Retinoblastoma

A Detailed Study of Tumor Suppressor Gene

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Edited by **Fergus Pearson**

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Preface

This book has been an outcome of determined endeavour from a group of educationists in the field. The primary objective was to involve a broad spectrum of professionals from diverse cultural background involved in the field for developing new researches. The book not only targets students but also scholars pursuing higher research for further enhancement of the theoretical and practical applications of the subject.

Retinoblastoma is described as a rare malignant tumor of the retina, generally affecting young children. The first gene discovered to have the capability of curbing tumor was Retinoblastoma. This breakthrough led to the rise of a new opportunity in the sphere of oncology, resulting in the detection of 35 tumor suppressor genes in the human genome. This text is an extensive collection of basic and advanced data which can cater to budding clinicians and experts simultaneously. Substantial amount of information on latest progress and state-of-the-art knowledge in intracellular molecular cross-talking of retinoblastoma protein with various cellular viral-like proteins has also been provided in this book.

It was an honour to edit such a profound book and also a challenging task to compile and examine all the relevant data for accuracy and originality. I wish to acknowledge the efforts of the contributors for submitting such brilliant and diverse chapters in the field and for endlessly working for the completion of the book. Last, but not the least; I thank my family for being a constant source of support in all my research endeavours.

Editor

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Part 1

Clinical Sciences

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Review of Clinical Presentations of Retinoblastoma

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1. Introduction

A retinoblastoma is a neuroblastoma. It is a rare eye tumor of childhood that arises in the retina and represents the most common intraocular malignancy of infancy and childhood -**1**. It may occur at any age-**2**, but most often it occurs in younger children, usually before the age of two years. Most affected children are diagnosed before the age of five years-**1,3**. Intraocular tumours may exhibit a variety of growth patterns and is commonly seen in advanced countries. Extraocular retinoblastoma is common in developing countries because of delay in diagnosis.-**4,5**.

In 60% of cases, the disease is unilateral (non hereditary) and the median age at diagnosis is two years. Retinoblastoma is bilateral (hereditary) in about 40% of cases with a median age at diagnosis of one year-**1**. Trilateral retinoblastoma is rare and refers to bilateral or unilateral retinoblastoma associated with an intracranial primitive neuroectodermal tumor in the pineal or suprasellar region-**6**. The median time interval from diagnosis of retinoblastoma to the development of a pineal region tumor was 24 months whereas the median time interval for the development of a suprasellar region tumor was 1 month-**6.** Untreated, retinoblastoma is fatal. In the developing countries, retinoblastoma presents with advanced disease with resultant 5 year survival of less than 50%-**7** whereas patients present with intraocular disease in the developed countries due to availability of resources for early detection and treatment. The survival rate in these nations has improved from approximately 30% in the 1930s to over 90% in the 1990s -**8,9.** In the middle income countries, the survival rate is about 70% -**10.** Retinoblastoma occurs equally in males and females and there is no predilection for any race or any particular eye-**11**.

2. What are the common symptoms of retinoblastoma

a. Leucocoria (white papillary reflex or cat's eye) is the most common accounting for about 60%- 80% of cases.-**1,4,5**. This is the most common type of presentation where there is high level of awareness such as in high income countries
b. Strabismus occurs in about 20% of cases-**1,4**
c. Orbital inflammation is seen in cases of tumour necrosis-**4**
d. Proptosis follows orbital invasion. Secondary microbial infections are often present. This is a common type of presentation in most developing nations-**12** due mainly to socioeconomic and cultural limitations resulting in delayed presentation -**10**

