RETINOBLASTOMA - AN OVERVIEW

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Retinoblastoma is the most common intraocular malignancy in children with a reported incidence ranging from 1 in 15000 to 1 in 18000 live births. The average age at diagnosis is 18 months, sporadic unilateral cases being diagnosed at 24 months and bilateral cases before 12 months.

Pawins described retinoblastoma as early as 1597. In 1809, Wardrop referred the tumor as fungus haematids and suggested enucleation as treatment. Initially it was called a glioma of the retina by Virchow (1864). Flexner (1891) and Wintrersteiner (1897) described it to be a neuroepithelioma because of the presence of rosettes. Later on the tumor was officially termed as retinoblastoma in 1926 by American Ophthalmological Society.

Genetics

The genetics of retinoblastoma has been the subject of many investigations. When retinoblastoma follows a genetic pattern, it is almost always an autosomal dominant with virtually complete penetrance. The retinoblastoma gene maps to a locus within the q 14 band of chromosome 13. 60% of retinoblastoma arises from the somatic nonhereditary mutations in retinal cells. These mutations generally results in unifocal and unilateral tumors. Approximately 40 % cases are inheritable form of retinoblastoma.

Clinical Manifestation of Retinoblastoma

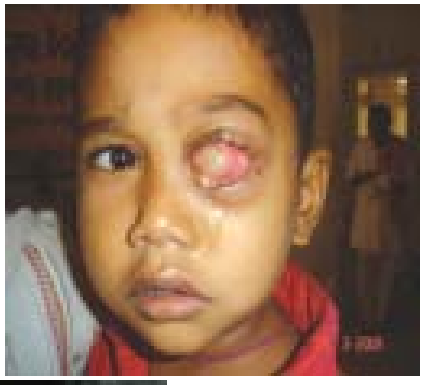
Leucocoria is the most common presenting feature of retinoblastoma, followed by strabismus, proptosis, painful blind eye and loss of vision. Table 1 lists the symptoms and signs of retinoblastoma.

Table-1 Common presenting features of retinoblastoma

1	Leucocoria	56%
2	Strabismus	20%
3	Red painful eye	7%
4	Poor vision	5%
5	Orbital cellulitis	3%
6	Asymptomatic	3%
7	Unilateral mydriasis	2%
8	Heterochromia iridis	1%
9	Hyphema	1%

Diagnosis of Retinoblastoma

A detailed ophthalmic evaluation including a dilated fundus examination under anaesthesia is usually the routine protocol in a child with suspected retinoblastoma. Ultrasonography B-scan shows a rounded or irregular intraocular mass with high internal reflectivity representing typical intralesional calcification. Computed tomography delineates extraocular extension and can detect an associated Pinealoblastoma. MRI is indicated in suspected cases of intracranial extension or optic nerve involvement.



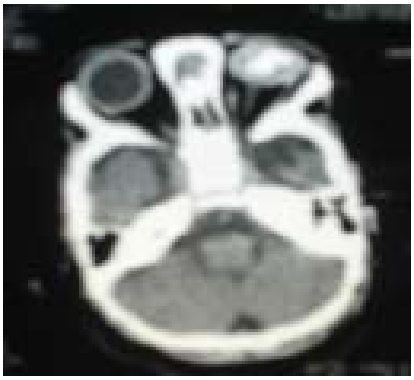


Figure 1, Figure 2
(3 year old child presenting as unilateral proptosis)

Histopathology of Retinoblastoma

Well-differentiated tumours show the presence of rosettes and fleurettes. The characteristic histopathologic features of retinoblastoma include Flexner-Wintersteiner rosettes, which consist of columnar cells arranged around a central lumen. Homer Wright rosettes consist of cells arranged around a central neuromuscular tangle. This is also seen in medulloblastomas and neuroblastomas.

Classification of Retinoblastoma

An ideal classification system for retinoblastoma should include two components: grouping and staging. Grouping is a clinical system of prognosticating organ salvage while staging prognosticates survival. The Reese Ellsworth classification was introduced to prognosticate patients treated with external beam radiotherapy (EBM).The new International Classification of Intraocular Retinoblastoma is a logical flow of sequential tumour grading that linearly correlates with the outcome of newer therapeutic modalities.

Table-2 Reese-Ellsworth Classification

Group I: very favorable for maintenance of sight

A. Solitary tumor, smaller than 4 disc diameters (DD), at or behind the equator.
B. Multiple tumors, none larger than 4 DD, all at or behind the equator.

Group II: favorable for maintenance of sight

A. Solitary tumor, 4 to 10 DD at or behind the equator.
B. Multiple tumors, 4 to 10 DD behind the equator.

Group III: possible for maintenance of sight

A. Any lesion anterior to the equator.
B. Solitary tumor, larger than 10 DD behind the equator.

Group IV: unfavorable for maintenance of sight

A. Multiple tumors, some larger than 10 DD.
B. Any lesion extending anteriorly to the ora serrata.

Group V: very unfavorable for maintenance of sight

A. Massive tumors involving more than one half the retina
B. Vitreous seeding.

Table-3 International Classification System for Intraocular Retinoblastoma

Group A : Small intraretinal tumors away from foveola and disc.

