ABSTRACT

Introduction: Retinoblastoma is a devastating autosomal dominant genetic disease usually seen in children. It causes tumors of the retina which can lead to severe visual impairments and in some cases death.

Body: A defective or absent pRB protein, from a mutated or deleted RB1 gene, causes genomic instability and allows retinoblasts to undergo rapid mitosis. This can lead to the formation of tumors within the retina. As retinoblastoma usually affects infants and young children, they may not notice any changes in their vision or ocular discomfort. The most commonly observed sign of retinoblastoma is leukocoria, caused by the light colored tumor within the eye. There are many treatment options available, some of which include chemotherapy, enucleation, external beam radiation, and radioactive plaques. If caught early, the prognosis is usually very good in the United States. Unfortunately, in second and third world countries the outlook can be significantly worse.

Discussion: Retinoblastoma is a complex disease which can have severe health impacts and endanger the life of the afflicted child. Although this disease is rare, it is the most common primary ocular malignancy in children. Retinoblastoma is caused by a disruption of the RB1 gene. Research has led to the triple hit hypothesis that three mutations are required for retinoblastoma formation. Tumors often appear early as translucent thickenings of the retina and evolve into dome-shaped, white, vascularized masses. The most common treatments include chemotherapy, radiation and enucleation. Early detection is best accomplished when young children receive comprehensive eye examinations. Catching the disease before it metastasizes greatly improves a child's chance of survival. Early diagnosis and subsequent treatment could ultimately save a child's vision or even his or her life.

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Keywords: Retinoblastoma, RB1, pRB, malignancy, tumor, cancer
INTRODUCTION

Retinoblastoma is the most common primary intraocular malignancy in children, and can have devastating effects on a child's vision and health.\(^1,2\) It is an autosomal dominant cancer of the retina which typically develops in children under the age of five or six.\(^1,3\) In the case of retinoblastoma, autosomal dominance does not guarantee that the affected person will develop retinoblastoma; it only indicates an increased risk.\(^3\) It is caused by mutations or deletions of the \(RB1\) gene, located on chromosome 13.\(^3,4\) Retinoblastoma is typically unilateral with a hallmark sign of leukocoria, noted in the affected eye.\(^1,3\) If caught early, especially before it metastasizes, the prognosis for patients can be very good, but if not, the patient's life may be at risk. This review is intended to inform the reader of the scientific and clinical aspects of retinoblastoma.

Epidemiology

Retinoblastoma affects approximately 1 in 15,000 to 20,000 people.\(^1,2,3\) In the United States, 250-350 children are diagnosed with retinoblastoma each year.\(^5\) It is responsible for approximately 11% of all cancers during the first year of life, and 4% of cancers during the first 15 years of life.\(^5,6\) After 6 years of age, its incidence is extremely low, peaking during the first few months of life. It is normally diagnosed around 12 months of age in children who have bilateral retinoblastoma, compared to 24 months for children with unilateral cases.\(^1\) The survival rate in the United States is very high, nearing 100%.\(^2,7\) Unfortunately, the prognosis in second and third world countries is not nearly as good, which is likely associated with lack of detection and poor access to medical care. The survival rate is 81% in China, 48% in India, and as low as 20-46% in Africa. Worldwide, it is estimated that 3,000-4,000 deaths occur annually due to retinoblastoma.\(^2\) There is no known racial or gender predilection.\(^1,7\)

