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Incidence and management of retinoblastoma

Abstract

This was a retrospective as well as prospective study of fifty (50) cases of retinoblastoma in series during the study period from January 2005 to December 2015, conducted at Liaquat Medical College Eye hospital and Indus Medical College Hospital, Pakistan. The average incidence of retinoblastoma in cases presented in our department was 4.5 cases per year with 0.8 cases per year bilateral and 3.7 cases per year with unilateral involvement respectively. The minimum age in this series was 15 days and maximum age was 8 years, mean age being 3.46 years. Out of these 50 cases, 27(54%) were male and 23(46%) were females. In most of the cases diagnosis was made on clinical grounds and histopathological reports of the biopsy specimens. Other measures like plain X-ray orbit, CT scan, ultrasonography (A and B Scan) and studies of blood chemistry were used where ever needed. Majority of our cases were found to be in a fairly advanced stage (an aplasia grade severe) that is extending beyond the sclera in the orbital tissues. In 4 cases cat's eye reflex noted. Out of these cases 3 were having involvement of the other eye extensively while in 4th case the other eye was not involved at all. Of the remaining cases 11(22%) were having vitreous seeding, 16(32%) showed extension up to the sclera and 22(44%) extended to involve the orbit. Only one case presented with the involvement of regional lymph nodes. All those cases that underwent modified exonerations were sent to radio isotope center for further management with radiation and/or chemotherapy depending upon the nature of spread. One patient who had the regional lymph nodes involvement, though did not show extra ocular spread in the orbit, underwent chemotherapy following enucleations.2 cases which were diagnosed in very early stage involving the posterior retina behind equator were managed by ^{60}Cobalt radioactive plaques insertion over the sclera at the site of lesion, left in place till such time as advised by the oncologist of the radio isotope center. A total of 28 enucleations and 19 modified exentrations were carried out. Recurrences were noted in 13 cases, no surgery was done in these cases and they were referred to radio isotope center at Jamshoro, Pakistan for further management with radiation or chemotherapy. In this series no case was found to have distant metastasis anywhere including long bones and other viscera of the body. 12 cases were lost to follow up at different stages of management and 6 of the cases died of unknown cause.

Keywords: khan NA, khan SA, khan aa, khan aisha, khan atiqa, khan sobia, retinoblastoma incidence and management, lmc eye hospital and indus medical college hospital, Pakistan

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Nisar Ahmed Khan, Saeed Ahmed Khan, Aftab Ahmed Khan, Aisha Khan, Atiqa Khan and Sobia Khan

Department of Ophthalmology, Indus Medical College Hospital, Pakistan

Correspondence: Nisar Ahmed Khan, Assistant Professor/ Consultant, Indus Medical College Hospital, Tando Mohammad Khan, Pakistan, Tel +92-300-3014168, Email nisargh2001@yahoo.com

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Introduction

Retinoblastoma is the most common primary malignant tumor of infancy and childhood [1–3] Retinoblastoma being described by Pawius in early 1597, Wardrop in 1809 suggested it as a fungus haematodes, Virchow in 1864 suggested it as glioma of retina while Flexner and Wintersteiner suggested as neuroepithelioma[4] ,comprises about 3 percent of all the malignant tumors of childhood [5] It is responsible for 1 percent of all deaths from cancer in pediatric age group.[6] It arises from any part of retina and may be unifocal or multifocal. It may involve one or both eyes.[7] It occurs in sporadic (95%) and inherited (5%) forms respectively [8] the latter includes most of the bilateral tumors and a small number of unilateral cases. There is no sex and race predilection. Its spread is mainly to the brain through the optic nerve though it may also metastasize rarely to other viscera and long bones of the body. Its local spread may involve the orbital contents and may progressively enlarge to fungating out as cauliflower mass from the orbit.[9]

