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Editor's Note

Dear Colleagues,

In my previous notes, I talked about the light at the end of the pandemic tunnel. Of course, I mean the vaccine. One would think that if there were a lifesaving intervention people would be fighting to get it. Yet we have lifesaving vaccines and people are running away from them. I am not talking about anti-vaxxers. I am speaking of normal, middle-of-the-road people who are either afraid of the vaccine or just don't believe that it is necessary. Most of these people are "on the fence" or "Fencers" as I call them. What is going on?!

Many of us who have been lifelong, ardent vaccine proponents are frustrated. I am personally not only frustrated by anti-vaxxers but also by many well-meaning vaccine zealots. If we are to convince millions who are not anti-vaxxers but simply concerned about the vaccine and are on the fence, we need to convince them. We are not going to convince them by being absolutists. We need to accept what we don't know and stress what we do know but also have the humility to say what we don't know.

Biological plausibility, scientific rationale, medical extrapolation, harm risk reduction, and public health versus personalized patient level decision making are things that we discuss in medicine all the time. However, these concepts are not always easy to explain, even to other healthcare professionals. Why else would less than 50% of healthcare workers get vaccinated?

We have a lot of work to do, and we must double up our efforts. Until we reach herd immunity, we are never going to get rid of the Coronavirus. As long as there are susceptible hosts, the virus will have opportunities to replicate. Replicating viruses mutate, and that is how we get variants. If we believe the Delta variant is bad, we haven't seen anything yet. If we don't control the pandemic now, we will for sure see even worse variants.

Then there are our children. At the time of this writing, children under 12 years of age are not eligible for the Coronavirus vaccine. How do we protect them right now and when they go to school in the Fall? The only way, currently, is to make sure that everyone around them is vaccinated so that we can "cocoon" the kids and protect them. It is with this in mind that I believe parents should demand that all eligible individuals in the school system be vaccinated against the coronavirus.

We need to protect the healthcare workers for their own sake and to make sure the healthcare system does not fracture because of absences due to the coronavirus. It is time for healthcare leaders to stand up and make coronavirus vaccinations mandatory for anyone working in a healthcare institution, not just hospitals. It will take courage for Presidents and CEOs to stand up for what is right. Leaders in a city or a region should collaborate in this effort so that this mandate is regional, preventing healthcare workers from moving to another institution to avoid vaccination. Healthcare institutions already have legal protection as a result of the Federal Court decision in the Texas case. In addition, several professional healthcare organizations have already recommended or implemented mandatory coronavirus immunizations or are moving in that direction.

Finally, and most importantly, not only do we need to make sure that Americans are vaccinated, but America must also make every effort to assure that the vaccine is globally available to all. It is not only the right thing to do, but also in our best interest. If we vaccinate the under-resourced parts of the world at the current rate, then it will take decades to control the pandemic. The United States must take the lead, as it did in the eradication of smallpox and in controlling the spread of polio. If we can't or won't do it, no one else will. We are the ones they are waiting for.

We talk about the "coronavirus epidemic of the unvaccinated" in the US. If the global population is not vaccinated, we will have a "pandemic of the unvaccinated". We led the global effort against smallpox and polio. We need to do the same for the Coronavirus.

Mobeen H. Rathore, MD, CPE, FAAP, FPIDS, FSHEA, FIDSA, FACPE
Editor, The Florida Pediatrician

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STUDENT ARTICLE

Chronic Recurrent Multifocal Osteomyelitis: A Forgotten Diagnosis

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ABSTRACT

Chronic recurrent multifocal osteomyelitis (CRMO) is a rare condition characterized by longstanding inflammatory bone lesions. Often initially misdiagnosed as infectious osteomyelitis, the time to accurate diagnosis is frequently lengthy and may lead to unnecessary diagnostic studies and ineffective treatment strategies. We discuss a case of a seven-year-old male who initially presented with right knee pain, followed by intermittent left ankle and hip pain, who was subsequently diagnosed with CRMO eight months later. This case report highlights to primary care providers the importance of considering CRMO as a potential diagnosis in children with recurrent bone pain.

INTRODUCTION

Chronic recurrent multifocal osteomyelitis (CRMO) is an uncommon auto-inflammatory condition generally found in pediatric populations. The disease consists of skeletal lesions, most commonly involving metaphyseal regions of long bones, clavicles, and vertebral bodies. However, CRMO is also closely associated with other inflammatory conditions of the skin and gastrointestinal system, such as inflammatory bowel disease, acne, and psoriasis. The pathophysiology behind CRMO is not yet entirely understood, but is thought to have a genetic component based upon an imbalance between pro- and anti-inflammatory cytokines.[1]

Patients generally present due to refractory bone pain with or without any physical findings such as erythema or swelling. Diagnostic evaluation usually begins with x-rays, then progression to Magnetic Resonance Imaging (MRI) and/or bone scans.[2] When the medical history, physical and radiologic findings are typical, the diagnosis can be made without a biopsy. However, since CRMO is primarily a diagnosis of exclusion, thus biopsies may be required to distinguish CRMO from infectious or malignant pathologies when presentation is unclear.[3]

We discuss a case of a seven-year-old male who initially presented with right knee pain, followed by intermittent left ankle and hip pain, who was subsequently diagnosed with CRMO eight months later.

CASE PRESENTATION

A seven-year-old male presented to his pediatrician with right knee pain after a fall off his bike. Over time, the knee pain improved, but he began experiencing intermittent pain in his left ankle and hip that worsened with activity. His pediatrician recommended ibuprofen and heating pad as needed. However, he continued experiencing refractory pain.

He was fully immunized with no significant past medical history or family medical history. He experienced no joint swelling, erythema of skin overlying joints, fever, weight loss or night sweats. He had no significant travel, exposure to wooded areas, or sick contacts.

Due to refractory pain, x-rays of the left hip and ankle were obtained and were normal except for soft tissue swelling. Laboratory tests were mostly within normal limits with the exception of a slightly elevated platelet count (523 K/mcL), an elevated erythrocyte sedimentation rate (ESR) (43 mm/h), and a slightly elevated peripheral blood neutrophil percentage (64%). MRI of the left ankle and pelvis was performed and demonstrated multiple focal bone lesions and areas of marrow edema and contrast enhancement (figures 1-3). The MRI findings led to concern for the possibility of osteomyelitis, histiocytosis, or malignancy.

Biopsies of the left proximal femur and the left distal tibia lesions were performed. Pathology of the left proximal femur showed hypocellular subcortical marrow without any evidence of inflammation or neoplasia. The left distal tibia, however, showed hypocellular subcortical marrow with histological features associated with chronic osteomyelitis. The lesions were negative for findings of neoplasia (figures 4-5). Tissue cultures for bacteria, fungi and mycobacteria were negative. The patient was referred to Pediatric Infectious Diseases. He was subsequently diagnosed with CRMO and was treated with naproxen with excellent response.

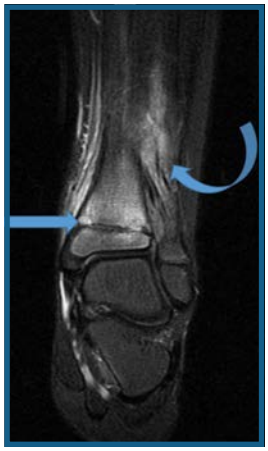

Figure 1

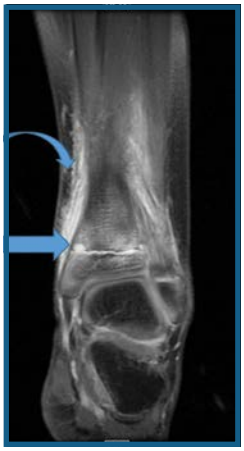

Figure 2

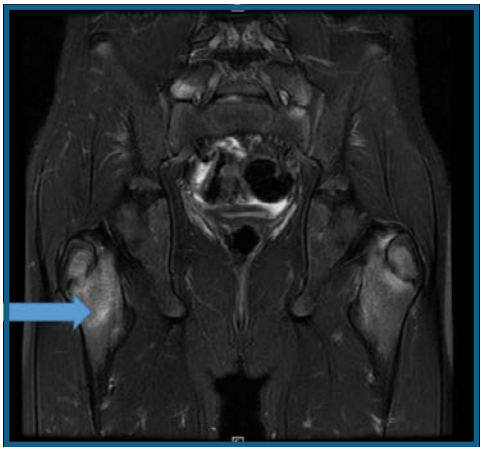

Figure 3

Figure 1: Coronal T2-weighted iterative decomposition of water and fat with echo asymmetry and least-squares estimation (IDEAL) MRI image of the left ankle shows focal hyperintense signal just superior to distal tibial physis (straight arrow) and within the soft tissues above the ankle (curved arrow).

Figure 2: Coronal T1-weighted MRI image of the left ankle after injection of intravenous gadolinium contrast shows increased focal enhancement just superior to distal tibial physis (straight arrow) and within the soft tissues above the ankle (curved arrow).

Figure 3: Coronal T2-weighted iterative decomposition of water and fat with echo asymmetry and least-squares estimation (IDEAL) MRI image of the pelvis and hips shows patchy hyperintense signal in the right proximal femur (arrow) representing marrow edema.

DISCUSSION

When a child presents with the primary symptom of refractory bone pain, the initial differential generally includes infectious osteomyelitis, benign bone tumors, and primary bone malignancies. The differential expands depending on other features of the history and clinical presentation. When coupled with leukocytosis, fever and weight loss, possibilities such as leukemia and lymphomas must be considered. In patients with a history of chronic steroid use, avascular necrosis must be ruled out. In patients with malnourishment concerns, the possibility of vitamin deficiencies, particularly vitamin C deficiency leading

