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The Role of Gender in Uveitis and Ocular Inflammation

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Abstract

Uveitides can be due to non-infectious and infectious etiologies. It has been observed that there is a gender difference with a greater preponderance of non-infectious uveitis in women than in men. This review will describe both non-infectious and infectious uveitides and describes some of the current autoimmune mechanisms thought to be underlying the gender difference. It will specifically look at non-infectious uveitides with systemic involvement including juvenile idiopathic arthritis, spondyloarthropathies, sarcoidosis, Behçet's disease, and Vogt-Koyanagi-Harada disease and at uveitides without systemic involvement including sympathetic ophthalmia, birdshot chorioretinitis, and the white dot syndromes. Infectious uveitides like acute retinal necrosis, progressive outer retinal necrosis, and cytomegalovirus mediated uveitis will be mentioned. Different uveitides with female- or male- predominance are presented and discussed.

Background

The burden of blindness worldwide is unequal with regards to gender, with women accounting for 64.5% of blindness.¹ While some of this discrepancy can be explained by factors such as poorer access to care, it is not sufficient to explain the entirety of the problem.² The uveitides are a collection of diseases that result in inflammation of the uveal tract that may also involve the retina and vitreous. The causes of uveitis can be either non-infectious (most are considered forms of autoimmune uveitis) or infectious. If left untreated, uveitis can lead to poor visual outcomes, including blindness. Interestingly, these diseases affect the genders differently, with some being more common in women and others more common in men.³ Along with the finding that the prevalence of autoimmunity in women is higher than in men, uveitides with autoimmune etiologies, such as those resulting from systemic lupus erythematosus (SLE) and sarcoidosis tend to be reported more frequently in women than in men.⁴ While the cause for this is unclear, recent evidence has pointed towards how sex hormones affect the autoimmune response; estrogen increases the response whereas androgens suppress it. However, other evidence suggests that estrogen's effect on autoimmunity may be dose dependent with lower levels being immune-stimulatory and higher levels immune-inhibitory.⁵ Furthermore, women respond to injury or infection with a dominant Th2 immune response (leading to increased antibody production), while men respond with a stronger Th1 response. This may play a role in the increased prevalence of

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Th2-mediated autoimmune disorders in women.⁴ Moreover, estrogen has recently been shown to play a significant role in the development and function of Th17 cells, as well as the production of IL-17.^{6, 7} It has also been noted that men and women may present with the same underlying cause of uveitis but with differing severity or ophthalmic manifestations.⁸ In addition, infectious uveitides do show gender differences in prevalence, primarily due to behavioral and/or cultural sources.⁹ All these reports point to gender differences in clinical manifestations and pathogenesis of uveitis that may be important for disease prevention and treatment.

Female predominant uveitides with systemic involvement

Systemic autoimmune diseases affect approximately 8% of population, mostly among women.⁴ Uveitides with systemic involvement are quite similar with a higher prevalence in women than men.³ Juvenile idiopathic arthritis (JIA) is a group of auto-immune arthritides that affect children below the age of 16.¹⁰⁻¹² It is more common in females and depending on the sub-type, 50-80% of JIA patients are female.¹³ Uveitis is a common manifestation of the disease, occurring in 10-45% of JIA patients.^{11, 12, 14} The most typical uveitic presentation is a chronic insidious bilateral anterior uveitis, which is thought to confer the greatest risk to vision due to the lack of a red eye and its onset in pre-verbal children.¹⁵ Female, anti-nuclear antibody (ANA) positive, oligoarticular arthritic JIA children are at the highest risk for uveitis.^{11, 12, 15-17} Whereas females are more likely to develop uveitis, males with JIA can present with enthesitis, which is linked to the presence of human leukocyte antigen (HLA)-B27 (60-70%).¹⁵ However, when uveitis is found in male patients, it is often more severe with a higher rate of ocular complications, including posterior synechiae.^{15, 18} Males also have a higher rate of complications; after 8 years of follow-up in a cohort of patients with JIA-associated uveitis, 40% of males had at least one ocular complication compared to 10% of females.¹⁹ This increased severity but reduced prevalence in the male gender is also seen in other autoimmune diseases.

SLE is an autoimmune disorder that causes immune complex mediated damage affecting many organs, which is associated with the production of auto-antibodies against nuclear material.⁷ Eighty-eight to 90.5% of SLE patients are women.^{7, 20, 21} SLE commonly affects Asian and African women in their reproductive years.²²⁻²⁴ Increased levels of estrogen and progesterone (e.g. pregnancy, post-partum status) can cause worsening of SLE.^{5, 7} This is likely due to upregulation of a Th2 immune response leading to increased antibody synthesis. Although ocular findings are not one of the components of the classification criteria for SLE, SLE is associated with keratoconjunctivitis sicca and posterior segment pathology.^{5, 25} SLE can cause lupus retinopathy with the clinical appearance of a Purtscher-like retinopathy.²⁶ Retinal vasculitis and retrobulbar optic neuritis are the uncommon inflammatory complications of SLE.²⁷ Although men have a lower prevalence of SLE than women, they are at higher risk for SLE-related complications, including systemic thromboses, nephropathy and CNS involvement. Thus, male gender has been proposed as a predictor for poor systemic outcomes but the exact etiology remains unclear.^{5, 28, 29}

Multiple sclerosis (MS) is a chronic episodic demyelinating non-infectious auto-immune disease of the central nervous system (CNS). MS is much more prevalent in women, with

78% of patients being female with a mean age of diagnosis around 37 years old.^{30, 31} MS varies geographically with a lower incidence in Asia and a higher incidence in countries away from the equator.³² This suggests a role for genetic, epigenetic, or noninfectious environmental factors.³¹ Hormonal changes have been implicated in the disease; it is known that women, though more likely to develop MS, will have fewer relapses during pregnancy, suggesting that changes to the hormonal profile of these women affects the course of the disease.^{30, 31} This hypothesis has been supported by further testing in rodent MS models, wherein T lymphocyte transfer from female rats was more effective at instigating disease than from male rats.³³ Ocular manifestations of MS range from optic neuritis, internuclear ophthalmoplegia, nystagmus, and uveitis including intermediate uveitis and retinal periphlebitis.³¹ Interestingly, 56% of cases are granulomatous and greater than 90% are bilateral.^{34, 35} Uveitis, in particular, shows a female predisposition, though it is uncertain whether this is solely because MS is more common in females (upwards of 88% of MS patients with uveitis are female).^{31, 34, 35} Idiopathic intermediate uveitis (IU) that often has similar clinical findings of MS is slightly more prevalent in females, with 56% of IU patients being female. However IU in children under the age of 16 are more common in males (61%).³⁶

Sarcoidosis is a systemic granulomatous inflammation in multiple organs of unknown etiology. Globally, it is slightly more prevalent in women (55-64% of those diagnosed are female).³⁷⁻³⁹ Though sarcoidosis can affect many organs and both genders, ocular involvement is more common to females.³⁸ Ethnically, it is 10-20 times more prevalent in African-Americans than Caucasians.^{5, 40} However, female gender and Caucasian race are associated with a worse visual outcome, with white females having the highest occurrence of cystoid macular edema.^{5, 39, 41-43} A second peak in sarcoidosis diagnoses occurs after the age of 50; 83.3% of patients diagnosed with late-onset sarcoidosis were female, compared to 50% in the younger cohort. Uveitis in this older group was also more likely in females (80%) compared to males.⁴⁴ In the eye, sarcoidosis commonly presents as a bilateral granulomatous anterior uveitis. Posterior/pan-uveitis and periphlebitis can also occur, and posterior segment involvement is associated with a worse visual outcome.^{5, 39}

Vogt-Koyanagi-Harada disease (VKH) is an autoimmune disorder that involves the eyes, ears, skin, hair, and meninges. Worldwide, women are more frequently affected than men. In Brazil, 70% of VKH patients were female,⁴⁵ in the USA, 78.7%,⁴⁶ and in India, 84.4%.⁴⁷ VKH tends to affect patients with Asian, Middle Eastern, Hispanic and Native American ancestry.^{48, 49} Acute VKH uveitis frequently presents with bilateral multifocal exudative retinal detachments. Other signs include mutton-fat keratic precipitates, anterior uveitis, iris nodules, posterior synechiae, vitritis, diffuse choroidal infiltration, Dalen-Fuchs nodules, and papillitis. Sugiura's sign and a sunset-glow fundus can occur in the convalescent (chronic) stage.⁵⁰ Long-term sequelae include choroidal neovascularization (CNV), sub-retinal fibrosis, and cataracts.^{48, 51} Similar to other uveitic conditions with systemic involvement, gender affects the prognosis;⁵⁰ a male VKH patient is significantly more likely to have a poorer visual outcome than a female patient. An Indian group found that 37.5% of their male VKH patients had vision worse than 20/80, compared to only 3.3% of their female VKH cohort.⁵² The reason for the poorer male visual outcomes is unclear, though

female sex hormones and HLA-DR genes have been associated with the female predisposition to the disease.^{50, 53-55}

Female predominant uveitides without systemic involvement

Birdshot chorioretinopathy (BCR) is a rare bilateral posterior uveitis. It is more common in women (58% of a cohort of 1157 BCR patients were female).⁵⁶ It has strong association with the HLA-A29 and tends to affect those of Northern European ancestry and those in middle age (average 48-53 years).⁵⁶ BCR patients usually produce pathogenic T cell subsets that are associated with IL-17 cytokines.⁵⁷

