A Literature Review on Fuchs Uveitis Syndrome

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Abstract: Fuchs uveitis syndrome (FUS) is a chronic unilateral non-granulomatous uveitis. Various theories have been proposed to explain its etiology and pathogenesis, including infectious, sympathetic, genetic, and immunological theories. The onset and progression of FUS are currently believed to result from the combined effects of multiple pathogenic mechanisms rather than a single etiology. The clinical manifestations mainly include insidious onset, unilateral involvement, mild anterior chamber inflammation, stellate or medium-sized KPs distributed diffusely or centrally, iris depigmentation with or without heterochromia, the absence of posterior synechiae, and the occasional occurrence of vitreous opacities. Common complications include cataracts and glaucoma. As the diagnosis relies mainly on clinical observations rather than laboratory tests, FUS is often misdiagnosed, especially in patients with dark brown irises. Many patients with FUS do not require specific treatment, but regular follow-up is necessary to monitor for elevated IOP and cataract development. Most patients have a good visual prognosis, which mainly depends on the outcome of cataract surgery and glaucoma control. Refractory glaucoma may lead to vision loss. We discuss the clinical manifestations, etiology, pathogenesis, diagnosis, treatment, and prognosis of FUS with a comprehensive description.

Keywords: Fuchs uveitis syndrome; Pathogenesis; Iris depigmentation; Cataract; Secondary glaucoma

1. Introduction

Fuchs uveitis syndrome (FUS) is a chronic non-granulomatous uveitis characterized by diffuse iris depigmentation and medium-sized or stellate keratic precipitates (KPs) that are diffusely distributed\textsuperscript{[1-4]}. In 1906, Ernst Fuchs\textsuperscript{[5]} first systematically described the clinical features and histopathological findings in patients with FUS and suggested possible etiologies. Over the following century, the disease has garnered significant attention from many scientists and ophthalmologists.

FUS is the second most common form of non-infectious uveitis, accounting for 1-20\% of all anterior uveitis cases\textsuperscript{[6]}. It can occur at any age, with patients ranging from 8 to 75 years old, but is most common in adults between the ages of 20 and 50. No gender differences have been observed\textsuperscript{[1]}. It occurs worldwide, with an incidence rate of 1.8-22.7\% in developed countries, but only 0-5.6\% in developing countries\textsuperscript{[2, 7]}.

In recent years, with increasing research in the fields of electron microscopy techniques, fluorescein angiography, microbiology, and immunology, there has been a deeper understanding of various aspects of the etiology, pathogenesis, and clinical features of FUS.

2. Etiology and pathogenesis

The etiology and pathogenesis of FUS are not fully understood. Various theories have been proposed to explain its pathogenesis, including infectious, sympathetic, genetic, and immunological theories\textsuperscript{[5, 8]}. However, no theory can fully explain all the clinical manifestations of patients with FUS. The onset and progression of FUS may be caused by multiple pathogenic mechanisms rather than a single etiology\textsuperscript{[5]}.

2.1 Infectious theory

Various viral infections have been reported to be associated with the pathogenesis of FUS, including herpes simplex virus (HSV), toxoplasma gondii, cytomegalovirus (CMV), rubella virus (RV), chikungunya virus, and other viruses.
2.1.1 Herpes simplex virus

The association between FUS and HSV infection was first described by Mitchell et al. [9] in 1996. Subsequently, Quentin et al. [10] examined aqueous humor samples from 52 patients with FUS and found that the Goldmann-Witmer coefficient values for herpes virus antibodies in all samples were within the normal range, indicating no intraocular synthesis of HSV antibodies. A case report by Barequet et al. [11] showed that HSV DNA was detected in the aqueous humor sample of a patient with FUS using polymerase chain reaction (PCR), which suggested that HSV may play a role in the pathogenesis of FUS.

