ORIGINAL ARTICLE

Retinoblastoma: Our Experience

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ABSTRACT

Aim: To analyze presentation, demographic data and management outcomes of retinoblastoma patients presented in last ten years.

Method: A total of 306 patients suffering from retinoblastoma were enrolled in this audit. All patient's data was taken from the record. All patients underwent indirect ophthalmoscopic examination under anesthesia (EUA).B scan, MRI brain plus orbit and baseline investigations including complete blood count, chest X-ray, liver function tests, renal function tests, serum electrolytes and hepatitis B,C screening were done in all patients. Stage of disease was assessed using international classification of retinoblastoma from A-E. All patients were managed according to the stage of disease.

Results: Total of 493 eyes of 306 patients of retinoblastoma were included in this audit. Of these, female patients were123 while male patients were 183. 187 patients had bilateral disease while 119 were unilateral.114 patients were between 0-12 months of age, 145 were between 13-24 months of age while 47 were of more than 2 years of age. Of total 493 eyes, 3 eyes were of stage A, 15 of stage B, 25of stage C, 300 of stage D and 150 were of stage E disease. 235 Patients got systemic chemotherapy. Cryotherapy was done in 356 eyes; intravitreal injections were given in 90 eyes, laser photocoagulation in 200,enucleation in 160and exenteration in 20eyes

Conclusion: High incidence of enucleation, advanced stage presentation, bilateral disease, and male predominance was found in our ten years audit.

Keywords: Retinoblastoma, Audit, Pakistan, Chemotherapy, Intra-vitreal Malphalan, Intra-arterial chemotherapy.

INTRODUCTION

Retinoblastoma is one of the commonest intraocular malignancies of childhood[1]. It is believed that it arises from multipotent precursor cells[2]. It affects 1/17000 live births worldwide[3]. An estimated 250-500 new cases of retinoblastoma occur in the United States yearly[4]. Approximately 60% of cases are bilateral and 40% are unilateral[5] with survival rate ranging from 86-92%[6]. Gender predisposition was noted with male predominance of 1.12:1[7]. Retinoblastoma is diagnosed in patients at an average age of 18 months, with 90% of cases diagnosed younger than 5 years[8].

Pathogenesis of RB is well defined with two types of mutations i.e. genomic and somatic mutations. Genomic mutation is associated with bilateral disease while somatic mutation is associated with usually less severe unilateral disease[9]. Mutation in the long arm of chromosome 13 band 13q14 is the key factor for pathogenesis of disease[10]. Castera et al identified MDM2 as the first modifier gene for retinoblastoma[11].

Retinoblastoma presents with diverse clinical presentations including leukocoria, strabismus, proptosis and buphthalmos[12]. Diagnosis of retinoblastoma is mainly clinical including indirect ophthalmoscopy; general anesthesia is required for infants and non-cooperative children[13]. Other diagnostic modalities include B-Scan, CT scan and MRI scan to look for tumor spread[14]. For optimal management of other family members molecular genetic testing is essential because of 1) Preservation of vision and reduction in morbidity can be achieved by surveillance of at-risk individuals since birth 2) Individuals at risk are spared from unnecessary examination under general anesthesia 3) Identification of an RB1 mutation allows reproductive options including prenatal testing and pre-implantation genetic diagnosis to be offered.

Picture of retinoblastoma can mimic like different other intraocular pathologies including Congenital cataract, Coats's disease, Toxocariasis, Retinoma and ROP[15].

With multiple advancements in last decade, different treatment protocols are in practice for the management of retinoblastoma including intravenous(I/V) chemotherapy[16], intra-vitreal chemotherapy, methotrexate[17], radiotherapy[18] and cryotherapy[19]. Intra-arterial chemotherapy is gaining popularity for retinoblastoma[20]. Being selective and focal approach it has fewer side effects as compared to I/V chemotherapy[21].

As rate of RB and RB associated mortality is high in third world countries so this study was conducted to evaluate the trend of Retinoblastoma in Pakistan. As Pakistan is a developing country so many modern techniques are being used now a days to manage this disease.

