Longitudinal Study of Peripapillary Thinning in Sickle Cell Hemoglobinopathies

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• PURPOSE: **To determine the rate of retinal nerve fiber layer (RNFL) thinning in patients with sickle cell hemoglobinopathies.**
• DESIGN: **This was a prospective cohort study.**
• METHODS: **Sixty-seven patients averaging 35.8 ± 11.5 years of age at enrollment with electrophoretically confirmed sickle cell hemoglobinopathies followed by the University of Illinois at Chicago retina clinic for ≥1 year were included. Exclusion criteria included a history of diabetes, uncontrolled hypertension, glaucoma, ocular opacities, other retinopathies, and previous retinal procedures. The optic nerve head RNFL thicknesses were measured with spectral-domain optical coherence tomography (Heidelberg Engineering, Inc) at enrollment and subsequent follow-ups. Linear mixed models were used to estimate rates of thinning.**
• RESULTS: **A total of 122 eyes were followed for 3.8 ± 2.0 years (range 1–8 years). Mean global peripapillary RNFL thickness was 100.9 ± 13.0 μm at baseline. Global peripapillary RNFL thickness decreased at a rate of 0.98 μm per year (95% confidence interval [CI] 0.77–1.19 μm/year). A history of stroke was associated with a faster rate of global RNFL thinning (1.72 ± 0.20 vs 0.79 ± 0.12 μm/year, $P < .001$), whereas a history of hypertension was associated with a slower rate of thinning (0.33 ± 0.27 vs 1.14 ± 0.12 μm/year, $P = .002$).**
• CONCLUSIONS: **Peripapillary RNFL thinning in patients with sickle cell hemoglobinopathies occurred faster in patients with a history of stroke and slower in patients with controlled hypertension. Future studies will compare these rates to those of healthy age- and race-matched individuals. (Am J Ophthalmol 2019;202:30–36. © 2019 Elsevier Inc. All rights reserved.)**

SICKLE CELL DISEASE IS CHARACTERIZED BY AN inherited abnormal hemoglobin protein chain that causes intermittent vaso-occlusive events and chronic hemolytic anemia.[1] The disease is more prevalent in the African American population and is estimated by the United States Centers for Disease Control and prevention to affect 1 in 365 African American births.[2] In the eye, patients with sickle cell disease may develop conjunctival abnormalities, anterior uveitis, and elevated intraocular pressure (IOP) in the setting of hyphema. Sickle cell retinopathy findings have been well described and range from nonproliferative to proliferative changes.[3] Based on spectral-domain optical coherence tomography (SD-OCT), patients with sickle cell disease have central macular splaying, outer retinal thinning, macular thinning, and peripapillary retinal nerve fiber layer (RNFL) thinning when compared with age- and race-matched control subjects.[4–6]

Peripapillary RNFL loss, African American race, elevated IOP, and increasing age are known risk factors for development and progression of glaucoma.[7] Our group previously found that patients with sickle cell disease have peripapillary RNFL thinning compared with age- and race-matched individuals without sickle cell disease, yet it is unknown whether this thinning progresses at a faster rate over time than expected for age or translates to an increased risk of developing glaucoma. In this study, we present a longitudinal analysis of peripapillary thickness using SD-OCT in patients with sickle cell hemoglobinopathies in order to quantify the rates of peripapillary thinning in these patients. We further identify systemic factors that are associated with the rate of peripapillary RNFL thinning.

METHODS

WE PERFORMED A PROSPECTIVE COHORT STUDY OF PATIENTS with sickle cell retinopathy. Patients were referred to the University of Illinois at Chicago Department of Ophthalmology from the Sickle Cell Clinic from 2009 to 2016 and had electrophoretic confirmation of sickle cell disease (Hgb SS), sickle hemoglobin C disease (Hgb SC), sickle hemoglobin O disease (Hgb SO), or β-thalassemia (Hgb SThal). This study was prospectively approved by the University of Illinois at Chicago Institutional Review Board. All patients gave written informed consent to participate before enrollment. Data collection and analyses complied with the Health Insurance Portability and Accountability Act.