2.1.2 Toxoplasma gondii

It has been reported that patients with FUS exhibit retinochoroiditis similar to that caused by toxoplasma infection. Some studies suggested that toxoplasma infection is closely associated with FUS [12-14]. Toledo de Abreu et al. [12] first associated FUS with ocular toxoplasmosis, reporting 13 cases of FUS with focal necrotizing chorioretinal toxoplasmic lesions. In the study by Schwab et al. [14], 13 out of 25 patients with FUS exhibited typical toxoplasmosis scars and were seropositive for anti-toxoplasma antibodies, suggesting a causal relationship between the two disorders. However, in the report by La Hey et al. [15], despite the significant clinical association found between FUS and toxoplasmosis-like chorioretinal scars, the aqueous humor samples from 88 patients with FUS tested negative for anti-toxoplasma antibodies.

Additionally, some case reports have shown an increase in anti-toxoplasma antibodies in the aqueous humor of patients diagnosed with FUS. In a study by La Hey et al. [16] in 1993, the calculation of the Goldmann-Witmer coefficient revealed that the aqueous humor of one patient with FUS tested positive for anti-toxoplasma IgG. Similarly, in 1999, Parrat et al. [17] reported a case of FUS associated with toxoplasmic chorioretinal scars, in which a high level of anti-toxoplasma antibodies was detected in the aqueous humor. In 2004, Ganesh et al. [18] observed a female patient who developed bilateral features of FUS after experiencing multiple episodes of bilateral toxoplasmic retinochoroiditis, and an enzyme-linked immunosorbent assay showed high titers of both anti-Toxoplasma IgG and IgM in her serum. Later, Teyssot et al. [19] demonstrated that ELISA serology for Toxocara canis yielded positive results for IgG, whereas serological analysis for Toxoplasma gondii was negative, suggesting that serological testing for toxocariasis may be useful in patients with FUS and retinal scars in the absence of toxoplasmosis. In 2013, Jad et al. [20] reported six cases of classic FUS secondary to ocular toxoplasmosis and measured the production of anti-toxoplasma IgG in the aqueous humor of five patients by calculating the Goldmann-Witmer coefficient, with positive results in four cases. These findings support our conclusion that FUS may develop following ocular toxoplasmosis over a period of time, which may be a secondary immune response to antigenic stimulation of a previous infection.

2.1.3 Cytomegalovirus

Cytomegalovirus infection can lead to various ocular manifestations, including iris atrophy [21], acute recurrent hypertensive anterior uveitis (Posner-Schlossman syndrome) [22], chronic anterior uveitis resembling FUS, and corneal endotheliitis [12, 23]. In Asia, the incidence of CMV infection in FUS cases ranges from approximately 16% to 42%, whereas in Western countries, FUS is predominantly associated with RV rather than CMV [24-27]. Chee et al. [25] found an association between FUS and CMV infection. They examined 36 eyes of 35 FUS patients and detected CMV DNA in the aqueous humor of 15 eyes using PCR, suggesting that CMV infection is an important cause of FUS.

2.1.4 Rubella virus

In previous studies, the RV was recognized as a causative factor in patients with clinical signs of FUS. In 2004, Quentin and Reiber provided the first conclusive evidence that RV plays a key role in the development of FUS [10]. Subsequently, other researchers have detected anti-rubella virus-specific antibodies in samples from patients with FUS, suggesting an association between FUS and RV [26, 28-32]. In a study by Wensing et al. [33], RV RNA was detected by PCR in the atrial fluid of patients with FUS. Suzuki et al. [30] isolated rubella virus particles from the aqueous humor of a patient with FUS, further confirming the presence of RV in this disease. Additionally, an epidemiological study demonstrated a decrease in the incidence of FUS since mass rubella vaccination began in the United States in 1969, a trend not observed in the control group [34, 35].