Genetics & Pathogenesis

The tumor suppressor gene associated with retinoblastoma, \(RB1\), is located on 13q14.2, meaning that it is found on the q (long) arm of chromosome 13, in band number 14, and within sub band 2.\(^1,3,5\) The \(RB1\) gene codes for the protein pRB, a nuclear protein, which is important for regulating cellular growth.\(^4,8\) The pRB protein normally binds to the E2F transcription factor complex, inactivating it, and thus prevents the movement of the cell from the G1 phase to the S phase of mitosis. Recent studies also suggest that pRB has roles in controlling cellular differentiation, regulating apoptosis, sustaining cell cycle arrest, and chromatin remodeling.\(^8\) The inactivation of the \(RB1\) gene is also seen in some other forms of second cancers.\(^3\) Typically, retinoblastoma is caused by a biallelic loss of function or deletion of \(RB1\) leading to genomic instability.\(^3,4\) Studies have demonstrated that at minimum a third mutation in a separate gene is required, beyond the biallelic mutations of the \(RB1\) gene, in order for retinoblastoma tumors to form. This third hit can occur in another a tumor suppressor gene or oncogene, such as \(MYCN\) (2p24.3), \(E2F3\) and \(DEK\) (6p22), \(CDH11\) (16q21), or \(p75NTR\) (17q21) and potentially allow for the transformation of retinomas to malignant retinoblastoma tumors.\(^4\) The genomic instability from the defect in \(RB1\) can also lead to problems in other genes, such as the ones listed above. Affecting other genes can help enable tumor growth within the eye and other tissues throughout the body.

The vast majority of the human genome is identical from person-to-person. However, differences exist in the parts of deoxyribonucleic acid (DNA) encoding for genes. The differences in DNA bases are known as single nucleotide polymorphisms (SNPs). Human somatic cells are normally diploid, meaning that they have two copies of each chromosome. SNPs permit cells to have different nucleotide bases within each chromosome allowing for heterozygosity, or having different copies of genes, as opposed to being homozygous. Deletion or inactivation
of the *RB1* gene, as seen in the case of retinoblastoma, is termed loss of heterozygosity (LOH), since there is only one functional *RB1* gene remaining.4 People who have LOH are at a much higher risk for developing retinoblastoma as it may only take one mutation to occur in the remaining RB1 gene within a retinoblast to begin the formation of a retinoblastoma.

Alfred Knundson proposed the two-hit theory of retinoblastoma carcinogenesis in 1971. His theory states that a cell needs to have two damaged alleles in order for a tumor to form. There are two forms of retinoblastoma based off of this model, inherited (familial) or sporadic. The first hit, or mutation, of inherited retinoblastoma is acquired from the germ cell of a parent. Thus, all the cells of the child would have one normal and one altered *RB1* gene. Due to this LOH, the developing fetus requires only a single mutational event in one of its retinoblasts in order to initiate a tumor.9 As these individuals have a defective *RB1* gene throughout all of their cells, they are also more prone to other second cancers such as osteosarcoma, melanoma, and various soft tissue cancers, depending on which gene(s) the third or any additional hits affect.3,5 Although very rare, trilateral retinoblastoma can occur when there is a pinealblastoma associated with bilateral ocular retinoblastoma.1,3 This is thought to occur because certain retinal and pineal gland tissues are similar.3 The trilateral form has a much higher mortality rate, accounting for over half of all retinoblastoma deaths during the first decade of life.7

Sporadic retinoblastoma is when the germ cell from each parent has a normal, functional *RB1* gene, but two somatic mutations occur in the *RB1* genes during fetal development, also known as Knudson’s two-hit theory. A distinguishing factor between the two is that inherited retinoblastoma is frequently bilateral as all cells are more prone to acquiring the 2nd hit needed to form retinoblastoma, whereas the sporadic variety is usually unilateral.9 Approximately 60-70% of retinoblastoma cases are unilateral, with the remaining 30-40% being bilateral.1

**Signs & Symptoms**

The hallmark sign of retinoblastoma is leukocoria, defined as a white reflex in the pupil.1,3 This is caused by the reflection of light off the yellow-white colored retinoblastoma tumor.1,10 The second most common sign of retinoblastoma is strabismus, which can manifest as either exotropia or esotropia.1 Strabismus is most likely caused by macular compromise so proper binocular fixation cannot be maintained in the affected eye. Other ocular signs of retinoblastoma include red eye, excessive tearing, buphthalmos, and corneal clouding.1 Iris discoloration from neovascularization, loss of fundus reflection secondary to intraocular bleeding of the tumor, clumping of white tumor cells on the iris or in the aqueous humor, hyphema, glaucoma, and sterile orbital cellulitis may also be observed.1,3 Symptoms may consist of ocular pain, redness, irritation, and decreased visual acuity.5 Young children are most often affected by retinoblastoma and may be less likely to notice or report any ocular discomfort or blurred vision.

