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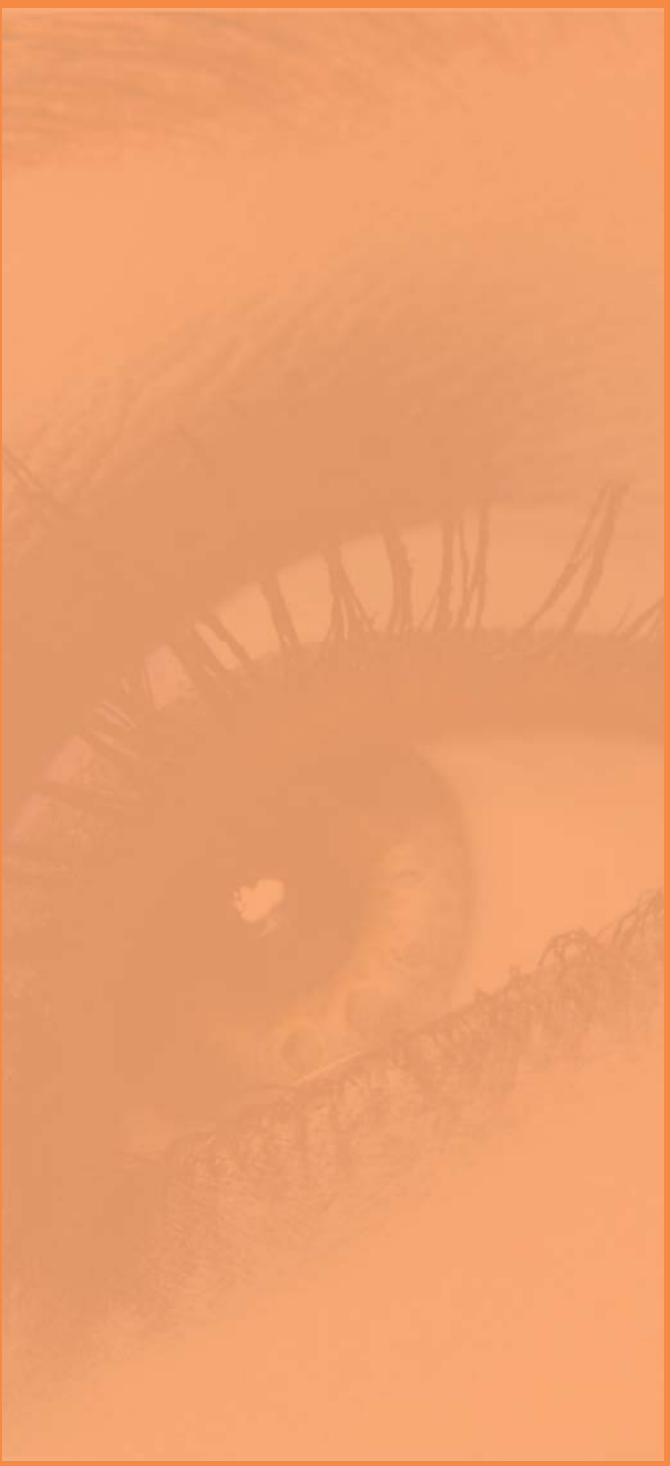

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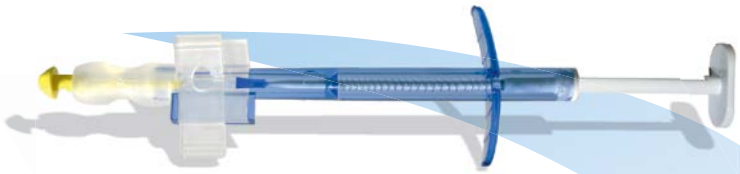

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+91- 733 957 0001 aurolab@aurolab.com www.aurolab.com
Contact us : africa.ba@aurolab.com +91 73050 34720

PUBLISHER

College of Ophthalmology of Eastern, Central and Southern Africa (COECSA)

A toolkit for glaucoma management in Africa

Glaucoma is the leading cause of irreversible vision impairment worldwide and the burden is largely in sub-Saharan Africa (SSA) where about 4% of adults aged 40 years and above have the condition[1]. Clinic-based data have increasingly shown younger adults presenting with severe glaucoma.

In February 2019, a strategic stakeholders' workshop was organised by Light for the World, in Addis Ababa, Ethiopia. Discussions at this workshop led to the development of the first *Toolkit for Glaucoma Management in Africa.* The practical toolkit is a guide on: "Where do I start from, in developing glaucoma care services?" Its development was made possible thanks to funding from Light for the World and the Else Kröner-Fresenius-Stiftung.

The *Toolkit for Glaucoma Management in Africa* was co-developed by more than a dozen high level, renowned glaucoma experts and general ophthalmologists from the region. It builds on the important International Council of Ophthalmology (ICO) Guidelines for Glaucoma Eye Care and counts with invaluable contributions from the ICO, the International Agency for the Prevention of Blindness (IAPB), the College of Ophthalmology for Eastern, Central and Southern Africa (COECSA), the Francophone African Ophthalmic Society (SAFO), the West African College of Surgeons (WACS), the African Glaucoma Consortium, the Ethiopia, Ghana, Nigeria and South Africa Glaucoma and Ophthalmological Societies, as well as the scientific community and major international training institutions. The toolkit is instrumental to guide ophthalmologists, glaucoma specialists and glaucoma care team members and programme planners to set up integrated glaucoma care services adapted to their very own context and to strengthen the health systems sustainably. Thus, it is "by Africans for Africans."

The intended outcomes of use of the toolkit are to shift paradigm to recognise that glaucoma blindness is avoidable, to strengthen clinical services, encourage earlier detection of glaucoma and strengthen health systems governance.

The toolkit has three parts: Part one is on how to deliver good clinical care of a glaucoma patient in the Sub-Saharan African setting; Part two on how to plan, set up and deliver glaucoma services; and Part three on generating information and on glaucoma research priorities for Africa. The toolkit is a useful guide for management of glaucoma.

The first chapter has checklists to facilitate clinical diagnosis of glaucoma. However, given the different options for treatment, we tried to avoid giving specific prescriptions since that would depend on availability of the said intervention in the country. In Part one, Chapter 2 of the toolkit, there is a clinical decision support tool, which considers the staging and severity of glaucoma and a risk assessment for progression of vision loss. This guides towards whether to choose surgery or medication or laser as the treatment of choice, where available. Chapter 3 guides the clinician towards making a diagnosis of the type of glaucoma with algorithms for dealing with specific situations for example, open-angle glaucoma, ocular hypertension, angle-closure glaucoma, cataract with glaucoma, glaucoma in pregnancy, etc. While Chapter 4 signposts selected weblinks for recipes and how-to perform the diagnostic and treatment procedures e.g. gonioscopy, selective laser trabeculoplasty, etc. Chapter 5 discusses current opinion on selected and topical issues. For example, the importance of OCT, the performance of Minimally Invasive Glaucoma Surgeries (MIGS), etc.

Part two focuses on how to set up an integrated glaucoma programme. Chapter 6 discusses levels of care and who does what and where with emphasis on integration and health systems strengthening. Chapter 7 suggests models of service delivery including financing care, facilitating early diagnosis and improving follow-up. An adapted list of essential equipment for glaucoma care is in Chapter 8. Chapter 9 highlights the need for advocacy and improving awareness for glaucoma. The key messages to consider for individuals, community or decision-makers are also highlighted. For example, we encourage or advise testing each eye every day - Just cover one eye at a time, and if you notice any difference, seek help.

Chapter 10 in part three is on Monitoring, Evaluation and Learning (MEL), listing the indicators for assessing a glaucoma care service. Chapter 11 focuses on research development and innovation for glaucoma service, indicating priority areas for research and the need for a glaucoma research and data repository to maximise the benefit of collaborations and shared learning.

The glaucoma toolkit was launched by IAPB during the World Glaucoma Week 2021. The IAPB launch outlined the development process of the toolkit and presented its content to the audience, including learnings from piloting its use in Nigeria. It was further launched in French - "Lancement Version française Boite à Outil sur le Glaucome" in Burkina Faso on 30th March 2021 hosted by the Société Burkinabé d'Ophtalmologie; and in Mozambique on 23rd June 2021. These country launches were strategy towards action plan with relevant stakeholders on how to use the toolkit in the different units across the country and how the toolkit can be integrated into existing training curricula for general ophthalmologists and allied eye care personnel.

The toolkit is ready for use as a practical guide for glaucoma management. Its incorporation in the training for ophthalmologists and eye care personnel is ongoing. In Burkina Faso, Ethiopia and Mozambique (Light for

the World glaucoma programme countries), two lines of training on the use of the toolkit are planned: (i) training for allied eye care personnel in identification, counselling and referral of glaucoma patients by ophthalmologists who have a strong understanding of the ICO Guidelines and the glaucoma toolkit; and (ii) training for ophthalmologists by glaucoma experts. The major training colleges involved in the development have already indicated that the toolkit for glaucoma management in Africa will be incorporated into their training curricula.

The next question is does benchmarking diagnostic protocols and patterns of care according to recommended guidelines have implications on quality of care?

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Kyari F, College of Health Sciences, University of Abuja, Abuja, Nigeria and London School of Hygiene & Tropical Medicine, London, UK.
Email: Fatima.Kyari1@Ishtm.ac.uk

Glaucoma awareness in Sub Saharan Africa region: Review and strategies

Gessesse GW, Mulugeta A, Giorgis AT, Ayele FA

Corresponding author: Dr Girum W Gessesse, P. O. Box 124012, Addis Ababa, Ethiopia.
Email: girumgw@yahoo.com

ABSTRACT

There is low level of awareness on glaucoma among the public in the region and there is a need for more research. Raising glaucoma awareness has multiple impacts that ultimately contribute to early detection, management and avoiding blindness due to the disease. There are various strategies for raising awareness on glaucoma and the experience in Ethiopia has shown the importance of raising glaucoma awareness in terms of early detection of disease, compliance to glaucoma management, acceptance of surgery, mobilizing stakeholders, and getting due attention to glaucoma as a public health problem.

Key words: Glaucoma, Africa, Primary open angle glaucoma, Blindness, Awareness

INTRODUCTION

Glaucoma is the leading cause of blindness after cataract[1]. It refers to a group of eye disease, in which optic nerve damage is the common pathology that leads to vision loss. An estimated 3% of the global and 4.5%of sub-Saharan African (SSA) countries population over 40 years of age currently have glaucoma. With growing elderly population, the prevalence is increasing globally and it was expected that 79.6 million people will have glaucomaby 2020[1,2].

According to WHO, 8% of all blindness worldwide is caused by glaucoma and these figure rises to 15% in SSA countries[2]. Glaucoma tends to be detected at later stage of the disease when it has advanced into vision impairment. It is characterized by distinctive peripheral visual field loss; patients may have "tunnel vision" but have normal central vision. Furthermore, of people living with glaucoma, 50% in developed and 90% in developing countries do not know they have the disease[3]. The fundamental factor in the prevention of vision loss caused by glaucoma is being able to identity it in its early stage. This is often problematic in SSA countries as the majority of people do not routinely visit eye care centers unless an eye problem become evident.

Patients with glaucoma are reported to have poorer quality of life,with decline of social function and mental health[4]. In low resource settings, managing patients with glaucoma has unique challenges. Inability to pay, treatment rejection, poor compliance, and lack of education and awareness are all barriers to good glaucoma care. Most patients are unaware of glaucoma disease, and the time they present many have lost significant vision[3].

Poor knowledge of glaucoma by the public may adversely influence individuals having regular sight tests. Individual's risk of vision loss could be reduced if those at risk of blinding eye diseases obtain a comprehensive ophthalmic examination on a regular basis[5].

Research and evaluation of the use of mass media in health promotion have shown that mass media can raise consciousness of public about some health issues and change behavior. Mass media intervention by themselves or in combination with other programs can significantly influence the health behaviors of population.

LEVEL OF AWARENESS ON GLAUCOMA

Studies done in Africa on glaucoma awareness among the general public, and glaucoma patients themselves showed low levels of awareness about the disease. Even among health professionals, awareness and understanding of glaucoma is low. There is a need to undertake more research in the region on awareness of the disease that will help in understanding the burden of the problem and to devise strategies for effective intervention.

(i) Awareness among glaucoma patients

In a study among Primary Angle Closure Glaucoma (POAG) patients in Lagos, Nigeria, 80% of respondents knew they were being managed for a disease called glaucoma while 20% of the respondents did not know they were being managed for a disease called glaucoma. Among those who had the knowledge, 37.5% lacked information about the fact that it could be heritable, 30.2% had not informed their families that they had been diagnosed to have glaucoma and 46.9% had first degree relatives who had not been screened for glaucoma[6].

In a study using Focus Group Discussions (FGDs) with glaucoma patients with advanced disease in northern Nigeria, many of the participants said they heard the term "glaucoma" for the first time during the study, despite the patients having late stage disease[7].

In a qualitative investigation among glaucoma patients in Tanzania, participants knowledge of glaucoma, particularly knowledge of the symptoms, diagnosis and treatments was limited to patients own individual experiences. Patients also had a poor understanding of the hereditary nature of POAG and inherent increased risk

for their families. Even those who knew of the risk were found to be unsure what action they should take[8].

In a study among glaucoma patients attending Kenyatta National Hospital, 53 (67.9%) patients were classified as having some knowledge about glaucoma. Patients also had wrong expectation of both treatment and surgery with 29.5% and 32.5% expecting cure from medical and surgical treatment respectively[9].

(ii) Awareness among the community

There is scarcity of data on awareness on glaucoma in a community setting. In a community-based study an adult rural population of Osun State, Southwest Nigeria; only 41 (15.8%) participants had ever heard of glaucoma. Responses to the causes of glaucoma included 48.8% participants who said 'I don't know' and 24.4% of participants who responded 'curse-from-God'. Responses to questions on treatment included 48.8% participants who responded 'I don't know how it can be treated' and 36.6% said 'medically'[10].

In a study among 340 people attending ophthalmic outreach services in Southwestern Ethiopia, only eight people (2.4%) were aware of glaucoma[11]. In a recent study among 300 residents of Abokobi, Greater Accra region, Ghana, 39% (118/300) of respondents indicated they had heard about the eye condition glaucoma. Majority (99.1 %) of respondents aware of glaucoma also agreed the disease can result in blindness with only 28% affirming that blindness from glaucoma is irreversible. Nearly half (49.7%) of the respondents perceived themselves to be at risk of developing glaucoma. Approximately, 20.7% of the respondents have had their eye screened with just a few (4.3%) screening for glaucoma[12]. In a study among new ophthalmic patients in Ethiopia, 28.4% were found to be aware of glaucoma and 75.8% of them had some knowledge of glaucoma as well[13].

(iii) Awareness among health professionals

In a study among workers in a Nigerian tertiary hospital, a total of 148 (68.6%) participants had heard of glaucoma comprising all participants from the clinical directorate and 28 (29.2%) participants from the administrative directorate. Eighteen (63.4%) from the administrative directorate had the knowledge that glaucoma would result in blindness without treatment, while eight (28.6%) felt that visual loss from glaucoma could can be restored[14].

