

# Retinoblastoma in a Referral Center in Nigeria: 7- year Review of Changing Pattern of Presentation and Lag Time

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## Abstract

**Background:** Improvement in survival from retinoblastoma (RB) improved to about 98% in developed countries because of early presentation and prompt intervention at designated RB care center, whereas in low-resourced countries, late presentations and poor survival are not unusual. This study reviews the changing pattern of presentations over a 7-year period when various efforts were deployed to improve early presentation and intervention in a low-resourced setting. **Materials and methods:** Data were extracted from RB clerk sheets that were used for documentation of clinical records of patients with RB managed at a single tertiary referral center for RB in Nigeria between 2013 and 2019. The data were analyzed for changing trend of clinical presentation and lag time. Ethical approval was obtained from the institution. **Results:** Two hundred and twenty-two eyes of 148 children were reviewed. There were 79 males and 69 (46.6%) females, and male to female ratio was 1.14:1. There were 74 (50%) unilateral, 72 (48.6%) bilateral, and 2 (1.4%) trilateral cases. **Discussion:** Overall, 66 (44.6%) and 82 (55.4%), patients had shown symptoms by 6 months and 1 year, respectively, whereas only 39 (25.7%) had presented by 1 year. Early disease stage presenting as leukocoria increased from 22.2% to 85.7%, whereas late presentation as proptosis declined from 55.5% to 10.7% between 2013 and 2019. Some cases were identified during vision screening performed by community health workers during routine immunization at primary healthcare clinics. At presentation, 188 (84.7%) RB eyes were intraocular, 32 (14.4%) orbital, and 2 (0.9%) had systemic spread. The median of the lag-time (delay) between when symptom was noticed to presentation reduced gradually each year by 1 month, from a median of 9 months in 2013 to 4 months in 2018. **Conclusions:** In Nigeria, early presentation as leukocoria increased, whereas late presentation as proptosis and lag time in RB reduced significantly from year 2013 to 2019 which was supported by deliberate efforts to educate the public and institute training across all levels of health care. In low-resourced country like ours, achieving early presentation of RB cases would increase the survival of affected children.

**Key Messages:** Late hospital presentation of retinoblastoma has gradually reduced in Nigeria. Greater deliberate efforts are required by government, communities, families, and all stakeholders through universally accessible, affordable, sustainable, cost-effective, and scalable initiatives. This will include public education, human capacity building, deployment of appropriate resource at all levels of health care to support early detection, prompt referral, and presentation for adequately funded experts care. Only then would survival become comparable to other developed nations.

**Keywords:** Affordable care, childhood immunization, early presentation, lag time, retinoblastoma

## INTRODUCTION

Retinoblastoma (RB) is the most common primary intraocular tumor in childhood<sup>[1]</sup> and is postulated to occur as a result of mutation in the tumor suppressor *RBI* gene (chromosome 13).<sup>[2]</sup> Globally, it is responsible for 3% of all childhood cancers<sup>[1]</sup> and occurs in approximately 1 in every 17,000 live births with an estimated 9000 new cases every year.<sup>[3]</sup>

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**Received:** 16 July 2021 **Revised:** 24 September 2021  
**Accepted:** 25 September 2021 **Published:** 29 August 2022

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**How to cite this article:** Ademola-Popoola DS, Yusuf IA, Obajolowo TS, Akinremi SO, Gobeh AS. Retinoblastoma in a Referral Center in Nigeria: 7- year Review of Changing Pattern of Presentation and Lag Time. *Niger J Ophthalmol* 2022;30:56-62.

### Access this article online

#### Quick Response Code:



#### Website:

[www.nigerianjournalofophthalmology.com](http://www.nigerianjournalofophthalmology.com)

#### DOI:

10.4103/njo.njo\_40\_21

Retinoblastoma has no sex or racial predilection<sup>[1]</sup> and over 90% of cases occur before the age of 5 years.<sup>[4]</sup> Africa and India have the highest incidence of RB in the world (80% of all new cases)<sup>[5]</sup> and sadly, 70% to 80% of these children will die primarily due to late presentation.<sup>[6,7]</sup>

In Nigeria, the estimated incidence of RB is 196 cases per year.<sup>[8]</sup> Clusters of studies in different institutions in Nigeria have reported varying hospital incidences and high rate of proptosis at presentation in different localities over the time span 1987 to 2017 with the number of patients reported ranging from 18 to 41 and proptosis as presentation between 29.7 and 65%.<sup>[9-15]</sup>

Retinoblastoma care was strengthened at the referral center in 2007, facilities were provided for chemotherapy, focal therapy (diode LASER transpupillary thermotherapy and cryotherapy), and enucleation. The few patients who require external beam radiation therapy are referred to a nearby facility about 150 km away. Patient's documentation was recorded into specially designed forms to capture details specific to RB at first and subsequent presentations to the unit.

