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PEDIATRIC RHEUMATOLOGY (TJA LEHMAN, SECTION EDITOR)

Current Perspectives on Ophthalmic Manifestations of Childhood Rheumatic Diseases

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Abstract Inflammatory eye diseases are an important manifestation of many pediatric rheumatologic conditions. Early screening and diagnosis are imperative as these illnesses can not only result in significant visual morbidity but are also an indicator of systemic inflammation. Time to presentation of ocular inflammation varies significantly and can range from many years prior to the onset of systemic symptoms to well after the diagnosis of the rheumatologic disorder. Due to this variability in presentation, careful monitoring by an ophthalmologist is vital to preventing ocular complications and preserving vision. Both local and systemic immunosuppressive medications have been effective in the management of ocular disease. In this review, we will focus on the known ophthalmologic manifestations of common pediatric rheumatologic diseases and discuss recent advances in therapeutic considerations for these conditions.

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Introduction

Pediatric rheumatologic diseases can affect the eye, periorbita, and orbit posing a serious threat to vision. Ocular manifestations include conjunctivitis, scleritis, keratitis, uveitis, retinal vasculitis, and optic neuritis. Of these findings, uveitis is the most common [1]. The diagnosis of ocular inflammation can be difficult and is frequently delayed in children secondary to limited history, patient compliance, and the chronic and insidious nature of several of these diseases. Significant vision loss has been reported in 25–33 % of children often secondary to band keratopathy, cataract, glaucoma, cystoid macular edema, macular ischemia, and, in younger children, amblyopia [2, 3]. Therefore, prompt diagnosis and management of ocular inflammation is crucial and necessitates close communication between pediatricians, rheumatologists, ophthalmologists, and other subspecialty providers.

In this review, we discuss the clinical features of ophthalmic manifestations commonly associated with pediatric rheumatologic conditions and discuss recent advancements in their management.

Childhood Arthritides

Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis (JIA), also known as juvenile rheumatoid arthritis (JRA) or juvenile chronic arthritis

(JCA), comprises a diverse group of arthritides with onset ≦16 years of age, duration greater than 6 weeks, and with no known etiology [4, 5]. It is based on the International League of Associations for Rheumatology (ILAR) classification and consists of 7 subtypes—oligoarticular persistent, oligoarticular extended, polyarticular rheumatoid factor (RF)-positive, polyarticular RF-negative, systemic, psoriatic, enthesitis-related, and undifferentiated JIA [5].

JIA is the most common systemic disorder associated with uveitis in children accounting for more than 75 % of cases of pediatric anterior uveitis [6]. Uveitis prevalence ranges from 10–20 % [7, 8] in the United States, although there is significant global variation [9]. It is a non-granulomatous anterior uveitis that occurs in up to 80 % of children [10•] and may develop prior to, simultaneously with, or after, the onset of arthritis. Female gender, arthritis subtype, young age, anti-nuclear antibody (ANA) positivity, and RF negativity have all been associated with an increased risk of uveitis [7].

Chronic anterior uveitis is the most common presentation [11]. It is usually silent and asymptomatic and may not be recognized until a child performs poorly on a visual evaluation as part of routine screening. The chronic, smoldering nature of the inflammation plays a greater role in visual morbidity than the actual degree of inflammation. Hence, children who develop uveitis prior to the onset of arthritis tend to have a worse visual prognosis [12]. Mean age of presentation is between 4–9 years [10•, 13–18]; however, intraocular inflammation usually has been present for many years prior to diagnosis. In a retrospective case series by Thorne et al. [13], the median duration of uveitis prior to presentation was 6 years. In fact, most cases are diagnosed in the absence of any ocular symptoms [16]. Hence, the American Academy of Pediatrics Sections of Rheumatology and Ophthalmology created screening guidelines wherein children who are of pauci- or polyarticular JIA subtype, ANA (+), short duration of arthritis, and young at arthritis onset are at a higher risk and require slit lamp examinations every 3–4 months [19]. However, these guidelines are based on the JRA classification scheme, and not the more recent JIA classification.