Figure 1 shows a photograph of typical large retinoblastoma. Tumors associated with retinoblastoma vary greatly in appearance. Discrete intraretinal tumors appear as white, dome shaped masses with blood vessels growing towards them. Small tumors often appear as translucent thickenings of the retina.1 Exophytic (growing outward towards the retinal pigment epithelium) retinoblastoma tumors are typically larger, and are associated with rhegmatogenous retinal detachments.1,10 On the other hand, endophytic (growing towards the vitreous) tumors are usually smaller, and their cells may accumulate in the vitreous.1 Occasionally, some tumors may have a mixed endophytic-exophytic growth pattern. Diffuse infiltrating retinoblastoma is a rare form which occurs when the tumor grows horizontally within the retina, as opposed to growing vertically as seen
in endophytic and exophytic growth patterns. It often appears as a thickening of the retina and may be mistaken for uveitis, endophthalmitis, or vitreous hemorrhage. Endophytic and infiltrating retinoblastoma tumors are associated with vitreous seeding. Vitreous seeding occurs when tumor cells break off and float freely in the vitreous. Seeding can make treatment much more challenging because in addition to targeting the main tumor in the retina, each cluster of cells in the vitreous must be targeted. These clusters can deposit elsewhere on the retina and start additional tumors. Vitrectomy has not been shown to be an effective treatment for untreated retinoblastoma with vitreous seeding and is generally not recommended, as the openings made in the globe to perform a vitrectomy may help enable tumor cells to spread into the orbit.

**DIAGNOSIS**

There are a variety of methods used to help diagnose retinoblastoma. The tumors can be imaged well by ultrasonography, as most large tumors have intralesional calcification making them highly reflective. Also due to calcification, retinoblastoma tumors can be imaged via computed tomography. Magnetic resonance imaging is the best method of examining the patient’s sellar and parasellar regions of the brain to check for trilateral retinoblastoma. It is also useful for studying the soft tissues of the orbit and optic nerve to check for extraocular spread of a tumor. Fluorescein angiography is typically not used as a diagnostic tool, but if it is performed on a discrete intraretinal retinoblastoma, the angiogram would reveal fast filling of the feeder artery, swift filling of the intralesional vessels, and then quick draining by the efferent vein.

**MANAGEMENT**

The most important treatment goal of retinoblastoma is to save the child’s life. The next step is to save as much of the child’s vision as possible. If detected early the prognosis is usually very good. If left untreated, children usually die within 2-4 years from the onset of symptoms.

Various methods are used to classify retinoblastoma. Historically, the Reese-Ellsworth staging system was utilized. This system divided retinoblastoma into 5 groups depending on the size, location, and number of tumors. It was used to predict the outcome of eyes treated with external beam radiation. Mainly due to the increased use of chemotherapy for treatment, the most common staging system currently utilized is the International Classification for Intraocular Retinoblastoma. It divides intraocular retinoblastomas into 5 groups, A through E, with A describing the eye that is likely to be preserved and E describing an eye which is very unlikely to be preserved. This system places a greater emphasis on the presence of vitreous seeding and less on tumor size and location compared to the Reese-Ellsworth system. Table 1 describes the International Classification for Intraocular Retinoblastoma system.