• **PATIENTS:** At each ophthalmology visit, patients were evaluated with Snellen best-corrected visual acuity (VA),

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TABLE 1. Baseline Patient and Eye Characteristics

Characteristic	All	Hgb SS	Hgb SC	Hgb SThal	*P* Value[a]
By patient					
Patients, n	67	38	22	6	
Age, y (±SD)	35.8 ± 11.5	35.1 ± 12.1	37.6 ± 11.2	35.6 ± 10.7	.724
Female, n (%)	50 (74.6)	25 (65.8)	19 (86.4)	5 (83.3)	.180
History of stroke, n (%)	12 (17.9)	9 (23.7)	2 (9.1)	1 (16.7)	.395
History of acute chest syndrome, n (%)	29 (43.3)	19 (50)	7 (31.8)	2 (33.3)	.318
History of avascular necrosis of any joint, n (%)	17 (25.4)	10 (26.3)	4 (18.2)	3 (50)	.281
History of hypertension, n (%)	14 (20.9)	8 (21.1)	6 (27.3)	0	.441
History of pulmonary hypertension, n (%)	7 (10.5)	6 (15.8)	1 (4.5)	0	.309
Glaucoma suspect, n (%)	5 (7.5)	3 (7.9)	0	0	.470
By eye					
Eyes, n	122	72	37	11	
Length of follow-up, y	3.8 ± 2.0	4.2 ± 1.9	4.0 ± 2.3	3.8 ± 1.6	.370
Refraction, diopters ± SD	−1.21 ± 1.96	−0.67 ± 1.44	−2.09 ± 2.38	−0.93 ± 1.00	.020
Intraocular pressure, mm Hg ± SD	15.7 ± 2.9	15.7 ± 3.0	15.6 ± 3.1	15.6 ± 2.4	.720
Cup-to-disc ratio ± SD	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	.750
Sickle retinopathy stage ± SD	2.0 ± 0.5	2.0 ± 0.4	2.1 ± 0.5	1.6 ± 0.8	.099

Hgb SC = sickle hemoglobin C disease; Hgb SS = sickle cell disease; Hgb Sthal = β-thalassemia; SD = standard deviation.
[a]*P* value of differences in the characteristics between the sickle hemoglobinopathy types.

Goldmann applanation tonometry, slit-lamp biomicroscropy, and dilated fundus examination. Data recorded included VA, refraction, IOP, optic nerve cup-to-disc ratio, and sickle retinopathy stage (Goldberg classification scale)[8] as determined by a retina specialist (J.I.L.). The Goldberg classification system includes: stage 0 = no retinopathy; stage 1 = peripheral arterial occlusion; stage 2 = peripheral arteriovenous anastomoses; stage 3 = neovascular and fibrous proliferation (sea fan); stage 4 = vitreous hemorrhage; and stage 5 = tractional retinal detachment. Patients with baseline diabetes mellitus or uncontrolled systemic hypertension (HTN) were excluded from this current study because of the potential confounding effects of these diseases on the optic nerve and retina. Eyes with lens or other ocular media opacities, history of laser or cryotherapy treatment, glaucoma, or clinical evidence of any other maculopathies were also excluded. Patients identified as glaucoma suspects based on enlarged cup-to-disc ratios were referred to the glaucoma clinic and included if they were not diagnosed as having glaucoma based on examination and visual field testing. If an eye received laser or retinal surgery during the follow-up period, data for that eye were excluded from the time of treatment and forward because of confounding effects of the treatment on RNFL thickness.

Medical history of sickle hemoglobinopathy type, stroke, acute chest syndrome (ACS) caused by vaso-occlusive crisis of the pulmonary vasculature, avascular necrosis (AVN) of any joint, HTN, and pulmonary HTN at enrollment and during the follow-up period were recorded from electronic chart review of the ophthalmology and Sickle Cell Clinic notes.

• **OPTICAL COHERENCE TOMOGRAPHY:** Patients underwent SD-OCT imaging (Spectralis; Heidelberg Engineering, Inc, Carlsbad, California, USA) of the optic nerve head at enrollment and subsequent visits, typically annually. In this longitudinal study, we included patients who had ≥1 follow-up RNFL scan at ≥1 year after enrollment. All images were obtained by trained ophthalmic photographers. In brief, a scan circle with a diameter of 3.45 mm was positioned manually at the center of the optic disc. For each scan, the signal strength, centration, and peripapillary RNFL segmentation were checked for accuracy and quality control; scans with signal strength <15 were excluded. The measurements used for analysis were obtained from the progression series in the native software, so all images in a series for each eye were aligned to a single reference scan. Data collected included thickness in the global area and the 6 regional sectors (nasal, inferonasal, inferotemporal, temporal, superotemporal, and superonasal).

