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Glaucoma Cascade Screening in a High Risk Afro-Caribbean Haitian Population: A Pilot Study

Ta C. Chang, MD, Linda Celestin, BS, COA,* Elizabeth A. Hodapp, MD,* Alana L. Grajewski, MD,* Anna Junk, MD,* Adam L. Rothman, MD,* Eric R.H. Duerr, MD,* Swarup S. Swaminathan, MD,* Steven J. Gedde, MD,* Terri L. Young, MD,† Janey Wiggs, MD, PhD,‡§ Mildred M.G. Olivier, MD,‖ Raquel Quintanilla, MD,* Esdras Arrieta, MD,* Eleonore J. Savatovsky, MD, PhD,* Elizabeth A. Vanner, PhD,* and Richard K. Parrish, MD**

Précis: Glaucoma cascade screening in first-degree relatives (FDRs) of young Haitian glaucoma patients had high yield for diagnosing manifest and suspected glaucoma in 30.8% of those screened despite modest participation.

Purpose: To evaluate the outcomes of glaucoma cascade screening in FDRs (parents, siblings, and offspring) of Haitian juvenile open-angle glaucoma (JOAG) patients.

Patients and Methods: Consecutive index patients (Haitians with JOAG) were identified, and the number/type of FDRs residing in South Florida were recorded. These FDRs were invited for free glaucoma screening, which included a comprehensive ophthalmic exam, gonioscopy, automated visual field testing and optical coherence tomographic analysis of the retinal nerve fiber layers. FDR characteristics and clinical findings from screening are reported.

Results: A total of 77 FDRs were invited, 26 (33.8%) agreed to undergo screening (18 females, 9 males), which revealed 2 (7.7%) with manifest glaucoma (mean age 77.5 y; one of whom was previously unaware of his glaucoma diagnosis), 6 (23.1%) with suspected glaucoma (mean age 29.8 ± 18.3 y), and 18 (69.2%) without manifest or suspected glaucoma (mean age 37.2 ± 21.8 y). Siblings of index patients were least likely to participate in cascade glaucoma screening when compared with index patients' parents or offspring. FDR eyes with manifest glaucoma had significantly worse best-corrected visual acuities, higher intraocular pressures, thinner central corneal thicknesses, and thinner circumferential papillary retinal nerve fiber layer thicknesses than those without glaucoma.

Conclusion: Glaucoma cascade screening of Haitian JOAG patients' FDRs revealed that 30.8% had suspected or manifest glaucoma. Future efforts centered on provider-initiated recruitment and improving public glaucoma awareness and education may increase screening participation.

Key Words: juvenile open angle glaucoma, first-degree relatives, Afro-Caribbean Haitian, cascade screening participation

(*J Glaucoma* 2022;31:584–589)

Glaucoma is the leading cause of irreversible blindness worldwide, and its prevalence varies by ethnicity and geography.[1,2] Individuals of African and Afro-Caribbean descent are at high risk of developing glaucoma.[3] The prevalence of primary open angle glaucoma (POAG) in Haiti is estimated to be between 14.2% and 19.1%,[4,5] in contrast to 10.3% in the neighboring island of Barbados,[3] or 1% to 2% in individuals of European descent.[6] In affected Haitians, the disease is diagnosed at an average age of 52.3 years, and 35.1% present with end-stage disease.[3,4] Two cross-sectional studies underscore this high prevalence and early-onset of POAG among individuals of Haitian descent: the first identified intraocular pressure (IOP) over 25 mm Hg in 11.3% of Haitians aged 30 to 49 years (in contrast to 3.6% among American Caucasians), while the second found 5.3% of Haitians living in South Florida younger than 40 years to have suspected or confirmed glaucoma.[7–9] These findings suggest that young Afro-Caribbean Haitians bear a high POAG burden during their most productive working years. Many may in fact fall under the classification of juvenile open angle glaucoma (JOAG) with disease onset before age of 40 years. JOAG is highly heritable[10–12] with several known Mendelian loci (including *MYOC*, *CYP1B1*, *LTBP2*, *OPTN*, and *TBK1*),[13–18] and first-degree relatives (FDRs) of individuals with glaucoma have a 22% lifetime risk for glaucoma, compared with 2.3% among others.[19] Taken together, the FDRs of Haitian JOAG patients comprise a very high-risk group for developing glaucoma. Cascade screening—the systematic examination of relatives

Received for publication September 11, 2021; accepted January 12, 2022.