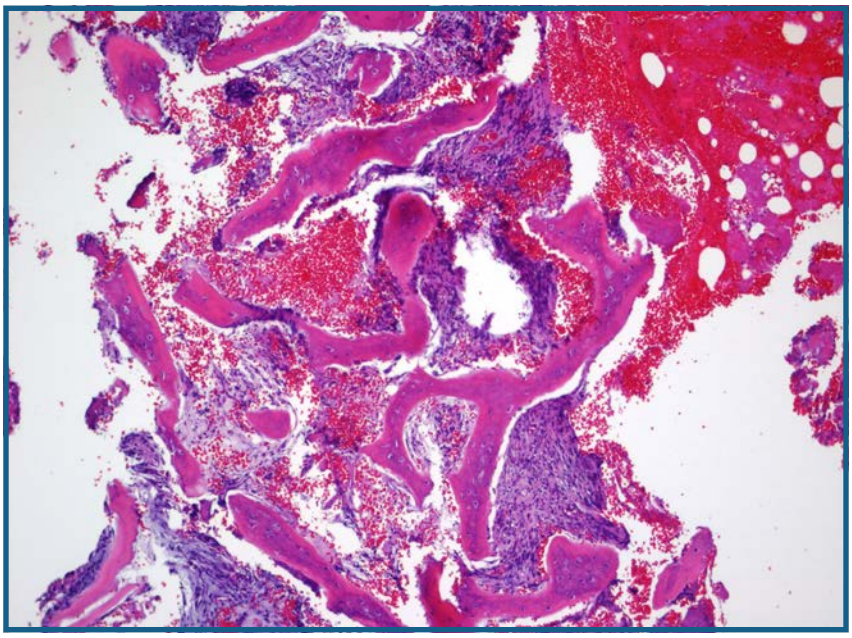

Figure 4: Histopathology of the left distal tibia on low power

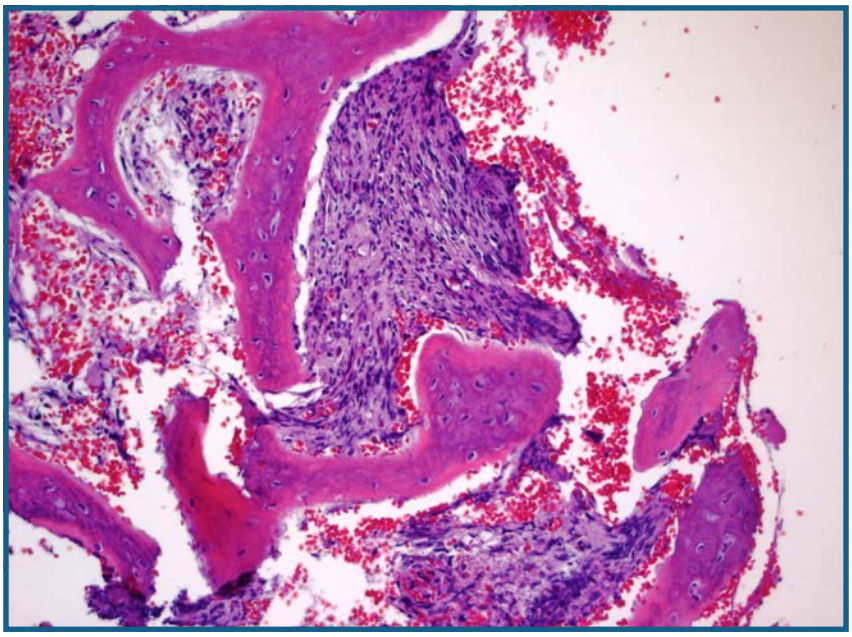

Figure 5: Same on high power, showing hypocellular subcortical marrow with features associated with chronic osteomyelitis, and no evidence of neoplasia.

to scurvy, must be considered. CRMO can be a particularly elusive diagnosis. Laboratory studies such as peripheral white blood cell counts, ESR and C-reactive protein (CRP) are often normal or only slightly elevated.[1]

X-rays are frequently the first imaging step in the diagnosis. While they are often normal in early disease, they may reveal areas of lytic changes surrounded by sclerosis. In the past, x-rays were often followed by a technicium-99 bone scan to survey the extent of involvement, but bone scan has now been mostly supplanted by use of MRI. This is a much more sensitive study and can often reveal changes earlier on, such as edema and soft tissue involvement of the surrounding area.[2] When biopsy is indicated, the histopathologic findings generally include an inflammatory infiltrate consisting of lymphocytes, plasma cells, histiocytes, and occasional neutrophil granulocytes.[4]

The patient in this particular case had a diagnostic delay of almost eight months. Unfortunately, this length of delay in diagnosis is typical in CRMO, since it is very uncommon condition not often considered in a physician's differential diagnosis in a patient complaining of bone pain. Indeed, the average time of symptom onset to CRMO diagnosis is 15 months.[5] In order to avoid delays in diagnosis, physicians must be diligent in including CRMO in the differential for such cases. Because CRMO is so often presumed to be infectious osteomyelitis, the work-up must be focused on discriminating between the two entities. The diagnostic modalities of choice for both infectious osteomyelitis and chronic recurrent multifocal osteomyelitis are generally an MRI followed by bone biopsy if deemed necessary. However, in infectious osteomyelitis, bone cultures from biopsy typically are positive for a specific organism, whereas in CRMO cultures are be negative by rule. Thus, providers may waste significant time and costs by repeating cultures in CRMO in what are futile attempts to identify an infectious etiology. The presence of typical MRI findings coupled with a negative culture is highly suspicious of CRMO, and further work-up is often not required.

Antibiotics have been proven to play no role in the management of CRMO. Nonetheless, a study published in 2018 reported that one-third of 284 surveyed patients with CRMO received antibiotics prior to their diagnosis, and one-fourth of those patients received them for greater than six months.[6] Such antibiotic courses are lengthy, expensive, and entirely unhelpful for CRMO and also come with significant side effect profiles, increased risk for *Clostridium difficile* infection, and potential to contribute to overall antimicrobial resistance.

Treatment of CRMO typically begins with nonsteroidal anti-inflammatory drugs (NSAIDs), which have been associated with a response rate of up to 80%.[2] In patients who fail to respond to NSAIDs, trials of temporary or chronic oral corticosteroids have been used, often with great benefit. In refractory patients, various agents such as methotrexate, TNF-alpha inhibitors, bisphosphonates, and IL-1 receptor blocking agents have been attempted with mixed results.[3]

The intent of this report is twofold – to share an interesting case of an uncommon disease, and to remind medical practitioners to consider CRMO as a potential diagnosis in chronic and/or recurrent bone pain in children. While CRMO is infrequent, it is important to keep the disease in mind in patients with confounding refractory bone pain and the characteristic imaging findings. With greater awareness of this condition, perhaps medical providers will be able to prevent unnecessary diagnostic evaluations, reduce unneeded courses of antibiotics, and shorten the time to effective treatment.

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STUDENT ARTICLE

Vernal Keratoconjunctivitis in an Adolescent Female

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CASE PRESENTATION

A 15-year-old African American female was referred to an academic ophthalmology clinic by her ophthalmologist for management of bilateral (OU) keratitis being treated with daily dexamethasone drops. She initially presented to her primary provider with bloodshot eyes with complaints of a foreign body sensation and episodes of "white spots" on her eyes. She was referred to a pediatric ophthalmologist who noted that she had severe photophobia, and her vision was 20/200 OU. She was subsequently started on dexamethasone drops which relieved many of these symptoms and partially improved her vision. Recently however she had worsening blurriness when opening her eyes that was partially resolved with blinking. She denied any visual disturbance, pain, or conjunctival injection. A review of systems was positive only for atopic dermatitis.

Visual testing showed uncorrected distance visual acuity of 20/20 OD (right eye) and 20/70 OS (left eye). Her intraocular pressures were within normal limits at 16 mmHg OD and 13 mmHg OS (normal range: 12-22mmHg). Neurologic examination showed that her pupils were equal, round, and reactive to light bilaterally with full visual fields and intact extraocular movements. Detailed examination via slit lamp revealed significant, large papillae and follicles over the upper tarsal conjunctiva OU (Figures 1 & 2). Corneal examination showed mild inferior scarring and thinning OD and central thinning and scarring OS with vessels encroaching into the cornea (Figure 3). The remainder of the examination including the anterior chamber, iris, and lens revealed no changes or pathology.

The patient was subsequently diagnosed with vernal keratoconjunctivitis (VKC) involving the corneas. It was presumed that she had previous shield ulcers that had healed with residual scarring of the corneas. The patient was switched to 0.05%

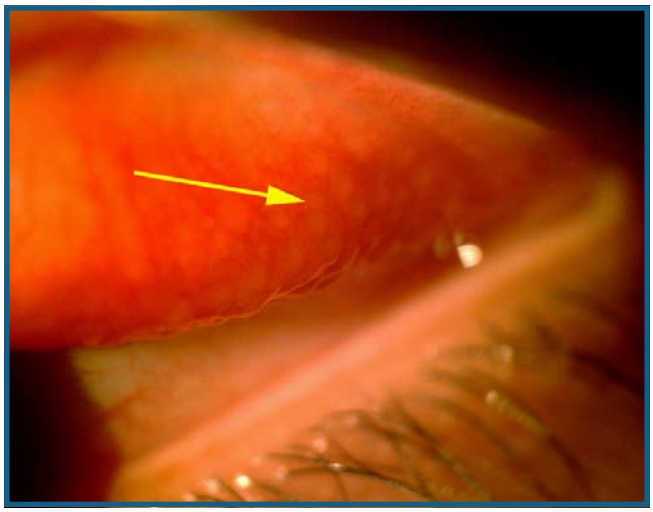

Figure 1: Follicular reaction on the upper tarsal conjunctiva

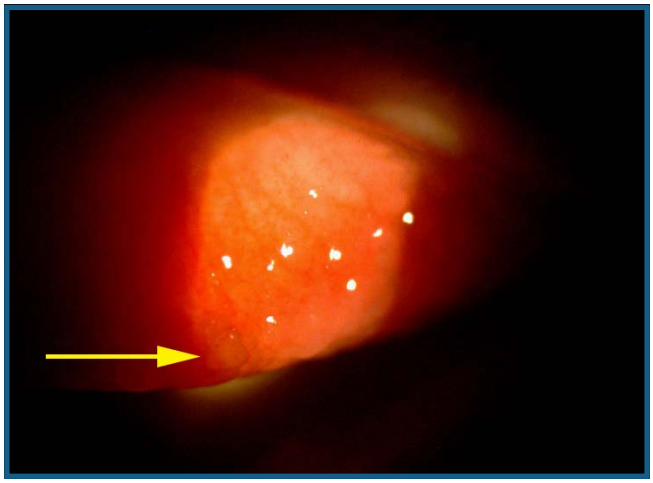

Figure 2: Giant papillae (arrow) on the upper tarsal conjunctiva

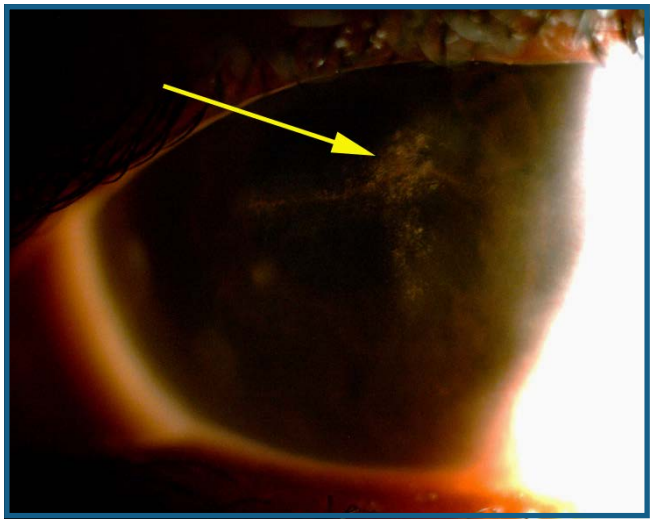

Figure 3: Central corneal scarring from healed shield ulcer

cyclosporine (Restasis®, Allergan) and olopatadine (Pataday®, Alcon) drops to reduce her long-term steroid dependence with the understanding that she would occasionally require steroids (e.g. dexamethasone drops) for future disease flares. Given the vision changes in her left eye, she was counseled that she could possibly benefit from contact lens fitting in that eye in the future if desired.

