Fuch's UvietisSyndrome : A Variable Clinical Spectrum

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Abstract

Fuch's uveitis syndrome (FUS) is a form of uveitis that is often difficult to diagnose because it has a variable clinical spectrum.ThiscasereportofFUSisintendedtofamiliarize the clinician with this under diagnosed condition to facilitate timely identification and propermanagement.

Background

Fuch's uveitis syndrome (FUS) was first recognized in 1843 by Lawrence, who described the dual clinical combination of heterochromia and cataract.[1] It was not until 1906, however, that Ernest Fuchs further defined and studied 38 patients with thecomplicatedcharacteristicsofheterochromia,iridocyclitis, and cataracts.[2] This triad of clinical findings would later bear his name.

FUS is presently defined as a syndrome typically recognized by the most common triad of clinical characteristics: heterochromia or iris atrophy, iridocyclitis, and cataract. However, characteristic keratic precipitates, absence of posteriorsynechiae,developmentofcataracts,vitrealopacities, iris nodules and, less commonly, glaucoma are also part of the clinical spectrum. The presentation and characteristic featuresofthissyndromearemoreextensiveandvariablethan previously thought.[1] Furthermore, the clinical signs of FUS are not always present at the same time. This, coupled with thefactthattherearenospecificdiagnosticlaboratorytests that can lead the clinician to the diagnosis of FUS, can make identification a challenge. [3]

Over the years, this syndrome has been referred to as Fuchs' heterochronic cyclitis, Fuchs' heterochronic iridocyclitis, Fuchs' heterochromic uveitis syndrome, and more recently as Fuchs' uveitis syndrome. Prior nomenclature included heterochromia as part of the name designation insinuating the presence of this feature in all cases. However, it is now knownthatirisatrophycanbeverysubtleorevenoverlooked, especially in dark irises, and is typically not present in bilateral cases. Furthermore, including iridocyclitis within the name ignores vitreal involvement. It is well documented that vitreal opacities and choriogenin scars can coexist in a subset of cases and thus it is not entirely accurate to use the term iridocyclitis.[4] Additionally, Cunningham and Baglivo elucidated on whether or not Fuchs' should be labeled as a syndrome or a disease.[2]To be defined as a disease wouldinfer thatithasawellcharacterizedpathophysiologicalmechanism, whichcurrentlyFuchs'lacks.[2]Thusitwouldmakemoresense to classify it as a syndrome, since FUS is currently no more than a constellation of recognizable signs and symptoms.[2] Consequently,asmorestudiesandpublicationsarecompleted, the clinical features of this syndrome are being redefined. The name of this syndrome seems to be incorporating less specific terms and moving toward more of an umbrella term. For this reason, we have chosen to use the name Fuch's uveitis syndrome (FUS) throughout thispaper.

Case Description

A 45-year-old, Caucasian, male presented for a routine comprehensiveeyeexam.Hischiefcomplaintwasthathehad recentlynoticedamild,dull,achewithinbotheyesinaddition toincreasedredness.Healsorelayedthatthesesymptomswere baseline for him but were exacerbated at times. He deniedany discharge, itching, tearing, mucous, photophobia, or loss of vision. The patient had a history of bilateral floaters that were longstanding and stable. His best corrected acuities were OD 20/20 and OS20/20.

Entrance exam for pupils, confrontational fields, and extra-ocular movement were unremarkable. Biomicroscopy revealed diffuse injection in the right eye and in the left eye, a characteristic perilimbal flush. Diffuse, medium sized, white,

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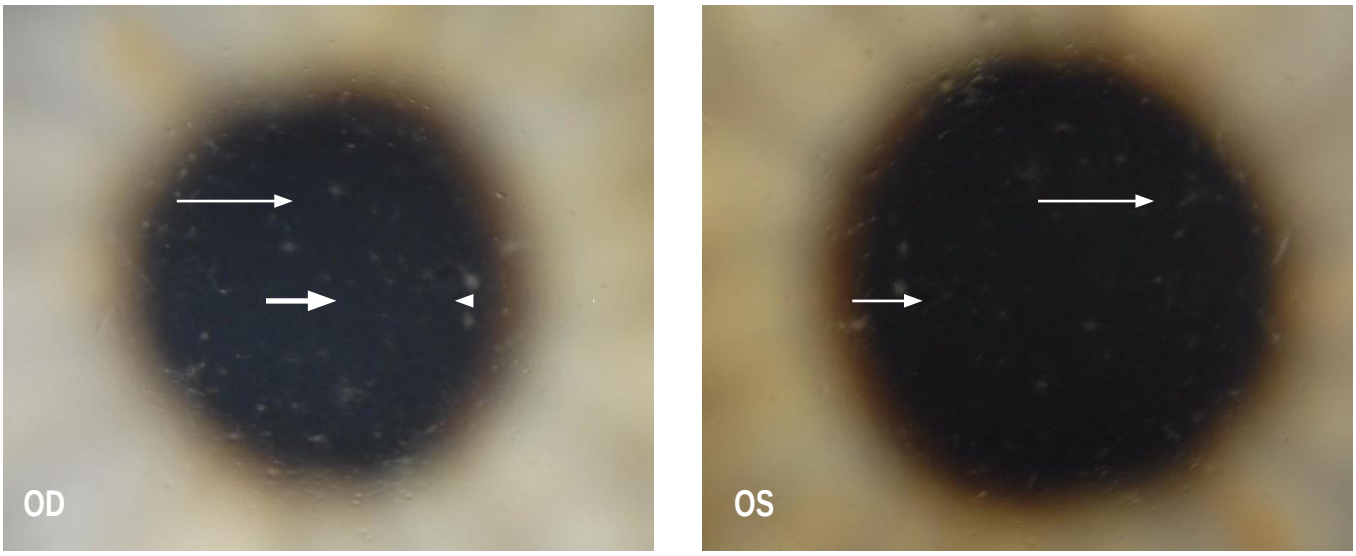

Figures1and2showdiffusestellatekeraticprecipitatesinbothODandOS.Thinlongerarrowspointtothestellateshapeofkeraticprecipitatesand thethickshortarrowpointstofibrinextension.

