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Cascade screening for glaucoma in high-risk family members of African-Caribbean glaucoma patients in an urban population in London

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ABSTRACT

Background/aims Cascade screening has been used successfully in relatives of patients with inherited cancers and other genetic diseases to identify presymptomatic disease. This study was designed to examine if this approach would be successful in a high-risk group: first-degree relatives (FDR) of African-Caribbean glaucoma patients resident in London.

Methods African-Caribbean patients (probands) with glaucoma from an inner London hospital setting in a deprived area were asked to disseminate personalised information to their FDR over the age of 30 and to arrange a free hospital-based screening. Data collected, including optical coherence tomography imaging, were reviewed by a glaucoma specialist and if glaucoma was diagnosed or suspected, local specialist referral via family doctor was made.

Results 203 probands were recruited from glaucoma clinics. 248 suitable FDR were identified as potentially eligible to attend screening. 57 (23%) FDR made contact with the research team of whom 18 (7%) attended a subsequent screening visit. No patients were diagnosed with glaucoma; one participant was diagnosed as glaucoma suspect. Reasons for poor uptake included reluctance by probands to involve their family members, and retirees spending significant time abroad.

Conclusion Cascade screening of FDR of African-Caribbean glaucoma patients in inner city London was unsuccessful. Research confidentiality guidance prohibiting research teams directly contacting family members was a barrier. Greater community engagement, community-based screening and permission to contact FDR directly might have improved uptake.

INTRODUCTION

Glaucoma is the leading cause of irreversible blindness, accounting for approximately 8% of blindness globally.¹ Blindness due to glaucoma has been found to be four to five times more common among people of African descent (PAD) compared with people of European descent.^{2,3} Glaucoma affects over 4% of the PAD adult population, compared with 2% in those of European ancestry (and 16% in subjects over 70 years compared with 6%).⁴ PAD typically develop glaucoma almost a decade earlier than other ethnic groups with Primary Open Angle Glaucoma (POAG),⁵ and are more likely to have advanced field loss at presentation. In the UK, PAD are 4.5 times more likely to have a late presentation than their white counterparts.⁶ A faster rate

of disease progression is also associated with this cohort of patients.⁷ Glaucomatous damage has a significant impact on morbidity and quality of life. It affects many aspects of daily living including mobility, increased risk of falls, driving ability, difficulty reading, facial recognition as well as anxiety and depression.⁸ If glaucoma is detected early, interventions can be made which preserve vision and reduce the chance of any further loss of sight.

Glaucoma screening for the entire population is not cost-effective, and lacks sensitivity and specificity.⁹ Most population-based epidemiology studies show half the patients with glaucoma are undiagnosed. Screening at-risk groups might be more effective. One of the major risk factors for glaucoma is family history: the Glaucoma Inheritance Study in Tasmania identified 60% of glaucoma as familial, but also that 25% of people with glaucoma are unaware of their family history.¹⁰ Familial glaucoma is more severe than sporadic glaucoma, and first-degree relatives (FDR) are 10 times more likely to develop glaucoma than the general population.¹¹ Family history is also an important risk factor in PAD.¹²

The term cascade screening is typically used to describe the systematic process of screening close relatives of a patient with an inherited disease. It has been widely used for genetic cancers such as Hereditary Breast and Ovarian Cancer Syndrome, Lynch syndrome (hereditary non-polyposis colorectal cancer) and in non-cancer-related diseases such as familial hypercholesterolaemia.^{13–15} Cascade screening has been used successfully in relatives of patients with advanced glaucoma who have Myocilin gene mutations.¹⁶ A programme in Tasmania identified undiagnosed glaucoma in 5% of FDR of glaucoma patients.¹⁷ Given the high prevalence of glaucoma in PAD and the importance of family history, the aim of this study was to examine if a cascade screening approach would be successful in diagnosing unidentified glaucoma in a high risk group: FDR of African-Caribbean glaucoma patients in an urban British population.

MATERIALS AND METHODS

The study recruited African-Caribbean adult glaucoma patients (probands) from St Thomas' Hospital glaucoma clinics. The hospital is set in Lambeth and Southwark local authorities, deprived boroughs in London; 37% of residents are of black and minority ethnicity, with the large



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majority being of West African and Caribbean origins. PAD were self-defined as originating from any of the black racial groups of Africa or the Caribbean. Glaucoma was defined as POAG, with a typical optic neuropathy (optic disc cupping with cup:disc ratio >0.6) and characteristic visual field such as arcuate, hemifield and nasal step defects with corresponding optic disc cupping. Consultants and their teams at the glaucoma services identified potential probands at their routine glaucoma appointments.