We have studied fifty (50) cases of retinoblastoma at Liaquat Medical College Eye Hospital and Indus Medical College Hospital, Pakistan. In this study, the incidence of retinoblastoma during study period from January 2005 to December 2015, presentation of these cases and their management were discussed. Most of the cases presented in advanced stage (anaplasia grade severe). They were managed by surgery (enucleations and modified exentrations) and radiotherapy. In few cases radioisotope (^{60}Cobalt) and chemotherapy were used. Although other methods of treatment like laser therapy, cryotherapy and photocoagulation are also in use for the management of retinoblastoma in early cases.[10,11] As the more advanced diagnostic

measures and treatment options are emerging with further research to improve and prolong the survival rate of retinoblastoma patients in western world. In our country little work has been done in this regard. The aim of our study is to know the rate of incidence in our society and to make efforts to detect this fatal disease as early as possible and its management utilizing the available diagnostic and therapeutic means.

Material and methods

Fifty (50) cases of retinoblastoma in series were included in this study conducted at Liaquat Medical College Eye Hospital and Indus Medical College Hospital, Pakistan. Only those cases were included in this study that were recruited from January 2005 to December 2015 and were diagnosed histopathologically as retinoblastoma. In this study out of fifty cases, 27(54%) were male and 23(46%) were female, 41(82%) were unilateral while 9(18%) were bilateral cases. Most of the unilateral cases were presented in advanced stage of retinoblastoma while in bilateral cases tumor in one eye was in advanced stage as compare to the other eye. The overall average incidence of retinoblastoma remained 4.5 cases per year with 0.8 case were bilateral and 3.7 cases were unilateral respectively.

Diagnosis was primarily based on clinical examination of eyes confirmed by the histopathological findings of the biopsied specimen. Patients underwent a complete work up including; family history, physical examination, A and B -Scan ultrasonography (wherever needed), computerized tomography (CT) of the orbits and brain, chest X-ray (PA View), plain X-ray orbits (PA and lateral views), blood chemistry. Bone Scan and abdominal ultrasonography were also performed. It is unfortunate that most of the cases were in advanced stages (anaplasia grade severe). Only 1(2%) unilateral and the other eye of 3(6%) out of 9 (18%) bilateral cases presented with leukokoria (white pupils) or cat's eye reflex, in these cases tumor remained restricted to retina, 11(22%) were with vitreous seeding, in 16(32%) there was involvement of sclera while 2(44%) cases presented with cauliflower mass fungating out of orbit. 1(2%) case presented with the extension of tumor to the regional lymph nodes.

Management

Treatment modalities of retinoblastoma includes; surgery (enucleations and modified exentrations), radiotherapy (radioactive plaque therapy and radiation), photocoagulation, cryotherapy and chemotherapy. In our study we adopted surgical methods appropriate for the cases and radiotherapy which was carried out in radio isotope center.

Enucleation

Enucleations done in 28(56%) of cases with three types of presentations:

1. Those cases 1(2%) in which tumor remained restricted to retina.
2. Those cases 11(22%) in which there was vitreous seeding and,
3. Those cases 16(32%) in which the whole of the eye ball filled with the tumor mass but did not extend to the extra ocular tissues.

Enucleations were performed under general anesthesia, the eye ball enucleated with as large as possible stump of optic nerve. After securing the hemostasis the tenon's capsule and conjunctiva were closed separately using 8.0 vicryl or black silk. The specimen of the tumor and optic nerve were sent to pathology department of Liaquat Medical College Jamshoro for histopathological examination.

Modified exenteration

Modified exenterations adopted in 19(38%) of cases in which there was spread of tumor to the orbit. Whole of the orbital contents were removed leaving the skin of eyelids. The skin of eyelids was saved to cover the raw surface of the orbit at the end of the surgery. This technique was adopted to minimize the healing period and to obtain a better cosmetic appearance of the orbit post-operatively. It is our observation that even in cases with extensive size and involvement of the orbital contents, the skin is found to be free of tumor spread and can be saved without any risk for this purpose.

