RESEARCH COMMUNICATION

Retinoblastoma in Karachi, Pakistan

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Abstract

The objective was to assess epidemiologic aspects of retinoblastoma development in Karachi, Pakistan. Incident cases, diagnosed clinically or microscopically and registered at Karachi Cancer Registry (KCR) during 1st January 1998 to 31st December 2002 were reabstracted, rechecked and reanalyzed for this purpose. One hundred and one cases of retinoblastoma were reported to KCR over the 5 years (1998-2002). Fifty-seven were residents of Karachi, 34 (59.6%) males and 23 (40.4%) females. The gender ratio (M:F) was 1.5. The mean age at diagnosis was 3.96 years (95% CI 2.92; 4.99) and 3.85 years (95% CI 2.72; 4.98) in males and females respectively. The annual crude incidence of retinoblastomas in Karachi was 4.0/100,000 and 2.4/100,000 in children under the age of 5 and 10 years respectively, the corresponding age standardized rates being 5.3/100,000 and 4.8/100,000. The age groups at risk of developing retinoblastoma, associated morbidity and possibility of almost 100% 5-year survival with available treatments, calls for ophthalmologic screening of all infants below 1 year, and high-risk children until the age of 7 years. In order to detect retinoblastoma, as early as possible, health education for parents and health providers, and improved training of ophthalmologists is essential. Genetic testing for siblings and children of retinoblastoma cases and identification of high-risk children would be helpful, but lacks financial feasibility in developing countries at present. Future health care planning should focus on capacity building for neonatal ophthalmologic screening, handling of parents' and children' emotional reactions and opportunities for education, occupational training and cosmetic rehabilitation for surviving retinoblastoma patients.

Key Words: Malignant tumours - eye - retinoblastoma - Karachi, Pakistan

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Introduction

The objective of this study was to assess epidemiologic aspects of retinoblastoma development in Karachi. The city is located on the coast of Arabian Sea, latitude: 24 -56'-00" and longitude: 67 -01'-00". It has a population of 1,724,915 with 929,394 (54%) males and 795,521 (46%) females. The population of children, 0-14 years is 705449, 42.5% of the total population of Karachi (Table 1). (Census 1998)

Retinoblastoma is a rare primary malignant intraocular neoplasm of childhood displaying photoreceptor differentiation. The tumour is categorized into hereditary (familial) or nonhereditary (nonfamilial) types, with a significant association between sporadic retinoblastoma (bilateral and unilateral) and late para, indicating fresh germline mutations. The familial form is significantly associated with early para, suggesting early parental age. (Sivakumaran et al, 2000) Hereditary retinoblastoma has a germinal mutation of Rb gene located in 13q14 and an autosomal dominant inheritance with 80% penetrance. Presenting multiply (average number is three) in both eyes and in younger patients, about 5% are accompanied by a pineal tumor or paracellular neuroectodermal tumor (trilateral retinoblastoma). (Kaneko, 2000) Secondary malignancies such as osteosarcoma, rhabdomyosarcoma, cutaneous melanoma, fibrosarcoma, other rare spindle cell sarcomas, brain tumors e.g. pinealoblastoma and acute leukemia are more frequent and the main cause of death with hereditary retinoblastoma. Cumulative mortality rate from second malignancies is 26% for bilateral cases at 40

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Table 1. Census 1998

Age Group	Male pop.	Female pop.	M:F
0-4	125575	123074	1.02
5-9	125395	118618	1.06
10-14	112527	100260	1.12
15-19	95993	82513	1.16
20-24	85090	68667	1.24
25-29	69182	59430	1.16
30-34	55689	42659	1.31
35-39	49521	41893	1.18
40-44	44159	37150	1.19
45-49	35491	26900	1.32
50-54	31738	16267	1.95
55-59	21013	14355	1.46
60-64	17170	11677	1.47
65-69	8322	6105	1.36
70-74	8412	7547	1.15
75+	8407	7839	1.07
	893684	764954	1.17

years. Unilateral retinoblastoma carries approximately 15% chance of germline mutation and 1.5% cumulative mortality rate. (Kaneko, 2000; Kiratli et al, 1998; Chauveinc et al, 2001) Secondary malignancies occur approximately 1.2 years earlier inside than outside the radiation field, and with a bimodal distribution of latency periods. This suggests different mechanisms may be involved in radiocarcinogenesis, radiation-induced mutation of the second RB1 allele may be the cause after a short delay, while other genes may be affected in those occurring after a longer delay. (Chauveinc et al, 2001)