DISCUSSION

Vernal keratoconjunctivitis (VKC) is a condition of chronic allergic inflammation of the external eye. The condition is more common in hot, arid regions of the world, but is also seen in the United States.[1,2] It tends to occur seasonally (hence "vernal" referring to the Spring) though many patients have recurrent symptoms throughout the year. The condition tends to affect young patients and is more common in males than females.[3] Many patients outgrow the condition as they progress through puberty, while some have symptoms that persist into adulthood. As seen in this patient, a personal or family history of atopy is common. Published studies suggest nearly half of patients with VKC have a family history of autoimmune or immunologic disorders.[4,5]

The pathophysiology of VKC has not been fully elucidated, but immunoglobulin E (IgE)-mediated Type 1 hypersensitivity, T helper cell type 2 (Th2)-mediated Type 4 hypersensitivity, and eosinophil-mediated processes are all believed to be involved.[6,7,8] Due to the difference in prevalence between boys and girls, there may also be an endocrine component, but no formal pathways have yet been identified.[1,9] Ocular allergy testing and the development of ocular biomarkers may help better elucidate the underlying processes.[10]

Patient-reported symptoms often include severe itching, photophobia, tearing, foreign body sensation, discharge (often described as thick or "ropy"), pain, and blurry vision.[11] Three subtypes of VKC exist: conjunctival, limbal, and mixed. The classic examination finding in VKC is giant (greater than 1mm in diameter) "cobblestone-like" papillae on the upper tarsal conjunctiva (Figures 1 & 2) that are visualized by flipping over the upper lid. Other signs include hyperemia, thick discharge, ptosis (droopy eyelid), blepharospasm, opacification of the limbal conjunctiva and peri-limbal Horner-Trantas dots. These punctate white dots represent accumulations of epithelial cells and eosinophils and are consistent with the history of "white dots" reported in this patient report.[1,11] Often most concerning is that progression of the disease can lead to corneal involvement and subsequent vision loss. Corneal involvement ranges from mild punctate erosions to large erosions and ulcers. Some erosions heal completely, others can progress to large shield ulcers (Figure 3) with subsequent neovascularization (as seen in this patient) and vision loss.[12]

As VKC is a chronic condition, treatment similarly requires long-term medication use and routine follow-up. Basic non-pharmacologic approaches include the avoidance of nonspecific triggers such as allergens (e.g., environmental, dander, etc.), the use of cool compresses, and the use of preservative-free artificial tears.[13,14] A proposed grading system exists and may aid in treatment decisions, however the first-line treatment is typically a dual-acting mast cell stabilizer and antihistamine such as olopatadine as prescribed to this patient.[14,15] If the patient does not respond to initial therapy within a few weeks, referral to an ophthalmologist is warranted for possible corticosteroid or other therapeutic considerations. Topical calcineurin inhibitors have been shown in randomized trials to significantly improve signs and symptoms of VKC.[16] Topical cyclosporine is especially preferred in patient with shield ulcers, as was seen in our patient, since they do not inhibit ulcer healing. Even with improved control with cyclosporine, patients may still require occasional topical corticosteroid treatment for flares, as was discussed with this patient.[16] A wide range of other therapies have been studied for VKC including vasoconstrictors, NSAIDs, antimetabolites, and newer monoclonal antibodies such as omalizumab (anti-IgE) with varying success.[13, 17, 18]

Many patients with VKC experience resolution of the disease with puberty. Chronic treatment until resolution may be required and treatment regimens should be tailored based on individual response to treatment and symptom severity.

CONCLUSION

Vernal keratoconjunctivitis is an uncommon, chronic inflammatory condition of the external eye that presents with severe itching, photophobia, tearing, foreign body sensation, discharge, pain, and blurry vision. Examination findings classically include large "cobblestone-like" papillae of the upper tarsal conjunctiva and possible disease involvement of the limbus and/or cornea. Initial treatment includes avoidance of allergens and treatment with a topical dual-acting mast cell destabilizer and antihistamine. Patients who do not respond to initial treatment should be referred to an ophthalmologist to explore other treatment options including calcineurin inhibitors, corticosteroids, and more.

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STUDENT ARTICLE

The Challenge of Diagnosing Common Variable Immunodeficiency in the Face of Immunosuppression and Nephrotic Syndrome

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Children with common variable immunodeficiency are often challenging to diagnose. We present a case of common variable immunodeficiency and nephrotic syndrome and discuss features, including immunosuppression, which made the diagnosis challenging. This case underlines the importance of suspecting underlying immunodeficiencies in children who are therapeutically immunosuppressed, but infections persist once such therapy is stopped.

INTRODUCTION

Combined variable immunodeficiency (CVID) represents a heterogeneous group of disorders characterized by hypogammaglobinemia, poor or absent response to immunization, and increased susceptibility to recurrent and chronic infection.[1] Diagnosis of CVID typically occurs in the third decade of life. However, the second-highest incidence falls between ages 5 to 10 years. Typical presentation in both adults and children include pneumonia, sinusitis, gastroenteritis and otitis media. Autoimmune disorders, splenomegaly, and bronchiectasis are also common findings.[1,2] Typical presentations of CVID may require extensive evaluations and time to diagnose.

We present the second reported case of CVID in a patient with a history of nephrotic syndrome caused by minimal change disease (MCD). Unlike the first reported patient, the diagnosis of nephrotic syndrome and subsequent immunosuppressive therapy preceded the diagnosis of CVID, making the diagnosis of CVID even more challenging.

Recurrent infections in patients taking immunosuppressive medications requires the clinician to distinguish medication-induced complications from possible underlying conditions.

CASE REPORT

A 9-year-old boy with nephrotic syndrome, recurrent infections, and a chronic cough presented to his pediatrician in April with one day of fever up to 105.4°F and one episode of non-bloody, non-bilious emesis. The pediatrician obtained a complete blood count which was notable for a leukocyte count of 26,000 cells per μL with a neutrophil predominance and then referred the child to the emergency department (ED).

In the ED, the patient presented with fever and otherwise normal vital signs. The patient was in no distress, and other than the fever, had a normal physical examination including clear lungs bilaterally. C-reactive protein was elevated to 9.2mg/dL. A chest X-ray showed consolidation of the left lower lobe. Medical record review revealed 4 prior pneumonias in the last 2 years, with two hospitalizations in 2020, prompting a more thorough history.

The patient was born at term without complications. His early childhood was complicated with recurrent ear infections and multiple ED presentations for fever. At 20 months of age, following five episodes of otitis media in a six-month period and persistence of middle ear effusions, the patient underwent bilateral tympanostomy tube placement that ultimately did not resolve the ear infections.

In 2012, at 27 months of age, he presented to the ED with testicular swelling. Urinalysis indicated significant proteinuria resulting in an evaluation by nephrology and a diagnosis of nephrotic syndrome. Because the patient relapsed during steroid therapy, a renal biopsy was obtained which demonstrated minimal change disease (MCD). For the next 2 years the patient experienced multiple relapses requiring escalation from steroids to cyclosporine, tacrolimus, and rituximab.

Despite gaining better control of edema and proteinuria with initiation of tacrolimus in 2014, his frequent presentations for otitis media, pneumonia and diarrhea continued and were attributed to immunocompromised status secondary to pharmacotherapy for nephrotic syndrome. Tacrolimus therapy was discontinued in late 2017, and the patient achieved remission of nephrotic syndrome in January 2018. He continued to follow-up with nephrology. In February he 2020 was found to have a low serum IgA level of 8mg/dL during a gastroenterology evaluation for his recurrent diarrhea.

Given the patient's history of recurrent infections before immunosuppressive therapy commenced and which continued after the treatment had stopped, we initiated a workup for immune deficiency. The evaluation revealed low serum levels of IgG (235.2 mg/dL), IgM (<15 mg/dL), and IgA (5.3 mg/dL) with poor pneumococcal antibody titers after immunization consistent with CVID. He received IVIG on the second day of hospitalization with no adverse reactions and remained afebrile without use of antipyretics for the duration of his hospital stay. He was discharged with antibiotics and follow up with infectious disease for monthly IVIG infusions.

DISCUSSION

Our patient presented with persistent infections in his first two years of life, but his diagnosis of CVID was not made until he was 9-years-old. This is not uncommon. In a study of 95 patients with CVID, mean time from first presenting symptoms to correct diagnosis was 8.5 years.[3] Although autoimmune processes are often implicated in nephrotic syndrome, and CVID is strongly associated with autoimmune disease, this is only the second reported case of nephrotic syndrome in a patient with CVID. In fact, in a 30-year retrospective review of both pediatric- and adult-onset CVID, cytopenias such as autoimmune thrombocytopenia and autoimmune hemolytic anemia made up the largest proportion (33%) of autoimmune disorders with no mention of kidney disease.[4]

Renal involvement is rare in both pediatric and adult populations carrying a diagnosis of CVID.[5] In a cohort study, excluding infectious etiologies like urinary tract infection and pyelonephritis, only one out of 69 pediatric patients with CVID developed renal sequelae over a follow-up period of five years.[1] Concurrent MCD and CVID appear only once in a comprehensive literature search. In a 2008 case report, a 12-year-old patient with known CVID developed nephrotic syndrome while receiving monthly IVIG infusions.[6] The diagnosis of nephrotic syndrome is usually straightforward given the recognizable signs and symptoms of edema, proteinuria and hypoalbuminemia, even in a patient with other co-morbidities. Aside from other edematous states, most co-morbidities would not delay the diagnosis of nephrotic syndrome, but the opposite is not true. Complications of the immunosuppressive treatment of nephrotic syndrome can mimic immune deficiencies and further obscure the already challenging diagnosis of CVID. Our patient continued to develop pneumonias after discontinuation of immunosuppressive therapy and was even known to have low IgA and recurrent diarrhea. We suspect that anchoring and availability bias may have contributed to the delay in diagnosis given his long history of immunosuppression and infections.

Our case highlights an important presentation of MCD and CVID given the challenges of diagnosing CVID with concurrent immune suppression. Obtaining a thorough history, including recurrent, chronic and unusual infections is of utmost

importance before prescribing immunosuppressant therapy. Understanding the expected frequency, type and severity of infections intrinsic to each medication or combination of medications is also important, though complex, and may require consultation with infectious disease experts. Finally, a patient's susceptibility to infections should normalize once immunosuppressant therapy ceases. Clinicians should discuss this expectation with patients and families, and in partnership with them, monitor for continued infections allowing for earlier recognition of an underlying immunodeficiency.