MATERIAL AND METHODS

A total of 306 patients suffering from retinoblastoma were enrolled in this audit. All patients' data including age, sex, address, laterality, stage of disease, family history, medical history and surgical history was taken from the record. All patients under went detailed indirect ophthalmoscopic examination under anesthesia (EUA). B sacn and MRI brain and orbit were performed. Baseline investigation including complete blood count, chest X ray, liver function tests (LFTs),renal function tests(RFTs) and serum electrolytes and hepatitis B,C screening was done in all patients. Stage

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of disease was assessed using International classification of retinoblastoma. Patients were treated with systemic chemotherapy, laser photocoagulation, cryotherapy and intra-vitreal chemotherapy (from 2014), enucleation and exentration. During systemic chemotherapy certain investigations including MRI brain and orbit, B scan, complete blood count, LFTs, RFTs and serum electrolytes were done to monitor the disease progression or regression and drugs toxicity. All the patients during treatment were followed four weekly. At follow-up,EUA with indirect fundus ophthalmoscopy was done in all patients and repeated MRI scans B scans were done as needed. After treatment, four weekly follow-up for first year (follow up included examination under anesthesia with indirect fundus ophthalmoscopy and MRI orbit and brain and B-scan as needed), 8 weekly follow-up for second year, three monthly follow-up for third year and six monthly follow-up till the age of eight years were done. Post treatment till six years indirect fundus ophthalmoscopy was done under general anesthesia while during next two years indirect fundus ophthalmoscopy was done without anesthesia. Statistical analysis was done by SPSS version 20.

RESULTS

A total of 306 patients of retinoblastoma were included in this audit presented in last ten years (January 2007 to December 2016). 493 eyes were diagnosed as retinoblastoma. Female patients were 123 (40.1%) while male patients were 183 (59.9%). 187(61.1%) patients had bilateral disease while rest of the cases were unilateral 119 (38.9%).
With respect to age distribution there were 114(37.2%) patients in 0-12 months of age group, 145 (47.3%) patients were in 13-24 months of age group and 47(15.3%) patients were in > two years of age group (Table 01). Mean age was calculated to be 14±6 months. Among total 493 eyes 3 (0.6%) were of stage A, 15 (3.04%) of stage B, 25 (5.07%) of stage C, 300 (60.85%) of stage D and 150 (30.42%) were of stage E disease (Table 2). Orbital disease was present in 60(12.17%) eyes. 235 patients (76.79%) got systemic chemotherapy. Cryotherapy was done in 356 (72.2%) eyes. Intra-vitreal injections were given in 90 (18.25%) eyes and laser photocoagulation was done in 200 (40.56%) eyes, enucleation was performed in 160(32.45%) eyes and exenteration was performed in 20(4.05%) eyes (Table 3). 4(1.30%) deaths were reported from January 2007 to December 2016.

Table 1: Age distribution

Age group (months)	%age
0-12	114(37.2%)
13-24	145(47.3%)
>24	47(15.3%)

Table 2: Stage presentation

Stage Presentation	%age
Stage A	3(0.6%)
Stage B	15(3.04%)
Stage C	25(5.07%)
Stage D	300(60.85%)
Stage E	150(30.42%)

Table 3: Treatment modalities (n=235)

Treatment modalities	%age
Enucleation	160(32.41%)
Exanteration	20(4.95%)
Cryotherapy	356(72.2%)
Laser photocoagulation	200(40.56%)
Intra-vitreal injections	90(22.31%)

DISCUSSION

Retinoblastoma is the most common intra ocular malignancy of childhood[22] with incidence of 1 in 18000 live births[23] and is the second most common malignant intraocular tumor after uveal melanoma[24]. In 1957 retinoblastoma was first described as fungus hematodes and enucleation was considered as the primary mode of management[25]. In 1864 retinoblastoma was considered to be derived from glial cells and hence called as glioma of retina[25]. Flexner (1891) and Wintersteiner (1897) described it as neuroepithelioma later. In 1926 American Ophthalmological Society described it to be originated from retinoblasts hence named retinoblastoma[25].

