RETINOBLASTOMA: IMPORTANT UPDATE FOR PEDIATRICIANS

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RETINOBLASTOMA - TREATMENT PRINCIPLES:

1. PRESERVE LIFE
2. PRESERVE THE EYE
3. PRESERVE VISION
4. MINIMIZE SIDE EFFECTS OF TREATMENT IN VERY YOUNG PATIENTS

RETINOBLASTOMA - GENERAL

WHAT IS IT?

Most common eye (intraocular) tumor in children
Highly malignant tumor of immature retina
Rare: 6000 cases/year worldwide,

300 cases/year in US/Canada
Typically affects children under 5 years of age
Can be unilateral or bilateral

RB CLINICAL PRESENTATION

#1 presenting sign = leukocoria (60%) **late sign**
Red reflex screening is necessary prior to discharge from the nursery and at all well visits

#2 presenting sign = strabismus (20%) due to tumor growing in front of the macula with loss of vision **early sign**
Pediatricians play a crucial role in early identification

#3 presenting sign = inflammatory (20%) and worse prognosis

RED REFLEX NOT RED EYE

Red reflexes:

Red reflex screening is necessary prior to discharge from the nursery and at all well visits.
LEUKOCORIA DIFFERENTIAL DIAGNOSIS

- CATARACT
- COLOBOMA
- COATS DISEASE (40%)
- PERSISTENT FETAL VASCULATURE (PHPV OR PFV) (28%)
- RETINOPATHY OF PREMATURITY
- TOXOCARIASIS
- UVEITIS
- VITREORETINOPATHIES
  - FEVR (Familial Exudative VitreoRetinopathy)
  - NORRIE’S DISEASE (MALES)
  - INCONTINENTIA PIGMENTI (IP)
- RETINAL DETACHMENT (MANY ETIOLOGIES)
- ASTROCYTIC HAMARTOMA (TUBEROUS SCLEROSIS)
- RETINOPATHY OF PREMATURITY (ROP)
- RETROLENTAL FIBROPLASIA (RLF)
- VITREOUS HEMORRHAGE
- ENDOGENOUS ENDOPHTHALMITIS

LEUKOCORIA DIFFERENTIAL DIAGNOSIS: COATS DISEASE

PERSISTENT HYPERPLASTIC PRIMARY VITREOUS (PHPV)

FAMILIAL EXUDATIVE VITREORETINOPATHY (FEVR)

RETINOPATHY OF PREMATURITY (ROP)

RETINAL COLOBOMA & ASTROCYTIC HAMARTOMA (TUBEROUS SCLEROSIS)
RETINOBLASTOMA EPIDEMIOLOGY

- Incidence estimated at 1/15,000-20,000 live births
- 90% occur under age 5 years
- 4% of all childhood cancers < 15 years old
- No gender or race predilection
- No socioeconomic factors
- Hereditary and non-hereditary

HOW DOES HEREDITARY AFFECT THE CLINICAL PRESENTATION OF RETINOBLASTOMA?

- Hereditary form has germline mutation
  - Younger age (7 months) at presentation, bilateral, multi-focal, located posteriorly
- Sporadic form requires two postnatal mutations
  - Older age (24 months) at presentation, unilateral, unifocal, peripheral tumor

CLINICAL EVALUATION OF RETINOBLASTOMA

- Ophthalmic examination with fundus photographs
- MRI brain to rule out Trilateral Retinoblastoma (esp in bilateral cases)
- Avoid CT scan (minimize ionizing radiation exposure)
- Ultrasound to identify calcification if necessary
- If spread from eye => Bone marrow biopsy, Lumbar puncture, blood work

CLINICAL FINDINGS AND CLASSIFICATION

- Tumor growth pattern
  - Endophytic, exophytic, mixed, diffuse-infiltrating
- Duration of tumor presence
- Vascularization
- Calcifications
- Vitreous Seeding
- Retinal detachment
- Retinal hemorrhage

ENDOPHYTIC AND EXOPHYTIC GROWTH PATTERNS OF RETINOBLASTOMA

- Endophytic higher propensity for vitreous seeding
- Exophytic presents with RD, masking the underlying tumor mass

ENDOPHYTIC RETINOBLASTOMA

- Grows from retina into vitreous and spills tumor seeds into the vitreous
EXOPHYTIC RETINOBLASTOMA
Grows beneath the retina between the retina and the choroid (vascular bed between the sclera and the retina) can lead to subretinal seeds.

