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Alexandra Abdala-Figuerola, Rosalba Y. Bobadilla Mayorquín & Alejandro Lichtinger

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REVIEW

Challenges in the diagnosis of Fuchs uveitis syndrome in children

Alexandra Abdala-Figuerola [a], Rosalba Y. Bobadilla Mayorquín[b] and Alejandro Lichtinger[a]

[a]Department of Cornea and Refractive Surgery, Instituto de Oftalmologia 'Conde de Valenciana,' Mexico City, Mexico; [b]Department Uvea, Instituto de Oftalmologia 'Conde de Valenciana,' Mexico City, Mexico

ABSTRACT

Introduction: Fuchs uveitis syndrome in children is a rare entity and establishing the diagnosis can be challenging. A better understanding of the disease with a detailed examination and complementary tests should be performed to reach the diagnosis.

Areas covered: The objective of this review is to describe the clinical manifestations, epidemiology and pathogenic theories proposed for Fuchs uveitis syndrome in children. We propose an algorithm that includes personal history, clinical features and ancillary tests to establish the diagnosis.

Expert commentary: The prevalence of FUS in children is low, mostly due to the lack of suspicion and a delay in the diagnosis. In order to have a prompt diagnosis, ophthalmologists should be able to identity and distinguish this entity. Although the diagnosis is still based on clinical findings, complimentary ancillary tests may be helpful.

1. Introduction

Pediatric uveitis is an uncommon condition that represents only 5–10% of all cases of uveitis [1]. However, BenEzra et al. reported a much higher incidence of 33.1% in patients under 18 years old in a series of 821 cases, probably the highest incidence ever reported in the literature [2].

Uveitis in the pediatric population has a very diverse etiology that differs from the adult population, thus requiring special attention to prevent severe visual impairment [3].

The majority of uveitis cases in children is idiopathic, bilateral, and chronic in nature with a female predilection [2,4]. The most frequent etiology in childhood is uveitis associated with systemic diseases, specifically juvenile idiopathic arthritis (JIA) [5,6] and pars planitis [7]. Other causes include autoimmune and infectious diseases, such as Behcet disease, sarcoidosis, Vogt–Koyanagi–Harada syndrome, sympathetic ophthalmia, toxocariasis, toxoplasmosis, and tuberculosis, although their incidence varies among studies [2,3,5,8]. Pediatric uveitis has a high complication rate, with significant visual loss in 25–33% of all cases [8], mostly due to cystoid macular edema followed by cataract and band keratopathy. Visual impairment can also be the result of macular chorioretinal scars, hypotony, and secondary glaucoma [3,7,8]; hence, a prompt diagnosis and treatment are crucial to prevent further complications.

Fuchs uveitis syndrome (FUS), also called Fuchs heterochromic iridocyclitis, Fuchs hetrerochromic cyclitis, or Fuchs herochromic uveitis [9], was first described by Ernst Fuchs in 1906, after analyzing a series of 38 young patients with chronic ocular inflammation, iris heterochromia, and cataract [10].

FUS is an uncommon cause of chronic intermediate, non-granulomatous, unilateral uveitis in children, frequently undiagnosed or misdiagnosed over the first decades of life [11]. It is challenging for physicians to identify FUS at an early age, often due to the subtle changes present at this stage [12], causing a delay on the diagnosis of 3–3.7 years on average after their first examination [11,13,14].

2. Epidemiology

The prevalence of uveitis in children is 30/100,000 [4], with an annual incidence of 4.3–6.9 per 100,000 [4]. Although it can be assumed that the numbers are probably higher because children are taken less frequently to the ophthalmologist.

The etiology and frequency vary widely among studies depending on age and geographic location. The three principal causes of uveitis in children over a 10-year period in a Swiss study were idiopathic (34.2%), associated with JIA (22.8%), and toxoplasmosis (15.2%) [6], which differs slightly from a similar study performed in the United States, in which the third cause was pars planitis (17.1%) instead of toxoplasmosis [15].

FUS has an incidence rate of 0.2/100,000 [16], and it is responsible for 0.6–10% of all uveitis cases in the general population [17,18] and 8.5% in children [19].

There is no gender predilection in FUS, and the age at diagnosis is usually between the third to fourth decades of life [11,20–22]. Tappeiner et al. reported that the average age for the diagnosis of uveitis in their series was 12 ± 4.2 years, while the diagnosis of FUS was delayed until age 22.7 ± 10.7 years [12].