From the *Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, FL; †Department of Ophthalmology and Visual Sciences, University of Wisconsin-Madison, Madison, WI; ‡Department of Ophthalmology, Massachusetts Eye and Ear, Harvard Medical School; §Ocular Genomics Institute, Harvard Medical School, Boston, MA; and ‖Rosalind Franklin University of Medicine and Science/The Chicago Medical School, North Chicago, IL.

The project was supported by NIH Center Core Grant P30EY014801, Research to Prevent Blindness Unrestricted Grant, 2021 Glaucoma Research Foundation Shaffer Grant and Grant Number UL1TR002736, Miami Clinical and Translational Science Institute, from the National Center for Advancing Translational Sciences and the National Institute on Minority Health and Health Disparities. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

Disclosure: The authors declare no conflict of interest.

Reprints: Ta C. Chang, MD, 900 NW 17th Street, 450N, Miami, FL 33136 (e-mail: t.chang@med.miami.edu).

DOI: 10.1097/IJG.0000000000001996

of individuals who manifest a highly heritable condition—has been used successfully to identify many presymptomatic diseases, but has not been previously applied as means for early glaucoma detection in the Haitian community. In this pilot study, we examined for the first time the findings of glaucoma cascade screening in FDRs of Haitian JOAG patients living in the United States.

PATIENTS AND METHODS

The study protocol was approved by the University of Miami Miller School of Medicine Institutional Review Board. It was fully compliant with the requirements of the United States Health Insurance Portability and Accountability Act, and adherent to the tenets of the Declaration of Helsinki.

Recruitment

Beginning in September 2019, consecutive index Haitian JOAG patients from the Bascom Palmer Eye Institute Glaucoma Service were approached for cascade screening recruitment. The ascertainment criteria for JOAG is defined below, and all index patients had manifest POAG presented before the age of 40 years. The number and relationships of all FDRs (eg, parents, full-siblings, and offspring) living in South Florida were recorded. The index patients were given the business card of the principal investigator (T.C.C.) providing contact information, and were asked to invite their South Floridian FDRs (both adults and children) by word-of-mouth for cascade screening by contacting the principal investigator via a telephone call or email. Once contacted, a dedicated Haitian cultural liaison/research coordinator (L.C.) assessed the FDRs by phone for their willingness to participate in a free cascade screening visit. If willing, they were scheduled to be evaluated in a clinic on a day of their choosing.

Cascade Screening

Written informed consent was obtained in English and/or Haitian Creole by one of the investigators, with the cultural liaison/research coordinator translating as needed. During the screening visit, study participants underwent a comprehensive ophthalmologic examination by a fellowship-trained glaucoma specialist (T.C.C., A.L.G. or A.L.R.). The examination included manifest refraction, tonometry, pachymetry, gonioscopy, optical coherence tomographic (OCT) analyses of the circumferential papillary retinal nerve fiber layer (RNFL) thickness (Zeiss Cirrus HD-OCT; Carl Zeiss Meditec Inc., Dublin, CA), and automated visual field testing (Humphrey Field Analyzer, protocol 24-2 or 24-2C, stimulus size III or V based on best-corrected visual acuity; Carl Zeiss Meditec Inc.). At the conclusion of the cascade screening visit, the FDR was categorized as having either "manifest glaucoma," "suspected glaucoma," or "no glaucoma," based on the criteria outlined below. All examined participants were referred for long-term ophthalmic care based on clinical findings.

Study Definitions

In an individual aged 18 or more years, 3 findings were considered (adopted from *Clinical Decisions in Glaucoma, 2nd Edition*[20]): (1) IOP >21 mm Hg; (2) focal RNFL defect by OCT or optic disc notching on direct/indirect disc examination; and (3) visual field defect corresponding to the RNFL defect and/or disc notching. If all 3 findings were present in 1 or both eyes, the participant was categorized as having "manifest glaucoma." If no findings were present, the participant was categorized as having "no glaucoma," while the remaining (some but not all 3 conditions) were categorized as "suspected glaucoma."

