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ORIGINAL ARTICLE

Clinical epidemiology of retinoblastoma at the Philippine General Hospital: 1998-2008

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ABSTRACT

Objective

This study determined the clinical characteristics of retinoblastoma (RB) from 1998 to 2008 and compared the epidemiological and clinical patterns with those of the period from 1967 to 2001.

Methods

We reviewed the clinical records of 152 patients with RB from 1998 to 2008 in terms of demographic and ophthalmological data and clinical staging or classification.

Results

Sixty-three percent of cases were unilateral and 37% were bilateral. Three (3%) of 95 unilateral cases and 7 (12%) of 57 bilateral cases had family history of RB ($p = 0.038$). The mean age at onset was 17.8 months for unilateral and 7.4 months for bilateral cases, while the mean age at diagnosis was 26.4 months and 13.7 months respectively. The delay from onset to diagnosis was 69% in unilateral and 56% in bilateral RB groups. Financial cost (71.4%) was the leading reason for delay, followed by misdiagnosis (24.5%), and inaccessibility of medical facility (2.0%). The most common manifestations were leukocoria (77%), extraocular findings of orbital mass (9%), and proptosis (6%). Advanced intraocular stage was seen in 63 – 71.6% among those with unilateral and 56 – 60% in those with bilateral tumor.

Conclusions

The onset of disease had not changed over the years, but patients in general were brought earlier for consultation. Most cases presented in the advanced stage. Decreasing the occurrence of extraocular RB through early consultation and treatment can improve patient survival.

Keywords: *Retinoblastoma, Intraocular tumor, Epidemiology*

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RETINOBLASTOMA (RB) is the most common primary intraocular malignancy of childhood, accounting for around 4% of all pediatric malignancies.[1-2] It is a highly malignant tumor of the eye that manifests most often in the first 3 years of life.[3] About 250 to 300 new cases of RB are diagnosed in the United States each year and 5,000 worldwide.[4]

Leukocoria (cat's eye reflex) and strabismus are the most common presenting signs or symptoms of RB,[5-6] reported in both local and international studies. Metastasis generally develops within 1 year of the diagnosis of the intraocular tumor. Risk factors include invasion beyond the lamina cribrosa onto the optic nerve, choroid (>2 mm dimension), sclera, orbit, and anterior chamber. Invasion of the optic nerve or choroid generally involves a large RB tumor, over 15 millimeters at its greatest dimension, along with elevated intraocular pressure and total retinal detachment.[7]

Because RB is highly malignant and the mortality rate reaches 99% if left untreated, the primary goal of management is patient survival. Preservation of the globe and visual acuity are secondary goals. In the 1960s when external beam radiotherapy (EBRT) was the most popular conservative (non-enucleation) treatment, Reese–Ellsworth classification based on location, multifocality, and size of the tumor was created.[8] At that time, peripheral RBs at the ora serrata, multifocal tumors, and larger tumors were more difficult to treat than smaller, single, macular tumors. Hence, peripheral, multifocal, and large tumors were assumed to be more aggressive and earned a higher ranking in the Reese–Ellsworth classification, implying a worse ocular prognosis.

In the mid-1990s, there was a gradual shift in conservative treatment methods for retinoblastoma from EBRT to CRD (combined with focal therapies).The limiting factors for RB control in the CRD era were different than in the EBRT era and related predominantly to the management of associated vitreous and subretinal seeds. The problem of subretinal seeding and differentiation between focal and diffuse vitreous seeding was not addressed in the Reese–Ellsworth classification. For these reasons, it was found to be a poor predictor of CRD success.[9]

The International Classification of Retinoblastoma (ICRB) was formulated based mainly on extent of tumor seeding in the vitreous cavity and subretinal space with minor consideration of tumor size and location.[9] It was intended to predict globe outcome and has shown to be predictive after CRD. Patients within groups A, B, and C had considerable chances for globe salvage and avoidance of EBRT. Patients within group D had much lower chance of success, with approximately one half requiring EBRT or enucleation.[10]

Unilateral RB is generally managed with enucleation if the eye is classified as Reese-Ellsworth group V, and chemoreduction or focal measures are intended for groups I-IV. In bilateral RBs, chemoreduction is required in most cases unless there is extreme asymmetric involvement, with one eye having advanced disease necessitating enucleation and the other minimal disease treatable with focal methods.[1-2, 10]

In a local study, Espiritu et al. noted that the epidemiological and clinical patterns of retinoblastoma cases seen at the University of the Philippines–Philippine General Hospital (UP–PGH) may be changing over time and required continuous monitoring of incidence and characteristics.[11]

The UP–PGH is a tertiary government hospital that receives most retinoblastoma referrals in the Philippines. These cases were initially seen by the retina service of the Department of Ophthalmology. In 1997, the Retinoblastoma-Ocular Oncology Unit was established and handled all these referrals. With the vast number of clinical records available at the unit, the demographics and clinical characteristics of retinoblastoma cases in the last decade can be studied.

