Fuchs’ Heterochromic Uveitis: an under diagnosed Entity

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Abstract

Fuchs’ Heterochromic Uveitis (FHU) is considered to be a rare chronic intraocular inflammatory disease. Alike other syndromes of unknown etiology, the diagnostic criteria and associated clinical features are continually changing, contributing to misdiagnosis. This article is a review of FHU and considers its principal clinical features, management, complications and prognosis.

Keywords: Fuchs’ Heterochromic Uveitis; Inflammation; Iridocyclitis; Iris; Uveitis

Introduction

First described in 1906, Fuchs’ Heterochromic Uveitis (FHU) is a chronic intraocular inflammatory disease affecting approximately 2% to 11.5% of all patients with uveitis [1,2].

The classic triad of signs of this non-granulomatous uveitis includes iris Heterochromia, cataract and keratic precipitates [3]. Currently, Heterochromia is not required for the diagnosis, which remains clinical, based on a thorough ophthalmic examination. Revised diagnostic clinical features are presented in Table 1.

| Absence of posterior synechiae, prior to cataract surgery |
| Diffuse iris stromal atrophy with or without heterochromia |
| Frequent presence of cataracts and glaucoma |
| Lack of acute symptoms of severe pain, redness and photophobia |
| Low-grade anterior chamber reaction |
| Presence of cells and opacities in the anterior vitreous |
| Typical diffusely spread, small or medium-sized white stellate keratic precipitates |

Table 1: Clinical features of FHU [4-6].

The condition appears to be unilateral in 90% to 95% of patients and typically presents during mid-adult life with complaints of floaters and gradual visual impairment [7,8]. These complaints which correlate, respectively, to vitreous opacities and cataract, are the most common symptoms of FHU, at the time of presentation. Some patients have no significant symptoms and are just identified during a routine ophthalmic exam [9]. Inflammation in FHU is usually low-grade but difficult to control due to lack of response to steroids. [1,8]. Occasionally, ocular discomfort is experienced but secondary glaucoma is the most damaging complication [10]. Though evidence from different studies points to an association between FHU and Rubella virus (RV), its etiology is still elusive [11]. This review aims to highlight the clinical features, latest research and treatment options of this under diagnosed and most likely over treated uveitis.

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Etiopathogenesis

FHU has no gender predisposition, no racial or ethnic predilection and the influence of genetic factors is considered to be very low or absent [12].

Although some cases have been described in association with other ocular disorders, including infections with Toxoplasma [13], Toxocara [14], Chikungunya virus [15] and Herpes simplex virus [16], as well as Retinitis Pigmentosa [17], previous trauma [8] and corneal autoantibodies [18] its cause(s) remain unknown.

After molecular and histologic studies found evidence of an underlying immunologic mechanism, recent interest has arisen from the findings by several groups of local intraocular IgG antibody production against Rubella Virus (RV) in FHU eyes suggesting that RV infection might be the initial trigger for the following immune reaction [11,19].

In 2004, Quentin and Reiber studied the presence of specific antibodies in the aqueous humor (AH) of 52 FHU patients and found that all patients had markedly elevated intraocular titers to RV (using a modified Goldmann-Witmer coefficient to calculate the antibody index) and a substantial subset had positive reverse transcription polymerase chain reaction (RT-PCR), demonstrating active virus presence in the AH [11]. This connection was also established by published series from different regions around the world [18-22].

Further indirect support for a potential relationship between RV and FHU was derived from epidemiologic reports indicating a lower incidence of FHU in the United States following the institution of vaccination against RV, with a parallel increase of foreign-born cases [23].

In addition, immunoscope analysis of T-lymphocytes revealed the prevalence of CD8 (+) T-lymphocytes on the cellular infiltrate during active inflammation phase, suggestive of viral pathogenesis [24]. The viral etiology could also explain the limited response to steroid medications. Although heterogeneity prevails, some in vivo studies using confocal microscopy (IVCM) suggest similar KP pattern among infectious uveitis and FHU [25]. Vitreous involvement was confirmed by the elevation of different kinds of inflammatory cytokines and chemokines in the vitreous fluid of patients with FHU [26].

