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RETINOBLASTOMA

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Retinoblastoma
Introduction

It is the most common primary intraocular malignancy of childhood which arises from primitive retinal cells

- **Incidence:**
  - 1 in 17000 live births
  - About 3% of all childhood cancers

- **No sexual or racial predisposition**

- **Mean age of diagnosis:**
  - known history: 4 months
  - bilateral disease 40% : 12 months
  - unilateral disease 60% : 24 months
  - 90% of cases : under 3 years of age

- **Trilateral RB** : bilateral RB with ectopic intracranial RB (usually pineal gland or parasellar region)
History

- Peter Pawius of Amsterdam provided the description of a tumor resembling RB. He described as “Substance similar to brain tissue mixed with thick blood and like crushed stone” in 1597.
- James Wardrop, a scottish surgeon first recommended enucleation for saving lives in patients of retinoblastoma in 1809.
- Verhoeff confirmed the origin from undifferentiated retinal cells, named retinoblastoma in 1900’s.
- American Ophthalmology Society first adopted the term retinoblastoma in 1926.
Pathology

• Histology:

Tumor composed of small basophilic cells (retinoblasts) with large hyperchromatic nuclei and scanty cytoplasm

- Many retinoblastomas are undifferentiated but differentiation are characterized by formation of rosettes, of which there are 3 types -
  a. Flexner–Wintersteiner rosettes
  b. Homer–Wright rosettes
  c. Fleurette, occasionally, photoreceptor differentiation of individual retinoblasts (fleurettes) are also seen
Flexner-Wintersteiner (FW) rosette with clear lumen at the center (H and E, ×400)
Homer Wright (HW) rosette with central tangle of neural filament. There is no clear lumen at the center
Fleurettes consist of small clusters of eosinophilic bulbous processes extending into lumen resembling photoreceptors
Growth Patterns

• Endophytic:
  - White to cream-colored mass breaks through internal limiting membrane
  - No surface vessels or small, irregular tumor vessels
  - Associated with vitreous seeding

Endophytic tumour with vitreous seeding
Growth Patterns

• **Exophytic:**
  - Yellow-white lesion in subretinal space
  - Overlying retinal vessels increased in caliber and tortuosity
  - Associated subretinal fluid and RD that can obscure the tumour

Exophytic tumour

May be difficult to visualize through deep detachment
Growth Patterns

- **Diffuse infiltrating:**
  - Flat infiltration of retina without discrete tumor mass
  - Conjunctival chemosis, pseudohypopopion, vitritis

- Large tumor can be both endophytic and exophytic

Intraretinal tumour

whole eye section shows a mixed endophytic (into the vitreous) and exophytic (into the subretinal space) growth pattern
Flow chart showing Routes of Spread

- **Direct local Tumor infiltration**
- **Subarachnoid Space Of optic nerve**
- **Anterior spread to Conjunctiva, Eyelids & Extra ocular tissue**
- **Hematogenous dissemination From orbital, bone or lymphatic invasion**

  - **Choroid invasion**
    - **Scleral invasion**
      - Orbital soft tissue, bone & brain invasion
  - **CSF dissemination To brain & spine**
  - **Lymphatic dissemination**
Genetics

- Malignant transformation of primitive retinal cells before final differentiation
- Mutational inactivation of both alleles of Retinoblastoma (RB1) gene on chromosome 13q14
  - Heretable (germline, autosomal dominant) 40%
    - 5-10% have a family history
    - 90-95% new germinal mutation
    - 85% bilateral, multiple tumors
    - 15% unilateral
- Non heretable (sporadic/somatic) 60%
  - unilateral, not transmissible
  - arise at somatic level in a single retinal cell
Clinical Features (Presentations)

• **Symptoms:**
  1. Child is brought to ophthalmologist with history of yellow/white reflex in pupillary area sometimes called cat’s eye
  2. Squint, usually convergent, at times divergent
  3. Cataract/ Bulging eye/ large eye

• **Signs:**
  1. Leukocoria (60%)
  2. Strabismus (20%)
  3. Secondary glaucoma
  4. Buphthalmos (large eye, corneal edema, blue sclera)
  5. Pseudohypopyon /ocular inflammation /Proptosis
  6. Mydriasis/ hyphema /dysmorphic appearance
Clinical Features (Presentations)

Unilateral leukocoria
Bilateral leukocoria
Secondary glaucoma and buphthalmos

Iris nodules and pseudohypopyon
Orbital inflammation
Orbital invasion
Clinical Stages

