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Pediatric Uveitis

Developed by Virginia Goetz and Dr. Dax Rumsey for PedsCases.com.
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Introduction:

Hi everyone and welcome to Pedcases. My name is Virginia Goetz and I am a second-year medical student at the University of Alberta. I worked alongside Dr. Dax Rumsey, a Pediatric Rheumatologist at the Stollery Children's Hospital and University of Alberta in Edmonton, Alberta, to bring you information about pediatric uveitis. In this pedscase, we will explore this topic through the discussion of clinical cases that may appear in your practice. We hope you find this podcast helpful and interesting.

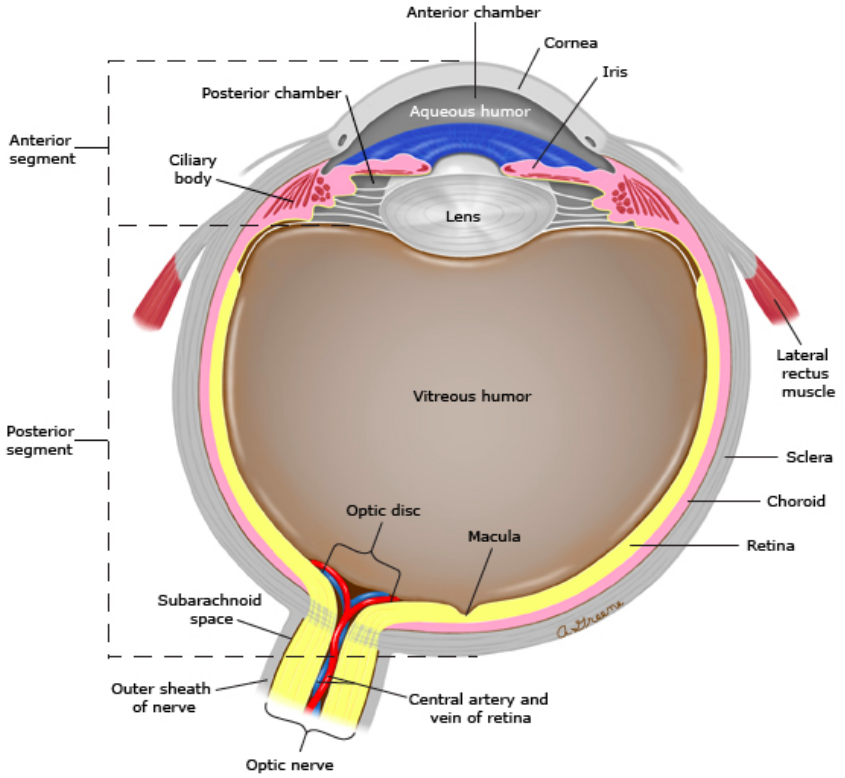
Objectives:

By the end of this podcast, you should be able to:

1. Generate a differential diagnosis for a child presenting with photophobia, redness, and tearing.
2. Discuss the fact that chronic uveitis (aka 'white uveitis') can present with no symptoms and is often associated with a rheumatic disease, most commonly juvenile idiopathic arthritis (JIA).
3. Review the relevant anatomy, classification, and potential complications of uveitis.
4. Differentiate the differences in etiology and presentation of a child with sudden-onset acute uveitis and insidious chronic uveitis.
5. Describe the diagnosis and management of a child presenting with either acute or chronic uveitis.
6. Delineate the prognosis for both acute and chronic uveitis.

Background Info:

- Uveitis is inflammation of the uvea, which is the middle layer of the eye, consisting of the iris, ciliary body, and choroid. It can be further classified based on anatomic location:
    1. **Anterior uveitis (most common)**: involving the anterior chamber of the eye, predominantly the iris; often called 'iritis'.
    2. **Intermediate uveitis**: primarily involving the vitreous.
    3. **Posterior Uveitis**: involving the choroid and/or retina.
    4. **Panuveitis**: inflammation in all three anatomic locations.