The white dot syndromes are a group of rare posterior uveitic diseases.⁵⁸ Most of these conditions described below are more common in women.⁵⁶ Multiple evanescent white dot syndrome (MEWDS) classically presents as numerous small discrete white lesions at the posterior pole and mid-periphery in young myopic women between the ages of 20 to 45. Of the reported 77 MEWDS patients, 74% were female. MEWDS is thought to have a viral etiology and usually resolves spontaneously.⁵⁶ Multi-focal choroiditis with pan-uveitis (MFC) differs from MEWDS in that patients are more likely to have irreversible visual impairment. In this cohort, 75% of 406 MFC patients were female. MFC patients usually present with a bilateral vitritis along with punched out chorio-retinal scars with pigmented borders at the posterior poles and peripheries. MFC tends to be a chronic disorder with a poor visual prognosis due to CNV. The cause is unknown.⁵⁶ Punctate Inner Choroidopathy (PIC) is also similar to MEWDS and is similarly associated with young myopic women. In the cohort, 85% of 471 PIC patients was female.⁵⁶ Similar to MFC, CNV can occur in PIC leading to vision loss.⁵⁶ Acute zonal occult outer retinopathy (AZOOR) is the last of the white dot syndromes that is more common in women. In the cohort, 79% of 150 AZOOR patients were female. AZOOR classically presents in a young woman with photopsia. There is rapid loss of large areas of outer retinal function but with minimal fundus changes. The cause is unknown and no effective treatment has been found. Further, in all the white dot syndromes, no gender differences in disease severity or symptoms have been noted.⁵⁶

Male predominant uveitides with systemic involvement

Spondyloarthropathies are a group of inflammatory arthritides. Uveitis occurs in up to 37% of spondyloarthropathy patients.^{59, 60} These diseases tend to be more prevalent in males.⁶¹ For example, up to 80% of ankylosing spondylitis patients are male.⁶² Up to 90% of ankylosing spondylitis patients, 40-80% of reactive arthritis patients, and 40-50% of psoriatic arthritic patients are positive for HLA-B27.⁵⁹⁻⁶¹ HLA-B27 anterior uveitis is more prevalent in males with 66.5-75% of patients being male.^{63, 64} This is important because HLA-B27 anterior uveitis is one of the most common types of uveitis in Western countries, accounting for 50-80% of anterior uveitis patients.^{60, 61, 63, 65-67} Recently, a genome-wide association study showed that a single allele of HLA-B27 conferred an odds ratio (OR) of 66.8 for developing acute anterior uveitis and homozygosity conferred an OR of 130.6 when compared to HLA-B27 negative controls.⁶⁸ In general, an HLA-B27 associated uveitis has a poorer prognosis than a HLA B27 negative uveitis.^{69, 70} Male gender is also a risk factor for an associated occlusive retinal vasculitis, a younger age of onset, and single visit vision loss

of 20/50 or worse.^{61, 71-74} However, there is no gender difference in the risk of hypopyon, vitritis, cystoid macular edema, secondary glaucoma or final visual acuity.⁶¹

Behçet's disease (BD) is a rare immune-mediated systemic vasculitis of unknown etiology. In BD, 54-85% of patients are male.⁷⁵⁻⁷⁸ It predominantly affects patients with ancestry from the Silk Road (especially from Turkey). Uveitis occurs in 50-90% of BD patients.^{79, 80} BD frequently presents as a bilateral panuveitis, particularly with a retinal vasculitis.^{75, 81} Other features include oral and genital ulcers, vascular complications, arthritis, skin lesions and central nervous system lesions.⁸ There is a strong association with HLA-B51.^{82, 83} BD tends to be more severe in males, patients with a younger age of onset, and in HLA-B51 positive patients.^{79, 84} Men also are more likely to have a poorer response to therapy for ocular BD.^{85, 86} This is thought to be due to the higher incidence of retinal vasculitis and posterior segment involvement in men than in women.⁵

The systemic vasculitides are a group of conditions associated with uveitis, which were classified according to the size of the involved blood vessels. The 2012 International Chapel Hill Consensus Conference updated the nomenclature. The new term "anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV)" now encompasses: granulomatosis with polyangiitis (GPA instead of Wegener's granulomatosis), eosinophilic granulomatosis with polyangiitis (EGPA instead of Churg-Strauss Syndrome) and microscopic polyangiitis (MPA).^{5, 87} No obvious gender difference for AAV has been reported.⁸⁸ In one study, 53.8% of AAV patients were male.⁸⁹ Interestingly, mildly increased male prevalence was pronounced in patients over 50 years of age.⁹⁰ The most common ophthalmic manifestations of ANCA-associated vasculitides are conjunctivitis, episcleritis, and scleritis. Uveitis tends to occur in less than 10% of patients and is thought to be spillover of inflammation from adjacent scleritis or keratitis.⁹¹⁻⁹⁴ Occlusion of retinal veins and arteries is uncommon but can occur in GPA and EGPA.⁹⁵⁻⁹⁸

Male predominant uveitides without systemic involvement

Sympathetic ophthalmia (SO) is a rare condition that occurs after the uvea of one eye is subjected to a penetrating injury (e.g. by trauma or surgery). Pathologically, it is similar to VKH, but SO lacks VKH's extra-ocular manifestations. Injury to the "exciting eye" results in an inflammatory response that develops later (90% of cases are within one year) in the uninjured "sympathizing eye".⁵⁰ As men are more likely to suffer penetrating ocular trauma due to occupational and lifestyle factors, there seems an increased prevalence in men with 50-72.1% of SO patients being male.^{50, 99, 100} In post-surgical cases, there have been no reported gender differences.^{50, 99} SO classically presents as acute bilateral granulomatous inflammation with mutton-fat keratic precipitates, aqueous cells and flare, iridocyclitis, and posterior synechiae. Posterior segment signs include vitritis, optic disc swelling, and Dalen-Fuchs nodules with choroidal infiltration and thickening.^{50, 101-104}

Acute posterior multifocal placoid pigment epitheliopathy (APMPPE) is the only member of the white dot syndromes to be more prevalent in men. Of 405 APMPPE patients, 54% were male.⁵⁶ APMPPE presents with bilateral multiple yellow-white placoid lesions at the

posterior pole. The lesions fade over 1-2 weeks, usually with significant sequelae. Although the etiology is not fully understood, a viral factor is thought to be involved.⁵⁶

Infectious uveitides

In infectious uveitides for which there is no element of sexual transmission, the prevalence of ocular disease is roughly equal between men and women. However, variation exists between different infectious uveitides due to the influence of occupational exposures, sexual behaviors, and other environmental factors that differ between the sexes.⁹

Some infectious conditions are more prevalent in men. Eighty-seven to 90% of systemic and ocular syphilis occurs in men.^{9, 105, 106} The high prevalence of syphilis in men is thought to be due to unsafe sexual practices mainly among men who have sex with men, who account for 73% of infectious syphilis. Ocular syphilis can cause an anterior, intermediate, posterior, or pan-uveitis along with optic neuritis and interstitial keratitis.¹⁰⁶

Acute retinal necrosis (ARN) is a rare but devastating condition that usually occurs in immunocompetent individuals. The causative agents are thought to be varicella zoster virus (VZV), herpes simplex virus (HSV) and possibly Epstein-Barr virus (EBV) and cytomegalovirus (CMV). ARN is characterized by discrete foci of peripheral retinal necrosis, circumferential spread, occlusive arteriolar retinopathy, vitreous or anterior chamber reaction, and rapid disease progression.¹⁰⁷ Secondary retinal detachment is a known possible complication of ARN.¹⁰⁸ ARN has an increased prevalence in men with 56-72% of ARN patients being male.^{77, 107-109} Further, ARN severity is correlated with gender; in one study of 22 individuals with ARN, male gender was a risk factor for severe vision loss at 6 and 12 months ($p = 0.019$ and $p = 0.008$ respectively).¹⁰⁹

Progressive outer retinal necrosis (PORN) is another viral-mediated infectious uveitides which is more prevalent in men (83-86%).^{110, 111} PORN occurs in immunocompromised individuals and is due to varicella zoster or herpes simplex viral infection.¹¹² It usually presents as a minimal non-granulomatous anterior uveitis without vitritis but is associated with a bilateral necrotizing retinitis. The retinitis starts at the posterior pole and spreads peripherally. Like ARN, PORN can also lead to secondary retinal detachment.¹¹³

CMV retinitis (CMVR) is a similar viral-mediated infectious uveitides that is more common in men. In human immunodeficiency virus (HIV) infected patients, up to 77% of CMV retinitis patients are male.¹¹⁴ Though uncommon in non-HIV infected patients, 60-80% of these CMV retinitis patients are male.^{115, 116} CMVR is characterized with dense, white confluent retinal lesions with hemorrhages and vascular sheathing. Similar to ARN and PORN, a secondary retinal detachment can occur.¹¹³ CMV can also cause anterior uveitis. Similar to CMVR, there is a male predominance with 56-78% of CMV anterior uveitis patients being male.¹¹⁷⁻¹²⁰ CMV anterior uveitis can be acute or chronic. It can present like Posner-Schlossman syndrome or Fuchs' heterochromic iridocyclitis and may be associated with acute relapsing or chronic raised intraocular pressure (IOP).¹¹⁸