Thus, this study determined the clinical characteristics of RB cases seen at UP–PGH from 1998 to 2008 and compared them with local data from previous decades (1967 to 2001) and other centers. It determined the changes in trends in terms of demographics, time of consultation, treatment parameters, and other clinical characteristics.

METHODOLOGY

This study is a retrospective review of medical records of all patients diagnosed with RB between 1998 and 2008 at the UP–PGH Retinoblastoma Clinic. Each chart was assigned a number to keep the name of the patient confidential. Demographic data collected included age at first symptom/sign, age at diagnosis, sex, family history of RB, age at first treatment, lag period between first symptom/sign and diagnosis, and lag period between diagnosis and treatment. Ophthalmological data collected consisted of visual acuity, laterality, and clinical staging. Data were recorded in Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) and analyzed using SPSS for Windows. Patients with unilateral and bilateral RBs were compared. T-test for equality of means was used with a p value of <0.05 considered significant. The data gathered were also compared with earlier local data.

RESULTS

RB patients included 78 males and 74 females, with a mean age of 24.2 ± 14.2 months at initial consultation. Ninety-five (62.5%) of the 152 patients had unilateral tumor while 57 (37.5%) had bilateral tumors. Of the patients with bilateral tumors, 25 (43.9%) sought consul-

Table 1. **Characteristics of children diagnosed with retinoblastoma from 1998 to 2008.**

Variables	Unilateral Retinoblastoma (N = 95)	Bilateral Retinoblastoma (N = 57)	*p*
Age in months, X(SD)	27.9 (±13.6)	18.0 (±13.4)	0.000
Sex			
Female	49 (52%)	25 (44%)	0.357
Male	46 (48%)	32 (56%)	
Mean age at first symptoms, months	17.8 (±15.3)	7.4 (±7.7)	0.000
Age at initial diagnosis, months	26.4 (±13.8)	13.7 (±11.0)	0.000
Age at first treatment, months	28.2 (±14.7)	16.0 (±10.9)	0.000
Presence of family history, %	3% (3)	12% (7)	0.028
Lag between first symptom and diagnosis, months	9.1 (±8.6)	5.9 (±7.5)	0.022
Lag between diagnosis and treatment, months	1.1 (±2.4)	1.0 (±2.0)	0.660

tation for symptoms/signs in both eyes, while 32 (56.1%) sought consultation for one eye but were found to have bilateral RBs. One patient presented with a unilateral tumor at age 1.5 months and developed RB lesions in the fellow eye after 4 months. Three patients with unilateral and 7 with bilateral RBs had a family history of RB ($p = 0.03$). Among those with unilateral RB, the mean age at initial symptom/sign was 17.8 months, which was significantly older than in the bilateral group ($p < 0.001$). The mean age at diagnosis was 26.4 months in those with unilateral and 13.7 months in those with bilateral RBs ($p < 0.001$). The mean lag time from discovery of initial sign or symptom to diagnosis was 9.1 for the unilateral and 5.9 months for the bilateral groups ($p = 0.03$). Sixty-six (69%) with unilateral RB and 32 (56%) with bilateral RBs consulted late (Table 1).

Delay from Onset to Diagnosis

The delay from initial sign or symptom to diagnosis of less than 1 month was 3.2% (3/95) of the unilateral and 21.1% (12/57) of the bilateral RB groups; delay of 1 to 3 months was 24.2% (23/95) of the unilateral and 28.1% (16/57) for the bilateral groups; delay of greater than 3 months was 72.6% (69/95) of the unilateral and 50.9% (29/57) of the bilateral groups. The bilateral group significantly presented earlier compared with the unilateral group.

Combining both unilateral and bilateral groups, 9.9% (15 of 152) had a delay from initial symptom to diagnosis for less than a month; 25.7% (39 of 152) had a delay between 1 to 3 months; and 64.5% (98 of 152 patients) had a delay in consultation of greater than 3 months.

Financial cost (71.4%) was the leading reason for the delay from initial symptom to diagnosis, followed by misdiagnosis (24.5%) and inaccessibility of medical facility (2%). In 1% of cases, the reasons were not indicated, while in another 1% the patients were initially treated with herbal medications.