Previously retinoblastoma was considered as a disease, which only leads to death, but in last few decades advances have revolutionized that concept with good anticipated prognosis[26]. Our study showed that there was male predominance in retinoblastoma, which was the same as in other international publications[27]. Most of the cases were bilateral in our study but no specific trend was seen in different publications with respect to laterality[28].

Retinoblastoma was more prevalent in 7-12 months of age group in our study while in another study it was more prevalent among 1-6 months of age group[29]. Minimum number of patients were of >24 months of age group. A study conducted in United States showed that greater than 14 months of age group was associated with minimum number of patients associated with retinoblastoma[30]. In our study a total 493 eyes were examined and treated. Out of these, 110 (22.31%) eyes got enucleated, which was higher than some international studies[31].

Systemic chemotherapy was administered for the treatment of disease. Local therapy including cryotherapy and laser photocoagulation was administered. There are studies showing role of local therapy as adjuvant to systemic chemotherapy in reduction of vitreous seeding[32, 33,34]. Local therapies are more useful in case of small tumors and when already size is reduced following chemoreduction. Cryotherapy was useful in the treatment of equatorial and peripheral small retinoblastoma where adequate view of fundus is not seen. Tumor destruction is usually achieved with one or two sessions of triple freeze-thaw cryotherapy delivered at 1-month intervals. Laser photocoagulation is indicated in posterior located lesions[32]. Laser photocoagulation aims at vascular coagulation and tumor ischema[33]. Tumors with location near to fovea and optic nerve require transpupillary thermotherapy as radiation may harm vision at these sensitive areas. Being time consuming and cumbersome procedure it is not in use frequently now a days[34].

Radioactive plaque brachytherapy is another mode of focal treatment; in this modality radioactive plaque is placed at the tumor base to irradiate the lesion. It is limited to tumors less than 16 mm in base and 8 mm in thickness.

Plaque radiotherapy is used as primary as well as secondary chemotherapy in cases which are resistant to chemotherapy and radiotherapy[33].

Stage D and E tumors are best managed by enucleation but if salvage of eye is considered then intra-vitreal chemotherapy is the best option[34].Ghassemi and Shields published a study and they concluded that intra-vitrealmalphalan showed best results in recurrent vitreous seedings with minimum side effects. Kaneko et al[32]concluded that intra-vitrealmalphalan has tremendous effects in recurrent vitreous seeding as well as adjuvant therapy. Periocular chemotherapy i.e carboplatin and topotecan is another important mode of focal chemotherapy.

As retinoblastoma is a radiosensitive tumor so external beam radiotherapy (EBRT) can be used to irradiate whole eye in case of advanced tumor but it is associated with secondary cancers i.e., osteosarcoma and pinealoma[34].

In our study stage of disease was evaluated by international classification of retinoblastoma[35]. Stage D was most frequent among all stages followed by stage E. A study was published that showed stage C-D being most frequent presentation of retinoblastoma among all stages[36]. Another study was conducted in Brazil, they concluded that stage D being most frequent stage of Retinoblastoma among all stages[37].

Kaneko *et al described an* advanced mode of delivery for chemotherapy via intra-arterial route[38]. Shields and Shields described the efficacy of intra-arterial chemotherapy results. They showed that intra-arterial chemotherapy was 100% successful in Group C and D while 33% in Group E retinoblastoma[39]. Intra-arterial chemotherapy has fewer side effects as compared to systemic chemotherapy. Side effects of local (IAC) chemotherapy include hematoma at entry site, pancytopenia, carotid vascular spasm and stroke.

Our study emphasized on gender predisposition, laterality, age distribution and demographic distribution of disease among population of Pakistan that will help in future to combat with this disease[40].

CONCLUSION

High incidence of enucleation, advanced stage presentation, bilateral disease, and male predominance was found in our ten years audit.

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