There are infectious uveitides without gender preference. Toxoplasma is a gender-neutral infection that can result in uveitis. Brazil has a high prevalence of toxoplasma

chorioretinitis, and toxoplasma seropositivity occurs across both sexes in the same households. Sharing of and ingestion of contaminated food or similar environmental factors within the same family could account for this gender neutrality.^{9, 121}

Discussion

In general, autoimmune diseases are mediated by Th1, Th2, and Th17 cells. Th1 cells are responsible for cell-mediated immunity, whereas Th2 cells are responsible for humoral-mediated immunity. Excessive Th1 response, via production of interferon (IFN)- γ often results in tissue damage, while an excessive Th2 response leads to hypersensitivity through IL-4 mediated B cell recruitment.¹²² The role of Th17 cells and their production of IL-17 in autoimmunity are being studied in a variety of models.¹²³⁻¹²⁹ Animal models of uveitis (experimental autoimmune uveitis, EAU) have demonstrated that EAU is predominantly a Th1/Th17 mediated disease.¹³⁰ Further, Th17 response has been associated with the pathogenesis of VKH,¹³¹ and IL-17 is raised in ocular sarcoidosis and in active VKH.¹³²⁻¹³⁵ This matches other systemic autoimmune conditions where pro-inflammatory IL-17 has also been found to be overexpressed in MS,¹²⁵ rheumatoid arthritis (RA),¹³⁶ and SLE.^{127, 129}

However, differences in the way the sexes respond to infection and develop autoimmunity have also been described. Women primarily respond to infection and vaccination with classical Th2 mechanisms (leading to increased antibody production), whilst men develop a stronger Th1 response.^{4, 137} This fact has been postulated as one reason why Th2-mediated autoimmune conditions like RA are more prevalent in women.⁴

Other immunologic pathways underpinning the gender difference in autoimmunity must also be present. Increasingly, it is recognized that the gut microbiome and intestinal mucosal inflammation has a role in systemic autoimmune diseases.¹³⁸ The gut mucosa of female mice have higher concentrations of plasma cells, gut imprinted $\alpha 4\beta 7$ T cells, and of CD45+ IL-17, IL-22 and IL-9 producing cells than male mice.⁷ The microbiome has been linked to the female predominant conditions of RA and MS and is thought to have an effect on IL-17 mediated pathways.¹³⁹⁻¹⁴¹

Overall, non-infectious uveitis tends to be more prevalent in women. However, with HLA-B27 associated disease, the uveitis tends to be more prevalent and severe in men. JIA-affected boys who are HLA-B27 positive have a 40% ocular complication rate, compared to a 10% ocular complication rate in girls.^{15, 16, 19} The explanation as for why HLA-B27 has a larger effect on ocular complications in males compared to females is still unknown, though recent evidence suggests altered gut microbiota may play a role in HLA-B27 associated disease.¹⁴²

It may not just be differences in the HLA gene loci to explain for the gender difference in severity of the uveitis. Interestingly, the CCR5-403 AA genotype was only found in male patients with BD. These associations may point to gender-associated genetics that have been heretofore unexplored.¹⁴³

X chromosomes and hormone-mediated modulation may be another possible reason for the gender difference. Pregnancy illustrates this. A successful pregnancy requires the tolerance

of a semi-allogeneic fetus.^{144, 145} Increased levels of estrogen and progesterone in pregnancy results in the suppression of Th1 responses and the up-regulation of Th2 responses.¹⁴⁶⁻¹⁴⁸ Thus, it is hypothesized that pregnancy ameliorates Th1 associated autoimmune conditions like RA but exacerbates Th2 associated autoimmune conditions like SLE.¹⁴⁵⁻¹⁵² Though largely unexplored, Th17 cells may also play a role in the altered autoimmunity in pregnancy.^{123, 153-156} These hypotheses have been supported by animal work confirming a role for sex hormones in uveitis. Rodent EAU models showed that estrogen enhanced uveitis in females, and that these results correlated with the ocular levels of Th1 (IFN- γ) and Th2 (IL-10) cytokine messengers.¹⁵⁷

X chromosome inactivation may also play a significant role in gender differences in autoimmunity. It is known that a variety of immune system genes, including TLR7 and CD40R, are located on the X chromosome and that during X chromosome inactivation, approximately 15% of the genes on the second X chromosome are not completely silenced.^{158, 159} This incomplete inactivation has been hypothesized to be a significant cause of autoimmunity in women via the activation of TLR7 and formation of age-associated B cells (ABCs) are found only in the spleens of female mice and produce high levels of autoantibodies upon stimulation.¹⁵⁹ These ABCs express IFN γ R on their surfaces and are able to respond to the high levels of IFN- γ secreted in models of SLE. This hypothesis has been supported in humans by studies showing that males with Klinefelter's syndrome (XXY) have the same risk of developing SLE as females and show similar levels of X chromosome inactivation.¹⁶⁰

However some gender differences in uveitis, particularly with infectious etiology, are mediated by behavioral factors. In India, *Leptospira* infectious uveitis is more prevalent in men with up to 75% of patients being male.¹⁶¹ Exposure to this spirochaete bacterium usually occurs via farming, a task usually undertaken by men. Similarly, syphilis and HIV are more common in men. This is thought to be due to an increase since 1999 of unsafe sexual practices mainly among homosexual males.^{105, 106}

Finally, how can we make use of the gender differences to aid patient management? Firstly the above knowledge can be applied to prevent uveitis. For example, increased public education of safe sexual practices could reduce the incidence of syphilitic uveitis.¹⁰⁶ Increased awareness among family medicine practitioners that women are more likely to have non-infectious uveitis and autoimmune diseases should allow for early diagnosis and adequate treatment.⁵ Similarly increased awareness among pediatric rheumatologists of the increased ocular complication rate of JIA-affected boys should ensure that JIA-affected boys are referred for uveitic screening and closely follow-up.¹⁵

One way to capitalize on the gender difference would be the use of hormonal manipulation to provide a more tailored yet efficacious therapy for future uveitis patients. Supplemental estrogen in the form of contraceptive pills has been proposed to increase the risk of SLE flares. Thus, clinicians should be judicious in their prescribing of hormonal therapy for SLE patients.⁵ This contrasts with sarcoidosis, which has a second peak presentation in women over the age of 50. This increased prevalence in postmenopausal women suggests a role for

sex hormone replacement. Thus hormonal therapy may be considered as a possible therapeutic adjunct for sarcoidosis patients.^{162, 163}

Conclusion

Male predominant autoimmune diseases, such as BD usually manifest clinically before the age of 50 and are characterized by acute inflammation and a Th1 response. HLA-B27 associated anterior uveitis in men is an example of this. Female predominant autoimmunity, such as RA and SLE tends to present later in life and occur likely via Th2 and autoantibody related mechanisms. Recognition of the gender difference in autoimmunity including uveitis should allow new preventative and therapeutic strategies for patients in the future.⁴

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References

1. Abou-Gareeb I, Lewallen S, Bassett K, et al. Gender and blindness: A meta-analysis of population-based prevalence surveys. *Ophthalmic Epidemiol.* 2001; 8:39–56. [PubMed: 11262681]
2. Lewallen S, Mousa A, Bassett K, et al. Cataract surgical coverage remains lower in women. *Br J Ophthalmol.* 2009; 93:295–298. [PubMed: 19091848]
3. Chan CC, Goldstein DA, Davis JL, et al. Gender and uveitis. *J Ophthalmol.* 2014; 2014:818070. [PubMed: 25136455]
4. Fairweather D, Frisancho-Kiss S, Rose NR. Sex differences in autoimmune disease from a pathological perspective. *Am J Pathol.* 2008; 173:600–609. [PubMed: 18688037]
5. Choudhary MM, Hajj-Ali RA, Lowder CY. Gender and ocular manifestations of connective tissue diseases and systemic vasculitides. *J Ophthalmol.* 2014; 2014:403042. [PubMed: 24757559]
6. Singh RP, Hasan S, Sharma S, et al. Th17 cells in inflammation and autoimmunity. *Autoimmun Rev.* 2014; 13:1174–1181. [PubMed: 25151974]
7. Gaudreau MC, Johnson BM, Gudi R, et al. Gender bias in lupus: Does immune response initiated in the gut mucosa have a role? *Clin Exp Immunol.* 2015
8. Ucar-Comlekoglu D, Fox A, Sen HN. Gender differences in Behcet's disease associated uveitis. *J Ophthalmol.* 2014; 2014:820710. [PubMed: 24864195]
9. Davis JL. Sex and reproduction in the transmission of infectious uveitis. *J Ophthalmol.* 2014; 2014:683246. [PubMed: 25105020]
10. Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: Second revision, Edmonton, 2001. *J Rheumatol.* 2004; 31:390–392. [PubMed: 14760812]
11. Ravelli A, Felici E, Magni-Manzoni S, et al. Patients with antinuclear antibody-positive juvenile idiopathic arthritis constitute a homogeneous subgroup irrespective of the course of joint disease. *Arthritis Rheum.* 2005; 52:826–832. [PubMed: 15751057]
12. Hahn YS, Kim JG. Pathogenesis and clinical manifestations of juvenile rheumatoid arthritis. *Korean J Pediatr.* 2010; 53:921–930. [PubMed: 21218013]
13. Heiligenhaus A, Heinz C, Edelsten C, et al. Review for disease of the year: Epidemiology of juvenile idiopathic arthritis and its associated uveitis: The probable risk factors. *Ocul Immunol Inflamm.* 2013; 21:180–191. [PubMed: 23713827]
14. Kalinina Ayuso V, Makhotkina N, van Tent-Hoeve M, et al. Pathogenesis of juvenile idiopathic arthritis associated uveitis: The known and unknown. *Surv Ophthalmol.* 2014; 59:517–531. [PubMed: 25130893]
15. Moradi A, Amin RM, Thorne JE. The role of gender in juvenile idiopathic arthritis-associated uveitis. *J Ophthalmol.* 2014; 2014:461078. [PubMed: 24701346]