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stellate keratic precipitates were seen diffusely distributedon the endothelium of both eyes (See Figures 1 and 2). Grade 1+ cells were present in the anterior chamber of OD and 2+ cells in OS without posterior synechiae. Mild diffuse iris atrophy was noted OU. Goldman applanation tonometry (GAT) revealed intraocular pressures of 9 mm Hg OD and 11mmHGOS.Gonioscopyconfirmednoperipheralanterior synechiae. Dilated fundus examination was negative for vitritis,butrevealedmildnuclearscleroticcataractsOU,with healthy,smallcuppingandanunremarkableperipheralexam.

His systemic medical history was only noteworthy for hyperlipidemia. His ocular history was extensive and dated back to 1982 when he was first diagnosed with chronic bilateral non-granulomatous iritis of unknown etiology. He reported a full uveitis work-up in 1982 which had been completed in the private sector. Copies of the results were obtained and reviewed when the patient transferred his eye caretothisfacility.Theresultswereunrevealingforsystemic disease (see Table 1 for lab tests and results of the uveitis work-up).

In 2006 -2007 the patient was diagnosed with two bilateral recurrentuveitisflare-upsatannualroutineeyeappointments. In both episodes he was treated acutely with prednisolone acetate 1% ophthalmic suspension OU and tapered over the course of 2-3 months. With both recurrent episodes, the patientneverreturnedtotheclinicforfollowupappointments once he was tapered off of themedication.

Given the patient's extensive history of bilateral non-granulomatous uveitis, on his June 11, 2009, visit, the patient was diagnosed with a recurrent bilateral uveitis flare- up. Homatropine 5% ophthalmic solution BID OU and prednisolone acetate 1% ophthalmic suspension every two hours OU were initiated. Also at this exam, the patient was referred to a uveitis specialist to determine the appropriate management for this persistent and recurrent uveitis.

The patient was seen by the uveitis specialist one week later and his diagnosis was determined to be bilateral Fuch's uveitis syndrome. The diagnosis was supported by stellate keratic precipitates, iris atrophy and no posterior synechiae. This confirmed why his past systemic workups had been negativeandwhytheuveitiswaspersistent,despitetreatment.
The uveitis specialist recommended a taper schedule over the next few weeks which consisted of taking prednisolone acetate 1% ophthalmic suspension every two hours OU x 10 days,thenfourtimeadayx2weeks,followedbythreetimes a day x 1week, once a day x 1 week, and then once every other day for week. He recommended switching the patient to a maintenance dose once daily OU of fluorometholone 0.1% ophthalmic suspension. The more mild steroid was recommended to limit secondary complications of steroid use. The uveitis specialist reported that the goal of treatment was to control symptoms as there is no curative treatmentfor this type of uveitis. The current management would consist of monitoring the patient for complications of FUS such as cataracts and glaucoma and keeping the patient comfortable. Currently this patient is managed with flurometholone 0.1% ophthalmic suspension once daily OU and remains comfortable. IOPS remain in the low teens with mild nuclear sclerotic cataracts OU and currently no evidence of posterior subcapsularcataracts.

Table 2: Differential Diagnosis of FUS	
Glaucoma, Pigmentary	Ocular Manifestations of HIV
Glaucoma, Uveitis	Posner-Schlossman Syndrome
Herpes Simplex	Retinitis, CMV
Herpes Zoster	Sarcoidosis
HIV	Toxoplasmosis
HLA-B27 Syndromes	Tuberculosis
Horner Syndrome	Uveitis, Intermediate

Discussion

Epidemiology

FUSaccountsforapproximately2-11%ofallanterioruveitis cases. [3] The syndrome occurs more commonly in the 3rd to 4th decades of life with no sex or race predilection and approximately90%ofcasesareunilateral.[5]FUSisanunusual form of uveitis. It's pathogenesis still remains a mysterywith speculation on a common immunologic pathway triggered by a multitude of factors. Recent literature focuses on the infectious rubella virus as a potential etiologictrigger.

