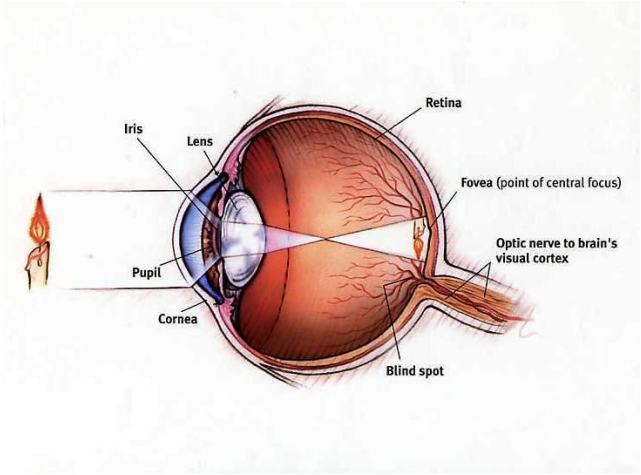
Pathology Report: **Retinoblastoma**

Definition:

Retinoblastoma (Rb) is a rare, malignant tumor that develops in the immature cells of the retina, or light detecting tissue of the eye. It is the most common malignant tumor of the eye in children, and is rapidly developing. It usually occurs in children younger than 5 years old, most often in children 2 years old or younger. In very rare cases, it can occur in adults.

The retina is made up of nerve tissue that senses light as it comes through your eye. The retina sends a signal through your optic nerve to your brain where it is interpreted as images.



Background:

Of all childhood cancers Rb has one of the best cure rates in the developed world at 95-98%. More than 9 out of 10 survive into adulthood. Bilateral cases (both eyes) in the UK are usually diagnosed within 14-16 months, while unilateral (one eye) diagnosis usually peaks between 24-30 months. In certain hereditary Rb cases the pineal gland (or very rarely other midline intracranial locations) are also affected and that's classified as trilateral Rb. This usually occurs more than 20 months after Rb is diagnosed.

There is currently research being joint funded by The Childhood Eye Cancer Trust in Birmingham, UK attempting to establish the different types of Rb and subsequently determine better treatment pathways.

Key Signs, Symptoms:

- The most common and observable sign is the abnormally large white reflection in the pupil (does not solely lead to Rb diagnosis.)
- The appearance of only one red eye in photographs.
- Deterioration of vision, red and irritated eye with glaucoma.
- Faltering growth and delayed development.
- Can cause children to develop an eye that turns in.

- Eye enlargement in developing countries commonly found.
- Depending on position, tumor can be visible during simple eye exam.

Causes and Classification:

Chromosome 13 is responsible for controlling retinal cell division. In children with retinoblastoma, retinal cell division continues unchecked, causing retinal tumors. The cells continue to grow and multiply because of the mutation, where as healthy cells would die. Rb cells can spread further into the eye and nearby structures, although that is not common. It can also metastasize to other areas of the body including the brain and spine.

Leaders in the Field:

- Memorial Sloan Kettering Cancer Center in New York City is the leading location for Rb. They have had a Rb program for 100 years, and have treated the most amount of cases. They have the only genetic counselor in the world dedicated solely to Rb. Research from them turned out to be pivotal in my nephew's case.
- University of Minnesota Children's Hospital in Minneapolis is the second most experienced center for Rb in the US.

Genetic Testing:

This is very important to determine if it's hereditary Rb, and if siblings need to be closely monitored, as well as the fact that these individuals are more likely to develop other cancers later in life. It runs in the family if there is a RB1 gene mutation. Tests include detecting the mutation in the blood with high sensitivity molecular testing, as well as testing the tumor.