16. Edelsten C, Reddy MA, Stanford MR, et al. Visual loss associated with pediatric uveitis in English primary and referral centers. *Am J Ophthalmol.* 2003; 135:676–680. [PubMed: 12719076]
17. American Academy of Pediatrics Section on Rheumatology and Section on Ophthalmology. Guidelines for ophthalmologic examinations in children with juvenile rheumatoid arthritis. *Pediatrics.* 1993; 92:295–296. [PubMed: 8337036]
18. Woreta F, Thorne JE, Jabs DA, et al. Risk factors for ocular complications and poor visual acuity at presentation among patients with uveitis associated with juvenile idiopathic arthritis. *Am J Ophthalmol.* 2007; 143:647–655. [PubMed: 17224116]
19. Edelsten C, Lee V, Bentley CR, et al. An evaluation of baseline risk factors predicting severity in juvenile idiopathic arthritis associated uveitis and other chronic anterior uveitis in early childhood. *Br J Ophthalmol.* 2002; 86:51–56. [PubMed: 11801504]
20. Cervera R, Doria A, Amoura Z, et al. Patterns of systemic lupus erythematosus expression in Europe. *Autoimmun Rev.* 2014; 13:621–629. [PubMed: 24418306]
21. Tedeschi SK, Bermas B, Costenbader KH. Sexual disparities in the incidence and course of SLE and RA. *Clin Immunol.* 2013; 149:211–218. [PubMed: 23578823]
22. D'Cruz DP, Khamashta MA, Hughes GR. Systemic lupus erythematosus. *Lancet.* 2007; 369:587–596. [PubMed: 17307106]
23. Rees F, Doherty M, Grainge M, et al. The incidence and prevalence of systemic lupus erythematosus in the UK, 1999-2012. *Ann Rheum Dis.* 2014
24. Watson P, Brennan A, Birch H, et al. An integrated extrapolation of long-term outcomes in systemic lupus erythematosus: analysis and simulation of the Hopkins Lupus Cohort. *Rheumatology (Oxford).* 2014
25. Yap EY, Au Eong KG, Fong KY, et al. Ophthalmic manifestations in Asian patients with systemic lupus erythematosus. *Singapore Med J.* 1998; 39:557–559. [PubMed: 10067401]
26. Wu C, Dai R, Dong F, et al. Purtscher-like retinopathy in systemic lupus erythematosus. *Am J Ophthalmol.* 2014; 158:1335–1341. e1331. [PubMed: 25205559]
27. Read RW. Clinical mini-review: Systemic lupus erythematosus and the eye. *Ocul Immunol Inflamm.* 2004; 12:87–99. [PubMed: 15512979]
28. Ding Y, He J, Guo JP, et al. Gender differences are associated with the clinical features of systemic lupus erythematosus. *Chin Med J (Engl).* 2012; 125:2477–2481. [PubMed: 22882925]
29. Stefanidou S, Benos A, Galanopoulou V, et al. Clinical expression and morbidity of systemic lupus erythematosus during a post-diagnostic 5-year follow-up: A male:female comparison. *Lupus.* 2011; 20:1090–1094. [PubMed: 21700658]
30. Harbo HF, Gold R, Tintore M. Sex and gender issues in multiple sclerosis. *Ther Adv Neurol Disord.* 2013; 6:237–248. [PubMed: 23858327]
31. Gordon LK, Goldstein DA. Gender and uveitis in patients with multiple sclerosis. *J Ophthalmol.* 2014; 2014:565262. [PubMed: 24891944]
32. Rosati G. The prevalence of multiple sclerosis in the world: An update. *Neurol Sci.* 2001; 22:117–139. [PubMed: 11603614]
33. Voskuhl RR, Pitchejian-Halabi H, MacKenzie-Graham A, et al. Gender differences in autoimmune demyelination in the mouse: Implications for multiple sclerosis. *Ann Neurol.* 1996; 39:724–733. [PubMed: 8651644]
34. Sen HN, Davis J, Ucar D, et al. Gender disparities in ocular inflammatory disorders. *Curr Eye Res.* 2015; 40:146–161. [PubMed: 24987987]
35. Zein G, Berta A, Foster CS. Multiple sclerosis-associated uveitis. *Ocul Immunol Inflamm.* 2004; 12:137–142. [PubMed: 15512983]
36. Paroli MP, Abicca I, Sapia A, et al. Intermediate uveitis: Comparison between childhood-onset and adult-onset disease. *Eur J Ophthalmol.* 2014; 24:94–100. [PubMed: 23813110]
37. Siltzbach LE, James DG, Neville E, et al. Course and prognosis of sarcoidosis around the world. *Am J Med.* 1974; 57:847–852. [PubMed: 4432869]
38. Judson MA, Boan AD, Lackland DT. The clinical course of sarcoidosis: Presentation, diagnosis, and treatment in a large white and black cohort in the United States. *Sarcoidosis Vasc Diffuse Lung Dis.* 2012; 29:119–127. [PubMed: 23461074]

39. Lobo A, Barton K, Minassian D, et al. Visual loss in sarcoid-related uveitis. *Clin Experiment Ophthalmol*. 2003; 31:310–316. [PubMed: 12880455]
40. Reich JM. Course and prognosis of sarcoidosis in African-Americans versus Caucasians. *Eur Respir J*. 2001; 17:833. [PubMed: 11401082]
41. Obenaus CD, Shaw HE, Sydnor CF, et al. Sarcoidosis and its ophthalmic manifestations. *Am J Ophthalmol*. 1978; 86:648–655. [PubMed: 568886]
42. Stavrou P, Linton S, Young DW, et al. Clinical diagnosis of ocular sarcoidosis. *Eye (Lond)*. 1997; 11:365–370. Pt 3. [PubMed: 9373478]
43. Khalatbari D, Stinnett S, McCallum RM, et al. Demographic-related variations in posterior segment ocular sarcoidosis. *Ophthalmology*. 2004; 111:357–362. [PubMed: 15019390]
44. Varron L, Cottin V, Schott AM, et al. Late-onset sarcoidosis: A comparative study. *Medicine (Baltimore)*. 2012; 91:137–143. [PubMed: 22543629]
45. Belfort Junior R, Nishi M, Hayashi S, et al. Vogt-Koyanagi-Harada's disease in Brazil. *Jpn J Ophthalmol*. 1988; 32:344–347. [PubMed: 3230721]
46. Lertsumitkul S, Whitcup SM, Nussenblatt RB, et al. Subretinal fibrosis and choroidal neovascularization in Vogt-Koyanagi-Harada syndrome. *Graefes Arch Clin Exp Ophthalmol*. 1999; 237:1039–1045. [PubMed: 10654175]
47. Murthy SI, Moreker MR, Sangwan VS, et al. The spectrum of Vogt-Koyanagi-Harada disease in South India. *Int Ophthalmol*. 2007; 27:131–136. [PubMed: 17318321]
48. Lertsumitkul S, Whitcup SM, Chan CC, et al. Subretinal fibrosis in Vogt-Koyanagi Harada syndrome. *Ophthalmology*. 2001; 108:1371. [PubMed: 11470684]
49. Ohno S, Char DH, Kimura SJ, et al. Vogt-Koyanagi-Harada syndrome. *Am J Ophthalmol*. 1977; 83:735–740. [PubMed: 868972]
50. Wang Y, Chan CC. Gender differences in Vogt-Koyanagi-Harada disease and sympathetic ophthalmia. *J Ophthalmol*. 2014; 2014:157803. [PubMed: 24734166]
51. Moorthy RS, Inomata H, Rao NA. Vogt-Koyanagi-Harada syndrome. *Surv Ophthalmol*. 1995; 39:265–292. [PubMed: 7725227]
52. Elias A, Gopalakrishnan M, Bhat S, et al. Vogt-Koyanagi-Harada disease clinical course, therapy, complications and prognostic factors. *World Journal of Retina and Vitreous*. 2012; 2:46–52.
53. Alaez C, Flores AH, Concha del Rio LE, et al. Major histocompatibility complex and strong human leukocyte antigen-DRB1 and gender association with Vogt-Koyanagi-Harada syndrome in Mexican Mestizos. *Hum Immunol*. 2011; 72:1198–1203. [PubMed: 21964432]
54. Sanghvi C, Aziz K, Jones NP. Uveitis and the menstrual cycle. *Eye (Lond)*. 2004; 18:451–454. [PubMed: 15131672]
55. Chan CC, Reed GF, Kim Y, et al. A correlation of pregnancy term, disease activity, serum female hormones, and cytokines in uveitis. *Br J Ophthalmol*. 2004; 88:1506–1509. [PubMed: 15548800]
56. Faia LJ. Gender differences in birdshot chorioretinopathy and the white dot syndromes: Do they exist? *J Ophthalmol*. 2014; 2014:146768. [PubMed: 24678412]
57. Kuiper J, Rothova A, de Boer J, et al. The immunopathogenesis of birdshot chorioretinopathy; A bird of many feathers. *Prog Retin Eye Res*. 2015; 44c:99–110. [PubMed: 25434765]
58. Abu-Yaghi NE, Hartono SP, Hodge DO, et al. White dot syndromes: A 20-year study of incidence, clinical features, and outcomes. *Ocul Immunol Inflamm*. 2011; 19:426–430. [PubMed: 22106911]
59. Suhler EB, Martin TM, Rosenbaum JT. HLA-B27-associated uveitis: Overview and current perspectives. *Curr Opin Ophthalmol*. 2003; 14:378–383. [PubMed: 14615643]
60. Chang JH, McCluskey PJ, Wakefield D. Acute anterior uveitis and HLA-B27. *Surv Ophthalmol*. 2005; 50:364–388. [PubMed: 15967191]
61. Smith WM. Gender and spondyloarthropathy-associated uveitis. *J Ophthalmol*. 2013; 2013:928264. [PubMed: 24455197]
62. Masi AT, Medsger TA Jr. A new look at the epidemiology of ankylosing spondylitis and related syndromes. *Clin Orthop Relat Res*. 1979; 15–29. [PubMed: 389516]
63. Tran VT, Auer C, Guex-Crosier Y, et al. Epidemiology of uveitis in Switzerland. *Ocul Immunol Inflamm*. 1994; 2:169–176. [PubMed: 22823117]

