Retinoblastoma (RB) — Inheritance, Staging and Special Types

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The retinoblastoma is a tumor of infancy and childhood and accounts for about 2% of all malignant neoplasia in children. Experts recommend a simple screening test to diagnose retinoblastomas early: The frontal photography of an infant using flash reveals the most common symptom of retinoblastoma – leukocoria – and can be essential for an early diagnosis in order to facilitate adequate therapy.

Definition of Retinoblastoma

Retinoblastoma – A malignant tumor of the retina

Retinoblastoma has the highest prevalence among intraocular tumors in children. It is a malignant tumor of the retina emanating from embryonic cells. The disease may affect one or both eyes and can appear sporadically or cumulatively in families. Healing rate is almost at 100% if the tumor is solely intraocular.

Epidemiology of Retinoblastoma

Retinoblastoma presents an incidence of 0.4 in 100,000. The main age of its manifestation is the first year of one's life. 80% of diseased children are younger than 4 years. Girls and boys are both affected equally.
Pathogenesis of Retinoblastoma

Genetic causes of retinoblastoma

The **two-hit-hypothesis** of Knudson states that only a loss of both alleles of the **retinoblastoma-gene** is required to trigger the development of retinoblastoma. This gene is located on chromosome 13 and is involved in regulating the **cell cycle**. There are two types of retinoblastoma. First, there is the **hereditary type**, that accounts for 45% of cases and the second type, the **sporadic type**, that accounts for the remaining 55%. In the hereditary type, all somatic cells have lost one allele, therefore, the loss of a second allele in a retinal cell consequently induces the growth of retinoblastoma. In 95% of the cases, such secondary somatic mutation occurs, so that the inheritance is typically **autosomal-dominant** with incomplete, but very high penetration. Bilateral retinoblastomas are almost always hereditary.

If one of the parents is diseased with retinoblastoma, there is a 50% chance for the offspring to inherit the mutated Rb-gene.

A multifocal appearance of the retinoblastoma is possible. Characteristic is an invasion into the vitreous body, further spreading along the optic nerve into the brain, causing the development of meningeosis. In addition to this, expansion across the sclera into the eye socket and alongside the ciliary arteries is possible. Metastasis occurs after invasion takes place through the Bruch’s membrane into the highly vascular choroid by means of **hematogenous**, finally spreading into **bones**, **bone marrow**, and **lymph nodes**.

<table>
<thead>
<tr>
<th>Hereditary type</th>
<th>Sporadic type</th>
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<tbody>
<tr>
<td>Early diagnosis, about 12 months old</td>
<td>Late diagnosis, about 23 months old</td>
</tr>
<tr>
<td>Bi- and unilateral appearance</td>
<td>Unilateral appearance</td>
</tr>
<tr>
<td>First mutation occurring in germline</td>
<td>Two somatic mutations</td>
</tr>
<tr>
<td>50% risk that offspring is getting affected</td>
<td>Offspring is at same risk as the remaining population</td>
</tr>
<tr>
<td>Increased risk of further malignant tumors like osteosarcomas</td>
<td>No increased risk of further malignant tumors</td>
</tr>
</tbody>
</table>
Clinical Symptoms of Retinoblastoma

The most common symptom, which can be observed in 3 out of 4 children, is leukocoria or amaurotic cat’s eye reflex. The white pupil is caused by the tumor infiltrating the vitreous body. The consequent loss of vision often remains unnoticed by parents. Other symptoms are strabismus and a reddened aching eye caused by emerging glaucoma due to the growth of the tumor. Increasing impairment of vision or even blindness is caused by the destruction and detachment of the retina or the infiltration of the macula. Macular Degeneration is the number 1 cause of irreversible blindness (U.S.).

<table>
<thead>
<tr>
<th>Dry (aka nonexudative) macular degeneration</th>
<th>Wet (exudative) macular degeneration</th>
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</thead>
<tbody>
<tr>
<td>90% of all cases</td>
<td>10% of cases</td>
</tr>
<tr>
<td>Yellow-white deposits (drusen) in the retinal pigment epithelium (RPE) tissue beneath the macula</td>
<td>Abnormal blood vessel growth beneath the macula</td>
</tr>
<tr>
<td>Waste products from photoreceptor cells</td>
<td>Leak blood and fluid</td>
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<td></td>
<td>Rapid progression</td>
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In rare cases, unilateral mydriasis, heterochromia iridium or hyphema can be observed.

Retrolental fibrovascular membranes in the course of retinopathy of prematurity, uveitis, and toxoplasmosis must be taken into consideration in the differential diagnosis of leukocoria.
Diagnosis of Retinoblastoma

Versatile examinations for complete diagnostics of a retinoblastoma

Medical diagnosis is made with the help of examining the ocular fundus. A retinal tumor can be observed, which often contains calcium deposits and is usually the cause of retinal detachment. Also, the infiltration of the vitreous body or the anterior chamber can be visualized clearly using indirect ophthalmoscopy. Staging and planning of therapies is made on the basis of a spinal tap and a bone marrow examination. In CT- and MRT-scans, the intraocular expansion can be evaluated. If skeletal metastasis is suspected, a scintigraphy using Technetium 99 m may be required.
Note: A biopsy of the retinoblastoma is not indicated since tumor cells could be dispersed and carried over to adjacent structures of the eye bulb.