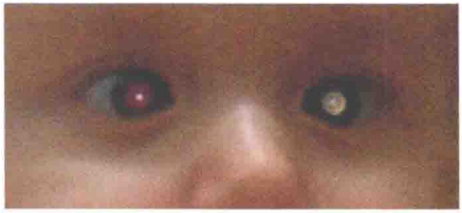

Fig. 1. Left leucocoria in a child with retinoblastoma. Courtesy. Wikipedia

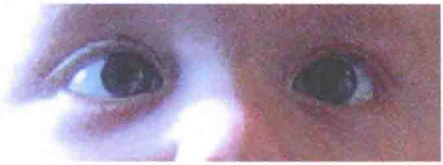

Fig. 2. Crossed eye in a child with retinoblastoma. Courtesy. Wikipedia

Fig. 3. Courtesy. www.arquivosdamorte.com

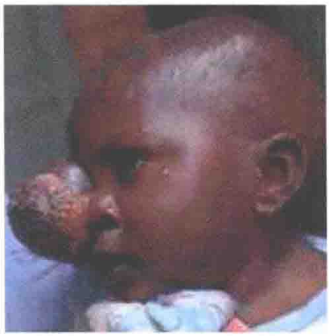

Fig. 4. Courtesy. projectmedishare.wordpress

Advanced extra ocular retinoblastoma in African and South American children above

e. Metastatic spread involves the brain/central nervous system, bones (especially skull bones and long bones), liver, spleen, Lymph nodes etc. This is worse in undeveloped economies due to late presentation and paucity of means of diagnosis -(**-1,4,5,12**)

f. Decrease in visual acuity-**12**

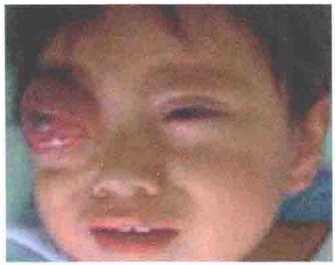

Fig. 5. Courtesy. inctr.ctisinc.com.

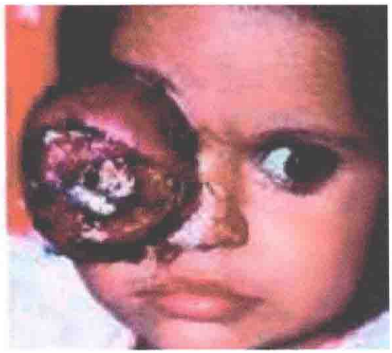

Fig. 6. Courtesy. www.jornallivre.com.br

3. What are the common signs of retinoblastoma

The clinical signs-**5,12** vary with the stage of the tumour at the time of presentation.

a. Early intraretinal tumour is a flat lesion which appears transparent or translucent. This type is commonly seen in high income countries where increase in awareness and early presentation are the norms
b. Endophytic tumour projects from retinal surface toward the vitreous as a friable mass, frequently associated with fine blood vessels on its surface-**4**. The tumour resembles cottage cheese if calcified. Vitreous seeding may be present

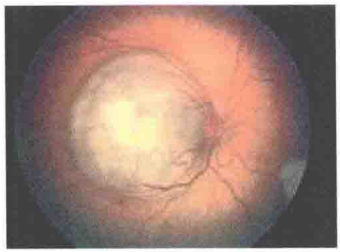

Fig. 7. Endophytic tumour. Courtesy. www.retinoblastomainfo.com

c. Exophytic tumour. This grows from the retina outward into the subretinal space with progressive retinal detachment. It may become a multilobulated mass with overlying retinal detachment. As the orbital structures are invaded, proptosis increases. Sometimes the grossly detached retina may be visible just behind the clear lens. Presence of vitreous hemorrhage may make the fundus hazy. Clinically, they may resemble coats disease

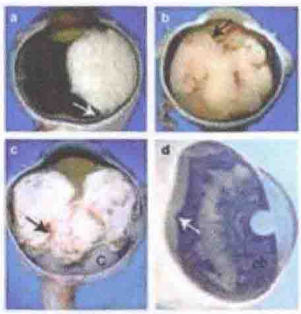

Fig. 8. Fundus pictures of Retinoblastoma. Courtesy. journals.cambridge.org

Fig. 9. Large exophytic retinoblastoma with calcification producing exudative retinal detachment. Courtesy. Wikimedia commons

d. Occasionally, a retinoblastoma can assume a diffuse infiltrating feature characterized by a relatively flat infiltration of the retina by tumour cells without an obvious mass. In such cases, diagnosis may be more difficult and this pattern can simulate uveitis or endophthalmitis