2.1.5 Chikungunya virus

Mahendradas et al. [36] first reported a case of bilateral FUS associated with chikungunya virus infection in the left eye, detecting chikungunya virus RNA in the aqueous humor. This suggests a
potential association between the Chikungunya virus and FUS. However, it remains unclear whether the Chikungunya virus is a causative factor for FUS.

2.2 Sympathetic theory

The sympathetic theory suggests that the normal process of uveal pigmentation in FUS may be inhibited by some predisposing defect in the sympathetic nervous system [37, 38]. Since the last century, there have been many case reports of FUS associated with sympathetic dysfunction [39, 40]. Melamed et al. [41] proposed that the iris heterochromia in FUS may be due to defects in melanin production resulting from abnormal adrenergic innervation. Several studies have shown that iris stromal melanocytes receive direct adrenergic innervation [42-44]. In conclusion, the sympathetic theory suggests that sympathetic dysfunction may be the cause of reduced iris pigmentation in patients with FUS and Horner syndrome, as the reduced innervation of iris stromal melanocytes may lead to defects in melanin production. In addition, patients with FUS exhibit a reduced density of sympathetic nerve distribution in the uvea, resulting in vasodilation, ciliary congestion, increased capillary permeability, and disruption of the blood-aqueous barrier function, which causes increased aqueous humor protein concentration, the formation of KPs, vitreous opacity, cataract, and glaucoma [37].

2.3 Genetic theory

Genetic theory suggests that iris heterochromia and uveitis are fundamentally linked to genetic factors [5, 37, 38]. In 1956, Makley et al. [45] reported that both identical twins were diagnosed with FUS. However, in the studies by Jones and Read, no concordance in FUS among identical twins was observed, nor was a Mendelian inheritance pattern found for FUS, and the temporal relationship between the onset of heterochromia and FUS in patients with congenital heterochromia remains unclear [46]. Due to the lack of large-scale case studies, the exact role of genetics in the pathogenesis of FUS cannot yet be confirmed.

2.4 Immunological theory

The immunological theory posits that immune responses to uveitis-causing antigens in the retina and uvea, such as melanin-associated antigens in the uvea, retinal S-antigen, and interphotoreceptor retinoid-binding protein, may be an important mechanism in the development of FUS [1]. La Hey et al. [47] first described the presence of autoantibodies against corneal epithelial cells in almost 90% of patients with FUS, providing further evidence that immune mechanisms may play an important role in the etiology of FUS. Although there is a lack of additional evidence to support this doctrine, many scholars now agree that FUS is associated with an immune response [37, 48-51].

3. Clinical features

According to the guidelines of the International Uveitis Study Group [51], the typical features of FUS include chronic unilateral non-granulomatous inflammation primarily involving the anterior uvea, an insidious onset, low activity, an equal male-to-female ratio, and most commonly occurring between 20 and 50 years of age. The condition is insensitive to hormonal therapy and usually has no associated systemic disease. Cataract and glaucoma are the main complications. The prognosis is generally good. However, according to the reports from the Netherlands [3], Spain [52], the United Kingdom [4, 53], Mexico [54], the United States [55, 56], Turkey [57], and China [2], there are significant differences in the clinical presentations of patients from different ethnic groups.

Patients with FUS predominantly present with unilateral involvement [2, 5, 50], and in the study by Yang et al. [2], less than 10% of patients had bilateral involvement. The most common symptom is blurred or decreased vision [5, 53, 58]. Many patients have mild chronic iridocyclitis, which is characterized by a few anterior chamber cells and mild anterior chamber flare [58, 59]. Most patients do not present with signs of acute iridocyclitis, such as ciliary congestion, miosis, photophobia, tearing, and eye pain, and tend to have no obvious ocular symptoms. It is worth noting that a small number of patients may experience eye redness, photophobia, and tearing during the first episode, but these symptoms usually disappear during recurrences. Additionally, some patients may exhibit an obvious inflammatory response in the anterior chamber after undergoing surgical treatment, during which ciliary congestion may occur [4, 52].
KPs in patients with FUS are predominantly medium-sized or stellate, with fibrous filaments often connected between KPs [1, 2, 60]. Typically, there are three distribution patterns: diffuse distribution on the entire corneal endothelium, distribution on the central corneal endothelium, and triangular distribution on the inferior corneal endothelium, with diffuse distribution being the most common [2, 61, 62]. While KPs in other types of anterior uveitis tend to diminish as the inflammation subsides, those in FUS often persist for long periods, sometimes lasting for months or even years, and do not subside rapidly even with the use of glucocorticoid eye drops [1, 61].