Pathogenesis

ThepathogenicmechanismofFUSremainselusive.Overthe years, several theories have been proposed, however, many of these cannot be substantiated. More recently, attentionhas been focused on the role of the rubella virus as a potential etiologic factor for FUS. However, other clinical studies provide evidence that demonstrate the rubella virus may not be the only virus or causative factor involved in initiating the immune response seen inFUS. -

There are well-documented cases of the coexistence of FUS and sympathetic syndromes such as Parry-Romberg (hemi facial atrophy) and Horner's syndromes. Calmettes and Makley have confirmed two cases of Horner's and FUS developing after sympathetic denervation secondary to stellateganglionectomy.[6,7]

Furthermore, five cases of concurrent FUS and congenital Horner's syndrome have been reported in a retrospective study by Regenbogen and Naveh-Floman.[8]Similarly, LaHey and Baarsma documented a concurrent case of progressive Parry-Romberg syndrome and FUS, possibly linking a common sympathetic defect.[9] The neurogenic theory of Passow[8] assumes the changes noted in FUS are a result of injurytothesympatheticnervoussystem.[8]Thecoexistenceof FUS and Horner's is based on the mutual commonality, loss of sympathetic innervation. Iris heterochromia and pupillary changes have been reported as clinical signs of impaired sympatheticinnervation.Alackofsympatheticinnervationto both the iris vasculature and stromal melanocytes is believed toresultindefectivemelaninproductionandincreased vascular permeability. A defective production of melanin leadstoirishypochromiawhiledenervationofthevasculature leads to the leakage of protein and white blood cells into the anterior chamber. Although this theory may explain a select few cases it does not account for the majority of cases that lack the concurrence of both sympathetic disease andFUS.[10]

At one time, the possibility of hereditary FUS was contemplated, however past studies of FUS in familial cases cannot be substantiated. The small number of familial FUS casesincomparisontotheoverallnumberFUScasesweakens thistheory.Furthermore,LoewenfeldandThompsonin1973, retrospectively reviewed 1500 cases with FUS and found only five families with two cases of FUS.[11]

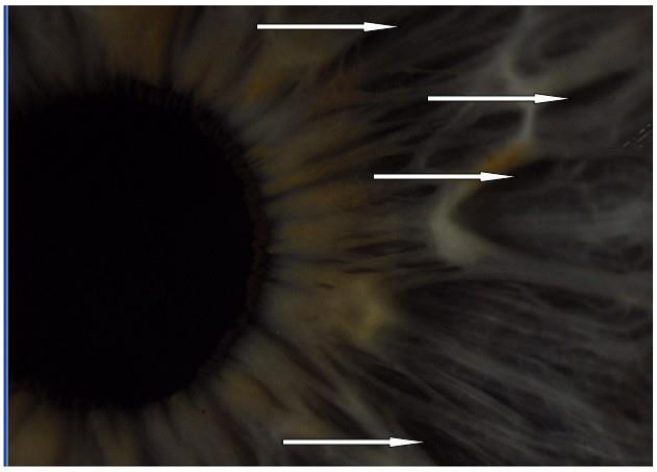
Additionally, Jones and Read reported a case in which FUS developedinonlyonechildofmonozygotictwins,disproving the familial association.[12]

Other theories involving vascular abnormalities secondary to an immune complex vasculitis have been considered in the roleoftriggeringFUS.Itwasthoughtthatimmunecomplexes found in the vessel walls of FUS patients were responsible for the vascular abnormalities and chronic inflammationseen in FUS. [10] It has also been postulated that an autoimmune reaction against altered uveal tissue secondary to a trigger, such as infection, leads to the inflammatory reaction seen in FUS. However, no anti-uveal antibodies can be repeatedly confirmed acrossstudies.

Infectious etiologies have also been considered, mostnotably toxoplasmosis *gondii*.The coexistence of chorio-retinal lesionscharacteristicoftoxoplasmosis*gondii*inFUSpatients was not uncommon. Multiple studies have documented the simultaneous presence of peripheral lesions and FUS with variable frequency ranging from 7.5% to as high as 65%.[10]Because these scars have attributes of typical toxoplasmosis scars; it was originally thought that toxoplasmosis *gondii* could be the etiologic trigger for FUS. Presently, definitive laboratory evidence has not been established and recent studies tend to refute this original association of FUS and toxoplasmosis *gondii*. [13] Quentin et al., found only two of 16 FHCcaseshadincreasedtoxoplasmosisantibodyproduction, and one of these cases with unilateral FUS had bilateral peripheral chorioretinal scars formerly diagnosed as bilateral toxoplasmosis.[3]Similarly, Devissor et al, found chorioretinal scars in rubella associated uveitis patients, however not one ofthesepatientstestedpositiveforthetoxoplasmosisgenome or for the toxoplasmosisantibody.

Chee et al investigated the role of the cytomegalovirus (CMV) in triggering hypertensive anterior uveitis in immunocompetentpatients.Theyfoundthat22.8%ofpatients withhypertensiveuveitiswerepositiveforCMVDNA.Of

Figure3 : arrow points to the anterior border layer: seen as orange color overlying blue iris



Arrows denote areas void of stroma with visualization of pigment epithelium

Table 1: Lab tests and results of the uveitc work up

TEST	RESULT
HLA-B27	negative
ANA	negative
Rheumatoid Factor, RF	negative
ACE, serum lysozyme and Chest X-ray	negative
Lyme Titer	negative
RPR	negative
Toxoplasmosis gondii	negative
PPD	negative
ESR	Within normal range

thesepatients,75%hadbeenclinicallydiagnosedwithPosner Schlossman syndrome and 20.8% diagnosed with FUS. All of their treated eyes responded favorably to the anti-viral, gancyclovir. There were relapses with discontinuation of the antiviral,butagoodclinicalresponsewithre-initiationofthe anti-viral medication. Thus, their results showed CMV may play a role in select cases of FUS, as well as otherpreviously diagnosed idiopathic uveitis cases.[14]

