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Retinoblastoma: An Overview

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ABSTRACT

Retinoblastoma is the most common primary intra-ocular malignancy of childhood and infancy with worldwide incidence of approximately 1 in 18,000 live births. Retinoblastoma is a highly malignant tumor that arises from an accumulation of proliferating embryonic retinal cells. Early diagnosis and treatment of the tumor is essential for child's survival and salvaging of eye to give useful vision. It is important for the treating doctor to give correct and adequate genetic counseling to the parents of child about chances of their second child being affected by retinoblastoma, and chance of the tumor being inherited in further generations.

Keywords *- Ocular Tumour, Chemotherapy, Enucleation, Brachytherap*

INTRODUCTION

Retinoblastoma is the most common intraocular malignancy in children [1] with a worldwide incidence of approximately 1 in 18,000 live births. It constitutes 4% of all paediatric malignancies. It may present any time from birth to 5 years of age. The mean age at presentation is 2.5 years in India. [2] Most common first symptom is white reflex [Figure-1] followed by squint and redness. Uncommon clinical presentations include uveitis

like picture with pseudohypopyon, pthisis bulbi, hyphema, bupthalmos, aseptic orbital cellulitis, proptosis and fungating mass. Patients with metastases may present with bone pains, vomiting and headache or scalp masses.

Figure 1- Leukocoria (white reflex) in retinoblastoma.

Extraocular retinoblastoma which is very rare in developed countries contributes approximately half of all retinoblastoma in developing nations.[3,4] While survival for intraocular retinoblastoma is almost 100%, it is only 50-70% for extraocular tumor and 50-75% in cases of distant metastases not involving central nervous system. [5,6,7] Therefore the overall survival for retinoblastoma is significantly lower in the developing world. A child suspected with retinoblastoma must undergo a preliminary assessment in the clinic which includes a visual acuity assessment, slit lamp examination, indirect ophthalmoscopy and ultrasonography. Ultrasound of the eye [Figure-2] can pick up calcification in 87% to 97% of cases of retinoblastoma. [8] CT Scan is most popularly used imaging modality in cases of suspected retinoblastoma [Figure-3] .

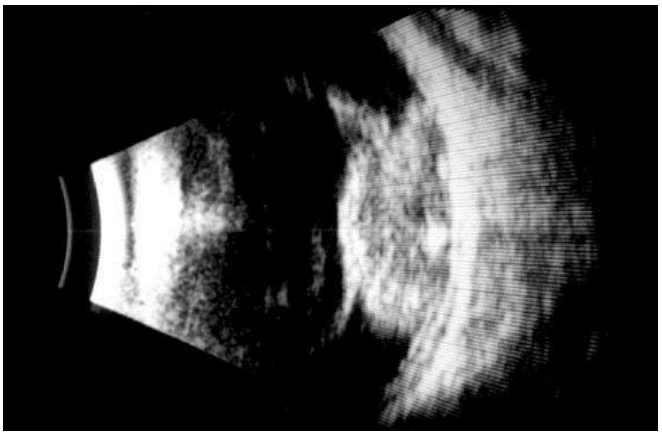

Figure 2- B Scan ultrasonogram showing a dome shaped mass lesion with low to medium internal reflectivity.

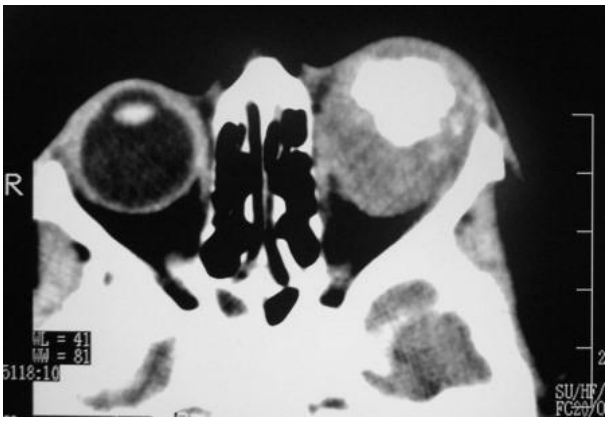

Figure 3: CT Scan of orbit showing a well-defined mildly enhancing mass lesion.

Magnetic resonance imaging (MRI) of brain and orbit is performed to rule out extraocular extension and bilateral retinoblastoma. MRI is very useful in confirming the diagnosis of retinoblastoma in doubtful cases with no calcification.

Examination under anaesthesia (EUA) is critical for diagnosis and management of retinoblastoma. Following parameters should be evaluated during EUA:

- Intraocular Pressure Measurement
- Anterior segment examination under microscope to rule out iris

neovascularization, hyphema, iris nodule or hypopyon.

- Corneal Diameters
- Fundus examination using indirect ophthalmoscope with scleral indentation and tumor documentation.

