



# RETINOBLASTOMA



**Eye Learn**  
All about the Eye

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# RETINOBLASTOMA

Genetics and inheritance of retinoblastoma.

\*\*\*Pathology of retinoblastoma.

\*\*\*Write down modern histopathology classification of Retinoblastoma and give its clinical significance and effect on management.

\*\*Write down prevalence of various forms of retinoblastoma. How will you counsel a parent with one child having a retinoblastoma?

\*\*Describe the common causes of leukocoria. What is retinoblastoma gene and inheritance?

\*\*\*\*Give the international classification of retinoblastoma. Discuss the management of retinoblastoma with recent advances in detail.

\*\*\*\*\*Discuss the differential diagnosis of retinoblastoma. Discuss the factors which affect the genetic counseling for patients of retinoblastoma.

## RETINOBLASTOMA

- Most common primary intraocular malignancy of the childhood and accounts for 3% of all childhood malignancies.
- Second MC (after uveal melanoma) intraocular malignancy in all age groups.
- 1 in 14,000 to 1 in 20,000 live births.
- B/L in 30-40% of the cases.

## HISTOPATHOLOGY

- Tumours are composed of small basophilic cells (retinoblasts) with large hyperchromatic nuclei and scanty cytoplasm.
- Many retinoblastomas are undifferentiated but varying degrees of differentiation are characterized by the formation of structures known as rosettes (Flexner–Wintersteiner, Homer–Wright and fleurettes).

## GENETIC COUNSELLING

- RB1 gene, tumor suppressor gene, long arm of 13 chromosome at locus 14 (13q14).
- Size of deletion ----- more aggressive the tumor.
- 1-3% RB have mutation in N-MYC (not RB1).
- Both copies must be mutated for RB.
- B/L – 98% chance of germline mutation.
- 10% cases have a family history
- 90% are sporadic – of these 60% are UL with no germline mutation, remaining have new germline mutation and multiple tumors will develop



- Heritable (hereditary, germline) retinoblastoma accounts for 40%.
- Non-heritable (non-hereditary, somatic) retinoblastoma. The tumour is unilateral, not transmissible and does not predispose the patient to second non-ocular cancers. Ninety per cent of children with unilateral retinoblastoma will have the non-hereditary form.
- Genetic testing
  - o PCR
  - o FISH
  - o Multiplex ligation-dependent probe amplification (MLPA)
  - o RNA analysis

If parent:	has bilateral retinoblastoma		has unilateral retinoblastoma		is unaffected	
Chance of offspring having retinoblastoma	45% affected	55% unaffected	7%–15% affected	85%–93% unaffected	<<1% affected	99% unaffected
Laterality	85% bilateral	15% unilateral	0%	85% bilateral	15% unilateral	0%
Focality	100% multi-focal	96% multi-focal, 4% uni-focal	0%	100% multi-focal	96% multi-focal, 4% uni-focal	0%
Chance of next sibling having retinoblastoma	45%	45%	45%	45%	45%	45%
					7%–15%	
						5%*
						<1%*
						<1%*
						<1

\*If parent is a carrier, then 45%

## DIAGNOSIS – clinical dx

- Clinical examination
- Mean age of dx depends on 1. Family history and 2. Laterality
  - o Pt with known FH of RB – 8 months
  - o Pt with B/L disease – 12 months
  - o Pt with U/L disease – 24 months



1 Presenting Signs and Symptoms of Retinoblastoma	
Among Patients <5 Years	Among Patients ≥5 Years
Leukocoria (most common)	Leukocoria (35%)
Strabismus (≈20%)	Decreased vision (35%)
Ocular inflammation (≈5%)	Strabismus (15%)
Pseudohypopyon	Floaters (5%)
Hyphema	Pain (5%)
Iris heterochromia	
Spontaneous globe perforation	
Proptosis	
Cataract	
Glaucoma	
Nystagmus	
Tearing	
Anisocoria	

## - SYMPTOMS

- Leukocoria (white pupillary reflex) is the commonest presentation (60%) and may first be noticed in family photographs
- Strabismus is the second most common (20%); fundus examination is therefore mandatory in all cases of childhood squint.
- Painful red eye