Labaletteetal,throughtheirresearchconfirmedCD8-positive T cells in the aqueous humor of Fuchs' patients signifyingan antigenic triggering process.[15] Quentin and Reiber,expanded upon this and have provided quantitative data of aqueous antibodiesinbothacuteandchronicintraocularinflammation. Conclusive evidence from their works have suggested that an intraocular immune response against the rubella virus is involved in the pathogenesis for FUS. They have focused on analyzing the Antibody Index (AI) which represents the "relative value for the quantity of intraocularly synthesized specific antibodies."[3] Their study measured the AI in the aqueous humor of many eyes and determined the intraocular antibodysynthesisforthediseasesofmeasles,rubella,varicella zoster, herpes simplex, and toxoplasmosis. Of significance, all 52 of their patients with clinically diagnosed FUS had the presenceoftherubellaantibodywithastatisticallysignificant AI.Furthermore,0%ofthe83caseswithclinicallydiagnosed idiopathic anterior uveitis, toxoplasmosis retinitis, varicella zoster and herpes simplex iritis did not have a statistically significant AI for the rubella antibody. Similarly, the non-inflammatory control group with senile cataracts also had no cases of a statistically significant AI for the rubella virus. [3] Interestingly, the rubella antibody was found intraocularly in 73% of multiple sclerosis (MS) patients with the diagnosis of uveitis intermedia or periphlebitis retinae. But with MS patients,thisincreasedrubellaantibodysynthesisrepresented a "polyspecific immune response" instead of a "virus driven antibody response" as seen in FUS.[3] Furthermore in the subset of MS patients, increased antibody synthesis was also seen for the measles, herpes simplex virus, varicella zoster virus, and toxoplasmosis *gondii* indicating the polyspecific response was the cause for increased antibody synthesis.[3]A seven fold increase in the AI was seen when evaluating FUS versus MS, and of even more significance, the actual rubella antibodyfractioninFUScomparedtoMSwasapproximately 40 times higher. Thus, signifying the viral driven response is specific for rubella inFUS.[3]

Quentin and Reiber also analyzed the AI from both the unaffected fellow eye and the cerebrospinal fluid (CSF) of a select few Fuchs' patients. It was found that these select patients had a normal AI in the unaffected eye and CSF, indicating that FUS is a local process specific to the eye and in most cases is unilateral.[3]

Similarly de Groot-Mijnes in their study found 13 out 14 of their FUS patients had the presence of intraocular immunoglobulinGproductionagainsttherubellavirusandin these same patients, antibody production for herpes simplex virus, varicella zoster virus, or toxoplasmosis *gondii* was undetected.[16]

As for the intraocular persistence of the rubella virus itself in FUS patients, Quentin et al. discovered the presence of the viral genome via method, polymerase chain reaction (PCR), in 18% of FUS patients.[3] However, if FUS patients less than 40yrsofagewereisolated,thispercentageincreasedto56%.[3]This signifies the predilection of the persistent rubella virus in the younger population, but the duration of this persistence is still unclear. De Groot and associates provided insight for why the viral genome and antibody synthesis may not always correlate in infectious uveitis cases. They studied and compared both viral load and antibody synthesis production in other infectious uveitis etiologies such as herpes simplex virus, varicella zoster virus, or toxoplasmosis *gondii*. They usedtheinformationprovidedbytheselaboratorytestsfo

confirm the diagnosis of the suspected uveitis infectious agent.Theresultsofthesetestshaveprovidedsomeinsightas towhyconfirmedinfectiousuveitiscasesshoweddifferences between the PCR results and antibody synthesis production. It was postulated that both antibody synthesis and viral load may vary depending on the stage the disease was in when the diagnostic tests were performed. After initial insult, the pathogen is either eliminated or the antigen load is reduced to an undetectable level and thus this could explain why the active virus is not detected with all FUS, especially older patients.[17]

Although the exact presence and role of active virus in FUS remains elusive, we can conclude that detection of a local persistent rubella virus provides information on the pathomechanism for the cause of FUS. [3] Furthermore, the role of a persistent rubella virus is supportive evidence that corticosteroid therapy is not a viable treatment option for FUS as seen with other intraocular inflammatoryconditions.

The theory of FUS being driven by the rubella virus hasbeen bolstered by the epidemiologic association which has shown decreasing FUS cases occurring with the implementation of the rubella vaccination program in the United States. Birnbaum et al, analyzed the percentages of patients with FUS, idiopathic chronic iridocyclitis, and idiopathic chronic granulomatous iridocyclitis born over the periods from1919-1998. They grouped these 3 subsets of patients based on the year they were born and studied the percentage of cases per decade over an eighty-year span. From 1919 to 1958, the averagenumberofpatientsseenwithFUSmadeup4.48%of all uveitic cases seen at the University of Illinois. Starting in theyear1969,aftertheimplementationoftherubellavaccine, the number of FUS cases decreased dramatically. Between 1969-1978, the percentage of FUS dropped to 1.18% and in the next decade following, dropped even further to 1% of all uveitic cases whose etiology was attributed to FUS. This is significant when compared with prior decades before the initiation the rubella vaccine. The trends for the percentages in the two other subsets, idiopathic chronic iridocyclitis and idiopathic chronic granulomatous iridocyclitis, did not show a statistically significant change in cases per decade as with FUS. Interestingly, Birbaum et al also looked at the percentages of cases for this same period of time comparing USbornversusnon-USbornwithFUS.TheproportionofFUS patients born outside the US appears to have increased. Most ofthecountriesrepresentingthesepatientsdidnotimplement the rubella vaccine program until the 1980's or later. While the FUS increased over the more recent years for foreign born FUS cases, it has remained stable for foreign borncases of idiopathic chronic iridocyclitis, and idiopathic chronic granulomatous iridocyclitis. This negates the possibility that foreignbornincreaseinFUScasesisaresultofanoverall increase in foreign born patients seen by the uveitis clinic at the University of Illinois. [18]