The treatment modalities used for retinoblastoma depend on numerous factors, including size and location of the tumor, whether it is bilateral or unilateral, vision/potential vision in the affected eye, associated problems from the

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**Figure 1:** A photograph showing a large retinoblastoma in the posterior pole. Picture courtesy of Aerts et al. Retinoblastoma. Orphanet Journal of Rare Diseases 2006 1:31.
tumor, and the age and systemic health of the patient. Systemic chemotherapy is the main treatment performed on children with bilateral retinoblastoma and is often the first treatment for unilateral retinoblastoma if the eye may be saved.\textsuperscript{1} It is usually dosed with a combination of carboplatin, etoposide, and vincristine.\textsuperscript{1,11} Chemotherapy is often performed in several rounds over weeks to months.\textsuperscript{1} Enucleation may be performed in advanced cases, usually when the eye is not able to be preserved, such as in grade E retinoblastoma. During enucleation, a minimum of 5mm of the optic nerve should be removed since it is the main route for tumor cells to exit the eye. External beam radiation is a very effective method of causing regression in vascularized retinal tumors, but with the advent of chemotherapy it is not used as often as it was in the past.\textsuperscript{1} This is due to the fact that it can induce cataract formation, cause orbital bone growth arrest and consequent facial deformities in children under the age of one, and the tumor could still recur.\textsuperscript{1,11} Plaque radiation therapy is another option for retinoblastoma treatment. This describes a radioactive device (plaque) that is placed on the sclera overlying the intraocular tumor, and then removed after a certain period of time, to provide a specific amount of radiation.\textsuperscript{1} This method is limited to more localized retinoblastomas, since the treatment is very confined to the area near the plaque.\textsuperscript{11} Laser photocoagulation and thermotherapy are typically used to treat small tumors, or in conjunction with other treatment options.\textsuperscript{1,2,14} Observation without treatment can be performed in select situations, such as if the tumor spontaneously arrests and become dormant.\textsuperscript{1} Pre-malignant retinoblastoma tumors, known as retinomas, should also be carefully monitored throughout the patient’s life so that any signs of activation can be detected quickly.\textsuperscript{1,3} Signs of activation may include morphing in the size or shape of the tumor.

Fortunately, the survival rate for retinoblastoma in the United States is very high at around 96.5%.\textsuperscript{7} Treatment is often a multidisciplinary effort between primary eye care providers and specialists in various fields, such as pediatric oncology, pathology, and radiation oncology.\textsuperscript{3} Genetic testing may also be recommended to determine whether it was inherited or a sporadic genetic event. Later in life, genetic counseling may help the teenager or adult evaluate the risk of passing retinoblastoma on to his or her children.

**DIFFERENTIAL DIAGNOSES**

There are many possible differential diagnoses for retinoblastoma based on the clinical signs. The most common disorder mistaken

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<thead>
<tr>
<th>Group A – Very Low Risk</th>
<th>Tumors 3 mm or smaller</th>
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<td>Eyes with small discrete tumors not threatening vision</td>
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<tr>
<th>Group B – Low Risk</th>
<th>Tumor greater than 3 mm in size</th>
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<tr>
<td>Eyes with no vitreous or subretinal seeding</td>
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<tr>
<th>Group C – Moderate Risk</th>
<th>Vitreous or subretinal seeding within 3 mm of the tumor</th>
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<tr>
<td>Eyes with focal vitreous or subretinal seeding of any size or location</td>
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<tr>
<th>Group D – High Risk</th>
<th>Vitreous or subretinal seeding greater than 3 mm from the tumor</th>
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<tr>
<td>Eyes with diffuse vitreous or subretinal seeding</td>
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<tr>
<th>Group E – Extremely High Risk</th>
<th>Tumor occupying over 50% of globe</th>
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<tr>
<td>Eyes destroyed by the tumor with one or more of the following:</td>
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The description for the various stages of retinoblastoma from the International Intraocular Retinoblastoma Classification system.\textsuperscript{13}

**Table 1:**

**International Intraocular Retinoblastoma Classification**

- **Group A – Very Low Risk**
  - Eyes with small discrete tumors not threatening vision
  - Tumors 3 mm or smaller