Cases of intermediate, posterior and panuveitis have also been reported although less commonly [10•, 13, 15]. Symptoms when present include pain, redness, photophobia, pupil irregularity, and loss of vision. Because of its indolent nature, many patients have sustained ocular complications prior to diagnosis. In a series by Woreta et al. [18], 67 % of patients had vision-threatening complications, most commonly band keratopathy (metastatic calcification of the cornea), posterior synechiae (adhesions between the iris and lens), cataract, and ocular hypertension. Presenting visual acuity (VA) ranged from normal to severely impaired with approximately 50 % experiencing visual impairment [20].

Using optical coherence tomography (OCT), Paroli et al. [21] studied 14 patients (24 eyes) with JIA-associated uveitis. They noted that 13.8 % had macular edema (cystic swelling of the outer retina) by clinical exam whereas OCT examination showed a higher frequency of 25 %. Hence, the rate of ocular complications in uveitis is significant and warrants routine screening.

While numerous local and systemic immunosuppressive therapies are available, visual outcomes vary. Risk factors associated with poor outcomes include male gender [7, 22, 23], ANA positivity [13], active intraocular inflammation [13], and age less than 7 years [7]. Long-term follow-up studies have demonstrated that 10–38 % of patients develop vision loss of 20/200 or worse [24].

Juvenile Spondyloarthropathies

Juvenile spondyloarthropathy (JSA) is a group of arthritides with a prevalence of 7.4 % for enthesitis-related arthritis (ERA), 6.3 % for psoriatic arthritis, and 19.7 % undifferentiated arthritis [5, 25]. Inflammatory back pain (sacroiliitis) is more common in adults whereas peripheral and hip arthritis are more frequent in children [26].

A component of the minor criteria for the diagnosis of JSA is a personal or family history of acute anterior uveitis [27•] which has been found in 10–23 % of patients [28, 29]. Anterior uveitis is also an independent risk factor for the development of sacroiliitis [28]. Patients generally present with an acute, unilateral non-granulomatous uveitis. Bilateral ocular involvement is common but usually does not occur not simultaneously [30]. Children with spondyloarthropathy may develop pain, photophobia, and redness which differs from asymptomatic disease seen in oligoarticular JIA.

Hypopyon (layering of white blood cells within the anterior chamber) may also be observed in children, similar to adults. The *HLA-B27* [31] is a genetic risk marker associated with 80–90 % of patients with spondyloarthropathy [32], wherein there is activation of the innate immune response as opposed to antigen presentation [33, 34]. Identification of an association with HLA-B27 spondyloarthropathy is paramount, since patients with infectious uveitis (i.e. endophthalmitis) may present with a hypopyon. Post-streptococcal uveitis secondary to recent infection with group A streptococcus is a rare subset of uveitis associated with HLA-B27 positivity [35]. It is an immunologic sequelae after acute streptococcal pharyngitis with a mean delay in presentation of 10 days (range 1–6 weeks) and associated with elevations in anti-streptolysin-O and anti-DNAase B antibody titers [36]. It is usually a bilateral non-granulomatous uveitis although posterior segment manifestations have been reported [37]. Hence, patients with HLA-B27 positivity may develop a severe exacerbation of uveitis

in the setting of recent streptococcal pharyngitis, which requires prompt treatment.

Reactive Arthritis

Another post-infectious, inflammatory disorder associated with HLA-B27 positivity is reactive arthritis (formerly known as Reiter's syndrome). In adults, it is characterized by the triad of urethritis, conjunctivitis, and peripheral arthritis. Most common infectious triggers are Chlamydia trachomatis in older children, whereas Yersinia enterocolitica and Shigella flexneri are common in younger children [38]. Some 75–90 % of cases are associated with HLA-B27 positivity [39]

Peak age of onset is between 8 and 12 years [40]. Children rarely present with the previously described clinical triad as ocular disease tends to evolve over the first few weeks after disease onset [41]. Over 75 % of children will present with ocular involvement, most commonly mucopurulent bilateral conjunctivitis in 50 % of cases. It is often self-limiting and resolves within 1–2 weeks. Bilateral non-granulomatous anterior uveitis may also be a presenting finding especially in the HLA-B27 positive population [42]. Less commonly, keratitis, scleritis, papillitis, intermediate/posterior uveitis, cataract, and glaucoma occur [43].