Specifically, from year 2007, specific efforts were implemented to improve on advocacy, education of critical stakeholders in early detection, referral, and treatment of RB cases; the unit worked with Nigeria television authority to do documentaries on RB which was aired nationally; jingles were aired on the local radio stations and during live broadcast. Talk shows on RB were held at various community and religious gatherings.

Enucleation with orbital implants and prosthetic fit was introduced in year 2007, and in 2011, the center acquired Iridex diode 810 LASER with LASER indirect ophthalmoscope to deliver transpupillary thermotherapy, being the first of it dedicated to RB care in the country.

In addition, scheduled lectures were given to nurses, community health officers, immunization staff, medical students, and ophthalmologists in training at formal and informal events. Immunization staff were trained in the state from year 2016 to do red reflex test for babies at some large volume rural and urban clinics during routine childhood immunization,<sup>[16]</sup> and large format posters were placed at immunization clinics and eye clinic.

Presentations were made at the national ophthalmology meetings every year, and an international RB workshop was organized in year 2018 for stakeholders in RB across the country including ophthalmologists, oncologists, nurses, and pathologists.

The unit also dedicated a half-day clinic on Wednesday to RB and retinopathy of prematurity follow-up, fundus images obtained by smartphone were used for caregivers education and patient support and national RB professional and caregivers' chat groups were created on WhatsApp to improve communication and referral. Some of the care givers also created Facebook support groups. This report presents

the single largest data on presentation of RB over a 7-year period from a single main RB referral center in Nigeria, the most populous country in Africa, with the aim that the report will be used to further improve the outcome for children who develop RB.

## SUBJECTS AND METHODS

Retrospective review of clinical records of RB cases at a single center over a 7-year period between 2013 and 2019 was carried out. Ethical approval was obtained from the institution.

The information analyzed were retrieved from patient's clinical proforma (RB clerk sheets) used for clinical documentation for RB are age and mode of presentation, age at which RB symptom was first noticed, family history of RB, laterality, and clinical grading of the tumor using the intraocular classification of retinoblastoma (ICRB).<sup>[17]</sup>

The data were analyzed for the trend over a 7-year period of the study with IBM Statistical Package for Social Sciences (SPSS) version 23 (IBM Corp, Armonk, New York, USA) and results were presented as charts and tables.

Frequency tables of all variables were generated and Chi-squared test was used to test for association between two categorical variables and a *P*-value of less than 0.05 was taken as significant.

## RESULTS

Two hundred and twenty-two eyes of 148 children records were reviewed. Seventy-nine (53.4%) patients were males, whereas 69 (46.6%) children were females. There were 74 unilateral, 72 bilateral, and 2 trilateral cases (included in the analysis of bilateral cases). Laterality of disease had no sex predilection ( $P=0.41$ ). Among unilateral cases, the right eye was involved in 34 (45.9%) and the left eye in 40 (54.1%) patients.

Among the bilateral cases, four of the children were twins; one each of two dizygotic sets of twins and both of one monozygotic twins who both had group E and orbital disease in right and left eyes, respectively. There were two cases of bilateral disease that evolved within a 3-month period from an initial unilateral presentation.

The number of RB cases reported per year increased over the 7-year period with the largest number being in 2018 (33 cases, 22.3%) [Figure 1] and an average of 22 cases were reported per year, with unilateral and bilateral being at an average of 11 cases each.

