·Clinical Research·

Clinical presentation of retinoblastoma in Malaysia: a review of 64 patients

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Abstract

• AIM: To analyze the demography, presenting clinical features, spread of the disease of retinoblastoma in patients who were treated in two tertiary hospitals in Malaysia.

• METHODS: In this retrospective study, information of gender, age, race, presenting clinical features, findings of CT scan orbits and brain, lumbar puncture and bone marrow aspiration results were collected from the medical records of retinoblastoma patients diagnosed in Hospital of Universiti Sains Malaysia and General Hospital of Kuala Lumpur over a period of ten years. The data were collected in the same type of proforma from both hospitals.

• RESULTS: A total of 64 patients were treated in both hospitals together, of whom boys and girls were almost equally affected. The mean age of children at presentation was 24.2 (range 3-84) months, 53 (82.8%) children were under 36 months old. The disease was unilateral in 39 (60.9%) patients. The most common presenting signs were leukocoria in 46 (71.8%), followed by proptosis in 21 (32.8%) patients. Routine screening of the siblings of affected children revealed retinoblastoma in 2 patients. There was intracranial extension in 8 (12.5%) and metastasis in bone marrow in 6 (9.3%) patients.

• CONCLUSION: Leukocoria is the most common presentation of retinoblastoma in Malaysia. However, the disease was intraocular in 40 (62.5%) and extraocular (orbital involvement, intracranial and distant metastasis) in 24 (37.5%) patients.
KEYWORDS: retinoblastoma; leukocoria; strabismus; proptosis
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INTRODUCTION

Retinoblastoma is the most common primary intraocular malignancy in children. It is a rare tumor, occurring in only about 1 in 20 000 live births. Leukocoria (white papillary reflex) is the most common presenting signs, accounting for about two-thirds of cases. The other modes of its presentation are strabismus, secondary glaucoma, proptosis, anterior chamber inflammatory signs and spontaneous hyphema[1].The modes of presentation may vary in the developing countries which is characterized by late presentation with orbital involvement (proptosis) [2-4] and metastasis [5]. Under-standing the modes of presentation is important for timely diagnosis because survival of children is highly dependent on the degree of advancement of the disease.

There is paucity of published data on various modes of clinical presentation of retinoblastoma in Malaysia. Therefore, we reviewed the case records of retinoblastoma patients treated in Hospital of Universiti Sains Malaysia (HUSM, the tertiary teaching hospital in Kota Bharu, north-east peninsular Malaysia) and in General Hospital of Kuala Lumpur (GHKL, the apex hospital in the capital city of Malaysia) to analyze the demography of patients, clinical features, and spread of the disease at presentation.

MATERIALS AND METHODS

The case records of all patients of retinoblastoma treated over a period of ten years (1990-1999) in HUSM and GHKL were reviewed. The age, gender, race of patients, eye involved, presenting clinical features, CT scan findings of orbits and brain at presentation (to evaluate the spread of the disease into orbit and brain), lumbar puncture and bone marrow aspiration results (for assessment of metastasis) were noted from the case records of the patients. The parents of 4 children in HUSM and 2 children in GHKL refused bone marrow and lumbar puncture tests because of religious beliefs; and thus they were not included in the analysis of data. Ultrasound abdomen, X-ray chest PA view was done whenever needed. The diagnosis was made clinically, supported by computed axial tomography scanning of orbits and brain. Ellsworth [6], Grabowski and Abramson[7] classifications were used to stage the disease as

intraocular and extraocular. The patients with disease within the eyeball (intraocular) were considered as stage I, those with orbital extension as stage II, those with central nervous system metastasis as stage III, and those with haematogenous metastasis as stage IV. The findings of patients from both hospitals were noted in a same type of proforma.

RESULTS

Demography of Patients Sixty-four patients (26 in Hospital of Universiti Sains Malaysia, Kubang Kerian and 38 in General Hospital of Kuala Lumpur) treated over a period of ten years were included in this study; of whom 31 (48.4%) were boys and 33 (51.6%) were girls; 49 (76.6%) were Malays, 10 (15.6%) were Chinese and 5 (7.8%) were Indians. The disease was unilateral in 39 (60.9%) and bilateral in 25 (39.1%) patients. The mean age of patients at presentation was 24.2 (range 3-84) months; 53 (82.8%) were under 36 months old (Table 1). However, the age at presentation was higher in unilateral cases (mean age 24.5 months, range 4-84 months) than in bilateral cases (mean age 17.7 months, range 3-60 months).