In an individual aged under 18 years, 5 findings were considered (adopted from the Childhood Glaucoma Research Network diagnostic criteria[21]): (1) IOP >21 mm Hg; (2) cup/disc ratio asymmetry by 0.2 or more; (3) focal thinning of the optic disc rim on direct/indirect disc examination or as noted on OCT RNFL; (4) presence of Haab striae, corneal edema, or increased corneal diameter; and (5) visual field defect. If 2 or more findings were present in 1 or both eyes, the participant was categorized as having "manifest glaucoma." If no findings were present, the participant was categorized as having "no glaucoma," while the remaining were categorized as "suspected glaucoma."

Data Collection

For all participants, age, sex, and travel distance data were collected. The travel distances between the participants' residences and the Bascom Palmer Eye Institute (the Miami and Plantation campuses were where screenings took place) were calculated using a free online map tool (https://www.google.com/maps). For index patients, the age of glaucoma onset, and the total number of laser and/or incisional glaucoma procedures (including revision of prior glaucoma procedures) were recorded. For FDRs, the best-corrected visual acuity (BCVA), IOP, central corneal thickness (CCT), and OCT-RNFL thickness measurements were collected. Legal blindness was defined as BCVA of 20/

TABLE 1. Characteristics of Index Juvenile Open Angle Glaucoma Patients With Eligible First-degree Relatives

	Index JOAG Patients (N = 18)		
	With Unscreened FDR (n = 4)	With Screened FDR (n = 14)	*P*
Age (y)	47.8 ± 20.4	43.7 ± 22.0	0.7477*
Female, n (%)	2 (50.0)	8 (57.1)	1.0000†
Age of glaucoma onset (y)	18.3 ± 14.1	24.3 ± 11.4	0.2789‡
Proportion who are legally blind, n (%)	2 (50)	7 (50)	1.0000†
Number of prior glaucoma procedures	2.0 ± 1.2	1.1 ± 1.2	0.2177‡
Distance from hospital (miles)	11.0 ± 7.2	31.6 ± 37.5	**0.0437**‡
Number of available FDR	4.0 ± 1.2	4.4 ± 2.7	0.8714‡

Bold value indicates statistically significant.
*Independent samples *t* test.
†Fisher exact test.
‡Mann-Whitney Wilcoxon Rank-Sum test.
FDR indicates first-degree relatives; JOAG, juvenile open angle glaucoma.

200 Snellen-equivalence or worse in the better-seeing eye and/or a visual field of 10 degree or worse. Snellen visual acuities were converted to logarithm of the minimum angle resolution (LogMAR) equivalents, with 2 and 3 representing count fingers and hand motion vision, respectively.

Statistical Analysis

Categorical variables are presented as frequencies and percentages, and continuous variables are presented as means ± SD, as well as 5-number summaries (5NS: minimum, first quartile, median, third quartile, maximum). For person-level attributes, group differences were compared (1) with independent samples *t* tests for continuous, normally distributed variables, (2) for continuous, non-normally distributed variables with the (a) Mann-Whitney Wilcoxon Rank-Sum test (when there were 2 groups) or with the (b) Kruskal-Wallis test (when there were 3 groups) which used the Dwass, Steel, Critchlow-Fligner Method for pairwise post hoc comparisons, and (3) for categorical variables with the (a) χ^2 or (b) Fisher exact test when the assumptions of the χ^2 test were invalid. For eye-level attributes, group differences were compared with methods to account for the correlation between the 2 eyes of each subject (1) for continuous, normally distributed variables using generalized estimating equations and (2) for continuous, non-normally distributed variables using the macro *cluswilcox* (downloaded June 14, 2021 from https://sites.google.com/a/channing.harvard.edu/bernardrosner/channing/incorporating-cluster-effects-for-the-wilcoxon-rank-sum-test-1/cluswilcox/purpose?authuser=0). A *P*-value <0.05 was considered statistically significant.

