All About Retinoblastoma

What is retinoblastoma?

The retinoblastoma gene is a type of gene known as a "tumor suppressor gene." Tumor suppressor genes act as a "brake" on cell division. The retinoblastoma gene (RB or RB1) is present in all cells of the body. If an unwanted mutation forms in one of the cells of the body, the retinoblastoma protein (also known as pRB) acts as a brake to prevent that mutant cell from dividing. However, if the retinoblastoma gene is damaged (mutated), a defective pRB may be produced and the cell can then divide unchecked, leading to cancer.

Retinoblastoma arises from the retina of the eye. The retina is the light-sensitive lining in the back part of the eye. It can affect one or both of the eyes. It causes a tumor to form within the eye, which can then grow and destroy the internal structures of the eye. Retinoblastoma is generally limited to the eye but can spread. The majority of children who develop retinoblastoma are cured.

Retinoblastoma is an uncommon childhood cancer, affecting about 300 children in the United States every year. Although retinoblastoma can be diagnosed at any age, most children are diagnosed before the age of 2, and a majority of cases are diagnosed in children younger than 5 years of age.

Retinoblastoma is thought to occur based on the "two-hit" hypothesis. There are two copies of the retinoblastoma gene in each cell, and in order for retinoblastoma to occur, both copies of this gene need to be defective. There are two patterns of retinoblastoma that can occur: an inheritable, or germline form and a sporadic form. There are two ways that the inheritable form can occur. One way is through direct inheritance of one defective gene from a parent. This also means that one parent is a "carrier" of the defective gene. However, if the parent never developed a second retinoblastoma mutation, he or she would have never manifested any symptoms of the disease. So, there may not be a family history, even though one of the parents is a carrier of the gene.

The second way is through a germline mutation of one copy of the retinoblastoma gene. A germline mutation occurs when the retinoblastoma gene is mutated during conception, and this new mutation can then affect all cells in the body. Hence, all children with the inheritable form of retinoblastoma already have one defective retinoblastoma gene, and only one additional mutation is required to cause the disease. In the sporadic form of the disease, the child does not inherit a defective copy of the gene, and thus in order for the child to develop the disease, two "hits" are required to cause defects in the two normal copies of the retinoblastoma gene.

The inheritable and sporadic forms of retinoblastoma also manifest themselves in different fashions. Either form of retinoblastoma can affect just one eye. However, only the inheritable form of retinoblastoma can cause disease in both eyes. The inheritable form of the disease causes tumors in one eye about 15% of the time, tends to occur at an earlier age, and is associated with multiple tumors in the eye. As the inheritable form tends to occur in younger children, infants presenting with one or both eyes affected many times have the inheritable form of the disease. Studies have found that people who are diagnosed with the inheritable form of retinoblastoma are at increased risk for developing another cancer.

Studies have shown that children diagnosed with the hereditary retinoblastoma are at an increased risk of developing a secondary cancer later in life. They will be monitored closely for cancers such as sarcomas, melanoma, lung, lymphoma, bladder, uterine, breast, brain, mouth and nose.

Who is at risk for retinoblastoma?

Retinoblastoma appears to equally affect boys and girls, as well as African Americans and Caucasians. The retinoblastoma
gene is located on chromosome 13q. Children who have a parent or sibling with this disease or children with a known mutation of chromosome 13q are at increased risk for developing retinoblastoma.

Aside from the genetic risk factors, the specific exposures or other conditions which lead to retinoblastoma are not well known. Hence, there are no good guidelines regarding how to best prevent retinoblastoma. However, for children who are known to have a family history of retinoblastoma, frequent follow up examinations may allow for early detection of the disease. If there is a family history of RB, the child should be examined by an eye doctor (ophthalmologist) soon after the child is born. These exams should continue every three to four months until the child is three to four years of age. The exams are then done every six months until the child reaches five to six years of age.

If a child is noted to have no red reflex (as described below), they should be brought to medical attention.

**What Screening Tests are Available?**

Children have evaluation of their eyes during pediatric visits. During these visits, the pediatrician will check for several things, including the red reflex, the corneal light reflex, and the general function of their eyes. The red reflex is caused by light being reflected from the retina. The retina has numerous blood vessels and a reddish appearance, thus light reflected from the pupil appears red. The red reflex is the same phenomenon responsible for “red eye” seen when taking photos with a flash. In children with retinoblastoma, this reflex causes the light reflected from the pupil to appear white rather than red. This is known as leukocoria, and is seen as the first sign of retinoblastoma in many children. If the parents notice that the child's eyes appear to have a white reflection, they should inform their pediatrician.