Among final year health science university students in Ghana, all 273 respondents were aware of glaucoma but only 37.7% had knowledge of it. Only 28.6% respondents had previously undergone glaucoma screening[15].

Among workers at the University of Benin Teaching Hospital in Nigeria, 168 (74.3%) were aware of glaucoma. The knowledge of glaucoma was good among 31% of those who were aware of glaucoma, fair in 31.5% and poor in 37.8%[16].

Among health workers in Federal Medical Birnin Kebbi, Kebbi State, Nigeria 204 (76.1%) of the hospital workers had heard about glaucoma; 202 (75.4%) of the workers believed that glaucoma causes irreversible blindness[17].

Experience on glaucoma awareness, Ethiopia

Activities of glaucoma awareness creation started in 2007 by the Glaucoma Group of the Ophthalmological Society of Ethiopia (OSE). Since then a number of activities have been conducted to raise awareness and knowledge among the general public and glaucoma patients. Television, radio and newsletters have been the major means used to transfer educational message and to conduct live discussion on glaucoma. The mass media have been found to be the best means to access millions of population at a time all over the country and beyond. Brochures, posters and glaucoma guide, written in English and five local languages and distributed to all regions through the Federal Ministry of Health were the other methods of education used. The World Glaucoma Week and World Sight Day have been used as appropriate times to conduct screening and to held glaucoma health education programs at hospital outpatient waiting areas by trained nurses, and most of the aforementioned activities.

The impact of the awareness activates has been reflected by raising level of awareness from 4% in 2006 to 28% among ophthalmic patients at a tertiary center in 201118, which could be much higher at present time. Studies among community have identified the level of glaucoma awareness to be raised to 33% in 2015, which was 2.4% in 200911. Glaucoma patients have become more attentive about their disease and medications, and improvement on acceptance of surgery has been noticed as well. People with family members with glaucoma are coming to ophthalmic attention and they are keen to know their level of intraocular pressure and status of their optic nerve heads. Besides, many of patients coming for other eye problems ask their doctors whether they have glaucoma or not. Ophthalmologists and residents have become more interested in glaucoma. Availability and variety of anti-glaucoma drugs has been increasing, though, affordability remains as a limitation for utilization. Better awareness among the health decision makers has also resulted in getting due attention to glaucoma as a public health problem.

The Ethiopia experience on raising glaucoma awareness among the public in general and the affected individuals, in particular, has tremendous effect in early case detection and improving compliance to glaucoma management and follow-up, and hence in prevention of the irreversible blindness from glaucoma.

IMPACT OF RAISING GLAUCOMA AWARENESS

Among many factors contributing to the burden of glaucoma related blindness, awareness about the disease in the general public is a critical factor for early recognition and management of glaucoma. Raising public and health professionals' awareness and knowledge about glaucoma has multiple impacts that ultimately contribute to avoiding blindness due to the disease.

(i) Public and health professionals'

It is a common experience for practitioners to see some people confusing trachoma from glaucoma. Defining glaucoma in a simple language that people are able to understand can improve the knowledge and perception of the public towards the disease. As the level of awareness increases, it is expected that there will be an increase flow of people to eye centers for glaucoma screening, and those who visit eye centers for various reasons could also ask to be checked for glaucoma. Eye care providers could be more aware of glaucoma and become knowledgeable as a result of increased flow of patients for glaucoma evaluation and management. Awareness creation among other health professionals will also help for early referral of patients at risk s to eye care providers/ophthalmologists.

(i) Improving the knowledge and perception of glaucoma patients about the disease

Appropriate management of glaucoma usually requires lifelong follow-up of patients. Improved awareness, knowledge and better perception of glaucoma patients are key to the development of a positive outlook. A positive outlook can motivate patients to improve adherence and persistence to treatment and proper follow up as well as accepting surgery, if needed. It can also ensure that family members undergo glaucoma screening regularly thereby enhancing prompt diagnosis and reducing the risk of blindness from glaucoma. As the family members get better knowledge about the visual impacts of glaucoma, the affected patient is more likely to get the necessary psychological and social support.

Table 1: Levels of intervention and expected impacts of raising glaucoma awareness

Level of Intervention	Impact
General public	1. Increase number of people presenting to eye centers for glaucoma screening
Health professionals	2. Early referral of patients at risk to ophthalmologists/ eye care centers
	3. More interest in the field of specializing in glaucoma by residents and ophthalmologists
Glaucoma patients	4. Helps family members to undergo glaucoma screening
	5. Increases possibility for family/social support of affected patients
	6. Improves adherence to medications
	7. Acceptance to surgery and proper postoperative follow up
Health institutions	8. Better attention to glaucoma evaluation
	9. Improvement on the diagnostic and surgical facilities as well as human resource development

(ii) Impact on health institutions and professionals

As public awareness increases, demand for glaucoma services will be increased and as a result institutions will be enforced to be better prepared in terms of improving the diagnostic and surgical facilities as well as human resource development. Professionals will also be devoted to glaucoma, paying attention to glaucoma evaluation and management, and there will be a need for updating oneself and hands on training on glaucoma care. Residents and ophthalmologists will also show more interest in the field of specializing in glaucoma.

(iii) Policy makers

Improved glaucoma awareness will also help policy makers to give priority about the disease and incorporate it into National strategic plans. This will lead to support to all activities targeted at raising awareness, management of the disease as well as human resource development. Similarly, including glaucoma drugs within the 'essential drug list' of the country will facilitate availability of medications for glaucoma care.

STRATEGIES FOR RAISING AWARENESS ON GLAUCOMA IN COECSA REGION

Public education involves utilizing most persuasive messaging to help proactively engage key audiences in the issue and asking them to respond to a specific call to action. This glaucoma awareness raising strategy outlines the key activities to be undertaken in order to effectively inform the public and engage stakeholders in the prevention of blindness due to glaucoma.

The strategy objectives

1. Increase public awareness on glaucoma
2. Mobilize stakeholders to combat blindness due to glaucoma

Key targets

The target audiences of glaucoma awareness-raising activities are all people, more emphasis to adult population who are older than 40 years.

Key messages

The success of glaucoma public awareness- raising program hinges on the public's improved understanding of glaucoma as a silent and irreversible cause of blindness that can be prevented by early detection and lifelong treatment. Thus, clear, consistent and coherent messages have to be communicated to the public in local languages.

The key messages should include
1. What is glaucoma and how is it different from other causes of blindness
2. Who is at risk to develop glaucoma
3. How the diagnosis of glaucoma is made
4. When should an individual get checked for glaucoma
5. How is glaucoma managed and the need for lifelong follow up

Methods and activities to launch public awareness activities

This has to be tailored based on the availability of resources, literacy status of key targets, culture and other factors, as what works so well in one region may not be feasible in another. Generally, combinations of the following methods are necessary for effective communications with the public.

I. Leverage various media and opportunities

A. Traditional Media
   1. Post advertisement in national newspapers in local languages
   2. Distribute leaflets, brochures on glaucoma written in local languages
   3. Use of posters and banners in health institutions and public area
   4. Preparation of books on glaucoma in the local language
   5. Arranged advertisement on FM Radio and a quiz program with attractive awards to encourage the patients to learn more about the disease
   6. Exploit the opportunities on scheduled health related programs on TVs and radios including live transmissions to convey message about glaucoma and answer questions from the public
   7. Regular health education programs to general as well as ophthalmic patients(including glaucoma patients)

B. Social media (Twitter, Facebook) - a glaucoma group account can be opened and messages on glaucoma can be posted to address the ever growing social network users

II. Mobile phone short glaucoma messages can be sent to large number of people, encouraging to be checked even if they are not symptomatic or their eyes look normal. This can be aligned with World Sight day and World Glaucoma week activities.

III. Utilize opportunities to address glaucoma when people gather for outreach cataract campaign, town hall meetings and other traditional meetings (in rural areas)

IV. Use of key informants (patients with the disease, religious leaders, political leaders, celebrities) who are influential in their communities will improve the acceptance of the message by the general populations

V. Organising conferences, press release, march with T- shirts with message on glaucoma, etc. (during the World Glaucoma week)

Activities expected from the glaucoma specialist group includes

1. Producing and disseminating public information materials in local languages
2. Making information on glaucoma accessible online and through social networks
3. Engaging with the media on a regular basis
4. Linking the awareness raising campaign to World Sight day and World Glaucoma week

Mobilizing stakeholders

Combating blindness due to glaucoma is a collective responsibility. All stakeholders including, glaucoma patients and their associations, ophthalmologists, optometrists, ophthalmic nurses and other treating physicians, government bodies (Ministry of Health and Ministry of Education), the private sector, professional societies, civil society organizations, community leaders and religious establishments should play their own role in raising the awareness of the public on this blinding disease to promote an early health seeking behaviour of the people.

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- the manuscript has been read and approved by all the authors, that the requirements for authorship has been met, and that each author believes that the manuscript represents honest work.

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Outcomes of conjunctival flap in severe microbial keratitis

Tran T[1], Kanji R[2], Al-ramady A[2], Kintoki G[2], Onyango J[2], Leck A[3], Macleod D[4], Hu V[3], Burton M[3], Arunga S[2,3]

[1]Department of Ophthalmology and Visual Neurosciences, University of Minnesota, Minneapolis, Minnesota, USA
[2]Department of Ophthalmology, Mbarara University of Science and Technology, Mbarara, Western Region, Uganda
[3]Clinical Research Department, International Centre for Eye Health, London School of Hygiene & Tropical Medicine, London, UK
[4]Tropical Epidemiology Group, London School of Hygiene & Tropical Medicine, London, UK

Corresponding author: Dr Tu Tran, University of Minnesota, Minneapolis, Minnesota, USA.
Email: tranminhtumat@gmail.com

ABSTRACT

Objectives: To describe the 3-month outcomes of conjunctival flap in managing severe Microbial Keratitis (MK).
Design: This was a prospective cohort study.
Setting: Patients were enrolled at two major eye hospitals in Mbarara, a major city in the Southwestern sub-region of Uganda, over a one year period.
Subjects: Individuals of any age that met the case definition of severe microbial keratitis, in which perforation occurred acutely or was impending.
Interventions: A complete Gunderson conjunctival flap was done in all suitable patients. Demographics, health access, clinical, and microbiological data were recorded.
Main outcome measures: Statistical significance testing was done to assess predictors of evisceration at the 3-month follow-up time point.
Results: Among 57 patients (57 affected eyes), median age was 44 years (IQR 38, 60) and 47.4% were women. Trauma was associated with 35.1% of cases. Median time to presentation was 23 days (IQR 12, 34). Etiology was 80.7% purely fungal pathogens, 10.5% mixed bacterial/fungal, and 8.8% undetermined. Mean infiltrate and epithelial defect sizes were 7.2mm (SD 2.3) and 6.0mm (SD 2.5), respectively. Presenting visual acuity was <3/60 in 78% of eyes. At 3-months, 19 eyes (34.5%, 95%CI 23.5-48.2) had improved best-corrected visual acuity, though 9 eyes required evisceration (15.8%, 95%CI 8.3-28.0). There were no clinically or statistically significant predictors for evisceration at 3 months.
Conclusions: Conjunctival flap is a reasonable rescue procedure, especially if therapeutic penetrating keratoplasty is an eventually feasible option. However, there are considerable risks of vision loss or lack of improvement and eventual need for evisceration.
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Key words: Conjunctival flap, Corneal ulcer, Microbial keratitis, Evisceration, Uganda

INTRODUCTION

Microbial Keratitis (MK) is a sight-threatening ocular emergency from infection of the cornea by microorganisms. This can present as ulceration of the cornea with stromal infiltration in severe cases[1]. MKis a significant cause of unilateral blindness globally with an estimated incidence of 1.5 to 2 million cases per year[2],which is an underrepresentation of the true burden due to under-reporting by population surveys in Low- and Middle-Income Countries (LMICs)[3], where the burden disproportionately falls on the rural poor. Nevertheless using these data sources, there were 4.2 million prevalent cases globally in 2015 including individuals who were visually impaired (<6/18 best-corrected visual acuity) or blind (<3/60) from corneal opacity[4]. Large-scale global efforts have been responsible for the sharp reduction in prevalence of trachoma from 4.4 million visually impaired or blind in 1990 to 2.0 million in 20154. This success should motivate similar policy and implementation mechanisms to control the "silent epidemic" of MK.

Unfortunately, the status quo is unacceptable and a considerable proportion of patients present to tertiary level healthcare facilities in Sub-Saharan Africa (SSA) with severe MK, which can be defined as;(i) Stromal infiltrate size >3mm by the longest diameter, (ii) Best-Corrected Visual Acuity (BCVA) of<6/60 at baseline, and/or (iii) Impending perforation or acute perforation. Severe MK is associated with poor visual prognosis in Tanzania[5,6] and southern India[7]. In High-Income Countries (HIC), corneal

tissue is readily available for therapeutic penetrating keratoplasty (PK), while 53% of the world has no access to corneal tissue[8]. Most of these individuals reside in SSA countries. Therefore, conjunctival flap has been the most reasonable alternative to prevent corneal perforation and preserve the globe[9],[10]. While the long-term goal must be to increase corneal tissue availability in SSA countries, the incident and backlog cases of severe MK warrant near-term measures to provide the best functional outcomes for patients. Losing an eye has detrimental psychological consequences to the patient. Stabilizing the ocular surface and preventing enucleation can be achieved successfully with conjunctival flap[11],[12]; complications such as flap retraction and button-holing can be managed with a revision operation and occur as much as 24% in all cases among all indications for conjunctival flap[12].

To the best of our knowledge, no prospective cohort study has been performed in SSA reporting outcomes of conjunctival flap in management of severe MK. In this large consecutive cohort study from Uganda, we describe outcomes at 3months and assess predictors for failure of conjunctival flap requiring evisceration.

MATERIALS AND METHODS

Setting and participants: From December 2016 to March 2018, patients were enrolled from two major eye hospitals in Mbarara, a major city in the Southwestern Sub-region of Uganda[13]. Patients' ocular history, self-reported onset of symptoms,alternative treatments prior to presentation, and indicators of socioeconomic status were collected. All patients were assessed by an attending ophthalmologist (S.A.).The MK case definition included: (i) Corneal epithelium defect(>1mm diameter) with underlying stromal infiltrate oralternatively a deep corneal abscess (>1mm) and(ii) Associated signs of inflammation, such as conjunctival hyperemia, anterior chamber reaction, with/withouthypopyon. Individuals meeting MK case definition were then asked for consent to enroll in this study; exclusion criteria were: emergent cases without time to triage, children under age 18 years, and inability to provide consent whether due to refusal or lack of capacity.