- **Group B – Low Risk**
  - Eyes with no vitreous or subretinal seeding
  - Tumor greater than 3 mm in size
  - Tumor within 3 mm of the foveola
  - Tumor within 1.5 mm of the optic disc
  - Subretinal fluid less than 3 mm of the base of the tumor

- **Group C – Moderate Risk**
  - Eyes with focal vitreous or subretinal seeding of any size or location
  - Vitreous or subretinal seeding within 3 mm of the tumor

- **Group D – High Risk**
  - Eyes with diffuse vitreous or subretinal seeding
  - Vitreous or subretinal seeding greater than 3 mm from the tumor

- **Group E – Extremely High Risk**
  - Eyes destroyed by the tumor with one or more of the following:
    - Tumor occupying over 50% of globe
    - Neovascular glaucoma
    - Opaque media from hemorrhage in the anterior chamber, vitreous, or subretinal space
    - Invasion of postlaminar optic nerve, choroid, sclera, orbit, or anterior chamber

The description for the various stages of retinoblastoma from the International Intraocular Retinoblastoma Classification system.\textsuperscript{13}
for retinoblastoma is Coat’s disease, which can also present with leukocoria.¹ Coat’s disease is a condition in which faulty blood vessels leak in the retina allowing lipids to accumulate, forming lesions similar to that of retinoblastoma. Other differentials of leukocoria include persistent hyperplastic primary vitreous, ocular toxocariasis, cicatricial retinopathy of prematurity, familial exudative vitreoretinopathy, incontinentia pigmenti retinopathy, and Norrie’s disease. Intermediate uveitis, microbial endophthalmitis or retinitis, and leukemic infiltration are all possible differential diagnoses of vitreous seeds. Some differential diagnoses of discrete retinal tumors include astrocytoma of retina, medulloepithelioma, retinal capillary hemangioma, and areas of myelinated retinal nerve fibers.¹

DISCUSSION

Retinoblastoma is the most common intraocular malignancy of childhood. It is a devastating disease with severe visual impacts and even the possibility of death. Having a basic understanding of the genetics and pathophysiology ultimately leads to better care for the patient as appropriate referrals can be made to specialists for treatment, and to be examined for second cancers associated with retinoblastoma. Providers should be able to discuss the genetics of the disease, allowing parents to better understand retinoblastoma and potentially help determine if other family members may be at risk as well.

Since young children do not usually notice problems with their eyes, dilated eye exams should be performed on a regular basis to catch any problems early. While vision screenings may be effective at catching advanced cases of retinoblastoma, screenings lacking red reflex testing or internal examination and may miss the disease. All children who have an immediate family history of retinoblastoma should also have an eye examination shortly after birth, and at regular intervals thereafter. The trademark sign of retinoblastoma is leukocoria. Other diseases may also present with leukocoria in children, but regardless of the cause, leukocoria warrants a swift, complete, dilated eye examination. With early detection, a child’s prognosis for survival is usually very good. Many treatment modalities are available, and numerous factors need to be taken into consideration when choosing an appropriate treatment plan. Fortunately, the survival rate in the United States is very high. Pediatric eye exams need to be stressed so diseases such as retinoblastoma and other conditions can be identified early. The InfantSEE® program, created by the American Optometric Association (AOA), is an excellent start to educating the public on the importance of comprehensive eye exams for infants and children. This public health program provides complimentary exams to children between 6 and 12 months of age by a participating provider. The AOA recommends children without high risk factors to be examined at 6 months, 3 years, before the first grade, and every 2 years thereafter.¹⁵ Optometrists and ophthalmologists play a key role in the detection of retinoblastoma through comprehensive eye exams and collaboration with other specialists for its treatment and management. It is critical that eye care professionals have a thorough understanding of the clinical signs and symptoms of retinoblastoma, particularly in its early stages. Thorough knowledge of the genetics and treatment options for the disease are critical when educating parents stunned by their child’s diagnosis.

REFERENCES