A distinctive feature of FUS is the depigmentation of the iris stroma, the atrophy of the anterior stroma, and the loss of the iris pigment epithelium. Heterochromia may develop if there is significant depigmentation of the iris [4, 63]. All patients with FUS have iris depigmentation, but its extent varies greatly between patients [2]. Iris depigmentation in patients with FUS is generally diffuse or uniformly distributed, which is an important sign for distinguishing this disease from other types of uveitis [2, 64, 65]. In Caucasians, due to the lower amount of pigment in the iris, iris depigmentation tends to result in iris heterochromia [60]. In patients with dark or brown irises, it is difficult to observe obvious iris heterochromia due to the high concentration of pigment in the iris [2, 37, 53]. A few patients have iris swelling with a spongy appearance [2]. Due to focal atrophy and depigmentation of the iris pigment epithelium, the pigment epithelium often exhibits a worm-eaten appearance. Areas of pigment epithelial atrophy can be visualized by transillumination of the pupil [2, 4]. Iris nodules in patients with FUS are predominantly Koeppen nodules, with occasional Bussaca nodules. Koeppen nodules are fluffy, located around the pupillary collar, and tend to be multiple, sometimes numbering up to dozens. Bussaca nodules differ from those seen in granulomatous uveitis in that they are sometimes present in large numbers on the surface of the iris but do not exhibit any obvious signs of anterior chamber inflammation [3, 56, 67, 68]. Patients with FUS rarely develop posterior synechiae [2, 65, 66]. However, it has been reported that a few patients can develop posterior synechiae after cataract surgery, which may be due to the difference between postoperative inflammatory responses and the inflammation associated with FUS [55, 55].

Russell bodies, which are tiny, glistening, refractile deposits on the anterior surface of the iris, have been reported in a very small number of patients with FUS. These iris crystals are caused by inclusion bodies within plasma cells [63, 69, 70]. In a few patients with FUS, the pupil may be slightly dilated or irregular, with diminished pupillary light and near reflexes [55, 71]. These abnormalities indicate inflammation affecting the pupillary sphincter or the dilator muscles [66]. The anterior chamber angle is open and wide in patients with FUS, and gonioscopy sometimes reveals neovascularization of the angle. Occasionally, scattered peripheral anterior synechiae can be observed in the anterior chamber angle [53, 72].

During anterior chamber paracentesis, filiform hemorrhage occurring on the opposite side of the puncture, usually depositing in the inferior angle of the anterior chamber, is referred to as Amsler's sign. This sign was first described by Amsler and Verrey [73], who performed anterior chamber paracentesis on 23 patients with FUS and found Amsler's sign in 22 cases. This hemorrhage is usually absorbed within hours to a day without sequelae, and the bleeding recurs in the same manner with repeated punctures. However, it does not occur in the unaffected eyes of patients. This study identified Amsler's sign as an important indicator of FUS, a view shared by many scholars but disputed by others. Currently, Amsler's sign is not used internationally as a diagnostic criterion [74, 75].

