CHALLENGES IN THE MANAGEMENT OF RETINOBLASTOMA AT PERIPHERAL EYE CLINICS IN GHANA

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Abstract

Introduction: Retinoblastoma is the commonest childhood intraocular tumour with fatal consequence if untreated. The study purposed to determine, from general ophthalmologists at peripheral eye clinics in Ghana, the clinical stage of the disease at presentation to such centres, the challenges associated with its management and to seek recommendations for improvement in the management of retinoblastoma.

***Methods*:** A comparative, cross-sectional study was conducted among general ophthalmologists over two time periods: Period 1 (2005-2007) and Period 2 (2014-2016). One ophthalmologist from each peripheral eye clinic in Ghana was interviewed face-to-face, by telephone or email using a structured questionnaire after verbal informed-consent.

***Results*:** Responses were received from 24 out of 26 general ophthalmologists in Period 1 and from 35 out of 37 in Period 2. On the average 82 and 95 cases were seen respectively for the two periods. Specifically, 69 cases were seen in the year 2007 and 64 in 2016. The estimated age-specific incidence rates (ASR) for Periods 1 and 2 were 20.3 and 17.3 per million person-years respectively. The common clinical presentations reported by the ophthalmologists were leukocoria followed by proptosis and redness of eyes in both study periods. Diagnosis of retinoblastoma using clinical features supported by imaging (ultrasonography and CT-Scan) was done by 10 out of 24 (41.7%) in Period 1, as compared with 18/35 (51.4%) in Period 2 (p=0.461). Majority of ophthalmologists referred all their patients for treatment elsewhere in both periods on account of lack of resources for management including lack of general anaesthesia. Management challenges included abandonment of treatment by caretakers, lack of resources for management and refusal of treatment by caretakers with reasons such as cost, distance, fear of surgery and fear of bigger hospitals. Recommendations for improvement in management included need for standardized treatment guidelines, early detection through health education and funding for care.

***Conclusion*:** Patients with retinoblastoma present with clinically advanced disease to ophthalmologists in peripheral eye clinics in Ghana. There is abandonment and refusal of treatment by caretakers in these centres citing cost and distance as some reasons, and very little improvement over the past decade. Early detection, health education among the general public and health workers, and standardised treatment guidelines are needed to improve on patients' management and survival.

Key Words: eye tumours, leukocoria, ophthalmologists, peripheral eye hospitals, retinoblastoma.

Introduction

Retinoblastoma is the commonest intraocular tumour in childhood.[1] It is sight threatening, and most importantly, if untreated, almost uniformly fatal[1-3]. In developed countries, more than 90% of children with retinoblastoma present with limited-stage disease and are cured on account of availability of resources for early detection and treatment; however, in developing countries, like Ghana, most patients present with advanced disease and survival rates are less than 50%.[2-10] Retrospective studies on patients with retinoblastoma presenting to the Ophthalmology and Paediatric Oncology Units at Korle-Bu Teaching Hospital (KBTH) found majority of the patients presented with clinically and histologically advanced disease.[11,12] The manifestations included leukocoria, proptosis, fungating mass, Reese-Ellsworth stage V disease and poor outcome.

Early diagnosis, prompt and appropriate treatment are some measures necessary to improve on the survival of such children with retinoblastoma in Ghana[10, 13]. In addition, it will require identifying the factors that contribute to the late disease presentation; how such patients are managed at the peripheral eye hospitals in Ghana and difficulties encountered in the management of these patients at these centres among others.

The objectives of the study therefore were to determine from general ophthalmologists at peripheral eye hospitals in Ghana, the clinical stage of the disease at presentation, the challenges associated with its management and to seek recommendations for improvement in the management of retinoblastoma.

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Secondly, to compare findings from 2 study periods, a decade apart to see if there has been any improvement in the factors understudied over the period. We hope this would help in part to plan interventions for improvement in the care and survival of children with retinoblastoma in Ghana.

Methods

Study design

This was a comparative, cross-sectional study.

Study Population

General ophthalmologists in government, quasi-governmental, mission and private hospitals and clinics in Ghana who consented verbally to participate in the study were recruited. Ophthalmologists in the 2 Teaching Hospitals with Paediatric Eye Units were excluded. One ophthalmologist per centre was interviewed. In centres where more than one ophthalmologist managed retinoblastoma, only one (the key person) was interviewed to avoid possible duplication of data. Ethical approval was by University of Ghana Medical School ethics and protocol review committee (now Ethical and Protocol Review Committee of College of Health Sciences, University of Ghana).