Additionally, Siemerick et al have documented a case of clinicalFUSwithpositiverubellaspecificintraocularantibody production in a non-vaccinated 13- year- old boy. Thepatient showedallofthecharacteristicclinicalsignsforFUSandwas positive for rubella virus antibody synthesis in two aqueous humor samples, taken at two different times. The aqueous humor sample was negative for the other potential antigens such as herpes simplex virus, varicella zoster virus and for toxoplasma *gondii*. Intraocular inflammation coupled with positive rubella antibody synthesis has provided evidence to confirm the role of the rubella virus in triggering the isolated uveitis seen in FUS.[19]

Although the most convincing evidence for the cause ofFUS appears to be the rubella virus, in a few cases of FUS there stillremainsambiguity.DeVisseretal,in2008,demonstrated with their works a relationship between the clinical signsand symptoms of positive rubella associated uveitis andFUS.[13]

According to them, 77% of rubella virus positive patients had met 3 or more of the criteria for clinical FUS, implying a causal relationship in a substantial number of cases [13]However, 15% of rubella negative associated uveitis met the criteria for clinical FUS, despite lack of rubella antibody production.[13] This would indicate that although the rubella virus may be the cause for the majority of the cases, it is not the only etiologicfactor.

Furthermore, the occurrence of both Horner's and FUS after stellate ganglionectomy would give the sympathetic theory credibility in a few select cases. FUS may have more than one cause, and these triggers lead to "release of potent autoantigens resulting in a common pathway of secondary autoimmune uveitis that becomes self-perpetuating." [10]

Viruses are increasingly being linked to what has previously been considered idiopathic ocular inflammations.[14] It is important to realize that the clinical manifestations seen in responsetotheviralantigensismostlikelynotspecifictothe virus itself but to how the host's immune system responds. Thegeneticmake-upoftheindividualandthespecificpattern responsetoaparticularviruswilldeterminewhatisclinically manifested by the patient.[14] Whether, FUS is triggered by rubella virus, herpes simplex virus, cytomegalovirus or even a sympathetic defect, the uveal tissue responds in a limited way, which results in the clinical spectrum that is diagnosed as FUS.[10,14] Other patients, affected by the same viruses may manifest a very different presentation, possibly Posner Schlossman syndrome or even a corneal endotheliitis. [14]

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FUS may be part of a stereotypical response to multitude factors. Currently the diagnosis of FUS is made on clinical observation and not laboratory testing. However, with the implicationoftheroleofvirusesasacausativefactorbolsters the need for confirmatory routine laboratory testing.Whether or not there is a specific FUS antigen or a multitude of triggers, confirming potential triggers will, hopefully, lead to better management.

Clinical Characteristics

Stereotypicalpatientsareyoungadultsthatpresentwithvisual symptoms, heterochromia, and unilateral clinicalfindings.[20] According to Velilla et.al. studied 27 eyes of 26 patients with diagnosed FUS, the most common presenting symptom reported was visual deterioration. Similarly, Jones studied 103 patients with clinically diagnosed FUS and decreased vision was the most common symptom reported by the patients at initial presentation.[1] The visual deterioration was either described as a mild disturbance of vision or asreduced visual acuity. [1] The visual acuity levels recorded by Velillaet al were 20/40 or better and the primary cause for the reduced acuity was usually cataracts. Other reported symptoms by patients but less common was discomfort, floaters, and the awareness of heterochromia.[20] The symptom of floaters and its occurrence in FUS is not consistent depending on study beingreviewed.InJones'sstudy,thesymptomsoffloaterswere found in approximately one third of FUS patients indicating it may be more common than noted in comparativestudies.[1]

Currently no diagnostic criterion for diagnosis of FUS has been universally accepted. However, the coexistence of several common clinical features allows for diagnosis. This rare form of uveitis can vary clinically however some commonclinicalsignscanaidinthediagnosis.Patientsoften havelittleornociliaryflush,whiteandstellatediffusekeratic precipitates, iris atrophy with or without heterochromia, posteriorsubcapsularlensopacities,andvitrealcells.[20]Vellila et al studied 27 eyes with diagnosed FUS found that 100% of patients presented at their initial exam with diffuse keratic precipitates.[20]Jones's study found 83.8% of patients to have keratic precipitates at initial exam, most of which were diffusely distributed across the corneal endothelium. Less commonly the precipitates were distributed centrally and infrequently inferiorly. [1] Other common findings were lens opacities (77.8%), Heterochromia (70.4%) and an anterior chamber reaction (66.6%). Other findings occurring with less frequency were iris stromal atrophy (14.8%), glaucoma (14.8%), vitreal opacities (14.8%), and iris nodules(7.4%).[20]

