RETINOBLASTOMA PRESENTING AS METASTASIS

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Objective: The purpose of this study was to evaluate the frequency of metastatic retinoblastoma on initial presentation. **Design:** Prospective study. **Place and duration of study:** Supra Regional Centre for Retinoblastoma, Department of Ophthalmology, Khyber Teaching Hospital Peshawar Pakistan from 1st July 1999 to 31st January 2003. **Methods:** Data was collected from 80 registered Retinoblastoma patients admitted and examined under anaesthesia for tumours assessment. Diagnosis was supported with the help of CT scan and confirmed by histopathology of the enucleated specimen for evidence of optic nerve invasion by the tumour. **Results:** Twenty (25%) patients were presenting as Metastasis on initial presentation. Mean age was 3.5 years, range was 7 months to 12 years. Out of these 20 patients with metastasis, 10 were male and 10 were female. Eighteen (90%) of them were from lower socio-economic group. **Conclusion:** Failure in early diagnosis of retinoblastoma, advance age and unilateral disease are associated with extraocular spread; this tragic scenario can be prevented best be early detection and prompt treatment plan implementation.

Keywords: CT Scan, Optic nerve invasion, Orbital and Lymph node metastasis.

INTRODUCTION

With early diagnosis, the prospect of survival of Retinoblastoma patients has continuously improved. Recent studies indicate that Metastatic disease will develop in less than 10% of affected children.[1–3] Current treatment, with the objective of saving life of the child as well as sight is a modern day success story.[4–5] Advances in tools of diagnosis through indirect ophthalmoscopy, ophthalmic ultrasound and computer tomographic imaging has reduced the incidence of metastasis in Retinoblastoma patients. Knowledge and early recognition of risk factors for metastasis are crucial in avoiding this deadly outcome.

PATIENTS AND METHODS

This study is based on prospective analysis of data from 80 registered patients admitted for retinoblastoma between 1st July 1999 and 31st January 2003. The patients were examined under anaesthesia in well equipped operation theatre after filling the relevant proforma and initial interview. Examination was carried out with indirect ophthalmoscopy, in fully dilated pupils of both eyes. Number, extent, vitreous seeding as well as laterality were graphically recorded. C.T. Scan was done to confirm calcification and to see evidence of intracranial spread. Ophthalmol-Ultrasound scan was done to support diagnosis. A detailed systemic examination was done to exclude distant metastasis. Bone scan was done in suspected cases. Histopathological data was made available from enucleated patients, indicated for patients with advanced disease. During enucleation it was made sure that approximately 10 mm of optic nerve is cut with specimen eyeball. Pathologist was specifically requested for comments on optic nerve, choroid and necrosis. Clinical variables were investigated in reference to frequency with which they had occurred, by reviewing the proforma of patients. Horizontal corneal diameter was measured with callipers, and intraocular pressure recorded with Schiotz tonometer. Rubeosis irisdes was confirmed under operating microscope if any.

RESULTS

Total number of newly diagnosed patients was 80; out of which 44 (55%) were male and 36 (45%) were female. Mean age for the whole of these patients was 28.17 months (range 2 months to 12 years). Unilateral cases presented at mean age of 31.81 months, while bilateral occurred at 25.33 months of age, 40 were unilateral and equal number bilateral. Primary enucleation was done in 37 patients. All enucleated eyes had stage VB disease on Rees-Ellsworth classification. Amongst these enucleated patient s 18 were unilateral and 19 were bilateral.

Twenty (25%) out of the total 80 registered patients had metastatic disease. Of these, 10 were male and 10 were female. Mean age at presentation in these patients with metastasis was 3½ years, range was 7 months to 12 years. Patients with unilateral disease, in whom metastasis developed, were significantly older at diagnosis than unilateral cases without metastasis. (Figure-1)

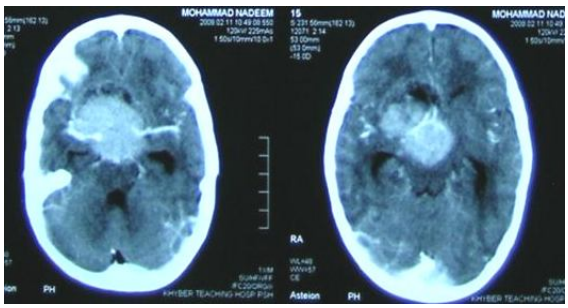

Figure-1: CT Scan of Orbit and Brain showing Intracranial spread in a Retinoblastoma patient

Amongst the unilateral cases 5 presented as intracranial extension, confirmed on CT Scan. Three had mandibular involvement proved on histopathological evidence of the swollen mass. 10 patients had optic nerve invasion, as reported on histopathology of the eyeball. One patient had orbital disease and one had lymph node (submandibular) involvement. (Table-1)

On retrieval of clinical data, other factors significantly associated with Metastasis were advanced stage of the disease, late enucleation, and multifocal disease.