Data collection and statistical analysis

Data was collected using a semi-structured questionnaire from September 2008 to June 2009 for Period 1 (2005-2007), and from September 2017 to April 2018 for Period 2 (2014-2016). The questionnaire explored the average number of patients diagnosed with retinoblastoma at the peripheral eye centres for the periods (and specifically for years 2007 and 2016), their clinical presentations, modes of diagnosis, treatment offered, resources available for management and challenges with the management of such children. Depending on the accessibility of the participants, the questionnaires were self-administered, mailed or administered by phone interviews. Where clarifications were needed from the participants, a follow-up phone interview was made. The mailing list of the Ophthalmological Society of Ghana (OSG) was used for the administration. Data was captured by the biostatistician using Statistical Package for Social Sciences (SPSS) Version 20 and checked for accuracy by the lead investigator. Continuous numerical data were reported as Mean and Standard deviation (SD) and categorical data as percentages (%). Continuous numerical data in the 2-time periods were compared using Independent t-test and categorical data were compared using the Chi-square test. P-values < 0.05 were considered statistically significant.

We estimated the age-specific incidence rate (ASR) for each period under study using the specific incidence for 2007 and 2016 and the corresponding population estimates for children less than 5 years (the age group with the highest incidence for retinoblastoma) i.e. [Number of cases] / [Number of person-years]. The estimated population for children less than 5 years in Ghana were 3.4 million for Period 1 and 3.7 million for Period 2[14].

Results

Responses were received from 24 out of 26 ophthalmologists in Period 1 and 35 out of 37 in Period 2 giving response rates of 92.3% and 94.6% respectively. The number of participating centres corresponded to the number of reporting ophthalmologists i.e. 24 and 35 for period 1 and period 2 respectively; however, the total number of ophthalmologists at post in these participating centres were 30 and 56 in Period 1 and Period 2 respectively. Majority of the ophthalmologists who participated in this study were from private, quasi-governmental and mission hospitals and clinics. An average of 82 cases of retinoblastoma were seen in Period 1 and 95 cases in Period 2. Sixty-nine cases were seen specifically in the year 2007 and 64 cases in 2016 (Table 1). The estimated ASR for the study periods 1 and 2 were 20.3 and 17.3 per million person-years respectively.

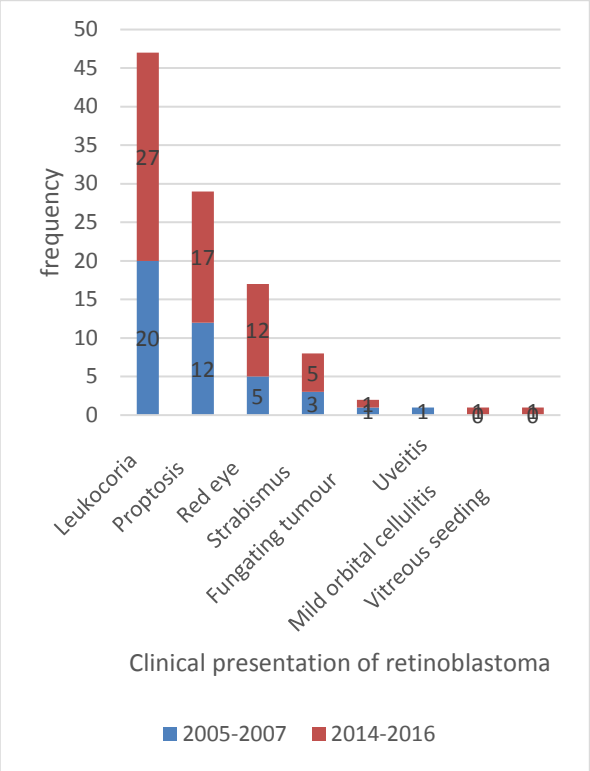

Fig 1: Clinical presentation of retinoblastoma to ophthalmologists at peripheral eye clinics

The common clinical presentations reported were leukocoria followed by proptosis in both periods (Figure 1). Reasons for late presentations to the peripheral eye centres included use of alternate medicine (34%), caretakers of patients being ignorant of prognosis (25%), and cost of care (12.5%) in Period 1 and for Period 2 the main reasons were cost of treatment

(31.4%) ignorance of prognosis (25.7%) and use of alternate medicine (14.3%) (Table 2).