Radioactive plaque therapy

In 2(4%) cases radioactive plaque therapy was done using ^{60}Cobalt scleral plaque. In these cases the tumors were small and located on the posterior retina. Enucleations and radiotherapy were avoided in these cases because these plaques gave a small, controlled amount of radiation to save the retina and orbit from complications of radiation. These plaques were left in place for the desired period guided by the radio-isotope department Jamshoro and removed after the full radiation dose was supposed to be complete.

Radiotherapy

In 22(44%) cases, radiotherapy considered and patients received radiation in radio isotope center (department of nuclear medicine) at Jamshoro. This management modality used in those cases in which there was involvement of sclera or there was local spread of tumor to the orbit. In our cases, radiation therapy followed the surgical methods of enucleations and modified exentrations. Results of radiation therapy are far better when combined with enucleations and modified exentrations than only radiation if used alone.

Chemotherapy

In only 1(2%) case that had extension of the tumor to regional lymph nodes, chemotherapy along with surgery and radiation was used. Cryotherapy and laser therapy were not used in this study due to the advanced presentation of tumors in retinoblastoma cases. The above methods of treatment used in our department at Liaquat Medical College Eye Hospital, Indus Medical College hospital and Radio-isotope center at Jamshoro, Pakistan. We kept the patients under our constant follow up, daily for one week then weekly for six weeks, monthly for six months. During our follow ups 13(26%) patients after treatment had recurrences of tumor, particularly those with modified exenterations. They were again sent back to radio isotope center for further treatment. During our follow up of up to 3 years not a single case was found with secondary spread or metastasis in the distant organs or bones of the body. 12(24%) of the cases were lost during follow up. 6(12%) died during follow up but the cause remained obscured. Some of the photographs of our cases showing mode of presentations and management Figure 1.

Citation: Khan NA, Khan SA, Khan AA, et al. Incidence and management of retinoblastoma. *Adv Ophthalmol Vis Syst.* 2018;8(1):40–45.
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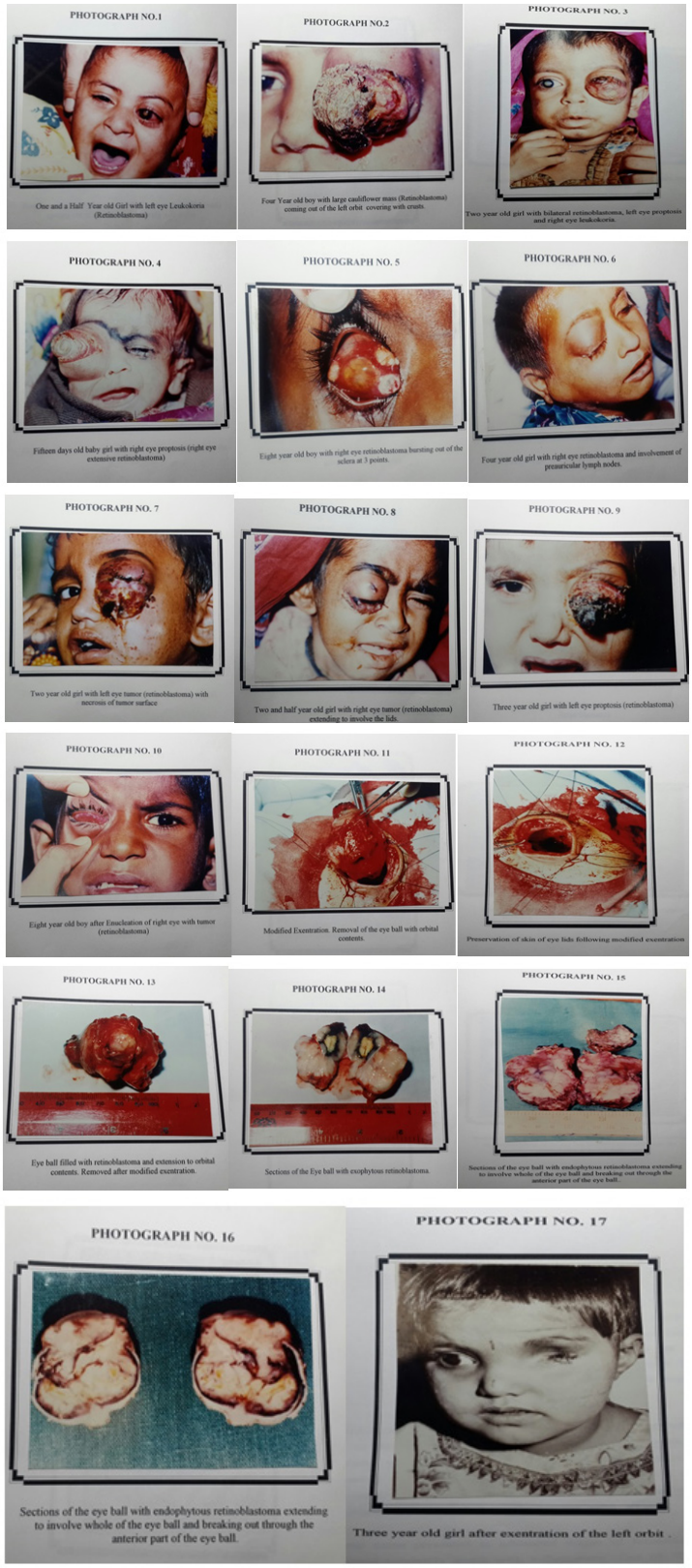