- In addition to anatomic classification, it is also important to classify uveitis as acute versus chronic because this has implications on management and prognosis.
    1. **Acute uveitis**: instances in which the onset was sudden, often symptomatic, and the duration of time the child has the disease is limited to <3 months.
    2. **Chronic uveitis**: used to describe a child who has persistent, often asymptomatic disease (>3 months) and prompt relapses of disease (within 3 months after discontinuation of therapy).
- Children presenting with uveitis may complain of photophobia, ocular pain, redness, tearing, and other signs that will be discussed later. The exception occurs in children with uveitis associated with Juvenile Idiopathic Arthritis (JIA) or with chronic, idiopathic uveitis, who are often asymptomatic.
- Uveitis may result from many causes including infections, systemic immune-mediated disease, and syndromes confined primarily to the eye. Many cases are also idiopathic or have no identifiable cause. This podcast will largely focus on pediatric uveitis related to systemic inflammatory diseases, in particular JIA. However, basic details on other causes will be provided.
- Uveitis associated with JIA accounts for 20-40% of cases of pediatric uveitis.
- With this basic background in mind, let's approach our first case.

Case 1: Acute Uveitis

- You are a medical student working in a general family medicine clinic.
- You are asked to see a 12-year-old boy named Max.
- No significant previous past medical history, healthy child.
- Max complains of a painful, red eye with some tearing.

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DDx:

- The symptoms of uveitis are non-specific. Thus, it is important to keep a broad differential diagnosis in mind for a child presenting with a red, sore eye.
- Take a moment to consider what other conditions (both common and uncommon) might lead a child to present with similar symptoms.
- Potential causes of red, sore, and tearing eyes include the following, with the first 3 being by far the most common:
    1. Allergic reaction
    2. Trauma
    3. Infectious (viral and bacterial) – could cause conjunctivitis or uveitis
    4. Drug reaction
    5. Rheumatic diseases associated with uveitis
        - Kawasaki disease – most commonly conjunctivitis, but could be associated with uveitis
        - A specific category of JIA known as enthesitis-related arthritis (ERA)
        - Bechet's disease
        - Early-onset sarcoidosis
    6. Other rare causes of uveitis
        - E.g. Tubulo-interstitial nephritis and uveitis (TINU) syndrome

- Narrowing down our DDx will depend on taking a good history and planning appropriate physical exam maneuvers and investigations.
- Take a moment to consider what questions you would like to ask Max and his mother.

History

Questions that are important to add to the basic history for this case:

History of the Presenting Illness:

- Is vision affected? This can be discerned by asking if the patient can still read normally (both near and far). It is important that a patient with impaired vision receive a detailed neurologic and ocular exam and be urgently referred to ophthalmology, if appropriate.
- Is there a foreign body sensation? Can you feel anything abnormal inside the eye or anything moving around? This is important because if there is a foreign body in the eye, it needs to be removed. A reported "scratchy" or "gritty" sensation in the eye could indicate allergic conjunctivitis, viral conjunctivitis, or dry eyes.
- Is there photophobia? Have bright lights been bothering you more than normal? Patients with iritis may have photophobia.
- Was there any trauma to the eye? Trauma can cause redness and soreness (i.e. a corneal abrasion).
- Do you wear contact lenses? In a patient who wears contact lenses, you may be suspicious for keratitis, which is inflammation of the cornea.
- Describe the consistency of the tearing. Is it primarily watery or purulent? Watery discharge is common in allergic or viral conjunctivitis and dry eyes. If the discharge is more opaque and purulent, then it might be a sign of bacterial conjunctivitis.

Associated Symptoms

- Any other infectious symptoms? This might include fever, cough, sore throat, ear ache, or rash. This can help discern if the child may have a bacterial or viral infection that can be causing uveitis symptoms.

- Is there any joint pain or swelling or inflammatory back pain? Enthesitis-related arthritis, a form of juvenile arthritis, is associated with acute, symptomatic uveitis.
- Any other systemic symptoms to suggest an underlying rheumatic disease, such as rashes, cardiorespiratory symptoms, or oral ulcers?

Other History

- Any risk factors for HIV? Children exposed to HIV are at a higher risk for the infectious causes of uveitis.
- Any history of herpes in the child or family? Herpes is known to cause infectious uveitis.
- Does the family have a cat? Both cat scratches and exposure to cat litter boxes can transmit infectious agents that cause uveitis (i.e. Bartonella henselae and toxoplasmosis, respectively).

To summarize, acute uveitis typically presents with ocular pain, redness, photophobia, and/or decreased visual acuity. Several other ocular conditions can present with similar signs and symptoms. If uncertain about the diagnosis, then the patient should be referred to an optometrist or ophthalmologist for further assessment, including a slit lamp examination. If there is concern for an underlying infectious, rheumatic, or other disease, then appropriate work-up and management should be initiated, as well.