Clinical Features Leukocoria was the most common (71.8%) presenting clinical feature followed by proptosis (32.8%) in our study (Table 2). Three patients presented with signs of orbital cellulitis. Retinoblastoma was diagnosed in 2 children on routine screening of siblings of the affected patients.

Spread of tumour There was direct intracranial extension into optic chiasma in 4 patients, while metastatic lesions were seen in cerebrum 1, meninges 1 and cavernous sinus 2 patients. Out of 10 patients with orbital involvement, the tumor mass was noted extending into maxillary sinus in 3 patients (Table 3). Bone marrow aspiration was positive for malignant cells in 6 cases, of whom osteolitic lesions were seen in skull bones in 2 cases, in the ribs in 2 cases, and cervical lymphadenopathy were noted in 2 cases. Malignant cells were seen in cerebrospinal fluid in 4 out of 8 cases with intracranial metastasis.

Taking into account of the clinical features and the investigation findings, the disease was categorized into stage I in 40 (62.5%): 35 unilateral and 5 bilateral cases, stage II in 10 (15.6%): 4 unilateral and 6 bilateral cases , stage III in 8 (12.5%), and stage IV in 6 (9.4%) patients. Ellsworth stage III or IV were noted in all the cases of stage I disease. All the patients in stage III and IV were having bilateral retinoblastoma. However, the disease was in Ellsworth stage I or II in one eye of these patients.

Treatment Depending on the stage of the disease at presentation, the treatment was determined i.e. enucleation for stage I, orbital external beam radiotherapy (4000 Gr in 20 divided doses) followed by enucleation for stage II, chemotherapy (6 cycles of intravenous cyclophosphamide and vincristin) and/or orbital radiotherapy for stage III and IV. The discussion was done with parents were explained about the proposed treatment and consent was obtained for the same. Adjunctive therapy (cryotherapy/laser photocoagulation) was given in all eyes of children who had Ellsworth I or II stage of the disease. Children whose enucleated eyeball showed histological infiltration of optic nerve were subjected to orbital radiotherapy postoperatively.

Histopathological findings Enucleation was performed in 50 eyes (35 in stage I of unilateral disease, 5 in the more

Table 1 Age at presentation and laterality in retinoblastoma patients (n=64)

Age(mo)	Unilateral cases	Bilateral cases	Total (%)
3-12	4	8	12(18.7)
13-24	12	12	24(37.5)
25-36	13	4	17(26.6)
34-48	6	2	8(12.5)
49-60	1	-	1(1.5)
61-72	1	-	1(1.5)
73-84	1	-	1(1.5)

Table 2 Clinical features at presentation in retinoblastoma patients (n=64)

Clinical features[a]	Number(%)
Leukocoria	46(71.8)
Proptosis	21(32.8)
Redness of eyes	15(23.4)
Secondary glaucoma	12(18.7)
Retinal detachment	10(15.6)
Vitreous seedling	7(10.9)
Squint	6(9.3)
Orbital cellulites	3(4.6)
Hyphema	3(4.6)
Nodules in the scalp	2(3.1)
Hypopyon	1(1.5)

[a]Some of the children had more than one sign at the time of presentation

Table 3 Radiological findings (CT scan of orbits and brain) in retinoblastoma patients (n=64)

CT scan findings[a]	Number(%)
Calcification	42(65.6)
Optic nerve thickening	26(40.6)
Extension into orbit	10(15.6)
Intracranial extension/metastasis	8(12.5)
Extension into maxillary sinus	3(4.6)

[a]More than one sign was present in some of the patients at the time of presentation

advanced eye in bilateral disease in stage I, 10 eyes in stage II after giving orbital radiotherapy). The eyeballs were subjected for histopathological examination. Rosettes (26, 52%) were the most common type of histological finding in our study. Optic nerve infiltration was noted in 16 (32%) patients (Table 4).

