, JOAG, and physiologic cupping.

Eyes with PCG were defined as having past intraocular pressure (IOP) of >21 mm Hg and clinical signs of glaucoma that started in the neonatal or infantile period. Eyes with JOAG were defined as eyes of children presenting after the 2nd year of life with cup:disk ratio of >0.5 and glaucomatous optic nerve head appearance, a history of IOP >21 mm Hg, and otherwise normal anterior segment with open angles. Eyes with physiologic cupping were defined as having a cup:disk ratio of ≥0.5 with a healthy and symmetric rim (cup:disk asymmetry of <0.1), IOP ≤21 mm Hg on multiple testing, and without any other clinical features suggestive of glaucoma. Normal eyes were defined as having a cup:disk ratio of <0.5 with a healthy and symmetric rim (intra-eye cup:disk ratio difference of <0.1), IOP of <21 mm Hg, no history of increased IOP or any ocular pathology in either eye (other than refractive error), and vision correctable to 20/20.

Children with neurologic disorders, refractive error (spherical equivalent of >5 D of hyperopia or myopia), aphakia, pseudophakia, and prematurity were excluded, because these characteristics have been reported to affect OCT-measured thickness of the macula and pRNFL.[16-18] Also excluded were eyes with any qualitative retinal abnormalities on a masked review of each of the 61-line macular OCT scans by two authors (ME, KJ). Eyes with secondary glaucoma from diseases such as Sturge-Weber and Axenfeld-Rieger syndromes were also excluded.

One eye per child was selected for data analysis as follows. For children with primary glaucoma (PCG or JOAG), the eye with the higher cup:disk ratio was selected if this eye was not already excluded by any of the above criteria. For children with physiologic cupping and normal eyes, the right eye was selected. For each child, the age at the SD-OCT, sex, race, visual acuity, and cup:disk ratio were obtained from the clinical record.

The Spectralis segmentation software (Heidelberg, Germany, beta version) was used to automatically segment and measure each individual layer of the macular Spectralis SD-OCT scan (mNFL, GCL, IPL, inner nuclear layer [INL], outer plexiform layer [OPL], outer nuclear layer [ONL], photoreceptor layer [PL], and retinal pigmented epithelium [RPE]; see Figure 1). The thickness was recorded for each layer in each area of the Early Treatment Diabetic Retinopathy Study (ETDRS) map, dividing the macula into 9 regions consisting of 3 concentric circles with diameters measuring 1 mm (fovea), 3 mm (inner ring), and 6 mm (outer ring). The total volume for each layer inside the 6 mm ring was used for comparison across the different diagnostic groups. The GCC was calculated by adding average mRNFL, GCL, and IPL. These data were exported into a Microsoft Excel database (Microsoft Corporation, Redmond, WA).

Statistical analysis of data was performed using JMP Pro software program (version 11; SAS Institute Inc, Cary, NC). Unpaired *t* tests were used to compare the total volume of each layer between the groups. Bonferroni correction was used for the multiple comparisons of the retinal layers (*P* value was divided by 9 for each layer of the retina [mRNFL, GCL, IPL, INL, OPL, ONL, PL, RPE] and the pRNFL; thus statistical significance was determined for *P* values of $<0.05 \div 9 = 0.00556$). Data are presented as mean with standard deviation unless otherwise stated.

Results

A total of 80 eyes of 80 children were included: 12 with JOAG, 25 with PCG, 28 with physiologic cupping, and 15 normal eyes. Patient demographics are provided in Table 1. First, eyes with glaucoma (PCG and JOAG) were compared to nonglaucomatous eyes (physiologic cupping and normal eyes). The 37 eyes with glaucoma