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Epidemiologic Features of Retinoblastoma in Shiraz, Southern Iran

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Abstract

Background: Retinoblastoma (RB) is the most common primary intraocular cancer of childhood. There is no published report on this affliction at our center as a referral center in southern Iran. This study aimed to perform a 15 years epidemiological assessment of RB, in Fars Province, Southern Iran.

Methods: We retrospectively analyzed medical records of all patients with RB diagnosed in Khalili Hospital affiliated to Shiraz University of Medical Sciences in Shiraz, Southern Iran. All available pathologic slides were reviewed and staging of tumors were revised using the TNM classification of 2008.

Results: Sixty-seven patients were enrolled in this study (46.3% females and 53.7% males). Among the cases, 71.6% had unilateral and 28.8% bilateral RB. The mean age of symptom presentation and diagnosis were 20.5±16.5 and 26.3±20.1 months, respectively, which were significantly lower in bilateral cases. Leukocoria was the most common presenting symptom (56.7%), followed by strabismus (10.4%). The result of histopathological review showed that RB in 70% of patients was at T1, T2 and T3 stage, but 30% were at T4 stage.

Conclusion: Demographic and clinical variables of RB under the present study are comparable with published reports but our patients were diagnosed at the later stage, leading to poorer prognosis. It is necessary to expand the existing organizations into a comprehensive population-based registry system to obtain a clearer picture of the epidemiology of RB in our region.

Keywords: Epidemiology; Retinoblastoma; Iran

Introduction

Retinoblastoma (RB) is the most common primary intraocular cancer of childhood. The frequency of RB ranges from 1 in 15000 to 18000 live births, depending on the country.[1-7] Considering epidemiology of eye cancer, however, we come to the conclusion that "RB is the most frequent primary intraocular cancer and is gaining importance rapidly".[8] RB is the first disease for which a genetic etiology of cancer has been described; it is caused by a mutation in the RB1 gene.[9] It can affect one or both eyes and the disease can be inherited. Altered discoloration of the pupil and strabismus are the usual symptoms that lead to medical attention. Cure rates are high in children when the tumor is confined to the eye and has not spread systemically or into the orbit or brain.[10]

RB is a life-threatening disease; survival has been found to be highly dependent on the degree of advancement of the disease.[4] If untreated, RB leads to the death of almost all patients due to intracranial extension and dissemination of the disease within two years. Although the 5-year survival rate for RB has increased to over 90% in developed countries, it is still not the case in developing countries.[1] Early detection of the disease, referral to specialized centers, and new methods of treatment improves outcomes among the RB patients.[1-3]

To our knowledge, few prior reports have assessed RB in Iran. The available ones have also focused on

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certain centers in Tehran.[1,11,12] There is, indeed, no information about this disorder in our center as a referral center in southern Iran. This study aimed to perform a 15 year epidemiological assessment of RB, in Fars Province, south of Iran.

Materials and Methods

We retrospectively analyzed the medical records of all patients diagnosed with RB in Khalili Hospital affiliated to Shiraz University of Medical Sciences in Shiraz, Southern Iran as a referral center. We enrolled 67 patients who were diagnosed with RB between January 1995 and January 2010. Demographic and clinicopathological data included sex, age at first presentation, age at diagnosis, laterality, familial history of RB, presenting signs, the person who first realized the presence of the eye problem, treatment modalities adopted, and patient survival for those whose data were available (20 cases, 29.8%) obtained from the patients' medical records.

All available pathologic slides were histopathological reviewed again by an ophthalmopathologist (23 slides, 34.3%) and staging of tumors was revised using the TNM classification of 2008.[12] The TNM classification included both clinical and pathological criteria: TX: primary tumor cannot be assessed; T0: There is no evidence of primary tumor; T1: Tumor is confined to the retina (no vitreous seeding or significant retinal detachment); T2: Tumor has spread contiguously to adjacent tissues or spaces (vitreous or subretinal space); T3: Invasion of the optic nerve and/or optic coats has occurred and T4: There is extraocular tumor.

Statistical analyses were performed using SPSS software (SPSS for Windows 15.0, SPSS, Chicago, IL, USA). Descriptive statistics for each variable was obtained. The Chi-Square and Fishers Exact tests were used to compare the qualitative data. In addition, the Mann-Whitney test as a non-parametric test was performed to compare the quantitative data of the unilateral and bilateral cases. *P* values less than 0.05 were considered statistically significant.