DIFFUSE INFILTRATIVE RETINOBLASTOMA
Spreads along retina to front of eye with tumor seeds spilling into the anterior chamber. Described in older age group, > 5 years old.

PATHOLOGY
Gross: White, fleshy, cottage cheese
Histopath: round, blue cells
Homer-Wright Rosettes: central neuropil
Pleomorphic Homer-Wright Rosettes: tumor center – ELM of retina
Well-differentiated Fleurettes: photoreceptor

REES - ELLSWORTH CLASSIFICATION - 1963
Group I: Very favorable for maintenance of site
A. Solitary tumor, smaller than 4 DD, at or behind equator
B. Multiple tumors, none larger than 4 DD, at or behind equator

Group II: Favorable for maintenance of sight
A. Solitary tumor, 4-10 DD, at or behind equator
B. Multiple tumors, 4-10 DD, at or behind equator

Group III: Possible for maintenance of sight
A. Any lesion anterior to equator
B. Solitary tumor, larger than 10 DD behind equator

Group IV: Unfavorable for maintenance of sight
A. Multiple tumors, some larger than 10 DD
B. Any lesion extending anterior to ora serrata

Group V: Very unfavorable for maintenance of sight
A. Massive tumors >1/2 of retina
B. Vitreous seeding

INTERNATIONAL CLASSIFICATION FOR INTRAOCULAR RETINOBLASTOMA (ICRB) - 2003
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
* 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 ¼ retina

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 vitreous disease may include "greasy" seeds or avascular tumor mass
* 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

ICRB GROUP A = SMALL TUMORS, AWAY FROM OPTIC DISC AND MACULA
RB CLINICAL PRESENTATION

#1 presenting sign = leukocoria (60%) **“later sign”**
Red reflex screening is necessary prior to discharge from the nursery and at all well visits.

#2 presenting sign = strabismus (20%) due to tumor growing in front of the macula with loss of vision **“early sign”**
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ICRB GROUP B – DISCRETE TUMOR CONFINED TO THE RETINA – NO SUBRETINAL SEEDING (ENDOPHYTIC PATTERN)

ICRB GROUP C = TUMOR <1/4 RETINA WITH LOCALIZED SEEDS, EXOPHYTIC (SUBRETINAL) TYPE

ICRB GROUP D

EXOPHYTEC

ENDOPHYTEC
RETINOBLASTOMA GENETICS
RB1 gene located on Chromosome 13q14.2 is the
main gene known to initiate retinoblastoma
RB1 was the 1st tumor suppressor gene identified
cloned in 1984 and subsequently sequenced
Lead to discovery of new class of anti-oncogenes
RB plays a central role in the cell cycle
- regulates exit from cell-cycle and apoptosis
uncontrolled cell division (cancer) caused by:
  - RB mutation or
  - RB inhibition by oncoproteins (SV40, Adenovirus,
and HPV)
  - BRCA2 (Ch 13), CDKN2 (p53/BRCA1) (TP53
cooperate with RB alterations)

THE EVOLVING GENETICS OF RETINOBLASTOMA
RB1 gene has two structurally related RB-like genes (RBL1, RBL2)
Localized to Chromosomes 20q11.2 and 16q12.2
RB may also arise from MYC mutation in absence of RB mutations
(tumors diagnosed at an earlier age than tumors w/ RB mutations)

RETINOBLASTOMA BIOLOGY
Pathophysiology of RB helped advance knowledge and management of solid tumors
in children
Although initially thought to result from “two-
hits”, now known that mutations of both alleles
of RB1 gene necessary in most cases but not
sufficient for phenotypic expression. A 3rd hit is
required for malignant tumor development.
RB can occur between the start of the 3rd
month postconception and 4 years of age
(final maturity of retinoblasts)
Germinat mutation in all cells predisposes to
other malignancies

RETINOBLASTOMA AND CANCER BIOLOGY
Rb1 tumor suppressor gene normally regulates cell growth
Mutation => non-functional protein => uncontrolled cell
division
RB1 encodes protein (pRB) => general cell cycle regulator
and central importance for p53-mediated tumor suppression
Deregulation of this pathway is common in most human
cancer
The genetics of RB is a rare exception in human cancer
Mutational inactivation of a single gene is necessary and
rate-limiting for RB cancer development