CONTACT Alejandro Lichtinger ✉ Drlichtinger@yahoo.com 🖂 Department of Cornea and Refractive Surgery, Instituto de Oftalmologia 'Conde de Valenciana,' Chimalpopoca 14, Cuauhtémoc, 06800 Mexico City, Mexico

3. Clinical features

At the initial stages of FUS, patients are asymptomatic. The most common complaints are decreased visual acuity and floaters. Exceptionally, ocular or periocular pain, photophobia, and red eye have been reported, usually associated with complications of FUS [11,12,14,20].

The typical presentation in FUS is a mild chronic intraocular inflammation with unilateral involvement reported in 90% of the cases [23], while bilateral involvement has been described in 5.2–10% [11,22].

The classic clinical findings are small- to medium-sized nonpigmented, diffusely distributed, and non-confluent stellate keratic precipitates (KPs) and generalized iris atrophy or moth-eaten appearance with iris heterochromia. Anterior chamber (AC) activity (presence of cells) is usually mild to moderate and can be accompanied by anterior vitreous haze [11–13,23]. It is common to observe either Koeppe or Busacca nodules.

Absence of posterior synechiae is a typical finding of FUS, and although they do not develop in spite of chronic intraocular inflammation [8,11,24–26], some authors report that they can develop after surgical procedures [25].

The hallmark of the disease is iris heterochromia (77%) (with hypochromia of the affected eye) [13,14], which can be absent or be undetectable in highly pigmented eyes [14,23,25]. On the other hand, inverse heterochromia is only observed in people with light-colored iris, due to a progressive atrophy of the anterior stoma that allows the visualization of the pigmented epithelium, thus appearing darker in the affected area [26]. Iris atrophy is more frequently generalized; however, when it develops in a localized pattern, it is present either on the iris periphery or adjacent to the pupil [11]. When FUS is bilateral, changes in the iris color can be difficult to detect; therefore, some authors recommend to photograph and compare with specific computerized software searching for subtle changes in color [25].

Iris nodules are a common clinical finding that can be present at the onset of FUS; Jones reported them in 20% of cases [25]. Out of the three types of iris nodules, this entity can present with two of them: Koeppe which are localized on the pupillary margin and more frequently seen in FUS than Busacca nodules, which are found on the iris surface [22,23,25]. Russell bodies, which are plasma cells filled with immunoglobulins (Igs) are seen clinically as small glistening deposits on the anterior surface of the iris and reported in only 1% to 2% of patients [22].

KPs are an extremely common feature of FUS; different types have been described, but the stellate pattern distributed all over the corneal endothelium is the most common. Although FUS is not a granulomatous type of anterior uveitis, mutton-fat KPs have been reported [23,25,26]. A study by Tappeiner et al., involving 23 children with unilateral FUS, presented fine KPs in 76.9% of cases, stellate KPs in 34.6%, and mutton-fat KPs in 73.1% [12]. The pattern and distribution of KPs can vary during the course of the disease or after cataract surgery [12].

Patients with FUS mostly have minimal or no AC activity, with reports in which more than half of the patients had no AC reaction at all [11] or all of them had a maximal 1+ (less than 15 cells) during follow-up [12].

Vitreous involvement can be a common finding [14,26] with opacities present in 66.6% of cases reported by Jones et al. [11], while Tappeiner et al. [12] described anterior vitreous cells in 92.3% and vitreous haze ≥1+ in 61.5% of cases (Standardization of Uveitis Nomenclature system classification) [27].

Other less-frequent findings are anisocoria and neovascularization of the iris and iridocorneal angle, which can develop later in the disease [11,22,25,26]. Presence of iris neovascularization has been a subject of debate, and some authors state that there is no such finding; instead they propose that the observed vessels are the minor arterial circle of the iris that is visualized due to stromal atrophy; however, some authors believe in true neovascularization of the iris [25]. On the other hand, neovascularization of the iridocorneal angle when present can lead to AC bleeding, known as the Amsler–Verry sign [25], which is characterized by a filiform hemorrhage that can develop into hyphema in 6–22% of patients. This sign can appear after paracentesis, gonioscopy, minor trauma, pharmacological mydriasis, or even spontaneously [28].

Anisocoria can develop as a result of pupil dilator and/or sphincter muscles atrophy [20], secondary to nerve axon loss, cellular infiltration, and hyalinization of blood vessel walls [25].

4. Pathogenesis

Although the etiology of FUS is unknown, different theories exist that support different pathogenic mechanisms. Ernst Fuchs proposed that FUS was congenital or it was developed in the first years of life from an unknown origin, which altered the development of uveal pigmentation, thus affecting the iris configuration. This theory was later rejected since iris heterochromia is not always present either at birth or during the course of the disease [29].