### Age symptoms noticed, age at presentation, and lag time to presentation

#### *Age symptoms were noticed*

Generally, the median age at which RB symptoms were first noticed was 12 months (interquartile range [IQR] 3–24 months). This was 17 months (IQR 5.5–30 months) for

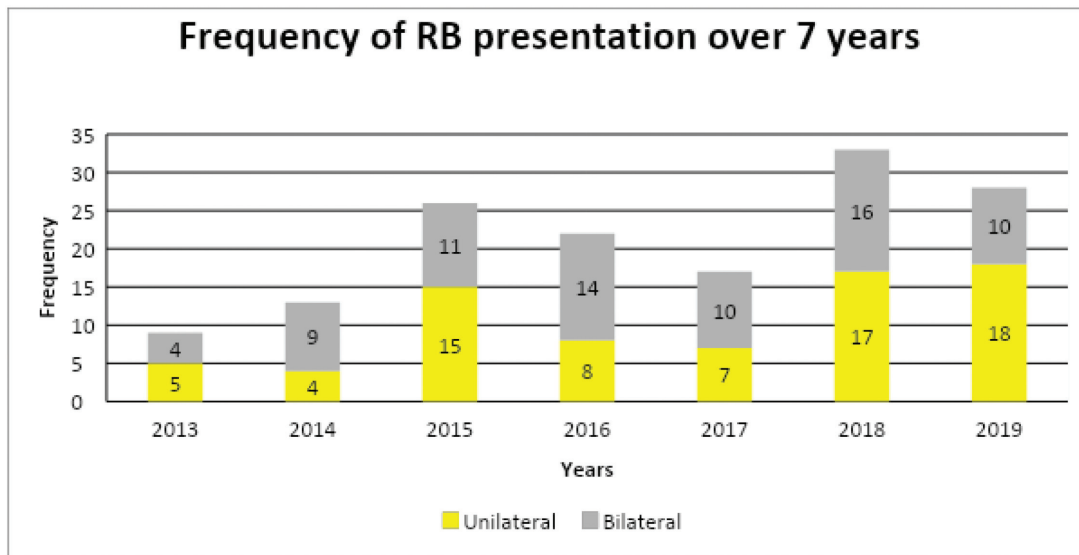


Figure 1: Frequency of retinoblastoma from 2013 to 2019.

Table 1: The age symptom was noticed, age at presentation, and lag time by laterality of retinoblastoma

Age (months)	Age symptoms first noticed(months)			Age at presentation to hospital (months)		
	Unilateral <i>n</i> = 74; <i>n</i> (%)	Bilateral/trilateral <i>n</i> = 74; <i>n</i> (%)	Total <i>n</i> = 148; <i>n</i> (%)	Unilateral <i>n</i> = 74; <i>n</i> (%)	Bilateral/trilateral <i>n</i> = 74; <i>n</i> (%)	Total <i>n</i> = 148; <i>n</i> (%)
≤1	5 (6.8)	17 (23.0)	22 (14.9)	0 (0.0)	3 (4.1)	3 (2.0)
>1–6	20 (27.0)	24 (32.4)	44 (29.7)	5 (6.8)	13 (17.6)	18 (12.2)
>6–12	9 (12.2)	7 (9.5)	16 (10.8)	6 (8.1)	11 (14.9)	17 (11.5)
>12–18	8 (10.8)	11 (14.9)	19 (12.8)	6 (8.1)	10 (13.5)	16 (10.8)
>18–24	8 (10.8)	5 (6.8)	13 (8.8)	20 (27.0)	11 (7.4)	31 (20.9)
>24–30	7 (9.5)	4 (5.4)	11 (7.4)	7 (9.5)	7 (9.5)	14 (9.5)
>30–36	8 (10.8)	4 (5.4)	12 (8.1)	14 (18.9)	10 (13.5)	24 (16.2)
>36	9 (12.2)	2 (2.7)	11 (7.4)	16 (21.6)	9 (12.2)	25 (16.9)
Range	0–74	0–48	0–74	3–120	1–94	1–120
Median	17	6	12	24.5	20	24
IQR	5.5–30	2–17.5	3–24	19–36	8.5–32.5	13–36
<i>P</i> -value		0.39		<i>P</i> -value	0.63	

IQR, interquartile range.

unilateral and 6 months (IQR 2–17.5 months) for bilateral cases. Furthermore, 66 (44.6%) and 82 (55.4%) patients had shown symptoms by 6 months and 1 year, respectively, whereas 34 (23%) cases showed after 2 years [Table 1].