Acute episodes of intraocular inflammation in reactive arthritis necessitate treatment. Often, topical and periocular corticosteroids are sufficient, however, many require systemic immunosuppression with one large study reporting 52 % of patients needing methotrexate [43].

Intermediate Uveitis and Pars Planitis

Intermediate uveitis encompasses a group of inflammatory ocular disorders involving the ciliary body, vitreous cavity, and peripheral retina. Common infectious etiologies include syphilis, tuberculosis and Lyme disease whereas noninfectious etiologies include sarcoidosis and multiple sclerosis.

Pars planitis is a distinct clinical phenotype of idiopathic intermediate uveitis that comprises 17 % of childhood uveitis and is the most common cause of intermediate uveitis in children [44]. It is characterized by inflammation of the pars plana, an approximately 6-mm anatomic zone spanning the ciliary body, ora serrata, and peripheral retina. Vitreous inflammation, which is observed as cells within the vitreous gel or haze obscuring funduscopic detail, is characteristic (Fig. 1). Workup of infectious and autoimmune causes of intermediate uveitis is characteristically negative, and diagnosis requires the exclusion of agents such as syphilis, tuberculosis, sarcoidosis, and multiple sclerosis. Advanced presentation may be observed in children given its chronic, insidious nature and the lack of external manifestations (i.e. red eye). Hence, children with pars planitis may have more severe manifestations secondary to late referral.

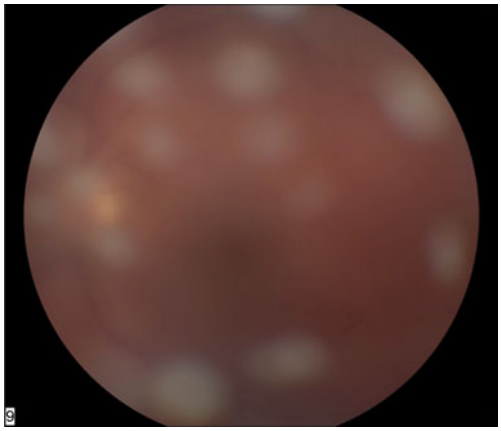

Fig. 1 Fundus photograph of a patient with pars planitis shows "snowballs" within the vitreous cavity and moderate vitreous haze, obscuring details of the optic nerve and retinal blood vessels

In contrast to the adult population, there is a higher incidence of males affected [45–47] with preponderance as high as 83 % [45]. The mean age at diagnosis ranges from 8 to 10 years [45, 48, 49]. The most common presenting symptom is blurred vision with a mean initial VA ranging from 20/40 to 20/150 [45, 50]. Cataracts, cystoid macular edema, and band keratopathy are the most common ocular complications of chronic inflammation. Less frequent complications include fibrovascular proliferation formation overlying the pars plana, vitreous hemorrhage, and macular pathology due to cicatricial changes over the retina from chronic inflammation.

Patients may respond well to either topical or periocular corticosteroids [45], although some patients require systemic immunosuppression. Occasionally, cryopexy for fibrovascular proliferations along the pars plana, or laser photocoagulation for areas of peripheral retinal ischemia associated with neovascularization and/or vitreous hemorrhage is performed.

Sarcoidosis

Sarcoidosis is a chronic, multisystem, non-caseating granulomatous disease that can also involve the eyes. Younger children (less than the age of 4) are more likely to develop ocular manifestations and arthritis while older children have systemic manifestations such as pulmonary involvement [51]. Ocular disease is rare accounting for approximately 2 % of pediatric uveitis [52] and is most commonly seen in African-Americans and Asians [51]. Disease prevalence varies from 0.06 per 100,000 person-years for children less than 4 and increases to 1.02 in adolescence [53]. Most cases occur between 13 and 15 years of age [54]. Although an

elevated angiotensin-converting enzyme level can be associated with sarcoidosis, it is not diagnostic.