Clinical data and microbiology: Slit lamp examination findings, including perforation status, were determined by an attending ophthalmologist (S.A.). Infiltrate size was determined using the greatest diameter of infiltrate (major axis) and widest perpendicular diameter (minor axis); the final infiltrate size is the geometric mean of these diameters14.Epithelial defect was determined using the same method with measurements taken under fluorescein staining. Corneal scrapings from the edges of the ulcer were used for microscopy (Gram, potassium hydroxide [KOH], calcofluor white [CFW] stains), culture agars (Sheep's Blood, Chocolate, Potato Dextrose), and Brain-Heart Infusion (BHI) broth. Corneal swabs were used for Polymerase Chain Reaction (PCR). Agar plates and broth were incubated at 35-37°C for up to 7 days for bacteria and at 25°C for 21 days for fungi.Organism identification and sensitivity testing were performed using standard microbiological techniques and reported using similar methods in Leck *et al*[15].

Surgical technique, medical management, and follow-up: If a patient was determined to have an acute perforation or the stromal infiltrate was deep enough such that perforation was impending, conjunctival flap surgical procedure was undertaken to prevent evisceration. Eyes already perforated with an overwhelming infection or extensive corneal necrosis with no healing potential underwent immediate evisceration (Figure 1).

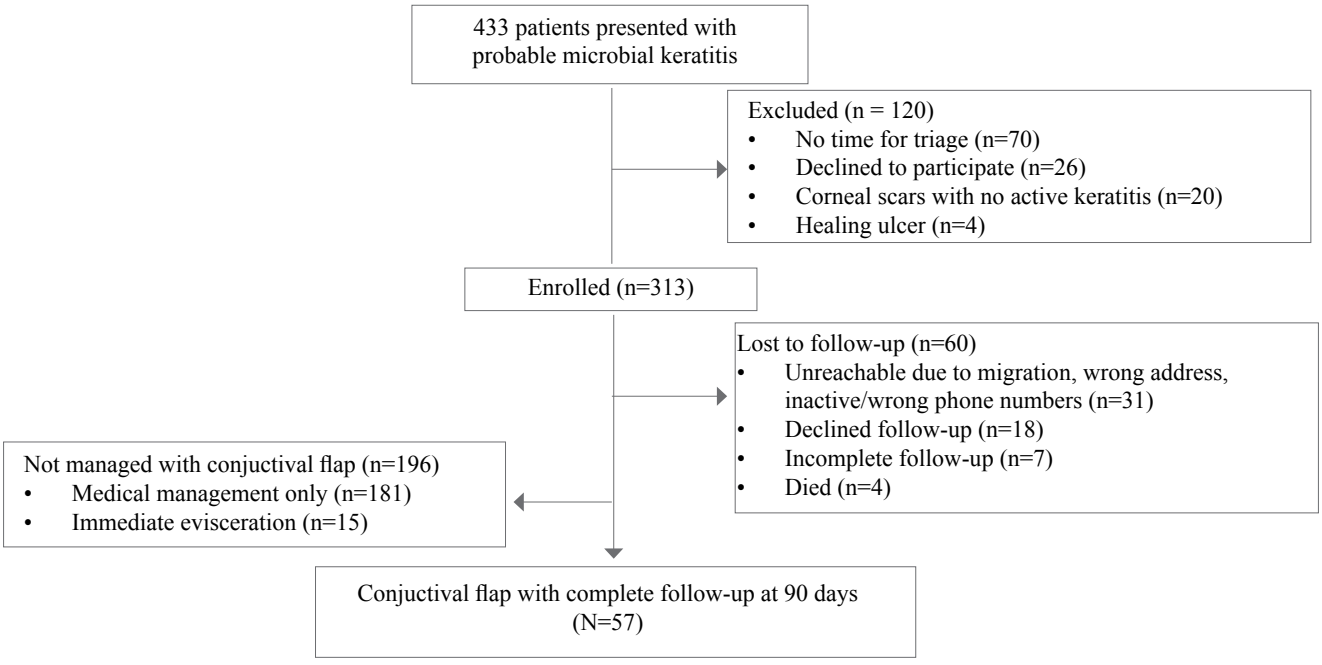

Figure 1: Study flow diagram

Conjunctival flap was carried out in a sterile operating theatre under an operating microscope by an attending ophthalmologist (S.A.) or a senior resident ophthalmologist (G.K.). All cases were performed under peribulbarblock with 3ml 2.0% lidocaine. A wide periorbital/hemifacial sterile field was established with 5.0% povidone iodine. The eye was draped, and a lid retractor was placed. A crescent blade was used to debride all necrotic tissue and denude corneal epitheliumto an area 1mm margin beyond the ulcer's extant. A complete Gunderson flap was then performed16. A traction suture (4-0 silk) was placed at the superior limbus to infraduct the globe, exposing superior conjunctiva. The conjunctiva was marked at the superior fornix, approximately 14mm superior to thelimbus. Admixture of 1% lidocaine and 1:100,000 epinephrine was injected into the subconjunctival space to facilitate mobilization. A 360° peritomy was performed, then a 20mm-length incision into conjunctiva was made at the superior fornix at the pre-marked location. The flap was created with sharp and blunt dissection with blunt-tipped scissors inferiorly toward the superior limbus. The flap was then mobilized inferiorly to completely cover the cornea. The flap was sutured in place at the superior and inferior limbus with simple, interrupted 10-0 monofilament nylon sutures. The flap remained tension-free. Empiric anti-microbial ophthalmic suspension wereapplied,and the eye was dressed.

Each patient was admitted and monitored post-operatively for one week. Dressing changes occurred every 24 hours. Pre-operative anti-microbial regimen was natamycin 5% and ofloxacin 0.3% every hour for first 3 days. When microscopy was available, the regimen was altered as follows. Fungal pathogens were treated with natamycin q1hour for 72 hours, then q1hour during waking hours for 2 weeks, q2hours during waking hours for 2 weeks, then four times per day until follow-up. Bacterial pathogens were treated with ofloxacin 0.3% ophthalmic solution q1hour for 3 days then 6 times per day for one week. Viralpathogens werepresumed herpetic andtreated with acyclovir 3% ophthalmic ointment 5 times per day for 3 weeks. Patients were evaluated at post-operative day 1 then 7, 21, and 90 days post initial presentation. Sutures were removed at day 21 visit. The primary outcome measures at 3months (90 days) were Best-Corrected Visual Acuity (BCVA), scar density, and need for evisceration. Independent variables were demographics, visual acuity at presentation, acuity of presentation, early operation, clinical characteristics of the ulcer, perforation status, microbiology, and medical comorbidities.

Data analysis: Summary statistics, error estimates, statistical significance testing of continuous and categorical variables, and regression modeling were performed in STATA 16 (Stata Corp, College Station, TX, USA). Data visualization was performed using STATA 16 and Microsoft Excel 2016 (Microsoft Corp, Redmond, WA, USA). Visual acuity was analyzed on the logMAR scale but converted to Snellen metric. Multivariable regression analysis was performed with the glmfunction to assess risk factors associated with evisceration at 3months (adjusted by age and gender). Forward selection stepwise regression analysis was used with variables tested for significance against a full adjusted model with likelihood ratio testing ($p< 0.05$) for retention. Univariable associations at $p < 0.3$ were considered for initial inclusion.Residual plots, AkaikeInformation Criterion (AIC) and Bayesian Information Criterion (BIC) were used to consider regression model fit.

Ethics statement: This study was approved by the London School of Hygiene and Tropical Medicine Ethics Committee (Ref 10647), Mbarara University Research Ethics Committee (Ref 10/04-16), and Uganda National Council for Science and Technology (Ref HS-2303). All patients provided written consent in their native language prior to participation in this study.

RESULTS

Demographics and clinical presentation: There were 57 patients for analysis, of whom none had previous ocular surgeries(Table 1). Median age was 44 years (interquartile range [IQR] 38, 60), and 47.4% were women. A majority (73.7%) were subsistence farmers, and 31.6% did not have a formal education. Per Uganda's criteria of health access as living within 5 km of a health facility, 75% of participants lived close to a primary care clinic or higher-level facility. However, the median distance to the definitive treating eye hospital was 118 km (IQR 76, 165).

In all cases of MK, median symptom duration prior to presentation was 23 days (IQR 12, 34). For those who eventually needed evisceration, median delay was 12 days versus 24 days among those who did not (p=0.209, Table 2). In terms of timeliness, only one participant presented within 3 days, and 14.4% presented within 7 days. The most frequently endorsed symptom at presentation was blurred vision (59.6%) followed by eye pain (35.1%). Trauma was sustained in 35.1% of cases with vegetation occurring in 30% of those traumatized. Nearly all patients (91.2%) sought other treatment, including Traditional Eye Medicines (TEM) (68.4%).TEM typically involve a plant-based extract from fresh leaves placed in the affected eye17. There was no association between patients who sought other treatment and delay in presentation. Regarding systemic diseases, diabetes mellitus and HIV infection was prevalent in 13.2% and 11.5%, respectively.

Best-Corrected Visual Acuity (BCVA) at presentation was worse than 3/60 in 87.7%. The BCVA at presentation was equally poor in non-eviscerated and eviscerated group (Table 2). The mean stromal infiltrate size, which is the geometric mean of longest diameter and largest perpendicular,was 7.2mm (SD 2.3) and the mean epithelial defect size was 6.0mm (SD 2.5). Both stromal and

Table 1: Participant demographics, socioeconomic indicators, health access

	Overall (n = 57)	Not eviscerated (n = 48)	Eviscerated (n = 9)	P value
Age (years)				
Mean (SD)	47.5 (14.8)	48.0 (14.9)	44.4 (14.5)	0.505
Median (IQR)	44 (38, 60)	45 (38, 61)	43 (36, 46)	
	20-85	20-85	25-70	
<30 years, n (col%)	6 (10.5)	5 (10.4)	1 (11.1)	
30-39 years, n (col%)	11 (19.3)	8 (16.7)	3 (33.3)	
40-49 years, n (col%)	18 (31.6)	15 (31.3)	3 (33.3)	
50-59 years, n (col%)	7 (12.3)	7 (14.6)	0 (0)	
>60 years, n (col%)	15 (26.3)	13 (27.0)	2 (22.2)	
Mean (SD)				
Women, n (col%)	27 (47.4)	22 (45.8)	5 (55.6)	0.722
Farmer, n (col%)	42 (73.7)	37 (77.1)	5 (55.6)	0.223
Education level				
None, n (col%)	18 (31.6)	16 (33.3)	2 (22.2)	0.774
Primary, n (col%)	27 (47.4)	21 (43.8)	6 (66.7)	
Secondary, n (col%)	9 (15.8)	8 (17.7)	1 (11.1)	
Tertiary, n (col%)	3 (5.2)	3 (6.2)	0 (0)	
Married, n (col%)	38 (66.7)	30 (62.5)	8 (88.9)	0.247
Distance to nearest health facility (km)				
Median (IQR), range	3 (1, 5), 1-45	3 (1, 5), 1-45	3 (2, 5), 1-5	0.435
Clinic, HC II, HC III, n (col%)	37 (63.2)	31 (64.6)	5 (55.6)	
HC IV and General hospital, n (col%)	16 (28.0)	12 (25.0)	4 (44.4)	
Don't know, n (col%)	5 (8.8)	5 (10.4)	0 (0)	
Distance to eye hospital (km)				
Median (IQR), range	118 (76, 165), 1.9-377.6	120 (76, 165), 1.9-377.6	112.4 (66, 265) 3-316.1	0.560

Acronyms: HC: health centre; IQR: interquartile range

infiltrate size was generally larger in the eviscerated group, but the difference was not statistically significant (p=0.525, 0.507). Common clinical signs were centrally-located ulcers (91.2%), raised slough (63.2%), serrated edges (88.9%), and white or cream-colored infiltrates (70.2%) (Table 2). Acute perforation was present among 40.4%; these individuals tended to present with longer delays than non-perforated given median of 24 days (IQR 14, 39) after symptom onset versus 17 days (IQR 12, 30) (p=0.173).The ulcer size was marginally smaller in individuals presenting with perforation: infiltrate size 7.01 (SD 1.96) versus 7.60 mm (SD 2.41) (p=0.339) and epithelial defect 5.58mm (SD 2.26) vs. 7.05mm (SD 2.60) (p=0.572).The proportion with perforation at presentation did not differ significantly between non-eviscerated and eviscerated group. The BCVA at presentation was also equally poor between perforated and non-perforated. Fungal pathogens were the main cause of severe MK in this cohort as they were isolated in 91.2% of cases with 80.7% of all cases growing only pathogenic fungus (Table 3).

Outcomes: At 3 months, 14 participants (24.6%) had good outcomes in which 2 healed, 4 had mild scar and 8 had moderate scarring, while 27 participants had dense scars and 7 had poor outcomes: 6 non-healing ulcers, 1 anterior staphyloma. The proportion of participants undergoing evisceration was 15.8% (95% CI, 8.3-28.0). The distribution of age, time from symptom onset to presentation, and perforation status are presented in Figure 2. The median presentation time was lowest in the eviscerated group, but the difference was not significant (p=0.684). The presenting BCVA was also not predictive of evisceration since the distribution of WHO category 3 (3/60 – 1/60) and category 4 (1/60 to light perception) were similar among all outcome groups (Figure 2D). For these patients with severe MK, changes in BCVA were not statistically significant, even when excluding the 9 individuals requiring evisceration. The proportion of patients with improved BCVA at 3 months was 34.5% (95%CI, 23.0-48.2). Overall visual outcome was poor with severe visual impairment (worse than 6/60) in 7.3% and blindness (worse than 3/60) in 72.7% (Figure 2E). There were no complications from the conjunctival flap procedure itself.

In assessing risk factors for evisceration, there were no significant predictors that could be delineated between the non-eviscerated and eviscerated group. The model provided no evidence for significant associations between the risk of evisceration and probable factors, such as demographics, delay to care, health access, clinical features on presentation, ulcer size, perforation, and baseline visual acuity (Table 3). Of note, surgeon level of experience (ophthalmologist or resident) did not impact outcome (p = 0.593) and was not included in the final model.

Table 2: Clinical history, signs at presentation and microbiology

	Overall (N = 57)	Not eviscerated (n = 48)	Eviscerated (n = 9)	P-value
Time from symptom onset to presentation (days)				
Early, 0-7 days, n (col%)	8 (14.0)	5 (10.4)	3 (33.3)	0.209
Intermediate, 8-14 days, n (col%)	12 (21.1)	10 (20.8)	2 (22.2)	
Late, 15-30 days, n (col%)	18 (31.6)	16 (33.3)	2 (22.2)	
Very late, >30 days, n (col%)	19 (33.3)	17 (35.4)	2 (22.2)	
Most important symptom (self-reported)				
Reduced vision, n (col%)	34 (59.6)	28 (58.3)	6 (66.7)	0.460
Pain, n (col%)	20 (35.1)	18 (37.5)	2 (22.2)	
Foreign body sensation, n (col%)	3 (5.3)	2 (4.2)	1 (11.1)	
Trauma, n (col%)	20 (35.1)	18 (37.5)	2 (22.2)	0.471
[1]Used traditional eye medicine, n (col%)	39 (68.4)	34 (70.8)	5 (55.6)	0.442
[2]Used other treatment, n (col%)	52 (91.2)	43 (89.6)	1 (100)	0.582
[3]Diabetes mellitus, n/N (col%)	7/53 (13.2)	7/44 (15.9)	0/9 (0)	0.334
[3]HIV infection, n/N (col%)	6/52 (11.5)	4/43 (9.3)	2/9 (22.2)	0.275
[4]Infiltrate size (mm) Mean (SD), range	7.2 (2.3), 0.9-11.5	7.1 (2.2), 0.9-10.9	7.6 (2.7), 1.7-11.5	0.525
[4]Epithelial defect size (mm) Mean (SD), range	6.0 (2.5), 0.5-10.8	5.9 (2.5), 0.5-10.8	6.6 (2.5), 1.7-10	0.507
[5]Ulcer located centrally, n (col%)	52 (91.2	44 (91.7)	8 (88.9)	0.787
Perforated, n (col%)	23 (40.4)	19 (39.6)	4 (44.4)	0.785
[6]Overall microbiological diagnosis, n (col%)				
Fungal species	46 (80.7)	38 (79.2)	8 (88.9)	0.822
Mixed fungal and bacterial species	6 (10.5)	5 (10.4)	1 (11.1)	
Undetermined	5 (8.8)	5 (10.4)	0 (0)	

Acronyms: BCVA: best-corrected visual acuity

[1]Traditional eye medicine involved any form of herbs the patient reported were placed in the affected eye.