Staging using the Reese-Ellsworth classification

I: Tumor diameter of less than 4 mm
- II: Tumor diameter of 4 – 10 mm
- III: Tumor diameter of more than 10 mm or anterior to equator
- IV: multiple tumors with a disc diameter larger than 10mm or lesion extending anteriorly to the ora serrata
- V: Tumor involving more than half of the retina or vitreous seeding

Therapy of Retinoblastoma

Characteristics of retinoblastoma are essential

Conservative treatment, thus a bulb preservative treatment, is only indicated if it is possible to obtain a certain degree of vision. Among these treatments are photocoagulation, cryotherapy and external beam radiotherapy, since the tumor is very sensitive to radiation. Check-ups on a regular basis are crucial, since osteosarcoma may form in the area where radiation is carried out or a radiogenic cataract may develop. A better treatment measure is brachytherapy using episcleral plaque-radiation. For this procedure, an applicator containing Ruthenium-106 is patched onto the sclera and removed after the cumulative dose has been applied. Adjuvant chemotherapy is recommended when the tumor has metastasized.
Enucleation of the eye is a valid option in patients with unilateral disease. Patients with bilateral retinoblastomas can keep the less affected eye and should be treated conservatively whereas the opposite eye can be enucleated.

**Special Types of Retinoblastoma**

**Trilateral retinoblastoma**

The trilateral retinoblastoma is very uncommon. It is hereditary retinoblastoma combined with a **brain tumor**. However, the brain tumor is not due to metastasis, but the histological findings are similar to those of retinoblastoma. Altogether, the trilateral retinoblastoma faces a poor prognosis.
Retinoma

The retinoma, also called retinocytoma, is a benign retinal tumor, which affects about 2% of children who carry the retinoblastoma gene mutation. Assumptions say that retinoma is a precursor of retinoblastoma or that it is retinoblastoma after spontaneous regression since its histology is quite similar.

Prognosis of Retinoblastoma

Good chances for retinoblastoma patients

The 5-year survival rate is about 97%. Prognosis is worse if the choroid or the optic nerve is infiltrated beyond the resection border or if a bilateral affection is on hand. Findings of distant metastases require high-dose chemotherapy combined with a reinfusion of stem cells, which is the sole curative approach for therapy and comes with it a clearly worse prognosis.

Note: Long-term survival of patients having the hereditary type of retinoblastoma is determined by the high rate of secondary malignant tumors.

Follow-Up Treatment of Retinoblastoma

If one parent has had bilateral or multifocal retinoblastoma, the patient is generally considered as a carrier of a constitutional mutation, which is inherited autosomal dominant. If inheritance of the RB1-mutation cannot be ruled out by a molecular genetic test, the ocular fundus of the newborn child has to be examined under anesthetic within the first two weeks of its life. Furthermore, the frequent examination of the ocular fundus should be performed by a pediatric ophthalmologist until the age of 3.

Descendants or brothers or sister of patients, having a sporadic type of unilateral retinoblastoma, do not have higher disease risks. However, it has to be ruled out whether it is unilateral retinoblastoma caused by germline mutations.

Due to the increased risk of secondary tumors after radiotherapy, especially in cases of constitutional heterozygosity, a life-long oncologic and ophthalmologic follow-up treatment of the affected patients is crucial.

Review Questions

The correct answers can be found below the references.

1. Which part of the body/organ is often affected by metastases of the retinoblastoma?

   A. Lung
   B. Liver
   C. Bone marrow
   D. Brain
   E. Skin

2. A 13-month old healthy boy is presented to you by his parents because his left eye had been reddened and aching for 2 weeks. The parents had already taken him to a pediatrician a week ago. His tentative diagnosis was viral
conjunctivitis and he was prescribed an eye ointment, which, however, did not alleviate the boy’s symptoms. Now the child’s father is even more worried since he read on the internet that such inflammation of the eye could indicate a tumor and he himself has also been wearing a glass eye ever since a tumor affected his eye when he was young. How high are the chances that the boy is affected by retinoblastoma if the father indeed has had hereditary type retinoblastoma?

A. Almost 100 percent  
B. Almost 50 percent  
C. 25 percent  
D. Same chance as the remaining population  
E. Approximately 0 percent, since children with retinoblastoma do not reach propagable age, therefore, the father cannot have had retinoblastoma.

3. How is stage V of the Reese-Ellsworth classification of the retinoblastoma defined?

A. Tumor with a diameter of more than 10 mm or anterior to the equator.  
B. Multiple tumors with a discus diameter greater than 10 mm or rostral to the ora serrata.  
C. The tumor takes one or vitreous sowing over half of the retina.  
D. The tumor occupies more than 3/4 of the retina or has formed distant metastases.  
E. Bilateral retinoblastoma.

References

Ludwig Gortner, Sascha Meyer, Friedrich Carl Sitzmann: Duale Reihe Pädiatrie, Thieme 2012

Correct answers: 1B, 2C, 3C

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