Clinical Precipitates

Characteristic endothelial keratic precipitates have been described in FUS and can provide useful insight, aiding diagnosis. In most cases of FUS, the keratic precipitates are diffusely dispersed over the entire corneal endothelium, whereasinotheretiologicuveiticcases,thepredilectionisfor inferior portion of the endothelium. Franceschetti, using slit lamp biomicroscopy described these keratic precipitates as round or star-shaped with fine filaments between the keratic precipitates. [21] Likewise, Jones described characteristic keratic precipitates as "stellate with fibrillary extension, and tiny interspersed fibrils."[1] Labbe' et al, using the higher resolving technique of In vivo-confocal microscopy (ICVM) characterized keratic precipitates in 13 diagnosed FUS patients as dendritic in shape with a small central body and numerous thin pseudopodia.[22] Furthermore, some of these pseudopodic extensions were found to make connections between different keratic precipitates. There was great consistency among all 13 FUS patients studied with ICVM, all demonstrating, these characteristic stellate precipitates.[22] Similarly,Mocanetal.,evaluated14patientswithknownFUS and their depiction of the keratic precipitates, "dendritiform" paralleledthefindingsofLabbeandassociates.[23]Interestingly, other ICVM studies looking at other infectious causes of uveitis tend to find this similar characteristic infiltrating and dendritic keratic precipitate. Whereas non-infectious uveitis keratic precipitates tend to be described as smooth, round, and globular. This may suggest that FUS represents "a true inflammatory component, related to a triggering infectious origin."[22] Furthermore, ICVM endothelial analysis of unilateral FUS patients confirmed endothelial changes only in the involved eye, which further supports an infectious precipitating trigger.[22]

Heterochromia, Iris Atrophy

Heterochromia has been considered an important feature of FUS and accounts for its incorporation into many of the namevariationsofFUS.Onlymorerecentlyhastheliterature moved from integrating heterochromia in the syndrome's name. Heterochromia in FUS denotes the lighter involved eye. However, this feature is very variable and depends on several factors such as the initial iris color, the intensity of anteriorstromalatrophyandtheamountofpigmentintheiris pigmented epithelium.[5] In all cases of FUS, the involved eye will have iris changes, however, heterochromia is not always obvious or always present. For instance, heterochromia is typically absent in dark color irides. Also, reverse heterochromia can exist.[5] This is when the inflamed eye has the darker iris because stromal atrophy exposes a substantial amount of the iris pigment epithelium.[5] These variations and subtleties can complicate diagnosis. Therefore, it is critical the clinician be aware of the nature and course of the iris changes seen in FUS as they can often beoverlooked.

IrisfindingsassociatedwithFUSmayincludeheterochromia, stromal atrophy, patchy atrophy of iris pigment epithelium, increased visibility of iris vasculature, loss of iris detail,less

commonly iris nodules, and rarely neovascularization of the iris or irido-corneal angle. Some of these findings may be very subtle and thus full awareness of the wide spectrum of iris presentations in FUS is critical.

Vastdifferencesinirisstructureandpigmentationexistamong patients,however,commonchangesamongFUSpatientswill allow for identification in an attuned clinician. Jones fully depicted the changes that occur in FUS by distinguishing the degree of atrophy in three separate layers of the iris: 1- anterior border layer, 2- stroma, and 3- pigmentepithelium in 103 patients diagnosed with FUS.[1] The anterior border layer of the iris is affected early on in the disease processand depigmentationofthislayerisusuallyresponsibleforcausing heterochromia.[1] This anterior border layer is described by Jones as an anterior stromal condensation densest in the collarette region of the iris. This layer is easier to visualize in the light iris and will typically appear as an orange blush. Often this layer is indistinguishable in patients with dark irides (Figure 3).[1]

The iris stromal layer and its ability to be visualized by the clinician will depend on the amount of pigmentation present. The denser the stromal pigmentation the less well defined the stroma will appear in slit lamp examination. A light iris will usually show radial fibrillary architecture with stromal vasculature evident and a distinct sphincter pupillae. Direct visualization of the deeper pigment epithelium layer can be seen through crypts in the stromal layer. Crypts represent absolute defects of the stroma and thus a direct view to the iris pigment epithelium (Figure 3). With progressive lossof stromal atrophy and visibility of the deeper pigment epithelium, a deeper blue hue to the affected iris may occur. This phenomenon is called reverse heterochromia and can appear in those with light blue irides.[1] On the contrary, adark iris will have a large supply of pigment cells resulting inasmoothfeaturelessappearance.Alargedegreeofstromal atrophy must occur in dark irides before macroscopic heterochromia becomes evident. This is why a critical slit lamp examination with bilateral iris comparison is necessary. The first signs of stromal atrophy in dark irides are usually notedastherevelationofirisdetail.Thearchitecturebecomes moreprominentasstromalpigmentandvolumearelost.Thus, stromal vessels, deep excavations, and the sphincter papillae become apparent.[1]

In general, stromal atrophy is harder to appreciate than anterior border loss and therefore is typically recognized on slit lamp examination in a later stage of FUS. It is critical for thecliniciantocompareboththeaffectedandunaffectedeyes when trying to evaluate the degree of stromal loss in FUS.[1]