Specifically, 5 (6.8%) unilateral cases had symptoms at birth, 25 (33.8%) within 6 months, 34 (46%) and 50 (67.6%) by 1 and 2 years, respectively. Conversely, among children with bilateral disease, 17 (23%) had shown symptoms within 1 month, and 41 (55.5%), 48 (65%), and 64 (86%) had symptoms noticed within 6 months, 1 year, and 2 years of life, respectively, whereas two children with bilateral disease had symptoms for the first time after 3 years.

The age at which the first symptoms were noticed was statistically related to higher parental education, father ( $P=0.03$ ) and mother ( $P=0.004$ ).

### Age at presentation

The age range at presentation was between 1 month and 10 years with a median of 24 months (IQR 13–36 months). Twenty-one (14.2%), 39 (25.7%), and 85 (57.4%) patients were presented by 6 months, 1 year, and 2 years of life, respectively, and 63 (42.6%) patients presented after 2 years [Table 1].

Three of the bilateral cases were identified at 6 weeks from vision screening by community health workers during routine immunization for children. The age at which symptom was noticed and the age of presentation were not statistically significantly affected by the laterality of disease [Table 1].

### Lag time between symptom and presentation

Lag time was shorter with higher education of the father ( $P=0.02$ ) but not to education of the mother ( $P=0.81$ ) or

gender of the child ( $P=0.53$ ). The median of the lag-time reduced gradually by 1 month from a median of 9 months in 2013 to 4 months in 2018 ( $P=0.00$ ). Nevertheless, it was between 1 and 3 years in about a quarter of the cases [Table 2].

### Family history of retinoblastoma

Four (2.7%) cases confirmed family history of RB. One (1.4%) was a unilateral case in which the mother had bilateral RB; three (4.1%) of them had bilateral disease; two in one of the parents and one in a first cousin; the previous history in the cousin helped with early presentation as the child presented within 1 week of life

with leukocoria that was detected by an aunt whose child was previously managed for RB detected at 9 months of life.

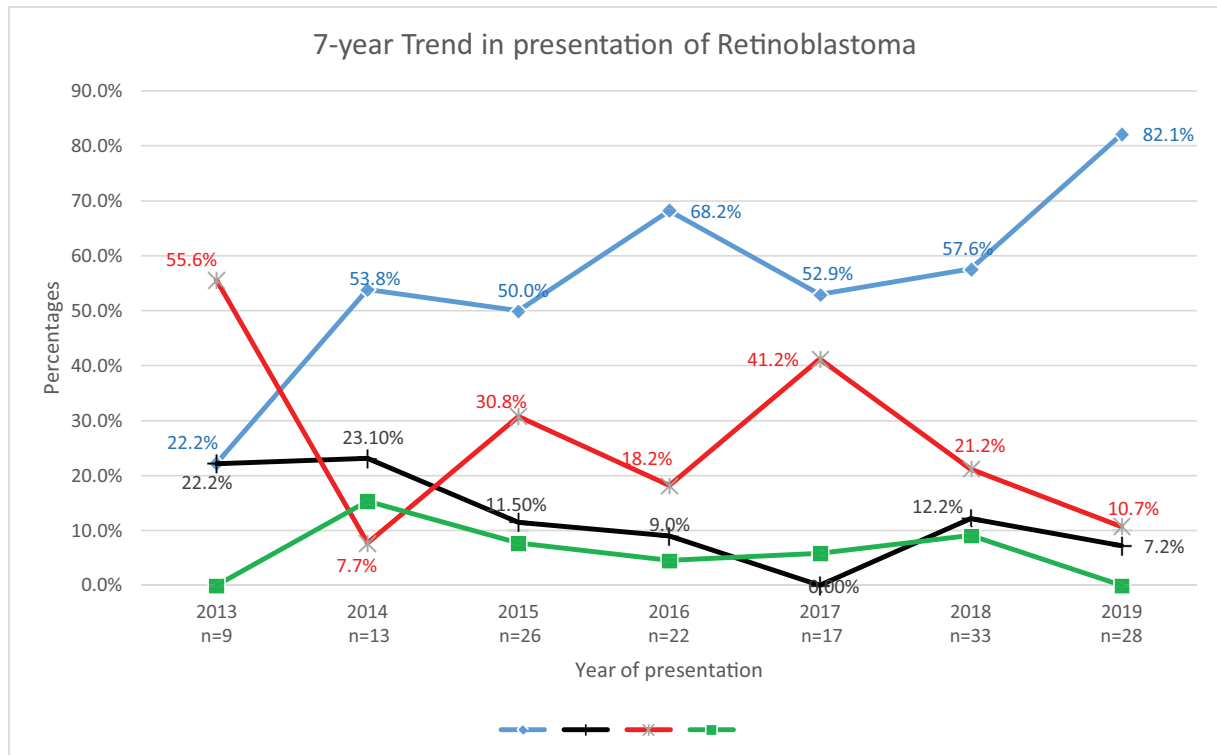
### Pattern of presentation of retinoblastoma