The most common misdiagnoses for RB were congenital cataract (25%) and eye infections (25%). Other misdiagnoses were uveitis/uveitic cataract (15%), glaucoma (15%), posttraumatic cataract (5%), strabismus (5%), blind eye (5%) and vitamin-A deficiency (5%). One patient was misdiagnosed to have glaucoma and underwent glaucoma surgery. Intraoperatively, an intraocular mass was noted. Most patients were initially seen by their local ophthalmologists (except for patients with vitamin-A deficiency who were seen by a general practitioner).

Most of the patients were from Metro Manila (28.9%), followed by provinces around Metro Manila such as Laguna (7.2%), Bulacan (5.3%), Cavite (3.9%), and Rizal (3.3%).

Age at Consultation

The mean age at initial diagnosis was 26.43 months for unilateral and 13.66 months for the bilateral RB groups ($p < 0.001$). The parents of 12 patients (6 in each group) refused treatment; these patients had no follow-up. The mean lag time between the diagnosis and first treatment was 1.1 months for the unilateral and 1 month for the bilateral groups ($p = 0.66$). Treatment was delayed for 14 months in 1 patient due to the parent's initial refusal. RB was in the advanced stage in the right eye (stage VB, E) and extraocular stage in the left; both eyes were eventually enucleated. After one cycle of chemotherapy, the tumor recurred 1 month postoperatively in the left eye and the patient was lost to follow-up.

Presenting Sign

Leukocoria was the presenting sign in 117 (77%) patients, followed by orbital mass (14), proptosis (6), and strabismus (4). Poor vision at presentation (defined as no dazzle, no light perception) was found in 91 (95.8%) patients with unilateral tumor. The other 4 patients had at least dazzle on visual examination. Among those with bilateral tumors, 15 (26.3%) presented with poor vision in both eyes, while 38 (66.7%) presented with poor vision in the worse and good vision (defined as with at least dazzle; central, steady and maintained; and finger play) in the better eye. Only three (5%) presented with good vision in both eyes.

Clinical staging

Tables 2 and 3 summarize the clinical staging at diagnosis according to the Reese–Ellsworth Classification and the ICRB. In the Reese-Ellsworth Classification, the most common stage was V-B; 71.6% in those with unilateral and 60% (34 for each eye) in those with bilateral tumors. The unilateral group presented at stage IV-A and higher while the bilateral group presented at varying stages. Among those with bilateral RBs, one eye usually presented in an advanced stage and the other at a lower stage or were incidentally found to have RBs at consultation. The same pattern was seen in the ICRB staging. The unilateral group presented at stage D and higher, while the bilateral group presented at all stages. Sixty-three percent (66) in the unilateral and 56% (32 for each eye) in the bilateral groups presented with stage E.

Table 2. **Clinical staging at diagnosis according to the Reese-Ellsworth Classification.**

Staging	Unilateral Retinoblastoma (N = 95)	Bilateral Retinoblastoma (N = 57, 114 eyes)
		Right / Left
Group IA	0%	7% (4), 9% (5)
Group IB	0%	4% (2), 2% (1)
Group IIA	0%	4% (2), 2% (1)
Group IIB	0%	12% (7), 0%
Group IIIA	0%	2% (1), 0%
Group IIIB	0%	2% (1), 5% (3)
Group IVA	1% (1)	2% (1), 4% (2)
Group IVB	0%	0%, 4% (2)
Group VA	3% (3)	0%, 0%
Group VB	72% (68)	60% (34), 60% (34)
Extraocular	24% (23)	9% (5), 9% (5)

Table 3. **Clinical staging at diagnosis based on the International Classification for Intraocular Retinoblastoma.**

Staging	Unilateral Retinoblastoma (N = 95)	Bilateral Retinoblastoma (N = 57, 114 eyes)
		Right / Left
Group A	0%	9% (5), 11% (6)
Group B	0%	11% (6), 7% (4)
Group C	0%	11% (6), 9% (5)
Group D	10% (9)	5% (3), 9% (5)
Group E	66% (63)	56% (32), 56% (32)
Extraocular	24% (23)	9% (5), 9% (5)

DISCUSSION

This study recorded 152 RB cases at the UP–PGH from 1998 to 2008. Similar retrospective studies reported 96 cases in Taiwan from 1978 to 2000, 90 in Thailand from 1997 to 2006, 141 in Turkey from 1981 to 2004, and 142 in Australia from 1974 to 2005.[13-16] Of the 152 cases, 62.5% were unilateral and 37.5% were bilateral, similar to those reported. Of the bilateral cases, 56.1% consulted for unilateral signs/symptoms but were found to have bilateral disease. One patient was initially diagnosed to have unilateral disease but developed tumor in the fellow eye after 4 months of monitoring. Thus, it is important to examine and monitor both eyes in apparent unilateral cases.