The pigment epithelium is also affected in FUS. Typically atrophy of this layer is seen as transillumination defects and loss of the pupillary pigment ruff. Predilection for pupillary involvement is specific in FUS but not pathognomonic. Transillumination defects in FUS are variable and typically occur after atrophy of the other layers. [1] Iris atrophy and depigmentation is a common and critical feature of FUSwith alllayersoftheirisbeingaffected.Clinically,however,atrophy isappreciatedfirstintheanteriorborderlayerfollowedbythe stroma and later pigment epithelium. The cause of this is not due to chronological order but is the result of the ability to visualize each layer's loss by slit lampexamination.[1]

Iris nodules have been reported in the literature to exist in FUS patients. Rothova et al from their study implicated that iris nodules without synechiae may be encountered as part of FUS and may be important in the identification of FUS especially in black patients.[24] In their small sampleof black patients diagnosed with FUS, they found the common characteristic of unilateral multiple transparent iris nodules diffusely scattered across the whole surface of the iris (Bussaca nodules) with an increase in density toward the pupillary margin (Koeppe nodules). [24] Jones found inhis study that 16.2% of FUS patients had iris nodules, and they were not associated with more severe inflammation. [1]Synechiae formation is not a typical feature in FUS, and lack of its presence actually aids in diagnosis. However, should it arise, it occurs transitorily in the area of Koeppe nodules and will typicalIy present as radial pigmented lines on the anterior lens capsule. [5]Similarly, Jones's study although not revealing of posterior synechiae associated with Koeppe nodules, did show radial stripes of pigment deposition on the anterior lens capsule.[1] This finding may suggest a previous site of adhesion. Even though the lack of posterior synechiae isanimportantfeatureofFUS,thesepatientsarenotguarded from its occurrence after cataract surgery. In Jones's study, 4 patients following cataract surgery demonstrated posterior synechiae secondary to uveitis.[1]

The appearance of abnormal iris vessels in FUS hasbeen described in many prior publications. However, the ambiguity and importance of these vessels still needs to be elucidated upon. It is known that rubeotic- like vessels and normal radial iris vessels can be found in FUS. The cause for their appearance is believed to be secondary to iris atrophy.[25] Normal iris vasculature will naturally become more apparent with atrophy and depigmentation of the iris itself. However, subclinical changes in iris angiography have also been reported in the past literature. [1] Such vessels have shown leakage on fluorescein angiography and speculation is that these vessels may be the responsiblefor someof the aqueous flare seen in FUS. [25,26] In addition, filiform hemorrhages following applanation tonometry, paracentesis, oraftercataractsurgeryhavealsobeendocumentedinthe

literature in FUS patients.[1,27] Furthermore, confirmed iris neovascularization in association with glaucoma following intracapsular cataract surgery was noted in a few select FUS patients in Jones's study. [1] Overall, the interpretation ofmany ofthesestudiesonabnormalvesselsisunclearand,hopefully, future studies will further elucidate their presence and role in FUS.

Pupil changes in FUS are not typical but may occur. Most pupils in FUS patients are anatomically round and react normally.Butinselectcases,atrophyofthedilatororsphincter pupillae, or partial loss of the pigment frill, may result in an irregular pupillary response to light. Also, the affected pupil could appear physiologically larger or smaller depending on thepatternofatrophy.[1]Vellilaetalreportedcataractsin77.8% of FUS eyes at presentation. [20] Posterior subcapsular cataract (PSC) was the typical type of cataract found in FUSpatients. [25] Cataract was also the primary cause of visual deterioration at the time of presentation. [20] The appearance of cataracts is probably related to the duration of the disease. [1] In any case, FUS should be high on the differentials for a young patient who presents with a unilateral cataract, especially PSC, and without a history of trauma or steroiduse.

Vitritis can also occur in FUS. Its prevalence varies across studies. In Jones', 66.6% of patients had some degree of vitreal opacification.[1]Velilla et al reported in their study 14.8% of their FUS patients having vitreal involvement at presentataion.[20] According to Mohamed et al, vitritis is a common finding, however, it is usually mild and not associated with retinal vasculitis. [25] In cases of FUS where vitreal opacification is severe, misdiagnosis for intermediate or posterior uveitis ispossible.[25]

But the absence of cystoid macula edema differentiates FUS from other chronic vitritis conditions.[25]

Glaucoma has been associated in FUS and its presence dependingonthestudyvariesfrom15%-59%ofFUSpatients [1,28] According to Jones, 26.2% of FUS patients were treated for glaucoma during some stage of the disease process. [1]Typicallytheglaucomaisachronicopenangleform.Several factors have contributed to this secondary glaucoma, such as trabeculitis, neovascularization of the iris stroma and angle, induced from steroid treatment, and induced from cataract surgery.[20]

Diagnosis and testing

At this time, there are no laboratory tests that can render the diagnosis of FUS. Rather, the diagnosis of FUS is a clinical one. The clinician should take a detailed history and perform a complete comprehensive examination, including dilation. Carefulanteriorsegmentevaluationisneededtolookforsigns suggestive of herpetic disease. A dilated fundus examination is paramount for ruling out toxoplasmosis retinochoroiditis or other posterior involvement. Even in cases where clinical examination is suggestive of FUS, mimickers of this disease (sarcoidosis,herpetic,andtoxoplasmosis)shouldberuledout with the proper laboratory testing. The differential diagnosis of FUS would include any conditions that can cause uveitis, pan-uveitis, iris heterochromia, as well as conditions that can cause chorioretinal scars (see Table2).

Treatment

Generally, topical prednisolone acetate 1% is initiated for treatmentoftheuveitis.Ifsymptomsimproveandallancillary andlaboratorytestingisnegative,thenafullcourseofsteroid with taper iswarranted.