All tumors are 3 mm or smaller in greatest dimension; confined to the retina All tumors are located further than 3 mm from the foveola and 1.5 mm from the optic disc.

Group B: All remaining discrete tumors confined to the retina.

All other tumors confined to the retina not in Group A. Tumor-associated subretinal fluid less than 3 mm from the tumor with no subretinal seeding.

Group C: Discrete local disease with minimal subretinal or vitreous seeding.

Tumor(s) are discrete. Subretinal fluid, present or past, without seeding involving up to one-fourth of the retina. Local fine vitreous seeding may be present close to discrete tumor.Local subretinal seeding less than 3 mm (2 DD) from the tumor.

Group D: Diffuse disease with significant vitreous or subretinal seeding.

Tumor(s) may be massive or diffuse. Subretinal fluid present or past without seeding, involving up to total retinal detachment. Diffuse or massive vitreous disease may include "greasy" seeds or avascular tumor masses. Diffuse subretinal seeding may include subretinal plaques or tumor nodules.

Group E: Presence of any one or more of these poor prognosis features.

Tumor touching the lens. Tumor anterior to anterior vitreous face involving ciliary body or anterior segment. Diffuse infiltrating retinoblastoma. Neovascular glaucoma. Opaque media from hemorrhage. Tumor necrosis with aseptic orbital cellulites. Phthisis bulbi.

Management of Retinoblastoma

There has been a significant change in the treatment of retinoblastoma in recent years. The primary goal of management is to save the patient's life and secondary to salvage the patient's eye and vision if possible. It needs a multidisciplinary team approach including an ophthalmologist, pediatric oncologist, radiation oncologist, genetist and an ophthalmic oncopathologist.

Enucleation: The choice for large unilateral tumors, especially with no visual potential. It should be done gently avoiding perforation. One should obtain as long a section of optic nerve (>15mm) stump as possible. This is best achieved via a temporal approach with slightly curved enucleation scissors. Results are good with a cure rate greater than 95%. Avoid biointegrated implant if postoperative radiotherapy is necessary.

External Beam Radiotherapy: EBR still plays a role in the management of retinoblastoma. Radiation is indicated in case of diffuse vitreous seeding (Reese-Ellsworth stage 5B), failure or intolerance to chemotherapy, or widespread recurrences. Local side effects include cataract, radiation retinopathy, optic neuropathy, chronic dry eye and atrophy of muscles and subcutaneous tissue. There is also a significant risk of development of sarcoma.

Plaque radiotherapy: It is a safe alternative to enucleation and is performed primarily in situations where chemotherapy is contraindicated. It is limited to tumor less than 16mm in base diameter and 8mm in thickness. The plaque containing radioactive iodine-125, are sewn to the eyes for 2 to 4 days, allowing for radiation to the underlying choroids, retina and tumor. Side effects include radiation retinopathy and optic neuropathy and are more prominent in children who have been exposed to chemotherapy.

Cryotherapy / Photocoagulation: Cryotherapy is used in small anterior tumors that are 3.5mm or less in diameter. It can cause shrinkage of the sclera, and extensive therapy predisposes the developing eye to myopia and increase the risk of retinal detachment. Laser photocoagulation is useful in tumor ? 2.5mm in thickness. Complications include retinal tears and detachments, preretinal fibrosis and vascular occlusion.

Chemotherapy: Recently the primary treatment of choice for retinoblastoma to reduce tumor bulk in an attempt to avoid external beam radiation (chemoreduction). It is indicated if or children whose enucleated globes show high risk of developing metastasis. The current protocol consists of combination of Vincristine sulfate, Etoposide phosphate and Carboplatin infused every four weeks typically for six months. Complications include neutropenia, infection, anaemia, hearing loss & later leukemia. It is not effective in treating diffuse vitreous seeding and tumor in the anterior chamber.

Table-4 Chemoreduction Regimen and Doses for Intraocular Retinoblastoma

Day 1 : Vincristine + Etoposide + Carboplatin
Day 2 : Etoposide

Standard dose (3 weekly, 6 cycles): Vincristine 1.5mg/sq.m(0.05mg/kg for children < 36 months of age and maximum dose < 2 mg.); Etoposide 150 mg/sq.m (5mg/kg for children < 36 months of age), Carboplatin 560mg/sq.m (18.6 mg/kg for children < 36 months of age)

High dose (3 weekly, 6-12 cycles): Vincristine 0.025mg/kg, Etoposide 12mg/kg, Carboplatin 28mg/kg.

Future Directions & Monitoring

Close monitoring of patients with retinoblastoma and their family members is crucial. If the retinoblastoma is in the hereditary form, the patients and siblings should be examined every 4 months until age 3 or 4 years and every 6 months until age of 6 years. EUA is indicated to obtain a thorough peripheral examination.

Screening of high risk children (e.g. those with a family history of RB) remains a vital tool in preventing visual loss from RB. At risk children should be screened shortly after birth and regularly through the first two years of life. Any report of abnormal pupillary reflexes in a preschool child requires immediate referral to a pediatric ophthalmologist for a dilated funduscopic examination. Finally a structured follow-up and supportive care is essential for the children to function productively and live with self-esteem.

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