CLINICAL DISSEMINATION OF RETINOBLASTOMA
OCCURS IN 3 MAIN WAYS
- Anteriorly from Vitreous / Subretinal space => orbit /
lymphatics
- Posteriorly through Optic Nerve to Brain/CSF
- Externally / Hematogenously from the choroid to systemic
circulation

RISK FACTORS FOR DISSEMINATION:
Optic Nerve or Orbital Invasion
Massive Choroidal Invasion (> 3mm)
HIGH RISK CHARACTERISTICS OF RETINOBLASTOMA

- Older age at time of diagnosis
- Delay from time of diagnosis until enucleation
- Presence of Hyphema [pseudohypopyon]
- Staphyloma
- Orbital cellulitis
- Elevated intraocular pressure
- Trilateral Retinoblastoma (PNET)

HIGH RISK PATHOLOGIC FEATURES

- Choroidal involvement > 3 mm thickness
- Post-laminar optic nerve extension
- Scleral invasion
- Anterior chamber involvement (pseudohypopyon)

- Other high risk characteristics:
  - Large tumor burden (ICRB Group E)
  - Eyes that progress despite chemotherapy, etc. (highly differentiated tumors)

  Increases risk of extra-ocular relapse (orbit, brain, elsewhere)

CURRENT TREATMENT OPTIONS AND RECOMMENDATIONS

- Stage [ICRB] / Laterality / age:
  - Direct local treatment: laser / thermotherapy
  - Chemoreduction
  - Ophthalmic Artery Chemosurgery
  - Plaque radiotherapy
  - Enucleation
  - Intravitreal injection

RETINOBLASTOMA TREATMENT

- Enucleation first described for RB in 1809 by Wardrop (Scotland)
- Current survival rates enucleated eyes w/advanced RB:
  - Prelaminar ON > 90%
  - Laminar ON 85%
  - Postlaminar 60%
  - At surgical resection site 35%
  - Massive Choroidal invasion 70%

CONVENTIONAL MANAGEMENT OF RE GROUPS I-III, (HISTORICAL PERSPECTIVE: EBRT UNTIL 1990’S)

- Late ‘60s- ‘80s: salvage rate with EBRT = 78.5-83% for RE I-III
  - 1990’s report of 78.5% (RE I-III) / 80% (RE I-III)
- However:
  - 53% required additional focal treatment (laser / cryo)
  - 4% died from metastases
- Kaplan-Meier estimate of second malignancies: 32% at 15 years, 50% by 50 years
- Greatest risk of 2nd malignancy in child tx’ed EBRT < 1 year of age (higher death risk from 2nd cancer)
- Leiomyosarcomas, osteosarcomas in radiation field
- CONCERN RE: 2ND MALIGNANCIES PROMPTED SWITCH TO MULTI-SYSTEM CHEMOTHERAPY IN THE MID-1990’S (VCE: Vincristine, Carboplatin, Etoposide)

CURRENT TREATMENT RETINOBLASTOMA

- Advanced disease: enucleation (85-90% cure)
  - adjuvant chemo if posterior ON invasion or massive choroidal invasion
- Unilateral, early-stage (esp young child at risk for bilateral if hereditable) – eye salvaging approach
  - Bilateral (hereditable): 2 agent chemo (VCE) if ICRB Group B, 3 agent chemo if Group C/D
- failures: inability of drug to reach target (diffusion) or well-differentiated tumor not cycling
- Consolidation: ocular cryotherapy if small anterior
  - laser / thermotherapy posterior
  - brachytherapy (plaque) if large
- Recurrent / metastatic RB:
  - 40-70% local isolated orbital
  - 30-40% CNS or distant metastases
CURRENT TREATMENT RETINOBLASTOMA

Orbital disease at time of diagnosis:
- Chemoreduction, enucleation, orbital irradiation
- Preauricular and cervical lymph nodes assessed / irradiated

CNS involvement: platinum based chemotherapy, possible neuroaxis irradiation

Distant metastases: high dose chemotherapy, autologous stem cell rescue

CHEMOREDUCTION

ICRB GROUP D (Diffuse, large tumor with subretinal fluid and seeds)
- Pre Chemotherapy Above
- Post Chemotherapy Below