Table-1: Mode of presentation in Retinoblastoma patients with metastasis

Clinical Presentation	Number (%)
Intra Cranial Extension	5 (25)
Mandibular involvement	3 (15)
Orbital Spread	1 (5)
Lymph Node involvement	1 (5)
Optic nerve involvement	10 (50)

DISCUSSION

Successful treatment of Retinoblastoma has been made possible with current protocol of treatment.[6–7] Early recognition of risk factors for metastasis offers the potential to improve survival and delay in diagnosis is an important variable.[8–9] Clinical genetic and histopathological features have been identified as risk factors for metastatic disease. Prompt treatment in this respect reduces the risk of metastasis, and fatality.[10] Clinical risk factors include demography, laterality, age at diagnosis and delay in diagnosis.[11]

Age at presentation in patients with metastatic disease is a statistically significant risk factor. In Tamboli series 95% of 220 patients with Retinoblastoma were diagnosed before the age 5 years and amongst these 40% were diagnosed before the age of 1 year. There is a trend towards less[12,13] metastatic disease in children diagnosed at an earlier age. Most children with Retinoblastoma are diagnosed before the 3rd year of life and new tumours can develop until they are 7 years of age.

Older age at diagnosis as a risk factor for metastasis had been pointed out by Megramm *et al*.[11] Our results amongst unilateral retinoblastoma support this significant observation.

Bilateral tumours are discovered at an earlier age and treated earlier than unilateral disease, although many studies suggest equal risk for both unilateral and bilateral diseases.

Kopelman *et al*, performed a multi variant analysis focusing on laterality of Retinoblastoma. They found that if patients with concurrent optic nerve invasion and orbital extension were removed from analysis, patients with bilateral Retinoblastoma were more likely to develop metastatic disease.[14] This is contrary to our study, which reveal intracranial extension in 4 patients, who had unilateral disease.

In a study performed by Messmer EP *et al*, the incidence of metastasis was considerably higher among patients with bilateral retinoblastoma (8.7%) than among the unilateral disease (3.7%).[15] Our series reveal 13% (16.25%) out of 80 patients as having metastasis with unilateral disease, as compared to 7 (8.75%) with bilateral disease.

The presence of tumours beyond lamina cribrosa is a risk factor for metastatic disease. Access to subarachnoid space allowed Retinoblastoma cells to spread to spinal fluid and CNS. MRI and CT Scan as well as ultrasonography have been useful in this regard. Glaucoma has been reported to be associated with metastasis.[16]

Extension of tumour beyond the line of transection needs additional treatment. Evidence of invasion of optic nerve need to be made available for quick action, in terms of radiotherapy, and prophylactic chemotherapy.[17]

Orbital invasion is a strong indication for systemic chemotherapy. Neovascular glaucoma seems to be considered as relative risk factor for orbital extension. Microscopic orbital extension is impossible to discover by clinical examination.[18] Larger extension of the orbit can be imaged by ultrasound CT Scan and MRI. Gross orbital extension can be difficult to miss and may simulate cellulitis and proptosis.

Kaan Gunduz in his study between 1999 and 2005 on Metastatic Retinoblastoma reported worst out come in these patient and all patients with CNS involvement had died.[19] Alex Melamud also reported hundred percent mortality in Retinoblastoma patients with Metastasis with in two years of diagnosis.[20]

Factors that delay Retinoblastoma diagnosis can be responsible for metastasis, e.g., cataract, misdiagnosis and lack of access to medical care as well as poverty.

CONCLUSION

In this era of highly precise and skilled facilities available, it is a tragedy that children in this part of the world should succumb to Retinoblastoma, when survival has reached nearly 100%, in developed world. Early detection and prompt treatment will contribute tremendously toward preventing metastatic disease. Similarly the concept of Supra Regional Centre in this regard will be a success, towards benefit of Retinoblastoma children.

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