On the whole, the pattern of presentation to the RB referral center was mostly leukocoria and/or squint in 104 (70.3%), proptosis 35 (23.6%), and others 9 (6.1%), including masquerade syndrome like aseptic orbital cellulitis/uveitis in 5 (3.4%), phthisis bulbi in 3 (2.1%), and buphthalmos in (0.7%). Specifically, the trend over the 7-year of the study showed that proptosis as a presentation reduced over time. In 2019, 89.3% presented as leukocoria/squint and 10.7% of children with proptosis, compared to 44.4 % and 55.6% and

**Table 2: Difference in age from symptom to presentation (months) to lag time**

Number of months	Unilateral $n = 74; n (%)$	Bilateral/trilateral $n = 74; n (%)$	Total $n = 148; n (%)$
≤1	8 (10.8)	7 (9.5)	15 (10.1)
>1–6	26 (35.1)	36 (48.6)	62 (41.9)
>6–12	18 (24.3)	15 (20.3)	33 (22.3)
>12–18	10 (13.5)	2 (2.7)	12 (8.1)
>18–24	5 (6.8)	3 (4.1)	8 (5.4)
>24–30	3 (4.1)	4 (5.4)	7 (4.7)
>30–36	0 (0.0)	3 (4.1)	3 (2.0)
>36	4 (5.4)	4 (5.6)	8 (5.4)
Range	0–74	0–93	0–93
Median	7	6	6
IQR	4–15.5	4–12	4–13

IQR, interquartile range.



**Figure 2:** Changing patterns of presenting symptoms and signs of retinoblastoma from 2013 to 2019.

leukocoria/squint and proptosis, respectively, in 2013 [Figure 2].

### Classification of retinoblastoma at presentation

The ICRB was used to classify the intraocular diseases: 188 (84.7%) eyes were intraocular, 32 (14.4%) orbital, and 2 (0.9%) had systemic spread at presentation. Among the 188 eyes with intraocular disease, 38 (20.2%) had between groups A and D: 26 (13.8%) eyes had either group A or B disease, 7 (3.7%) eyes had group C disease, 5 (2.7%) eyes had group D disease, 150 (79.8%) eyes had group E disease.

There was bilateral group E RB in 28 (18.9%) patients, whereas almost all (73 [98.6%]) of unilateral cases were also group E or worse disease [Figure 3].

Being groups A to C was not significantly related to age at which symptoms were noticed ( $P=0.795$ ) but was significantly related to the age at presentation ( $P=0.039$ ). It was also not affected by the lag time ( $P=0.194$ ). Expectedly, having orbital disease was significantly related to lag time ( $P=0.000$ ).

### Disease stage among cases reported between birth and 6 months of life

Among the cases, three of bilateral disease who presented to the hospital before 1 month of life: two of them had group B in one eye and group E disease in the other eye, whereas the third child had group E disease in both the eyes.

Eighteen (31 eyes) patients presented between 1 and 6 months of age: 5 (16.1%) unilateral group E disease and 13 bilateral cases. The bilateral eyes had 2 (6.5%) group A disease, 1

(3.2%) group B, 3 (9.7%) group C, and 20 (64.5%) group E diseases; there were no orbital disease.

### Disease stage among cases reported after 36 months of life

Among the 34 eyes of 25 (16.9%) patients who presented after 36 months of life, 16 (64.0%) had unilateral disease and 9 (36%) bilateral. Symptoms of RB had been noticed from birth in 2 (8.0%) cases, earlier than 12 months of life in 6 (24%), and among 17 (68%) children between 24 and 32 months of life.