Case 1:

- Back to the case!
- You take a thorough history, including all the questions discussed above.
- Max's mom indicates that his eyes started getting red about a week ago, but the pain and tearing have increased, prompting their visit today.
- No known trauma, allergies, or drug exposures.
- Max notes that he has had some difficulty reading in school recently because it seems more blurry than usual (decreased visual acuity).
- Max also notes that the bright light in the medical office right now is bothering him and he feels the need to squint (photophobia).
- Max denies having a recent infection and says he felt well until his eyes started becoming red and painful.
- His mom denies any fevers or weight loss.
- When asked about lower back pain or sore/swollen joints, Max says that he has noticed some discomfort sitting at school for long periods of time. He notes that he feels a bit sore "here" and points to his lower back. His mom also notes that Max has been complaining that his heels are sore and asking for looser and bigger shoes so that they don't push so hard and increase the pain.
- Satisfied with your history, think about the pertinent positives and negatives that inform your diagnosis.
- Move on to the physical exam.

Physical Exam

- You may start the physical exam with the patient's vital signs, height, and weight.
- You move on to assess the eye: assessment in the family practice office is limited and you will want to refer this patient for ophthalmologic evaluation. For now, you can look at a few basic things:
    1. Firstly, examine the pattern of redness and its location in the eye and severity.
    2. Examine the tearing - is it watery and clear or opaque?

3. Examine for any foreign bodies in the eye.
4. Measure visual acuity with a Snellen chart at 20 feet and measure near vision with a book at a comfortable distance.
5. Use a light to examine pupil dilation, reaction to light, and shape; check for red reflex.
6. Look for signs of chronicity of inflammation (e.g. posterior synechiae, which would present as an abnormally shaped pupil).
7. Perform a fundoscopic exam to evaluate the optic disc and related structures.
8. Examine for a layer of hypopyon (white cells) or hyphema (red cells) in the anterior chamber.

- Assess for possible JIA, including enthesitis-related arthritis:
    1. Examine all joints for swelling, tenderness and/or decreased range of motion.
    2. Examine for enthesitis around the knee, hip, foot, and ankle.
    3. Examine the back, including range of motion and palpation of the spine and SI joints.
    4. Examine the skin for rashes (possibly psoriatic arthritis).

Case

- Back to case
- Max's physical exam: normal vital signs, tracking growth chart well for height and weight, eyes are red, mild tearing is noted to be mostly a watery consistency, visual acuity is reduced, photophobia is noted with bright light.
- Tenderness around the SI joints as well as the Achilles tendon attachment at the calcaneus is tender and swollen on the right side. There is slightly reduced anterior spinal flexion.
- No joint swelling, warmth, erythema, or tenderness of any peripheral joints.
- No skin rashes.
- After your history and physical exam, you feel fairly confident that this is a presentation of acute uveitis in the context of enthesitis-related arthritis (ERA). You decide to perform further investigations. Take a moment and consider what investigations might be useful to you in this case.

Diagnosis and Investigations

- The patient will need to be referred to an ophthalmologist for an official diagnosis. The ophthalmologist will be able to perform a slit-lamp examination. The diagnostic signs of anterior uveitis on slit-lamp examination are the presence of inflammatory cells and increased protein concentration ("flare") in the aqueous humor of the anterior chamber of the eye. Deposition of inflammatory cells on the inner surface of the cornea may also be detected.
- Laboratory investigations for children with suspected uveitis may include:
    1. Anti-nuclear antibody (ANA).
    2. Urinalysis – to look for signs of tubulo-interstitial nephritis, such as proteinuria, hematuria, and sterile pyuria (present in the condition known as TINU, as above).
    3. HLA-B27 □ often positive in children with acute uveitis and enthesitis-related arthritis (ERA). This would be appropriate in Max's case, but usually must be ordered by a rheumatologist.
    4. Consider lyme serology, bartonella serology, toxocara serology, toxoplasmosis serology, herpes serology, CMV serology in appropriate historical and clinical

context not in Max's case because he has no history of these exposures and we are pretty confident his uveitis is related to ERA.
- Plain radiographs and MRI of the SI joints to observe any changes.

Case

- Along with your preceptor, you discuss your findings with Max and his mother and inform them that you think Max has acute uveitis associated with enthesitis-related arthritis (ERA), a form of JIA.
- They agree to your plan for further investigations and referral to an ophthalmologist and pediatric rheumatologist.
- Max's mother has questions about what they should do to treat Max and what they can expect going forward.