- Both types should include genetic counseling. The parents may have an eye exam performed on them by an opthamologist and counseling to determine if they should be tested for the gene mutation.
- Bilateral and about 15% of unilateral individuals show a mutation in the blood. If it is identified, siblings, children and relatives should be tested for the mutation.
- For the other 85% of unilateral patients do not need to be molecularly tested nor family members tested.
- If the RB1 mutation runs in the family, the mutation can be tested for in the amniotic cells of a pregnancy. A fetus that carries the mutation may be delivered early to treat any eye tumors which can lead to better outcomes for vision.

<u>Heritable:</u>

- More commonly bilateral (1/3 of cases)
- Usually occurs earlier in child's life than non-heritable
- Survivors of hereditary Rb have a higher risk of developing other cancers later in life, such as bone or soft tissue sarcoma or melanoma. Regular follow-ups are important.

- Mutation is on chromosome 13 called RB1 gene. The codes found in chromosomes control how cells grow and develop in the body. If a part of the code is missing or altered (mutation) a cancer may develop.
- If one parent carries a mutated gene, a child has a 50 percent chance of inheriting that gene.
- If the cancer is unilateral, the healthy eye should be checked on every 2-4 months for at least 24 months, as there is a chance that a tumor may form on the healthy eye.

Non-heritable:

- 55% of cases
- No history of disease in family
- Labeled sporadic
- Commonly unilateral (2/3 of cases)
- Not clear what causes the genetic mutations that lead to Rb

Tests and Diagnosis:

Rb is tested for at the 3 month well baby exam for all babies under regular medical care. If someone has a family history of Rb they should be getting regular eye exams to screen for it.

When to see a Dr:

- If you notice any changes in your child's eye that concerns you. Rb is very rare, there are other common eye conditions to explore.

Diseases that share similar signs or symptoms:

- Persistent hyperplastic primary vitreous
- Coats disease
- Toxocara canis
- Retinopathy of prematurity

Diagnosis and Spreading:

- Physical exam and history: Check for general signs of health, including checking for signs of disease such as lumps or anything unusual. Family history of Rb will be noted.
- Eye exam with dilated pupil: An exam where the pupil is dilated with medicated eye drops to allow doctor to look through the lens and pupil to the retina. The inside of the eye, retina, and optical nerve is examined under light. Depending on the child's age this may be done under anesthesia.
- Ultrasound exam: High energy sound waves are bounced off internal tissue and organs and make echoes. This is used to form a picture of body tissue called a sonogram. Ultrasounds can help define the height and thickness of tumor.

- CT or CAT (Computer Topography) Scan: Detailed pictures taken from different angles are made by a computer linked to an x-ray machine. A dye may be injected or swallowed to help organs or tissues show up better. CT scans should not be used routinely to avoid exposing child to ionizing radiation.
- MRI (Magnetic resonance imaging): A procedure that uses a magnet, radio waves, and a computer to make a series of detailed pictures inside the body or certain place like the eye. This can help determine if there are structure abnormalities (as well as CT scans.)
- Lumbar puncture (spinal tap) to determine spreading
- Bone marrow aspiration and biopsy to determine spreading
- Rb is usually diagnosed without a biopsy to prevent the cancer from spreading.

Stages:

Once a diagnonsis for Rb is made, further tests are done to find if cancer cells have spread within the eye or to other parts of the body. This determines the stage of the pathology.

- Intraocular: The cancer is only found in the eye. Cancer has not spread to tissues around the outside of the eye or to other parts of body.
- Extraocular (metastic): Cancer has spread beyond the eye potentially tissue around the eye, or it may have spread to the central nervous system (brain and spinal cord) or to other parts of the body such as bone marrow or lymph nodes.

3 ways cancer can spread in the body:

When cancer cells break away from primary tumor and travel to other places in the body another tumor may form. This is called metastasis. The secondary tumor is the same type of cancer as the original tumor. So cancer cells from Rb in bone marrow are still Rb cancer cells.