Probands who expressed interest in the study met a member of the study team for further information after their clinic appointment. Written informed consent was obtained after a full explanation of the purpose and consequences of this study. The probands were asked to list FDR (parents, siblings and children) over the age of 30 and living in the UK who would be able to attend a screening visit. The probands were then given personalised information leaflets about glaucoma for each eligible FDR, and details of the free screening programme. FDR were invited to telephone, email or write to the study team to arrange a screening visit at a time that suited them. Out of hours screening appointments were offered in an attempt to improve recruitment of those who were unable to take time off work to attend.

Probands consented to be reminded to speak to their family members about the study if their relatives did not make contact with the study team. If no contact from the relatives was made after 3 weeks, a follow-up telephone call was made to the proband to remind them to pass information on to their relatives. After a further 3 weeks with no contact being made, another follow-up call was made to the proband. In both calls, it was stressed that if the relatives were not able to attend screening, then they should get their eyes tested at a local optician for glaucoma.

Once the relatives made contact with the study organisers with a view to participating, they agreed a mutually convenient screening visit date and time at St Thomas' Hospital. After consenting, a trained research assistant performed a series of eye tests to screen for glaucoma. These included: visual acuity (standard logMAR visual acuity chart), autorefractometry, intraocular pressure (IOP) and central corneal thickness (CCT; Visionix, Luneau Technology Operations, Pont-de-l'Arche, France), optical coherence tomography (OCT) scanning to measure peripapillary retinal nerve fibre layer thickness and disc/retinal photography (iVue and iCam, Optovue, Fremont, California, USA). Screening visual fields were performed with the Humphrey Frequency Doubling Technology Perimeter (Carl Zeiss Meditec, Jena, Germany), and any abnormal fields were confirmed with 24-2 threshold perimetry. Gonioscopy was not performed. An optional blood sample for DNA extraction was also requested for future genetic studies.

The results were presented to the glaucoma specialist who reviewed OCT scans, optic disc images, visual fields and other information (IOP, CCT, autorefractometry) to determine if the patient had glaucoma. If the tests indicated glaucoma or glaucoma suspect, the patient's family doctor would be informed so a referral to a local eye service could be made (with prior consent). FDR with a previous diagnosis of glaucoma were invited to participate in the study. If this was the case, the patient would still attend the screening visit to consent and complete the questionnaire but would not have to complete the eye tests. With consent, this information would be extracted from the patients' medical records.

While no power calculations were performed for this study, the Tasmanian study by Staffieri *et al*¹⁷ examined 211 FDR of 133 available probands, and pilot data for our study suggested

