The Whiter, Brighter Pupil: Leukocoria in Children

Instructor:

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Section:

Functional Vision/Pediatrics

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COURSE DESCRIPTION:

This course will cover causes of monocular vision loss in young patients, including congenital cataract, retinoblastoma tumors of the eye and brain, and genetic conditions that can threaten both sight and, sometimes, the life of the patient.

LEARNING OBJECTIVES:

1. Which is the minimum number of tumors per eye that are seen to prove a case of genetic retinoblastoma?
2. What is the treatment of choice for retinoblastoma in recent years?
3. What is “trilateral” retinoblastoma? Where is the third tumor found in these cases?
4. Which cause of leukocoria is affected by diet?
5. Which cause of leukocoria is genetic and inherited less than 10% of the time?

The course begins on page 2
Hello and welcome to The Whiter, Brighter Pupil:
Leukocoria in Children. I am Dr. James Kudart and I am
an associate professor at Pacific University College of
Optometry. This presentation was co-created by my
colleague, Dr. Nadine Hanna from NOVA Southeastern
University. She will not be able to present with us
today, but the content remains equally both of ours, and
I wanted to insure that she gets full credit for what she
has created. There have been a few modifications to
this presentation since it was first created for the 2012
American Academy of Optometry meeting in Phoenix,
where it was first presented.

In Figure 1, we see two different causes of Leukocoria, not to be confused with Leukocornea, where the
cornea has become opaque. Leukocoria is a white pupil, often caught these days by social media using
digital photos. What we see here is retinoblastoma — the most worrisome cause of Leukocoria, in the
right eye in the top image, and in the left eye of the bottom image.

Here are some things we are going to study today regarding this issue, and we are going to spend about
half the time on white pupils caused by this rare but very serious cancer of the eye, Retinoblastoma. We
will talk about locations of the tumors when they do happen, and treatments. We will also talk about
some dietary causes of leukocoria, as well as genetic causes and some syndromes that will lead to it.
Along the way, we will also cover differential infectious causes, and, of course, the general cataract.

1. Which is the minimum number of tumors per eye that are seen to prove a case of genetic
retinoblastoma?
2. What is the treatment of choice for retinoblastoma in recent years?
3. What is “trilateral” retinoblastoma? Where is the third tumor found in these cases?
4. Which cause of leukocoria is affected by diet?
5. Which cause of leukocoria is genetic and inherited less than 10% of the time?

So, what causes white pupils? White pupils can be caused
by many things. In the case of Figure 2, we have the most
common cause, asymmetry of the refractive area, or
anisometropia. Here we have a Bruckner test reflex.
Bruckner is a great way to first detect anisometropia. This
is when you use your Direct Ophthalmoscope, or similar,
to put a spot of light over both eyes about a foot away
from the patient. What you see is the eye that is on-fovea
will have a darker pupil and an eye that is off-fovea, even
by a little bit, say in the case of micro-strabismus, in the
absence of media opacity, you will see a brighter pupil. It
could also happen if the refractive error is not the same in
the two eyes, and the light is not as well focused in one
eye as in the other. Thus, Bruckner is a great way to catch
anisometropia, which is the most common cause of apparent leukocoria.
Figure 2 (a) shows a 10 year old girl with an asymmetry in the reflex. Her prescription for the right eye ended up being a spherical equivalent of about -2.25D, 2.50D of which was with-the-rule astigmatism. Her left eye had a smaller prescription, the spherical equivalent being -1.25D, so the total anisometropia was about 1.00D with the right eye being more myopic.

In Fig 2 (b), we see the reflex of a 14 year old girl. There is barely any asymmetry noticeable, and that is because the patient had a prescription of OD: +5.50-2.50 x 090, and OS +6.50-3.50 x 090, which gives us a spherical equivalent within 0.50D in the +4.50D range.

Fig 2 (c) is a 13 year old male. This is the last example of our Bruckner reflex – this is sometimes called photorefraction. There is apparent asymmetry, as well. This particular example happens to be a very high myope, which all of us have seen on retinoscopy. The right eye here is -11.00D and the left eye is -13.00D. You can see that the right eye is a little bit brighter, with a better light focus on the back of the retina. The dimmer image is generally going to be the less focused image if there is no strabismus present or media opacity.

That is the “pseudo-leukocoria” that you want to be aware of, that is by far the most common cause. Now let’s talk about the pathological causes of leukocoria.

Table 1 lists the causes we are going to cover today in detail, starting with Retinoblastoma, moving on to congenital cataract and Coats’ Disease, and finally, wrapping up with Persistent Hyperplastic Primary Vitreous (PHPV). Along the way, we will talk about other conditions like toxocariasis that can mimic these things.

Figure 3, from a private practitioner’s office, is a pseudo-leukocoria that has a tendency to send parents, relatives and friends on social media into a panic, when the left eye looks like it’s dilated and very bright compared to the right eye. You would be worried about retinoblastoma here, but this is just due to position of gaze being off-axis compared to the axis of the camera flash.