More than 75% of children with retinoblastoma present with a 'white pupil' (leukocoria), or poorly aligned eyes (strabismus), or a red and painful eye (due to glaucoma). Other eye diseases which can cause these symptoms include panophthalmitis, congenital cataract, Toxocara canis, Coat' s disease, and persistent hypertrophic primary vitreous (PHPV). These diseases may mimic retinoblastoma, but examination under anesthesia, specialized blood tests, CAT scans, and ultrasound evaluations can help diagnose intraocular retinoblastoma in over 95% of cases. In order to be 100% correct a biopsy is essential but to be strongly avoided to prevent the spread of cancer cells.

In the past century focal conservative treatment has evolved for retinoblastoma as a result of early detection of the disease, however enucleation and external-beam radiotherapy are unavoidable in advanced retinoblastoma, especially with optic nerve, choroid, or orbit invasion and diffuse vitreous seeding. Plaque radiotherapy, cryotherapy, photocoagulation, thermotherapy, chemothermotherapy and advanced laser delivery systems are useful for controlling medium or small retinoblastomas, with focal vitreous seeding. It may be possible to eradicate viable tumor in all eyes with Reese-Ellsworth group I-IV retinoblastoma by chemoreduction followed by local treatments. Postenucleation adjuvant therapy is safe and effective in significantly reducing the occurrence of metastasis in patients with retinoblastoma manifesting histopathologic high-risk characteristics. The hydroxyapatite implant has provided improved cosmetic rehabilitation of the socket after enucleation. (Shields et al, 1996).

In the more developed countries, children with retinoblastoma typically survive their cancer due to advances in early diagnosis and treatment, survival rate being almost 100%. Despite this success, risk factors persist for metastasis that are thought to be related to patient age, sex, laterality, treatment, genetics, histopathology, and extraocular extension. Invasion of the uvea, orbit, and optic nerve continue to be the most important predictors of metastatic retinoblastoma. Bilaterality and delays in diagnosis are also important factors.

Enucleation and loss of vision are traumatic experiences for a young child and his family. In developed countries healthcare planning also focuses on handling of parents' and children' emotional reactions to the diagnosis and treatment (Ek, 2000). Unfortunately no such facilities exist in Karachi and probably in Pakistan to help these children find their places in the society. Education of patients and their family members, genetic counseling and development of new modalities of treatment for preserving eyeballs without inducing secondary malignancies are important.

Methodology

The Karachi Cancer Registry (KCR) records information on all people diagnosed with cancer in Karachi. For this publication, incident cases of retinoblastoma, diagnosed clinically or microscopically and registered at KCR during 1st January 1995 to 31st December 2002 were reabstracted, reanalyzed and follow-up data obtained. The medical records of 101 patients were traced, and information on laterality of tumor, spread of tumor, and mode of treatment, obtained. The residency status of cases was reascertained and rechecked. People residing in the specified geographical regions for more than six months were considered residents. Variables recorded were the hospital patient-number, date of incidence, name, age, sex, address, religion, ethnicity, topography, morphology, laterality, grading and staging.

The data were classified using ICD-O2 (International Classification of Diseases-Oncology, 2nd edition) and computerized using a customized version of CANREG-3 software provided by the International Agency for Research on Cancer (IARC). (WHO, 1990) This software includes facilities for the detection of duplicate registrations and for performing internal checks on the validity of the entered data. Both manual and computerized validity checks for the cancer data were performed as per recommendations of IARC and International Association of Cancer Registries (IACR). This involved factors influencing comparability i.e. classification and coding. (Parkin et al, 1994; Parkin et al, 1997; Skeet, 1991)

Table 2. Frequency of Retinoblastoma Cases Received at KCR

Regions	Frequency (%); n-101
Karachi	56.6
Sindh (other then Karachi)	31.8
Punjab	4.4
Baluchistan	5.8
NWFP	1.4