FHU is a constellation of clinical symptoms and may have diverse origins. As the various signs of FHU are not constantly present at the same time, it is yet unknown whether the clinical symptoms in RV-positive FHU are distinct from other FHU patients [27]. Further research is needed to confirm and clarify this syndrome’s Etiopathogenesis. However, in light of the above, this condition might represent a final common clinical phenotype of different pathogenic mechanisms, rather than the result of a single pathogenic process.

Clinical Features

FHU is characterized by a classic triad of iris Heterochromia, cataract and keratic precipitates (KP). [3]. However, heterogeneous clinical features may lead to misdiagnosis with important diagnostic delay, reaching, in some cases, almost 30 years [6].

Table 2 presents clinical features of FHU in different studies over the last 20 years.

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<tbody>
<tr>
<td>Age (years)</td>
<td>Avg. 35.5</td>
<td>Mean 30.2</td>
<td>Mean 31</td>
<td>Median 35</td>
<td>Mean 37</td>
<td>Median 35</td>
<td>Mean 35.2</td>
<td>Mean 36.32</td>
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<tr>
<td>Bilaterality</td>
<td>15.6%</td>
<td>3.9%</td>
<td>10.3%</td>
<td>13.5%</td>
<td>6%</td>
<td>11.4%</td>
<td>4.8%</td>
<td>10.5%</td>
</tr>
<tr>
<td>Cases</td>
<td>77</td>
<td>26</td>
<td>68</td>
<td>104</td>
<td>54</td>
<td>105</td>
<td>166</td>
<td>19</td>
</tr>
<tr>
<td>Cataract</td>
<td>73.0%</td>
<td>77.8%</td>
<td>69.3%</td>
<td>70.7%</td>
<td>92.5%</td>
<td>47%</td>
<td>85.6%</td>
<td>100%</td>
</tr>
<tr>
<td>Chorioretinal scars</td>
<td>18.4%</td>
<td>7.4%</td>
<td>1.3%</td>
<td>0%</td>
<td>11%</td>
<td>6%</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>21.3%</td>
<td>14.8%</td>
<td>4%</td>
<td>23.1%</td>
<td>11%</td>
<td>12.8%</td>
<td>27.6%</td>
<td>10.5%</td>
</tr>
<tr>
<td>Heterochromia</td>
<td>70.1%</td>
<td>70.4%</td>
<td>25%</td>
<td>12.7%</td>
<td>27.8 – 48.1 %</td>
<td>42.6%</td>
<td>13.9%</td>
<td>31.6%</td>
</tr>
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</table>

Bilateral disease ranges from 3.9% to 15.6%. It is worth mentioning that in those with bilateral disease no sequential involvement has been reported. Iris Heterochromia has been classically described in FHU and is attributed to a progressive atrophy of the anterior border layer and stroma of the affected iris leading to *hypochromia* of the affected eye [5].

However, in sporadic cases, *hyperchromia* may arise when marked atrophy exposes the underlying iris pigment epithelium. This feature is more easily detected in light brown or blue/green irises. In dark-colored irises, clinically evident heterochromia has a low frequency and might contribute to delayed diagnosis [5,30,35]. Frequently, the morphologic asymmetry between irises may be overlooked and, when suspecting of FHU, the examining physician must thoroughly shift from one eye to another paying special attention to the pupillary zone and iris collarette, looking for differences in color, thickness and anterior iris features, such as crypts (Figure 1).

![Iris nodules](image1.png)

<table>
<thead>
<tr>
<th>Clinical features of FHU.</th>
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<tr>
<td>Iris nodules</td>
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<tr>
<td>Keratic precipitates</td>
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<tr>
<td>Vitreous opacity</td>
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</tbody>
</table>

Iris nodules (7.4% to 30.7% of the patients in the reviewed studies) are an important feature in some patients with FHU. Still, the presence of the iris nodules coupled with subtle or absent heterochromia in a brown-eyed patient could mislead to diagnose the case as chronic granulomatous iridocyclitis. In this disease, the nodules are predominantly small, round, translucent and most predominant on the pupillary side of the colarette, though may be spread all over the surface of the iris [7,9]. The fact that there are no associated synechiae points in the direction of FHU [33].