**Leukocoria Cause #1: Retinoblastoma**

This is more worrisome, when we see something like Figure 4. This is, of course, retinoblastoma, and this is always the red-flag, albeit rare, cause of leukocoria. We are going to spend a disproportionate amount of time on this condition, even though it is the most rare of all causes. The left pupil here is white because there is a mass abutting the back of the lens. This is the most serious cause, and can be life-threatening. It happens in the very young pediatric population, which is why this is listed as a pediatric course for co-credit.
Let’s talk about Retinoblastoma definitions. The National Eye Institute (NEI) defines retinoblastoma as a cancer that forms in the tissues of the retina and it should happen before age 5. What may be surprising to you is that fewer than 10% of these come from a familial case. Thus, in 1/10 or fewer cases, it’s something that runs in the family, and if you have one sibling who has this, then you should check all of the family members that you can, especially the young ones. 1 in 4 are new mutations, but 2/3 of them are metastatic from elsewhere in the body. It is a cancer, and it is therefore, genetic, but it is not always inherited. In fact, most cases are not – they come from cancers elsewhere, even at this young age. The eye is a very small organ, and cancers that originate in the eye, genetic, inheritable, or otherwise, are not all that common. We should make a note that spontaneous metastasis are something we need to look for – the entire body needs to be checked by oncology.

This may be, and in fact has been noted to be, the most common eye tumor in kids. We are looking at only 1 in 15,000 to 20,000 children, and always before kindergarten or 1st grade age. It peaks in the toddler age group (1-2 years), before the kids are really able to talk to tell us that they cannot really see out of one eye, which is the consequence of this condition in whole or in part. 1 in 3 cases have retinoblastoma in both eyes, though it may present asymmetrically.

There is a trilateral type of retinoblastoma which is really scary. The third ‘eye tumor’ being the pineal gland. All of these children need to be checked to make sure that they don’t have a pinealoma in addition to retinoblastoma in one or both eyes. There are cases of familial retinoblastoma where an older sibling has been lost due to thinking that treatment of one eye was all that needed to be done. The earlier, the better, in regards to diagnosis.

**Causes of retinoblastoma**

How many of us can get the kind of view shown in Figure 6 even when a good dilation occurs in a child? This figure is probably taken under general anesthesia, but we need to be aware that if we get a cooperative child who can sit long enough to get a retinal photo, that will let us see a lot better than our view with BIO. This reference and photo comes from Dr. Jonathan D. Trobe from the University of Michigan Kellogg Eye Center.

Leukocoria is in the majority of cases (60%) the symptom or sign that allows us to detect the retinoblastoma. This type of tumor can proceed into the vitreous and can cause a turned eye if it interferes with vision – an inward or an outward-turned eye. Some of these cases are not discovered until a child fails a vision screening, which requires them to cooperate on an eye chart, often in the pediatrician’s office with ancillary healthcare personnel who are not specially trained on the eye.
We all know that cooperation is an issue when trying to get subjective findings on children, especially and most often, with visual acuity. Anterior segment signs can exist that will help us with our diagnosis, as we will see in a few minutes.

**Types of Retinoblastoma**

In the anterior segment, we can have extraocular retinoblastoma, usually occurring in other countries where health care is not as widely available. You can also have the posterior ones that are non-hereditary and hereditary, often multifocal hereditary. See table 2.

Let’s discuss each of these in turn.

If you see multiple tumors in one eye, as shown in Figure 7, then the chance of the retinoblastoma not being hereditary is very small. In other words, 2 or more tumors in one eye make it highly likely that you have one of the 10% of hereditary cases.

With the anterior segment, in case the retinoblastoma occurs near the ora serrata, it may seed its way into the iris and you might see the limbal seeding that we see in Figure 8 (left). Also, when you dilate, you get the leukocoria seen in the lower half of the pupil in Figure 8 (right).

Speaking of right, Kenneth W. Wright is an ophthalmologist author of a series of texts, a textbook that has been cut into a smaller series of clinical books, including the *Handbook of Pediatric Retinal Disease*, from 2006, which is a rare thing to find a book on this topic. I’ll share a few cases of Dr. Wright’s here.

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<table>
<thead>
<tr>
<th>Types of retinoblastoma</th>
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<tr>
<td>Anterior segment</td>
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<tr>
<td>- Extraocular Retinoblastoma</td>
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<tr>
<td>Posterior segment</td>
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<tr>
<td>- Sporadic Nonhereditary</td>
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<td>- Multifocal Hereditary</td>
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*Figure 7: Multiple tumors in one eye indicates hereditary retinoblastoma. Photo source: http://www.willseye.org/health-library/retinoblastoma*

*Figure 8: (Left): Limbal seeding in a retinoblastoma near the ora serrata. (Right): Leukocoria upon dilation of a retinoblastoma near the ora serrata. Photo source: http://www.thirdeyehealth.com/retinoblastoma.html*
Figure 9 is a case of extraocular retinoblastoma in the right eye of a child in Mexico, and the post-surgical results shown on the right. It’s rare in the US, but in third-world countries, or in patients who emigrate from third-world countries, you may well see this disease. This child is 3 ½ years old, the same age as my son at the time of this recording. The CT scan showed no evidence of intracranial disease – amazingly, the cancer had not metastasized beyond the eye. Radiotherapy was given with an external beam, and 60% of the dose was delivered across the midline to the right orbit. The right eye did become sunken and phthisical, and thus it was enucleated, or eviscerated. Since the disease did not invade the orbit, the optic nerve or the retro-bulbar space, so he got a prosthesis in the right eye, and safety glasses to protect his good left eye.