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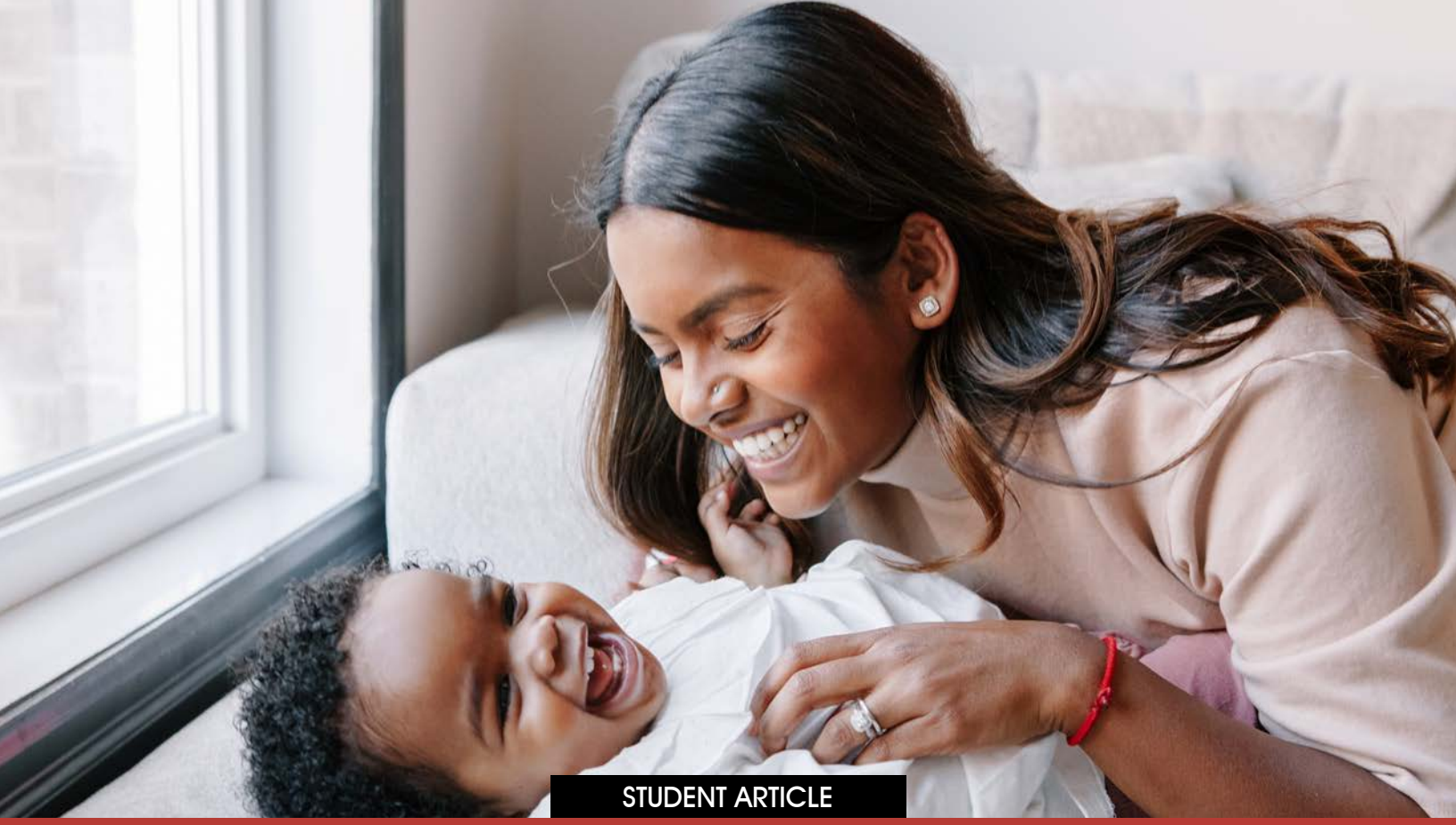

STUDENT ARTICLE

Poor Growth in an 8-month-old Infant: Don't Forget the Kidneys!

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CASE PRESENTATION

An 8-month-old female with a past medical history significant for milk protein allergy presented to clinic with a chief complaint of poor weight gain. At two months of age her weight was at the 30th percentile on the World Health Organization (WHO) Child Growth Standards, but as shown in Figure 1, she dropped to the 6th percentile. The infant's diet consisted of Nutramigen®, 24 Kcal/ounce, 2 to 3 ounces per feed for a total of 15 to 18 ounces daily. She had also been started on pureed fruits and vegetables. Previous attempts at increasing her weight include changing to Alimentum® formula, increasing the caloric density of the formula, and feeding therapy; however, none have made any significant improvement in weight gain over the last six months.

In regard to her history, the pregnancy was notable for intrauterine growth restriction, born at the 4th percentile with oligohydramnios. She was born to a 31-year-old mother (Gravida 2, Para 1) at 38 weeks and 3 days gestation by cesarean section due to a non-reassuring fetal heart rate tracing. She was admitted to the neonatal intensive care unit (NICU) for temperature instability and possible sepsis. However, all testing was reassuring, and she was discharged after three days with no issues. She was diagnosed with cow's milk protein allergy at 4 weeks of life after having bloody streaks in her stool. Since then, she was on Nutramigen® formula and doing well until the latest presentation.

Family history is notable for adult-onset hypertension in her father and maternal grandmother. The maternal grandmother has a history of renal calculi, and the mother has sickle cell trait. There is no family history of short stature, growth issues, or other renal diagnoses. The patient lives with her mother and father in a household with no pets or smokers. She does not attend daycare.

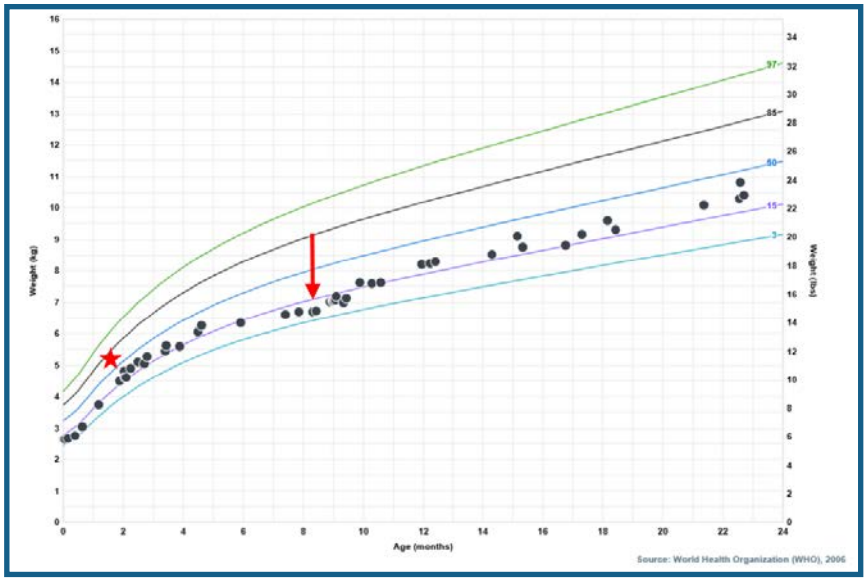

Figure 1. WHO Birth to age 2 years growth chart for our patient Star indicative of 2-month weight at 30th percentile. Arrow indicative of 8-month weight at 6th percentile at time of diagnosis and treatment initiation.

On examination, her weight was 7.025 kg (3rd percentile), height 68 cm (20th percentile), with Z-score of --2.52. Physical exam was unremarkable. Complete metabolic panel was significant for a bicarbonate of 16 mEq/L (18-25 mEq/L) with a normal anion gap. Urinalysis demonstrated a pH of 7 (normal 4-9) and urine electrolytes were sodium 21 mEq/L (normal 20-40 mEq/L), potassium 82.8 mEq/L (normal 25-125 mEq/L) and chloride 27 mEq/L (normal 20 mEq/L). The urine anion gap was +77 (nrmal = 0). She was diagnosed with renal tubular acidosis (RTA), most probably type 1, or distal RTA. A renal ultrasound showed normal kidneys without hydronephrosis, renal calculi, or other abnormalities.

DISCUSSION

Poor weight gain and malnutrition can be difficult to evaluate due to numerous diagnoses within the differential. Many organic disease processes, as well as social and environmental factors, must be considered and fully evaluated.[1] Renal tubular acidosis is a rare cause of poor growth, and in contrast to the adult form, is typically due to a genetic defect in children.[2] RTA is a group of disorders characterized by the inability of proximal renal tubules to reabsorb bicarbonate and distal renal tubules to excrete hydrogen ions, which leads to a primary metabolic acidosis with normal anion gap.[3] The three subtypes of RTA have different pathophysiologies due to genetic mutations or acquired disorders, but they all lead to a hyperchloremic, normal anion gap metabolic acidosis.

In children, the most common forms of RTA are characterized as type 1 (distal tubule) and type 2 (proximal tubule). Classic presenting symptoms in children include vomiting, diarrhea, constipation, poor weight gain or malnutrition (previously referred to as failure to thrive), and rickets.[2] A major concern in pediatric RTA patients is growth restriction.

Type 1, or distal renal tubular acidosis, is due to the inability of the distal tubule and collecting duct to properly excrete acid as hydrogen ions in response to the body's daily acid production. This results in a urine pH above 5.5 and to a positive urine anion gap.[2,4] There are genetic and acquired causes of type 1 RTA that can be autosomal dominant (often less severe cases) or recessive (often more severe) with or without deafness. Two other disorders that can cause a secondary type 1 RTA include Ehlers-Danlos syndrome and sickle cell anemia. Acquired cases may be due to medications, autoimmune disorders, or obstructive uropathy.[4,5]

In contrast, type 2 or proximal RTA is caused by a failure of bicarbonate reabsorption in the proximal tubule leading to excessive urinary loss of bicarbonate. Since distal acidifying mechanisms are appropriately functioning in type 2 RTA, urine is properly acidic if serum bicarbonate levels are low, and urine pH can be below 5.5. However, if serum bicarbonate levels rise to normal levels or above, the proximal tubule cannot properly reabsorb the bicarbonate. The distal tubule is not accustomed to such high levels of bicarbonate and cannot compensate. Thus, urine can be highly alkaline with high bicarbonate excretion.[5] Type 2 RTA can be primary or can simultaneously occur with other proximal tubular defects, in which case it is termed Fanconi syndrome. Isolated type 2 RTA is uncommon and usually transient or associated with another disorder.[2,5]

Type 4 hyperkalemic RTA is much less common, especially in children. It is due to inability to produce ammonia due to hyperkalemia. Urinary pH is normal in response to acidosis, and bicarbonate reabsorption is slightly reduced, but not to the same extent as with a proximal defect. Type 4 RTA can be seen with a number of causes of hyperkalemia, including aldosterone deficiency.[5]