## - SIGNS

- Morphology – Retinoblastoma begins as a translucent, gray to white intraretinal tumor, fed and drained by dilated, tortuous retinal vessels.
- As the tumor grows, foci of calcification develop, giving the tumor its characteristic chalky white appearance.
- Type of growth
  - Exophytic – grows below the retina, serous RD, obscuring visualization of the tumor
  - Endophytic – grow on the retinal surface into the vitreous cavity. Blood vessels difficult to visualize. Vitreous seeds formed, may pass into AC forming iris nodules, pseudohypopyon, sec glaucoma and rubeosis iridis.
  - Diffuse infiltrating retinoblastoma – rare variant, >5 years, dense vit cells, may be mistaken as intermediate uveitis

## INVESTIGATIONS

- Red reflex testing with a direct ophthalmoscope is a simple screening test for leukocoria
- EUA
  - General examination for congenital abnormalities of the face and hands.
  - Tonometry.
  - Measurement of the corneal diameter.
  - Anterior chamber examination with a hand-held slit lamp.
  - Ophthalmoscopy, documenting all findings with colour drawings or photography.
  - Cycloplegic refraction.
- USG – size, characteristic calcifications
- Wide-field photography (portable if necessary) is useful for both surveying and documentation
- CT also detects calcification, but chances of second malignancy
- MRI – optic nerve, orbit and brain
- Lumbar puncture – if suspected optic nerve involvement
- Genetic studies on tumour tissue and blood samples from the patient and relatives.



- Parents and siblings to be examined
- Complete physical examination by pediatric oncologist

## METASTASIS

- Most frequent site of metastasis is abdominal viscera, brain, distal long bones, lymph nodes, skull bones and spinal cord.
- ON into subarachnoid space
- Into choroid to emissary veins, erode sclera then extraocular
- In AC to TM into conj lymphatics and then to preauricular and cervical LN.

## DD

### Differential Diagnosis of Retinoblastoma

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Astrocytic hamartoma  
Coats disease  
Coloboma of choroid or optic nerve head  
Congenital retinal fold  
Organizing vitreous hemorrhage  
Persistent fetal vasculature  
Posterior cataract  
Retinal dysplasia  
Retinopathy of prematurity  
Toxocariasis (larval granuloma)  
Uveitis

#### I. PFV

1. Recognized days or weeks after birth
2. Microphthalmos, shallow AC, a hypoplastic iris with prominent vessels, and a retrolenticular fibrovascular mass that draws the ciliary body processes inward.
3. On indirect ophthalmoscopy, a vascular stalk may be seen arising from the optic nerve head and attaching to the posterior lens capsule.
4. Ultrasonography

#### II. Coat's disease

1. First decade of life, boys
2. Unilateral retinal telangiectasia associated with intraretinal yellow exudation without a distinct mass

#### III. Ocular Toxocariasis

1. Older children, eat soil, cats and dogs, posterior and peripheral granulomas
2. Absence of calcium
3. cause a cyclitic membrane and a white pupil. A granuloma at the posterior pole may resemble an endophytic retinoblastoma.



#### IV. Astrocytoma

1. Retinal astrocytoma, or astrocytic hamartoma, appears as a small, smooth, white, glistening tumor located in the nerve fiber layer of the retina.
2. It may be single or multiple, unilateral or bilateral.
3. It may grow and calcify, typically having a mulberry appearance.
4. Astrocytomas occasionally arise from the optic nerve head; such tumors are often referred to as giant drusen.

#### V. Medulloepithelioma

1. Inner layer of the optic cup, benign or malignant
2. 4-12 years, pigmented mass arising from the ciliary body

#### VI. ROP

1. cause retinal detachment and leukocoria. Diagnosis is usually straightforward because of the history of prematurity and low birth weight.

#### VII. Uveitis

1. may mimic the diffuse infiltrating type of RB
2. Conversely, retinoblastoma may be mistaken for uveitis, endophthalmitis or orbital cellulitis.

#### VIII. Vitreoretinal dysplasia

1. Due to faulty differentiation of the retina and vitreous that results in a detached dysplastic retina forming a retrolental mass with leukocoria
2. Other features include microphthalmos, shallow anterior chamber and elongated ciliary processes. Dysplasia may occur in isolation or in association with systemic abnormalities:
  - i. Norrie disease is an X-linked recessive disorder in which affected males are blind at birth or early infancy. NDP gene. Systemic features include cochlear deafness and mental retardation.
  - ii. Incontinentia pigmenti is an X-linked dominant condition. NEMO gene. Vesiculobullous rash on the trunk and extremities that with time is replaced by linear pigmentation. Other features include malformation of teeth, hair, nails, bones and CNS.
  - iii. Walker-Warburg syndrome is an autosomal recessive condition characterized by absence of cortical gyri and cerebellar malformations that may be associated with hydrocephalus and encephalocele. Peters anomaly, cataract, uveal coloboma, microphthalmos and optic nerve hypoplasia.