Divided into four stages:

1. **Quiescent stage.**
   - lasts for about 6 months to one year.
   - During this stage, child may presents with:
     1. *Leukocoria or yellowish-white pupillary reflex* (also called as *amaurotic cat’s eye appearance*)
        - commonest feature noticed in this stage
     2. *Squint*, usually convergent, may develop in some cases.
     3. *Nystagmus* is a rare feature, noticed in bilateral cases.
     4. *Defective vision*. Very rare
        - when the tumour arises late (3-5 years of age), the child may complain of defective vision
II. *Glaucmatous stage.*

- It develops when retinoblastoma is left untreated during the quiescent stage.
- This stage is characterised by severe pain, redness, and watering.

**Signs.**

- Eyeball is enlarged with apparent proptosis,
- conjunctiva is congested,
- cornea become hazy,
- *intraocular pressure is raised.*
- Occasionally, picture simulating severe, acute uveitis usually associated with pseudohypopyon and/or hyphaema may be the presenting mode (retinoblastoma masquerading as iridocyclitis)
III. *Stage of extraocular extension*.  
• Due to progressive enlargement of tumour, the globe bursts through the sclera, usually near the limbus or near the optic disc. It is followed by rapid fungation and involvement of extraocular tissues resulting in marked proptosis.

IV. *Stage of distant metastasis*.  
• Characterised by the involvement of distant structures:  
  1. *Lymphatic spread* first occurs in the preauricular and neighbouring lymph nodes.  
  2. *Direct extension* by continuity to the optic nerve and brain  
  3. *Metastasis by blood stream* involves cranial and other bones.  

Metastasis in other organs, usually the liver, is relatively rare.
Investigations

- Red reflex testing
- Examination under anesthesia
  - General examination
  - Tonometry
  - Measurement of corneal diameter, axial length of the eye
  - Examination with hand-held slit-lamp
  - Ophthalmoscopy, documenting findings with color drawing or photography
Investigations

- *Plain X-rays of orbit* may show calcification which occurs in 75 percent cases of retinoblastoma.
- *Lactic dehydrogenase (LDH) level* is raised in aqueous humour.
- *Ocular U/S (B-Scan)*
  - size of tumor, detects calcification
Investigations

- CT- may demonstrate a solid intraocular tumor with characteristic intratumoral calcifications

- Magnetic resonance imaging (MRI):
  - optic nerve involvement
  - the presence of an associated intracranial lesion → Tri-lateral RB
  - cannot detect calcification

- Systemic assessment
  - High-risk cases bone scans, bone marrow aspiration, lumbar puncture for CSF study
Staging/Classification system

- Two commonly used staging systems for retinoblastoma
  - the Reese-Ellsworth classification system
  - the International Classification of Retinoblastoma (ICRB) In
- the 1950's, the Reese-Ellsworth classification system was
  developed to predict the prognosis after treatment with radiation
- In the 1990s, Clinicians found the Reese-Ellsworth classification
  system no longer accurately reflect the prognosis with the newer
  treatment modalities and also increased risk of secondary tumors
  following radiation
- Thus, the International Classification of Retinoblastoma (ICRB) was
  developed to better predict the need for enucleation or external-
  beam radiation treatment
Reese-Ellsworth classification system

- **Group 1: Very Favorable**
  - a. Solitary tumor less than 4 DD in size, at or behind equator.
  - b. Multiple tumors, none over 4 DD in size, all at or behind equator.

- **Group 2: Favorable**
  - a. Solitary tumor, 4 to 10 DD in size, at or behind equator.
  - b. Multiple tumors, 4 to 10 DD in size, behind equator.

- **Group 3: Doubtful**
  - a. Any tumor anterior to equator.
  - b. Solitary tumor, larger than 10 DD, behind equator.

- **Group 4: Unfavorable**
  - a. Multiple tumors, some larger than 10 DD in size.
  - b. Any lesion extending anteriorly to the ora serrata.