Follow-up The time between the date of discharge from the hospital and the date of last follow-up was taken as duration of follow-up. Since there was a default of long term follow-up of many patients, survival rate could not be estimated in our study. Twelve patients (18.7%) were followed up for 6 months, 27 cases (42.2%) for 12 months, 10 cases (15.6%) for 24 months and 15 cases (23.4%) for 36 months or more. Orbital recurrence of the tumor occurred in 6 children who were given external beam radiotherapy.

The longest follow-up was 9.5 years in a female child with bilateral retinoblastoma. Enucleation of one eye was done at the age of 3 years in HUSM, and was referred to GHKL for external beam radiotherapy to the other eye. She developed radiation cataract in that eye 2.5 years after the radiotherapy treatment. Her best corrected vision was 6/24 following cataract surgery in HUSM (extracapsular cataract extraction and posterior chamber intraocular lens implantation). Fundus examination showed pale optic disc probably due to radiation optic neuropathy.

Table 4 Histopathological findings in retinoblastoma (n=50)

Histological findings[a]	Number (%)
Rosettes	26(52)
Pseudo rosettes	8(16)
Undifferentiated type	16(32)
Calcification	24(48)
Necrosis	14(28)
Haemorrhage	4(8)
Choroid infiltration	9(18)
Optic nerve infiltration	16(32)

[a]More than one histological findings were present in some of the eyeballs

DISCUSSION

Retinoblastoma has no sex predilection, and the average age at diagnosis is 18 months and vast majority become clinically apparent before the age of 3 years. Patients with bilateral tumors present earlier than those with unilateral involvement [1]. In our series also, there was not much difference in the occurrence of retinoblastoma in boys (48.4%) and girls (51.6%). The mean age of patients at presentation was 24.2 months which is slightly higher; however, 82.8% were below 36 months age. The mean age at presentation was less in bilateral cases (17.7 months) than in unilateral cases (24.5 months). Retinoblastoma was seen in 76.6% of Malays compared to Chinese and Indians. This is because of large proportion of population in Malaysia are Malays.

Leucocoria is the most common presenting sign of retinoblastoma followed by strabismus all over the world (Table 5). The figures vary from country to country, from time to time in the same country. This could probably be due to geographical variation of the disease, awareness of the disease among the public, availability of medical facilities in that country and number of patients examined. The frequency of common modes of presentation of retinoblastoma in our study is consistent with many studies from different parts of the world.

Leucocoria as presenting sign was seen in 22.6%[3] to 97.9%[12] of patients of retinoblastoma, while strabismus was noted in 5.6%[3] to 26%[17] of these patients at the time of diagnosis. In addition to the above, Abramson *et al* [8] reported many uncommon/rare presenting signs viz anisocoria, heterochromia iridis, inflammatory signs, nystagmus, microphthalmia/buphthalmos, proptosis, orbital cellulitis, hyphema, ptosis, aniridia, phthisis buli, vitreous haemorrhage *etc*. in their study of 1265 patients of retinoblastoma.

However, proptosis as the presenting sign at the time of diagnosis was reported in high frequency from some of the developing countries like Nigeria (84.6%) [4], Pakistan (52.8%)[3], Nepal (44.2%)[2], Thailand (26.7%)[14] and India (25.3%)[12]. Proptosis as presenting sign was reported in very low frequency from some of the developed countries like USA (0.5%)[8] and South Korea (1.4%)[22]; and this sign was not seen in any of the patients in Australia [16,21] and Singapore[11,23].

Bilateral retinoblastoma was seen in 39.1% of patients in our study which is similar to the figures reported from USA (41.5%) [8], Australia (41%) [21], India (37.2%) [12], and Thailand (36.7%)[15]. However, it was observed in very less percentage in countries like Nepal (9.3%)[2] and Singapore (17%)[11].