OPHTHALMIC ARTERY CHEMOSURGERY

- Introduced in US by Dr Abramson (Memorial Sloan Kettering) in 2007 for treatment of advanced intraocular retinoblastoma, with good initial success, treating ICRB B and C and RE I-III
- Used in 26 countries worldwide
- Reese (1950s) delivered intra-art Triethylene Melanamine (nitrogen mustard derivative) via direct carotid art puncture in order to lower dose of radiation by 50%
- Kaneko et al (Japan-1980s) used balloon catheter to occlude ICA past OA w/single agent Melphalan b/c of cultural challenge: families refused enucleation for unilateral RB (curative) for cultural reasons. Combined selective intra-art chemo with EBRT/hyperthermia/intravitreal injection of chemo and focal laser/cryo to save eye and were able to avoid enucleation in advanced eyes
- Super selective infusion by advancing a micro-catheter into the orifice of the ophthalmic artery – initial report 7/9 eyes scheduled for enucleation were saved
- Multiple reports for advanced eyes (RE IV-V) treated (NYC, Phila, Miami, Switzerland)
- Systemic toxicity limited (asx Grade 3 neutropenia)

PRE AND POST OPHTHALMIC ARTERY CHEMOSURGERY

IAC COMPLICATIONS

- Eyelid erythema and edema
- Emboli to retina or choroid => occlusive vasculopathy
- Vitreous hemorrhage
- Cerebral vasoconstriction

Systemic chemo may protect against trilateral RB
OTHER RECENT TREATMENT DEVELOPMENTS

Intravitreal chemotherapy

Techniques to prevent spread outside eye

ETIOLOGIES OF RB TREATMENT FAILURES

Chemo drugs fail to reach target:
- Persistence of Vitreous seeds (avascular)
- Persistence of Subretinal seeds
- Intraretinal tumor
- Highly differentiated tumor unresponsive to tumor - not dividing rapidly

SURVIVAL RATES OF RETINOBLASTOMA

Classes A through C: >90%
Class D - poorer
Invasion of Optic Nerve = Systemic chemotherapy >95% survival approx. 20% of eyes enucleated have high risk characteristics

NOVEL TREATMENTS ON HORIZON

Gene therapy (targeted killing):
- Intravitreal injection of adenovirus vector w/HSV thymidine kinase gene followed by IV ganciclovir
- Sustained drug release platforms – episcleral exoplant
- Nanoparticles: periocular injection sustained release nanoparticles w/carboplatin

PARENT RESOURCES

Childhood Eye Cancer Trust
The Retinoblastoma Online Support Group
Retinoblastoma Survivors Support Group
EyeCancer.com
AAPOS.org (FAQ on Retinoblastoma)

THANK YOU!

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Red reflexes:

GENETIC TESTING IN RETINOBLASTOMA
Melissa Samons, MS, CGC
Division of Genetics

HERITABLE AND NONHERITABLE RETINOBLASTOMA

<table>
<thead>
<tr>
<th>Tumor Presentation</th>
<th>Mutation</th>
<th>Family History</th>
<th>Probability of Germline RB1 Mutation</th>
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<td>Bilateral</td>
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<td>Negative</td>
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<tr>
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<td>X</td>
<td>Negative</td>
<td>14.93%</td>
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<tr>
<td>Multifocal</td>
<td>X</td>
<td>Positive</td>
<td>100%</td>
</tr>
<tr>
<td>Unifocal</td>
<td>X</td>
<td>Positive</td>
<td>100%</td>
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RB1 MUTATION TYPES

- Single-base substitutions, small intragenic deletions, insertions (70-75%)
- Large deletions
- Whole gene deletions
- Large insertions
- Hypermethylation of the promoter region
- Deep intronic splice mutations
- Chromosomal rearrangements
GENETIC TESTING COORDINATION

- Laboratory selection
- NYS approval
- Patient insurance
- Sample type
- Cost
- Turnaround time
- Informed consent
- Benefits and limitations
- Detection rate
- Post-test sample use
- Risks to other family members

RECURRENCE RISK FOR RETINOBLASTOMA WHEN NO GERMLINE RB1 MUTATION IS IDENTIFIED

<table>
<thead>
<tr>
<th>Tumor Presentation in Index Case</th>
<th>Family History</th>
<th>Risk to Sibs of an Index Case</th>
<th>Risk to Offspring of an Index Case</th>
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<tbody>
<tr>
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<td>50%</td>
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<tr>
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