- **Group 5: Very Unfavorable**
  - a. Massive tumor involving over half the retina.
  - b. Vitreous seeding
International Classification of Retinoblastoma (ICRB)

- **Group A**: Small intraretinal tumors (< 3mm) away from foveola and disc.
- **Group B**: Tumors > 3mm, macular or juxtapapillary location, or with subretinal fluid.
- **Group C**: Tumor with focal subretinal or vitreous seeding within 3mm of tumor.
- **Group D**: Tumor with diffuse subretinal or vitreous seeding > 3mm from tumor.
- **Group E**: Extensive retinoblastoma occupying >50% of the globe with or without neovascular glaucoma, hemorrhage, extension of tumor to optic nerve or anterior chamber.
Management
• Goals of treatment:
  - Save life
  - Preserve vision or salvage eye (i.e. avoid enucleation)
  - Minimize any complications or side effects of therapy
• Treatment options:
  - Enucleation & Exenteration
  - EBRTx.
  - Local therapies:
    - Plaque RTx.
    - Laser photocoagulation
    - Cryotherapy
    - Thermotherapy
  - Chemoreduction:
    - I.V.
    - Sub-Tenon
  - Chemotherapy
Treatment

- **Small Tumour** (<3mm wide x 2mm thick)
  - Laser photocoagulation
  - Transpupillary thermotherapy
  - Cryotherapy

- **Medium tumours** (12mm wide x 6mm thick)
  - Brachytherapy
  - Primary Chemotherapy (CEV) Carboplatin, Etoposide and Vincristine
  - External beam radiotherapy

- **Large tumours**
  - Chemotherapy followed by local treatment
  - Enucleation

- **Extraocular extension**
  - Adjuvant chemotherapy
  - External beam radiotherapy

- **Metastatic disease**
  - Chemotherapy
After radiotherapy or chemotherapy, tumours regress to a ‘cottage-cheese’ calcified mass, a translucent ‘fish-flesh’ mass, a mixture of both, or a flat atrophic scar.

Locally administered Carboplatin

Orbital implant (typically hydroxyapatite) is placed at the time of enucleation

Cross section of enucleated eye with optic nerve stamp
ENUCLEATION

• Surgical removal of the affected eye is an appropriate treatment option for many children with advanced unilateral sometimes in bilateral cases not amenable to any eye preserving therapy.

• If enucleation is performed, the ophthalmic surgeon should attempt to obtain a long section of the optic nerve, insertion of an orbital implant at the time of enucleation appears to be appropriate except when there is a strong likelihood of residual tumor in the orbit.

• The cosmetic results of enucleation are generally quite satisfactory as long as the child does not also undergo orbital radiation therapy.
Prognosis

- **Survival rates:**
  - 86-95% if localized intraocular disease
  - 60% if optic nerve involvement
  - 20% if tumor cells at surgical margins
  - 8 months if CNS involvement

- **Extraocular extension of tumor:**
  - most important risk factor for death

- **Secondary tumor development:** most common osteosarcoma
  - survival rate < 50%
  - without radiation: 26.5% within 50 years
  - with radiation
    - 10-20% within 20 years
    - 20-40% within 30 years
    - 58% by 50 years
Follow-up

- Recurrence usually occurs within 3 years.
- The risk period for extraocular spread after successful treatment is generally recognized to be 12 to 18 months.
- Ophthalmic examination needed:
  - First year: every 2-3 months
  - Second year: every 3-4 months
  - 3-5 years: every 6 months
  - > 5 years: every one year
- If treated conservatively EUA needed:
  - 2-8 weeks until the age of 3 years
  - then without anesthesia every 6 months up to 5 years
  - then yearly up to 10 years of age
Genetic counseling

- **Recommended for:**
  - Patients with family history of RB should undergo genetic counseling (blood sample only).
  - Parents having a child with RB (at the time of enucleation or during treatment).

- **Clinical Recommendation:** examination at birth & 4 monthly thereafter until 4 years of age

- **Sampling:**
  - in sporadic cases: tumor tissue & blood required
  - in inherited cases: only blood sample sufficient
Differential diagnosis

- Various conditions other than retinoblastoma, which present as leukocoria are collectively called as ‘pseudoglioma’.
  - Persistent anterior fetal vasculature (PHPV)
  - Persistent posterior fetal vasculature
  - Coats disease
  - Retinopathy of prematurity
  - Toxocariasis
  - Uveitis
  - Vitreoretinal dysplasia
    a. Norrie disease
    b. Incontinentia pigmenti
    c. Walker–Warburg syndrome
  - Other tumours
    a. Retinoma
    b. Retinal astrocytoma
Some pictures of DDs

Persistent anterior fetal vasculature (B) retrolental mass with inserted ciliary processes; (C) early involvement; (D) advanced case with cataract

Coats disease

Posterior pole toxocara granuloma

Vitreoretinal dysplasia

Retinoma

Persistent posterior fetal vasculature

Retinopathy of prematurity

Astrocytoma
Thank You