Among the respondents, diagnosis of retinoblastoma using clinical features supported by imaging (ultrasonography and CT-Scan) was done by 10 out of 24 (41.7%) during Period 1, as compared with 18 out of 35 (51.4%) in Period 2 (p=0.461) (Figure 2). Nine out of 24 (37.5%) ophthalmologists managed retinoblastoma by enucleation and histopathological analysis of the enucleated eyes in Period 1; and 4 out of 35 (11.4%) (p= 0.014) did same in Period 2. These four ophthalmologists who managed retinoblastoma with enucleation and histopathology in Period 2 also offered chemotherapy when needed. Thirteen out of 24 (54.2%) of the ophthalmologists managing retinoblastoma referred all patients to the tertiary eye centres in Period 1 as compared with 26/35 (74.3%) in Period 2 (p=0.109). Reasons for referral were mostly because of lack of resources for management e.g. lack of general anaesthesia/ anaesthetists (Figure 3, Table 2).

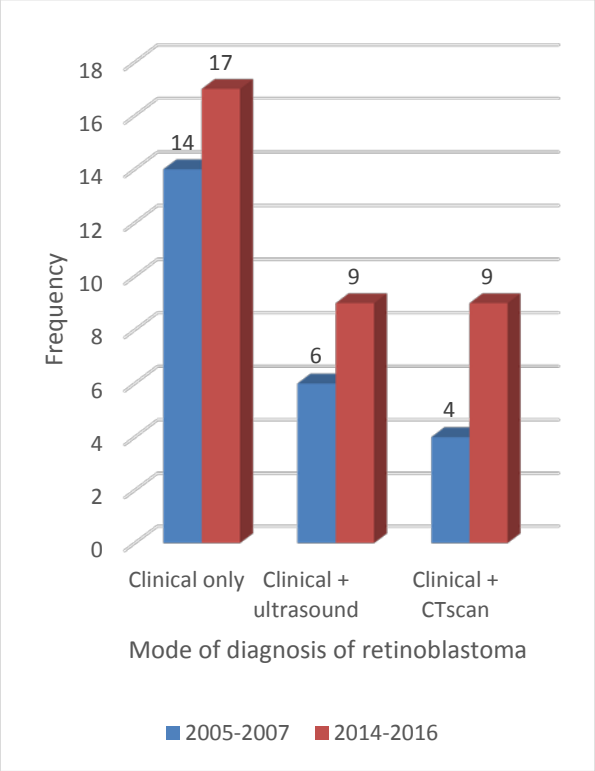

Fig 2: Modes of diagnosis of retinoblastoma by ophthalmologists at peripheral eye centres.

Challenges encountered by respondents in the management of children with retinoblastoma in the peripheral eye clinics in Period 1 included refusal of treatment by caretakers in 21 out of 24 respondents, with reasons such as cost, distance, fear of surgery and fear of bigger hospitals (Table 2).

Other difficulties included convincing parents for uptake of surgery and lack of facilities for management of retinoblastoma. Similarly, 6 out of 35 ophthalmologists in Period 2 reported refusal of treatment by caretakers as a challenge in the management of children with retinoblastoma. The main reasons for refusal of treatment were cost of treatment, fear of disfigurement and fear of death of the child.