- Through tissue: cancer invades surrounding normal tissue.
- Through lymph system: cancer invades lymph system and travels through the lymph vessels to other places in body
- Through the blood: Cancer invades the veins and capillaries and travels to other places in body

Prognosis depends on:

- Stage of cancer
- Age of patient
- How likely vision can be saved in one or both eyes
- Size and number of tumors
- Whether the patient has glaucoma (a group of eye conditions that lead to optic nerve damage, usually due to increased pressure in the eye known as intraocular pressure - IOP.)
- Whether trilateral Rb occurs

Western Medicine Treatment and Side Effects:

The priorities for Rb treatment are to preserve the life of the child, then preserve the vision and then to minimize complications or side effects of treatment. Position, size and quantity of tumors are considered when choosing treatment plan. The ophthalmologist in discussion with pediatric oncologist will determine treatment depending on the individual case. After treatment for Rb is finished, there should be follow-up exams continuing until the child is 5 years old.

What to expect from an initial Dr's appointment, questions they will ask:

- When did your child begin experiencing symptoms?
- Have your child's symptoms been continuous or occasional?
- How severe are your child's symptoms?
- What, if anything, seems to improve your child's symptoms?
- What, if anything, appears to worsen your child's symptoms?

Treatment:

- **Intra-arterial Chemotherapy**: New treatment where chemotherapy drug is injected directly into the ophthalmic artery, the blood vessel that leads to the eye. The patient is given anesthesia, a thin tube is inserted through the femoral artery in the groin and threaded up into the ophthalmic artery and injected into the eye. This minimizes the exposure of chemotherapy to the rest of the body. The average number of treatment sessions is 3, being delivered at 4 week intervals. The treatment is successful if the tumor shrinks. If there are residual tumors it can be treated with laser, or cryotherapy.
- **Enucleation**: Surgery to remove eye and part of optic nerve. This is done if the tumor is large and there is little to no chance vision can be saved. This is the most common treatment for Rb. After, the child may be fitted for a prosthetic replacement.
- **External Beam Radiation Treatment**: Been used since the early 1900's as a way to save the eye and vision. Rb is sensitive to radiation. Done 5 x per week over 3-4 weeks. Tumors usually get smaller, but rarely disappear. The pinkish grey tumor mass is replaced by white calcium. There are many side effects to this treatment including skin burns, cataracts, impaired vision, temporal bone suppression, tumor growth in other areas, and radiation retinopathy.
- **Radioactive Plaques**: Discs of radioactive material are inserted during an in hospital procedure. It is removed 3-7 days later. Side effects from the radioactivity possible.
- **Laser Therapy**: High temperature lasers are focused on the tumor through the pupil to kill cancer cells. Done under anesthesia, and non-invasive treatment.
- **Cryotherapy**: Smaller tumors are frozen while under anesthesia. A pen like probe is placed adjacent to the tumor and it's frozen. The procedure is usually repeated many times to destroy all cancer cells. The lids and eye can swell 1-5 days, sometimes to the point of being unable to open their eye lids.

- **Chemoreduction:** This is chemotherapy given intravenously where the drugs pass through the blood stream. This is most commonly the treatment for metastic Rb.

Complications:

- There is a risk with children treated for Rb of the cancer returning (recurrent Rb) in and around the treated eye. The child will schedule regular follow up exams to check for recurrent Rb. This may involve eye exams every few months for the first few years after treatment ends.
- Children with hereditary Rb have an increased risk of other types of cancers developing in other parts of the body. They should have regular exams to screen for other cancers.
- In intra-arterial chemotherapy, there have been instances where the artery turns away from the eye, thus making it difficult for the chemotherapy drug to be delivered to the site.
- Anesthesia can disrupt the child's sleeping schedule
- Chemo burns on head, if the intra-arterial chemotherapy misses the eye
- Late side effects of treatment may include
    - Physical problems such as seeing clearly
    - Changes in mood, feelings, thinking, learning or memory
    - Second cancers; children who've been exposed to radiation therapy have increased risks

Survivorship and follow up care:

Most children with Rb in the United States, more than 95%, survive cancer. It is important for children with vision in one eye to wear protective eyewear during sports and other activities. Rb is a life threatening disease, but it is rarely fatal if treated appropriately. Followup care and frequency depend upon the age of the child, suspicion of new tumors, whether one or both eyes are involved, and the type of treatment the child received.