RESULTS

A total of 26 consecutive, non-related index Haitian JOAG patients (12 females, 14 males) were approached to recruit their FDRs for cascade screening. They had a mean age of 48.2 ± 19.0 years (5NS: 12, 38.5, 51, 61.8, 78 y), with a mean age of disease onset of 25.5 ± 11.9 years (5NS: 8, 14, 29, 37.3, 40 y), and 1.5 ± 1.4 prior glaucoma procedures. Fourteen (53.8%) were legally blind, and 8 (30.8%) had no FDRs residing in South Florida. The remaining 18 had 77 FDRs available for screening (a mean of 4.3 FDR per index patient).

Of the 77 available FDRs, 39 (50.6%) responded to recruitment and were contacted by the Haitian liaison/research coordinator, and 26 (33.8%) from 14 index patients completed screening. Compared with the 4 index patient from whom we were unable to recruit any eligible FDRs for cascade screening, the 14 from whom we successfully recruited FDRs had no significant differences in age, sex, age of glaucoma onset, proportion with legal blindness, number of prior glaucoma procedures, and number of available FDRs, but the index patients who successfully recruited FDRs had greater residence distance from the screening site (Table 1).

TABLE 2. First-degree Relatives' Relationship to Index JOAG Patients

	FDR of Index JOAG Patients (N = 77)	
Relationship	**Screened, N (%)***	**Unscreened, N (%)**
Sibling	5 (15.2)	28 (84.8)*
Parent	10 (52.6)	9 (47.4)*
Offspring	11 (44.0)	14 (56.0)*
Total	26	51

*χ^2 test: sibling versus parent, $P = 0.0041$, sibling versus offspring, $P = 0.015$.

FDR indicates first-degree relatives; JOAG, juvenile open angle glaucoma.

Table 2 shows the familial relationship to the index case of screened and unscreened FDRs. Significantly fewer siblings were screened compared with the parents and offspring of index patients ($P = 0.0041$ and 0.015, respectively).

Of 26 FDRs (18 females, 69.2%) who completed cascade screening, the mean age was 38.6 ± 23.3 years (5NS: 6, 16.25, 33.5, 59, 90), with a mean distance traveled of 34.6 ± 13.4 km, which was not significantly different from that traveled by the index patients (60.8 ± 108.8 km, $P = 0.2575$). Manifest glaucoma, suspected glaucoma and no glaucoma were noted in 2 (7.7%), 6 (23.1%), and 18 (69.2%) FDRs screened, respectively (Table 3). Both FDRs with manifest glaucoma had prior eye examinations, although only one was aware of his manifest glaucoma status (50.0%). Of the 6 FDRs with suspected glaucoma, 2 (33.3%) had not had prior eye examinations.

The mean BCVA, IOP, refraction, CCT, and OCT-RNFL thickness of screened FDR eyes are summarized in Table 4. Eyes diagnosed with glaucoma had higher IOP, and thinner RNFL, which reflected our study definition for glaucoma. Furthermore, those eyes also had significantly worse BCVA and thinner CCT (Table 4). One of the patients with manifest glaucoma also had visually significant cataracts contributing to decreased BCVA.

Among the 13 FDRs who responded to recruitment but ultimately did not attend cascade screening, the reasons for not attending screening included being unable to take time off of work (despite offering screening clinic on both weekdays and weekends), transportation issues, and lack of interest in screening.

DISCUSSION

In this pilot study, we examined the cross-sectional findings of the glaucoma cascade screening in a large cohort

TABLE 3. Demographics of the First-degree Relatives Who Underwent Glaucoma Cascade Screening

	Overall, N = 26	No Glaucoma, N = 18	Suspected Glaucoma, N = 6	Manifest Glaucoma, N = 2
Age (y)	38.6 ± 23.3	37.2 ± 21.8*	29.8 ± 18.3*	77.5 ± 17.7*
Female, N (%)	18 (69.2)	14 (77.8)	4 (66.7)	0
Relationship to index patient, N (%)				
Parent	10 (38.5)	7 (38.9)	1 (16.7)	2 (100)
Sibling	5 (19.2)	3 (16.7)	2 (33.3)	0
Offspring	11 (42.3)	8 (44.4)	3 (50.0)	0

*Kruskal-Wallis test (Dwass, Steel, Critchlow-Fligner Method for pairwise comparisons); age comparisons—no glaucoma versus manifest glaucoma $P = 0.1414$, no glaucoma versus suspected glaucoma $P = 0.8548$, suspected glaucoma versus manifest glaucoma $P = 0.1122$.