• **DATA ANALYSIS:** Data analysis was performed with Stata software (version 12.1; StataCorp LP, College Station, Texas, USA). Analysis of variance was used to compare continuous variables among sickle subtypes and Fisher exact tests were used to compare categorical variables.

For each of the 6 regional sectors and in the global area, the rates of thinning per year and 95% confidence intervals (CIs) were estimated using linear mixed models with time

TABLE 2. Baseline Measurements in Each Peripapillary Retinal Nerve Fiber Layer Spectral-Domain Optical Coherence Tomography Sector

	Baseline Mean Thickness, μm ± SD				
Peripapillary Sector	All (N = 122)	Hgb SS (n = 72)	Hgb SC (n = 37)	Hgb SThal (n = 11)	*P* Value[a]
Global	101.8 ± 13.3	105.0 ± 13.4	98.7 ± 11.6	94.5 ± 11.2	.007
Nasal	74.8 ± 13.4	76.6 ± 12.6	71.3 ± 13.8	79.1 ± 13.5	.083
Inferonasal	124.4 ± 29.6	128.9 ± 28.4	122.3 ± 28.3	110.0 ± 35.5	.109
Inferotemporal	148.9 ± 25.7	154.8 ± 25.8	142.0 ± 21.9	137.0 ± 30.0	.012
Temporal	71.9 ± 11.3	71.6 ± 11.3	72.9 ± 11.8	71.4 ± 11.3	.849
Superotemporal	129.8 ± 22.6	133.4 ± 22.4	130.1 ± 19.7	109.2 ± 23.5	.004
Superonasal	116.4 ± 31.9	124.0 ± 34.7	108.6 ± 21.8	97.0 ± 29.3	.005

Hgb SC = sickle hemoglobin C disease; Hgb SS = sickle cell disease; Hgb Sthal = β-thalassemia; SD = standard deviation.
[a]*P* value of differences in the characteristics between the sickle hemoglobinopathy types.

TABLE 3. Rates of Peripapillary Retinal Nerve Fiber Layer Spectral-Domain Optical Coherence Tomography Thinning in Each Sector

Peripapillary Sector	Rate of Thinning (μm/year)	Standard Error (μm/year)	95% Confidence Interval (μm/year)	*P* Value[a]
Global	0.978	0.108	0.766 to 1.189	<.001
Nasal	1.038	0.119	0.804 to 1.272	<.001
Inferonasal	1.922	0.307	1.321 to 2.523	<.001
Inferotemporal	1.939	0.258	1.433 to 2.446	<.001
Temporal	0.680	0.080	0.524 to 0.836	<.001
Superotemporal	0.407	0.238	−0.060 to 0.873	.088
Superonasal	0.403	0.229	−0.060 to 0.876	.087

[a]*P* value that the rate of thinning is not 0.

as the independent variable and with patient and eye, which was nested in patient, as random effects. This model allowed analysis of both eyes from the same patient. All data are presented as positive rates of thinning representing decrease in thickness over time.

To assess the effects of a potential risk factor on the rate of thinning, the linear mixed model included time, the risk factor, and their interaction. A significant and positive interaction term indicated that the presence of a risk factor slowed down the rate of thinning. Conversely, a negative interaction indicated an increase in the rate of thinning in the presence of the risk factor. Risk factors assessed included baseline age, refraction, VA, IOP, cup-to-disc ratio, sickle retinopathy stage, glaucoma suspect status, and a history of stroke, ACS, AVN, HTN, and pulmonary HTN before enrollment or during the follow-up period. To determine the effect of systemic medical factors on the rates of thinning, rates were also estimated for eyes in the different subgroups, including sickle cell type (Hgb SS, Hgb SC, or Hgb SThal), history of stroke (Y/N), ACS (Y/N), AVN (Y/N), HTN (Y/N), pulmonary HTN (Y/N), and glaucoma suspect (Y/N).