[2]Other treatment includes traditional eye medicine and other treatments including eyedrops the patients could not report with specifics. Not all patients could describe what treatment was provided to them in detail.

[3]Not all patients consented to HIV and diabetes mellitus screening.

[4]These were calculated as the geometrical means using measurements per the Mycotic ulcer treatment trial (MUTT) protocol[14]. The upper limits exceeded normal 376 corneal diameter for some lesions, which extended up to the sclera.

[5]Non-central ulcers included 4 paracentral and 1 peripheral. Paracentral was when the ulcer was beyond 4 mm from the center of the cornea but was not a peripherally located either. The patient with the peripheral ulcer had an edge that reached within 2 mm from the cornea-limbus boundary.

[6]The order of material collection was 3 microscopy smears (gram, KOH, CFW), 3 agar inoculations (blood, chocolate, PDA) and 1 broth (BHI).

Table 3: Univariate and multivariate regression model of evisceration at 3 months on probable risk factors

	Univariable analysis			Multivariable analysis		
	Crude RR	95%CI	P-value	Adjusted RR	95%CI	P-value
Age (years)						
<50	Reference					
>50	0.45	0.10, 1.99	0.296			
Continuous variable (per 1 year increase)	0.98	0.94, 1.03	0.499	0.97	0.94, 1.01	0.190
Men	0.72	0.22, 2.41	0.594	0.56	0.19, 1.66	0.297
Education						
No formal education	Reference					
At least primary or beyond	1.62	0.37, 7.11	0.526			
Visual acuity at presentation (Snellen metric)						
6/10 – 3/60	Reference					
<3/60	1.12	0.16, 7.66	0.908			
Time from symptom onset to presentation						
Early, 0-7 days	Reference		0.305	Reference		
Intermediate, 8-14 days	0.44	0.09, 2.09	0.132	0.38	0.08, 1.78	0.222
Late, 15-30 days	0.29	0.06, 1.44	0.117	0.22	0.04, 1.30	0.095
Very late, >30 days	0.28	0.06, 1.37		0.27	0.05, 1.34	0.108

	Univariable analysis			Multivariable analysis		
	Crude RR	95%CI	P-value	Adjusted RR	95%CI	P-value
Reference operation (per 1 day increase)	0.98	0.93, 1.03	0.467			
Infiltrate size at presentation (per 1 mm increase)	1.11	0.82, 1.50	0.500			
Epithelial defect size at presentation (per 1 mm increase)	1.09	0.85, 1.40	0.500			
Hypopyon at presentation	0.94	0.28, 3.12	0.916			
Presence of satellite lesions at presentation	0.42	0.11, 1.50	0.180	0.44	0.11, 1.68	0.230
Perforated at presentation	1.18	0.35, 3.94	0.785			
Monomicrobial (fungus only)	1.91	0.26, 13.74	0.519			
HIV infection	2.19	0.58, 8.21	0.245			

Acronym: CI: confidence interval, RR: risk ratio

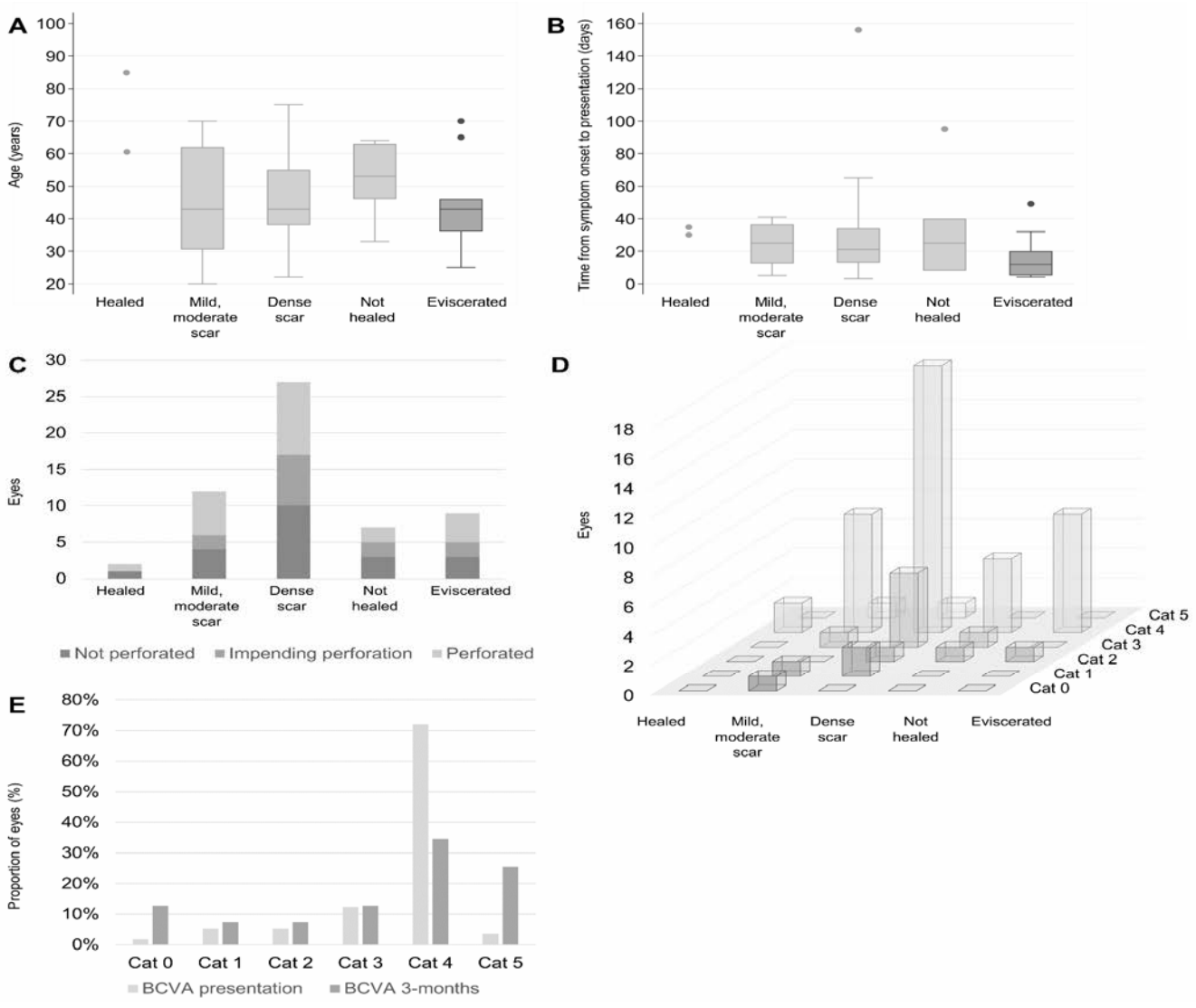

Figure 2: Outcome at 3 months grouped by status of the cornea.

(A) Age (years): median (IQR) are 43 (30.5, 62) among mild/moderate scar, 43 (38, 55) among dense scar, 53 (46, 63) among not healed, 43 (36, 46) among eviscerated (p=0.298). **(B)** Time from symptom onset to presentation (days): median (IQR) are 25 (13, 37) among mild/moderate scar, 21 (13, 34) among dense scar, 25 (8, 40) among not healed, 12 (5, 20) among eviscerated (p=0.684). **(C)** Perforation at presentation: bars show the number of individuals in each outcome category. Proportion of those presented with perforated ulcer are 50% among healed, 50% among mild/moderate scar, 37% among dense scar, 28.6% among not healed, and 44.4% among eviscerated (p=0.987). **(D)** Proportion of individuals at presentation and 3 months grouped by World Health Organization (WHO) best-corrected visual acuity; at 3 months, 7.3% were category 2, 12.7% were category 3, 34.6% were category 4, 25.5% were category 5 (p=0.181). Category 0 (> 6/18), Category 1 (6/18 – 6/60), Category 2 (6/60 – 3/60), Category 3 (3/60 – 1/60), Category 4 (1/60 – Light perception), Category 5 (No light perception). **(E)** BCVA at 3 months.

DISCUSSION

In this prospective cohort study, we have described clinical features and outcomes of conjunctival flap in patients with severe MK. In these cases, the visual prognosis is already poor and intervention is considered with the main goal of preserving the eye, which we achieved in 84% of patients. Based on our study results, we recommend an attempt to save the eye in all cases of severe MK unless there is extensive corneal necrosis or endophthalmitis. Without access to corneal tissue or amniotic membranes, the conjunctival flap procedure resulted in acceptable outcomes. Clinicians seek presenting factors that predict outcome to adjust treatment approach; however, there were no specific baseline clinical presentation or signs predictive of eventual evisceration. Therefore, clinical judgment on case-by-case basis is of utmost importance.

Outcomes: At 3 months,47.3% of patients had dense scars, a modest proportion of the cohort with improvement in BCVA (34.5%). However, the proportion of blindness worse than 3/60 was 72.7%. In Nigeria, the proportion of corneal scarring among a milder case mix of MK was 49.6%[18]. In a retrospective cohort from Tanzania with a preponderance of milder MK cases, the proportion<3/60 was 66.9% at 3 months[6]. In an Egyptian cohort of 20 MK patients (12 fungal), Abdulhalim *et al*[19] achieved 55% improvement in VA at 6 months with 80% globe preservation rate, and the ulcers were smaller (mean 4.98 mm vs 7.2 mm in our cohort). In a cohort of severe MK patients based out of Tamil Nadu, India, the proportion of worse than 3/60 went from 10% at presentation to 16% at 3-month follow-up[7], whereas our cohort with significantly worse baseline VA actually decreased from 87.7% to 72.7%. Investigators based in China have seemingly produced the most evidence on conjunctival flap in MK. In a cohort of 10 with fungal keratitis, VA improved in 60% of patients at 3 months though none of these patients had infiltrates reaching beyond the posterior half of the cornea20.A study from Changsha, China reported globe preservation of 80.6% (n = 29/36 MK patients)[21]. In Nizeyimana *et al.*'s[22] cohort of 16 fungal keratitis patients, globe preservation was achieved in 93.7% (n = 15/16), though 0% had improved VA at follow-up evaluations. Within this context, our cohort of severe MK with an approximate 60/40 split between impending and acute perforation, the outcomes are within expected range.

Without eye bank infrastructure and established corneal tissue imports, the conjunctival flap will be needed in the foreseeable future. Efforts must be made to improve outcomes. However, a paucity of modern conjunctival flap literature means the global data is very heterogenous across different continents with varying patient selection. Ultimately, the experiences in our setting suggest conjunctival flap is an appropriate treatment modality when no other options exist. A couple disadvantages of conjunctival flap should be noted. None of our participants had previous glaucoma filtering or posterior segment surgeries. Secondly, limbal stem cell loss may adversely affect further operations19, which is an important consideration as a temporary bridge to PK. From a visual outcomes standpoint, surgically managing severe MK is challenging as even penetrating keratoplasty results in 61.4% with <6/60 in Uttarakhand, India[23]. The same measure in our cohort was 80.1% even though conjunctival flap is not intended to improve VA. Since surgical options generally yield poor visual prognosis, prevention of MK incidence and progression is of the utmost importance.

Risk factors among severe microbial keratitis patients: Risk factors necessitating surgical treatment for MK have been previously studied and include: older age, low education, delayed presentation, outdoor manual labour (especially agriculture), prior treatment with topical steroids, poor visual acuity at presentation, central ulcer, large size ulcer, presence of perforation, and hypopyon[24]. Usual demographic factors appear blunted in our multivariable regression model as they are evenly distributed between the non-eviscerated and eviscerated group. This may be an effect of our cohort characteristics and does not necessarily invalidate significance of known risk factors. For example, our cohort had relatively low number of cases associated with trauma (35.1%), which is similar to 25% in a cohort from Tanzania6 but lower than the 48-64% from cohorts in India[14,24]. The proportion of male agriculture workers was high, suggesting a tendency for MK to affect adult males who work outdoors with higher occupational hazard exposure. Unlike Chidambaram *et al*'s[7] severe MK cohort, we did not find a significant association between female gender, older age, lack of education, ulcer size, and symptom duration. In fact, it appeared individuals with shorter presentation time were more likely to be in the eviscerated group. This is likely a surrogate for disease severity with symptoms more bothersome driving the individuals to seek attention sooner.

HIV infection did not appear to increase risk of evisceration in our cohort, though CD4 levels were not acquired. HIV infection has been implicated in increasing risk of herpes keratitis and keratouveitis since cell-mediated immunity is important in controlling corneal infections, though no direct evidence exist for control of corneal infections by extracellular pathogens, such as fungi. The HIV prevalence in our cohort is nearly double the prevalence in Ugandan adults; this cannot be merely coincidental, but perhaps the effects of immune suppression on evisceration is mediated by the similar level of MK severity. The severity was rather uniform between non-eviscerated and eviscerated groups. There were similar distributions between the groups in demographics, delays to care, 91% seeking alternative treatments prior including traditional eye medicines, presenting BCVA, infiltrate and epithelial defect sizes, central location of the ulcer, and perforation status. It is likely that once the

severity of MK has reached a certain level sharing all these clinical features, the visual prognosis will be poor and the risk for eventual evisceration is rather unpredictable. This was also observed in Nizeyimana *et al.*'s[22] cohort in which there was no difference in risk factors (age, gender, surgical duration, combined surgery) on complication rate and evisceration[22].