TABLE 4. Clinical Characteristics of the First-degree Relatives Who Underwent Glaucoma Cascade Screening

	Overall, N = 52 Eyes	Group 1 No Glaucoma, N = 36 Eyes	Group 2 Suspected Glaucoma, N = 12 Eyes	Group 3 Manifest Glaucoma, N = 4 Eyes	*P* for Group Comparisons
BCVA LogMAR (approximate Snellen equivalence)	0.12 ± 0.34 (20/27)	0.036 ± 0.059 (20/22)	0.15 ± 0.34 (20/29)	0.81 ± 0.86 (20/128)	Macro cluswilcox* *P* = 0.9539 (1 vs. 2) ***P* = 0.0065 (1 vs. 3)** *P* = 0.0735 (2 vs. 3)
IOP (mm Hg)	16.8 ± 4.1	16.2 ± 2.0	14.8 ± 2.6	27.5 ± 7.0	Macro cluswilcox* *P* = 0.2374 (1 vs. 2) ***P* = 0.0270 (1 vs. 3)** ***P* = 0.0461 (2 vs. 3**
SEQ refraction (D)	−1.47 ± 3.29	−1.08 ± 2.71	−3.25 ± 4.63	0.38 ± 0.60	Macro cluswilcox* *P* = 0.1885 (1 vs. 2) *P* = 0.5200 (1 vs. 3) *P* = 0.2153 (2 vs. 3)
CCT (μm)	528.3 ± 53.8	528.1 ± 46.5	560.1 ± 42.8	434.0 ± 29.0	GEE† model *P* = 0.1029 (1 vs. 2) ***P* < 0.0001 (1 vs. 3)** ***P* < 0.0001 (2 vs. 3)**
OCT RNFL thickness (μm)	95.7 ± 14.1	102.2 ± 6.8	87.4 ± 8.6	62.5 ± 17.4	Macro cluswilcox* ***P* = 0.0032 (1 vs. 2)** ***P* = 0.0198 (1 vs. 3)** *P* = 0.0970 (2 vs. 3)

Bold values indicates statistically significant.

*Macro *cluswilcox* (nonparametric analysis accounting for the correlation between 2 eyes of a person) downloaded June 14, 2021 from https://sites.google.com/a/channing.harvard.edu/bernardrosner/channing/incorporating-cluster-effects-for-the-wilcoxon-rank-sum-test-1/cluswilcox/purpose?authuser=0.

†Generalized estimating equations model.

BCVA indicates best-corrected visual acuity; CCT, central corneal thickness; IOP, intraocular pressure; LogMAR, logarithmic minimum angle of resolution; OCT, optical coherence tomography; RNFL, retinal nerve fiber layer; SEQ, spherical equivalence.

of FDRs of Afro-Caribbean Haitians with JOAG. The index patients had an early age of disease onset, a large proportion of legal blindness and a large number of available FDRs, which makes this population suitable for cascade screening.[22] Prior attempts at glaucoma cascade screening have mostly been performed on glaucoma associated with known genetic mutations.[23–25] One singular study of high-risk family members of heterogeneous Afro-Caribbean glaucoma patients based in the United Kingdom identified 203 index patients with 248 eligible FDRs, 18 (7%) of whom completed cascade screening. The current pilot study, the largest of its kind to the authors' knowledge, screened 33.8% of available FDRs, a nearly 5-fold increase in participation compared to the prior study.[26] This increased yield may be related to our use of a dedicated cultural liaison and research coordinator to communicate with our exclusively Haitian patients, and to the availability of weekend screening clinics.

We do not know why we were able to recruit FDRs from some index patients but not from the others, but the index patients' visual functions, age, age of glaucoma onset, and sex were not significant factors. On average, index patients with screened FDRs had traveled longer distances than those without screened FDRs, which may suggest a biased recruitment of FDRs from families with more transportation resources. It is possible that a larger proportion of the screened FDRs had previously accompanied the index patients to their glaucoma clinic appointments, and thus had more familiarity with clinical facilities and staff than those who were not screened. Similarly, if an eligible FDR overheard or participated in a dialogue between the physician and the index patient about cascade screening, they may have been more willing to participate, as cascade screening invitations that come directly from screeners (rather than indirectly via word-of-mouth from index patients) showed greater acceptance rates.[27] FDRs who were siblings of the index patients were less likely to be screened compared with parents and offspring. Prior studies of glaucoma patient FDRs have shown that, compared with parents and offspring, siblings of index patients had the lowest glaucoma awareness/knowledge,[28] which is one of the main factors affecting screening participation and may explain our observation.[29]