If,however,symptomsdonotimproveorwaxandwanethen an oral anti-viral medication is needed to rule out herpetic etiology. If both of these treatments do not yield favorable results and examination findings are consistent with FUS, then the topical steroid should be tapered slowly and the patient should be managed for the potential complications of FUS such as cataracts, ocular hypertension, and glaucoma, as these conditions may require additional medical and/or surgicaltreatment.

Unlike most uveitis syndromes, FUS typically does not respond to most corticosteroid treatment. As this is the case, most uveitis specialists will avoid the longstanding use of corticosteroids in FUS. With that in mind, therapeutic intervention may still be needed in certain cases in order to address acute flare-ups, significant vitritis, ocular hypertension, and cataract formation. Following such treatment, palliative therapies are suggested, and close monitoring is recommended.

Conclusion

In sum, FUS is an atypical form of uveitis that has a variable clinical spectrum making diagnosis difficult. It is considered to be an under-diagnosed syndrome, likely also because it lacks universal clinical criteria. The complaint of floaters and/or vision deterioration in a young adult with a unilateral uveitis in conjunction with a relatively quiet eye, shouldalert the clinician to the possibility of FUS.[20]Vellila et. al. found that delay in diagnosis can range from several days to 24 years.[20] Cunningham and Baglivo noted that the mean time for diagnosis is 3 years, during which time approximately two thirds of patients received anti-inflammatories including immunosuppressive treatments.[2] In the current case, the patient was diagnosed 27 years following his first incident of uveitis.

References:

1. Jones NP. Fuchs' heterochromic uveitis: a reappraisal ofthe clinical spectrum. *Eye* 1991;**5**:649-661.
2. Cunnigham ET, Baglivo E. Fuchs heterochromic iridocyclitis- syndrome,disease,orboth.*AmJOphthalmol*2009;**148:**479-481.
3. Quentin CD, Reiber H. Fuch's heterochromic cyclitis: rubella virus antibodies and genome in aqueoushumor. *Am J Ophthalmol* 2004;**138**:46-54.
4. Rothova A. The riddle of Fuchs heterochromicuveitis. *Am J Ophthalmol* 2007**;144**:447-8.
5. BonfioloAA,CuriALL,OreficeF.Fuchs'heterochromic cyclitis. *Seminars in Ophthalmology*2005;**20**:143-146.
6. Calmettes ML, Deodati R, Amalric P. UN cas d'association d'heterochromic de Fuch's et de syndrome de Claude Bernard. *Rev Oto-Neuro-Ophthalmol*1953;**25**:399-400.
7. Makley TA, Abbot K. Neurogenic heterochromia:report ofan interesting case. *Am J Ophthalmol*1965;**59**:927-8.
8. Regenbogen L, Naveh-Floman N. Glaucoma in Fuch's heterochromic cyclitis associated with congenitalHorner's syndrome. *Br J Ophthalmol*1987;**71:**844-9**.**
9. LaHeyE,BaarsmaG.Seerp.Fuch'sheterochromiccyclitisand retinalvascularabnormalitiesinprogressivehemifacialatrophy. *Eye*1993;**7**:426-8.
10. LaHeyE,DeJongPTVM,KijlstraA.Fuchs'heterochromic cyclitis:reviewoftheliteratureonthepathogeneticmechanisms. *Br J Ophthalmol*1994;**78**:307-12.
11. Loewenfeld IE, Thompson HS. Fuch's heterochromic cyclitis: a critical review of the literature. II. Aetiology andmechanism. *Surv Ophthalmol*1973;**17**:2-61.
12. Jones AP, Read AP. Is there a genetic basis for Fuch's heterochromicuveitis?Discordanceinmonozygotictwins.*BrJ Ophthalmol*1992;**76**:22-4.
13. DeVisserL,BraakenburgA,RothovaA,DeBoerJH.Rubella virus-associated uveitis: clinical manifestations and visual prognosis. . *Am J Ophthalmol*2008**;146**:292-7.
14. CheeS-P,BacsalK,JapA,Se-ThoeS-Y,LiChengCL,Tan BH.Clinicalfeaturesofcytomegalovirusanterioruveitisin immunocompetent patients. *Am J Ophthalmol* 2008**;145**:834-840.
15. Labalette P, Caillau D, Grutzmacher D, Dessaint J-P,Labalette M. Highly focused clonal composition of CD8(+) CD28(neg) T-cells in aqueous humor of Fuchs' heterochromic cyclitis. *Exp Eye Res* 2002;**75**:317-325.
16. DeGroot-MijnesJDF, deVisserL,RothovaA,SchullerM,van Loon AM, Weersink AJL. Rubella virus is associated with Fuchs heterochromic iridocyclites. *Am J Ophthalmol* 2006**;141**:212-4.
17. De Groot-Mijnes JDF, Rothova A, Van Loon Am, et al. PolymeraseChain reaction and Goldmann-Witmer coefficient analysis are complimentary for the diagnosis of infectious uveitis. *Am J Ophthalmol*2006**;141**:313-8.
18. BirnbaumAD,TesslerHH,SchultzKL,etal.Epidemiologic relationship between Fuchs heterochromic iridocyclitisand theUnitedStatesrubellavaccinationprogram.*AmJOphthalmol* 2007**;144**:424-8.

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