In children, as in the case we have presented, renal tubular acidosis, and specifically type 1 RTA, is more commonly a primary disorder. A thorough family history should be obtained, although many forms follow autosomal recessive transmission, and thus the child may be the first in the family diagnosed with the disease. Three genes have been identified in distal RTA: ATP6V1B1, ATP6V0A4, and SLC4A1, the last of which can be seen as either an autosomal dominant or recessive inheritance.[2] Other symptoms include vomiting, dehydration, polyuria, hypokalemia, hypercalciuria, and hypocitaturia.[1] These cases are also associated with sensorineural deafness.[2]

Though being a complex condition to diagnose, treatment for types 1 and 2 RTA is very rewarding. Consultation with a nephrologist to aid with treatment is highly recommended. Alkali therapy through sodium bicarbonate or a Shohl solution containing citric acid and sodium citrate are appropriate corrective therapies. A newer form of alkali therapy in the form of granules has been approved in Europe and is currently under study in the U.S. for type 1 RTA. Growth and serum bicarbonate level should be regularly monitored in the first 6 months to ensure proper dosing and to rule out other diseases. It is recommended to regularly image the kidneys by ultrasound to monitor for nephrocalcinosis seen in type 1 RTA. Studies have demonstrated various response rates to therapy, with some patients' growth returning to the curve in a few months, and others taking a number of years or not improving at all. Therapy can often be discontinued after resolution of metabolic acidosis, although regular monitoring is vital to ensure no complications arise.[3]

CONCLUSION

Our patient was started on potassium citrate suspension 4 mEq orally given 4 times daily in order to correct for both her acidosis and hypokalemia. At discharge, her acidosis had resolved, and she was gaining weight at a rate above 45g per day. Her weight recovered over the following months and has since remained at the 20th percentile for age. A repeat blood test one week after discharge revealed a normal serum bicarbonate level. At 18 months of age, it was determined that her weight gain and controlled acidosis warranted a trial of weaning off the potassium citrate solution. At the point of discontinuation, the metabolic acidosis returned within one month. Potassium citrate solution was reinstituted with ongoing primary care and nephrology follow up. She was thriving well and developmentally normal at her last visit at 23 months of age.

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STUDENT ARTICLE

Pre-Exposure Prophylaxis (PrEP) for HIV Use in the Adolescent

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INTRODUCTION

In 2018, 36.2% of new HIV infections in the United States were among persons aged 13-24 years, and 8.3% of infections were among individuals aged ≤19-years-old.[1] Data from the Centers for Disease Control and Prevention show relative stability of infection rates over the last decade in this age group.[1] The large proportion of affected young people highlights the pediatrician's role in preventing HIV infection in the United States.

Pediatricians have always played a large role in the prevention, screening, diagnosis, and treatment of sexually transmitted infections (STIs) in children and adolescents. Ideally, well child visits address "safer sex" practices and screening for intimate partner violence, STI risk, LGBTQ+ status, pregnancy risk, and other sexual health concerns. Given the high incidence of HIV infection in the adolescent and immediate post-adolescent period, it is crucial that pediatricians understand all of the tools in their repertoire to combat this epidemic.

In 2018, the U.S. Food and Drug Administration (FDA), expanded its approval of pre-exposure prophylaxis (PrEP) for HIV to the adolescent age group. The approval of PrEP in the adolescent age group gives pediatricians an additional tool to aid in the prevention of HIV infection. Despite approval, there are several barriers to the uptake of PrEP. There are only 100,000 individuals currently on PrEP of the 1.2 million individuals that have a strong indication to be on the medication in the United States.[2,3]

In Florida, the lifetime risk of an individual contracting HIV is 1 in 54 – making it one of the highest risk states in the country.[4] In 2018, there were over 110,000 people living with HIV in Florida with the highest burden of HIV among Black and Latinx populations.[5] Additionally in 2018, there were 4,573 Floridians with new HIV diagnoses – 79.5% of which were male and 17.3% of which were aged 13-24 years old.[5]

PrEP has been identified as a crucial part of the National HIV/AIDS strategy. It has been endorsed by the Centers for Disease Control and Prevention (CDC), the World Health Organization (WHO), the Society for Adolescent Health and Medicine,

and other groups.[6,] In 2018, there were 14,440 PrEP users in Florida – 95.3% identified as male and 11% were aged 13-24 years old.[5] While PrEP is only a piece of the solution, it is an important one.

This review will cover the uses and indications for PrEP, medication initiation and follow-up needed for PrEP, the side effects associated with different formulations of the medication, and barriers to access and uptake.

PRE-EXPOSURE PROPHYLAXIS – MEDICATION OVERVIEW

FDA-Approved Medications

There are currently two FDA-approved medications for pre-exposure prophylaxis against HIV for individuals that weigh ≥35kg – tenofovir disoproxil fumerate/emtricitabine (TDF-FTC), or Truvada® and tenofovir alafenamide/emtricitabine (TAF-FTC), known by trade name Descovy®. TDF/FTC, when taken daily, reduces the risk of contracting HIV from sexual contact by over 95%.[9] TAF/FTC has similar efficacy with less reported side effects. However, TDF/FTC is the only one of the two medications approved for use in individuals having receptive vaginal sex.[10,11]

Indications

PrEP is indicated for individuals who are at high-risk for HIV transmission.[12] According to the United States Preventative Services Task Force (USPSTF), these HIV negative individuals are in four different groups summarized in Table 1.

GROUP A	GROUP B	GROUP C	GROUP D
Sexually active men who have sex with men (MSM) who have ≥1 of the following:	Sexually active heterosexual individuals who have ≥1 of the following:	Persons who inject drugs who have ≥1 of the following:	Any individuals who fall into the below categories:
• A serodiscordant sex partner (i.e. a sex partner who is living with HIV) • Inconsistent condom use • An STI diagnosis of syphilis, gonorrhea, or chlamydia in the last 6 months • Men who have sex with men and women (MSMW)	• A serodiscordant sex partner • Inconsistent condom use with partners whose HIV status is unknown or is at high-risk for HIV transmission • An STI diagnosis of syphilis or gonorrhea in the last 6 months • Sexually active in an area with a high prevalence of HIV	• Any of the characteristics of Groups A, B, or D • Share drug paraphernalia	• Persons who engage in transactional sex • Persons who have been trafficked for sex work • Sexually active transgender men and women

Table 1: Indications for initiation of pre-exposure prophylaxis[7, 12]

Contraindications

Both current PrEP combinations are contraindicated in patients who:

- Are HIV positive
- Have severe renal impairment as defined by creatinine clearance < 30 ml/min[10,11]

Safety Profile and Side Effects

Generally, both medications are well-tolerated with few side effects and safety concerns. Reported side effects are noted in Table 2.

SIDE EFFECT	TAF-FTC (Descovy®)	TDF-FTC (Truvada®)
Diarrhea	5%	6%
Nausea	4%	5%
Headache	2%	2%
Fatigue	2%	3%
Abdominal Pain	2%	3%

Table 2: Side effect profiles reported as percentage of patients who experience these symptoms within 96 weeks[10]

TDF-FTC, the older of the two medications, has been associated with cases of mild worsening renal function, mild bone demineralization, and extremely rare cases of lactic acidosis and hepatic steatosis. The listed side effects, with the exception of fulminant hepatic steatosis, the rarest of the complications, resolve with discontinuation of TDF-FTC.[11]

MEDICATION INITIATION AND FOLLOW-UP

Step 1: Identifying Candidates for PrEP

The identification of adolescents who would benefit from PrEP should occur at routine well-child visits. However, acute care visits for sexual or mental health concerns also provide an opportune moment to discuss PrEP initiation. One critical component of well-child visits is a comprehensive and inclusive sexual history. A 2014 study found that only 3.3% of sexual histories taken by pediatricians were "inclusive," using language that avoids use of specific gender, sex, or sexual orientation.[13] Taking a comprehensive and inclusive sexual history can be accomplished by following the CDC's guide of the "5 P's" (Table 3). The goal of the sexual history is to understand the patient's STI risk based on their reported behaviors and anticipated future behaviors. For transgender or gender non-binary patients, it may be useful to have a candid conversation to understand sex behaviors. For example, it is important to clarify which anatomical parts are being used in order to properly stratify risk. This can take place during a routine HEADDSS assessment. As always, it is important to ask these questions in a developmentally-appropriate and private manner.

TAKING A COMPREHENSIVE AND INCLUSIVE SEXUAL HISTORY		
Partners	Identification of number and type of sexual contacts	• Are you currently sexually active? • Do you have sex with men, women, both or neither? • How many sexual partners have you had over the last 12 months? • Are you and your partner(s) monogamous? • Do you feel safe in your relationship(s)? • Have you ever experienced abuse or violence from your partner(s)?
Practices	Identification of sexual behaviors	• What type of sex do you have – oral, anal, vaginal, or other? • Have you or any of your partners ever engaged in transactional sex? • Have you or any of your partners ever used intravenous drugs? • Have you ever engaged in sexual behavior while under the influence of a drug or substance?
Protection	Identification of patient's knowledge and use of protection against STIs	• What do you do to protect against sexually transmitted infections? • How frequently do you use this protection – never, sometimes, always? • When do you use this protection – with oral, anal, and/or vaginal sex? • Do you know the STI status of your sexual partner(s)?
Past History	Identification of history of STIs	• Have you ever had a sexually transmitted disease – namely gonorrhea, chlamydia, syphilis, or HIV? • If yes, how did you get treated?
Pregnancy	For patients with a uterus and ovaries – identification of obstetric history, use of contraception	• Have you ever been pregnant? • If yes, how many times, and what were the outcomes of those pregnancies? • Are you currently trying to become pregnant? • If no, what are you using for contraception – are you never, sometimes, or always using this? • Are you currently satisfied with the contraception that you are using?

Table 3: The 5 P's of a comprehensive and inclusive sexual history[14]

It is important to ensure confidentiality and establish trust with the patient when taking a sexual history. Conversations about sexual behaviors may be especially difficult in patients who have recently had their sexual debut. However, having an understanding of the patient's behaviors and the partner(s)' behaviors is important to risk stratification concerning HIV transmission. Additionally, one must obtain a comprehensive and inclusive sexual history at every visit, since patients may not disclose all behaviors initially or their behaviors may change over time.

As a general guideline, the following five groups of individuals are considered to be at high risk for HIV and therefore should be counseled about HIV risk mitigation and PrEP.