Herbal Harm Reduction Plan:

Reduce Scarring and Inflammation of Eye:

- Radiation or chemo burns – Apply aloe vera, vit E, raw honey to prevent scar formation and encourage faster healing.
- Antimicrobial, vulnerary, drawing oil: Chickweed (pulls impurities, soothing, healing), violet leaf (good for cancer), calendula (vulnerary), gotu kola (cell regenerating), chamomile (vulnerary, anti-inflammatory) + lavender essential oil (antibacterial, and helps preserve)
- Chamomile fomentation on eye if experience the inflammation associated with cryotherapy

Sleep and Mood:

- To help calm child to be able to get back into normal sleep pattern after anesthesia:
    - Chamomile, lemon balm, catnip bath before bed to calm as gentle yet effective nervines
    - Chamomile (nervine, anti-inflammatory and carminative plus slight bitter to tonify digestive tract after chemo) + Lemon Balm (antiviral to protect child's health through

this taxing process, slight nervine, and anti-inflammatory) tea in child's formula or sippy cup before bed to calm, with other added benefits. Can also try Catnip and Vervain to aid with bringing on sleep, and sleep quality. *Bring water to a boil, turning off the burner, adding ½ teaspoon of the herb for babies. Steep for 10 minutes, strain well, and cool until the liquid is comfortable on your inner wrist. Make a fresh batch each day. This can be fed to your baby using a sterilized dropper.*

- Lavender essential oil sprayed in room to calm before bed. Also, anesthesia is a depressant and lavender is an anti-depressant. Lemon balm can also be added as an anti-depressant and calming source.

Support Liver and Organs of Elimination (against toxic load from Chemo):

- Chemotherapy (intravenous) specifically targets rapidly growing cells (cancer), but other rapidly growing cells also become a target in this process (bone marrow, hair follicles, gut lining, and also leads to general increased inflammation throughout body.)
  - Increase intake of mushrooms, bone broth, and fo ti (kidney support) due to suppressed bone marrow production
- Milk Thistle: Stated by Dr. Weil and Dr. Lowdog to be safe for children over the long term. Supports liver. The correct dosage for children is 5-10 mg per kilogram of body weight per day according to them. American Cancer Society states, *"One small study found that it seemed to help protect liver function in children getting chemotherapy for cancer… Early studies in test tubes and laboratory animals have suggested that silymarin may help with cancer prevention and treatment."* Additionally Milk Thistle is an antioxidant, protecting cells from damage from free radicals. Make powdered Milk Thistle into tea, or grind up and add to food.
- Astragalus: Hepaprotective and noted to be safe for children by Growingupherbal.com. Adaptogenic to help child deal with stress of treatment. Add powder to food or tea.
- Eleuthro: Antioxidant, immune tonic and adaptogenic to deal with stress on physical and emotional body of treatment and disease. Also, particularly noted to be good for those undergoing cancer treatment to reduce side effects and potentiate treatment effects. Noted to be safe for children by Growingupherbal.com. Add powder to food or tea.
- Dandelion root supports and repairs liver. Add small amount of tea to a drink.
- Add small amount of cilantro (or a replacement for baby/child palate) to diet, in order for phase 2 of the physiological process of detoxification to eliminate toxins from body.
- Incorporate a demulcent cold infusion of chamomile and marshmallow to child's diet while undergoing chemo, as well as before and after treatment to soothe their cellular membranes that were affected by the chemo drugs. This is also to provide a protective barrier for the myelin sheath of the neurons in your brain (http://www.the-scientist.com/?articles.view/articleNo/34848/title/After-Chemo/).
- Epsom salt baths to eliminate toxic load and helps with depression (magnesium absorbed through skin.) *"While increasing your magnesium levels, Epsom Salt also delivers sulfates, which are extremely difficult to get through food but which readily absorb through the skin. Sulfates serve a wide variety of functions in the body, playing a vital role in the formation of brain tissue,*

joint proteins and the mucin proteins that line the walls of the digestive tract. Sulfates also stimulate the pancreas to generate digestive enzymes and are believed to help detoxify the body's residue of medicines and environmental contaminants." (From PaleoMama)