Treatment and Follow-up for the Uveitis:

- Treatment needs to be prompt and aggressive to prevent or minimize visual complications.
- Treatment should be supervised by both a pediatric rheumatologist and ophthalmologist with experience managing these types of cases.
- **Initial therapy (first-line treatment)**: topical corticosteroids with or without mydriatics. This is to be continued up to 3 months providing the inflammation is controlled, before gradually tapering frequency of eye drops. If disease activity increases or is refractory to treatment then progress to second line treatment.
    1. The mydriatic agent can relieve pain due to spasm of the muscles controlling the pupil and will also help to prevent the formation of posterior synechiae that may interfere with the function of the pupil.
- **Second line treatment**: if the acute uveitis is recurrent/refractory, then there may be a need to add a systemic medication, such as methotrexate. If this controls the inflammation, continue using methotrexate and taper topical corticosteroids. If disease activity increases or is refractory to treatment, then progress to third line therapy.
- **Third line therapy**: add a biologic medication, most commonly an anti-TNF alpha agent, such as infliximab or adalimumab.
- Max will need to be followed regularly thereafter to ensure his acute uveitis has resolved and he has not had any recurrences or complications.
- A detailed treatment description of enthesitis-related arthritis goes beyond the limits of this discussion. However, medications would be chosen to treat both the uveitis and the arthritis. Good communication between the rheumatologist and ophthalmologist are essential in these cases.

Case

- Max is seen by the pediatric rheumatologist and the ophthalmologist. His workup by the ophthalmologist revealed that he did have acute anterior uveitis.
- His lab results were:
    1. HLA-B27 positive
    2. ANA negative
    3. CBC normal
    4. Urinalysis normal
- SI joint radiographs were also normal. MRI showed mild, bilateral sacroiliitis.

Case Conclusion

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- You see Max again in the rheumatology clinic on your pediatric rotation. His mother tells you that Max is managing well, his uveitis has settled down, and the pain related to his arthritis and enthesitis have been minimized. They thank you for following them along their journey and for your helpful counselling. To conclude the case, we will focus on some important take-home points.

Take-Home Points from Case 1

1. Remember to consider a wide differential diagnosis when evaluating a child who presents with uveitis-like symptoms.
2. Uveitis results from many causes which can be narrowed down through a careful history. Don't forget to ask about:

a. Visual symptoms (photophobia and decreased visual acuity)
b. Infectious symptoms and exposures
c. Tender and swollen joints and low back pain
d. Other signs and symptoms of a rheumatic disease, including rashes, cardiorespiratory symptoms, and oral ulcers.

3. Your uveitis physical examination in the family practice office should include external examination of the eye and fundoscopy. When assessing for suspected JIA, it should include a thorough joint exam.
4. Investigations should be guided by the history and physical exam.
5. The management of a patient with acute uveitis and suspected ERA requires consultation with an ophthalmologist and pediatric rheumatologist.
6. The main treatment options for acute uveitis include topical corticosteroids and, more rarely, oral/sc methotrexate and/or biologics.
7. Follow-up and continued screening is important in this patient group and will be determined by ophthalmology and rheumatology. Most patients do well when managed in a multidisciplinary team and if treated early and appropriately.

Now let's use apply some of our new knowledge to approach a second clinical case. This case will illustrate a different, but equally important, presentation of uveitis.

Case 2: Chronic Uveitis

Case

- You are on your pediatric emergency rotation and your preceptor asks you to see a 3-year-old Caucasian girl named Melissa.
- You review her triage note and see that she is presenting today with progressive swelling of the right knee**.** It is noted that the swelling has been going on for approximately 6 weeks.
- Knowing this, you generate a list of diagnoses as you approach the room and think about some questions on history that will help you narrow it down. Think for a moment what might be on your differential and what you would want to ask on history.
- You go in to the patient's room to chat with the family and gain more information.
- The parents say that she has been limping recently and it has been getting progressively worse, which has prompted their visit to the emergency department today.
- They describe that Melissa seems to be stiff, particularly in the morning and does not want to play for 2-3 hours after waking up. They have not noticed Melissa waking up in the night due to pain.