1. History of past or current STIs
2. Sexual activity in a location or in a network with a high prevalence of HIV. Given the prevalence of HIV in Florida, PrEP should be considered in all high-risk youth and young adults.
3. Any sex without the use of condoms
4. Self-identified as high-risk
5. Sexual partners with unknown HIV status[10]

The CDC has a tool for estimating HIV risk and risk-reduction using various methods. https://hivrisk.cdc.gov/#[7]

Step 2: Initiation of PrEP

After identifying the appropriate patient, the next step in initiating PrEP is obtaining baseline laboratories including a renal function panel, serologies for HIV, hepatitis B, hepatitis C, STIs at baseline, and a pregnancy test. Each of these is explained in more detail below:

- **HIV Testing – 4th Generation**. Since the medications which compose both TDF-FTC and TAF-FTC are used in the treatment of HIV, their solo use in a patient who is infected with HIV leads to viral resistance. Patients must abstain from sexual contact or consistently use condoms between HIV testing and therapeutic effect of PrEP. This is primarily to ensure that HIV is not contracted in the window period between HIV testing and PrEP therapeutic effect.
- **Kidney Function.** Both TDF-FTC and TAF-FTC have a relative contraindication for patients with CrCl < 60 ml/min or < 30 ml/min, respectively.
- **Hepatitis B Status.** Hepatitis B serologies should be drawn as part of the baseline assessment for initiation of PrEP. Individuals without immunity should be offered immunization. While hepatitis B infection is not a contraindication to PrEP initiation, in some patients with active or chronic hepatitis B infection, discontinuation of PrEP has led to severe acute exacerbations of viral hepatitis.
- **Hepatitis C Status**. TDF-FTC and TAF-FTC can interact with the newer antiviral medications that are used to treat hepatitis C such as sufosbovir.
- **Pregnancy Test**. Limited data indicate that TDF-FTC and TAF-FTC are safe during pregnancy and breastfeeding.
- **STI Testing**. Screen for syphilis, gonorrhea, and chlamydia in the blood, urine, pharynx, and rectum as indicated.[7, 10, 11]

Along with the laboratory testing shown in Table 4, there is also important counseling to be done for the patients at the initial visit. The cornerstones of counseling are:

Medication Adherence. It is extremely important to take PrEP as prescribed: daily. The medication is >95% effective when taken daily, and the effectiveness decreases with decreasing adherence. There are currently no reported cases of compliant individuals on PrEP who have contracted HIV. Studies have suggested that ways to improve medication adherence include patient education about the medication dosing and side effects, providing reminder systems and tools, and addressing social and financial needs that may impact adherence.[15]

STI Prevention. Since these patients are already identified as being high-risk for STIs, it is important to discuss that PrEP is only a part of a comprehensive STI-prevention plan. This includes encouragement of conversations with partners and use of condoms and other barrier protection.[7] Importantly, a recent systematic review concluded that it is unclear if PrEP use is associated with increased rates of other STIs.[16]

Step 3: Routine Monitoring and Follow-Up

Routine follow-up is key in ensuring adherence to PrEP, especially in the adolescent population. Current practice guidelines suggest follow-up appointments every three months; however, with the adolescent population there is indication that more frequent follow-up may be beneficial in improving adherence, especially at medication initiation.[10,11] The purpose of the follow

EVERY THREE MONTHS	EVERY SIX MONTHS
Reassess STI and HIV risk Counsel about adherence Perform HIV testing Indicated STI screening based on risk Repeat pregnancy testing and contraception counseling	Assess renal function

Table 4: Routine Follow-up visits [7, 10, 11]

up visits is to counsel about adherence and proper medication use, reassess HIV and STI risk, and do routine lab monitoring, as needed. Table 4 summarizes current best practice for follow-up.

With the recent increased adoption of telehealth visits, this modality may lend itself well for patients who may have barriers to care access. At follow-up visits, there should always be a discussion of continuing need for PrEP as sex behaviors may change over time.

The CDC has more comprehensive information about PrEP, including comprehensive clinical guidelines, resources for patient access, testing flowcharts and more at: https://www.cdc.gov/hiv/clinicians/prevention/prep.html

BARRIERS AND SOLUTIONS

While PrEP has proven benefit in reducing HIV infection rates among its users, there are identified barriers which have led to decreased use, uptake, and lack of adherence. Unfortunately, these barriers are amplified among the adolescent population, and adolescents have their own set of barriers which prevent uptake and adherence.

Confidentiality and Consent

A 2010 study found that only 20% of pediatricians had asked their patients about sexual orientation.[17] The 2018 Human Rights Campaign LGBTQ+ Youth Survey of >10,000 youth across the country found that 5% of youth had disclosed their sexual orientation to all of their healthcare providers, and 20% had disclosed to some of their healthcare providers.[18] These data highlight the importance of establishing a strong therapeutic relationship with patients, provider comfort in discussing sexual health, the normalization of sexual health conversations at well-child visits.

Guardian permission is frequently cited as a barrier to PrEP uptake among eligible candidates, especially among patients who may not have disclosed their sexual orientation, gender identity, and/or sex behaviors to their parents or peers.[19] These patients may fear rejection or punishment from their parents and therefore are not likely to agree to start PrEP. The legal-medical landscape of PrEP use in minors varies state-to-state. At the time of this writing, in Florida, based on explicit language in statute and/or regulation, clinicians are not able to offer prescription HIV or STI prevention services (including PrEP) to minors without parental consent. However, providers are able to offer HIV testing and treatment to minors without parental consent.[20] Therefore, in Florida, parents should be involved in the discussion of PrEP.

In other states allowing minor consent for PrEP, confidentiality is still a barrier. For patients that are under their guardian(s)' medical insurance, billing information could disclose PrEP visits and use to parents. Taken altogether, clinicians should partner with both the adolescent and the parent in navigating conversations about sexual health and PrEP in a way that is safe and respectful to all parties.

Cost

Cost continues to be a barrier both for patients who have insurance and patients who do not have insurance. TDF-FTC and TAF-FTC are increasingly covered by most major insurers, but some patients with insurance may still have difficulty with access and payment. At the time of this writing, Florida Medicaid covers the cost of both TDF-FTC and TAF-FTC.

The cost of clinic visits, lab testing, and the medication itself are all separate barriers.

With regard to medication access, there are several programs at the local, state, and federal level for both patients who are insured and uninsured. The Ready, Set, PrEP program sponsored by the United States Department of Health and Human Services was started in early 2020 to provide free PrEP to individuals without prescription drug coverage.[21] For insured and uninsured patients, Gilead, the parent company that produces Truvada® and Descovy®, has several co-pay and payment assistance programs which are available on their website.[22] At the time of this writing, both TDF-FTC and TAF-FTC are still under patent and there are no generic formulations available.

For clinic visits and lab tests, patients can access PrEP services at community health clinics, many of which offer PrEP services on a sliding-scale fee schedule. Additionally, there are fee assistance programs from Gilead and other patient assistance

programs which are available on the CDC's website: https://www.cdc.gov/hiv/risk/prep/index.html[7]

Stigma, Health Disparities, and Medical Mistrust

Historically HIV-prevention strategies have been targeted toward men who have sex with men; however, in 2017, approximately 24% of new HIV infections in the United States were due to heterosexual contact.[1] Moreover, recent evidence has shown the disproportionate rates of HIV transmission among racial and ethnic minorities, namely Black/African-American and Latinx groups. In 2017, the African American population and Hispanic population collectively accounted for 69% of HIV diagnoses, despite comprising only 31% of the U.S. population.[1] Furthermore, 69% of individuals that could benefit from PrEP are Black or Hispanic, yet these individuals comprise only 4% of the individuals that are prescribed it.[3, 23]

Particularly among communities of color and in the southern United States, there is a larger stigma surrounding sexual and gender minorities, HIV, and PrEP.[24] Many MSM or MSMW may identify as "straight" or "heterosexual" as there continues to be a large stigma surrounding these groups in some communities[24].

It is important to build a therapeutic alliance with patients, especially those who may benefit from PrEP use.

Patient Knowledge and Comfort

A 2018 survey found that only 54.8% of adolescents who were assigned the male sex at birth and have sex with men had ever heard of PrEP and 56.1% did not know how they would access PrEP.[25]

CONCLUSION

PrEP is an effective and safe tool to combat the HIV epidemic among our adolescents and young adults in the United States. There is a need for improved HIV prevention strategies in the young adult and adolescent population, as this group accounts for a significant proportion of new HIV diagnoses every year. Pediatricians, as stewards of health in this age group, have an important role to play.

Now more than ever, it is important to know which patients are at high risk for contracting HIV. This starts with sometimes difficult conversations regarding sexual activity and sexual health. There are several opportunities to discuss PrEP with adolescents. Both preventative health visits and acute care visits for sexual health concerns both should serve as an entry to discuss PrEP. As individuals with high risk are identified, it is important to discuss risk mitigation strategies, of which PrEP is one. Due to the complex interaction of confidentiality, cost, and stigma, it may take persistence and creativity to find the proper risk mitigation plan for each individual patient. The current laws in Florida make it even more difficult for providers to have conservations with patients about PrEP. This presents an opportunity for important advocacy to be had at the state level to have allowances for PrEP without parental consent as it is for nine other states.[20]

Per CDC and USPSTF guidelines, PrEP should be a topic in the care of the adolescent. The pediatrician can play a key role to improve the long-term health of this vulnerable population. With these tools, pediatricians can help put a stop to the HIV epidemic.

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STUDENT ARTICLE

Red Flags for the Red Eye: When Simple Subconjunctival Hemorrhage Is Not So Simple

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ABSTRACT

Subconjunctival hemorrhage (SCH) is a common disorder seen in the pediatric clinic and emergency room. While most isolated SCHs are benign, other more vision-threatening and life-threatening causes are important to consider when assessing SCH in the pediatric population. This article reviews SCH, its common associations, and tips on evaluating for potential emergencies.

INTRODUCTION

Subconjunctival hemorrhage (SCH) is one of the most common causes of eye redness in patients of all ages.[1] In a review of visits to a tertiary eye emergency department, SCH ranks within the top 20 most common diagnoses.[2] Within the eye clinic, it accounts for 2.9% of all eye findings.[1] Causes of SCH can be divided into atraumatic and traumatic, with the majority considered spontaneous and idiopathic. However, since other ocular and systemic emergencies may present as SCH, pediatricians may need to differentiate between benign and more worrisome causes of SCH to determine whether further evaluation is warranted.

APPEARANCE

SCH is characterized by a well-defined area of redness over the white sclera with absence of pain, discharge, or vision change.[3] It is caused by damage to a subconjunctival vessel leading to accumulation of blood between the conjunctiva and episclera.[4] The fibrous connections between these layers loosen over time, which may account for a more diffuse appearance in adults

Figure 1: Chemosis with elevated, "ballooned" appearance

versus a more focal appearance in children.[4] The conjunctival blood vessels may blend with the hemorrhage and appear obscured. Significant bleeding may cause chemosis or an elevated, "ballooned" appearance (Figure 1). In cases of trauma, bleeding is seen more commonly over the temporal rather than nasal aspect of the globe because of the exposed conjunctival surface area over the temporal globe, protection of the nasal globe by the nasal bridge, and better visualization of oncoming projectiles from the nasal side due to better binocular vision in the central visual field.[5,6] Over time, gravity causes the blood to collect inferiorly, and dehemoglobinization replaces the red color with a yellowish tinge.