In our screened FDR cohort, 30.8% had suspected or manifest glaucoma (23.1% and 7.7%, respectively). This finding is consistent with prior studies,[5,7–9] and is higher than in individuals of European descent.[6] Half of the FDRs with manifest glaucoma were unaware of their glaucoma status, which is similar to the proportion reported elsewhere,[30,31] whereas one-third of FDRs with suspected glaucoma had not had prior eye examinations. Taken together, these findings suggest that open angle glaucoma in FDRs of Haitian JOAG index patients may be underdiagnosed, underscoring the value of glaucoma cascade screening efforts, particularly in areas with high Afro-Caribbean populations, such as the Caribbean nations, the United Kingdom, and other parts of Europe as well as the United States.

Unsurprisingly, eyes with manifest glaucoma had higher IOP and thinner RNFL compared with those without manifest glaucoma, which reflected the diagnostic criteria used in this study. Eyes with manifest glaucoma also had significantly thinner corneas, which suggests that CCT may be an important risk factor for developing glaucoma in this cohort. The mean CCT in the overall study cohort was similar to those previously reported in Afro-Caribbean populations and was thinner than that of non-Hispanic Caucasians.[32–34] Thinner CCT has been identified as an independent risk factor for open angle glaucoma in the Barbados Eye Study,[34] and FDRs with suspected glaucoma and thin CCT may be at particularly high risk for developing glaucoma.

After the initial word-of-mouth invitation extended by the index patients, approximately half of eligible FDRs responded to the one-time invitations for cascade screening. While ophthalmic screening participation can be highly variable, prior studies have shown that neither financial incentives nor reminder text messages have increased screening participation,[35–37] whereas increased patient knowledge of disease consequences may increase participation.[29,36,38] FDRs of glaucoma patients have low awareness of the need for screening, and educational videos may be more effective than written pamphlet material in improving screening participation.[28,39] Hence, a reasonable approach to increase glaucoma cascade screening participation may be to incorporate—in the index patients' written after-visit summaries following a clinic appointment—a scannable matrix barcode linked to a sharable, online educational video to facilitate recruitment. Approximately two-thirds of FDRs who responded to recruitment followed through with screening, and this completion rate may be attributed to having a cultural liaison as an interface, which bypassed language and cultural barriers. While many reasons for screening failure such as lack of interest or failure to respond to follow-up phone calls/texts may be difficult to address, other factors such as transportation difficulties may be mitigated with resources such as public transportation and/or ride-sharing vouchers.

This study has several limitations. First, since no data (other than a blood relationship to the index patient) were available for FDRs who did not respond to recruitment, we were unable to identify FDR-level characteristics that would predict screening participation. Second, despite being the largest reported Afro-Caribbean cohort to have participated in glaucoma cascade screening, our pilot sample size was modest, partly attributed to COVID-19 related travel restrictions. Third, our index patients consisted of those diagnosed with JOAG, and the FDR profile and screening participation may have differed had we included older Haitian POAG patients. However, since the heritability of JOAG is greater than POAG, our FDR cohort represents the highest risk stratum in the absence of confirmed genetic diagnoses. In summary, in this pilot study, glaucoma cascade screening of FDRs of Afro-Caribbean Haitians with JOAG using a word-of-mouth method had high yield despite modest participation, revealing approximately one-third of those screened to have suspected or manifest glaucoma. This makes glaucoma cascade screening in high-risk FDRs a potentially useful public health approach in early glaucoma detection. Future efforts to increase participation may include increasing provider-initiated recruitment, targeted recruitment of the index patients' siblings and improving public glaucoma awareness.

ACKNOWLEDGMENTS

The authors wish to thank Bryan and Julie Butzow for their generous philanthropic support of The Samuel & Ethel Balkan International Pediatric Glaucoma Center. Their benevolence towards our Caribbean neighbors helped to make this research possible.

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