Among the nine bilateral cases were two (5.9%) eyes with group A disease, three (8.8%) group B, and one (2.9%) group C. In addition, there were 20 (58.8%) group E eyes (10 each from unilateral and bilateral cases) and 8 (23.5%) orbital disease from 6 eyes of unilateral and 2 from the bilateral eyes.

Figure 1 shows number of bilateral and unilateral RB each of 7 years of the review at a referral center.

Figure 2 shows changes in proptosis, leukocoria, squint, and other presentations of RB over 7 years. Figure 3 shows classification of intraocular RB by ICRB and local and systemic spread in unilateral and bilateral cases.

### DISCUSSION

This review of 222 eyes of 148 patients reported at a single center over a 7-year period represents the largest pool of patients recorded in the country so far. The large number is probably because of the various advocacy efforts, resources acquired, and the capacity that was developed over the years. The male to female ratio of the patients observed showed a

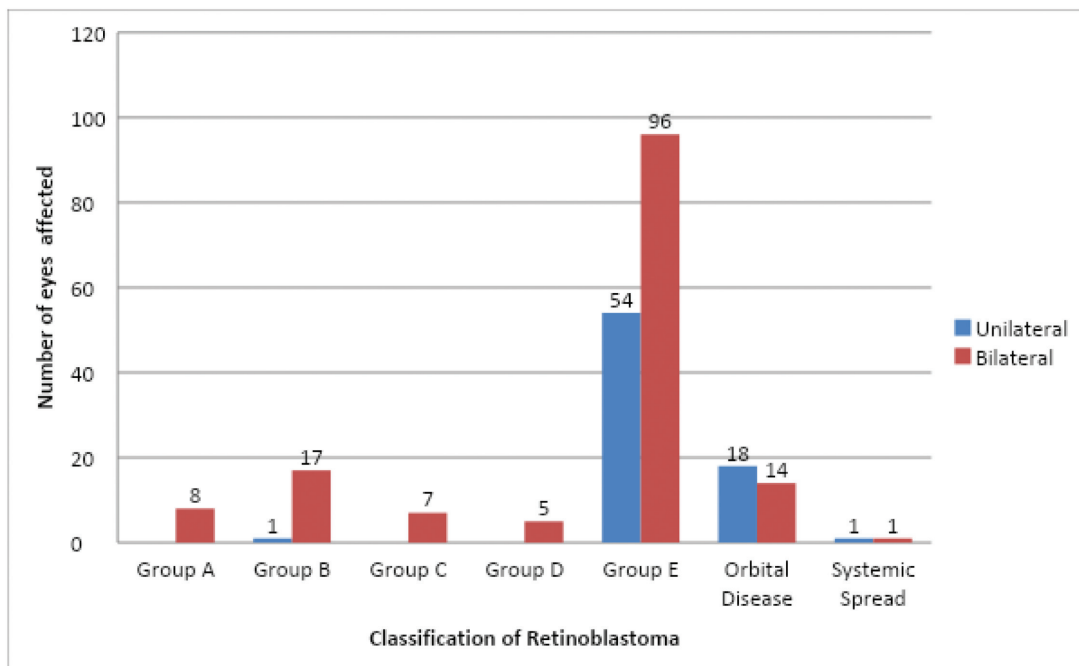


Figure 3: Classification of retinoblastoma at presentation.

slight male preponderance, similar to report of other studies.<sup>[18-21]</sup>

The increasing number of cases may reflect more of increasing awareness of the disease as well referrals from other eye centers and less likely due to any real increase in incidence. The large number of bilateral cases might be from the fact that referring centers are more likely to refer bilateral cases in a bid to salvage at least one eye.

Symptoms in bilateral cases were generally noticed much earlier (6 months) than unilateral cases (17 months) because of the usual earlier age of onset of bilateral, heritable disease. Unfortunately, this did not translate to earlier presentations, could be because the disease in the other were unnoticed by caregivers especially when not affecting visual function.