Results

Sixty-seven patients were enrolled in this study (Table 1). There were 31 (46.3%) patients from Fars

Table 1: General characteristics of patients with retinoblastoma

Variables		Patients (Total number:67)	*P* value*
Age at symptom presenting (month: Mean±SD)		20.5±16.5	
Age at diagnosis (month: Mean±SD)		26.3±20.1	
Symptom duration (month: Mean±SD)		3.3±6.2	
Residency Shiraz, No. (%)		10 (14.9)	
	Other cities of Fars province, n (%)	21 (31.4)	
	Other south provinces, No. (%)	31 (46.3)	
	Foringer, No. (%)	2 (2.9)	
	Unknown, No. (%)	3 (4.5)	
Sex	Female, No. (%)	31 (46.3)	0.541
	Male, No. (%)	36 (53.7)	
Family history for RB	Yes, No. (%)	5 (7.5)	0.001
	No, No. (%)	62 (92.5)	
Laterality	Unilateral, No. (%)	48 (71.4)	0.001
	Bilateral, No. (%)	19 (28.6)	
Main presenting symptom			
	Leukocoria, No. (o.%)	38 (56.7)	
	Strabismus, N (%)	7 (10.4)	
	Red eye, No. (%)	4 (6.0)	
	Decreased vision, No. (%)	2 (3.0)	
	Proptosis, No. (%)	1 (1.5)	
	Leukocoria and strabismus, No. (%)	3 (4.5)	
	Decreased vision and red eye, No. (%	2 (3.0)	
	Leukocoria and inflammation, No. (%)	1 (1.5)	
	Leukocoria and Red eye, No. (%)	1 (1.5)	
	Unknown, No. (%)	8 (11.9)	

* Chi-Square test.

province, 31 (46.3%) from others southern provinces, and 2 (2.9%) from foreign countries. The patients were equally distributed among both genders (p=0.541). There were 48 (71.6%) unilateral cases (28 involving the right eye) and 19 bilateral cases (28.8%), (p=0.001). Comparison of the baseline data between unilateral and bilateral RB cases were presented in Table 2.

The mean age at symptom presentation was 20.5±16.5 months (23.7±16.5 months in unilateral versus (vs.) 13.5±13.2 months in bilateral cases; p=0.045). The mean age at diagnosis was 26.3±20.1 months (30.3±21.3 months in unilateral vs. 17.2±12.2 months in bilateral cases; p=0.029). Nine cases (13.4%) were diagnosed after the age of 3, none of whom had positive family history and 1 was bilateral. The mean time lag between first presentation of the disease and RB diagnosis (delay in diagnosis) was 3.3±6.2 months, which was not significant between unilateral and bilateral patients (p=0.907).

With respect to family history, 5 (7.5%) of total which 3 (6.2%) cases of unilateral and 2 (10.5%) of bilateral had family history of RB, (p value=0.449). Age at diagnosis was not significantly different between those who had positive family history and those who did not, (16.8±14.4 months vs. 20.8±16.5 months; p=0.501).

Leukocoria was the most common presenting symptom (in 38 cases, 56.7%) noted in diagnosis of RB, followed by strabismus (in 7 cases, 10.4%), red eye (in 4 cases, 6.0%) and decreased vision (in 2 cases, 3.0%). Most often (in 98.3%), parents were the first persons who noticed abnormal appearance of the eye. Enucleation and exenteration were done in 50 (74.6%) and 8 (11.9%) cases, respectively. The parents had refused enucleation surgery in 6 (8.9%) cases, and surgery data were missing for 3 cases. Only 1 case did have bilateral enucleation.

As shown in Tables 3, treatment methods included enucleation, exenteration, radiotherapy, cryotherapy, laser photocoagulation. Chemotherapy as a systemic administration of different regimens has been used among our study group; vincristine, cisplatin, etoposide, and cyclophosphamide (OPEC regimen) and vincristine, carboplatin, etoposide, and cyclophosphamide (OJEC regimen).

Table 3: Different mode of treatments in patients with retinoblastoma

Mode of treatment	Patients No. (%) (Total number:67)*
Eye removal	58 (86.6)**
Enucleation	50 (74.6)
Exenteration	8 (11.9)
Refused from eye removal	6 (8.9)
Systemic chemotherapy	31 (46.3)
Radiotherapy	8 (11.9)
Cryotherapy	10 (14.9)
Laser photocoagulation	1 (1.5)

* Some patients received different mode of treatments, ** 3 cases surgery data were missing.