Fungal keratitis, referral system, and traditional eye medicines: Taking all cases of MK in our southwestern Uganda cohort (n = 313), fungal keratitis is responsible for 62%[13]. In this present study, fungal keratitis accounts for 80.7% of severe MK. This is not surprising given in sub-Saharan Africa, fungal species are the predominant if not one of the leading causative pathogens in MK[5,6,15,18,25]. Yet fungal keratitisis difficult to treat medically due to poor drug bioavailability, diminished corneal penetration, and the length of regimens. Fungal keratitis is associated with worse visual prognosis and higher rate of surgical intervention than bacterial keratitis[26,27]. Fungal keratitis can be worsened by use of combined steroid/antibacterial ophthalmic solutions commonly dispensed by lower level health facilities in Uganda. Diagnosis and treatment of MK should occur as soon as possible. This requires expedited referral to facilities that can perform a slit lamp examination and have access to topical natamycin. As in other SSA countries, there was a high rate of TEM use, potentially introducing pathogenic fungal spores into the eye and likely worsen progression of MK[28]. Traditional healers are well-integrated into their communities and are trusted; therefore, engaging with traditional healers to change their practice may be a practical approach rather than outright outlawing their work.

TEM and alternative treatments further delay care seeking as evidence by the high median time to presentation in our cohort. Clear and widely-adapted referral protocols are needed. Lower level health facilities should refer to facilities that can perform corneal scrapings to determine aetiology. Microscopy is useful in southwestern Uganda given such a high prevalence of fungal keratitis; sensitivity and specificity are approximately 90% and 95%, respectively for Gram, KOH, and CFW stains[27]. Ophthalmic clinical officers (OCOs – mid level ophthalmic care providers) are well positioned to implement this diagnostic workup and initial management. If a patient is likely to be lost to follow-up, we strongly encourage immediate referral to the tertiary level eye hospital despite the long travel distances. Microbiology lab and rapid diagnostics at these facilities enable more accurate diagnosis, and the OCO closest to the patient may manage follow-up and monitoring as the primary eye care provider.

Our study has three limitations. Despite our sample size being the largest to date in the literature, it is not adequately powered to fully assess specific clinical risk factors for evisceration, such as infiltrate and epithelial defect size. We believe a larger, multi-country collaborative clinical trial similar to the Asia Cornea Society Infectious Keratitis Study is needed in SSA. Another limitation is the data were collected from two eye hospitals within the same town, though these hospitals serve a catchment area of 5 million inhabitants and are the only tertiary eye hospitals in the Southwestern sub-region of Uganda. Finally, we did not have access to anterior segment Optical Coherence Tomography (OCT) at the time of this study. Anterior segment OCT could have improved precision in measurements of infiltrate and epithelial defect size pre- and post-operatively.

In conclusion, our results show conjunctival flap is an effective procedure in severe MK, restoring surface integrity and providing structural, immunologic, and metabolic support to promote corneal healing. This is important if the patient's goal is to avoid evisceration. Patients should be counseled that the visual prognosis is poor, but the flap may serve as bridge to PK.

Conflicts of interest: None to declare.

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Characteristics of babies referred to a tertiary eye hospital of Bangladesh for retinopathy of prematurity screening and management, a database analysis

Niyonzima JC, Nahar N, Chowdhury M, Kumar SD, Rahman M

SpahaniIslamia Eye Institute and Hospital, Dhaka, Bangladesh

Corresponding author: Dr. Jean Claude Niyonzima. Email: claudeniyonzima@gmail.com

ABSTRACT

Background: IspahaniIslamia Eye Institute and Hospital (IIEIH) is a not for profit hospital and a leading Retinopathy of Prematurity (ROP) screening center in Bangladesh.
Objective: The study had an aim to analyze the characteristics of referred babies and identify possible bottlenecks in the referral system.
Methods: Electronic records of babies referred to IIEIH for a period of three years (2016-2018) were analyzed retrospectively. All the babies registered in the electronic file were screened by any of the three consultants with a keen interest in ROP. Variables of interest were ROP stage, gestational age, birth weight, time to screening, referring institution and treatment modalities (laser, Anti-VEGF, retina surgery or combination). Data was exported to SPSS version 23 for Mac for descriptive and correlation analysis. A P-value of less than 0.05 was considered statistically significant.
Results: Eight hundred and eighty seven babies with ROP stage 1 or above were registered over the 3 years period, a large majority were referred mostly by neighbouring private institutions (75%), 60% of babies were moderate pre-terms according to WHO classification, the mean birth weight was 1563±397.1 grams. ROP stage 2 was dominant (37%) and 61% of any stage ROP babies had at least one treatment modality. There was an obvious delay in screening since only 55% of babies were screened within a period of less than 8 weeks. The younger the gestational age and the lower the birth weight, the higher the risk of presenting with ROP with advanced stage. (P-value<0.001).
Conclusions: The majority of babies with ROP came from private institutions and more than half of them needed at least one treatment modality. The delay in screening was a key bottleneck and needs to be addressed. We recommend more NICUS and more ROP services in public hospitals

Keywords: Retinopathy of prematurity, Screening, Treatment options, Referrals

INTRODUCTION

In 2014, Bangladesh ranked fourth in the top ten countries with the highest incidence of the pre-terms population behind India, China, and Nigeria. The same report showed an estimate of 19% of 3 152 549 live births were pre-terms, representing 4% of the global population of pre-terms[1].

ROP screening in Dhaka started in 2010, IIEIH and National Institute of Ophthalmology (NIO) were the only screening centers by then. They offered limited services for a period of 2 years. In 2013, Orbis International joined the centers and supported the human resources empowerment and raising awareness on ROP[2].

In a local press release, the ROP team at Ispahani Islamia Eye Institute and Hospital (IIEIH) in partnership with Orbis international warned there was rising incidence of blindness secondary to ROP thought to be linked to low rate of detection of ROP in the Neonatal Intensive Care Units (NICU) of the country or a late screening of babies who are already at advanced stage of the disease[3].

Besides these concerns, there was an international concern over the rising incidence of ROP in the developing countries referred to as "the third epidemic" of blindness directly linked to ROP[4].

It is now known that low gestational age, low birth weight, exposure to a high concentration of oxygen and neonatal sepsis are high-risk factors for ROP. WHO categorizes prematurity in 3 stages: extreme preterm <28 weeks, very preterm 28 to less than 32 weeks and late preterm between 32 and 37 weeks[5].

Some efforts have been deployed to improve the ROP screening in Dhaka and IIEIH is one leading referral center for ROP screening. At least 20 NICUs (only 3 are public) in the town of Dhaka are referring babies to IIEIH who either meet the objective criteria (gestational age <33 weeks or birth weight <2000 grams) or assumed to be at higher risk at the discretion of the neonatologists. Some babies may come from other centers, these are usually seen lately and may already have advanced disease.

In 2017, a study presented an overview of the screening program at IIEIH with a focus on the pattern

of ROP in the screened population. The major conclusion lines highlighted the significant public concern brought in by ROP morbidity and the need for a stronger government response[2].

This study objective was to analyze the characteristics of babies referred for ROP screening.

MATERIALS AND METHODS

This was a retrospective study conducted at IIEIH, an urban tertiary eye hospital of Dhaka, Bangladesh. The study period covered January 2016 till December 2018. The data was retrieved in the ROP screening electronic database an excel folder that stores patients' medical records numbers, gestational age, birth weight, ROP stage, time to screening, referring institution (private, public, not for profit or self-referrals) and treatment modalities (laser, Anti-VEGF, retina surgery or combination). Data was broken down monthly. Since the database was specifically designed for ROP, all the stored data was included in the study. There were no exclusion criteria.

The investigator did not get access to the whole database but was granted a copy of the data for the specific period of the study by the Head of the Department. To process the data, the investigator checked the data sheet for completeness before they were exported to SPSS version 23 for Mac for descriptive and correlation analysis. A one-sample t-test was used to test for correlation. Results were presented using tables, pie-charts, bar charts. A P-value of less than 0.05 was considered statistically significant.

The study was approved by Ispahani Islamia Eye Institute and Hospital Ethical Research Committee (IIEIH-ERC) and no patient consent forms were needed since the researchers used a database and did not involve any human or photography.

RESULTS

ROP in numbers and treatment modalities: We retrieved 2540 babies screened for the three years period in the database among which 887 had ROP of any stage. The ROP incidence was 34.9%. Demographics and some clinical data were not available in the database. The summary of the numbers of babies screened and treated are presented in Table 1.

More than half (53%) of the screened babies were eligible for at least one treatment modality. Laser is the most commonly prescribed and performed procedure. Cumulatively, 382(43%) babies underwent laser photocoagulation over the 3 years. Trends analysis for the same period shows there is a sharp increase in use of anti-VEGF(from 5 (2%) cases in 2016, 49 (17%)in 2017 to 68(13%) in 2018) and a shy decrease in numbers of babies who need vitreoretinal surgeries (from 19 (7%) surgeries in 2016, 19(6.5%) in 2017 to 16 (4.5%)in 2018). Some babies required a combination of 2 or 3 treatment options.

Table 1: Incidence of ROP and treatment needs

	2016	2017	2018	Total
Screened babies	953	778	809	2540 (100%)
ROP(Incidence)	246(25.8%)	292(37.5%)	349(43.1%)	887(34.9%)
No treatment	121	137	159	417
Laser treatment	102	89	118	309
Anti-VEGF injections	1	26	22	49
VR surgeries	18	13	11	32
Laser +Anti-VEGF	3	21	44	68
Laser +VR surgery	0	4	3	7
Laser +Anti-VEGF+VR surgery	1	2	2	5

Gestational age: The gestational age is presented in Figure 1. Five hundred twenty-eight babies (60%) were moderate or late preterm according to WHO classification. Of note, 216 babies were older than 33 weeks (24%) and 14 babies (2%) did not fit in any WHO category of prematurity although diagnosed to have various stages of ROP. The mean gestational age was 31.9± 2.3 weeks, with a range of 23 to 40 weeks.

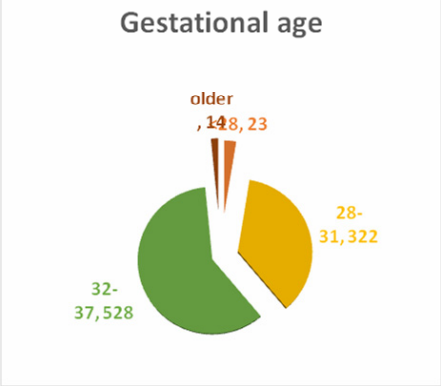

Figure 1: Gestational age according to WHO categories

Birth weight: The mean birth weight was 1563 ± 397 grams, with a range of 600 to 3700grams. The birth weight subcategories commonly used in ROP studies are summarized in Figure 2.Babies weighing 1501-2000 grams represented 34.6% of the total number of ROP babies, followed by babies weighing 1251-1500 grams (32.6%). Thirteen babies (1.5%) had birth weight exceeding 2500grams.

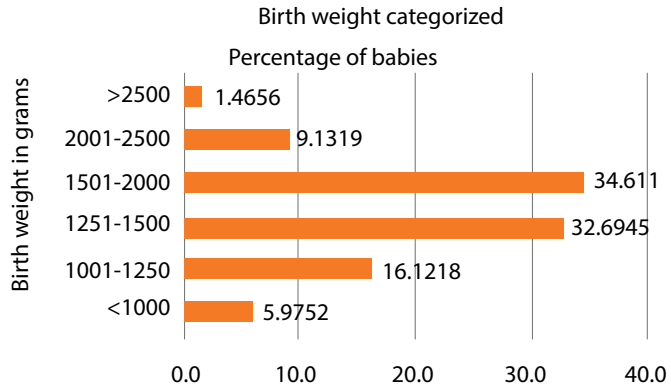

Figure 2: Birth weight subcategories

ROP staging: Stage 2 ROP was the most prevalent (37.1%) among babies seen. Stages 3 and 1 have almost a similar prevalence. Of note, the aggressive posterior ROP (APROP) prevalence was as high as 10.5%. Details are shown in Figure 3. Trend analysis over the period shows exponential increase of ROP stage 2 and a decrease of stages 4&5 (prone to surgical management).

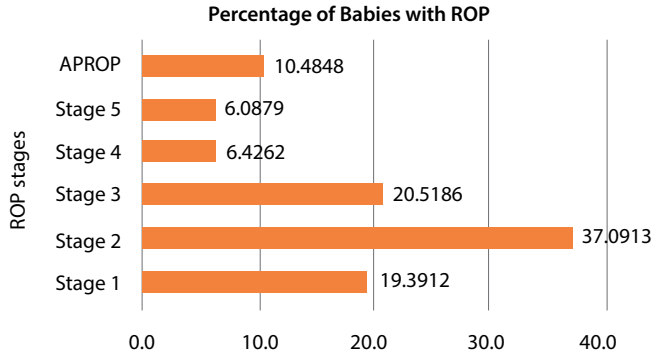

Figure3: ROP staging

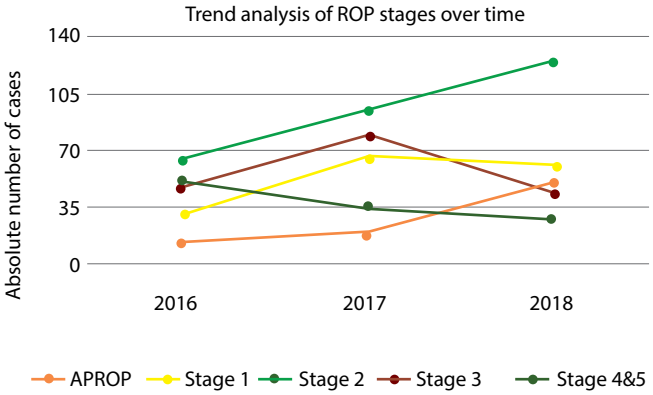

Figure 4: Trend analysis of ROP stages over time

Chronological age and time to screening: Barely half of the babies (55.3%) were screened before age 2months corroborating the widely recommended 4-6 weeks screening period, the mean time to screening was 1.7±1.19 months, with a range of 1 to 10 months. More details are presented in Figure 5.

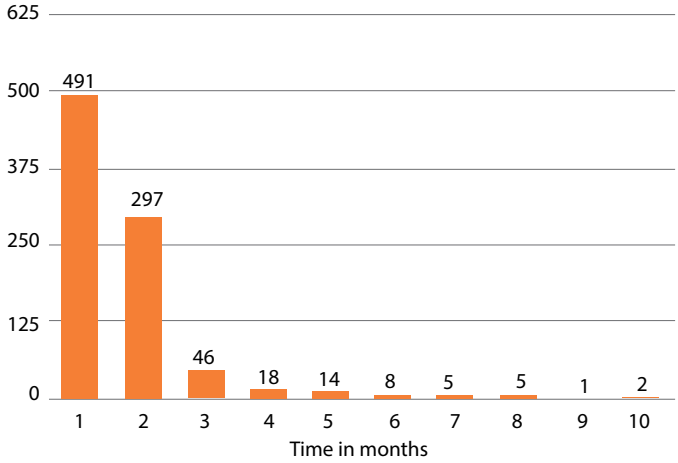

Figure 5: chronological age at time of screening

Origin of referrals: The majority of babies are referred by private practitioners (75.4%) mostly from Dhaka the main city. Public hospitals referred 18.4%. Note that almost 3% of babies came directly from the community(self-referred) (Figure.6).