A small number of patients with FUS may develop vitreous cells and opacities. Unlike other types of uveitis, these opacities are almost always white rather than brown. Jones et al. [53, 55] reported three patients with FUS who developed severe vitreous opacities, which occurred suddenly and without anterior segment inflammation, ultimately requiring surgical intervention. The formation of curtain membranes and dense veil-like membranous material is also occasionally observed in the vitreous. Yang et al. [2] conducted ultrasound biomicroscopy on several patients with FUS and found that the ciliary body in the affected eyes exhibited various types of exudates, mainly including mass-like, linear, or dotted forms at the pars plana and basal vitreous body. However, unlike other types of uveitis, FUS does not exhibit alterations such as swollen ciliary body, cycodialysis, or snowbank-like changes.

Chorioretinal lesions are relatively uncommon and may present as peripheral chorioretinal lesions [38, 55]. Of the 38 patients reported by Fuchs et al. [5, 76], chorioretinal lesions were observed in three patients. In 1955, Franceschetti et al. [63] concluded that the chorioretinal lesions observed in patients with FUS were indicative of a degenerative condition rather than an inflammatory one. However, it is challenging to definitively classify chorioretinal scarring as either degenerative or inflammatory based solely on its characteristics. Kimura et al. [77] suggested that while peripheral chorioretinitis is occasionally observed, this lesion is often overlooked due to the infrequent examination of the
Peripheral retina. When fundus fluorescein angiography is performed in patients with FUS, fluorescein leakage from mid-peripheral retinal capillaries and optic disc staining may be seen in some patients [2]. A few patients may experience vascular wall staining or focal chorioretinal atrophy [78-80].

4. Complications

The most common complication of FUS is secondary cataract. It typically presents as posterior subcapsular lens opacities in the early stages and may progress to complete opacification in the advanced stages. Due to the insidious onset of FUS, many patients already present with secondary cataracts upon their initial visit. The longer the duration of the disease, the greater the likelihood of developing intercurrent cataract. It is noteworthy that the cataract caused by FUS is not significantly distinguishable in appearance from cataracts caused by other types of chronic anterior uveitis, thus limiting the value of cataracts in the differential diagnosis of FUS [57, 81].

Secondary glaucoma is also a common complication of FUS, with an incidence ranging from approximately 6.3% to 59% [38, 82]. The intraocular pressure (IOP) tends to be mildly to moderately elevated, typically ranging from 22 to 35 mmHg, occasionally exceeding 50 mmHg [55, 83]. Notably, many cases of glaucoma occurring in patients with FUS are attributed to the use of glucocorticoids. Due to the long-standing KPs and anterior chamber flare, many patients use glucocorticoid eye drops long-term and may even undergo repeated subconjunctival injections of glucocorticoids or receive prolonged systemic therapy, which makes them susceptible to glucocorticoid glaucoma. Some reports suggest that many patients not diagnosed with FUS do not necessarily require long-term administration of topical or systemic corticosteroid therapy, which may lead to cataracts and severe glaucoma [84-86].

5. Diagnosis

The diagnosis of FUS is primarily based on clinical manifestations, and there are currently no internationally agreed diagnostic criteria due to the variations in clinical presentations among patients from different ethnic groups. Although FUS has typical clinical features such as diffuse iris depigmentation, characteristic KPs, mild anterior chamber inflammation, and the absence of posterior synechiae, its insidious onset makes accurate diagnosis challenging, often leading to misdiagnosis. Kimura et al. [77] proposed a typical triad (heterochromia, cyclitis, and cataract) based on clinical data from 750 American patients with uveitis (including 23 patients with FUS). Based on observations from 51 Dutch patients with FUS, La Hey et al. [3] modified the description provided by Kimura et al. and proposed a comprehensive set of diagnostic criteria. They classified the clinical manifestations of FUS into essential and associated signs, proposing that a definitive diagnosis requires the patient to present all essential signs and at least two associated signs (Table 1). The Standardization of Uveitis Nomenclature (SUN) Working Group [87] developed classification criteria for FUS using machine learning based on data from 1083 patients with anterior uveitis (including 146 cases of FUS). The aforementioned criteria, especially those proposed by La Hey, have been widely used in clinical practice for a long time. In recent years, Yang et al. [65] introduced a set of diagnostic criteria for FUS specifically tailored to the Chinese population based on an extensive dataset of Chinese patients, demonstrating high sensitivity and specificity (Table 1).