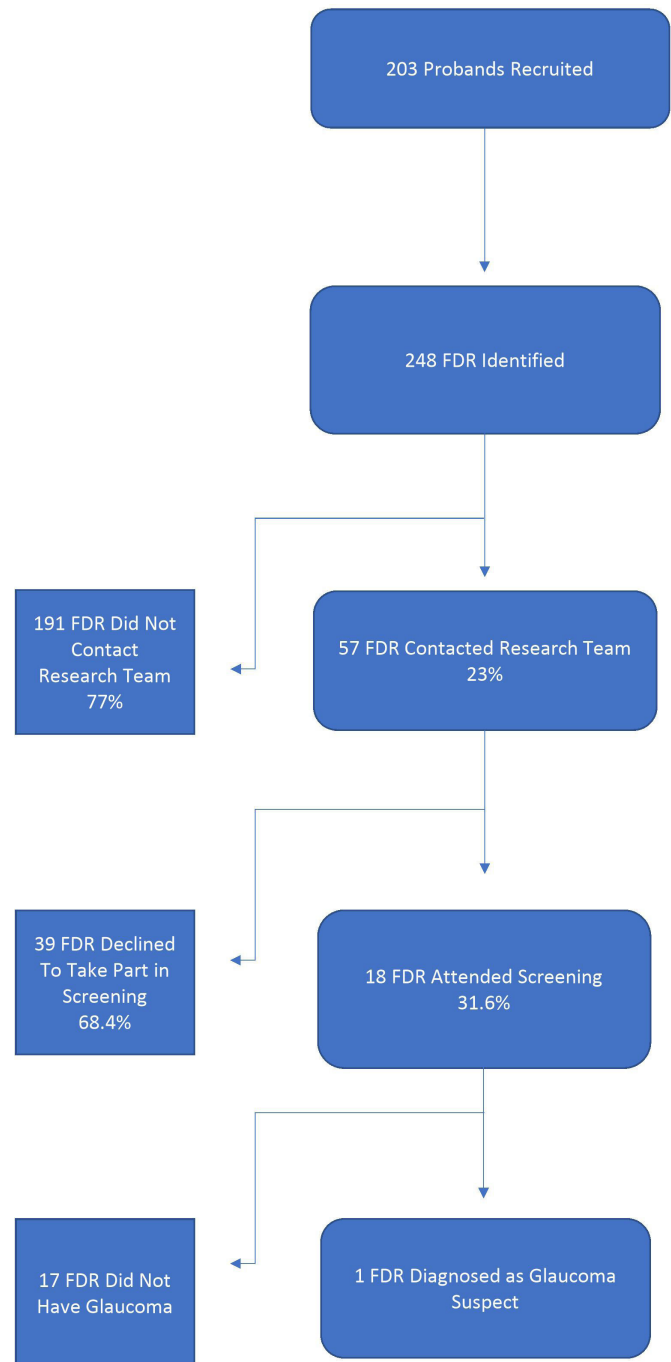


Figure 1 A flow chart showing each stage of the recruitment and cascade screening process. FDR, first-degree relatives.

UK PAD glaucoma patients each had 2 eligible FDR, so the aim was to recruit 200 probands.

RESULTS

203 patients with glaucoma (probands) were recruited to the study from routine glaucoma clinics. 110 (54%) of these were male and 93 (46%) female. Age range of the probands was between 32 and 90 years (mean: 65.7 years old, SD 14.5). Cup-to-disc ratio range was 0.5–1.0 (mean 0.8, SD 0.13). A total of 248 FDR were identified by the 203 probands as being potentially eligible to attend screening, an average of 1.2 FDR per proband (95% CI 1.08 to 1.37) (figure 1). As 146 probands (72%) identified any suitable relatives, this meant an average of

1.7 FDR (95% CI 1.56 to 1.84) per proband who were able and willing to identify an FDR. Of the 248 potential FDR, 57 (23%) contacted the research team enquiring about the screening process. Subsequently, only 18/57 FDR (31.6% of the total) attended a screening visit at the hospital. Of 57 FDR, 39 (68.4% of those who made contact) declined to take part in the screening process. Reasons stated included: not interested, busy, abroad, incorrect information given and misplaced leaflets.

During the study, various attempts were made to improve recruitment. Informal discussions with a group of six probands and others when they were telephoned to remind them to recruit family members revealed the strongest reasons for not informing their FDR were that parents said their 'children were very busy', and that they 'did not want to disturb' them. Also many probands and their siblings were first-generation migrants and many were retired, spending significant time abroad. Employment of a PAD nurse for recruitment did not improve uptake.

Of the 18 FDR who attended screening, 13 were female (72%) and 5 were male (28%). Age range was 32–74 years (mean: 46.4 years, SD 10.5). None were diagnosed with glaucoma and one participant was diagnosed as glaucoma suspect.

DISCUSSION

Targeted screening for eye disease has been used for ophthalmic conditions including diabetic eye disease screening and retinopathy of prematurity in those at risk.^{18 19} Cascade screening is a form of targeted screening based on family structure, as it increases the likelihood of detection of diseases of a hereditary nature. We believe glaucoma falls under this umbrella, particularly in PAD, but success depends on participation of those at risk. This requires clinicians, patients and their relatives to be educated on the risks of developing glaucoma and the requirement for appropriate assessment.⁹ This study failed, as only 23% of FDR contacted the research department to discuss screening, and 68% of this group declined to participate in the process. These results are in contrast with the Tasmanian study; while 34/133 available probands had no FDR or declined (26%, similar to the 28% in our study), 211/405 (52%) eligible FDR participated compared with 7% here. However, if an additional 173 FDR in the Tasmanian study who were 'not yet examined' were included, their participation rate would be 36%. Their study demonstrated a 'number needed to screen (NNS)' of 19 to identify one FDR with glaucoma,¹⁷ and additionally 15% of FDR were diagnosed as glaucoma suspect. The NNS in the unselected population-based Blue Mountains Eye Study in Australia was 66, demonstrating the potential to screen based on family members.²⁰ With no cases detected in our study, we cannot calculate an NNS.

Similar to the Tasmanian study, our study had an unequal distribution of male and female participants and it is often the case that women are more likely to participate in clinical and translational studies.²¹ Active community engagement by a dedicated research team has also been shown to increase trust and participation of black women in clinical research.²² Many strategies to increase male recruitment in this population have been trialled with limited success but one study highlighted greater levels of engagement through family referrals.²³ This is in contrast to our own findings and suggests that other strategies need to be employed. Indeed, the ReGAE study showed that men are less likely to access medical care generally, with that pattern extending into clinical research.²⁴

There are many potential reasons for the lack of success in this study. These include poor understanding of the disease and

low prioritisation of glaucoma in patients and relatives, cultural and social barriers to participation in a study of this sort, and poor engagement by the study team with the PAD community. It is possible that relatives may have felt that they were already adequately screened: in the UK, the National Health Service pays for a free annual optometric appointment including glaucoma screening for FDR (aged over 40) of patients with glaucoma, who are encouraged to advise their family members to be screened.