Leukocoria is due to tumor mass or retinal detachment appearance through the pupil. Strabismus is due to visual loss caused by tumor or retinal detachment involving the macula and/or optic disc. Orbital extension of the tumor results in proptosis, lid swelling and echymosis; and the disease is considered to be in moderately advanced stage[26]. The late presentation (proptosis) could probably be due to lack of awareness among the public about the occurrence of cancer in the eye in young children. The other reason we observed in our study is that some parents do not accept the

Table 5 Comparative frequency of common presenting signs of retinoblastoma in different parts of world

Author	Year	Country	No.of patients	Leuko-coria	Strabismus %	Proptosis %
Abramson *et al*[8]	1998	USA	1265	56.1	23.6	0.5
Tarkkanen & Tuoveinen[9]	1971	Finland	136	39.7	13.2	-
Bedford et al[10]	1971	UK	139	23.2	14.2	-
Tan *et al*[11]	1997	Singapore	41	82.9	19.5	-
Sahu *et al*[12]	1998	India	296	97.9	-	25.3
Chantada *et al*[13]	1999	Argentina	95	81.0	14.3	-
Peterson [14]	2000	USA	114	61.4	18.4	-
Patikulsila & Patikulsila[15]	2001	Thailand	30	60.0	10.0	26.7
Kao *et al*[16]	2002	Taiwan	96	78.1	12.5	16.7
Dondey *et al*[17]	2004	Australia	165	53.3	26.0	-
Shanmugam *et al*[18]	2005	India	355	74.6	6.2	1.1
Badhu *et al*[2]	2005	Nepal	43	32.5	-	44.2
Ozkan *et al*[19]	2006	Turkey	141	82.2	9.2	7.8
Chang *et al*[20]	2006	Taiwan	54	71.4	14.3	-
Berman *et al*[21]	2007	Australia	142	72.5	22.5	-
Chung *et al*[22]	2008	South	70	80.0	8.5	1.4
Aung *et al*[23]	2009	Singapore	30	50.0	20.0	-
Rai *et al*[3]	2009	Pakistan	53	22.6	5.6	52.8
Bonanomi *et al*[24]	2009	Brazil	28	75.0	10.7	3.6
Naseripour *et al*[25]	2009	Iran	105	64.8	28.2	-
Present study		Malaysia	64	71.8	9.3	32.8

diagnosis of cancer in the eye in young children and thereby try to seek treatment from traditional faith healers. After some months, they realize that it will not cure the disease. Then, they consult another doctor for medical help, and by that time the disease is in advanced stage and incurable.

All children with strabismus should be subjected to detailed fundus examination to exclude retinoblastoma as a cause for the squint which is a life threatening disease. Although uncommon signs are seen in very few children, it is worth keeping their association with retinoblastoma. All other causes of such symptom/sign should be excluded before labeling the patient as a case of retinoblastoma. By starting the treatment in-time in such patients, the life of the child can be saved.

In our series, three children presented with signs of orbital cellulitis. Two children had unilateral retinoblastoma while the third child had bilateral retinoblastoma. The diagnosis was confirmed by CT scan of orbits and brain which showed tumor mass in the globe with areas of calcification in the affected eyes. Although extremely rare, orbital cellulitis as presenting sign in patients of retinoblastoma has been well documented in the literature[27-30]. It is suggested that necrotic changes occurring in the ciliary body and iris root trigger an inflammatory response in adjacent orbital soft tissue. Another possible route for necrotic tumor to reach out of the eye is through trabecular mesh work [29,30]. Histological optic nerve infiltration was noted in 32% of patients in our study which is similar to a study reported by Biswas *et al* [31] from India (32.3%), but is less than 37% as reported by Badu *et al* [2] from Nepal. Bone marrow metastasis was seen in 9.3% of cases in our study, while the same was reported in 16.6% of patients from Taiwan[16].

Enucleation is a definitive treatment for retinoblastoma and is associated with a low complication rate but the patient can not have the choice of vision in the affected eye. External beam radiotherapy, although effective, can result in cosmetic deformity, cataracts, or retinopathy and carries an increased risk of a second non-ocular malignancy in the treatment field. Focal therapies such as cryotherapy, laser and plaque radiotherapy have been used to treat small tumors with no evidence of seeding. A combination of focal therapy with chemoreduction has provided an alternative to the treatment of large tumors with primary enucleation. Chemoreduction utilizes neoadjunctive chemotherapy to reduce the tumor volume and enable focal therapy[32,33].

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