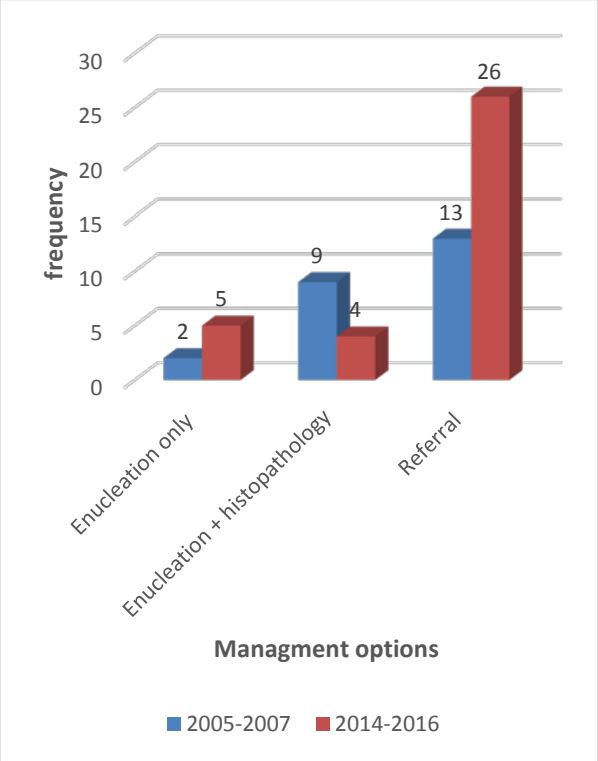

Fig 3: Retinoblastoma management options by ophthalmologists in peripheral eye clinics.

In addition, abandonment of treatment ranging from 1 to 6 children per year per centre was reported by 11 out of 24 ophthalmologists (45.8%) in Period 1 as compared to 7 out of 35 ophthalmologists (20.0%) in Period 2 (p=*0.034*). Reasons obtained from caretakers for such abandonment or default of treatment were similar in both periods and included avoidance of enucleation, prognosis not understood, cost of treatment, religious persuasions and seeking permission from families especially fathers.

Recommendations put forth by the ophthalmologists for improvement in the management of retinoblastoma in the country included the need for standardized treatment guidelines or protocols, early detection through health education, training of health personnel in the diagnosis and treatment of retinoblastoma, provision of resources for management and cheaper sources of funding for care.

Table 1. Ophthalmologists interviewed and reported retinoblastoma cases at peripheral eye clinics in Ghana

Region of the Country	**No. of Ophthalmologists interviewed**		**Average no. of Patients seen with RB**		**Specific no. of Patients seen with RB**	
	2005-2007	2014-2016	2005-2007	2015-2016	2007	2016
Upper East	1	1	5	5	5	3
Upper West	1	1	3	5	4	0
Northern	1	2	6	20	5	22
Brong-Ahafo	2	3	3	5	3	4
Western	1	1	10	1	11	0
Ashanti	4	4	20	6	13	5
Eastern	3	4	5	8	3	6
Volta	1	1	3	1	2	1
Central	1	3	2	9	2	5
Greater-Accra	9	15	25	35	21	18
Total	**24**	**35**	**82**	**95**	**69**	**64**

***Table 2.** Baseline information on peripheral eye clinics in Ghana.

Type of information	**2005-2007 N=24**		**2014-2016 N=35**	
Reasons why patients presented with late disease (Ophthalmologist's view)	N	%	n	%
Use of alternate medicine	10	41.7	5	14.3
Ignorance of prognosis	7	29.2	9	25.7
Cost of treatment	4	16.7	11	31.4
Fear of enucleation	3	12.5	2	5.7
Distance from clinic	2	8.3	3	8.6
Waiting to access NHIS	2	8.3	-	-
Others	2	8.3	5	14.3
Management challenges				
Centres with patients defaulting/ abandoning treatment	11	45.8	7	20.0
Average no. of patients defaulting/ abandoning treatment/centre/ year (Range)	2 (1-6)		1 (0-1)	
Centres with general anaesthesia services	17	70.8	16	45.7
Centres where caretakers refused treatment	13	54.2	6	17.1
Reasons for refusal of treatment				
Cosmesis / fear of disfigurement	8	33.3	1	2.9
Fear of death	5	20.8	3	8.6
Cost of treatment	4	16.7	5	14.3
Others (e.g. fear of bigger hospital, spiritual illness, ignorance, fear of surgery, hope of spontaneous recovery)	2	8.3	1	2.9

***Multiple response**

Discussion

The average number of new patients with retinoblastoma reported by the participating ophthalmologists in this study for the Period 1 was 82, with 69 seen specifically in 2007. The average number of cases for Period 2 was 95 cases, with 64 cases seen specifically in 2016**.** Their corresponding estimated ASR of 20.3 and 17.3 per million person-years compares favourably with the ASR for Ibadan, Nigeria, estimated at 19 per million person-years.[15] Ghana shares similar geographic and demographic features with Nigeria in the West African sub-region. These reported incidences of retinoblastoma for the two periods are higher than those seen in some developed countries such as United Kingdom where about 40 cases are seen a year[16] and less than 30 cases seen yearly in Canada[17]. The findings corroborate observations from developing countries indicating generally higher incidences, especially from Sub-Saharan Africa[18].