Ocular manifestations are reported in 20–30 % of pediatric sarcoidosis [55] of which the majority include anterior uveitis [56] and conjunctival granulomas [57]. Less common are intermediate and posterior uveitis, orbital/periorbital involvement, and scleritis. The clinical course of uveitis is diverse and can range from acute non-granulomatous iridocyclitis to chronic granulomatous iridocyclitis with posterior synechiae, cataract, and secondary glaucoma [58]. Posterior segment manifestations include vitritis, cystoid macular edema, periphlebitis, chorioretinitis, and optic neuritis. Younger children have shown a higher rate of vitreous hemorrhage [59] and lacrimal gland involvement [60]. Importantly, ocular sarcoidosis can occur in the absence of systemic disease.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic, autoimmune, connective tissue multisystem disorder with a relapsing and remitting clinical course. Approximately 15–20 % of patients develop symptoms in childhood. Prior to puberty, males and females are at similar risk of developing SLE, while after puberty there is a four-fold increased incidence in females [61]. During childhood, renal and CNS involvement are more prevalent and require immunomodulatory therapy [62].

Ocular manifestations may occur later in the disease and are less commonly observed in the juvenile form of SLE (jSLE) with one large study estimating a prevalence of 8 % [63]. Although other studies report higher rates, many of these findings are secondary to chronic corticosteroid use (i.e. cataract) as opposed to inflammatory sequelae secondary to SLE [64]. Similar to adult-onset disease, the most common ocular finding is keratoconjunctivitis sicca (KCS) [65], while the most visually devastating sequelae occur secondary to optic nerve involvement and retinal vaso-occlusion [66].

Antiphospholipid antibody (aPL) syndrome has been variably reported in cases of SLE. A recent review found the prevalence of anti-cardiolipin antibody at 44 %, anti-2-glycoprotein I at 40 % and lupus anticoagulant at 22 % in jSLE [67]. aPL has been associated with retinal vaso-occlusive disease. In one study, 77 % of patients with SLE and retinal involvement had positive aPL titers whereas only 29 % of SLE patients without retinal disease had positive titers [68].

Another important ocular finding of SLE is choroidopathy. It is a rare manifestation with less than 40 cases reported in the literature. The pathogenesis is multifactorial wherein uncontrolled hypertension [69], immune complex deposition in the choriocapillaris [70], and anti-retinal pigment epithelium antibodies [71] have been implicated. It is generally seen in patients with highly active disease including CNS vasculitis and nephropathy as well as hypertension. Although it is a marker of increased disease activity, lupus choroidopathy has been shown to be responsive to corticosteroids and other forms of immunosuppression. Given its associations with CNS and renal disease, the presence of choroidopathy is likely an indication for aggressive, long–term immunosuppression [72•].

Childhood Behcet's Disease

Behcet's disease is a major cause of pediatric uveitis with an incidence as high as 11 % in endemic nations [73]. It is a chronic multi-system inflammatory disorder with a peak age of onset in the 3rd decade of life; however, childhood and elderly cases have been described. It is characterized by recurrent oral and genital ulcerations and uveitis. The underlying pathophysiology is a necrotizing vasculitis affecting both the arterial and venous system of all organ systems [74].

Childhood Behcet's is rare, and in the Japanese population where the prevalence has been estimated up to 30 times higher than in the United States, pediatric disease comprises only 0.002 % [75]. The mean age of diagnosis ranges from 11 to 15 years [76–79]. The most common presentation in both childhood and adult cases is oral ulcerations [76, 79, 80]. Ocular disease is rarely an initial manifestation [76, 79, 81] and usually occurs 2 years after disease diagnosis [76].

Ocular involvement has been variably reported between 29 and 100 % and most commonly presents as a relapsing anterior or posterior uveitis, typically bilateral [74, 76, 77, 79, 81]. Compared with adult disease, childhood-onset is more severe with a higher degree of visual impairment especially in young males [77, 81, 82]. Patients with anterior uveitis tend to have a better visual outcome than those with posterior segment disease [81]. Vision loss is most commonly secondary to ischemic maculopathy, cataract, and optic atrophy [76, 83]. Final vision tends to be poor, usually 20/70 or worse [76, 81]. Other less common findings include conjunctivitis, conjunctival ulcers, scleritis/episcleritis, keratitis, and cranial nerve involvement [80]. Aggressive immunosuppressive therapy is crucial with reports showing 56–75 % of patients requiring treatment [76, 82, 84].

Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitides

The ANCA-associated vasculitides (AAV) are a group of small to medium-sized autoimmune vasculitides associated with c-ANCA and p-ANCA antibodies and include granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis [85]), microscopic polyangiitis (MPA), and Churg–Strauss syndrome (CSS). AAV can affect all organ systems; however, pulmonary, renal,

gastrointestinal, and central and peripheral nervous system involvement are most common.

Of these vasculitides, ocular involvement is most commonly seen in GPA. Typically, upper and lower respiratory tract inflammation with renal disease occur, although patients often present with non-specific symptoms such as shortness of breath, chronic cough, hemoptysis, and abnormal urinalysis [86]. In general, ocular findings are less common and affect only 37 % at presentation [86]. In children, conjunctival involvement occurs most frequently followed by episcleral/scleral and orbital disease [87]. Conjunctival disease most commonly affects the upper palpebral conjunctiva and begins as hyperemia but can progress to nodule formation and cicitricial changes. In severe cases, globe exposure occurs increasing the risk of secondary infectious keratitis. Histopathology may show an occlusive vasculitis [88]. The sclera can also be involved because of its high collagen content [89]. Necrotizing scleritis portends a poor ocular and systemic prognosis [88]. Orbital involvement can include periorbital edema, paniculitis, myositis, dacryoadenitis, and dacryocystitis/canaliculitis and is highly associated with nasal sinus involvement [90]. Because orbital tissues are frequently involved, a tissue diagnosis of GPA may be achieved via an orbital biopsy.

Sjogren's Syndrome

Sjogren's syndrome is characterized by decreased function of the salivary and lacrimal glands. Recently revised diagnostic criteria include 2 of the following: (1) (+) anti-SSA/Ro and/or anti-SSB/La OR (+) RF and ANA titer> 1:320, (2) keratoconjunctivitis sicca (KCS) with an ocular staining score >3 (derived from fluorescein staining of the cornea and lissamine green staining of the conjunctiva), and (3) labial salivary gland biopsy exhibiting focal lymphocytic sialadenitis [91]. Sjogren's syndrome can be isolated or associated with other auto-inflammatory diseases such as rheumatoid arthritis (20 %), systemic lupus erythematosus (15 %) and scleroderma (30 %) [92].

Primary Sjogren's syndrome (pSS) in childhood is rare, with a recent review identifying only 145 cases with 66.4 % having ocular involvement [93]. The mean age at diagnosis was 9.8 years [93] with a 7:1 female predominance [94]. The most common clinical manifestations are bilateral parotid swelling and recurrent parotitis [93, 95]. Sicca-related disease (KCS and xerostomia) are common presenting symptoms in adults, but occur later in children possibly secondary to underreporting if patients are not severely affected [95, 96]. Therefore, early ophthalmology referral of children with a history of recurrent parotitis is necessary for objective testing for KCS.

Commonly performed tests include Schirmer's testing and staining of the ocular surface. A Schirmer's test involves suspending strips of filter paper from the inferior conjunctival cul-de-sac in an anesthetized eye (measures basal tear production) or an unanaesthetized eye (measures basal and reflex tear production). A measurement less than 5 mm is typical of KCS. Ocular surface staining can be done with fluorescein (stains basement membrane in areas of absent epithelium), lissamine green (stains devitalized, swollen epithelial cells), or rose bengal dye (stains devitalized, swollen epithelial cells). Diffuse punctate staining, especially in the interpalpebral region, is characteristic of KCS.

Secondary Sjogren's syndrome (sSS) in childhood appears to be more common. A comparative study of children with pSS and sSS found a similar age of diagnosis (9.5 vs. 8.5 years), a female preponderance, and similar presenting symptoms. There were significantly more sSS patients with positive serologies (i.e. ANA, RF, anti-Ro, anti-La) observed [97].