64. Chung YM, Liao HT, Lin KC, et al. Prevalence of spondyloarthritis in 504 Chinese patients with HLA-B27-associated acute anterior uveitis. *Scand J Rheumatol.* 2009; 38:84–90. [PubMed: 18821178]
65. McCannel CA, Holland GN, Helm CJ, et al. Causes of uveitis in the general practice of ophthalmology. UCLA Community-Based Uveitis Study Group. *Am J Ophthalmol.* 1996; 121:35–46. [PubMed: 8554079]
66. Rodriguez A, Calonge M, Pedroza-Seres M, et al. Referral patterns of uveitis in a tertiary eye care center. *Arch Ophthalmol.* 1996; 114:593–599. [PubMed: 8619771]
67. Rothova A, Buitenhuis HJ, Meenken C, et al. Uveitis and systemic disease. *Br J Ophthalmol.* 1992; 76:137–141. [PubMed: 1540555]
68. Robinson PC, Claushuis TA, Cortes A, et al. Genetic dissection of acute anterior uveitis reveals similarities and differences in associations observed with ankylosing spondylitis. *Arthritis Rheumatol.* 2015; 67:140–151. [PubMed: 25200001]
69. Power WJ, Rodriguez A, Pedroza-Seres M, et al. Outcomes in anterior uveitis associated with the HLA-B27 haplotype. *Ophthalmology.* 1998; 105:1646–1651. [PubMed: 9754172]
70. Rothova A, van Veenedaal WG, Linssen A, et al. Clinical features of acute anterior uveitis. *Am J Ophthalmol.* 1987; 103:137–145. [PubMed: 3492916]
71. Monnet D, Breban M, Hudry C, et al. Ophthalmic findings and frequency of extraocular manifestations in patients with HLA-B27 uveitis: A study of 175 cases. *Ophthalmology.* 2004; 111:802–809. [PubMed: 15051216]
72. Uy HS, Christen WG, Foster CS. HLA-B27-associated uveitis and cystoid macular edema. *Ocul Immunol Inflamm.* 2001; 9:177–183. [PubMed: 11815886]
73. Braakenburg AM, de Valk HW, de Boer J, et al. Human leukocyte antigen-B27-associated uveitis: Long-term follow-up and gender differences. *Am J Ophthalmol.* 2008; 145:472–479. [PubMed: 18282492]
74. Agnani S, Choi D, Martin TM, et al. Gender and laterality affect recurrences of acute anterior uveitis. *Br J Ophthalmol.* 2010; 94:1643–1647. [PubMed: 20733025]
75. Citirik M, Berker N, Songur MS, et al. Ocular manifestations of late-onset behcet disease. *Ophthalmologica.* 2011; 225:21–26. [PubMed: 20693818]
76. Tugal-Tutkun I, Gupta V, Cunningham ET. Differential diagnosis of Behcet uveitis. *Ocul Immunol Inflamm.* 2013; 21:337–350. [PubMed: 23730816]
77. Nakahara H, Kaburaki T, Takamoto M, et al. Statistical analyses of endogenous uveitis patients (2007-2009) in central Tokyo area and comparison with previous studies (1963-2006). *Ocul Immunol Inflamm.* 2014; 1–6. [PubMed: 25154003]
78. Liberman P, Gauro F, Berger O, et al. Causes of uveitis in a tertiary center in Chile: A cross-sectional retrospective review. *Ocul Immunol Inflamm.* 2014; 1–7. [PubMed: 25437569]
79. Yazici H, Fresko I, Yurdakul S. Behcet's syndrome: Disease manifestations, management, and advances in treatment. *Nat Clin Pract Rheumatol.* 2007; 3:148–155. [PubMed: 17334337]
80. Yang P, Fang W, Meng Q, et al. Clinical features of chinese patients with Behcet's disease. *Ophthalmology.* 2008; 115:312–318. e314. [PubMed: 17692378]
81. Tugal-Tutkun I, Onal S, Altan-Yaycioglu R, et al. Uveitis in Behcet disease: An analysis of 880 patients. *Am J Ophthalmol.* 2004; 138:373–380. [PubMed: 15364218]
82. Hatemi G, Seyahi E, Fresko I, et al. Behcet's syndrome: A critical digest of the 2013-2014 literature. *Clin Exp Rheumatol.* 2014; 32:S112–122. [PubMed: 25268667]
83. Remmers EF, Cosan F, Kirino Y, et al. Genome-wide association study identifies variants in the MHC class I, IL10, and IL23R-IL12RB2 regions associated with Behcet's disease. *Nat Genet.* 2010; 42:698–702. [PubMed: 20622878]
84. Gul A. Behcet's disease as an autoinflammatory disorder. *Curr Drug Targets Inflamm Allergy.* 2005; 4:81–83. [PubMed: 15720240]
85. Yazici H, Tuzun Y, Tanman AB, et al. Male patients with Behcet's syndrome have stronger pathergy reactions. *Clin Exp Rheumatol.* 1985; 3:137–141. [PubMed: 4017311]
86. Ohno S, Ohguchi M, Hirose S, et al. Close association of HLA-B51 with Behcet's disease. *Arch Ophthalmol.* 1982; 100:1455–1458. [PubMed: 6956266]

87. Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum.* 2013; 65:1–11. [PubMed: 23045170]
88. Almouhawis HA, Leao JC, Fedele S, et al. Wegener's granulomatosis: A review of clinical features and an update in diagnosis and treatment. *J Oral Pathol Med.* 2013; 42:507–516. [PubMed: 23301777]
89. Heijl C, Harper L, Flossmann O, et al. Incidence of malignancy in patients treated for antineutrophil cytoplasm antibody-associated vasculitis: Follow-up data from European Vasculitis Study Group clinical trials. *Ann Rheum Dis.* 2011; 70:1415–1421. [PubMed: 21616914]
90. Herlyn K, Buckert F, Gross WL, et al. Doubled prevalence rates of ANCA-associated vasculitides and giant cell arteritis between 1994 and 2006 in northern Germany. *Rheumatology (Oxford).* 2014; 53:882–889. [PubMed: 24425780]
91. Thorne JE, Jabs DA. Ocular manifestations of vasculitis. *Rheum Dis Clin North Am.* 2001; 27:761–779. vi. [PubMed: 11723763]
92. Pakrou N, Selva D, Leibovitch I. Wegener's granulomatosis: Ophthalmic manifestations and management. *Semin Arthritis Rheum.* 2006; 35:284–292. [PubMed: 16616151]
93. Bullen CL, Liesegang TJ, McDonald TJ, et al. Ocular complications of Wegener's granulomatosis. *Ophthalmology.* 1983; 90:279–290. [PubMed: 6602963]
94. Haynes BF, Fishman ML, Fauci AS, et al. The ocular manifestations of Wegener's granulomatosis. Fifteen years experience and review of the literature. *Am J Med.* 1977; 63:131–141. [PubMed: 327802]
95. Wang M, Khurana RN, Sadda SR. Central retinal vein occlusion in Wegener's granulomatosis without retinal vasculitis. *Br J Ophthalmol.* 2006; 90:1435–1436. [PubMed: 17057178]
96. Iida T, Spaide RF, Kantor J. Retinal and choroidal arterial occlusion in Wegener's granulomatosis. *Am J Ophthalmol.* 2002; 133:151–152. [PubMed: 11755858]
97. Dagi LR, Currie J. Branch retinal artery occlusion in the Churg-Strauss syndrome. *J Clin Neuroophthalmol.* 1985; 5:229–237. [PubMed: 2934426]
98. Partal A, Moshfeghi DM, Alcorn D. Churg-Strauss syndrome in a child: Retina and optic nerve findings. *Br J Ophthalmol.* 2004; 88:971–972. [PubMed: 15205253]
99. Chan CC, Roberge RG, Whitcup SM, et al. 32 cases of sympathetic ophthalmia. A retrospective study at the National Eye Institute, Bethesda, MD., from 1982 to 1992. *Arch Ophthalmol.* 1995; 113:597–600. [PubMed: 7748129]
100. Castiblanco CP, Adelman RA. Sympathetic ophthalmia. *Graefes Arch Clin Exp Ophthalmol.* 2009; 247:289–302. [PubMed: 18795315]
101. Gupta V, Gupta A, Dogra MR. Posterior sympathetic ophthalmia: A single centre long-term study of 40 patients from North India. *Eye (Lond).* 2008; 22:1459–1464. [PubMed: 17618240]
102. Abu El-Asrar AM, Al Kuraya H, Al-Ghamdi A. Sympathetic ophthalmia after successful retinal reattachment surgery with vitrectomy. *Eur J Ophthalmol.* 2006; 16:891–894. [PubMed: 17191203]
103. Chu XK, Chan CC. Sympathetic ophthalmia: To the twenty-first century and beyond. *J Ophthalmic Inflamm Infect.* 2013; 3:49. [PubMed: 23724856]
104. El-Asrar AM, Al-Obeidan SA. Sympathetic ophthalmia after complicated cataract surgery and intraocular lens implantation. *Eur J Ophthalmol.* 2001; 11:193–196. [PubMed: 11456026]
105. Shockman S, Buescher LS, Stone SP. Syphilis in the United States. *Clin Dermatol.* 2014; 32:213–218. [PubMed: 24559556]
106. Mathew RG, Goh BT, Westcott MC. British Ocular Syphilis Study (BOSS): 2-year national surveillance study of intraocular inflammation secondary to ocular syphilis. *Invest Ophthalmol Vis Sci.* 2014; 55:5394–5400. [PubMed: 24925878]
107. Roy R, Pal BP, Mathur G, et al. Acute retinal necrosis: Clinical features, management and outcomes--A 10 year consecutive case series. *Ocul Immunol Inflamm.* 2014; 22:170–174. [PubMed: 24738972]
108. Khochtali S, Abroug N, Kahloun R, et al. Pattern of acute retinal necrosis in a referral center in Tunisia, North Africa. *Ocul Immunol Inflamm.* 2014; 1–7. [PubMed: 24945738]