Based on the clinical, imaging and histopathological findings, disease is staged. The international retinoblastoma staging system is currently widely used for staging. [9]

International Classification System for Intraocular Retinoblastoma

Group A: Very low risk • Eyes with small intra-retinal tumors away from critical structures: • Tumors are 3mm or smaller in greatest dimension • Confined to the retina • Located further than 3mm from the foveola and 1.5mm from the optic disc
Group B: Low risk Eyes with no seeding. Tumors are discrete but any size or location. • Any size or location not in group A • No seeding • Cuff of subretinal fluid < 3mm from the tumor
Group C: Moderate risk Discrete local disease with minimal subretinal or vitreous seeding. • Local fine vitreous seeding close to discrete tumor or • Local subretinal seeding <3mm from the tumor • Or both.
Group D: High risk Eyes with diffuse vitreous or subretinal seeding. • More extensive seeding than group C • Diffuse vitreous seeding or subretinal seeding (>3mm) from tumor margin or both.
Group E: Very high risk Presence of any one or more of the following poor prognostic features: • Irreversible neovascular glaucoma • Opaque media due to hemorrhage • Aseptic orbital cellulitis • Tumor anterior to anterior vitreous face • Tumor touching the lens • Diffuse infiltrating retinoblastoma • Pthisis bulbi

International Staging System For Extraocular Disease	
Stage O	Patient treated conservatively.
Stage I	Eye enucleated, completely resected histologically.
Stage II	Eye enucleated, microscopic residual tumor.
Stage III	Regional extension: a) Overt orbital disease b) Preauricular or cervical lymph node extension
Stage IV	Metastatic disease: a) Hematogenous metastasis with central nervous system (CNS) involvement 1.Single lesion 2. Multiple lesions b) CNS extension 1. Pre-chiasmatic lesion 2. CNS mass 3. Leptomeningeal and CSF disease

Genetics

First successful attempt to understand the genetics of retinoblastoma was made in 1971 by Alfred Kundson [10], until when the disease was thought to follow an autosomal dominant pattern of inheritance. It is now known that retinoblastoma can be inherited as familial tumor in which the affected child has a positive family history of retinoblastoma or as a sporadic tumor. All patients with familial retinoblastoma are at risk of passing the predisposition for developing the tumor to their offsprings.

In 1984, Murphee [11] with the help of established data suggested that gene responsible for retinoblastoma was located on a single locus in the region 13q14. This locus represents an allele located on 14th band on the long arm (q) of the 13th chromosome. This allele is known as RB1 gene. The deletion of 13q chromosome may be associated with other dysmorphic features such as microcephaly, broad prominent nasal bridge, hypertelorism, microphthalmos, epicanthus, toe abnormalities and psychomotor and mental retardation. [12]

Management

Management of retinoblastoma is a team work involving ophthalmologist, medical oncologist and radiation oncologist. Once the diagnosis of retinoblastoma is confirmed, further management depends on the stage at which the tumor is

detected. A working knowledge of the classification system is essential in order to accurately stage the tumor. Goals of the treatment include:

- Survival of child
- Globe salvage
- Vision salvage
- Cosmetic rehabilitation

Intraocular Retinoblastoma: The prognosis for survival is excellent for tumors confined to the globe. Systemic chemotherapy and focal treatment with laser photocoagulation/ transpupillary therapy/ cryotherapy has resulted in number of eyes being salvaged. Factors governing treatment include the extent of disease and potential for vision. In general, group A tumors are treated with focal therapy, while group B, C and D tumors are treated with systemic chemotherapy and focal consolidation. The most commonly used chemotherapy drugs are vincristine, etoposide and carboplatin.

Standard Chemotherapy Protocols for Retinoblastoma:

Drugs:

- Vincristine 1.5mg/mt^2 on Day 1(0.05mg/kg for children <3 years and maximum dose 2mg)
- Carboplatin 560mg/mt^2 on Day 1 (18.6 mg/kg for children <3 years)
- Etoposide 150mg/mt^2 on Day 1 and 2 (5mg/kg for children <3 years)

Before each cycle, it should be ensured that Absolute neutrophil count is >1000 and platelets >100,000/mm^3.

Examination under anaesthesia is done at regular intervals to assess tumor control. Side effects of systemic chemotherapy include nausea, vomiting, loss of appetite, diarrhea and fever. Myelosupression leading to anemia and neutropenia, upper respiratory tract infections and alopecia are other adverse effects. Children receiving systemic chemotherapy need close supervision under pediatric oncologist.

In addition to systemic chemotherapy, periocular carboplatin supplementation may be given for Group C and Group D tumors. Periocular carboplatin (20mg/2 ml) is given via subtenon or subconjunctival route.