Kawasaki Disease

Kawasaki disease (KD) is a systemic vasculitis and a leading cause of acquired heart disease in North American and Japanese children. Over the past 10 years, there has been an increase in the diagnosis of KD with an incidence of 218.6 per 100,000 children less than 5 years old in 2008, surpassing an incidence of 196.1 per 100,000 during the epidemic of 1982 in Japan [98]. Overall, incidence is highest between 6 and 11 months of age [98], wherein children less than 5 years old comprise 73 % of cases [99].

KD is a clinical diagnosis consisting of fever for greater than 5 days and at least 4 of the following: bilateral bulbar conjunctivitis, oropharyngeal changes (i.e. strawberry tongue, cracked lips, mucosal erythema), cervical lymphadenopathy, polymorphous rash, and skin changes of the extremity (i.e. erythema of palms or soles, periungal desquamation) [100]. The most common ocular finding is a bilateral non-exudative conjunctivitis involving only the bulbar conjunctiva. Symptoms include tearing, irritation, and mild photophobia. Corneal involvement tends to be mild and is usually in the form of punctate epitheliopathy [101]; however, severe disease such as disciform keratitis has been reported [102]. A mild bilateral non-granulomatous anterior uveitis is also commonly present early in the acute phase of the disease [103, 104]. The intraocular inflammation generally presents in the first week and usually has a self-limited course [103–105]. In fact, one study reported anterior uveitis in 83 % of patients during the first week of illness which dropped to 41 % 1 week after onset of symptoms [103]. Most cases resolve within 2–8 weeks and patients rarely have ocular

sequelae [105]. However, topical corticosteroids have been successfully used to treat inflammation [104]. Rarely, posterior segment abnormalities have been associated with KD including papillitis [106, 107], vitreous opacities [107], and retinal vasculitis [106]. Early treatment of the posterior segment manifestations with systemic or periocular corticosteroids is important to prevent ischemic injury to the retina and permanent vision loss [108].

Special Considerations

Therapeutic Considerations: Local and Systemic Corticosteroids, Non-Biologic and Biologic DMARDS

Corticosteroids

Corticosteroids are a mainstay of therapy for acute, sight-threatening non-infectious uveitis associated with systemic pediatric inflammatory disorders. This medication class inhibits both the innate and adaptive immune response by preventing proliferation and inducing apoptosis of T cells, B cells, and macrophages, as well as reducing levels of cytokines and prostaglandins [109].

Corticosteroids may be administered locally for ophthalmic disease via topical, periocular or intravitreal routes or systemically via oral or parenteral administration. The short-term use of topical corticosteroids is effective for anterior uveitis; however, because of poor vitreous and posterior segment (i.e. retinal, choroidal) penetration, periocular or systemically administered corticosteroids are often needed. Moreover, the use of topical corticosteroids exceeding three drops daily has been associated with incident cataract development. Specifically, the use $\leq$3 drops daily was associated with 0.01/eye-year incident risk of cataract versus 0.16/eye-year incident risk of cataract in patients using $\geq$3drops daily ($p<0.0006$) [110•].

Periocular administration is also available for severe posterior segment inflammation or anterior inflammation refractory to topical medications. For example, in patients with pars planitis, particularly in those with unilateral disease, asymmetric bilateral disease, or cystoid macular edema, the administration of periocular corticosteroids may be effective for acute disease control and to avoid the need for systemic medications [111]. However, the risk of glaucoma, cataract, and globe penetration should be considered.

Systemic corticosteroids are effective for the control of acute, bilateral disease in patients with systemic autoimmune disorders. However, long-term use may be associated with glaucoma and cataract in addition to systemic side effects hence should be avoided when possible.

Non-biologic DMARDS

The efficacy of disease-modifying antirheumatic drugs (DMARDS), particularly methotrexate, has been described for a variety of indications including JIA-associated uveitis and pars planitis [112, 113].

Biologic agents

Biologic agents, in particular the TNF alpha inhibitors, have been used successfully for the treatment of children with ocular inflammation [114–116]. In particular, infliximab and adalimumab have demonstrated efficacy in JIA-associated uveitis. Dosing of infliximab has ranged from 3 to 8 mg/kg although reports of higher doses from 10 to 20 mg/kg have been suggested [117]. Adalimumab has demonstrated efficacy both as an initial corticosteroid-sparing biologic agent, as well as in patients who are refractory to infliximab [118•, 119].