109. Sims JL, Yeoh J, Stawell RJ. Acute retinal necrosis: A case series with clinical features and treatment outcomes. *Clin Experiment Ophthalmol*. 2009; 37:473–477. [PubMed: 19624343]
110. Spaide RF, Martin DF, Teich SA, et al. Successful treatment of progressive outer retinal necrosis syndrome. *Retina*. 1996; 16:479–487. [PubMed: 9002130]
111. Sittivarakul W, Aui-aree N. Clinical features, management and outcomes of progressive outer retinal necrosis (PORN) in southern Thailand. *J Med Assoc Thai*. 2009; 92:360–366. [PubMed: 19301729]
112. Bartolini CE, Liang MC, Goldberg RA, et al. Progressive outer retinal necrosis secondary to herpes simplex virus type 2. *Ophthalmic Surg Lasers Imaging Retina*. 2014;1–2. [PubMed: 24988530]
113. Al-Dhibi HA, Al-Mahmood AM, Arevalo JF. A systematic approach to emergencies in uveitis. *Middle East Afr J Ophthalmol*. 2014; 21:251–258. [PubMed: 25100911]
114. Colby DJ, Vo DQ, Teoh SC, et al. Prevalence and predictors of cytomegalovirus retinitis in HIV-infected patients with low CD4 lymphocyte counts in Vietnam. *Int J STD AIDS*. 2013; 25:516–522. [PubMed: 24327723]
115. Agarwal A, Kumari N, Trehan A, et al. Outcome of cytomegalovirus retinitis in immunocompromised patients without Human Immunodeficiency Virus treated with intravitreal ganciclovir injection. *Graefes Arch Clin Exp Ophthalmol*. 2014; 252:1393–1401. [PubMed: 24557658]
116. Chan TS, Cheung CY, Yeung IY, et al. Cytomegalovirus retinitis complicating combination therapy with rituximab and fludarabine. *Ann Hematol*. 2015
117. Takase H, Kubono R, Terada Y, et al. Comparison of the ocular characteristics of anterior uveitis caused by herpes simplex virus, varicella-zoster virus, and cytomegalovirus. *Jpn J Ophthalmol*. 2014; 58:473–482. [PubMed: 25124341]
118. Accorinti M, Gilardi M, Pirraglia MP, et al. Cytomegalovirus anterior uveitis: Long-term follow-up of immunocompetent patients. *Graefes Arch Clin Exp Ophthalmol*. 2014; 252:1817–1824. [PubMed: 25138606]
119. Woo JH, Lim WK, Ho SL, et al. Characteristics of cytomegalovirus uveitis in immunocompetent patients. *Ocul Immunol Inflamm*. 2014;1–6. [PubMed: 25207970]
120. Su CC, Hu FR, Wang TH, et al. Clinical outcomes in cytomegalovirus-positive Posner-Schlossman syndrome patients treated with topical ganciclovir therapy. *Am J Ophthalmol*. 2014; 158:1024–1031. e1022. [PubMed: 25124264]
121. Portela RW, Bethony J, Costa MI, et al. A multihousehold study reveals a positive correlation between age, severity of ocular toxoplasmosis, and levels of glycoinositolphospholipid-specific immunoglobulin A. *J Infect Dis*. 2004; 190:175–183. [PubMed: 15195258]
122. Raphael I, Nalawade S, Eagar TN, et al. T cell subsets and their signature cytokines in autoimmune and inflammatory diseases. *Cytokine*. 2014
123. Furuzawa-Carballeda J, Vargas-Rojas MI, Cabral AR. Autoimmune inflammation from the Th17 perspective. *Autoimmun Rev*. 2007; 6:169–175. [PubMed: 17289553]
124. Hu Y, Shen F, Crellin NK, et al. The IL-17 pathway as a major therapeutic target in autoimmune diseases. *Ann N Y Acad Sci*. 2011; 1217:60–76. [PubMed: 21155836]
125. Lock C, Hermans G, Pedotti R, et al. Gene-microarray analysis of multiple sclerosis lesions yields new targets validated in autoimmune encephalomyelitis. *Nat Med*. 2002; 8:500–508. [PubMed: 11984595]
126. Sutton CE, Lalor SJ, Sweeney CM, et al. Interleukin-1 and IL-23 induce innate IL-17 production from gammadelta T cells, amplifying Th17 responses and autoimmunity. *Immunity*. 2009; 31:331–341. [PubMed: 19682929]
127. Doreau A, Belot A, Bastid J, et al. Interleukin 17 acts in synergy with B cell-activating factor to influence B cell biology and the pathophysiology of systemic lupus erythematosus. *Nat Immunol*. 2009; 10:778–785. [PubMed: 19483719]
128. Kezic JM, Glant TT, Rosenbaum JT, et al. Neutralization of IL-17 ameliorates uveitis but damages photoreceptors in a murine model of spondyloarthritis. *Arthritis Res Ther*. 2012; 14:R18. [PubMed: 22269151]