RESULTS

A TOTAL OF 122 EYES OF 67 PATIENTS, WITH AN AVERAGE age of 35.8 ± 11.5 years and an average follow-up duration of 3.8 ± 2.0 years (range 1–8 years) were included in this study (Table 1). Most patients were female (50/67 [74.6%]). Of the 67 patients, the majority had Hgb SS (38 [56.7%]), followed by Hgb SC (22 [32.8%]) and Hgb SThal (6 [9.0%]). One patient (1.5%) had Hgb SO disease.

Eyes with Hgb SS and Hgb SC eyes had higher average sickle retinopathy stages when compared with Hgb SThal eyes, but this finding was not statistically significant (Table 1). Patients with Hgb SS had higher rates of stroke, ACS, AVN, and pulmonary HTN compared with those with Hgb SC, but these differences also did not reach statistical significance.

Table 2 shows the baseline measurements in each peripapillary RNFL SD-OCT sector, while Table 3 shows the rates of peripapillary RNFL SD-OCT thinning in each sector. The average global RNFL thickness at baseline was 101.8 ± 13.3 μm (Table 2). The rate of global RNFL thinning was 0.98 μm per year (95% CI

0.77–1.19 μm/year; Table 3; Figure). Thinning was fastest in the inferotemporal (1.94 μm/year [95% CI 1.43–2.45 μm/year]) and inferonasal sectors (1.92 μm/year [95% CI 1.32–2.52 μm/year]).

When the rates of thinning across the sickle cell types were compared, the rate was fastest in eyes with Hgb SS (1.09 μm/year [95% CI 0.84–1.34 μm/year]) and slowest in eyes with Hgb SThal (0.03 μm/year [95% CI −0.85 to 0.91]; Table 4), but these differences were not statistically significant.

There was a statistically significant association between the rate of global RNFL thinning and history of stroke (interaction coefficient = −0.92, $P < .001$), as well as rate of global thinning and history of HTN (interaction coefficient = 0.83, $P < .01$; Supplemental Table 5 [Supplemental Material available at AJO.com]). Patients with a positive history of stroke had statistically significantly faster rates of global thinning at 1.72 μm per year (95% CI 1.33–2.11 μm/year) compared with those without a history of stroke (0.79 μm/year [95% CI 0.55–1.03 μm/year]; Table 4). In contrast, eyes in patients with a history of HTN thinned at a rate of only 0.33 μm per year (95% CI −0.20 to 0.85 μm/year), despite being older on average (45.5 ± 10.9 years), compared with 1.14 μm per year (95% CI 0.91–1.36 μm/year; average age 32.8 ± 10.3 years, P of age <.001; Supplemental Table 6 [Supplemental Material available at AJO.com]) in those without a history of HTN.

There was no statistically significant association between rate of thinning in any sector and IOP, sickle retinopathy stage, history of AVN, history of pulmonary HTN, glaucoma suspect status, or baseline thickness.

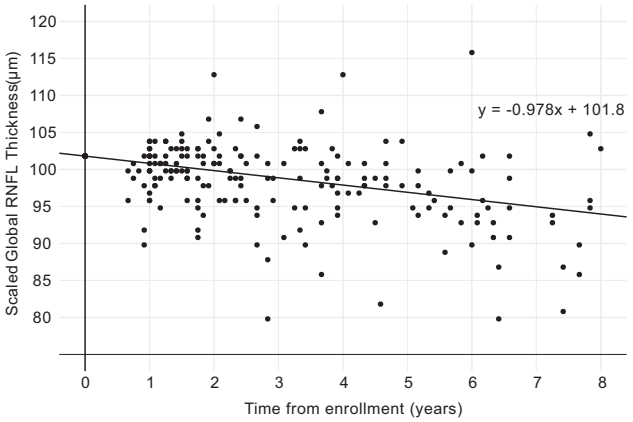

FIGURE. Plot of the scaled global retinal nerve fiber layer (RNFL) thickness at each timepoint from enrollment showing overall decrease in global RNFL thickness over time at an average slope of −0.978 μm per year. Each eye is set to a scaled baseline thickness of 101.8 μm, the average baseline global RNFL thickness.