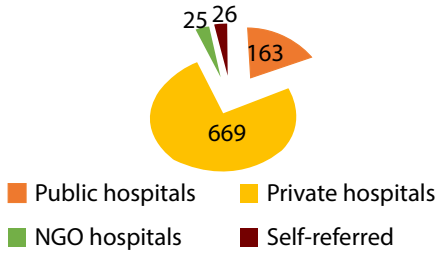

Figure 6: Origin of referrals

Correlation analysis between ROP stages and risk factors: There is a negative correlation between the gestational age, birth weight, and ROP stage, the lower the parameter, the higher the risk for severe ROP stage (P-value<0.001). Conversely, the babies who delayed coming to the hospital were likely to have a higher ROP stage (P-value<0.001). Values are displayed in Table 2.

Subset analysis: There were 14 babies older than 37 weeks of gestational age in the database. Four of these babies were treated. Three had a low birth weight of 1300 grams each, the fourth was seen later after 2 months and the weight was already 3000 grams. One baby had a stage 5 ROP, no surgical intervention was possible.

Table 2: Correlation analysis

Correlation Matrix

		Stage	Time to screening	Birth Weight	Gestational age
Stage	Pearson's r	—			
	p-value	—			
Time to screening	Pearson's r	0.219	—		
	p-value	< .001	—		
Birth Weight	Pearson's r	-0.122	-0.110	—	
	p-value	< .001	0.001	—	
Gestational age	Pearson's r	-0.221	-0.229	0.519	—
	p-value	< .001	< .001	< .001	—

*Correlation is significant at 0.01 level(2-tailed)

DISCUSSION

Ispahani Islamia Eye Institute and Hospital (IIEIH) screened more than 800 babies yearly and therefore the institute can be regarded as one of the most important ROP centers in the world. This is an important dataset for ROP screening compared to the numbers seen in the literature[6–10].

IIEH ROP experience shows how ROP screening and management services can be scaled up in a given hospital; from 50 ROP cases screened in year 2012 to a yearly average of 296 cases in the last 3 years is a giant step made forward[2].

The incidence of ROP among the referrals was 34.9%. Incidences reported in the literature vary and often depend on the screening guidelines of each country. In this study, although the screening guidelines targeted preterm babies younger than 33 weeks of gestational age or babies with a birth weight lower than 1500grams, there was a big number of babies (24%) older than that GA. Elsewhere, reported incidence was calculated at 32 weeks of GA and there is clear difference between developed and developing countries whereby ROP incidence appears to be lower in the former and higher in the latter: France (22.3%), Sweden(25.5%), United Kingdom (19.2%), India (37.2%), Kenya(40%), Saudi Arabia(41%), Iran (47.3%),Turkey (50.9%) and Istanbul (52.7%)[6,11–16].

Among the babies screened to have any ROP stage, 53% needed at least one treatment modality. As reported and supported by other researchers in this field, photocoagulation laser remains the most common treatment modality for ROP and was performed in 389 (43.8%) cases alone or combined with other treatment options. Trends analysis for the 3 years period shows there is a shy but steady increase in use of anti-VEGF(from 5(2%) cases in 2016, 49(17%) in 2017 to 68(13%) in 2018) and a decrease in numbers of babies who were admitted for vitreoretinal surgeries (from 19(7%) surgeries in 2016, 19 (6.5%) in 2017 to 16 (4.5%) in 2018). This was in keeping with the decreasing numbers of surgical cases as observed in the trend analysis.

The mean gestational age in this study is higher than those usually reported elsewhere, and some 14 babies were not preterm as they exceeded 37 weeks. Some of the babies had low birth weight or had other risk factors including but not limited to admission in a NICU for sepsis or anaemia necessitating transfusion. Among this sub-group, nine babies did not need any treatment, three had 1300 grams of birth weight and were treated by laser and one who reported lately after 8 weeks in NICU needed retinal detachment surgery. Other researchers have postulated ROP incidence was found to be more associated with low birth weight rather than gestational age[17].

Although ROP in big babies has been reported in India, the authors still put a caveat on the accuracy of the reported gestational age and recommended an emphasis on younger preterm rather than big babies so as not to waste man-hours[11,18].

The birth weight analysis shows a mean of 1563 ± 397 grams, this was comparable to the findings of Akçakayaet al19 in their study on ROP screening in a tertiary eye hospital in Istanbul where the birth weight mean was 1,549.4 ± 512.9 grams. Al-Amroet al9 in Saudi Arabia had a completely different scenario where ROP was only diagnosed in babies aged less than 32 weeks and who had a birth weight less than 1250 grams. IIEIH cut-off for screening is 32 weeks and is a referral center as opposed to other research centers that report data obtained from their hospitals' NICUs. Moreover, some babies were not referred by a health professional, which means they decided to consult when parents noted obvious symptoms like poor or no fixation or leukocoria. A subset analysis of 'self-referred' group showed 7 babies (26%) were classified ROP stage 5 of whom only one baby was admitted for surgery. This is a clue that these babies come very late to the hospital.

The time (postnatal age) to screening is also following the same trend as the gestational age and birth weight as it is longer than what we would expect. It is worth noting that 9% of babies came after 3 to 10 months of chronological age. Delayed screening is a matter of concern as it is an important prognostic factor for the successful management of ROP. Many clinicians and researchers report there is a short window for screening between symptoms appearance and complications occurrence. However, this has been a debate and may change from population to population[9].

The socioeconomic status of the families was not available in our database and such a piece of valuable information may shed more light on the issue of a delayed screening.

Our finding on ROP staging is in agreement with other researchers' reports as stage 2 was the most prevalent in our case series. Aggressive posterior ROP was 10.5% of the cases. Other authors reported a similar incidence of APROP in India (13.2%)20.The classification in zones was not available in the database and should be included in the future.

The referring institutions were private in the majority of cases. This is partly explained by the large number of private NICUs in Dhaka. We could not ascertain whether the babies were necessarily born in the referring hospitals or whether they consulted in a private institution later after birth. In the first hypothesis, two scenarios are possible; either ROP screening is effectively happening in the public hospitals and there is no need to refer or parents of babies born in public hospitals do not get to know about ROP screening. The former is less likely based on the previous studies[2,3].

In the second hypothesis, it would mean many parents trust private pediatricians and still visit them even after the babies were born in public hospitals. Whichever hypothesis is considered, public hospitals need their mother and child health strategy reinforced to bridge the gaps noted in ROP screening for a timely management.

CONCLUSIONS

IIEIH is an important ROP screening center given the numbers seen yearly and has achieved a great deal in scaling up services over the last few years. A database is an excellent tool that helps to monitor the progress, however socio-economic status, ROP zones, "plus disease" occurrence data are yet to be included. The delay in screening was evident. Babies with ROP risk factors are referred late and some have advanced disease that requires vitreo-retinal surgeries. The public hospitals need to increase the number and capacity of NICUs with ROP screening staff for a large public access.

Ethics approval and consent to participate: This is a database analysis; however, consent was taken from babies' parents before screening and treatment and agreed their data to be used for research purposes. The study was approved by IIEIH –ERC.

Consent for publication: The study was approved by the relevant authority (IIEIH-ERC).

Competing interests: None of the authors has competing interest to declare

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Sensitivity and specificity of McMonnies Questionnaire in diagnosing dry eye syndrome among patients aged 40 years and above in Uganda

Atto G[1], Twinamasiko A[1], Arunga S[1,2]

[1]Department of Ophthalmology, Mbarara University of Science and Technology, Uganda
[2]International Centre for Eye Health, London School of Hygiene & Tropical Medicine, UK

Corresponding author: Dr Gladys Atto, Department of Ophthalmology, Mbarara University of Science and Technology, Uganda. Email: attoglad@gmail.com

ABSTRACT

Objective: To evaluate the sensitivity and specificity of McMonnies Questionnaire (MQ) as a screening tool for Dry Eye Syndrome (DES) among patients aged 40 years and above attending Ruharo Eye Centre (REC).
Design: This was a cross-sectional hospital-based study.
Methods: The study was conducted during the months of September to December 2017. Both males (76) and females (91) who were aged 40 years and above using convenient sampling were included. All participants were screened for DES using McMonnies Questionnaire after which assessment for the signs of DES using Schirmer I, TBUT and Rose Bengal tests were done. We entered data into Excel and exported into Stata 13.0 for analysis.
Results: A total of 167 patients were enrolled, 91 (54.49%) were females. The female to male ratio was 1.2:1. The median age of the patients was 63 years (IQR: 54-72, range: 40-94). The median Schirmer I, TBUT and MQ scores were 14 mm (IQR: 5-22, range: 1-35), 6.67 seconds (IQR: 3.33-17, range: 1-34.33) and 12 (IQR: 9-17 range of 2-27). The prevalence of DES was 68%. The sensitivity and specificity of McMonnies Questionnaire in diagnosing DES were 81.6% (95% CI, 73.2 - 88.2) and 39.6% (95% CI, 26.5 - 54) respectively.
Conclusion: The McMonnies Questionnaire had a high sensitivity (81.3%)but low specificity (36.9%) in diagnosing DES. Therefore, when such a test is negative, it is good for ruling out DES but not suitable for identifying people at risk of the disease.

Key words: Dry eye syndrome, Sensitivity and specificity, McMonnies Questionnaire, Uganda

INTRODUCTION

The international Dry Eye Workshop 2007 (DEWS) defined Dry Eye Syndrome (DES) as a multifactorial disease of the tear and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface[1]. DES is very common, affecting especially those older than 40 years with prevalence estimates ranging from approximately 10-30% of the population in the United States to 27.5% in rural Indonesia and 18.4% in India[2–4].

A variety of diagnostic tests are in common clinical usage such as TBUT, Schirmer, tear osmolarity, ocular surface stains but there is no consensus as to which combination of tests should be used to define the disease either in the clinic or for the purposes of a research protocol[5]. Practitioners sometimes make use of dry eye questionnaires to identify patients at risk for dry eyes[6]. The McMonnies Questionnaire is among the earliest and most widely used screening instruments for DES and it was found to be a useful tool in detecting the presence of dry eye disease and those at risk of developing the disease[6].

MATERIALS AND METHODS

This was a cross-sectional hospital-based study carried out in Ruharo Eye Center (REC), South-western Uganda. Approvals were sought from the Faculty Research Committee and Institutional Ethical Review Committee of Mbarara University of Science and Technology and REC. Informed consent was obtained from all the participants. Participants were also informed that participation in the study was voluntary and that refusal to participate would not affect their routine care at the hospital.

Convenient sampling was used. A sample size of 167 patients was determined using Buderer's formula[7].Since the test was required to be more sensitive than specific, the sensitivity formula was used to determine the sample size. Therefore, using the formula below, the anticipated sensitivity SN = 0.98, absolute precision = 0.03 with 95% confidence level (two-tailed), expected prevalence = 0.18 from hospital-based study[2].

Sample size (n) based on sensitivity.

$$\frac{Z^2 1 - \alpha/2 \times SN \times (1-SN).}{L^2 \times Prevalence}$$

Data collection period lasted for a total of 4 months of non-consecutive days from September to December 2017. We included all patients aged 40 years and above who consented to the study and excluded patients with symptoms requiring acute eye care and those who had undergone eye surgery in the past 3 months.

Demographic details including, age, sex was recorded. All patients were symptomatically screened for dry eye using McMonnies Questionnaire (MQ) modified by Nichols etal8. The MQ grades patients' symptoms with scores ranging from 0-409 and classifies patients as: normal (<10), marginal dry eye (10-20) and pathological dry eye (>20). All patients (dry eye and no dry eye) were then subjected to clinical examination and clinical dry eye tests.

Clinical examination

Visual acuity assessment was done using tumbling Snellen E- chart at 6meters.Slit lamp examination of anterior segment was done to assess conjunctival hyperemia, presence of mucus filament, thickening of the lid margin and telangiectasia. Meibomian gland dysfunction was assessed by performing gland expression with digital pressure to the central lower lid to indicate whether the orifices are plugged or open. A normal secretion was clear while an abnormal secretion would be cloudy meibum or more viscous, granular, or toothpaste-like material on expression or absence of expressible material.

The Schirmer 1 test (without anaesthesia) was performed by placing the filter strips which were 5x35 mm (Devine Meditech) in the inferior temporal fornix with the eyes closed. The test result was considered positive if the length of wetting obtained was ≤ 10 mm in 5minutes.

Tear Break Up Time (TBUT) test was recorded with the patient on a slit lamp after corneal staining using fluorescein strips (Ophtechnics limited) 1 mg/ml staining. The strips were initially wetted with normal saline before being gently dabbed on the lower aspect of the bulbar conjunctiva. The patients were asked to blink several times and then look straight at a target; the time taken for the first dry spot to appear was recorded, and an average of three readings was taken as TBUT. The test was considered positive if the average TBUT was ≤ 10seconds.

Ocular surface evaluation on a slit lamp was done using Rose Bengal strips (Devine Meditech) 1.5mg/ml staining placed for 2min in the lower outer conjunctional cul-de-sac after wetting using normal saline. The Oxford grading scheme was used to score ocular surface damage10. The grading chart is made up of five panels, each of which represents typical gradations of stain on either cornea or conjunctivaas 0, I, II, III, IV and V depending on number of dots per panel. Minimum being grade 0 and maximum score V11.

Both eyes of patients were examined, however, for purposes of analysis, only the more severely affected eye was considered.

Since no single test is considered a "gold standard", a composite score was formed using Schirmer I test and TBUT to act as the gold standard. A score of "one" was assigned to a positive test and a score of "zero" to a negative test and summation of the scores were taken as the composite score. A composite score of one and above was taken as DES, for example, if the TBUT and Schirmer I scores were zero and one respectively, the result would be interpreted as positive; if both scored one, the result would still be positive but negative if both scores were "zero" as shown in Table 1.

Table 1

	Schirmer I	TBUT	Composite score	Diagnosis
Patient 1	1	1	2	DES
Patient 2	0	0	0	No DES
Patient 3	1	0	1	DES

Analysis

The data set was entered into Microsoft Excel and exported into STATA version 13.0 for analysis. The prevalence of DES among patients aged 40 years and above presenting at REC was expressed as a proportion of patients diagnosed with DES out of all the patients enrolled in the study, and the respective confidence intervals were provided.

Sensitivity was calculated using STATA as the proportion of true cases (people with DES) correctly categorized as having the disease by the MQ, and specificity as the proportion of true non-cases (healthy people) correctly categorized as being healthy.

The McNemar's test was used to test if there was a statistically significant difference between MQ and the composite score with a P-value of <0.05 being significant.