## CLASSIFICATION

### I. Reese-Ellsworth

1. In the era of EBRT
2. Based on 4 factors
  - i. Size
  - ii. Number
  - iii. Location
  - iv. +/- vit seeds
3. Not stages extraocular tumor, provides no prognostic information on survival and vision



**Table 1. — Reese-Ellsworth Classification for Conservative Treatment of Retinoblastoma\***

Group I: Very favorable	(a) Solitary tumor, less than 4 disc diameters in size, at or behind the equator
	(b) Multiple tumors, none over 4 disc diameters in size, all at or behind the equator
Group II: Favorable	(a) Solitary tumor, 4 to 10 disc diameters in size, at or behind the equator
	(b) Multiple tumors, 4 to 10 disc diameters in size, behind the equator
Group III: Doubtful	(a) Any lesion anterior to the equator
	(b) Solitary tumors larger than 10 disc diameters behind the equator
Group IV: Unfavorable	(a) Multiple tumors, some larger than 10 disc diameters
	(b) Any lesion extending anteriorly to the ora serrata
Group V: Very unfavorable	(a) Massive tumors involving over half the retina
	(b) Vitreous seeding

\* Refers to chances of salvaging the affected eye and not systemic prognosis.

II. International Classification System for Intraocular Retinoblastoma (Murphree)

1. Most commonly used system worldwide.
2. Based on 3 parameters
  - i. Size
  - ii. SRF
  - iii. Vit seeds
3. Eyes are assigned a letter from A to E (most to least salvageable with chemotherapy).

Group A	Small tumors (<3 mm) confined to the retina; >3 mm from the fovea; >1.5 mm from the optic nerve head
Group B	Tumors (>3 mm) confined to the retina in any location, with clear subretinal fluid up to 5 mm from the tumor margin
Group C	Localized vitreous and/or subretinal seeding
Group D	Diffuse vitreous and/or subretinal seeding
Group E	No visual potential or presence of 1 or more of the following: <ul style="list-style-type: none"> <li>• tumor in the anterior segment</li> <li>• tumor in or on the ciliary body</li> <li>• neovascular glaucoma</li> <li>• vitreous hemorrhage obscuring the tumor or significant hyphema</li> <li>• phthisical or prephthisical eye</li> <li>• orbital cellulitis-like presentation</li> </ul>

III. American Joint Committee on Cancer (AJCC)

1. Both intraocular and extraocular disease, but it is not used clinically by most ocular oncologists.

IV. TNM



## ASSOCIATED CONDITIONS

1. Retinocytoma
  - i. Clinically indistinguishable from RB
  - ii. Theories
    - i. It is RB that has differentiated
    - ii. Benign counterpart of RB
2. Primitive Neuroectodermal Tumor
  - i. PNET or trilateral retinoblastoma, BL RB with ectopic intracranial disease.
  - ii. The ectopic focus is usually located in the pineal gland or the parasellar region and has historically been known as a pinealoblastoma.
  - iii. This tumor affects up to 5% of children with a germline RB1 mutation.
  - iv. All patients with retinoblastoma should undergo baseline neuroimaging studies to exclude intracranial involvement.

**TREATMENT** - The approach to management is collaborative between the ophthalmologist, pediatric oncologist, ocular pathologist, geneticist, allied health professionals and parents.

Based on approach – LIFE >> EYE >> VISION

### A. Intraocular RB

- focal (cryotherapy, laser photocoagulation, transpupillary thermotherapy, transscleral thermotherapy, plaque brachytherapy),
- local (external beam radiotherapy, enucleation), and
- systemic (chemotherapy).
- While primary focal measures are mainly reserved for small tumors, local and systemic modalities are used to treat advanced retinoblastoma.

### B. Metastatic disease - intensive chemotherapy, radiation, and bone marrow transplantation.

#### I. Chemotherapy - mainstay of treatment in most cases

- i. Has replaced EBRT for globe salvage
- ii. IV VEC 3-6 cycles – vincristine, etoposide, carboplatin – successful for group A, B, C
- iii. After initial consolidation, treated with laser or cryo or brachy
- iv. Intra-arterial / intravitreal chemo – Melphalan – highly effective for subretinal seeds
- v. Chemoreduction may be followed by focal treatment with cryotherapy or TTT to consolidate tumour control

#### II. Laser photocoagulation

- i. Laser photocoagulation is used for small posterior tumors 4 mm in basal diameter and 2 mm in thickness.
- ii. The treatment is directed to delimit the tumor and coagulate the blood supply to the tumor by surrounding it with two rows of overlapping laser burns.
- iii. Complications include transient serous retinal detachment, retinal vascular occlusion, retinal hole, retinal traction, and preretinal fibrosis.