Figure 1 Some of the photographs of our cases showing mode of presentations and management.

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Results

This study includes fifty (50) consecutive cases of retinoblastoma. Out of fifty cases 27(54%) were male and 23(46%) were female Table 1with mean age of 3.46 years (15 days to 8 years) Table 2, 9(18%) were bilateral while 41(82%) were unilateral, among unilateral cases 28(56%) involving right eyes while 13(26%) with involvement of left eyes Table 3. Among bilateral cases 5(five) were diagnosed in between 4 to 6 years while 3 between 2 to2- ½ years. Unilateral cases presented between the ages of 15 days to 8 years with mean age of 3.46 years Table 4. In our study which extended from January 2005 to December 2015, we found the incidence of retinoblastoma in patients who presented at Liaquat medical college eye hospital and Indus Medical College Hospital was 4.5 cases per year with 0.8 cases per year bilateral and 3.7 cases per year unilateral respectively Table 5.

Table 1 Sex Distribution of 50 Cases of Retinoblastoma

Sex	No of cases	Percentage of total
Male	27	54%
Female	23	46%

Table 2 Age at presentation

Total cases	Minimum age	Maximum age	Mean age
50	15 days	8 years	3.46 years

Table 3 Laterality of 50 cases of retinoblastoma in series

Laterality	No of cases	Percentage of total
Bilateral	9	18%
Unilateral	41	82%
Right Eye	28	56%
Left eye	13	26%

Table 4 Incidence of retinoblastoma in children under the of 8 years by year of birth

Year of birth	Incidence		Total no of cases
	Unilateral	Bilateral	
2005	3	1	4
2006	5	-	5
2007	4	1	5
2008	2	2	4
2009	4	-	4
2010	4	-	4
2011	5	1	6
2012	2	1	3
2013	5	1	6
2014	3	1	4
2015	4	1	5

Table 5 Mode of presentation of 50 cases of retinoblastoma in series

Mode of presentation	No of cases	Percentage of total
Restricted to retina	1	2%
Restricted to vitreous cavity	11	22%
Involvement of sclera	16	32%
Involvement of orbit	22	44%

Out of fifty (50) cases 1(2%) presented with tumor which was restricted to retina only, 11(22%) cases presented with vitreous seeding along with involvement of retina. 16(32%) cases were in more advanced stage involving sclera, among these cases 1(one) case presented with the involvement of regional lymph nodes. Remaining 22(44%) cases were extended to involve the orbit Table 6. Most of our cases presented in advanced stages (anaplasia grade severe) of retinoblastoma and were managed surgically along with radiotherapy. Out of 50 cases, 47(94%) managed surgically. Among these surgically managed cases 24(48%) after surgery sent for radiotherapy as they were in more advanced stages. 1(2%) case were sent for chemotherapy as it presented with the involvement of regional lymph nodes and was not manageable by surgery and radiation alone Table 7. Out of 47(94%) surgically managed cases, enucleations were done in 28(56%) while 19(38%) were under gone modified exentrations Table 7.