Interestingly, five years later at age 8 ½, he was free of retinoblastoma, but had developed an osteosarcoma of the left arm. One wonders in this case if the cancer had metastasized to the left arm, or the other way around.

The sporadic retinoblastoma might look like Figure 10. We will have a single tumor in the eye, maybe in just one eye. For two months the family had noticed a white pupil. The left eye was, thankfully, intact and the family history was negative for any type of cancer.

You can sometimes see, as you can see here, calcium inclusion bodies, which will be bright white refractile minerals (from the center of the tumor out in a straight line to 9:00) and the glial cells may be disturbed by that, of course. The official description is a “creamy, yellow-white, yogurt-like appearance” of this viable retinoblastoma.

This patient was diagnosed past age 2, so it was thought to be a sporadic tumor, but the doctor wasn't sure because there are 15% of the genetically-predisposed kids that get a single tumor in a single eye. To re-state: 1 in 10 of retinoblastoma cases will be hereditary, and of those, 15% will have a single tumor in a single eye.
When you see multifocal retinoblastoma (Fig 11), more than one tumor in a single eye, or if you see it bilaterally, the chance of it being a spontaneous finding becomes less likely. In fact, the mathematics indicate that the cancer cells occur once per million retinoblast cells (the cells that form retinal tissue) so the frequency of even one tumor rising without a genetic predisposition is one in one trillion retinoblasts.

There are a lot of retinoblasts that make up an eye; children have 3 million of them at birth. 3 cells per eye is what is expected to be abnormal, and potentially cancerous in a non-predisposed child. The patients who are genetically predisposed to retinoblastoma have an average of three tumors per eye. For clinical purposes, if you see more than two tumors in the same eye, it’s a genetic case until proven otherwise. If you see a single tumor, in most cases, it will not be genetically based.

**Genetic Testing for Retinoblastoma**

Figure 12 shows a prominent anterior segment retinoblastoma, and one wonders that, even on a light colored eye, how it was allowed to progress as far as it did. What we are seeing is that the unilateral cases, even if they get to the anterior segment, are usually not inherited, as we discussed previously.

There is a retinoblastoma gene – the RB1 gene. You look for it in the family and in family members, especially children – even those children who come later, if our patient is the oldest child and they have younger siblings or those who will be born in the future. You have to examine the whole family, and as we will see coming up, don’t neglect the older kids – check them, as well.

Some retinoblastoma metastasis are quite aggressive. The growth rate of these tumors is rather remarkable considering that they are diagnosed at age 1½ or 2 years old. Figure 13 shows one that is seeding itself into the vitreous and growing out like a ‘Hershey’s kiss’ appearance. It’s hard to get it all in focus, much like a retinal detachment, which this type of tumor can also cause.

This is called a progression of malignancy. These cells overgrow and crowd out healthy cells in the eye, leaving this life-threatening tumor, especially when we get beyond the eye into the brain. A smooth tumor is probably better for prognostic indicators than an elevated one like this.
I would like to present a couple of cases here, none of which are my own, but I will share with you what happens when you treat, for example in this case, with steroids. This child is 7 years old – 5 years older than the average diagnosis for retinoblastoma. He presented with pain and redness in the left eye for 1 week. He had hand motion vision in that eye, with a mild anterior chamber reaction. The vitreous had an intense reaction – the posterior chamber had a vitritis. The other eye showed none of this.

The doctor tried to rule out infectious causes such as toxocariasis, toxoplasmosis, etc. The ultrasound and CT scan showed the posterior pole mass but no evidence of calcification. The diagnosis of retinoblastoma was under consideration, but the lack of calcification makes that less likely. The child was put on a course of steroids to clear up the vitritis, as we often do, in order to get a better look inside the eye and to relieve symptoms.

After three days of oral steroids, the repeated CT scan showed calcification, but all other findings were out of character for retinoblastoma. This diagnosis would not have been made without a high index of suspicion. Normally they would have presumed toxocariasis or toxoplasmosis – certainly those are much more common in this age group.

Figure 15 is an example of what Toxocariasis might look like. You can see that while there are some darkened scars there, the toxocariasis protozoan cannot live in the eye for very long. In fact, it does not live in the human body very long at all, but it does cause damage while it’s dying. That damage is when we have ocular larvae migrans (OLM) as you can see here, happening in 10% of toxocariasis, which can lead to uveitis. Of 100 uveitis patients, 1% of them will be from toxocariasis. The patient is also going to have the same kind of blurred vision, floaters, pain and photophobia as when they have an acute condition. This particular patient was 76 years old and was seen at Pacific University.