Other Complimentary Therapies:

- Rose Quartz to provide child with loving support
- Clear Quartz is cleansing so good for those going through Chemo
- Optical Calcite is associated with physical eyes as well as 3rd eye, sense of sight and spiritual sight. Also has a cooling affect if placed on body/eyes.
- Acupuncture for vision issues not associated with Rb, but that may be occurring in second eye, if it has not been removed. Andy Rosenfarb, noted optical acupuncturist, cites a lot of success in extreme far sightedness.
- Vision Therapy: A type of physical therapy for eyes and brain used to treat common visual problems such as lazy eye, crossed eyes, double vision, convergence insufficiency and some reading and learning disabilities. The tumor in some children's eye/s may form into calcified form blocking all or some of their vision. This could be a productive therapy to address this.
- Craniosacral Therapy: is a form of bodywork or alternative therapy focused primarily on the regulating the flow of cerebrospinal fluid by using therapeutic touch to manipulate the synarthrodial joints of the cranium. To do this, a practitioner will apply light touches to a patient's skull, face, spine and pelvis. Cerebrospinal fluid circulates through the eye and it's noted stagnated fluid is not good for the eye. This therapy may get fluid moving to promote eye health. *Note: It could be controversial to actually apply pressure or massage eye as it's not known if this spreads cancer.*
- Electronic usage reduction: Electronic usage is damaging to eyes because by focusing for any length of time at one distance sets up visual confinement which will solidify fluids in the eye tissue. The lymph, cerebrospinal fluid and blood that pass through the eyes stagnate due to this closed system of movement.
- Intravenous IV vitamin C during chemotherapy has been shown to kill cancer cells. Many laboratory studies have been done to find out how high-dose vitamin C may cause the death of cancer cells. The anticancer effect of vitamin C in different types of cancer cells involves a chemical reaction that makes hydrogen peroxide (found in many traditional healing waters, ex: Water of Lourdes), which may kill cancer cells. Riordan Clinic online states the therapy is safe for children receiving chemo.

Nutritional Therapy:

- Increase intake of fermented foods. Fermenting makes nutrients more bioavailable. Sauerkraut in particular contains glucosinolates which has been shown to have anti-cancer activity.
- Increase intake of mushrooms. Shitake, and Turkey Tails in particular have been shown to be strong anti-cancer agents increasing the natural killer cells reinforcing our immune system to be able to fight cancer. They also increase function of liver. Maitake, and Agaricus blazei have also

been shown to be anticancer in various ways by improving immune function, being anti-tumor agents, etc.

- Combine fermented miso with seaweed in Miso soup and it is a powerful anticancer food. Seaweeds are incredibly protective against cancer, and have been shown in studies to having the ability to cure cancer in some instances. Seaweeds also contain colloidal minerals that facilitate in unloading toxins from body for chemo patients. Also iodine in seaweed has anticancer properties, inhibiting cells from forming cancer.
- Add turmeric to curries, and other dishes. Turmeric is an incredibly powerful herb for cancer. It is anti-inflammatory and antioxidant to protect the myelin sheath against damage from the chemo. Also great for the liver. Particularly cancer in children is usually very inflammatory and rapid growing. Could not find information on if Turmeric is safe at therapeutic doses, safer to cook with it for children.
- Reduce sugar intake to a minimum. Simply, sugar feeds cancer growth.

Sources:

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