129. Wong CK, Lit LC, Tam LS, et al. Hyperproduction of IL-23 and IL-17 in patients with systemic lupus erythematosus: implications for Th17-mediated inflammation in auto-immunity. *Clin Immunol.* 2008; 127:385–393. [PubMed: 18373953]
130. Forrester JV, Klaska IP, Yu T, et al. Uveitis in mouse and man. *Int Rev Immunol.* 2013; 32:76–96. [PubMed: 23360160]
131. Wang C, Tian Y, Lei B, et al. Decreased IL-27 expression in association with an increased Th17 response in Vogt-Koyanagi-Harada disease. *Invest Ophthalmol Vis Sci.* 2012; 53:4668–4675. [PubMed: 22669715]
132. Wu W, Jin M, Wang Y, et al. Overexpression of IL-17RC associated with ocular sarcoidosis. *J Transl Med.* 2014; 12:152. [PubMed: 24885153]
133. Jiang S, Liu X, Luo L, et al. Elevated serum IL-23 correlates with intraocular inflammation after cataract surgery in patients with Vogt-Koyanagi-Harada disease. *Br J Ophthalmol.* 2010; 94:1078–1082. [PubMed: 19910285]
134. Chi W, Yang P, Li B, et al. IL-23 promotes CD4+ T cells to produce IL-17 in Vogt-Koyanagi-Harada disease. *J Allergy Clin Immunol.* 2007; 119:1218–1224. [PubMed: 17335887]
135. Bordaberry MF. Vogt-Koyanagi-Harada disease: Diagnosis and treatments update. *Curr Opin Ophthalmol.* 2010; 21:430–435. [PubMed: 20829689]
136. Kotake S, Udagawa N, Takahashi N, et al. IL-17 in synovial fluids from patients with rheumatoid arthritis is a potent stimulator of osteoclastogenesis. *J Clin Invest.* 1999; 103:1345–1352. [PubMed: 10225978]
137. Klein SL, Marriott I, Fish EN. Sex-based differences in immune function and responses to vaccination. *Trans R Soc Trop Med Hyg.* 2015; 109:9–15. [PubMed: 25573105]
138. Yurkovetskiy L, Burrows M, Khan AA, et al. Gender bias in autoimmunity is influenced by microbiota. *Immunity.* 2013; 39:400–412. [PubMed: 23973225]
139. Brusca SB, Abramson SB, Scher JU. Microbiome and mucosal inflammation as extra-articular triggers for rheumatoid arthritis and autoimmunity. *Curr Opin Rheumatol.* 2014; 26:101–107. [PubMed: 24247114]
140. Joscelyn J, Kasper LH. Digesting the emerging role for the gut microbiome in central nervous system demyelination. *Mult Scler.* 2014; 20:1553–1559. [PubMed: 25070675]
141. Van Praet JT, Donovan E, Vanassche I, et al. Commensal microbiota influence systemic autoimmune responses. *EMBO J.* 2015
142. Lin P, Bach M, Asquith M, et al. HLA-B27 and human beta2-microglobulin affect the gut microbiota of transgenic rats. *PLoS One.* 2014; 9:e105684. [PubMed: 25140823]
143. Chen Y, Vaughan RW, Kondeatis E, et al. Chemokine gene polymorphisms associate with gender in patients with uveitis. *Tissue Antigens.* 2004; 63:41–45. [PubMed: 14651522]
144. Buyon JP, Nelson JL, Lockshin MD. The effects of pregnancy on autoimmune diseases. *Clin Immunol Immunopathol.* 1996; 78:99–104. [PubMed: 8625564]
145. Wilder RL. Hormones, pregnancy, and autoimmune diseases. *Ann N Y Acad Sci.* 1998; 840:45–50. [PubMed: 9629235]
146. Buyon JP. The effects of pregnancy on autoimmune diseases. *J Leukoc Biol.* 1998; 63:281–287. [PubMed: 9500514]
147. Doria A, Iaccarino L, Arienti S, et al. Th2 immune deviation induced by pregnancy: The two faces of autoimmune rheumatic diseases. *Reprod Toxicol.* 2006; 22:234–241. [PubMed: 16704920]
148. Elenkov IJ, Hoffman J, Wilder RL. Does differential neuroendocrine control of cytokine production govern the expression of autoimmune diseases in pregnancy and the postpartum period? *Mol Med Today.* 1997; 3:379–383. [PubMed: 9302687]
149. Elenkov IJ, Wilder RL, Bakalov VK, et al. IL-12, TNF-alpha, and hormonal changes during late pregnancy and early postpartum: Implications for autoimmune disease activity during these times. *J Clin Endocrinol Metab.* 2001; 86:4933–4938. [PubMed: 11600565]
150. Keeling SO, Oswald AE. Pregnancy and rheumatic disease: "By the book" or "by the doc". *Clin Rheumatol.* 2009; 28:1–9. [PubMed: 18987777]

151. Jara LJ, Vera-Lastra O, Miranda JM, et al. Prolactin in human systemic lupus erythematosus. *Lupus*. 2001; 10:748–756. [PubMed: 11721702]
152. Ostensen M, Villiger PM, Forger F. Interaction of pregnancy and autoimmune rheumatic disease. *Autoimmun Rev*. 2012; 11:A437–446. [PubMed: 22154710]
153. Akdis M, Palomares O, van de Veen W, et al. Th17 and Th22 cells: A confusion of antimicrobial response with tissue inflammation versus protection. *J Allergy Clin Immunol*. 2012; 129:1438–1449. [PubMed: 22657405]
154. Bettelli E, Oukka M, Kuchroo VK. Th-17 cells in the circle of immunity and autoimmunity. *Nat Immunol*. 2007; 8:345–350. [PubMed: 17375096]
155. Torchinsky MB, Blander JM. T helper 17 cells: Discovery, function, and physiological trigger. *Cell Mol Life Sci*. 2010; 67:1407–1421. [PubMed: 20054607]
156. Ernerudh J, Berg G, Mjosberg J. Regulatory T helper cells in pregnancy and their roles in systemic versus local immune tolerance. *Am J Reprod Immunol*. 2011; 66(Suppl 1):31–43. [PubMed: 21726336]
157. Buggage RR, Matteson DM, Shen DF, et al. Effect of sex hormones on experimental autoimmune uveoretinitis (EAU). *Immunol Invest*. 2003; 32:259–273. [PubMed: 14603994]
158. Carrel L, Willard HF. X-inactivation profile reveals extensive variability in X-linked gene expression in females. *Nature*. 2005; 434:400–404. [PubMed: 15772666]
159. Rubtsova K, Marrack P, Rubtsov AV. TLR7, IFN γ , and T-bet: Their roles in the development of ABCs in female-biased autoimmunity. *Cell Immunol*. 2014
160. Scofield RH, Bruner GR, Namjou B, et al. Klinefelter's syndrome (47,XXY) in male systemic lupus erythematosus patients: Support for the notion of a gene-dose effect from the X chromosome. *Arthritis Rheum*. 2008; 58:2511–2517. [PubMed: 18668569]
161. Chu KM, Rathinam R, Namperumalsamy P, et al. Identification of *Leptospira* species in the pathogenesis of uveitis and determination of clinical ocular characteristics in south India. *J Infect Dis*. 1998; 177:1314–1321. [PubMed: 9593018]
162. Zurkova M, Turkova M, Tichy T, et al. Sarcoidosis of female reproductive organs in a postmenopausal woman: a case report and review of the literature: Is there a potential for hormone therapy? *Menopause*. 2014
163. Birnbaum AD, Rifkin LM. Sarcoidosis: sex-dependent variations in presentation and management. *J Ophthalmol*. 2014; 2014:236905. [PubMed: 24987524]
164. Al Dhahri H, Al Rubaie K, Hemachandran S, et al. Patterns of uveitis in a university-based tertiary referral center in Riyadh, Saudi Arabia. *Ocul Immunol Inflamm*. 2014; 1–9. [PubMed: 25058456]
165. Yang P, Ren Y, Li B, et al. Clinical characteristics of Vogt-Koyanagi-Harada syndrome in Chinese patients. *Ophthalmology*. 2007; 114:606–614. [PubMed: 17123618]
166. Sukavatcharin S, Tsai JH, Rao NA. Vogt-Koyanagi-Harada disease in Hispanic patients. *Int Ophthalmol*. 2007; 27:143–148. [PubMed: 17380271]
167. Lyons JL, Rosenbaum JT. Uveitis associated with inflammatory bowel disease compared with uveitis associated with spondyloarthritis. *Arch Ophthalmol*. 1997; 115:61–64. [PubMed: 9006426]
168. Zippi M, Corrado C, Pica R, et al. Extraintestinal manifestations in a large series of Italian inflammatory bowel disease patients. *World J Gastroenterol*. 2014; 20:17463–17467. [PubMed: 25516659]
169. Tugal-Tutkun I, Quartier P, Bodaghi B. Disease of the year: Juvenile idiopathic arthritis-associated uveitis--Classification and diagnostic approach. *Ocul Immunol Inflamm*. 2014; 22:56–63. [PubMed: 24410427]
170. Foeldvari I. Ocular involvement in juvenile idiopathic arthritis: Classification and treatment. *Clin Rev Allergy Immunol*. 2014
171. Marrie RA, Cutter G, Tyry T. Substantial adverse association of visual and vascular comorbidities on visual disability in multiple sclerosis. *Mult Scler*. 2011; 17:1464–1471. [PubMed: 21844067]
172. Herrera-Esparza R, Avalos-Diaz E. Infliximab treatment in a case of rheumatoid scleromalacia perforans. *Reumatismo*. 2009; 61:212–215. [PubMed: 19888506]