It is notable that, while initial reports described the efficacy of etanercept for uveitis associated with JIA [120], more recent reports have differed. Specifically, one large questionnaire-based study suggested no difference in uveitis flare-ups in patients on etanercept versus those not using etanercept [121]. Moreover, the initiation of etanercept has been associated with an acute drug-related uveitis [122].

Other promising biologic agents for pediatric uveitis described in smaller series and case reports include abatacept [123], golimumab [124], and daclizumab [125]. While these reports are encouraging, the majority of the patients were incompletely responsive to TNF-alpha inhibitors. Hence, their use as a first-line corticosteroid-sparing medication warrants further study.

Retinal Toxicity Due to Anti-malarial Agents

Antimalarial agents such as chloroquine and hydroxychloroquine have commonly been used as steroid-sparing agents for chronic immunosuppression in both pediatric and adult rheumatologic disease. Ocular toxicity has been described and includes keratopathy, ciliary body dysfunction, lens opacities, and maculopathy [126].

Retinal findings are most commonly reported in the literature and can be visually debilitating if not properly diagnosed. Specifically, an irreversible drug-induced maculopathy may occur. Evidence from the adult literature shows increased risk of toxicity with a cumulative dose greater than 1,000 g of hydroxychloroquine. Other risk factors include greater than 5–7 years duration of therapy, impaired renal or hepatic function, obesity, pre-existing retinal pathology, and advanced age [127]. Abnormalities in color vision may be an indication of early toxicity. However, there have not been sufficient studies

in the pediatric literature to set standards for retinal toxicity.

Because insufficient evidence exists, the American College of Rheumatology has advocated an annual eye exam for children taking hydroxychloroquine [128]. A Humphrey visual field with a 10–2 testing algorithm, multifocal electroretinogram, spectral-domain optical coherence tomography, and fundus autofluorescence have all been recommended as acceptable screening tools for diagnosing early retinal changes secondary to hydroxychloroquine and chloroquine [127].

A Multidisciplinary Approach to the Management of Children with Ocular Inflammation

There has been vast improvement in the visual outcomes of children with ocular inflammatory disorders over the last decade. This has been secondary to improved routine uveitis screening for children with JIA, better partnerships between pediatric ophthalmologists and rheumatologists, and the advent of targeted biologic therapies. Close communication and collaboration between specialists is crucial to identify patients at-risk for poorer outcomes, coordinate therapeutic decisions according to ocular inflammation while mitigating drug toxicities, and ensure optimal visual and quality-of-life (QOL) outcomes for children.

While outcomes may be monitored objectively through the clinical ocular exam (e.g., visual acuity, level of anterior chamber and vitreous inflammation using slit lamp examination biomicroscopy and dilated funduscopic examination), our ability to correlate improvement of ophthalmic outcomes with improved QOL is the subject of ongoing research. Specifically, there is a need for subjective measures to assess the short-term and long-term impact of ocular involvement in a child's life. Our group has developed an instrument to measure visual function and vision related QOL in children with uveitis entitled, "Effects of youngsters' eyesight on quality of life (EYE-Q)" [129•, 130]. We hope this tool will augment current evaluations, enable a comprehensive assessment of the impact of uveitis and perhaps be utilized for children with other ocular disorders. A coordinated, multi-disciplinary approach engaging perspectives from both the rheumatologist and ophthalmologist are a requisite for the coordinated care of patients with complex ocular conditions.

Conclusions

Systemic autoimmune disease can affect every organ system including the eye, and pediatric disease holds no exception. Ocular manifestations may be silent or appear incongruously with systemic findings. They can be vision threatening and are often an index of disease activity. Early diagnosis is essential and requires close collaboration between the ophthalmologist and rheumatologist. With the advent of newer biologic agents, better control of ocular and systemic inflammation may be possible ultimately improving disease morbidity.

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Compliance with Ethics Guidelines

Conflict of Interest Neal V. Palejwala declares that he has no conflict of interest.

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