In eyes with advanced intraocular disease and no potential for vision, enucleation is performed. The basic precautions to be taken during enucleation surgery include careful handling of the globe to avoid perforation and obtaining a long stump of the optic nerve (preferably >15mm). Careful histopathological examination of the enucleated globe is mandatory for detection of high risk histopathological features. These include tumor invasion of anterior chamber, iris, ciliary body, massive choroidal invasion, involvement of the transection end of the optic nerve, scleral and extrascleral invasion. Adjuvant chemotherapy with six cycles of systemic chemotherapy is recommended after enucleation in these cases to protect from distant metastasis or local recurrence.

Extraocular Retinoblastoma: Several factors such as delay in diagnosis, inadequate treatment facilities, financial constraints lead to spread of tumor outside the eye. In cases with the overt spread, MRI scan of brain and orbit is mandatory

to detect the extent of optic nerve involvement and orbital spread. Metastatic work up includes complete hemogram, liver function tests, kidney function tests, serum electrolytes, chest X-ray, ultrasonography whole abdomen, CSF analysis, bone marrow aspiration/ biopsy, fine needle aspiration cytology of lymph node and whole body PET scan wherever possible.

Exentration is rarely carried out these days and multimodal treatment approach with systemic high dose chemotherapy, enucleation and orbital radiotherapy has shown good results. Initially, neo-adjuvant chemotherapy is administered for 3 cycles. Systemic chemotherapy helps in shrinking the tumor and makes it amenable to enucleation. The most common used drugs are vincristine, etoposide, carboplatin and cyclophosphamide. Following chemo-reduction, MRI brain and orbit is performed and external beam radiotherapy is given to the orbit in a dose of 45Gy. This is followed by additional cycles of systemic chemotherapy.

For patients with metastatic disease, high dose marrow ablative chemotherapy and autologous hematopoietic stem cell rescue have been used. For intracranial disease, intrathecal methothrexate and craniospinal irradiation have been tried. The prognosis for metastatic disease, especially CNS metastasis, is grim and long term survival is less than 10%.

Role of External Beam Radiotherapy

Indications:

- In cases of extra and intraocular retinoblastoma that fails to respond to chemotherapy.
- In cases where histopathological examination of the enucleated globe shows tumor invasion to the cut end of the optic nerve or microscopic extra-scleral extension.

Adverse Effects:

- Increased risk of developing secondary cancers
- Orbital hypoplasia
- Cataract
- Radiation retinopathy.

Follow up: Regular follow-up is very important even after completion of therapy for detecting side-effects of treatment, local recurrence or systemic metastasis. Children with sporadic disease should be followed up for at least 5 years and those with germ line disease have to be followed up for life.

Advances in approach for drug delivery: Concerns about side-effects of systemic chemotherapy had led to development of newer approach for delivering chemotherapy to globe. There have been reports suggesting that intra-arterial infusion of chemotherapy is effective in intra-ocular retinoblastoma. The technique involves super-selective infusion of melphalan into ophthalmic artery. This is achieved by femoral artery puncture and catheterization of the internal carotid artery. Micro-catheters are then introduced into the ophthalmic artery and melphalan is introduced. Recently, Gobin et al [13] reported on their experience with selective ophthalmic artery cannulation on 95 eyes of 78 patients with unilateral or bilateral advanced intra-ocular retinoblastoma. There were no permanent extra-

ocular complications, suggesting that intra-arterial chemotherapy is safe and effective for treatment of advanced intra-ocular retinoblastoma.

Genetic councelling: The ophthalmologist who manages an infant with retinoblastoma should be responsible for adequate genetic councelling of parents.

Only 6% of newly diagnosed retinoblastoma patients will have a family history of retinoblastoma (familial) and are also heritable, whereas 94% will have no family history (sporadic). Approximately 15-20% of unilateral sporadic retinoblastoma are caused by germinal mutations that by chance affect only one eye. Such patients can transmit the disease to the offsprings. The remaining 80-85% are somatic mutations that occur only in the retina and are non-hereditary and thus such patients cannot transmit the disease [14]. Patients who have bilateral retinoblastoma are more likely to have the heritable disease.

The retinoblastoma gene is about 80% penetrant so that only 40% of the offspring will manifest the clinical findings of the gene and some offspring may only be carriers of the gene without developing retinoblastoma [15].

The parents may be reluctant to inform the child that he had cancer during infancy. The patient may grow up and have children without realizing that there is possibility of transmitting a malignant gene.

CONCLUSION

Children and adolescents with cancer should be referred to medical centers that have a multi-disciplinary team of cancer specialists with experience of treating the pediatric cancers. This multidisciplinary team approach incorporates the skills of the primary care physician, an ophthalmologist with extensive experience in treatment of children with retinoblastoma, pediatric surgical subspecialists, radiation oncologists, pediatric medical oncologist/ hematologists, rehabilitation specialists and other supporting staff to ensure that children receive treatment, supportive care and rehabilitation that will achieve optimal survival and quality of life. Dramatic improvements in survival have been achieved for children and adolescents with cancer. Childhood cancer survivors require close follow up because cancer therapy adverse effects may persist or develop months or years after treatment.

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