DISCUSSION

WE REPORT AN AVERAGE GLOBAL RNFL THINNING RATE OF 0.98 μm per year in primarily African American patients with sickle cell hemoglobinopathies followed for an average of 3.8 years. This rate is faster than that previously reported in normal eyes (0.52–0.54 μm/year),[9,10] but comparable to that of older glaucoma suspect patients without visual field damage (0.82 μm/year).[11] Specifically, Miki and associates[11] reported a rate of thinning of 0.82 μm per year (average baseline global RNFL thickness 89.8 ± 11.7 μm) in 256 glaucoma suspect patients averaging 64.0 ± 11.3 years of age (31% of African descent) without visual field damage imaged on Spectralis SD-OCT. In normal eyes, Leung and associates[9] reported a rate of 0.52 μm per year (95% CI 0.17–0.86, average baseline global RNFL thickness 99.80 ± 8.58 μm) in 70 eyes of Asian subjects averaging 56.4 ± 6.7 years of age. Wu and associates[10] similarly estimated a rate of 0.54 ± 0.23 μm per year (average global RNFL thickness 95.9 ± 11.2 μm) in 75 eyes of 40 subjects averaging 51.7 ± 12.7 years of age, 42% of whom were of African descent. In these studies, measurements were obtained on the Cirrus SD-OCT imaging system (Carl Zeiss Meditec Inc., Dublin, California, USA) and might not be fully comparable to the Spectralis SD-OCT used in our study.

As these previous studies[9–11] examined patients who were 20 to 30 years older than our average study population age of 36 years, the rate of RNFL thinning observed in patients with sickle cell disease in our study may be faster than expected for healthy people of similar age. This interpretation, however, is significantly limited by the absence of a control group of healthy African American subjects. Although we intended to conduct longitudinal follow-up on the previously reported age- and race-matched control group,[4] too few subjects returned for reimaging to include for comparative longitudinal analysis. Analysis of the 7 eyes of 4 healthy African American volunteers averaging 34.7 ± 6.2 years of age at enrollment who were reimaged 5.3 ± 3.1 years later showed that the global RNFL thickness of the control eyes thinned at a rate of 0.17 ± 0.11 μm per year (95% CI 0.04–0.39 μm/year). This rate is slower than that of patients with sickle cell hemoglobinopathies, but further study is needed in a larger age- and race-matched cohort.

An increased rate of RNFL thinning may translate to an increased risk of glaucomatous visual field damage, because patients with sickle cell hemoglobinopathies also share multiple risk factors for glaucoma, including vascular ischemia and African descent. In the study by Miki and associates[11] of glaucoma suspect eyes followed for a median of 2.2 years, eyes that developed visual field damage (n = 40) had a global RNFL thinning rate of 2.02 μm per year, which was more than twice as fast as 0.82 μm per year in eyes that developed no visual field damage (n = 414).

TABLE 4. Rates of Global Peripapillary Retinal Nerve Fiber Layer Spectral-Domain Optical Coherence Tomography Thinning in Different Subgroups

Risk Factor (Eyes, n)	Rate of Thinning (μm/year)	Standard Error (μm/year)	95% Confidence Interval (μm/year)	*P* Value[a]
Sickle cell type				
Hgb SS (72)	1.091	0.126	0.843–1.338	<.001
Hgb SC (37)	0.954	0.233	0.498–1.410	<.001
Hgb SThal (11)	0.030	0.448	−0.848 to 0.907	.947
Stroke				
Yes (21)	1.717	0.198	1.329–2.106	<.001
No (101)	0.790	0.121	0.552–1.027	<.001
Acute chest syndrome				
Yes (54)	1.078	0.128	0.827–1.330	<.001
No (68)	0.889	0.167	0.561–1.217	<.001
Avascular necrosis of any joint				
Yes (31)	1.114	0.118	0.883–1.345	<.001
No (91)	0.941	0.134	0.679–1.202	<.001
Hypertension				
Yes (25)	0.325	0.268	−0.201 to 0.851	.226
No (97)	1.136	0.115	0.911–1.361	<.001
Pulmonary hypertension				
Yes (12)	0.975	0.172	0.638–1.312	<.001
No (110)	0.977	0.120	0.743–1.211	<.001
Glaucoma suspect				
Yes (7)	0.871	0.262	0.357–1.386	.001
No (115)	0.991	0.113	0.769–1.213	<.001

Hgb SC = sickle hemoglobin C disease; Hgb SS = sickle cell disease; Hgb Sthal = β-thalassemia.
[a]*P* value that the rate of thinning is not 0.