The anterior chamber (AC) reaction is usually mild and flare is hardly identified. Some patients experience periods without detectable AC cellular activity and about half of them reach a stage where inflammation is no longer seen [9]. In contrast, a small number of eyes exhibit a more aggressive form of FHU with marked AC reaction [9]. Keratic precipitates are observed from 80% to 100%. These KP have distinctive features with a characteristic morphology and distribution. They are generally grayish, numerous, translucent, small to medium in size and typically scattered all over the entire corneal endothelium. Some KP demonstrate starlike radial extensions and between them delicate fibrillary structures form a meshwork [9]. (Figure 2)

In recent years, the evaluation of KP observed in various uveitic syndromes using IVCM has gained considerable attention [36]. IVCM evaluation has underlined the probable association of certain KP morphologies with distinct uveitic syndromes [37]. The dendritiform KP pattern is a highly characteristic feature of FHU and is detected in an overwhelming majority of cases. Endothelial cell loss and decreased percentage of hexagonal cells were also found to be present in some patients with FHU [25].

Abnormal anterior segment vasculature is also an important feature of FHU. As a result of iris atrophy, normal iris vessels become conspicuous when compared to the opposite eye. In contrast to these vessels, iris neovascularization may be observed in up to 20% of the affected eyes. Iris fluorescein angiography exhibited narrow radial iris vessels with sector perfusion defects and scattered foci of leaky tufts of vessels in an even higher proportion [38].

The Amsler–Verrey sign describes the characteristic AC bleeding that is noted in patients with FHU. Amsler proposed that a sudden decrease in intraocular pressure causes the rupture of anomalous vessels. It may arise during cataract surgery but it can also occur either spontaneously or associated with minor trauma [39]. However, the clinical utility and usefulness of this sign has been questioned [40].

The presence of cells in the anterior vitreous (retrolental space) and eventually vitreous opacities are an integral part of FHU that has been neglected over the years and can lead to misdiagnosis of intermediate or posterior uveitis [33]. Floaters might become so disturbing that will require vitrectomy [6,9].

Corneal astigmatism appears to be a common finding in eyes with FHU, and so disparity in corneal astigmatism between the two eyes, when accompanied by typical characteristics, may raise the clinical suspicion of this syndrome [41]. Ciliary body involvement is a feature of FHU that can be accessed through ultrasound biomicroscopy, which can detect exudates adjacent to the ciliary body [31].

A study reported fundus fluorescein angiographic (FFA) findings in 44 eyes with FHU, namely, nearly constant disc hyperfluorescence, absence of cystoids macular edema and, more rarely, peripheral retinal vascular leakage [42]. These features are not usually associated with FHU and might represent an additional factor leading to misdiagnosis.

Recently, fluffy white iris precipitates were identified in FHU patients, during routine physical examination of the angle by gonioscopy. These may also represent an additional clinical sign [43].

**Figure 2:** Typical stellate or dendritic grayish keratic precipitates with fine interspersed fibrils. Drawing adapted from Jones, N. P. (1991). [10]
Clinical Management (Complications and Prognosis)

Glaucoma, cataract and vitreous opacification are the three main sight-threatening complications of FHU.

Uveitis

Anterior chamber reaction is usually mild and patients rarely complain of inflammation related symptoms. Topical steroids should be used with caution owing to their potential to worsen cataract and induce glaucoma in susceptible individuals.

Corticosteroids should be reserved to specific circumstances, namely, dense accumulation of KP, precipitates on the lens surface, patients with flare-ups of inflammation and during the pre and post ocular surgery period [44].

Cataract

Cataract develops in most patients with FHU, conceivably from sustained low-grade inflammation and steroid treatment. On the reviewed studies (Table 3), the incidence of cataract ranged from 43% to 100%.

The lens opacities are usually posterior subcapsular in morphology and may rapidly progress [45]. Cataract extraction in FHU appears to provide excellent visual acuity results and is reported to have better outcomes than other uveitic cataracts [45,46].

Table 3 presents cataract extraction outcomes in FHU patients in different studies over the last 20 years.