These differences in incidence between developed and developing countries may be due to differing exposure to infections or other environmental factors inducing the necessary mutations in utero or during infancy leading to more sporadic types[19]. It has been observed that very little difference exists in incidence of bilateral retinoblastoma cases, which are mostly germline mutations and heritable, between regions of the world or ethnic groups[20]. This differentiation however, was not examined in this current study.

Clinical presentation of retinoblastoma in children in peripheral eye clinics in Ghana is reported to be characterized by signs of late disease such as proptosis (28.5% in Period 1 vs 26.6% in Period 2), redness of eye (11.9% vs 18.8%) and fungating mass (2.4% vs 1.6%). There has been very little change over the decade under review in this current study. Signs of late disease tends to characterize presentations in developing countries such as Nigeria, where proptosis (84.6%) was the most common clinical presentation among 20 children with retinoblastoma[9]. In Ghana, the most common clinical presentation of retinoblastoma in a tertiary eye clinic where 23 children were studied, was leukocoria (87%) followed by proptosis (34.8%)[12]. Similar clinical presentations of leukocoria (71.8%) and proptosis (32.8%) were found in a review of 64 children with retinoblastoma in Malaysia[21]. The clinical presentations of retinoblastoma in this current study, thus corroborate findings from other Sub-Saharan African countries like Nigeria, East Africa and Congo [5,7-9,22,23] and from India[24]. However, it contrasts findings from USA, where a retrospective study of 1265 patients with retinoblastoma at New York Hospital in the USA, demonstrated leukocoria as present in 56.2% of patients followed by strabismus (23.6%), with orbital disease being extremely rare[25]. The finding of leukocoria corroborates findings worldwide as the commonest presentation of retinoblastoma[12,24,25].

Lack of awareness of retinoblastoma by the public and heath care workers, poor access to eye care doctors, initial employment of alternative forms of care and delayed diagnosis are some known factors that account for advanced disease presentation[8,9,26-30]. Early diagnosis is important in improving survival of patients. Distance from eye centres, cost of transportation and treatment of retinoblastoma mainly in tertiary eye centres may lead to delay in initiating treatment and may promote adoption of alternative medical care which may further reduce survival rates. Some of these factors were alluded to in the reasons for late disease presentations in this study. In Honduras and Brazil, public health campaigns to create awareness among the population and healthcare workers have led to improvement in early diagnosis and reduction in extra-ocular retinoblastoma[26,29]. This intervention may contribute to a reduction in late disease presentation, if employed in Ghana.

The diagnosis of retinoblastoma is clinical using indirect ophthalmoscopy. Imaging modalities such as ultrasonography, computed tomography and magnetic resonance imaging are helpful in establishing the diagnosis, excluding diseases that simulate retinoblastoma and in staging the disease[31]. In this study, about half the number of ophthalmologists in peripheral eye clinics diagnosed retinoblastoma only clinically without supportive imaging modalities in the first period of study (58.3%), and in Period 2 (48.6%). This practice is not acceptable, as it may result in misdiagnosis and inappropriate staging of the disease and treatment of patients.

Histologic analysis of enucleated eyes is useful in confirming the diagnosis and identifying high risk histopathologic features such as scleral invasion, massive choroidal invasion (>3mm in maximum diameter) and post-laminar optic nerve invasion.[32] Histology will also help in determining the presence of microscopic residual diseases such as involvement of optic nerve resection margin or trans-scleral involvement[31]. Without recognizing these features and hence not offering adjuvant chemotherapy, the risk of systemic metastasis would increase leading to death[32]. It is of concern that only 37.5% of ophthalmologists interviewed managed retinoblastoma by enucleation and histopathological analysis in Period 1; and even significantly lesser proportion (11.4%, p= 0.014) did so in Period 2. The rest either managed with enucleation only or referred all cases to the tertiary centres for further management. This practice of performing enucleation without histopathological analysis, is also unacceptable, and if continued, would delay detection of microscopic extra-ocular disease and thus contribute to poor patient outcomes.