Table 4 presents the results of a histopathology review of available slides in our patients (23 cases, 34.3%). Vitreous was the most common organ affected by RB (in 18 cases, 78.3%). Also 8 (34.8%) cases were moderately differentiated and 6 (26.1%) cases were undifferentiated. RB for 14 patients (60.9%) was contained within the eye (T1 and T2), in 2 patients (8.7%), RB invaded the optic nerve (T3), and 7 (30.4%) patients had extraocular tumor extension (T4). The only patient who developed secondary cancer was a unilateral case who developed osteosarcoma 9 years after the RB diagnosis. She had no positive history of radiotherapy in the course of RB treatment. According to our available data, 8 (11.9%) patients had positive evidence of metastasis, in half of whom there was metastasis to the CNS. In addition to our research, 5 patients died due to RB, and 15 patients survived up to January 2010.

Table 2: Comparison between unilateral and bilateral retinoblastoma among studied patients

Variables	Patients		
	Unilateral (n=48)	Bilateral (n=19)	*P* value
Age at symptom presenting (month: Mean±SD)	23.7±16.5	13.5±13.2	0.045*
Age at diagnosis (month: Mean±SD)	30.3±21.3	17.2±12.2	0.029*
Symptom duration (month: Mean±SD)	3.7±6.9	2.3±4.0	0.907*
Sex; Male, No. (%)	23(47.9)	12(63.1)	0.220**
Positive family history, No. (%)	3(6.2)	2(10.9)	0.449+

* Mann-Whitney Test as non parametric Test, ** Chi-Square Test, + Fishers Exact Test.

Table 4: Available pathologic data in patients with retinoblastoma

Variables		Number of patients (%) (Total=23)
Positive evidence of organ involvement *	Sclera	7 (30.4)
	Optic nerve	9 (39.1)
	Vitreous	22 (95.6)
	Orbit	6 (26.1)
	Choroid	12 (34.8)
Cell type	Highly differentiated	6 (26.1)
	Moderately differentiated	8 (34.8)
	Un differentiated	6 (26.1)
	Necrotic	3 (13)
TNM classification	pT1	4 (17.4)
	pT2a	5 (21.7)
	pT2b	5 (21.7)
	pT3	2 (8.7)
	pT4	7 (30.5)

* Some cases had several organ involvement, pT: Primary tumor, pT1: Tumor confined to the retina, the vitreous, or subretinal space; pT2a: Tumor invades optic nerve up to, but not through, the level of the lamina cribrosa; pT2b: Tumor invades choroid focally; pT2c: Tumor invades optic nerve up to, but not through, the level of the lamina cribrosa and invades the choroid focally; pT3: Significant invasion of the optic nerve; pT4: Extraocular tumor extension

Discussion

RB is a malignancy that arises in primitive neuroectodermal cells of the retina.[14] With early detection and effective treatment, RB remains the most curable of all childhood cancers with a survival rate currently exceeding 90%.[15] Approximately 80% of children with RB are diagnosed before the age of 3 years.[16] This is compatible with our results that 86.6% of patients were diagnosed up to 3 years old.

Patients with bilateral disease usually present at a younger age (14–16 months) than patients with unilateral disease (29–30 months).[16,17] In our study, the mean age of symptom presentation was 20.5±16.5 months (23.7±16.5 in unilateral vs. 13.5±13.2 in bilateral cases). The mean age of diagnosis was 26.3±20.1 months (30.3±21.3 in unilateral vs. 17.2±12.2 in bilateral cases). A study from Tehran, Iran reported that the mean age of diagnosis was 27.4 months in unilateral and 30 months in bilateral.[1] The same study reported the patient age at diagnosis tended to be relatively late in Taiwan.[2] Patient ages at diagnosis of unilateral and bilateral cases were 20.7 and 7.5 months in Japan.[18] The median age of diagnosis in the USA has been reported to be 12 months in bilateral and 24 months in unilateral cases.[15] The reasons for late diagnosis in Nigeria (30.7 months) included late presentation for unknown reasons, missed diagnosis, and mismanagement in a previous hospital.[19]

In the current study, the mean time lag between first presentation of the disease and diagnosis was 3.3 months. The same study in Taiwan reported the mean duration of symptoms as 2.96 months.[2] In developing countries, RB is unfortunately accompanied by delayed diagnosis that leads to disease presentation in advanced and high mortality stages.[20]

The results of histopathological review of available slides in our patients (23 cases) showed 78.3% had a vitreous, 34.8% choroid, 34.8% optic nerve, 21.7% sclera, and 21.7% orbit involvement. In 34.8%, RB was moderately differentiated and 26.1% was undifferentiated. RB in 70% patients was at T1, T2 and T3 stage, but 30% were at T4 stage. A comparable study which reviewed the status of the children with unilateral RB in Toronto, during the period 1988 to 2008, showed that 96% of the patients had T1, T2 and T3 stage and only 4% had T4 (extraocular tumor extension).[21] According to this comparison, our patients were diagnosed at a higher stage and had poorer prognosis.