RESULTS

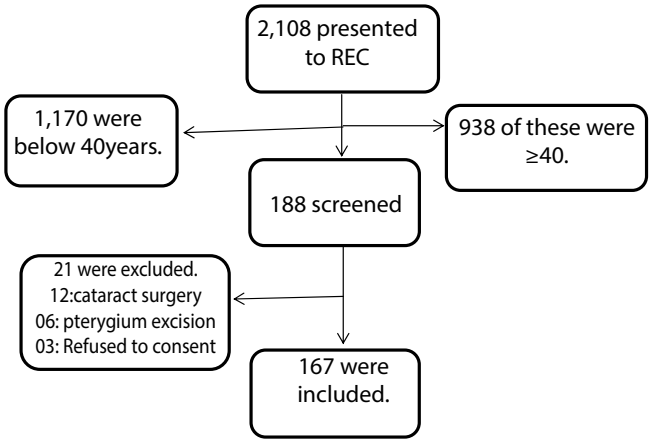

Figure 1: Flow chart

Table 2: Baseline characteristics and examination findings(n=167)

Variable	Description	Frequency	Percentage
Sex	Male	76	45.5
	Female	91	54.6
Age (years)	40-50	30	18.0
	51-60	44	26.4
	61-70	47	28.1
	>70	46	27.5
Examination findings			
Eyelids	Normal	164	98.2
	Retracted	0	0
	Ectropion	1	0.6
	Entropion	2	1.2
	Lagophthalmos	0	0
Eyelid margin	Normal	160	95.8
	Erythema	1	0.6
	Abnormal Deposits	1	0.6
	Keratinized	5	3.0
Meibomian gland orifices	Plugged	11	6.6
	Open	156	93.4
Eyelashes	Normal	164	98.2
	Trichiasis	3	1.8
	Distichiasis	0	0
Conjunctival hyperaemia	Absent	92	55.1
	Mild	57	34.1
	Moderate	18	10.8
	Severe	0	0
Pannus	Present	165	98.8
	Absent	2	1.2
Mucus filament	Present	35	21.0
	Absent	132	79.0

Prevalence of Dry Eye Syndrome (DES)

The McMonnies Questionnaire diagnosed the highest number of patients, 74.9% as having DES followed by the composite score with 68%. The 68% prevalence of DES as determined by the composite score was higher than that obtained by the individual tests as shown in Figure 2. The proportion of females and males who had DES was 70% and 66% respectively.

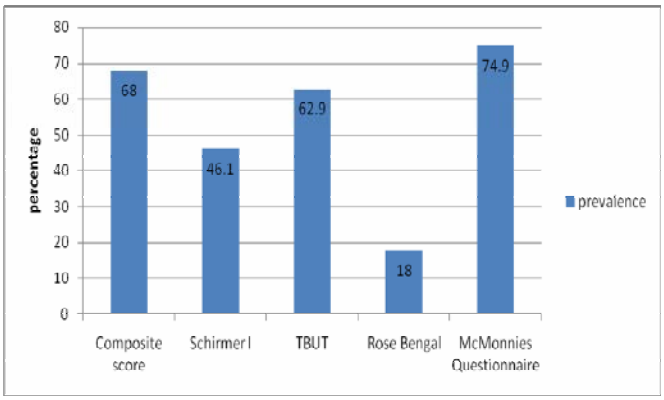

Figure 2: The prevalence of DES as determined by MQ and the different clinical tests (n=167)

Sensitivity and specificity of McMonnies Questionnaire in diagnosing DES

The sensitivity and specificity of McMonnies Questionnaire in diagnosing DES were 81.6% (95% CI,73.2 - 88.2) and 39.6% (95% CI,26.5 - 54) respectively. A positive predictive value of 73.4% and a negative predictive value of 50% were found as shown in Table 3.

Table 3: Two by Two

	Composite score positive	Composite score negative
MQ positive	93a	32b
MQ negative	21c	21d

Sensitivity= a/(a+c) x 100
Specificity= d/(d+b) x 100
Positive predictive value=a/a+b
Negative predictive value=d/c+d
McNemar's test X2= (b-c)2/(b+c) p>0.05
Accuracy=a+d/a+b+c+d X 100

Table 4: Sensitivity and specificity of McMonnies Questionnaire in diagnosing DES

Validity indices	Score	95% CI
Sensitivity	81.6%	73.2% - 88.2%
Specificity	39.6%	26.5% - 54%
Positive Predictive Value	73.4%	65.8% - 81.8%
Negative Predictive Value	50%	34.2% - 65.8%
Likelihood ratio (+)	1.35	1.07 - 1.71
Likelihood ratio (-)	0.465	0.279 - 0.774

DISCUSSION

This study found the sensitivity and specificity of McMonnies Questionnaire (MQ) in diagnosing DES to be 81.6% and 39.6% respectively. Previous studies using this questionnaire revealed varying values of sensitivity and specificity ranging from (34%–98%) and (36%–97%) respectively which might partly be explained by the difference in the experimental population [8,9,12,13]. McMonnies *et al*[13], for instance, studied a group of 50 women with Sjögren syndrome who had severe DES while our study included all patients aged 40 years and above, irrespective of their diagnosis. Furthermore, different scoring methods of the MQ have been used since its development.

In our study, we adopted the modified scoring system developed by Nichols and associates[8] which could possibly explain why the two findings were similar (82% and 36%) in contrast to the weighted algorithm based on clinical experience used by McMonnies *et al*[13] whose sensitivity and specificity estimates were higher (92% and 93% respectively) but one cannot rule out the possibility of selection bias since they assessed efficacy based on the data from the same sample of patients from whom the cutoff values for diagnosis were derived and not from an independent sample of new patients.

We thought of looking at age and gender stratifications of sensitivity and specificity by MQ, but we did not feel that these comparisons would be necessarily fair because the scoring algorithm for the McMonnies Index automatically weights women higher than men, and older individuals higher than younger individuals.

The prevalence of DES determined by MQ was 75% (125), quite higher than that of Schirmer and TBUT alone (46.1% and 62.9% respectively) which might probably reflects its poor correlation with other dry eye clinical tests as reported in other studies[14,15]. The overall prevalence of patients with DES in our population was as determined by the composite score was68%, similar to the 58.4% obtained from an Indian-based hospital study but higher than the 37.6% reported in the 40-49 year age group obtained from a population based study in Indonesia4. The high prevalence in our setting may be partly explained by the fact that our study utilized a composite score of Schirmer and TBUT that would be expected to capture more cases of DES than would be the case if individual tests were used. Considering that our data collection took place in a dry season, we might have probably overestimated the prevalence since dry conditions are known to exacerbate symptoms of dry eye nevertheless, the result still reflects how common DES is among this age group, a finding quite in agreement with many other studies even if their prevalence values were not as high as that obtained in our study[16,17].

The authors of this study chose TBUT and Schirmer tests for composite gold standard because they proved to be highly sensitive in most studies[10,18,19].

In conclusion, MQ had a high sensitivity but low specificity for diagnosing DES; when such a test is negative, it is good for ruling out DES but not suitable for identifying people at risk for the disease. An ideal screening test should have both a high sensitivity and specificity. We therefore recommend further studies with a larger sample size to further evaluate the screening properties of the questionnaire.

Availability of data and materials: The datasets used during the study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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From strabismus to pseudo-strabismus and familial exudative vitreoretinopathy, a clinical journey of phenotypically identic twins with symmetric ocular features

Pathan AH, Niyonzima JC, Sazzad Iftekhar QS

Ispahani Islamia Eye Institute and Hospital, Dhaka, Bangladesh

Corresponding author: Dr Jean Claude Niyonzima. Email:claudeniyonzima@gmail.com

ABSTRACT

Familial Exudative Vitreoretinopathy (FEVR) is a rare genetic condition and several genes have been identified. Clinically, it can cause macular dragging and therefore pseudo-strabismus or exudative or tractional retinal detachment leading to loss of vision in severe cases. Other symptoms including refractive error, cataract and glaucoma have been documented. The main differential diagnosis remains retinopathy of prematurity. We report two phenotypically identic twins that were seen in a lower level hospital and diagnosed with strabismus presumed to be secondary to myopia. A multidisciplinary team including optometrist, paediatric and vitreo-retinal ophthalmologists re-examined the twins and found eccentric fixation and features of FEVR on fundoscopy and angiography. There was a high chance that the twins would have been managed only with spectacles missing the opportunity to be followed up for a more severe vitreoretinal proliferative disease. This case report underlines the genetic basis of the disease with symmetrical and equally distributed myopia, macular dragging and subsequent pseudo-strabismus and FEVR angiographic features. A multidisciplinary team-work was of utmost importance. Beside refractive error correction, the twins also benefited from laser photocoagulation to the avascular retinae to prevent further progress of the proliferative vitreoretinopathy. A good clinical history is enough to rule out retinopathy of prematurity and focus on other causes of retinal fibrovascular membranes in the pediatric population. The fluorescein angiography can be decisive in the clinical setting while genotyping is essential for genetic counseling. Clinicians in low income countries may depend solely on a good clinical history and examination but a high index of suspicion in presence of clinical features of FEVR is key.

INTRODUCTION

Familial Exudative Vitreoretinopathy (FEVR) is a rare, genetic condition described for the first time by Criswick and Schepens in 1968[1]. Key features include peripheral avascularity, ectopic macula, tractional bands also described as macular tags, subretinal exudation, retinal ischemia, new vessels proliferation, vitreous haemorrhage and retinal detachment in late stage.

FEVR, unlike its main differential diagnosis that is retinopathy of prematurity, can exhibit a slow and progressive development at any age of life[1,2].

FEVR in homozygous twins has been previously reported but, to our best knowledge, this is the first report a combination of pseudo-strabismus, myopia and symmetric images of FEVR in twins is reported.

CASE REPORT

Two phenotypically identic twins were referred to a tertiary level eye hospital in Bangladesh for assessment of their vision. The father reported their family had not previously noted any eye nor vision abnormality until the teacher sent them an alert over their children visual difficulties with subsequent learning problems. They then started realizing their twins had eye deviation problems and decided to seek for medical attention.

The twins were born at term with no perinatal morbidity, they had no history of signs of poor vision and had never been examined by an eye health professional. There was no history of strabismus or loss of vision in their family. At presentation, the pair of male twins were seven years old and in apparent fair general health and growth for the age. The physical examination is presented separately for each of the twins.

Twin A

Presenting visual acuity was 3/60 OD and 6/60 OS and the best corrected visual acuity was 6/36 OD and 6/18 OS.The cycloplegic retinoscopy was -5.00DS/-0.50DCx 90^0 OD and -3.50DS/-0.50DCx90^0 OS.

The orthoptic assessment found a free and full ocular motility in all gazes, no nystagmus was noted. Corneal light reflex assessment showed a nasal displacement in the right eye whereas it was on the temporal side of the left eye. On prism cover test, there was no deviation and the absence of binocular single vision subsequently confirmed by the Titmus test.

The anterior segment had no particularity. The fundoscopy of the right eye found a peripheral temporal 'V' shaped avascular zone with straitened vessels proximally. There were no fibrovascular bands. For the left eye, there was a fibrovascular band starting at the disc

and extending towards the foveal area without a clear involvement of the late. The far temporal periphery was quite avascular.

Twin S

Presenting visual acuity was 6/60 OD and 6/36 OS and the best corrected visual acuity was 6/24 OD and 6/18 OS.The cycloplegic retinoscopy was -5.00DS/-0.50DCx 90^0 OD and -1.0DS/-0.50DCx80^0 OS.

The orthoptic assessment found a free and full ocular motility in all gazes and no nystagmus. The corneal light reflex was displaced nasally in the left eye and temporally in the right eye. However, as observed in twin A, there was no deviation noted when the prism cover test was performed, likewise, the binocular single vision was absent. The anterior segment had no particularity. The fundoscopy found images similar to those of twin A. For the right eye, the macula was apparently free, and no obvious peripheral avascularity unlike the left eye that exhibited fibrovascular bands originating from the disc without involving the fovea itself and a peripheral temporal avascular zone.

Table 1: Summary of clinical features

	Laterality	Corneal light reflex displacement	Refraction	Macular tagging	Presenting visual acuity
Twin A	OD	Nasally	-5.00DS/-0.50DCx 90^0	Absent	3/60
	OS	Temporally	-3.50DS/-0.50DCx90^0	Present	6/60
Twin S	OD	Nasally	-5.00DS/-0.50DCx 90^0	Absent	6/60
	OS	Temporally	-1.0DS/-0.50DCx80^0	Present	6/36
Symmetry	Symmetric	Symmetric	Symmetric	Symmetric	

Investigations

Colour fundus photo picked areas of avascularity that were subsequently confirmed on fluorescein angiography (Figures 1 and 3).

For twin A, areas of vascular straightening and areas of hypoperfusion were noted in the peripheral temporal quadrants, leakage was also noted in the late phase in the transitional zone between perfused and non-perfused areas (Figure 2).

Twin S had also vascular straightening and peripheral avascular zones in the temporal and inferior far periphery. In the left eye, mild leakage was noted as opposed to right eye (Figure 4).Genetic testing was not possible in a context of limited resources.

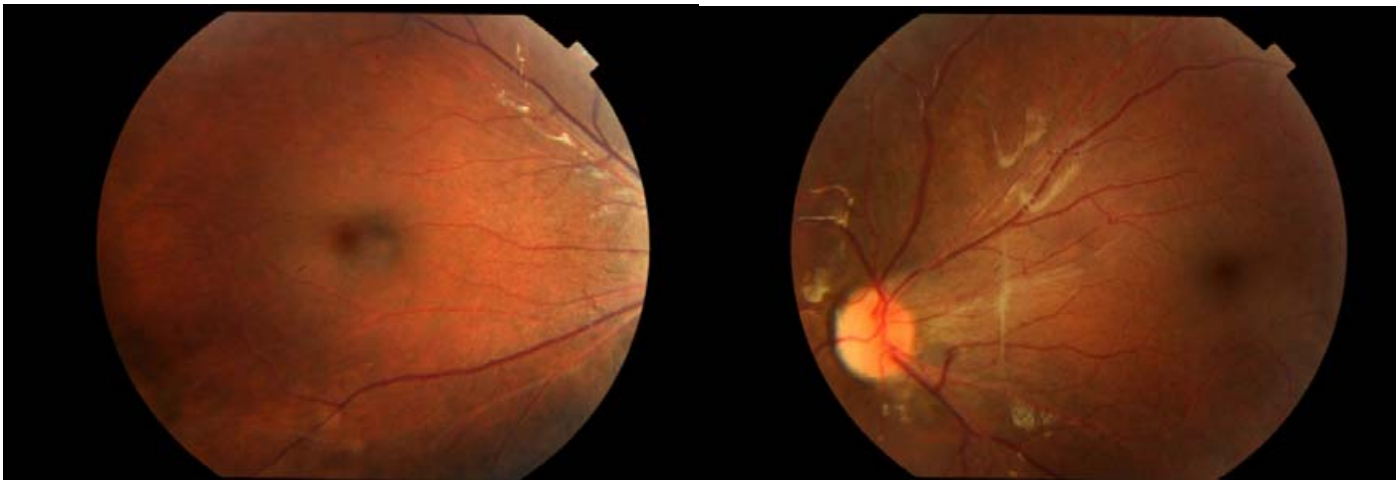

Figure 1: Colour fundus photos show bilateral vessels straightening and left disc dragging