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<tbody>
<tr>
<td>Cases</td>
<td>20</td>
<td>77</td>
<td>35</td>
<td>20</td>
<td>41</td>
<td>103</td>
</tr>
<tr>
<td>Follow-up</td>
<td>15 months</td>
<td>34 months</td>
<td>24 months</td>
<td>24 months</td>
<td>18 months</td>
<td>12.9 months</td>
</tr>
<tr>
<td>Technique</td>
<td>ECCE, PCIOl</td>
<td>ECCE, PCIOl</td>
<td>ECCE, Phaco, PCIOl</td>
<td>Phaco, PCIOl</td>
<td>Phaco, PCIOl</td>
<td>ECCE, Phaco, PCIOl</td>
</tr>
<tr>
<td>VA &gt; 5/10</td>
<td>95%</td>
<td>83%</td>
<td>90%</td>
<td>100%</td>
<td>100%</td>
<td>92.5%</td>
</tr>
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</table>

Table 3: Cataract extraction outcomes in FHU.

In the reviewed studies, extracapsular cataract extraction (ECCE) or phacoemulsification (Phaco) with IOL implantation was safe in patients with FHU. Almost every patient achieved a visual acuity of 5/10 or better without major intraoperative or postoperative complications. As in any other eyes with chronic iridocyclitis, the use of anterior chamber lenses is discouraged in eyes with FHU [51].

Although postoperative inflammation may be severer than that encountered in the general population, topical instillation of steroid eye drops appears to be effective in controlling postsurgical inflammation and cellular precipitates on the IOL surface [26]. Posterior capsule opacification does not appear to be more frequent in FHU patients, however, laser capsulotomy should be also accompanied by topical steroid therapy [44].

Vitreous opacification

Vitreous opacification can be highly significant in patients with FHU. On the above presented studies (Table 2), the incidence of vitreous opacity ranged from 14.8% to 100%. Pars plana vitrectomy (PPV) has already an established role in the surgical management of other forms of chronic uveitis complicated by significant vitreous opacification [52]. PPV appears to be a safe and effective treatment for symptomatic vitreous opacification which can be combined with cataract extraction, if required [53]. Vitrectomy surgery results are encouraging with most of the patients recuperating a visual acuity of 7/10 or better and no apparent exacerbation of inflammation [53,54].

Glaucoma

Glaucoma is the most serious, vision-threatening complication of FHU. Its pathogenesis in FHU is still poorly understood, and in most cases it is chronic open-angle glaucoma [11]. On the above presented studies (Table 2), the incidence of glaucoma ranged from 4% to 27.6%.

Fuchs’ Heterochromic Uveitis: an under diagnosed Entity

Occasionally the contralateral eye also develops glaucoma [44]. Younger age of FHU patients, difficulty in controlling intraocular inflammation and high pre-intervention intraocular pressure (IOP) makes the management of glaucoma secondary to FHU a challenge. IOP appears to be more difficult to control and requires more aggressive treatment when compared to other uveitic glaucoma forms [55]. Topical anti-glaucoma agents are the first-line therapy in glaucoma secondary to FHU [55]. However, IOP usually becomes refractory to medical therapy and even despite surgery, a significant proportion of the eyes fail to respond to treatment [56]. When maximal topical therapy fails to control the IOP, different treatment options can be considered. These include oral carbonic anhydrase inhibitors, argon or selective laser trabeculoplasty, non-penetrating glaucoma surgery, goniosurgery, trabeculectomy with or without adjuvant anti-metabolites (5-fluorouracil or mitomycin C), glaucoma drainage devices or cycloablative procedures [11,55-57]. Although there is no gold standard approach for the surgical management of glaucoma secondary to FHU, trabeculectomy with adjuvant anti-metabolites is usually considered the first surgical option once medical therapy has failed [55]. (Figure 3)

Figure 3: Patient with FHU, following combined phacoemulsification and trabeculectomy of the affected eye (A). The asymmetry between iris features of both eyes is easily accessed.

Conclusions

FHU is a largely underdiagnosed uveitis. It is important to make the diagnosis of FHU to avoid superfluous investigations and potentially adverse steroid treatment. It is of note that the classically described heterochromia is not required for the diagnosis, and special attention should be paid to more subtle structural iris changes. Although the prognosis is generally favorable, patients should be counseled regarding the need for appropriate screening for glaucoma. Rubella virus appears to be involved, yet, despite much interest in investigating the underlying pathology, the exact cause remains elusive. Parspectesis and collection of aqueous humor for determination of antirubellar antibody production can provide valuable diagnostic information, particularly in unclear inflammatory eye diseases, suspicious of FHU.

Conclusions


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