Returning from differentials to a second case of retinoblastoma, Figure 16 shows a 4 month old child. There was a mass detected in the right eye, which was also noted to be a little microphthalmic compared to the left eye at the time of birth. The child developed a right esotropia (RET) at 2 months of age. The best view of the inside of the right eye that they could get of the retina is shown in Fig 16(b).
Figure 16: (a) 4 mo old child with microphthalmia and interior mass, OD. (b) Retina, OD. Photo source: Wright 2, Fig 9-4

Clinically, it looks like a white mass centered around the optic nerve with a pigmented ring around its base. There were 45 radial vessels entering the mass around the perimeter. The left eye appeared normal. There was no calcification shown, so it looked like a developmental anomaly. Retinoblastoma was not considered to be a strong possibility because, usually this tumor, as you have no doubt noticed, does not arise from the optic nerve.

Repeat examination 5 months later showed the mass had doubled in size. CT scan confirmed increased size with no evidence of calcification. The right eye was subsequently enucleated for diagnostic reasons. Unfortunately, histopathology showed that total retinal detachment with retinal dysplasia had occurred. The mass appeared to be a malformation and not, in fact, retinoblastoma, but who could blame the surgeons for playing it safe on this one? When we compare Fig 16(b) to our previous case – Figure 14, the initial findings with no calcification made Case 1 look like it was not a retinoblastoma in a 7 year old child. Here, in Case 2, the lack of calcification made it appear as though it was not a retinoblastoma, though all other findings indicated it may be. Also, the child was of the right age for retinoblastoma.

Case #3

Figure 17: (a) 12 YO female with proptosis. (b) CT scan showing enucleated eye 10 years prior. Photo source: Wright 2, Fig 9-13

In case 3, we have, while the photo looks older, a 12 YO female. She presented with some proptosis of the left eye. This child had a history of retinoblastoma. She had an eye enucleated as you can see from Fig 17(b). The right eye had been enucleated at age 2, 10 years previously.

The left eye had been treated with beam radiotherapy and cryotherapy in order to prevent tumors from seeding there. There was no history of recurrence, but she reported a fullness in that remaining left eye when the child was 11 years old.
There were three exams done in the 8 months between age 11 and age 12, showing no active retinoblastoma. Then an orbital aching, headache, nausea and vomiting, and a 15 lb weight loss sent her to multiple pediatricians. They diagnosed her with Chronic Viral Syndrome.

The proptosis and inability to move the left eye finally had the patient examined again. There was congestion and chemosis noted at this exam. In Fig 17(a) the patient is actually trying to look up and cannot. Thus, we have an elevator palsy happening here.

Looking at the CT appearance, you can see in the ethmoid sinus there is a rather large tumor. Symptoms have been present for 8 months prior to diagnosis, and the failure of the physicians to consider a second malignant neoplasm in someone who had ocular cancer at age 2 caused the delay in diagnosis. Some have said that a bracelet or Medicard should be carried by these patients for life once they have been a cancer survivor as a toddler.

**Case #4**

*Figure 18: (a) and (b) lesions before treatment. (c) and (d) those same lesions after treatment. Photo source: Wright 2, Fig 9-9*
In Case #4, this 7 YO male had sustained head trauma, I believe from a school sport activity or gym class. The emergency room physician noticed that the left eye had an APD. Because of the pupillary defect in the left eye, they sent the patient to ophthalmology. Ophthalmology noticed a multifocal retinoblastoma of the left eye, but the patient had no previous diagnosis. Note that this is 5 years after this should be found, and presumably should cause horrible symptoms if not, unfortunately, take the life of the child.

In Fig 18(a) and (b) we see two large lesions at age 7, and then Fig 18(c) and (d) show the regression of those respective lesions by age 10 – it looks like we have only calcium left here, giving the tumor a cottage-cheese appearance. Over time, this was monitored because the child had made it so far, and it continued to regress over time. This was diagnosed at Oregon Health Science University in Portland, OR.

One more differential you will want to consider is the case of phakomatoses. Figure 19 is a case of astrocytoma. Hamartomas in the retina might occur in the disorder Tuberosclerosis, which means they are probably throughout the central nervous system and perhaps visible elsewhere on the skin. These patients may be mistaken for having rosacea, for example, or a bad case of acne vulgaris.

Seeing a montage picture of the retina, Figure 19, is a right eye with a peripapillary astrocytoma and an inferior hemorrhage. These sometimes block blood flow by causing a branch retinal vein occlusion (BRVO) which is also seen here. Fortunately the BRVO is in a distal branch.

OCT (Fig 20) shows the astrocytoma, as would B-scan ultrasound. This is less dangerous, by far, than retinoblastoma, despite having a similar calcified appearance.

Figure 21 shows an enucleated eye that had been allowed to fill with the retinoblastoma before it was removed. These days, though, enucleation is the last resort and chemotherapy is the first choice. That is followed by freezing with cryotherapy of the tumor, radioactive seeding and laser therapy, followed by focal radiation therapy, in decreasing order of preference for treating retinoblastoma.