In our study, no patient developed glaucoma during the course of follow-up, and although glaucoma at presentation was an exclusion criterion for this study, no patient was excluded based on a history of glaucoma alone. In a small retrospective review of patients with sickle cell disease, the prevalence of glaucoma was likewise low (Crossan A, et al. IOVS 2014;55:ARVO E-abstract 4275). Another small case-control study found a similar prevalence of sickle cell trait between patients with open-angle glaucoma and matched control subjects.[12] The absence of a correlation between glaucoma and sickle cell disease may be related to the young age of the sickle cell patients studied, because glaucoma risk increases with age.[13] Although the patients in our study might be expected to develop glaucoma at younger ages, they remain relatively young to have glaucoma.

Our analyses suggest that controlled HTN is potentially protective against RNFL thinning in patients with sickle cell hemoglobinopathies as evidenced by the statistically significantly slower rate of thinning in those with a history of controlled HTN. In contrast, a large population-based study reported by the European Eye Epidemiology consortium found that a history of HTN was associated with reduced RNFL thickness.[14]

The role of blood pressure (BP) on glaucoma risk has been examined with mixed results. Specifically, lower systolic BP was associated with a reduced risk of progression and incidence of open-angle glaucoma in the Early Manifest Glaucoma Trial[15] and Barbados Eye Studies,[13] which studied a population of African descent closely resembling our patients. In contrast, HTN and increased BP were associated with an increased glaucoma risk in the Blue Mountains Eye Study[16] and among older subjects in the Baltimore Eye Survey.[17] Ocular perfusion pressure, which is the relationship between systemic BP and IOP, reflects the vascular status of the optic disc and has been hypothesized to play a role in the development of glaucoma.[18] It is possible that in our study population predisposed to vaso-occlusive disease, systemic HTN may be protective in maintaining vascular flow and higher perfusion pressure around the optic nerve and thus slowing RNFL thinning. Of note, patients with uncontrolled HTN were excluded from the analysis, and therefore our results cannot be generalized to such patients.

In addition, our study demonstrates that a history of stroke is associated with a statistically significantly increased rate of RNFL thinning, which is consistent with findings from the European Eye Epidemiology consortium that stroke is associated with decreased peripapillary RNFL thickness.[14] The association between stroke and glaucomatous optic neuropathy that leads to RNFL thinning has been described in several large studies.[19–22]

These findings are also consistent with the vascular theory of glaucomatous optic neuropathy, where blood vessel disease leads to ischemic optic nerve damage.[23] Eyes with sickle cell disease may be susceptible to ischemia in addition to reperfusion damage with mild, repeated episodes of vaso-occlusion surrounding the optic nerve inducing oxidative stress.[23] The history of stroke in certain patients with sickle cell disease may represent a systemic tendency toward vaso-occlusive events that may involve the optic nerve with subsequent RNFL thinning.

In regard to topographic variation, we found the rate of thinning to be fastest in the inferotemporal sector, which is a pattern that has been previously described in both glaucoma patients and healthy control subjects by See and associates[24] using confocal scanning laser tomography. The inferotemporal neuroretinal rim, therefore, may be more susceptible to thinning, but further research is needed to determine the implication of this finding as a predictor of global thinning. Consistent with previous reports, the macular OCTs in patients with sickle cell disease have been previously described to have focal temporal retinal macular thinning.[4,25,26] This finding is thought to be caused by increased risk for terminal arteriolar occlusions along the temporal horizontal raphe, which is a watershed zone. The RNFL layers from these areas contribute to the superior and inferior peripapillary RNFL, which might be expected to thin at a faster rate with repeated occlusions.

The strengths of this study include the longitudinal prospective nature of the study design and the long follow-up of ≤8 years. This study is, however, notably limited by lack of an age- and race-matched control group. These findings may also not reflect the natural history of RNFL thinning in eyes with advanced sickle retinopathy. Most of our patients had stage 2 disease and those who developed stage 3 (neovascularization) or greater had their data censored if they underwent intervention, such as laser, which may thin the RNFL.[27]

Through this longitudinal study of peripapillary RNFL thinning in patients with sickle cell hemoglobinopathies, we show that the rate of thinning increases in patients with a history of stroke and decreases in those with a history of well-controlled HTN. These findings may help guide management and screening of these patients, who may be at increased risk of glaucomatous optic neuropathy. Future studies will follow these patients into older adulthood in order to assess the actual impact of peripapillary thinning on development of glaucoma and visual function.

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