COMMON CAUSES

Most cases of SCH are classified as idiopathic since no significant history is often found.[6] Mild eye rubbing, coughing, or sneezing, easily forgotten by the patient, can be the trigger for hemorrhage. However a detailed history is crucial in avoiding an incomplete diagnosis. In older patients, the most common causes of spontaneous, atraumatic SCH include hypertension, Valsalva effect (including vomiting, coughing and sneezing), diabetes, and anticoagulant/antiplatelet therapy.[4,6] It is thought that weaker vessels walls accompanied by a predilection for spontaneous bleeding may add to the mechanism in the adult population. Additionally, acute hemorrhagic conjunctivitis, most commonly caused by enterovirus 70, was a common cause of SCH of all ages, but there has been a significant decline in these cases in recent decades.[7] Nevertheless, severe conjunctivitis remains a common cause of SCH in children.

The pediatric population has a unique risk profile. While atraumatic SCH from severe vomiting, coughing, or constipation is commonly seen,[8] it has been shown that trauma and contact lens usage make up a significant proportion when compared to the older population.[7] This may be due to the active nature of children and the relatively popularity of contact lenses in the younger population. There is a tendency for higher numbers of SCH in children in summer months suggesting that summer vacation may be an important causative factor in trauma-related eye injuries.[7]

DIFFERENTIAL DIAGNOSES

SCH can be associated with other ocular and systemic findings as discussed in the following sections:

OCULAR TRAUMA

When a SCH is noted in association with a history of significant trauma, deeper ocular injuries must be excluded. Eyelid lacerations accompanied by SCH should raise concern for additional globe and orbital involvement.

Corneal abrasions and *corneal foreign bodies* may present with additional tearing, decreased vision, and positive fluorescein staining under cobalt blue light. *Traumatic iritis* may present with blurry vision, photophobia, and fine white blood cells in the anterior chamber on slit lamp exam. *Hyphema*, an accumulation of blood in the anterior chamber, appears with blood layered inferiorly between the cornea and iris or may diffusely obscure the iris and pupil. A *traumatic retinal detachment* may present with a decreased peripheral visual field, with or without an afferent pupillary defect. Injuries associated with metal from *metal projectiles* (e.g., hammering) or explosions (e.g., fireworks) should prompt a CT scan to rule out intraocular or intraorbital foreign body. It is important to note that metallic projectiles with significant velocities may penetrate the eye without a visible entry wound. An extensive, *bullous SCH* may indicate an underlying *scleral laceration* and an open globe, which would require exploration and repair in the operating room. A significant SCH with proptosis and elevated intraocular pressure may indicate a *retrobulbar hemorrhage*, a condition that can compromise the optic nerve and necessitates emergent ophthalmology evaluation and management. Periorbital bruising and decreased extraocular movement may indicate *orbital and facial fractures*. If the conditions of open globe, retrobulbar hemorrhage or fractures are suspected, emergent CT imaging is warranted to assist in confirming these diagnoses. This is especially important in very young children where even short-term compromise of equal binocular vision can result in amblyopia (lazy eye).

NON-ACCIDENTAL TRAUMA (NAT)

Non-accidental trauma makes up a nebulous and small fraction of all presenting eye cases. Review of cases at a tertiary eye hospital in England noted 2 cases of battered baby syndrome out of 3210 cases of eye trauma within a 24-week period.[12] A separate study suggested that ocular changes were the presenting sign to the ophthalmologist in 6% of suspected NAT patients.[8] Conversely, in children diagnosed with NAT, the incidence of ocular findings can vary from 22% to 46%.[8] The presence of retinal hemorrhages is the most common ocular finding,[13] but SCH in NAT has been documented as well. One group identified three cases of spontaneous bilateral subconjunctival hemorrhage as the initial presentation of NAT.[14] One patient had facial petechiae, and all three patients had concerning skeletal x-ray findings. A separate review of 1466 inpatient consults to the child protection team at a tertiary children's hospital identified 14 cases where SCH was noted on exam.[8] None of these patients had history of excessive Valsalva, and none had retinal hemorrhages or conjunctivitis, but bruising in other areas of the body were documented in 79% of the cases. While the group could not determine the prevalence of NAT among all children who present with SCH per se, the group felt SCH could occur in isolation and without other overt signs of abuse and should remain in the differential diagnosis after all other causes have been ruled out. A review of pre-ambulatory children presenting to emergency departments or urgent care clinics with visible injuries found a number of skeletal surveys concerning for NAT despite the notation of "minor" injuries, including 33% of individuals with apparently isolated subconjunctival hemorrhage.[15]

Of note, the differential diagnostic approach in an early newborn should include normal SCH after vaginal delivery or cesarean section as uterine contractions during labor can cause thoracic or abdominal compressions and elevated episcleral venous pressure.[15] Nevertheless, non-accidental trauma should also be considered in any infant with SCH that lacks relevant history given the larger implications. Consultation with a child abuse specialist should be considered in such cases.

INFECTIONS

Conjunctivitis and keratitis may present with SCH, but are usually associated with discharge and decreased vision. The list of viral, bacterial and parasitic infections associated with conjunctivitis is broad and includes enteroviruses, coxsackievirus, herpes zoster, adenovirus, rubella, rubeola, hantavirus, *Bordetella pertussis*, *Haemophilus influenzae*, *Streptococcus pnuemoniae*, *Moraxella catarrhalis*, *Staphylococcus aureus,* Leptospira, Trichinella, and cerebral malaria.[8] SCH and periocular pain has been documented to precede pediatric herpes zoster ophthalmicus.[9] In the case of keratitis, new white lesions over the cornea may be noted by family members. *Pre-septal and orbital cellulitis* may present with periocular erythema, ecchymosis, or edema. Orbital cellulitis presents with fever and is often accompanied by a history of sinusitis or trauma, decreased extraocular movements, afferent pupillary defect, and proptosis. CT of the maxillary/face and head, a complete blood count (CBC), and blood cultures are appropriate tests in the diagnostic evaluation of orbital cellulitis.

CONJUNCTIVAL AND ORBITAL VASCULAR TUMORS[4]

SCH could be a sign of a periorbital vascular anomaly. Conjunctival vascular anomalies include Kaposi sarcoma, lymphangiectasias, lymphangioma, cavernous hemangiomas, and arteriovenous malformations. A history of recurrent SCH should alert the physician to a possible ruptured aneurysm due to hereditary hemochromatosis. Adnexal lesions such as anaplastic carcinoma of the lacrimal gland and orbital lymphoma have been associated with cases of recurrent SCH in older patients.

SYSTEMIC BLEEDING DISORDERS

Systemic bleeding disorders associated with SCH include thrombocytopenic purpura, hemophilia, anemia, leukemia, splenic disorders, and uremia.[4] Case reports have documented the presence of bilateral SCH as the initial presentation for congenital fibrinogen deficiency[10] and Kasabach-Merritt syndrome.[11] Obtaining a good history regarding easy bruising or frequent nosebleeds, or history of recurrent SCH, should prompt a work up for bleeding diatheses.

HOW TO APPROACH THE EYE EXAM

A detailed history and exam is paramount in obtaining the correct diagnosis. History should include inquiries concerning any trauma, Valsalva, or anticoagulation therapy. Issues associated with excessive bleeding, hypertension and diabetes are also important to know.

Examination should begin with a general physical exam and then a careful eye exam, starting from anterior to posterior. This should include visual acuity, eye pressure, pupil reactivity, extraocular movement, and confrontation to visual fields. An abnormality in any of these exam components would exclude an isolated SCH.

Visual acuity is usually assessed using the Snellen letter eye chart or an Allen chart displaying shapes for younger children. In the ER, a hand-held near vision card can provide an approximate near vision assessment. Visual acuity in infants may be evaluated by object tracking with each eye individually. Intraocular pressure is usually determined with a tonometer; however, a non-ophthalmologist can palpate the globes, which should feel slightly soft. If there is any concern for an open globe, intraocular pressure should be deferred.

Pupils should be examined for symmetry and equal reactivity to light. A swinging flashlight test is used to assess for an afferent pupillary defect which usually indicates a significant ocular or neurological defect. Similarly, limitation in extraocular movement of one or both eyes may indicate an orbital fracture or mass, or neurological issue.

Examination of the anterior segment is best performed by slit lamp since it magnifies the image, thus allowing visualization of subtle findings. If a slit lamp instrument is unavailable, use of a pen light can provide a gross assessment, especially if a hand-held magnifying lens is used in conjunction with it. The posterior segment exam can be accomplished by a primary care provider using a direct ophthalmoscope. The retina should appear attached and with an orange-red reflex. The optic disc should have sharp borders without hemorrhages. A pediatric eye exam can challenging for a primary care provider, but asymmetry in any part of the exam can help narrow the differential.[16]

TREATMENT, MANAGEMENT AND PROGNOSIS

Despite being a topic of research for decades, there is no treatment that can accelerate the rate of healing of SCH. The extravasated blood is typically reabsorbed over a period of 2 to 3 weeks without residual scarring or visual compromise. The hemorrhage may spread circumferentially, obeying the force of gravity before it fades. Patients should be aware that the coloring of the affected conjunctiva can progress from red to greenish yellow to yellow as the hemoglobin is catabolized.[17] For foreign body sensation, artificial tears may aid in minimizing discomfort. The appearance of a SCH can be startling, so patient reassurance is an integral part of management. Additional treatment and management depend on the presence of further findings. If the hemorrhage fails to resolve or is recurrent, workup for a more serious etiologies is warranted.

CONCLUSION

Pediatricians will often encounter the SCH in clinical practice. SCH is a very common and often harmless problem in of itself, but pediatricians should stay alert for potential underlying vision-threatening and life-threatening conditions, including deeper globe and orbital trauma, infections, bleeding diatheses, and non-accidental trauma. Ophthalmology consultation should be considered for more complicated cases, but the general pediatrician plays a crucial role in obtaining important information for the correct diagnosis and treatment.

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STUDENT ARTICLE

What Can Be Learned from an Adolescent with Marfan Syndrome and Mental Health

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ABSTRACT

This case describes an adolescent with Marfan Syndrome (MFS), focusing on the psychologic aspects of the case. While cardiology, ophthalmology, and orthopedics are crucial to the care of the MFS patient, it is vital to consider psychologic manifestations of living with the syndrome, especially in younger populations. This report will explore strategies for effective psychologic assistance as supported by the case and the literature.