- Other than the swollen knee, the parents report Melissa is a well child and she has not shown any other signs of illness. She has not had any recent fevers, infections, trauma, or travel outside of Canada.
- Your review of systems also reveals that she has not had any rashes, weight loss, abdominal pain, or ocular symptoms.
- Melissa has no significant past medical or surgical history and no relevant family history.
- Satisfied with your history, you leave the room to go debrief with your preceptor and discuss the case. Think for a moment what you might consider on your differential diagnosis and what you think is going on in Melissa's case.

Differential Diagnosis

- You summarize for your preceptor the pertinent details on Melissa's history.
    1. **Pertinent positives:** visibly swollen knee joint, limp, morning stiffness, insidious onset over the past 6 weeks.
    2. **Pertinent negatives**: lack of fever, infectious symptoms, constitutional symptoms, or trauma; unremarkable past medical and family histories.
- Based on these details, you and your preceptor agree that JIA is at the top of your differential. Other diagnoses you will keep in mind include:
    1. Reactive arthritis
    2. TB arthritis
    3. Lyme disease
    4. Chronic osteomyelitis
    5. Trauma
- You discuss your plan for the physical exam and possible investigations with your preceptor before you head back into the room.

Physical Exam

- The details of the physical exam for a child presenting with joint pain and swelling are beyond the scope of this pedscase. To quickly review, the physical exam will need to include:
    1. General appearance, vitals, height, and weight
    2. Examination of the heart, lungs, skin, and eyes since these organ systems are often affected in children with joint pain or swelling.
    3. Pediatric musculoskeletal screening exam, i.e. the Pediatric Gait Arms Legs Spine (pGALS) examination.
    4. A focused joint exam of the affected knee and any other joints that seem to be affected. This includes inspection, palpation, and range of motion of the joints.

Investigations

- A detailed discussion of investigations to order for this child presenting are beyond this case.
- In Melissa's case, you discuss ordering:
    1. CBCd
    2. CRP
    3. Liver and kidney tests
    4. Urinalysis
    5. ANA and RF
    6. An X-ray of the affected knee

Case

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- The results of Melissa's physical exam reveal normal vitals, height and weight that are in the 50th percentile for her age, normal cardio. and respiratory exams, normal skin findings, and no visible ocular abnormalities.
- Melissa walks with a limp and cannot run well. There is no leg length discrepancy.
- Your focused joint exam reveals a swollen right knee that is tender with range of motion. You also notice that Melissa has a slightly swollen left elbow and left wrist. Therefore, she appears to have 3 affected joints in total.
- Her laboratory results show CBCd normal, liver and kidney tests normal, urinalysis normal, and elevated CRP.
- ANA and RF pending.
- Her knee x-ray showed soft tissue swelling only.
- You discuss the results of the physical exam and investigations with your preceptor. You agree that this appears to be a presentation of JIA, specifically the oligoarticular category and that Melissa should be referred to pediatric rheumatology. Additionally, you remember that uveitis is associated with oligoarticular JIA and that it is important to refer children for a slit lamp examination because presentations of uveitis in this category of arthritis are most often asymptomatic. Your preceptor is impressed with your suggestion and asks you to tell them more about uveitis in oligoarticular JIA. How does Melissa need to be screened for uveitis moving forward?

Chronic Anterior Uveitis

- In Case 1, we discussed acute uveitis with the example of Max, a young boy who presented with symptomatic uveitis in the context of ERA. There are 7 categories of JIA and ERA is the only category that is associated with acute, symptomatic uveitis. The other categories, including oligoarticular JIA, as in Melissa's case, are associated with chronic, asymptomatic (aka "white") uveitis.
- Risk of chronic uveitis is related to the category of JIA, sex of the child, and the age at onset of JIA. The risk is highest in girls with oligoarticular JIA with an early onset (<7 years), who are ANA positive. Melissa fits this high-risk category (as her ANA ended up being positive).
- In almost half of all patients with uveitis, it occurs just before arthritis is diagnosed, at the time of diagnosis, or shortly thereafter. Therefore, Melissa must be urgently referred for an eye exam because she may already have uveitis and, if not, is at risk for developing it soon.
- As discussed in Case 1, the diagnosis of uveitis will require slit-lamp examination by an optometrist or ophthalmologist. Should a patient be diagnosed with uveitis by an optometrist, they should then be referred to an ophthalmologist for treatment and follow-up thereafter.
- Along with initial slit lamp examination, it will also be important that Melissa follows repeat screening at prescribed intervals. Because she is in the highest-risk group (early age of onset, oligoarticular JIA, and ANA positive), screening eye exams must be performed every 3 months for the first 4 years, every 6 months for the following 3 years, and then annually thereafter.
- Notably, many cases of chronic uveitis are idiopathic or not associated with any known infection or underlying systemic disease. These cases are still often co-managed by ophthalmology and rheumatology.
- Your preceptor accompanies you back to the room to discuss this with the family.