173. Mikkila HO, Seppala IJ, Viljanen MK, et al. The expanding clinical spectrum of ocular lyme borreliosis. *Ophthalmology*. 2000; 107:581–587. [PubMed: 10711899]
174. Rosenbaum JT, Rahn DW. Prevalence of Lyme disease among patients with uveitis. *Am J Ophthalmol*. 1991; 112:462–463. [PubMed: 1928255]
175. Gupta V, Shoughy SS, Mahajan S, et al. Clinics of ocular tuberculosis. *Ocul Immunol Inflamm*. 2015; 23:14–24. [PubMed: 25615807]
176. World Health Organization. Global Tuberculosis Report 2013. 2013.
177. Al-Mezaine HS, Kangave D, Abu El-Asrar AM. Patterns of uveitis in patients admitted to a University Hospital in Riyadh, Saudi Arabia. *Ocul Immunol Inflamm*. 2010; 18:424–431. [PubMed: 20735294]
178. Abu El-Asrar AM, Abouammoh M, Al-Mezaine HS. Tuberculous uveitis. *Int Ophthalmol Clin*. 2010; 50:19–39. [PubMed: 20375860]
179. Maenz M, Schluter D, Liesenfeld O, et al. Ocular toxoplasmosis past, present and new aspects of an old disease. *Prog Retin Eye Res*. 2014; 39:77–106. [PubMed: 24412517]
180. Glasner PD, Silveira C, Kruszon-Moran D, et al. An unusually high prevalence of ocular toxoplasmosis in southern Brazil. *Am J Ophthalmol*. 1992; 114:136–144. [PubMed: 1642287]
181. Vanaclocha F, Crespo-Erchiga V, Jimenez-Puya R, et al. Immune-Mediated Inflammatory Diseases and Other Comorbidities in Patients With Psoriasis: Baseline Characteristics of Patients in the AQUILES Study. *Actas Dermosifiliogr*. 2014
182. Fotiadou C, Lazaridou E, Kemanetzi C, et al. Recalcitrant psoriatic uveitis and anti-tumor necrosis factor-alpha monoclonal antibodies: Experience from a psoriasis referral center. *Int J Dermatol*. 2014
183. Burden-Teh E, Murphy R. Psoriasis and uveitis--Should we be asking about eye symptoms? *Br J Dermatol*. 2014; 170:756–757. [PubMed: 24205953]
184. Lima FB, Abalem MF, Ruiz DG, et al. Prevalence of eye disease in Brazilian patients with psoriatic arthritis. *Clinics (Sao Paulo)*. 2012; 67:249–253. [PubMed: 22473406]
185. Tay-Kearney ML, Schwam BL, Lowder C, et al. Clinical features and associated systemic diseases of HLA-B27 uveitis. *Am J Ophthalmol*. 1996; 121:47–56. [PubMed: 8554080]
186. Zheng MQ, Wang YQ, Lu XY, et al. Clinical analysis of 240 patients with HLA-B27 associated acute anterior uveitis. *Eye Sci*. 2012; 27:169–172. [PubMed: 23225836]
187. Kola M, Kalkisim A, Karkucak M, et al. Evaluation of choroidal thickness in ankylosing spondylitis using optical coherence tomography. *Ocul Immunol Inflamm*. 2014; 22:434–438. [PubMed: 24988331]
188. Kassimos DG, Vassilakos J, Magiorkinis G, et al. Prevalence and clinical manifestations of ankylosing spondylitis in young Greek males. *Clin Rheumatol*. 2014; 33:1303–1306. [PubMed: 24647983]
189. Ho HH, Chen JY. Ankylosing spondylitis: Chinese perspective, clinical phenotypes, and associated extra-articular systemic features. *Curr Rheumatol Rep*. 2013; 15:344. [PubMed: 23797415]
190. Stolwijk C, Essers I, van Tubergen A, et al. The epidemiology of extra-articular manifestations in ankylosing spondylitis: A population-based matched cohort study. *Ann Rheum Dis*. 2014
191. Verma A, Stevenson B. Leptospiral uveitis - There is more to it than meets the eye! *Zoonoses Public Health*. 2012; 59(Suppl 2):132–141. [PubMed: 22958257]
192. Shukla D, Rathinam SR, Cunningham ET Jr. Leptospiral uveitis in the developing world. *Int Ophthalmol Clin*. 2010; 50:113–124. [PubMed: 20375866]
193. Nakagawa F, Phillips AN, Lundgren JD. Update on HIV in western Europe. *Curr HIV/AIDS Rep*. 2014; 11:177–185. [PubMed: 24659343]
194. Monroe AK, Burkholder BM, Butler NJ, et al. Sclerouveitis associated with Rosai-Dorfman disease in an HIV-infected patient. *Ocul Immunol Inflamm*. 2014; 22:236–238. [PubMed: 24564426]
195. Rose-Nussbaumer J, Goldstein DA, Thorne JE, et al. Uveitis in human immunodeficiency virus-infected persons with CD4+ T-lymphocyte count over 200 cells/mL. *Clin Experiment Ophthalmol*. 2014; 42:118–125. [PubMed: 23777456]

196. Tan S, Duan H, Xun T, et al. HIV-1 impairs human retinal pigment epithelial barrier function: Possible association with the pathogenesis of HIV-associated retinopathy. *Lab Invest*. 2014; 94:777–787. [PubMed: 24840331]
197. Sampaio-Barros PD, Pereira IA, Hernandez-Cuevas C, et al. An analysis of 372 patients with anterior uveitis in a large Ibero-American cohort of spondyloarthritis: the RESPONDIA Group. *Clin Exp Rheumatol*. 2013; 31:484–489. [PubMed: 23899968]
198. Selmi C, Gershwin ME. Diagnosis and classification of reactive arthritis. *Autoimmun Rev*. 2014; 13:546–549. [PubMed: 24418301]
199. Amer R, Priel E, Kramer M. Spectral-domain optical coherence tomographic features of choroidal neovascular membranes in multifocal choroiditis and punctate inner choroidopathy. *Graefes Arch Clin Exp Ophthalmol*. 2015
200. Shen Z, Zhang L, Li Z, et al. Comparison on clinical characteristics of multifocal choroiditis and punctate inner choroidopathy. *Eye Sci*. 2011; 26:161–165. [PubMed: 21913348]
201. Tugal-Tutkun I, Otuk-Yasar B, Altinkurt E. Clinical features and prognosis of herpetic anterior uveitis: A retrospective study of 111 cases. *Int Ophthalmol*. 2010; 30:559–565. [PubMed: 20857175]
202. Jap A, Chee SP. Viral anterior uveitis. *Curr Opin Ophthalmol*. 2011; 22:483–488. [PubMed: 21918442]
203. Shao EH, Menezo V, Taylor SR. Birdshot chorioretinopathy. *Curr Opin Ophthalmol*. 2014; 25:488–494. [PubMed: 25211040]
204. Chan CK, Wu ZH, Luk FO, et al. Clinical characteristics of intermediate uveitis in Chinese patients. *Ocul Immunol Inflamm*. 2013; 21:71–76. [PubMed: 23323585]
205. Wakefield D, Easter J, Penny R. Clinical features of HLA-B27 anterior uveitis. *Australian Journal of Ophthalmology*. 1984; 12:191–196.
206. Loh AR, Acharya NR. Incidence rates and risk factors for ocular complications and vision loss in HLA-B27-associated uveitis. *Am J Ophthalmol*. 2010; 150:534–542. e532. [PubMed: 20643395]
207. Ushiyama O, Ushiyama K, Koarada S, et al. Retinal disease in patients with systemic lupus erythematosus. *Ann Rheum Dis*. 2000; 59:705–8. [PubMed: 10976084]

Table 1

Gender differences in the prevalence of systemic diseases with ocular involvement

Disease	% Female	% Uveitis	Other Ophthalmic Manifestations
SLE	88–90.5	2.9	Episcleritis, scleritis, keratoconjunctivitis sicca, lupus retinopathy, optic neuritis
MS	78	3	Optic neuritis, internuclear ophthalmoplegia, nystagmus
VKH	70–84	84–100	Cataract, ocular hypertension, subretinal fibrosis, band keratopathy, choroidal neovascularization
RA	66–75	unknown	Episcleritis, scleritis, keratoconjunctivitis sicca, peripheral ulcerative keratitis, corneal melt
Inflammatory bowel disease	53–82	1.7–7.4	Episcleritis
JIA (non enthesitis-related subtype)	50–80	10–45	Band keratopathy, cataract, glaucoma, macular edema
Lyme disease	60	<5–50	Conjunctivitis, episcleritis, keratitis, retinal vein occlusion, strabismus
Sarcoidosis	55–64	8.6–83	Adnexal granuloma, keratoconjunctivitis sicca
Tuberculosis	50	0–2.8	Adnexal granuloma, conjunctival granuloma, scleritis, keratitis, optic neuritis
Toxoplasma	50	2–18	Scleritis
ANCA-associated vasculitis	46–50	0–10	Episcleritis, scleritis, peripheral ulcerative keratitis, vascular occlusion, optic neuritis
Psoriatic arthropathy	40	0.2–25	Keratoconjunctivitis sicca
Spondyloarthropathy	33–40	19–37	cystoid macular edema, secondary glaucoma
Behçet's disease	15–46	50–90	
JIA (enthesitis-related subtype)	25–33	10–15	Band keratopathy, cataract, glaucoma, macular edema
Ankylosing spondylitis	18–38	11–40	Increased choroidal thickness
Leptospirosis	25	2–90	Papillitis
Reactive arthritis (Reiter's syndrome)	18–19	50–75	Conjunctivitis
Syphilis	10–13	0.6	Interstitial keratitis, optic neuritis

SLE: systemic lupus erythematosus; VKH: Vogt-Koyanagi-Harada disease; JIA: juvenile idiopathic arthritis; MS: multiple sclerosis; RA: rheumatoid arthritis; ANCA: anti-neutrophil cytoplasmic antibody

Table 2

Gender differences in the prevalence of non-systemic ocular diseases

Disease	% Female	Other Ophthalmic Manifestations
PIC	85	Choroidal neovascularization
AZOOR	79	
MFC	75	Cataract, choroidal neovascularization, cystoid macular edema, epiretinal membrane
MEWDS	74	
HSV anterior uveitis	55–88	Raised intra-ocular pressure
Birdshot chorioretinopathy	58	Cystoid macular edema
Idiopathic uveitis	39–58	Cataract, raised intra-ocular pressure, cystoid macular edema, epiretinal membrane
APMPPE	46	
VZV anterior uveitis	45	Raised intra-ocular pressure
SO	27.9–50	Dalen Fuchs nodules, optic disc swelling
ARN	28–44	
HLA-B27+ anterior uveitis	22–46	
CMV uveitis	20–44	Corneal endotheliitis, Posner Schlossman syndrome, raised intra-ocular pressure
PORN	14–17	

PIC: punctate inner choroidopathy; AZOOR: Acute zonal occult outer retinopathy; MFC: Multifocal choroiditis with pan-uveitis; MEWDS: Multiple evanescent white dot syndrome; HSV: herpes simplex virus; SO: sympathetic ophthalmia; APMPPE: acute posterior multifocal placoid pigment epitheliopathy; ARN: acute retinal necrosis; HLA: human leukocyte antigen; VZV: varicella zoster virus; CMV: cytomegalovirus; PORN: progressive outer retinal necrosis