The 7-year average of 23.6% proptosis as presentation is similar to the reported between 19% and 29.7% rate of proptosis by other earlier reports in Nigeria.<sup>[12,14,22]</sup> However, there was a significant reduction of proptosis presentation from 55.6% in 2013 to 10.7% in 2019, even though it was still higher than the 6% reported from India<sup>[23]</sup> and from more developed countries. Much lower rates of proptosis (if any) were found in the studies from the developed world, as reflected in a recent review of global RB presentation in the year 2017.<sup>[24]</sup>

The value of education in health awareness was demonstrated by the influence of education of both parents on the age at which symptoms were noticed, and health-seeking behavior was demonstrated by the age at presentation that was affected by the education of father and not mother. This is not unexpected in a typical patriarchal society of this study that sometimes discountenance a woman in decision making.

Considering the fact that about 45% of the cases had noticed symptoms by 6 months of life, whereas only about (14.4%) a third of those actually presented within the same period makes the first 6 months in the first year of life the most critical period for RB surveillance especially before discharge from hospital and during routine childhood immunization and well-baby clinics at the primary health centers.<sup>[16]</sup> This is also supported by the significant relationship between early age at presentation and the diagnosis of early stage (groups A–C) disease compared to those who presented late.

Over the 7-year of this study, there was a statistically significant reduction in lag time to presentation and consequently the demonstrated improvement in the stage of the disease over the years. This is believed to be mostly as a result of increasing awareness, improvement in communication with the ready access of Nigerians to mobile phones, advocacy as well as the improved capacity for RB care.

Nevertheless, the persistence in prolonged lag time among about a quarter of the cases is worrisome, even though it is from other developing countries.<sup>[25]</sup> This might be related to

the issues of direct and indirect cost of RB care in Nigeria. Out of pocket payment for care and the logistic difficulties of travelling long distances to seek care are believed constitute hindrance to early presentation.

A study from Uganda reported lag time of 3 to 36 months for unilateral cases and 3 to 8 weeks for bilateral cases.<sup>[26]</sup> The lack of orbital disease in the first 6 months demonstrates the value of early detection which was responsible for preservation of vision in one eye of such babies.

Presentation of groups A to C disease in one eye of bilateral cases even after 36 months of life points the possibility of late onset disease and the need to continue routine RB surveillance in cases presenting with unilateral disease especially where genetic typing is not accessible to at-risk children. Asymmetrical presentation in bilateral RB is not unusual, and the presence of advanced disease in one eye of patients that presented within 1 month suggests a congenital aggressive disease and a pointer to the need for intrauterine screening for earlier detection especially for babies with family history of RB.

Studies have revealed that all bilateral cases and 10% to 15% of unilateral cases have been documented to have germ-line mutation with a risk of 40% to both the siblings and offspring.<sup>[27]</sup> This study recorded associated family history in 2.7% which is in contrast to 9.7% recorded in Uganda<sup>[26]</sup> and 0% recorded in previous studies in Nigeria<sup>[9,14]</sup> but similar to 4% in India.<sup>[23]</sup> The low figures documented in our study as well as other Nigerian studies may be attributed to patients not being aware of the health challenges of fellow family members or might deliberately withhold information for sociocultural reasons.

This review showed that most patients with unilateral RB presented around 24 months of life, this is not surprising as unilateral RBs are mostly somatic and are known to develop much later compared to bilateral RB. Our study revealed that as high as 25 (16.9%) patients with unilateral RB noticed symptoms within 6 months of life. This may be related to the amplification of the MYCN oncogene documented by Rushlow *et al.*<sup>[28]</sup> as this has been shown to initiate early onset aggressive unilateral nonfamilial RB.

MYCN PROTOONCOGENE, bHLH TRANSCRIPTION FACTOR; MYCN MYC encodes a basic helix-loop-helix-leucine zipper (bHLH-LZ) transcription factor (TF), Myc family of oncogenes, bHLH transcription factor, genes play important roles in regulating cell growth and division (proliferation) and the self-destruction of cells (apoptosis). MYCN proto-oncogene, MYCN gene belongs to MYC family (MYC, MYCN and MYCL). The oncogenes are found in many types of cancers notably neuroblastoma, also in retinoblastoma, medulloblastoma, rhabdomyosarcoma, astrocytoma, Wilms' tumour, and small cell lung cancer in which they are deregulated. Amplification is described as when there are more than 10 copies of the gene present in a cell.

Increasingly, presentation of RB at early stages was achieved in our low-resource setting. The various efforts deployed are scalable and therefore commended to government and other stake holders in similar low-resourced settings. This will hopefully improve the overall survival until it becomes comparable to what obtains in developed countries.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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