Case

- Melissa's family is happy to hear you have a likely diagnosis for her and that she will be referred to pediatric rheumatology for further work-up and management of her suspected JIA. (Treatment for oligoarticular JIA will not discussed here).
- They ask you about the treatment, complications, and prognosis of chronic uveitis if Melissa is determined to have that.

Treatment of Chronic Uveitis

- The treatment of chronic uveitis is very similar to acute uveitis as discussed in case 1. This includes topical corticosteroids, oral/sc methotrexate, and biologics.
- However, chronic uveitis more commonly requires treatment beyond topical corticosteroids that acute uveitis does.
- You explain that chronic uveitis treatment would likely require long-term use of therapy and even with therapy-induced remission, uveitis relapses may occur. Thus, Melissa will need to undergo long-term screening.

Complications and Prognosis of Chronic Uveitis

- The course of chronic anterior uveitis in patients with JIA is variable. It may last for months, years, or even persist into adulthood.
- Sometimes the course is intermittent (relapsing and remitting) and sometimes it is persistent.
- Complications of chronic uveitis are frequent and increase with the duration of active disease. Long-term complications are more likely with chronic uveitis than with acute uveitis.
- Possible complications of uveitis can include: synechiae (adhesions between the iris and lens or iris and cornea), band keratopathy (deposition of calcium in the corneal epithelium), cataract (opacification of the lens), glaucoma (optic nerve injury resulting from increased intraocular pressure), hypotony (very low intraocular pressure), and decreased visual acuity/blindness.
- These complications are more common with chronic uveitis or recurrent, refractory acute uveitis.
- The activity of uveitis does not necessarily parallel arthritis activity. It may be active while the arthritis is in remission.
- Visual loss is more likely in chronic uveitis, but less likely when uveitis is detected early and treated appropriately.
- Chronic uveitis may have a lasting impact on a child's quality of life.

Case Conclusion

- Melissa's initial slit-lamp examination revealed anterior chamber inflammation of the right eye.
- Melissa was treated with NSAIDs, methotrexate, and topical corticosteroids for her oligoarticular JIA with associated uveitis.
- Sustained clinical benefit was rapidly obtained, with resolution of articular manifestations and uveitis. She was able to come off the steroid eye drops.
- Melissa continued regular follow-up with both her pediatric rheumatologist and ophthalmologist.
- This concludes our second case. Let's summarize some important take-home points from this case.

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Take-Home Points from Case 2

1. Remember to consider a wide differential diagnosis when evaluating a child who presents with joint pain and swelling.
2. JIA is the most common chronic rheumatic disease of childhood, and oligoarticular JIA represents about 50% of all JIA cases, with chronic uveitis occurring in approximately 30% of children with this category of JIA.
3. The high-risk group for chronic uveitis includes children with:

a. Oligoarticular JIA
b. Age of onset <7 years
c. Female sex
d. ANA positivity

4. The management of a patient with oligoarticular JIA with associated chronic anterior uveitis requires consultation with a pediatric rheumatologist and ophthalmologist. It is important that the child is referred to both specialities immediately at the time of diagnosis/suspected diagnosis. For many children, an optometrist can do the initial screening. If uveitis is found, then they will be transferred to an ophthalmologist's care.
5. Treatment options for chronic uveitis include topical corticosteroids, oral/sc methotrexate and other Disease Modifying Anti-Rheumatic Drugs (DMARDs), and biologics.
6. Continued uveitis screening of children with JIA is incredibly important to prevent and minimize the long-term complications of chronic uveitis. Screening intervals are determined based on risk, with high risk groups like Melissa being screened every 3 months.
7. Remember that uveitis can be idiopathic, as well (i.e. not associated with any infection or other systemic disease). These cases are still often treated the same way, with involvement of both ophthalmology and rheumatology.

Thank you for taking the time to listen to our podcast. We hope you found the cases and information provided on uveitis helpful and interesting. Have a great day!

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