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<th>Essential findings*</th>
<th>Associated findings**</th>
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<td>Absence of acute symptoms (severe redness, pain and photophobia)</td>
<td>Unilaterality of the uveitis</td>
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<tr>
<td>Characteristic KPs and/or minimal cells and flare in the aqueous (1+ or 2+)</td>
<td>Heterochromia</td>
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<td>Diffuse iris stromal atrophy</td>
<td>IPE atrophy</td>
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<td>Absence of synechiae</td>
<td>Subcapsular cataract</td>
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<td>Elevated IOP</td>
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<td>Vitreous opacities</td>
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<td>Chorioretinal lesions</td>
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Abbreviation: KPs, keratic precipitates; IPE, iris posterior pigment epithelium; IOP, intraocular pressure

*All essential findings must be present.
**At least two associated findings must be present.
6. Treatment

Many patients with mild iridocyclitis do not require specific treatment, but regular follow-up is necessary to monitor for elevated IOP and cataract development. If there are many anterior chamber cells and pronounced anterior chamber flare, topical glucocorticoid eye drops can be used for treatment. However, excessive frequency of administration and prolonged treatment duration are not recommended. Subconjunctival glucocorticoid injections or systemic administration are also not recommended [5, 66, 88, 89]. Additionally, the topical application of non-steroidal anti-inflammatory drugs (NSAIDs) can also reduce inflammatory responses.

Intercurrent cataracts can be treated with phacoemulsification and intraocular lens implantation according to the patient's needs. Anterior chamber cells, anterior chamber flare, KPs, or iris nodules are not contraindications for surgery. Most patients with FUS are reported to achieve good visual outcomes after cataract surgery [88, 90-95]. Glucocorticoid and non-steroidal anti-inflammatory eye drops should be administered before and after cataract surgery to alleviate the postoperative inflammatory response in the anterior chamber.

Secondary glaucoma can generally be effectively controlled with medication. If the patient's IOP remains uncontrolled and refractory glaucoma occurs, different types of glaucoma surgery can be considered depending on the patient's specific condition [96-99].

7. Conclusion

Fuchs uveitis syndrome is a chronic unilateral non-granulomatous uveitis. Since the first description of FUS, various theories have been proposed to explain its etiology and pathogenesis, including infectious, sympathetic, genetic, and immunological theories. The onset and progression of FUS are currently believed to result from the combined effects of multiple pathogenic mechanisms rather than a single etiology. The clinical manifestations mainly include insidious onset, unilateral involvement, absence of symptoms and signs of acute iridocyclitis, mild anterior chamber inflammation, stellate or medium-sized KPs distributed diffusely or centrally, diffuse iris depigmentation and atrophy, possible Koeppie nodules, the absence of posterior synechiae, and the occasional occurrence of vitreous opacities and peripheral chorioretinal lesions. Common complications include cataracts and glaucoma. Many patients with FUS do not require specific treatment, but regular follow-up is necessary to monitor for elevated IOP and cataract development. Most patients with concurrent cataracts can undergo cataract extraction and intraocular lens implantation, yielding favorable surgical outcomes. Secondary glaucoma in many patients is associated with the long-term use of glucocorticoids. Therefore, glucocorticoids should be used cautiously, with topical eye drops administered for short-term treatment only when there is severe anterior chamber inflammation. Secondary glaucoma can generally be effectively controlled with medication, and surgical treatment can be considered for refractory glaucoma cases. Most patients have a good visual prognosis, which mainly depends on the outcome of cataract surgery and glaucoma control. Refractory glaucoma may lead to vision loss. We believe that with the advancement of medicine, there will be further understanding or breakthroughs regarding the nature of FUS.

References