Table 6 Management

Management modality	No of cases	Percentage of total
Surgery	47	94%
Radiation therapy	24	48%
Chemotherapy	1	2%

Table 7 Surgical management

Surgical management	No of cases	Percentage of total
E nucleations	28	56%
Modified exestuations	19	38%

19(38%) cases in which modified exentrations performed and in 3(6%) cases enucleations were performed and sent for additional radiotherapy. In 2(4%) cases ^{60}Cobalt radioactive plaques were used to avoid the hazards of excessive radiation Table 8. Out of 19(38%) cases in which modified exentrations plus radiotherapy was done, 13(26%) had recurrences of tumor, were managed by further radiotherapy and chemotherapy in radio isotope center at Jamshoro Table 9. In our study no familial involvement was found in any case and thus all were diagnosed as sporadic cases. Most of the cases belong to rural areas and only small number belonged to urban areas Table 10. Most of them belonged to poor socio -economic class Table 11.

Table 8 Radiotherapy

Radiotherapy	No of cases	Percentage of total
Radiation therapy	22	44%
Plaque therapy (using 60Cobalt radioactive plaques)	2	4%

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Table 9 Incidence of recurrence

Total no of cases	Recurrence	Percentage of total cases	Further treatment
50	13	26%	Radiotherapy & chemotherapy
Total no of Cases	Recurrence	Percentage of Total Cases	Further Treatment
50	13	26%	Radiotherapy & chemotherapy

Table 10 Belonging area in series of 50 cases of retinoblastoma

Belonging area	No of cases	Percentage of total
Rural area	36	72%
Urban area	14	28%
Belonging Area	No of Cases	Percentage of Total

Table 11 Socioeconomic condition

Status	No of cases	Percentage of total
Poor	31	62%
Middle class	13	26%
Rich	6	12%

Poor class, monthly income: Rs. 5000–7000/month

Middle class, monthly income: Rs. 7000-12000/month

Rich, monthly income: more than Rs. 30000/month

Discussion

Fifty (50) cases of retinoblastoma included in this study conducted at Liaquat Medical College Eye Hospital and Indus Medical College Hospital. Only those cases were included in this study who were diagnosed histopathologically as retinoblastoma and recruited from January 2005 to December 2015. The rate of incidence of retinoblastoma in this study was 4.5 cases/year with 0.8 case/year bilateral involvement and 3.7 cases/year unilateral involvements. Among unilateral cases right eye involvement was more than twice the involvement of left eye but in literature this difference is not significant. As there is no sex and race predilection in literature.[12] In our study, 27(54%) were male and 23(46%) were female as compared by the study done by Sanders B.M and co-workers[13] during study period from 1969 to 1980, out of 431 cases, male were 221 while female were 210. This too shows that there is no sex and race predilection. 33 cases of retinoblastoma mentioned by Khan AA[14] while Munir-ul-Haque M.[15] mentioned 186 cases of retinoblastoma in his study from 1962 to 1987 (Table 12). Abramson David H. and Frank Christoper M [16] reported 816 bilateral cases among 1506 cases of retinoblastoma during 1914 to 1984. In our study there occurred no spontaneous regression in any case leading to phthisis whereas Sanders B.M and co-workers [13] claimed 2(two) such cases who showed spontaneous regression.