These days, outcomes are quite good for retinoblastomas that are treated. Some of these regress on their own or are detected later in life.
Retinoblastomas have one of the best cure rates of all childhood cancers – up to 98% surviving, possibly losing vision, but not losing their life, and not having the cancer continue.

You may well see, as I have seen, patients who have grown up and have had retinoblastoma treated in both eyes. The other thing you may notice is that these patients may look like they are microphthalmic when in fact, they weren’t to begin with. After chemo, cryo, radiation therapy, etc, the eyes may be sunken into the orbits rather extremely. In these cases, it becomes rather difficult to fit contact lenses, or even to do Goldmann tonometry, or many other anterior segment procedures. Be aware of that, and patients will generally be happy to tell you their story – you will learn a lot.

Try to catch these early, and thank goodness for the social media photos to help us to do so.

**Leukocoria Cause #2: Congenital Cataract**

Let’s spend the rest of our time talking about another cause of congenital leukocoria – congenital cataracts. Figure 22 is an open-source picture of bilateral cataracts due to German Measles, which is an uncommon cause. We have talked about Rubella and Pertussis being on the rise, but German Measles I have not seen too many cases of, personally. However, there are survivors of it out there – 15% of the cases of nuclear cataracts in newborns are due to this.

The photo shows actually liquified cataracts that have little islands of normal lens in them, but also have live virus in them, so the surgeons have to be very careful when removing these. Often, when congenital cataracts are taken out, in any case, the posterior capsule is not salvageable because the cataracts have hardened to the capsule and regular phacoemulsification (like for a senile cataract) is not possible with congenital cataracts. An anterior vitrectomy becomes necessary, and then the IOL becomes tricky when the patient is of an age to get an IOL.

You need to know that the fetal lens has zones to it (Fig 23) that may be different than the adult lens. The fetal lens is shown there on the right in blue, and the adult lens is on the left in purple. We have here the distinct zones, including nuclear zone, cortical zone, epithelial zone, and a lens capsule which we are used to. The new lens fibers, going through the fetal nucleus is not as compact as the adults, and the Y-suture formation can be seen there. Remember, the tunic of hyaloid vessels and arteries covers the fetal lens and is supposed to dissolve before birth. Sometimes its partial dissolution leads to congenital cataract.

Now besides the cortical, nuclear, and particularly the posterior sub-capsular cataracts that are characteristic of congenital cataracts, there are other types, as well. Figure 24 is a myotonic dystrophy
cataract, also known as a congenital polar cataract or the ‘Christmas Tree cataract’, and you can see how it’s so refractile that refraction causes a colorful, tinsel-like appearance to this cataract. These are probably due to cysteine in the lens, and is likely a cataract that the patient can live with for awhile, but probably, like most small congenital cataracts, will ripen at a younger age than normally expected. Patients may be in their 20’s and 30’s when they have the cataract removed.

There is also a congenital nuclear cataract that may look like a sand dollar-like appearance that you see in Figure 25. This certainly would be operable if the patient was having disturbed sight, which I imagine they would be before dilation. It also looks like the pupil is not quite round on the dilation. The Y sutures can be seen here, both front and back. This is associated with microphthalmos, microcornea, and fetal alcohol spectrum disorders (FASD).

Many of us may have seen some version of a Cerulean Cataract, or Blue-Dot Opacities, which occur frequently in Down Syndrome, and need to be looked for as the congenital cataract of choice, along with brush field spots of the iris that are connective tissue that occur in Down and non-Down syndromes. These are very diffuse cataracts, and may not disturb vision enough to have them removed in infancy or early childhood.

Then we have the Congenital Zonular Cataract, or the Oil-droplet Cataract, which occurs in galactosemia, when the patient cannot digest milk sugar. (Fig 26) They test for this with what they call the “Heel-prick test” at birth, when they test the blood to see if there are any of these congenital disorders that cause brain damage if you are exposed to the offending nutrients. In this case, dairy products must be avoided for life. Fortunately, many non-dairy alternatives are available, especially in the United States and North America. These cataracts happen with exposure to galactose, but this is the one type of cataract that can actually reverse itself if the offending agent is removed early enough.

In Fig 27 we can see just how hard these cataracts can get, even in little children. All of the teratogenic diseases, sometimes abbreviated with the acronym TORCH, standing for Toxoplasmosis, Other, Rubella, Cytomegalovirus, and Herpes Virus, can call cause birth defects, as well as defects in the eye and brain.

The Rubella itself can cause, in addition to cataracts, a sort of pigmented retinopathy known as ‘salt and pepper fundus,’ and hearing loss. After 6 weeks of gestation, if the mother contracts Rubella, then the virus cannot cross the lens capsule at that point, so to develop
cataracts, the virus must be transmitted very early in gestation – in the first month to a month and a half of pregnancy.

Birth defects can still occur in up to the first trimester from Rubella, and the virus can persist living in the lens until the child is 3. Notice how dense the cataract in Figure 27 is anteriorly, then there may be a slightly clearer zone posteriorly.