The corneal light reflex is the shine that is present on the surface of the eyes when light is reflected off of them. Both eyes should reflect the light in the same place on each eye. If the light is not reflected back symmetrically from each eye, this may mean the eyes are not aligned with one another properly. This is known as strabismus, and can be a presentation of retinoblastoma (though less frequently).

Retinoblastoma is a visual diagnosis. A fundoscopic eye exam (examination of the back of the eye, or retina) using an ophthalmoscope is also done to look into the eye. The pupil needs to be dilated for a better view of the inside of the eye, and may need to be done under anesthesia because of the young age of the children examined.

If retinoblastoma is suspected, further imaging studies, such as MRI may be ordered. There are also genetic tests available to determine if the retinoblastoma gene is present to confirm the diagnosis. This test also determines if the child has the inheritable form or the sporadic form of the disease. If they are found to have the inheritable form, parents and siblings should be tested and be referred to a genetic counselor. Blood tests may also be ordered to check for abnormalities in these family members.

**What is the staging for retinoblastoma?**

Retinoblastoma is divided into 2 main groups: intraocular and extraocular. Intraocular meaning the cancer is within the eye. Extraocular meaning the cancer has spread outside the eye. The International Classification system is used by most physicians and divides intraocular retinoblastoma into 5 groups.

**The International Grouping System:**

Group A: Small tumors that are less than or equal to 3 mm in size and only in the retina.

Group B: Larger tumors that are bigger than 3 mm and only in the retina.

Group C: Tumors with small amounts of tumor under the retina or into the jelly-like material in the eye. Tumor under the retina is called subretinal seeding, tumor in the eye is called vitreous seeding.

Group D: Widespread subretinal or vitreous seeding and retinal detachment.

Group E: Large tumor that has spread to the front of the eye. It can bleed and can cause glaucoma.

It is also important to know whether the retinoblastoma is unilateral (affecting one eye) or bilateral (affecting two eyes).
Treatment is typically based on the tumor that has the higher "group" classification.

In order to see if the retinoblastoma has spread, the physician will order blood counts and imaging of the brain. Abnormal blood counts could indicate the retinoblastoma has spread. A brain MRI checks for another brain tumor which is associated with retinoblastoma (called a pineoblastoma). When this is present at diagnosis it is sometimes called trilateral disease. Luckily, there is a decreased incidence of pineoblastoma since chemoreduction of tumors has been used.

**What are the treatments for retinoblastoma?**

The goals of retinoblastoma treatment are first to save the child’s life, and second to preserve as much vision as possible. Children with less involved tumors (Group A and B) are great candidates for therapies that treat the tumor and preserve vision, where children with more extensive tumors may not have their vision maintained, or in some cases, even have to have their eye surgically removed.

Chemotherapies used for retinoblastoma include carboplatin, etoposide and vincristine. These medications are given by IV (intravenous), with the exact doses varying based on the group of the tumor. Long-term effects of this chemotherapy have been studied and there is a small risk of hearing loss as a result of the treatment. There is also a possible, but not likely, issue with fertility or development of secondary cancers due to this chemotherapy.

Some groups also use chemotherapy that is given in the blood vessels that directly supply the eye (called intra-arterial chemotherapy). This is a newer technique, so less research is available to know the long term effects of this treatment.

Cryotherapy, photocoagulation and radiation are other treatments that have been used. Cryotherapy works by freezing the cancer cells, which damages them permanently and causes them to die. Photocoagulation is the use of a laser to burn tumors. Thermotherapy is a similar technique, which uses microwaves to burn the tumor. Radiation used to be used frequently for retinoblastoma, but has fallen out of favor because of the long-term effects of giving radiation to the eye and brain in young children.

**Follow-Up Testing**

The cure rate for retinoblastoma is over 90%, though the exact cure rate will depend on the extent of disease. A child who does not develop recurrence of retinoblastoma within five years after treatment is considered cured.

For children who have the inheritable form of retinoblastoma, follow-up is life-long in order to check for the development of second cancers. These cancers are most often of the bone or soft tissues (sarcomas). It is essential that children with the inheritable form not smoke, as this has been shown to increase the risk of another cancer developing. It is also critical to monitor for disease in the opposite eye in children who are only affected in one eye. Disease in the other eye occurs most commonly in the inherited form of the disease, and children with this form should have frequent eye exams. Generally, if retinoblastoma is going to affect the other eye, it does so within three years of the diagnosis. Screening MRI’s are done every six months after the diagnosis of retinoblastoma, until the age of five.

**References For More Information**

Retinoblastoma – the American Cancer Society

Retinoblastoma – St. Jude Children’s Research Hospital

The Eye Cancer Network: Provides disease specific educational information, support and networking for eye cancer patients and their caregivers.