The person-years of population at risk by sex and 5-year age-groups were estimated based on the 1998 census (copy obtained from the Sindh Bureau of Statistics), assuming an annual growth rate of 1.94%. The growth rate was based on the inter-census growth-rate and measures for inflow and outflow of population, calculated by the Federal Bureau of Statistics. Standardized incidence rate was calculated with an external reference population, the 'world' population with a given 'standard' age distribution. (Segi, 1960) 'The standardized rate is the incidence rate that, theoretically, would have been observed if the population had a standard age distribution. The methodology applied was direct standardization, using 5-year age groups. The rates given are the annual incidence per 100,000 population, averaged over the number of years for which data are presented'. (Parkin et al, 1997) Incidence tables were based on ICD-10. (WHO, 1992)

Results

One hundred and one cases of retinoblastoma were reported to KCR in 5 years (1998-2002). Fifty-seven were residents of Karachi, 34 (59.6%) males and 23 (40.4%) females. The rest were from different geographical regions of Pakistan (Table 2). In Karachi the gender ratio (M:F) was 1.5. The mean age at diagnosis was 3.96 years (95% CI 2.92; 4.99) and 3.85 years (95% CI 2.72; 4.98) in males and females respectively. Approximately half the cases were observed below 3 years of age (61.5% males; 50% females). Only 7.7% of the cases in males and 14.3% in females were observed below the age of one year whereas 11.5% of the males and 7.1% of the female cases were observed above 7 years of age. Cases reported from Sindh, other than Karachi and other provinces of Pakistan also show a late presentation (Table 3)

The annual crude incidence of retinoblastoma in Karachi is 4.0/100,000 and 2.4/100,000 in children under the age of 5 and 10 years respectively. The age standardized rates are 5.3/100,000 and 4.8/100,000 in children under the age of 5 and 10 years respectively. The overall incidence remained constant over the 5-year period.

The presenting complains were leukocoria in 5.7% and an orbital mass in 70% of the cases. At the time of presentation, the left eye was involved in 70% of the males and the right eye in 70% of the females. Nine percent of the female cases reported with bilateral malignancy, but none of males. Optic nerve was involved in 60% of the cases, 8.3% of the cases showed extension into the orbit and brain. Thus only 41.7% of the cancers were localized to the eye. No secondary malignancies were observed in our series. All cases of retinoblastoma were enucleations and histologically confirmed. Flexner-Wintersteiner rosettes occurred in 50% of the cases.

The overall histological characterization of ocular malignancies in males was squamous cell carcinoma (29.7%), retinoblastoma (23.1%), lymphoma (13.2%), rhabdomyosarcoma (9.9%), melanoma (8.8%), and adenocarcinoma (4.4%). In females the histological characterization was squamous cell carcinoma (36.8%), retinoblastoma (22.4%), rhabdomyosarcoma (12.0%), melanoma (8.2%), adenocarcinoma (8.2%) and lymphoma (6.1%).

Discussion

The incidence of retinoblastoma in Karachi is comparable to low risk regions of the world. There is a possibility of under-reporting of childhood cancers in developing countries; however, a longer survival and morbidity ensure the retinoblastoma patients' entry into the health-care system. Neglect of retinoblastoma is more likely to manifest as a late presentation.

The incidence in Karachi is comparable to rates observed Asian populations but lower than other regions of the world. (Table 4). (Parkin et al, 1998) In Mumbai the crude rates are 4.0 and 3.1 and the corresponding age adjusted incidence rates are 4.2/100000 and 3.3/100000 for males and females respectively. (Yeole and Advani, 2002) In Singapore, the incidence rate is 2.4/100,000 for children under 9 years and 11.1/100,000 for children under 5 years. (Saw SM et al, 2000) Globally the incidence of retinoblastoma has been almost uniform over time, with significant geographical variations. The rates when calculated for different age groups (0-4, 5-9, 10-14 or 0-14) also show variations and a lack of comparability if non-identical age groups are used.

Karachi is a referral centre for cancer treatment from the rest of Pakistan because of the availability of better

Table 3. Mean Age of Retinoblastoma Cases in Pakistan

	Male	Female
Karachi	3.96 years (95% CI 2.92; 4.99)	4.10 years (95% CI 3.00; 5.10)
Sindh (other then Karachi)	4.30 years (95% CI 2.70; 5.99)	3.90 years (95% CI 2.50; 5.30)
Pakistan (other then Sindh)	4.20 years (95% CI 2.20; 6.10)	3.60 years (95% CI 1.50; 7.40)