Probands and relatives may feel that glaucoma is not a sufficiently serious disease to warrant screening, particularly if the former are relatively asymptomatic with their disease. It may be that a diagnosis of, say, breast cancer is more concerning to individuals than glaucoma. The American Compadre study of 669 PAD women with a family history of breast cancer could not contact 64%.²⁵ Of the 240 woman who could be contacted, 55% did not fully complete the study. Of the 131 woman who did not complete the study, 46% missed their telephone appointment, 26% did not send in their consent form and 27% actively declined to take part. Therefore, even in genetic breast cancer screening, recruitment of PAD can be challenging. Data from the UK are similar: one study found PAD are more likely to miss breast cancer screening appointments compared with Caucasians (37.4% vs 23.1%).²⁶

We may have failed to educate our participants that glaucoma can also be a life-changing condition if left untreated, even in the early stages of the disease. A Jamaican study highlighted the importance of education on screening for prostate cancer. Men who had not been advised to have prostate cancer screening were 92% less likely to be screened than those who were advised.²⁷ That study also highlighted socioeconomic status as a significant factor for not attending screening as well as men who only visited healthcare providers when they felt unwell.

The most common barriers included probands not wanting to disturb their busy relatives, and FDR often being overseas. The length of time for examination, potential inconvenience of the tests and possible time required off work may have hindered participation, factors which have been cited in similar studies.¹⁷ It may be that glaucoma patients did not want to worry their relatives, and communication of information to relatives for patients who may have recently been diagnosed themselves may be a significant burden. There is well-documented mistrust about research participation in PAD communities in the USA stemming from historical events including the Tuskegee syphilis study which may be an important barrier regardless of prior research participation or socioeconomic status.^{28 29} Collaboration at a community level with the research participants directly has been shown to increase research participation and improve the health and well-being of affected community members. This can be through community-based participatory research and community advisory boards processes.^{30 31}

The ReGAE study from the UK highlighted multiple cultural barriers to PAD in glaucoma healthcare.²⁴ Patients did not always seek help as eyes were not seen as 'part of health' and visits to optometrists were mostly driven by symptoms or secondary to a general practitioner visit with other symptoms. An account is given of a patient cheating in a school eye test as he did not want to acknowledge the problem and wear spectacles. Many patients were concerned about the financial implications of testing with one patient going so far as to say, 'we are frightened on spending money on our health'. Even the purchase of new spectacles is only driven by damage to previous glasses, or by fashion, rather than deteriorating vision.²⁴ In deprived communities, cost will invariably play a role and we attempted

to mitigate this by offering out-of-hours screening, free eye tests and to pay for travel expenses. Financial incentives have been shown to improve enrolment as was discussed in a Cochrane review to improve retention in randomised trials.³²

In our study, we had to rely on the probands contacting the FDR which made it even more challenging for successful recruitment into the study. Due to research ethics guidance on confidentiality, researchers are generally not allowed to approach FDR directly. Unlike the Compadre study,²⁵ FDR needed to physically attend a hospital appointment which may also contribute to the poor recruitment rate. A study focusing on diabetes in South London, a similar community to ours, utilised family doctor surgeries to identify patients and were able to consent 1735/2406 identified participants (of whom 39% were PAD).³³ The primary outcome measure was a routine blood test (glycated haemoglobin (HbA1c)) and perhaps, as this was community rather than hospital-based, patients were more likely to attend. The study also investigated low attendance at structured education sessions for patients newly diagnosed with diabetes, and lack of awareness was a barrier to attendance.^{34 35} Community-based screening may be a more successful approach and targeted screening in this case might lead to earlier treatment and/or prevention of disease. To reach and encourage individuals to attend screening and follow-up examinations may require a more tailored approach. Strategies such as marketing with community partners, radio advertisement and postcards have been trialled with some success.^{36 37} A shared care screening model from The Netherlands showed similar rates of diagnosing glaucoma (5%) in community-based screening in local retail optician clinics compared with hospital-based screening.³⁸

In conclusion, despite 72% of glaucoma probands identifying FDR eligible for glaucoma screening, only 23% of FDR contacted the research team, and only 7% attended a screening visit. Cascade screening of FDR of African-Caribbean glaucoma patients in an inner city area appears unsuccessful. We believe research ethics guidance preventing direct contact with family members was a significant barrier in this study. A future research study on a similar population, community-based and with more community engagement, and with research ethics permission to contact relatives and not just probands, might be more successful.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study was approved by the North West – Haydock Research Ethics Committee (Approval number: 14/NW/1215.). We adhered to the principles of the Declaration of Helsinki.

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Data availability statement Data are available on reasonable request.

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