INTRODUCTION

Marfan Syndrome (MFS) is an inherited connective tissue disorder that affects 1 in 3000 to 5000. Mutations involve fibrillin-1, which is a crucial component of elastic and non-elastic connective tissues.[1] Signs and symptoms of MFS are highly variable, but are known to include aortic disease, mitral valve prolapse, ectopia lentis, dural ectasia, excess linear growth in long bones, arachnodactyly, pectus deformity, hindfoot valgus, scoliosis, and protrusio acetabuli.[1] These features are characterized in the Ghent scoring system to establish the diagnosis.[2] Workup after diagnosis may include genetic testing, echocardiogram, eye examination, and electrocardiogram.[3] Cardiology, ophthalmology, and orthopedic surgery consults are frequently placed, and specialists continue to follow patients throughout their lifetime. Treatment is largely supportive, including bracing for scoliosis, glasses for ocular concerns, and pain management, and may also include cardiovascular or other surgeries.[3] MFS patients have lifespans reaching the 70s in modern day, even with the high rate of heart involvement.[1]

CASE REPORT

A 16-year-old African American female with an established diagnosis of MFS presented with her mother to her primary care office for a well-child visit. She had a history of prior aortic root surgery and knee surgery. She was followed by ophthalmology and cardiology. Physical examination revealed severe arthrogryposis in the joints, scoliosis, exotropia especially in the right eye with an inability to converge, ectopia lentis, hyperlaxity of joints, and club foot malformation.

The patient reported that, over the last few years, she had experienced increased bullying in school due to her condition. Her mother noted a sad affect, social isolation, decreased appetite, quiet demeanor, and falling grades. The patient had not had suicidal ideation. In October 2020, the patient's PHQ-9 score was 15, indicating moderate-severe depressive symptoms.

Due to the integrated care model of the primary care physician's office, a prompt behavioral health assessment by a psychologist was completed. Assessment and follow-up revealed adjustment disorder with mixed emotional features, major depressive disorder, and generalized anxiety. She began individual therapy sessions with the behavioral health staff addressing coping strategies for bullying, self-esteem, and academic achievement. In January 2021, her PHQ-9 score decreased to 4. Her overall demeanor was brighter, and her grades had started to improve. Continued monitoring by behavioral health was a priority in the care of this patient. The patient did not receive psychotropic medications.

DISCUSSION

MFS can be disfiguring, isolating, stressful, and worrisome for all age groups affected, especially the pediatric population. School bullies can be relentless, and a medical condition with various obvious physical manifestations make for an easy target. This case illustrated the profound impact that managing MFS can have on the psyche of an adolescent. An important aspect of care described in this case study was the integrated health model with easy access to behavioral health services at the patient's primary care office, including assessment of conditions, therapy, and medical treatment, if necessary. Focusing on coping mechanisms proved to be an effective strategy engaged by this behavioral health team.

The psychiatric aspect of the management of MFS has not taken appropriate precedence previously. Recent studies have attempted to further explore this topic.

The Pediatric Heart Network Marfan Trial compared Pediatric Quality of Life Inventory Generic Core Scales between MFS patients and healthy population norms. Those ages 5-18 years with MFS had lower mean scores for physical and psychosocial domains, and those ages 19-25 years had higher psychosocial scores than healthy norms.[4] Curiously, the severity of MFS-related physical findings were not associated with lower quality of life scores.[4] These data were significant as they noted that perhaps the adults in the study had already developed coping skills to manage their challenges and allow for higher levels of psychosocial functioning despite their physical manifestations of the syndrome. These lower quality of life scores in the children and adolescents should alert pediatricians and other specialists involved in the care of MFS patients to increase monitoring of psychological and neurodevelopmental issues and provide earlier opportunities for appropriate treatment. Furthermore, Nielson's article, "A Review of Psychosocial Factors of Marfan Syndrome: Adolescents, Adults, Families, and Providers," analyzed various reports to craft treatment recommendations including encouraging social activity involvement, development of coping strategies, provider discussion of concerns with the patient and family, and a multidisciplinary team approach to best care for MFS patents.[5] These strategies can foster resilience and a strong understanding of each patient's unique challenges.

As strides are being made to include psychologic evaluation as an element of first line MFS management, this case report illustrated the importance of screening tools such as the PHQ-9, regular visits with a primary care physician who can engage appropriate mental health care providers, and family involvement as part of the treatment plan. The literature echoes these notions. In future research, it would be worthy to explore the effects of different therapeutic methodologies on psychosocial concerns in MFS as well as other strategies to help those with MFS cope with their unique challenges.

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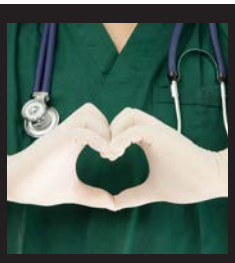
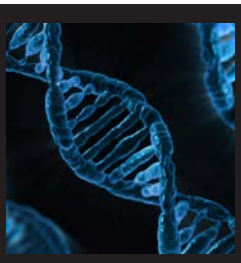

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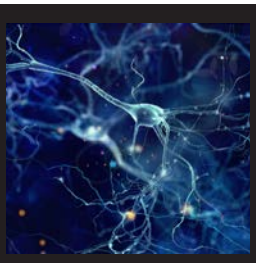


September 3-5, 2021

Hosted at & Live-Streamed from Disney's Yacht & Beach Club Resorts

AMA, AOA, ANCC, AAPA, and ABP MOC Part 2 credits available!

Friday, September 3
Obesity & Nutrition Symposium
Mental Health Symposium
Resident Brain Bowl Competition
Family Reception

Saturday, September 4
Primary Care Track
Hospitalist Track
2 Florida Mandatory Courses
Medical Student Research Forum

Sunday, September 5
Plenaries: The New Normal, Racism in Medicine, What's New with COVID-19
Workshop: Starting & Running a Private Pediatric Practice

Keynote: "the pediatrician is to sit in... legislatures." ~ Dr. Abraham Jacobi

In-Person and Virtual Tickets Available.
View the Full Agenda and Register at bit.ly/FPP2021-Home

Continuing Education Credit: AKH Inc., Advancing Knowledge in Healthcare, designates this live activity for a maximum of 25 *AMA PRA Category 1 Credit(s)*™. Successful completion of this CME activity, with individual assessments and feedback, enables participants to earn 25 points in the American Board of Pediatrics' Maintenance of Certification program. This activity is designated for 25 ANCC Contact Hours and 25 AAPA Category 1 CME credits. The Philadelphia College of Osteopathic Medicine designates this program for a maximum of 25 hours of *AOA Category 1-A credits*. See the final CE activity announcement for specific details. The full agenda & accreditation information is available online at bit.ly/FPP2021CE. Direct questions/comments to 850-224-3939 or info@fcaap.org.

Interested in joining the FCAAP Editorial Board or submitting an article for a future publication?

Contact FCAAP Director of Communications & Events Melanie Range at mrange@fcaap.org for more information!

FCAAP

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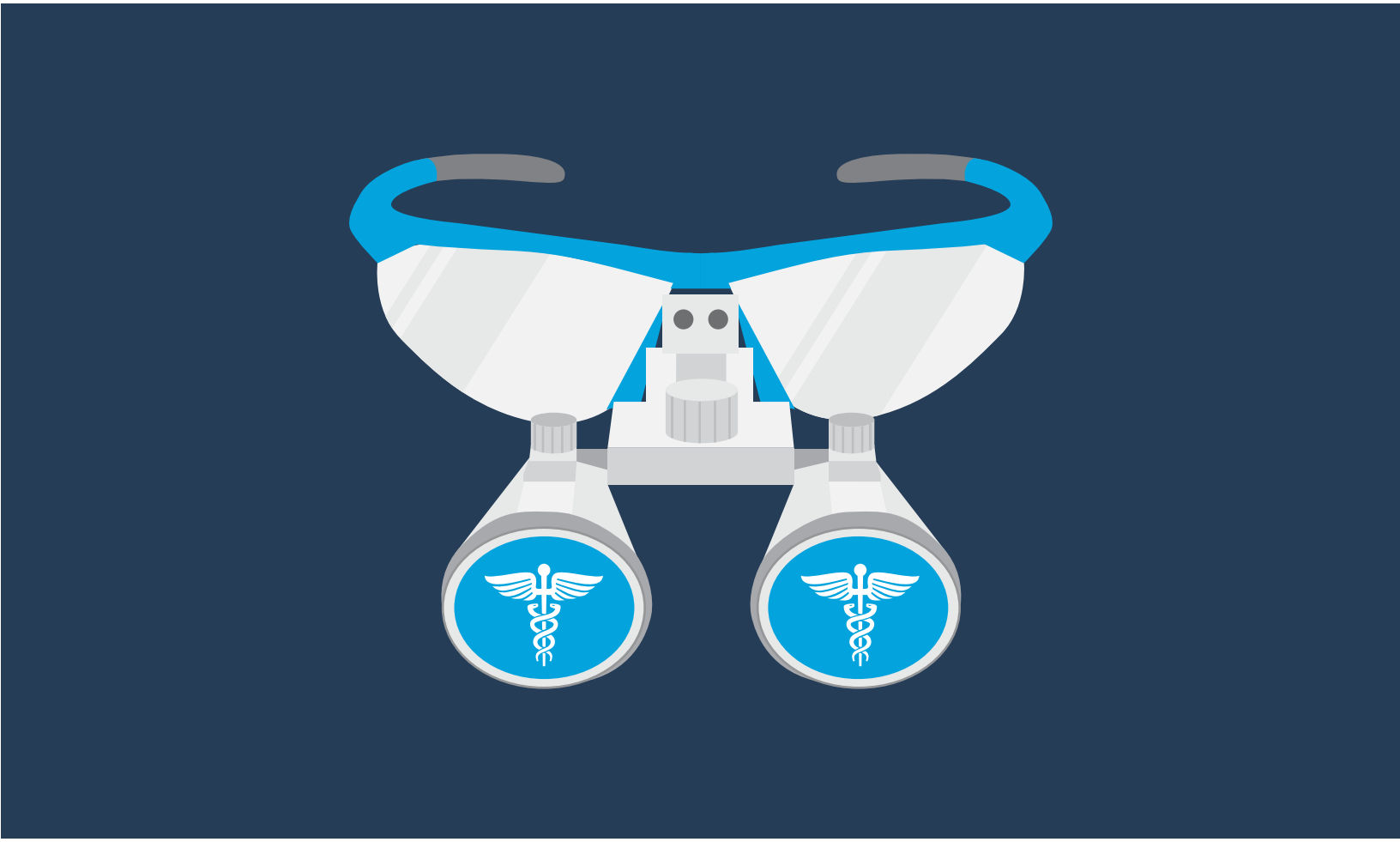

Announcing the 2021 Dividend for Florida Members

The Doctors Company has awarded $440 million in dividends to its members—including 4.5 percent to qualified Florida members. Unlike some insurers who are guided by their investors, we've always been guided by the belief that the practice of good medicine should be advanced, protected, and rewarded.

Join us and discover why delivering
the best imaginable service and unrivaled
rewards is at the core of who we are.

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