The mean age in our cases was 4.6 years (15 days to 8 years) while it was 18 days to 10 years in the study done by Sanders B.M. and co-workers[13] and in study done by Khan AA.[14] And co-workers it was 18 months to 10 years. This showed that the maximum age at presentation was slightly high as compared to our study Table 12. Our study showed that all of our cases were sporadic and there was no familial involvement seen. In the study by Sanders B.M and co-workers[13], out of 431 cases, 15 unilateral and 38 bilateral cases showed family history of retinoblastoma. In literature the presentation of the lesions are leukokoria (cat's eye reflex), strabismus, proptosis, cauliflower mass fun gating out of the orbit and involvement of regional lymph nodes or distant metastasis to long bones or other viscera of the body.[17] In our study majority of the cases presented with proptosis 16(32%), cauliflower mass fun gating out of the orbit, 22(44%), involvement of regional lymph nodes 1(2%), while remaining cases presented with leukokoria. In our study none of the cases showed any strabismus, this also shows a different pattern in presentation from the non-pigmented races in whom strabismus is one of the common findings. In studies conducted by Sanders B.M and co- workers,[13] Khan A.A and co-workers[14] and Munir-ul-Haque M.[15] The modes of presentation were otherwise similar Table 12.

Diagnostic measures depend upon the presentation of lesion. In our study most of the cases were in advanced stages so the clinical examination and histopathological reports of biopsied specimen confirmed the lesion. Although other tests were also performed like ultrasound (A and B Scan ultrasonography), CT scan, Plain X-ray orbit, ultrasound of abdominal viscera, Blood chemistry etc. where ever applicable. The early cases of retinoblastoma can be managed by chemotherapy and using local non-invasive measures like laser photocoagulation and cryotherapy.[18] In our study we used to treat these cases mostly by surgery (enucleating[19] and modified exonerations) and radiotherapy and in few cases radio-active plaque were used. Only in very advanced case with the involvement of regional lymph nodes, chemotherapy was used, the same mode of management were utilized by Sanders B.M and co-workers[13], Khan A.A and co-workers[14] and Munir-ul-Haque M[15] Table 12.

The recurrence rate in our study was 13 (26%) as compared to the study of Sanders B.M and co-workers[13] where the recurrence rate was only 4 cases. We sent our cases of recurrence to radio isotope center for further radiation and chemotherapy, Khan A.A and co-workers[14] also utilized the same modes of management in cases with recurrences while Sanders B.M and co-workers[13] used to enucleate the eyes Table 12. The high recurrence rate in our cases seems to be due to advanced stages of the tumors (an aplasia grade severe) which involved the whole orbit and proliferated out in cauliflower fashion. Even after exestuations tumor cells can escape total removal. This also indicates that though radiotherapy has got its value in combating and ameliorating the tumor but it is not completely fool proof as some cells of the tumor might be resistant to radiation and thus may be responsible for recurrence at variable periods.

Conclusion and recommendations

Retinoblastoma is a fatal malignant tumor of childhood. If not early diagnosed and managed may be life threatening. We came across with cases who were mainly in advanced stages having presentation of proptosis or with a cauliflower mass fungating out of the orbit. If these cases had come in early stages they could have been saved. Fifty

cases were included in our study of which majority were in advanced stage. The prevailing modes of management for retinoblastoma are discussed. Considering the facilities available in our institute, the best way of managing these tumors was adopted. We combined surgery with radiation or chemotherapy where ever needed to get the best results. Out of fifty cases which were followed during January 2005 to December 2015 recurrence was noted in 13 cases, which is very high as compared to other studies. The reasons for this high recurrence rate in our cases were explained.

In modern management of early retinoblastoma with confinement to the retina or even with vitreous seeding, chemoreduction, destruction of tumor with chemotherapy using anticancerous drugs along with cyclosporine and using less invasive methods like laser photocoagulation and cryotherapy is possible and there is no need for enucleations or radiation therapy. To avail the modern methods of treatment for retinoblastoma, it is necessary to diagnose the lesion as early as possible, so the need arises to literate the people about the salient features of this fatal lesion. We must adopt a national policy particularly in health sector to post an ophthalmologist and provide the facilities of ultrasound (A and B Scan ultrasonography) at district level so that the cases can be diagnosed early and referred to proper institutions for early treatment.

Conflicts of interest

Author does not have any conflicts of interest.

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