4. Less frequent signs of clinical presentations

a. Secondary glaucoma with or without buphthalmos-**4,13**. This is rare. Pain may be a feature
b. Anterior segment invasion-**4, 13.** Multifocal iris invasion may be associated with hyphema and iris neovascularization; painful red eye with pseudohypopyon due to tumour seeding into the anterior chamber. This is mostly unilateral involvement with no family history.-**4**
c. Associated conditions. 13q deletion syndrome has retinoblastoma, dysmorphic features, mental retardation which may be associated in some patients-**1**

5. Differential diagnosis of retinoblastoma

Some patients diagnosed initially with possible retinoblastoma prove, on referral to ocular oncologists and radiologists, to have pseudoretinoblastoma-**4,5,13** and not retinoblastoma The more frequently encountered being

Persistent hyperplastic primary vitreous
Coats disease
Ocular toxocariasis
Others include:
Preseptal or orbital cellulitis in extraocular spread
Cataract
Retinopathy of prematurity
Uveitis
Myelinated nerve fibre, optic nerve glioma, medulloepithelioma
Organizing vitreous hemorrhage
High myopia
High anisometropia
Retinal detachment

6. Classifications of retinoblastoma (Rb)

Several classifications of retinoblastoma have been developed to assist in prediction of globe salvage with preservation of useful vision where possible. There are two classifications for intraocular retinoblastoma currently in use.

1. Reese-Ellsworth classification. Originally used to predict visual prognosis of affected eyes and globe salvage after external beam radiotherapy. It is still useful to compare newer treatment modalities with older ones-**5**

Reese-Ellsworth classification of Retinoblastoma

Group i. Favorable

a. Solitary tumour less than 4 disc diameter in size at or behind the equator
b. Multiple tumours, all less than 4 disc diameters in size all at or behind the equator.

Group ii. Favorable

a. Solitary tumour, 4 to 10 disc diameters in size at or behind the equator
b. Multiple tumours , 4 to 10 disc diameters in size behind the equator

Group iii. Doubtful

a. Any lesion anterior to the equator
b. Solitary tumours larger than 10 disc diameters behind the equator

Group iv. Unfavorable

a. Multiple tumours, some larger than 10 disc diameters
b. Any lesion extending to the anterior ora serrata

Group v. Very Unfavorable

a. Massive seeding involving over half of retina
b. Vitreous seeding

2. ABC classification of retinoblstoma-**5**

To predict the preservation of the eye using all modern therapeutic methods

Group A. Small tumours <3mm (about 0.1 inch) confined to the retina
Group B. Larger tumours confined to the retina
Group C. Localized seeding of the vitreous or under the retina <6.00mm (0.2inch) from the original tumour
Group D. Widespread vitreous or sub retinal seeding which may have total retinal detachment
Group E. No visual potential, eye cannot recover

Others

3. Philadelphia Practical Grouping System of Retinoblastoma Based on Clinical Features.-**14**

To quantify retinoblastoma and its associated features without need to refer to complex qualification criteria. Proceeding from the lowest to the highest grouping is meant to imply worse ocular prognosis. This is a simpler and newer classification to Reese-Ellsworth.

Group	Abbreviations	Features	success*
1.	T	Tumour only#	100%
2.	T+SRF	Tumour + subretinal fluid	91%
3.	T + FS	Tumour +focal seeds SRS ≤ 3mm from tumor VS ≤ 3mm from tumor	59%
4.	T +DS	Tumour +diffuse seeds SRS >3mm from tumor VS > 3mm from tumor	12%
5.	High Risk	Tumor plus(any one) a. Neovascular glaucoma b. Opaque media from hemorrhage c. Invasion of post laminar optic nerve, choroid (<2mm), sclera, orbit or anterior chamber.	NA

*success after treatment with systemic chemotherapy with or without local consolidation is defined as avoidance of enucleation or need for external beam radiotherapy.
# Regardless of tumour number, size or location
DS=Diffuse seeds, FS=Focal seeds, SRF=Sub retinal fluid, SRS=Sub retinal seeds, T= Tumour, VS=Vitreous seeds, NA= Not applicable because these patients had primary enucleation.

4. International retinoblastoma classification

It is useful in guiding the selection of the most appropriate treatment methods and predicting chemo reduction success.-**15,16**