Table 4. Age-standardized and Cumulative Incidence Rates (0-14) per Million

	ASR M.	ASR F.	ASR Cum.	M:F	Cases
Uganda, Kampala	13.6	8.7	11.1	1.4	22
Zimbabwe, Harare	12.3	8.9	10.5	1.3	21
Kuwait, Kuwaitis	1.9	0.7	1.3	3	4
Kuwait, non-Kuwaitis	1.7	1.6	1.6	1	4
Egypt, Alexandria	0.5	0.8	0.7	0.6	8
India, Bombay	5.7	4.4	5.0	1.4	162
US SEER, white	4.8	5.0	4.9	1.0	172
US SEER, black	5.6	5.1	5.3	1.1	32
Karachi	1.9	1.4	1.6	1.5	57

Ref: Parkin et al 1998; M - male, F- female

treatment facilities. Nevertheless, a late presentation of retinoblastoma was observed in Karachi for the patients' residents of Karachi and various regions in Pakistan, viz. Sindh, Punjab, Baluchistan and NWFP, who reported to KCR. A late presentation has been observed by previous researchers in Pakistan and other developing countries. (Mouratova, 2003; Soomro et al, 2000; Akang et al, 2000; Mullaney et al, 1996; Moukouri et al, 1994) Late presentation in developing countries is probably an indicator of negligence and lack of awareness of patient and clinicians. In the more developed countries, retinoblastoma usually presents before 3 years of age. Children can be born with retinoblastoma, or more commonly develop new tumors within the first 3 years of life. The average age of children diagnosed with retinoblastoma is 18 months, whereas in our series it was approximately 4.0 years, reflecting the late presentation. Internationally new retinoblastoma are almost never seen after the age of seven, whereas in Karachi, 11.5% of the males and 7.1% of the female reported to treatment centers after crossing the 7th year of life.

Delayed presentation is often attributed to the initial clinical presentation of retinoblastoma, which can mimic other non-malignant conditions, thus leading to a delay in diagnosis and grave consequences. The patient may be the decisive factor in delaying medical evaluation of first symptoms, but the lack awareness and negligence by physicians and other service providers is not unknown. Delayed diagnosis in developing countries makes enucleation unavoidable and often shortens the survival time. (Nwosu et al, 1994) The diagnosis of retinoblastoma should always be kept in mind whenever an intraocular mass is revealed or where there are unexplained atypical ocular signs. In order to detect retinoblastoma as early as possible, health education for parents and health providers, about the first symptoms of the malignancy and improved training of ophthalmology specialists is essential.

The male female ratio of retinoblastoma fluctuates around unity in most populations. (Table 4). (Parkin et al, 1998) In Karachi (1998-2002) there was a higher proportion of males (M:F-1.5), an observation also made in earlier series. This may indicate an increased risk of retinoblastoma in the male child, but may also indicate a lack of attention for the female child.

Optic nerve involvement was observed in approximately half the surgical specimens which presented as enucleations, no apparent efforts having been made to detect optic nerve involvement preoperatively. This could have been done with reasonable accuracy using computed tomography and MRI, yet due to massive involvement of the eye in the majority of our patients, the preoperative knowledge would not have affected the treatment or prognosis. (Jacquemin et al, 1998)

No secondary malignancies were observed in our series. This was expected as we have a late presentation and short-term follow-up. The overall statistical risk of second cancers for children with retinoblastoma is 1% per year, or 20% at 20 years and 40% at 40 years, that risk is doubled if the child receives external beam irradiation before the first year of life. In our series we had a delayed presentation and none of the children received radiation before the age of one year. The other causes of increased risk of second cancers in children with retinoblastoma are hereditary or germ line mutations, bilaterality, multiple tumors, age below one year, and systemic chemotherapy.

Conclusions

The incidence of retinoblastoma, the age groups at risk, associated morbidity and possibility of almost 100% 5-year survival with available treatments, calls for ophthalmologic screening of all infants below 1 year, and high risk children until the age of 4 years. This screening should be an integral component of the National Cancer Control Program of Pakistan. Genetic testing for siblings and children of retinoblastoma cases and identification of high-risk children would be helpful, but lacks financial feasibility at present. Future healthcare planning should focus on capacity building for neonatal ophthalmologic screening, handling of parents' and children' emotional reactions to the diagnosis and treatment, and opportunities for education, occupational training and cosmetic rehabilitation for surviving retinoblastoma patients.

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