For treatment, of course, a lensectomy needs to be done. If it’s bilateral, you have a little bit of time, but if it’s unilateral, you need to patch the good eye at birth until the cataract can be removed at, say, 2-3 weeks of age under general anesthesia, unlike what they do with adults these days. Otherwise you will get a terrible deprivalional amblyopia underneath this. Of course, unfortunately, one fact that isn’t always known by patients or even eye doctors, is that it’s not just the cataract itself, but there’s often defects in the optic nerve, the whole way through the globe in the eye that had the congenital cataract – it’s really a birth defect that may affect both the anterior and posterior segment. You may not get good vision out of that eye, no matter how vigilant you are at removing the problem.

Juvenile glaucoma occurs in 1 of 5 of these patients later on, so they need to be monitored closely for that. That is one reason that we don’t seem any of these – they all go to pediatric ophthalmology, so unless you are co-managing with them, it’s less likely that you will see this as frequently as it does, in fact, occur.

I have included this sad picture of a poor child with poorly-adjusted aphakic spectacles, which are still used in some conditions – particularly if you have the posterior capsule disruption and a vitrectomy. Even at this age, the surgeon may not have enough space for an anterior segment IOL. You can prescribe aphakic contact lenses, which are, of course, preferred, but not always low-maintenance, even if you have medical necessity on the insurance for the patients to get them.

Our surgeons in Oregon will remove the cataract at birth. Before school starts, they will usually put an IOL in, but not during the same surgery. In the meantime, the patients will need some kind of correction in order to prevent the eyes from not focusing and the cortex from not developing.

For awhile, they were making an Air Optix O2 lens that was made-to-order that was up to +20.00D, but the SilSoft Super Plus from Bausch & Lomb is lens that has remained on the market. This is a hyper-Dk lens. It’s a soft lens, but the Dk is 340, and only 0.2% water content. Only a very wet baby eye could be comfortable with this lens, I think. It’s a very expensive lens; I think wholesale cost at the time of this recording was $136.00 per lens. It won’t absorb fluorescein and other...
things, which is nice, but it’s meant to be kept as a daily wear lens or an extended wear lens for up to a year or so, and then replaced. Notice that it comes in base curves as steep as 7.5 and in powers as high as +32.00D in 1.00D steps.

With your first order, they will often send you a teddy bear to give to the child.

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**Base Curves:** 7.5, 7.7, 7.9 mm  
**Diameter:** 11.3 mm  
**Powers:** +23.00D to +32.00D (1.00D steps)  
**Optical Zone:** 7.0mm  
**Center Thickness:** 0.51mm - 0.71mm

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**Leukocoria Cause #3: Coats’ Disease**

The third differential cause of white pupil, or leukocoria, is Coats’ Disease. Figure 30 is a child named Ryan from a parent’s blog, he is not a patient of mine, and the parent’s blog is HIPPA-exempt. ([http://savingryanseye.blogspot.com/2009/04/ryans-battle-with-coats-disease-brian.html](http://savingryanseye.blogspot.com/2009/04/ryans-battle-with-coats-disease-brian.html)) You can see clearly that he has a white pupil in his right eye and Ryan, like so many with Coats’ Disease, is a male patient, with a unilateral presentation.

Dr. Coats was a Scottish ophthalmologist from 100 years ago. He saw massive retinal exudates, particularly on one side. It turned out that 4 out of 5 of these unilateral cases are how Coats’ presents. Also, 75% of patients are males. There are adult forms of Coats’ that happen in senior citizens, but that was not well-known until recently.

When you look at the retina in Figure 31, and it was bilateral, but you didn’t know the age of the patient, you may be thinking Type II Diabetes. It looks like we have cotton wool spot presentations, there is infarction, perhaps. However, this is an 11 YO male who failed a school vision screening for football. It was discovered somehow, aside from the pupil defect, which was bad enough that the darkest gradient on the neutral density filter could not be put over the other eye to even out the pupils – making the rAPD OS greater than 1.8 log units. Almost 100 times greater than the other eye. Pinhole gave no improvement. Visual acuity was 20/300 in that eye, and there were cholesterol deposits.

When a fluorescein angiogram (FA) was taken of the same eye (Fig 32 (left)), we can see here what it looks like. The right eye was unremarkable, but in the left eye
we have the characteristic light bulb aneurysm at the end vessels, which we have a close-up of in Figure 32 (right). Note the hypofluorescence at the macula, and the lack of leakage in this early-stage FA. Most vessel dilation and telangiectasia is seen here. Figure 32 (middle) is a later-stage FA.

FA is a great way to diagnose Coats’ if you can do this on a child. Some worry about the rare anaphylactic reaction, but the dosage of the fluorescein can be controlled, and it can also takes about 30 seconds for it to reach the eye after it’s injected into the back of the hand. I’ve done these myself on older patients.

You see the light bulb aneurysms, or bulb-like telangiectasias as they are also called, in a girl with Coats’ Disease looking pretty noteworthy. If you just see this in one eye, girl or boy, that is suspect for Coats’ Disease. You will notice that these patients are a little older than what we saw with congenital cataracts and retinoblastoma.