Increasingly, many general ophthalmologists (54.0% in Period 1, and 74.3% in Period 2; p=0.109), referred children with retinoblastoma to the two main tertiary eye centres in Ghana for treatment with the main reason being lack of resources including general anaesthesia and anaesthetists. It is worthy of note however, that 71% of respondents in Period 1 and 46%

in Period 2 reported having general anaesthesia services. Further investigations need to be done to ascertain how best to get at least the centres that have general anaesthesia services to perform enucleation with histopathological analysis. This will reduce the proportion of referrals to the tertiary centres which may be too distant for parents and caretakers to access care for their children and may subsequently lead to a delay in initiation of treatment or abandonment of treatment. A retrospective study of retinoblastoma referral pattern in Kenya found that 35% (58/168) of children were lost to follow up after referral.[33]

Refusal of treatment or abandonment of treatment will promote systemic spread of the disease and reduce the survival rates. Luna-fineman et al reported that 22% of 172 children diagnosed with retinoblastoma in Central America either refused or abandoned therapy[34]. In a prospective study of 105 patients with retinoblastoma in Malaysia, 31% children deferred treatment for 6 months or more and 26% children were lost to follow-up.[27] A retrospective study of 23 patients with histologically confirmed retinoblastoma in a tertiary hospital in Ghana found 35% children abandoning treatment.[12] Leander et al reported that one third of their patients either refused or abandoned treatment[26]. Bekibele et al in Nigeria reported that 11(42%) of patients refused treatment[35]. This present study showed 54% of the ophthalmologists in peripheral eye centres encountered refusal of treatment by caretakers in Period 1, with the number reducing to 17% in Period 2. The reasons for their refusal included cost, distance, fear of surgery and fear of bigger hospitals. In addition, between one to six children had their treatment abandoned by their caretakers per year in more centres (45.8%) in Period 1, but these numbers also reduced to about one per centre in Period 2 and in fewer centres (20.0%), p= 0.034. These positive trends, if continued, would contribute to early treatment and improvement in survival. Refusal and or abandonment of treatment may be reduced by public education and appropriate counselling and formation of support groups of caretakers of children with retinoblastoma and surviving retinoblastoma patients[26, 36]. The development of a retinoblastoma programme in Central America has reduced the abandonment/refusal rate and has improved the care of retinoblastoma by ophthalmologist and paediatric oncologist[36].

To improve access to appropriate care and survival of children with retinoblastoma in Ghana, suggestions proposed by the ophthalmologists included the establishment of a national retinoblastoma programme with a focus on setting up guidelines and protocols for retinoblastoma care, training of ophthalmologist in peripheral eye centres on the appropriate management of retinoblastoma, awareness creation on how to recognize retinoblastoma among the public and all health care workers especially community and public health nurses, paediatricians, general practitioners and family physicians; advocacy for inclusion of retinoblastoma screening in the National immunization programme, advocacy for the inclusion of total retinoblastoma care in the National Health Insurance Scheme of Ghana, and provision of resources for retinoblastoma treatment in the peripheral eye centres. The advantage Ghana has is that, 46% of the peripheral eye centres presently have the resources (human and infrastructure) for the provision of general anaesthesia, mainly in Government hospitals, therefore retraining of the ophthalmologists to improve on their surgical skills coupled with arrangement for enucleated eyes to be sent to regional hospitals with the services of a pathologist, would contribute to better patient outcome.

Strengths and limitations

The retrospective nature of this study coupled with possible recall bias of the general ophthalmologists may be limitations for this study. However, this is the first published data that has highlighted the magnitude of retinoblastoma and challenges involved in its management in peripheral eye clinics in Ghana, where the bulk of these patients are seen. In addition, the study explores providers' viewpoint unlike most studies that dwell only on the patients. Recommendations from these providers when taken on board would strengthen teamwork and collaboration between peripheral and tertiary referral centres. The findings may help the country, in part, to adopt strategies for early detection, appropriate management and timely referrals of patients with retinoblastoma.

Conclusion

The estimated ASR for Ghana in this study, compares with those in developing countries where rates are generally much higher than developed countries. Patients with retinoblastoma present with advanced disease clinically to general ophthalmologists at peripheral eye clinics in Ghana. There is widespread abandonment or default of treatment, and refusal of treatment by caretakers among other challenges encountered by the ophthalmologists in these centres with very little improvement over the decade of study. Early detection, intensive health education including health promotion among the general public and health workers, and standardised treatment guidelines are needed in order to improve on patients' management and survival.

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