Similar to previous reports, bilateral cases manifested earlier than unilateral cases. There was a ten-month difference in age of onset between unilateral and bilateral cases, although there was no significant change in the age of onset compared with earlier local studies. The mean age of presentation was 18 months for unilateral and 8 months for bilateral RBs, suggesting that patients found to have signs and symptoms before age 12 months should be suspected of bilateral disease.

The percentage of familial incidence has not increased compared to data from previous years.[5,11-17] In this study, the familial incidence was 3% for the unilateral and 7% for the bilateral groups. No gender predilection was found, consistent with local and international reports.[5,11-17]

Consistent with previous reports,[5,11-17] the most common presenting sign was leukocoria. Signs suggestive of extraocular extension such as proptosis declined from 16% in 1967 to 1977[11] to 6% in 1985 to 1995,[11] while findings of orbital mass dropped from 27% to 11%.[11] In this study, there was a slight increase in the number of patients who presented with proptosis (Figure 1). Although 64.5% of patients had a delay from initial symptom to diagnosis of greater than 3 months, most still presented with leukocoria and few of the extraocular signs.

Financial cost was the most common reason for delay from onset to diagnosis. However, this study failed to determine the nature of the financial burden that could include cost of consultation, laboratory tests, or travel to a medical facility. Future data gathering should include reasons for the delay from onset to diagnosis so that appropriate public-health measures could be undertaken.

Majority of cases presented in the advanced intraocular stage for both unilateral and bilateral RB cases. Decreasing the occurrence of extraocular RB through early consultation would further increase survival of patients.

The onset of disease has not changed over the years. Although consultation remained delayed (mean delay of 9.1 months for unilateral and 5.9 months for bilateral cases), results showed that the lag time had become shorter and patients were brought in earlier for consultation (Figure 2). This may be a result of greater public awareness, im-

proved public-health programs, and increased access to health facilities.

Because of proximity, most of the patients were from Luzon, specifically Metro Manila and the surrounding provinces of Cavite, Laguna, Bulacan, and Rizal. There were some referrals from the 3 major island groups of the country, but many were treated at local centers with inadequate facilities and expertise. We recommend, therefore, a national retinoblastoma registry to assess the nationwide incidence. In addition, we recommend the establishment of RB treatment centers in key provinces in the Philippines. Since the major cause of delay from onset to diagnosis was financial such as transportation costs, there is a need to establish regional centers with qualified eye MDs that will be accessible, adequate, and affordable.

In summary, accessibility to medical care leading to early consultation and treatment will definitely increase survival rates in this potentially fatal disease.

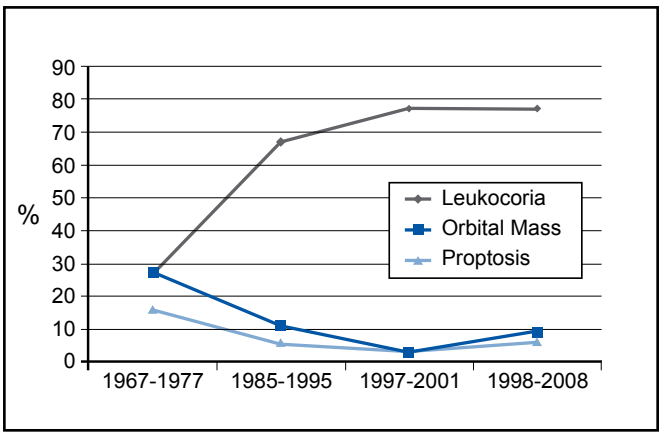

Figure 1. Presenting signs/symptoms of retinoblastoma.

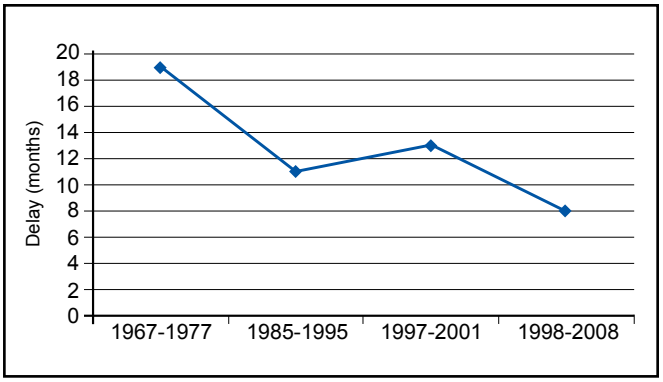

Figure 2. Decreasing trend in the delay from onset to diagnosis of retinoblastoma.

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