**Stages of Coats’ Disease**

The white pupil will be caused in the one eye by the first stages of Coats’ Disease. You want to catch Coats’ before it reaches Stage 3 – the exudative detachment (Fig 34) because total detachment happens in Stage 4, and irreversible blindness in Stage 5. The goal is, while in 80% of the time you will still have one good eye that remains good throughout life, the goal is to preserve as much peripheral vision in the Coats’ eye as you can.

**Table 3**

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<th>Stages of Coats’ Disease</th>
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<td><strong>Stage 1</strong></td>
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<td><strong>Stage 4</strong></td>
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<td><strong>Stage 5</strong></td>
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Unfortunately, when the patient is young, not even preschool age, the Stage 1 cases are usually not caught without proper, dilated vision exams for these children. Depending on how much the fovea is involved, Stage 2, which is the average stage in which Coats’ is caught, carries with it a guarded prognosis potentially, depending on how much of the retina is involved. You will not reverse the damage that has been done in a retina like that in Fig 33.

**Pseudoretinoblastoma in Coats’ Disease**

Now Coats’ may appear to be like retinoblastoma, in fact, it has been called Pseudoretinoblastoma. You don’t want to give the child chemotherapy if they have Coats’ Disease, but notice in Figure 35, again we have a young child – not as young as you would expect for retinoblastoma – but if we have an older child with a unilateral presentation, keep Coats’ Disease in mind for a differential to retinoblastoma.

We don’t generally enucleate these eyes unless they are painful and blind. A phthisical eye would be, as in adults, the only time you would do this. In this case, the Coats’ Disease had gotten far enough along that it was causing a pressure spike of 35 mmHg in the right eye, the eye that was affected by the disease. (IOP was 14 mmHg OS) A retinal detachment had occurred, as well. Thus, you do want to get ultrasound through this eye if you can, to get an idea of what all is going on. Certainly an oral steroid could be used, as well, but in many states you would want to be doing that with ophthalmology.

![Figure 34: Retinal detachment visible through the pupil in a patient with Stage 3 Coats’ Disease](Photo source: www.aapos.org/terms/conditions/34)

![Figure 35: Pseudoretinoblastoma in Stage 4 Coats’ Disease](Photo source: www.diagnosticpathology.org/content/1/1/24)

Figure 36 is a composite picture of an eye 6 months after diagnosis in a 14 YO girl who had a controlled diet that limited her cholesterol intake to zero, which may have slowed the disease. What we are seeing here, which is like so many things such as CMV Retinopathy in AIDS and that sort of thing, is breaks in Bruch’s membrane. Laser photocoagulation, much like a Panretinal photocoagulation (PRP) must be done to save the central vision in this eye as best one can. In this case, we have retinal ischemia going on, and it looks just like diabetic retinopathy except that the patient is too young and does not have diabetes. There is a vitreous hemorrhage occurring at the arrow in this figure.

![Figure 36: Retinal hemorrhage in Coats’ Disease](Photo source: http://bjo.bmj.com/content/88/7/970.full)
**Coats’ differential: Toxocariasis**

Look how similar Coats’ may appear to Toxocariasis. (Fig 37)

Again, we talk about getting this worm from dogs, but in this case, this infection is just happening in one eye. We have a posterior pole granuloma, and we need to look to see if it looks calcified, as it would in the case of retinoblastoma, once again. There is a vitritis over the top of this, and the lesion is well-demarcated after you give the patient a steroid, particularly an oral steroid. We also have retinal folds and an APD. This particular patient, from Pacific University’s online digital collection, was actually 64 years old. Peripapillary detachments can occur in this condition, as well.

Looking at this composite retinal picture, Figure 38, this Coats’ Disease patient (the same one from Figure 36, who was an absolute vegetarian and had no cholesterol intake) managed to avoid getting to this stage of Coats’ until age 14. Her diet gave her a few more years’ worth of healthy vision than normal.

They are investigating using Avastin and Lucentis, the antiVEGF inhibitors, on this condition. Cryotherapy is the treatment of choice, followed by laser and then PRP, as was done in this image.

**Leukocoria Cause #4: Persistent Hyperplastic Primary Vitreous**

Our last differential for Leukocoria is Persistent Hyperplastic Primary Vitreous (PHPV). This is a cause of leukocoria that many may not think of right away. The child in Figure 39, has Walker-Warburg Syndrome, which is a major cause of PHPV. This patient’s name is Gabriella, and she is not a patient of mine — again, from a HIPPA-exempt parent blog. She has bilateral aphakia due to the PHPV. This is sort of like getting congenital cataracts in both eyes, but instead it’s the posterior capsule becomes opacified because the hyaloid canal has become fibrous.

It’s hard to get pictures on this, but Figure 40 shows what this looks like, even under general anesthesia, with a speculum in the eye. You know that we have Bergmeister’s Papillae and Mittendorf’s Dot, which might be the posterior and anterior aspects of the hyaloid artery, which feeds the lens in fetal development. When the hyaloid artery doesn’t dissolve, and at worst become vitreous floaters before birth, then what’s...
left is PHPV. This has been known for over 50 years (since 1955). We see an association perhaps with Coats’ Disease sometimes, and I have an article I can send you, if you are interested in that.