#### III. TTT

- i. In thermotherapy, focused heat generated by infrared radiation is applied to tissues at subphotocoagulation levels to induce tumor necrosis. The goal is to achieve a slow and sustained temperature range of 40 to 60-degree C within the tumor, thus sparing damage to the retinal vessels.



- ii. TTT using infrared radiation from a semiconductor diode laser delivered with a 1300-micron large spot indirect ophthalmoscope delivery system has become a standard practice. It can also be applied transpupillary through an operating microscope or by the transscleral route with a diopexy probe.
- iii. The tumor is heated until it turns a subtle gray.
- iv. S/E - The common complications are focal iris atrophy, focal paraxial lens opacity, retinal traction and serous retinal detachment.

#### IV. Cryotherapy

- i. Cryotherapy is performed for small equatorial and peripheral retinal tumors measuring up to 4 mm in basal diameter and 2 mm in thickness.
- ii. Triple freeze thaw cryotherapy is applied at 4-6-week intervals until complete tumor regression.
- iii. Cryotherapy produces a scar much larger than the tumor. Complications of cryotherapy include transient serous retinal detachment, retinal tear and rhegmatogenous retinal detachment.

#### V. Plaque radiotherapy (Brachytherapy)

- i. Plaque brachytherapy involves placement of a radioactive implant on the sclera corresponding to the base of the tumor to transsclerally irradiate the tumor.
- ii. The most commonly used isotopes are iodine-125 and ruthenium-106.
- iii. Primary plaque brachytherapy is currently performed only in situations where chemotherapy is contraindicated. It is most useful as secondary treatment in eyes that fail to respond to chemoreduction and external beam radiotherapy or for tumor recurrences.
- iv. S/E - radiation papillopathy and radiation retinopathy.

#### VI. EBRT

- i. Presently it is indicated in eyes where primary chemotherapy and local therapy has failed, or rarely when chemotherapy is contraindicated.
- ii. Two major concerns
  - i. Germline mutation – second malignancy (osteosarcoma)
  - ii. Radiation related sequelae - midface hypoplasia, radiation-induced cataract, and radiation optic neuropathy and retinopathy

#### VII. Enucleation – it is a definitive rx of RB. Indicated when;

- i. the tumor involves more than 50% of the globe
- ii. orbital or optic nerve involvement is suspected
- iii. anterior segment involvement is present
- iv. neovascular glaucoma is present
- v. the affected eye has limited vision potential

The goal of enucleation techniques is to minimize the potential for inadvertent globe penetration while obtaining the greatest possible length of resected optic nerve, typically longer than 10 mm.

## PROSPECTIVE TRIALS

- Children's Oncology Group (COG)
  - o To improve the outcomes and
  - o clarify the toxicities of rx



## SPONTANEOUS REGRESSION

- In rare instances, retinoblastoma can undergo complete and spontaneous necrosis and is recognized clinically after involutinal changes such as phthisis have occurred.

## PROGNOSIS

- Intraocular tumor – 95% survival rates
  - Death occurs due to extraocular extension of tumor, through the sclera or, by invasion of the optic nerve.
- Children BL RB who survive have increased risk of nonocular malignancies

Tumors Arising in the Field of Radiation of the Eye		Tumors Arising Outside the Field of Radiation of the Eye	
Pathologic Type	Percent	Pathologic Type	Percent
Osteosarcoma	40	Osteosarcoma	36
Fibrosarcoma	10	Cutaneous melanoma	12
Soft-tissue sarcoma	8	Primitive neuroectodermal tumor	9
Anaplastic and unclassifiable	8	Ewing sarcoma	6
Squamous cell carcinoma	5	Papillary thyroid carcinoma	6
Rhabdomyosarcoma	5	Assorted other	30
Assorted other	24		

## HIGH RISK RB

- Anterior chamber seeding
- Iris infiltration
- Ciliary body infiltration
- Massive choroidal infiltration
- Invasion of the optic nerve lamina cribrosa
- Retrolaminar optic nerve invasion
- Invasion of optic nerve transection
- Scleral infiltration
- Extrascleral extension