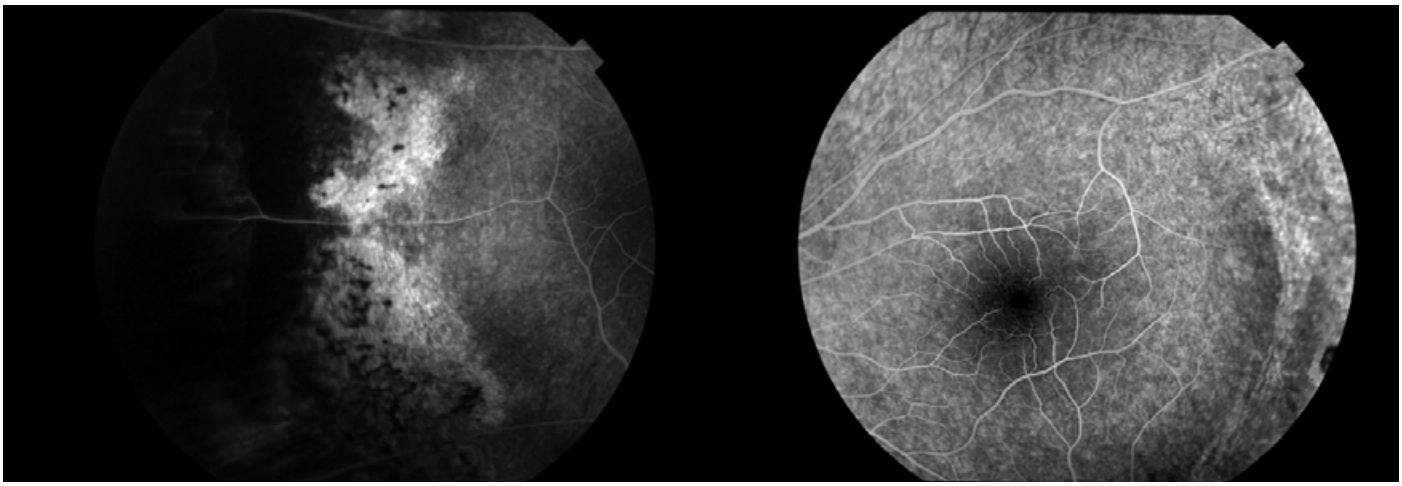

Figure 2: Fluorescein angiography images confirm temporal periphery avascularity and late leakage

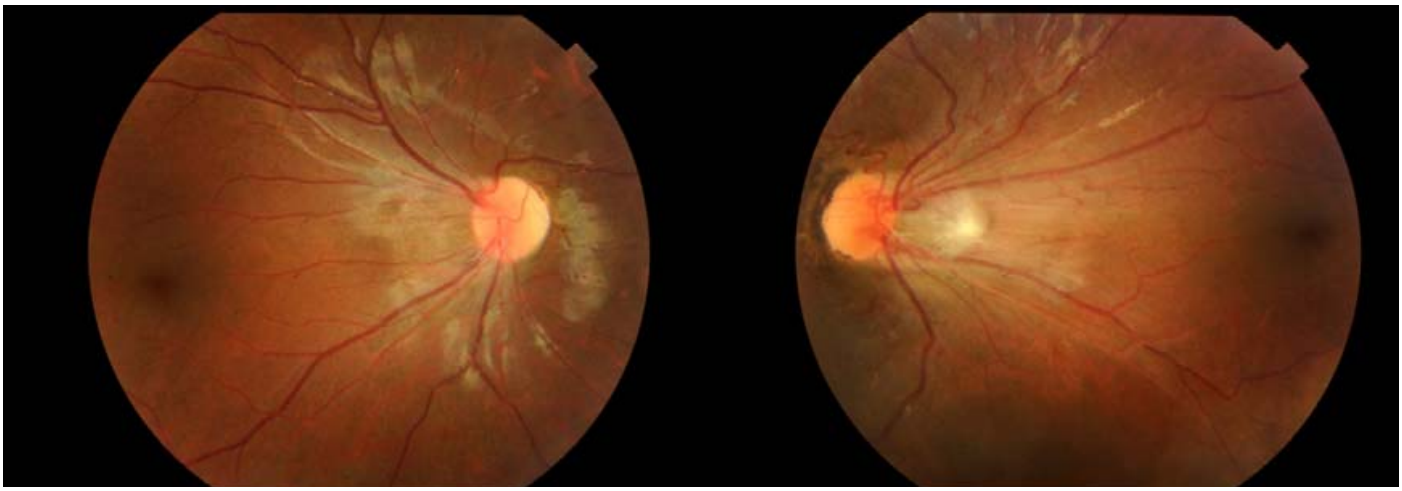

Figure 3: Colour fundus photo with bilateral vessels straightening and left disc dragging

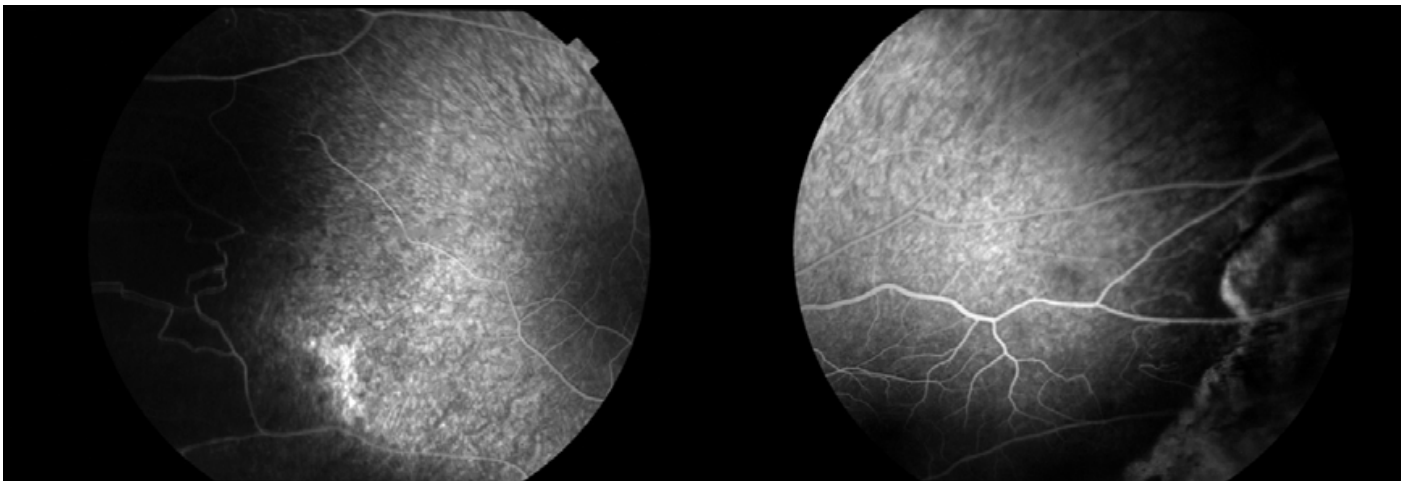

Figure 4: Fluorescein angiography images confirm peripheral temporal avascularity and late leakage

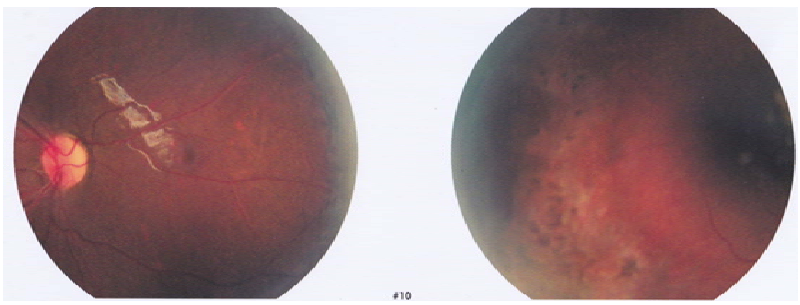

Figure 5: Twin A fundus photos after laser photocoagulation, note laser marks in the periphery

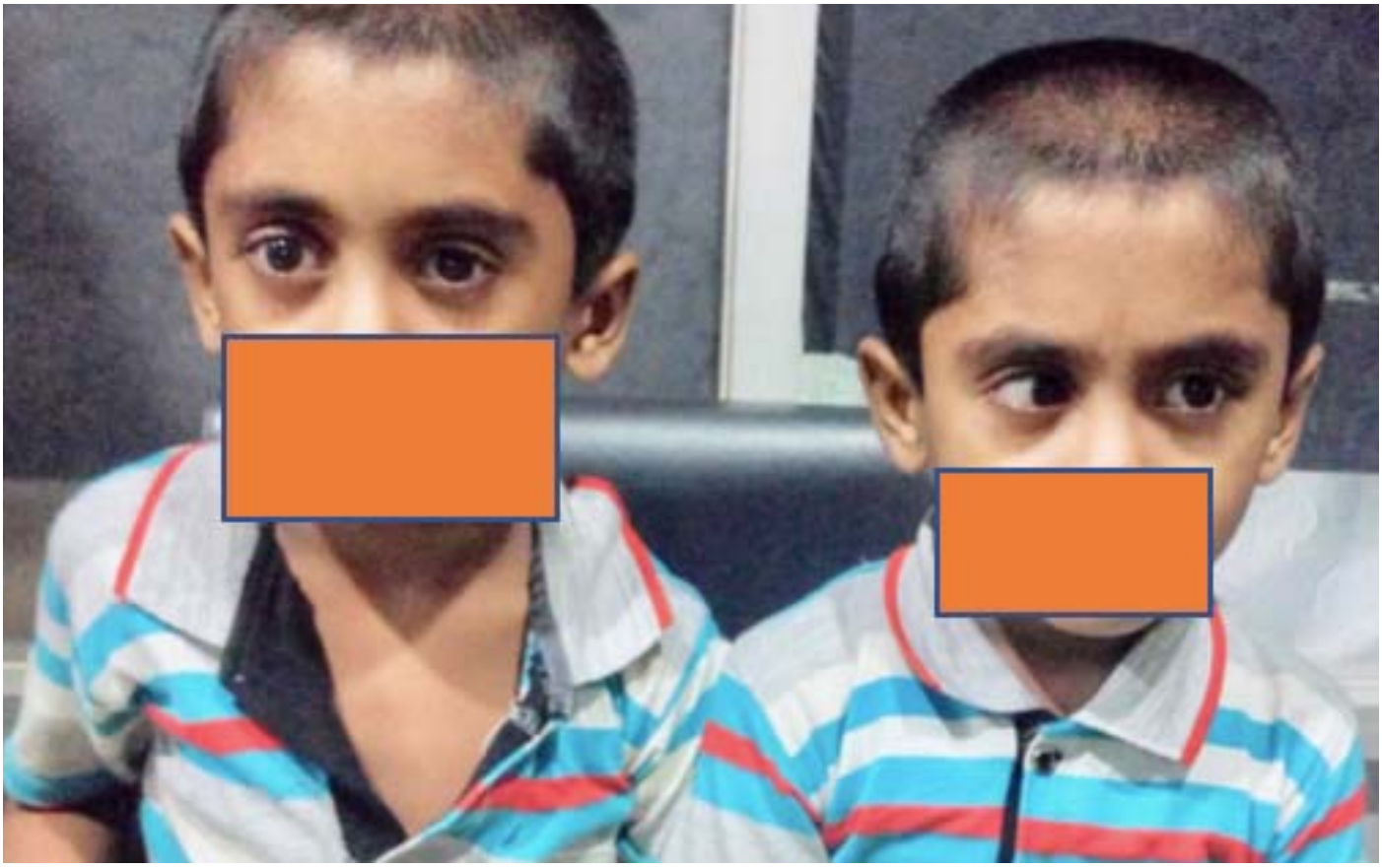

Figure 6: The corneal light reflexes showing the pseudo strabismus in both twins

Outcome and follow-up

The twins will be followed up regularly by both the paediatric ophthalmologists and vitreoretinal surgeons to assess the long-term progress of the disease.

DISCUSSION

FEVR is a rare condition and has been reported in various ways, each author trying to bridge the gap in the better understanding of the condition. The pathogenesis of the disease is now very clear, four genes mutations have been clearly linked to the disease although genetic penetrance and clinical phenotypes have been found to be variable even within the same family and between eyes of the same patient. The disease is genetically transmitted in three ways: autosomal dominant (most common), autosomal recessive and x-linked recessive. The mutations causing FEVR were identified to occur in Norrie Disease Protein (NDP), Frizzled-4 (FZD4), Low-density Lipoprotein Receptor- Related Protein 5 (LRP5), and tetraspanin-12 (TSPAN12)[9-12]. Although genetic studies were not available in our twins' study, the symmetric images found in these identic boys enhance the inherited mode of the disease as previously stated by other authors.

FEVR patients were extensively studied but the pattern and pathophysiology of strabismus remains poorly understood to date. Strabismus and pseudo-strabismus are both reported in conditions affecting the macular anatomy. In 2012, Exotropia was also reported by Natung *et al*[13]. In a study conducted among babies diagnosed with ROP, both myopia and strabismus were present. The mean spherical equivalent was -2.4±4.4D and 41.1% of babies presented with strabismus (26.8% esotropia and 14.3% exotropia)[14]. Esotropia has also been reported in FEVR. In two articles, the FEVR was unilateral and the same eye developed esotropia[15,16]. However other researchers supported that strabismus in FEVR was an effect of macular ectopia secondary to the dragging effect[17]. In our twins, since the macular ectopia was temporal, one would expect an exotropia secondary to efforts to re-center fixation on target. Conversely, orthoptic assessment found rather eccentric fixation than a squint.

It is possible to hypothesize the genetic pathogenesis of FEVR in our twins based on the symmetrical presentation of the ocular findings. In 1950, Waardenburg used the same principle stipulating: "If for a given trait, uni-ovular twins differ much less than bin-ovular twins, the trait may be accepted as essentially hereditary. If they differ just as much, the trait is mainly environmental"[18].

Extensive research has been conducted by various authorities to establish the genetic myopiagenesis as well and up to 200 genetic loci were identified. It is worth noting that a lot needs to be done to understand the phenotypic variance and to discern the molecular signaling cascade of myopia[19].

Since esotropia and exotropia are both described, it would be very important to study in a large cohort study the type of macular eccentricity and the type of tropias. Most cases of FEVR may be asymptomatic and may not need any treatment and several authorities have advocated for treatment of cases that have documented progression[1].

Regularity of follow-ups is a key player to track the progression if any and institute the treatment timely otherwise genetic counseling may help to tell who else in the family is at risk.Correction of the refractive error may help to achieve some useful vision.

CONCLUSIONS

Although rare, FEVR should be suspected and ruled out in all patients with atypical late onset strabismus or pseudo-strabismus. FEVR signs and symptoms may develop slowly from early childhood to adulthood. There is a risk that optometrists may associate the strabismus to the refractive error but a careful bilateral fundus examination by an ophthalmologist is a must as findings may only be evident in the peripheral retina. Fluorescein angiography is the investigation of choice that confirms the peripheral retina avascularity and guide the laser treatment before serious complications set in.

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Regent Court, Block A, Suite A7, Argwings Kodhek Road, Hurlingham, P.O. Box 4539-00506, Nairobi, Kenya,
Office line: +254 724 111 059, Mobile: +254 732 240 671
www. coecsa.org/info@coecsa.org