Sometimes PHPV will be fibrovascular, and can appear a lot like retinoblastoma, again. In the case of Figure 41, what we are looking at is persistent hyperplastic vitreous that didn’t extend all the way to the lens, but is not sticking just where the ophthalmic artery would leave the eye. It’s obscuring much of the posterior pole around the optic nerve.

It may resemble Retinopathy of Prematurity (ROP) with a dragged-disc appearance. Or, in the case of Fig 42, even a Morning Glory Disc appearance, I would say. We have this white, fibrous tissue and pigment around the outside of normal vessels, very much like we would have in a Morning Glory Disc. The patient with Walker-Warburg Syndrome is probably going to be nonverbal, nonambulatory, and intellectually handicapped – we will need to keep all of that in mind. This may be different than the Morning Glory Disc patient, who doesn’t have involvement beyond the eye.

Small eyes, microphthalmia, are common with this, and also esotropias when this occurs asymmetrically.

Figure 43 shows us what PHPV looks like from the anterior segment with an ocular speculum in place there. In Walker-Warburg, by the way, the main reason the patients don’t walk is the condition is primarily a malformation of the cerebellum affecting balance and eye movements. It is in the family of Arnold-Chiari malformations. Dr. Walker got to name two diseases, Dandy Walker being the other one, which can lead to hydrocephalus.

Some of these patients, it used to be thought that they would not live long enough to enter into school, and would be special needs cases, in any case. Thus, if you are not seeing congenital low vision and special needs, you may not be running into these patients, and may think they are extremely rare. For all intents and purposes, they would be, in the average optometric practice. They are not so rare if you see special needs and congenital low vision, as I have done for years in private practice. Also, if you work with pediatric ophthalmology, you will see these much more often.

Figure 44 shows what PHPV may look like again. The pictures are poor quality because with vitritis, it is hard to see the posterior pole. Traction on the disc and fibrous tissue extending from disc to lens makes it even more difficult to see the posterior pole. You can imagine how hard it is for patients to see out of this.


On Figure 45 (left) we see a patient that looks older than 3YO with PHPV. The patient has microphthalmia and what looks like a leukocornea on the left eye. On the right side, these patients are from Canada – one is 4 months old, the other is 10 months old. They are not siblings, they both have PHPV. In the Canadian providence from which they come, they get 1-2 cases each year.

Is this PHPV or Retinoblastoma?

Looking at some differentials here to wrap things up, Figure 46 shows a 3YO with an intraocular mass. It sure could be

Figure 46: PHPV or Retinoblastoma? Photo source: Wright 2, Fig 9-3
retinoblastoma – it’s looking all lumpy and calcified. The cornea of the right eye is a little microphthalmic, though I don’t know if you’d call it a cornea that is 11mm when it’s supposed to be 12mm microphthalmic, but I would call it that. Once they did ultrasound, there was a stalk going from the lens all the way back to the optic nerve head indicating it’s the much safer PHPV rather than cancer. This changes the treatment entirely to maybe just a vitrectomy, if that.

In Figure 47 we have again the traction caused by toxocariasis. Toxocariasis keeps coming back to haunt us.

In fact, when we presented this at Academy, it was an entire segment of the course. We could probably spend more time on it here, as well. I will leave this topic to Dr. Hanna if you have questions for her – being down in Florida, she is more of an expert in this topic than I.

When you look at this long fibrous tissue and the pars planitis you see here is mimicking PHPV with the peripheral granuloma. This will be elevated if you can get a 3D view of it using BIO or High Plus slit lamp.

Figure 48 is Ryan, the child from the parent’s blog at the beginning of this lecture who recovered from his Coats’ Disease. He will always have it, but he is doing OK. That right eye is still looking a little bright around the pupil.

You want to be aware that some cases of white pupil are due to media opacities, and these are generally the cause. Media being anything from cornea through the vitreous.

We looked at vitreal causes with PHPV, retinal causes including Coats’ Disease and the Retinoblastoma, and lenticular causes with congenital cataracts.

We need to remember that the most common cause is anisometropia, or in fact, strabismus not due to a blind eye with a tumor in it. Any size strabismus, including micro-esotropia will lead to a difference in brightness of Bruckner reflex, and that difference will also show up on flash photography.

**Review Capsule**

To study for your test, if you are taking this for credit, here are some review questions you may want to look into that will help for both credit and clinical practice.

1. Which brand of aphakic contact lenses comes in the highest powers? What do they cost?
2. Which systemic disease, a syndrome, causes PHPV?
3. Astrocytoma is a differential diagnosis for which case of leukocoria?
4. Which differential diagnosis in leukocoria causes vitritis at least 25% of the time?
5. Which cause of leukocoria might be mistaken for retinopathy of prematurity (ROP)?
I wanted to end with a picture of Dr. Hanna and I outside of our talk at Academy in Phoenix, AZ a couple of years ago. I hope you enjoyed this presentation. Both of us are happy to entertain questions, but most significantly me, as I am running the webpage for Continuing Education at Pacific University.

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**References:**