In our data, the laterality of RB disease (our study 28.8%, Taiwan 25%, and USA 29% were bilateral cases) and presenting signs were similar to those previously described in several comparable studies.[2,3,10,15] The most common presentation of RB in our study was leukocoria, which was often noticed by a parent (in 98.3% of our cases, parents noticed abnormal appearance of the eye). Leukocoria is an abnormal white discoloration in the pupil which is the

result of an altered pupillary red reflex in the eye. The second most common sign is strabismus that results from a loss of central vision in the eye causing ocular misalignment.[10,15] In patients with more advanced disease, the presenting signs and symptoms correlate with the degree of extraocular invasion can result in orbital swelling and proptosis.[10] In this study, one case presented by proptosis and another one by orbital inflammation. The incidence of unilateral RB is not similarly distributed among the world and is higher in developing countries[10,14,22] (Africa 34.2, Asia excluding Japan 18.8, Japan 8.3, Europe 10.2, Latin America 19.8 birth rate/1000[7]). The reason for this higher incidence is not clear. Lower socioeconomic status, high presence of human papilloma virus, HIV epidemic, very low birth weight, decreased intake of vegetables and fruits during pregnancy, and lack of prenatal vitamin supplementation and folate may increase the risk of having a child with sporadic RB.[10,14,22,23]

About 1/3 of the patients with RB present with bilateral disease and carry a germ line mutation of the RB1 gene; affected individuals carry a 45% risk of having an affected offspring. On the other hand, most unilateral cases are sporadic and only 10-15% of them are heritable, so most are at no risk of transmitting the disease to their offsprings.[24] Up to 12% of the RB cases in some developed countries inherit a RB1 mutation from an affected parent. Little information published regarding familial retinoblastoma in developing countries.[24] Family history was positive in 5 (7.5%) cases, 2 of whom were bilateral. Also other similar studies reported positive family history, for example, Tehran 4.8%, Taiwan 5.8%, and USA 6.8%.[1,2,8] Patients with familial RB were fewer to be diagnosed by screening in developing countries so diagnosed at a later age, advanced stage and poorer prognosis. By early detection of familial RB, it would be possible to reduce the treatment intensity.[24] So genetic counseling in families with RB is an important aspect.[10] In addition, the American Academy of Pediatrics recommends that a red reflex examination be completed in all infants younger than 2 months, and the physical exam should include examination of the red reflex as a screening test for visual anomalies.[25] These interventions can lead to early diagnosis that cannot only be life saving but also can be globe saving in the affected eye.

Also children with the heritable form of RB are at high risk for developing subsequent malignancies, most commonly sarcomas and cutaneous melanoma. This risk is greater for those children who were exposed to ionizing radiation at age <1 year. Patients should be counseled on the signs and symptoms of second tumors and should have a complete examination yearly.[10,15] In the current study, a patient who was a unilateral case and had negative family history developed osteosarcoma later in life,.

The coats disease, *Toxocara canis* eye infection, and persistence of the primitive vitreous are some of the differential diagnoses of RB.[15,22] In this study, a case who was presented by leukocoria and for whom enuclusion was done with RB diagnosis was found to suffer from coats disease according to her pathology. Coats disease is characterized by pathologic telangiectatic retinal vessels that leak and lead to accumulation of subretinal fluid and lipid, which appear as leukokoria. Coats disease is the most common condition mistaken for RB, but it is differentiated by a lack of calcification of the retinal mass.[15,22]

Although due to the retrospective nature of this study, some data were missed and the diagnosis, treatment, and outcome process could not be assessed in detail because of a lack of population-based registry system in our center, this study is relevant because it is the first one in Southern Iran. There is a need for the development of a registry system to know the impact of RB in our center. Several programs can be useful in improving prognosis and quality of life for these patients: parents' education for early detection, referral of ocular anomalies in the primary care setting, long-term follow up of the children who survive RB, and informing parents about risk of RB development among their offspring.[26] In addition, medical services with trained personnel,[24] careful examination, standard treatment protocol and genetic counseling for those who have a child with RB or have positive familial history of RB should be accessible. If these conditions are available, RB can be detected in the first few weeks of life and this can lead to a significantly reduced visual and systemic morbidity and mortality.

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