FUS has been associated with toxoplasmosis [10,25,29,30], sarcoidosis [31], toxocariasis [32,33], herpes simplex virus [34], Horner's syndrome [35], Usher's syndrome [36], cytomegalovirus (CMV) [37], rubella infection, and vaccines among others [38,39], which reflect the uncertainty of the pathogenesis.

4.1 Infectious theory

Toxoplasmosis and toxocariasis have been associated with FUS. The prevalence of chorioretinal scars related to toxoplasmosis in FUS patients varies widely in the literature from 7% to 65% [10,25,26,29], and levels of IgG against *Toxocara canis* have been detected by serology analysis (enzyme-linked immunosorbent assay) [32] in these patients; herpes simplex virus and CMV have been detected in aqueous humor and identified by polymerase chain reaction (PCR) in some studies [34,37]. Meanwhile, an association with rubella virus has become relevant in FUS over the past years; Quentin and Reiber reported a series of patients with confirmed diagnosis of FUS in which rubella antibodies were detected in aqueous humor in all of them [38]. Another study that supports this theory performed by Birnbaum et al. showed a significant decrease of FUS in patients that received rubella vaccine according to the USA vaccination program [39].

4.2 Sympathetic theory

A lesion on the sympathetic nerve system may be followed by iris heterochromia, which interferes with the normal uveal pigmentation process [29]. However, Loewenfeld and Thompson later rejected this theory since they found Horner's syndrome in only 1–4% of cases in a series of 1746 patients with FUS; its incidence was too low to have a direct association and did not explain the chronic intraocular inflammation [40].

4.3 Embryological theory

An abnormality of the neural crest causes a deficient migration of melanocytes [41,42]. This theory cannot explain the other clinical findings present in FUS besides iris heterochromia.

4.4 Genetic theory

This hypothesis of genetic association began with early observations of different family members with FUS. One of the first cases reported by Makley in 1956 was of monozygotic twins who both had FUS [43]. Later on, Loewenfeld and Thompson found only five families with two members having FUS in a series of 1500 cases [40]. The frequency of familiar cases is very low and does not show a Mendelian inheritance pattern; therefore, there are not enough data to support this theory [44].

4.5 Immunological theory

There have been reports of intraocular inflammatory activity associated with cytokine expression (interleukin [IL]-4, IL-10, IL-12, and interferon) and cellular activity (CD3, CD4, and CD8) in the AC, leading to a loss of immunologic privilege that may translate into the development of autoantibodies directed against uveal tissue [29,45].

4.6 Vascular theory

This was proposed based on the Amsler–Verry sign and the neovascularization of the iridocorneal angle, but it was rapidly excluded due to the absence of systemic manifestations of vascular disease [23,29].

5. Diagnosis

Establishing FUS diagnosis in children is challenging, mostly due to the lack of symptoms and subtle initial signs. However, a correct diagnosis is still based on classical clinical findings rather than laboratory studies [12,22].

In 1906, FUS diagnosis was based on the criteria proposed by Ernst Fuchs [10], which were later modified by Franceschetti in 1955 to include additional features [46].

As in every uveitis case, an algorithm approach is desirable. We suggest an algorithm to study patients suspected of having FUS (Figure 1), which is based on an anterior uveitis approach for children [5,7,8,12,20,21,26,34,38].

The first step of the proposed algorithm is a thorough personal history, since 60–90% of the diagnosis is based on a detailed medical background [47,48], followed by physical and ophthalmic examination and laboratory tests tailored by clinical findings.

The personal history must include nonpathologic and pathologic records, age, gender, race, socioeconomic status, recent travels, vaccination, and previous disorders, giving specific attention to autoimmune and infectious diseases [49].

An organized and systematic slit-lamp examination is recommended to avoid missing any specific signs that may lead to the diagnosis. The classical finding is iris heterochromia, but its absence should not rule out the diagnosis. Other reported ocular manifestations such as KPs, iris atrophy, iris nodules, AC reaction, and vitreous opacities may be subtle and difficult to observe.

A complementary guideline based on statistical probability developed by Beneyto et al., using the Bayesian method, in a Spaniard population, concluded that the combination of iris nodules with one of the following: cataract, glaucoma, or vitritis had a high probability (more than 50%) of FUS. However, the Bayesian method lacks reproducibility among different populations because it would require the specific incidence and specific data of each population in order to determine the probability of having FUS [13].

If clinical findings are not conclusive, additional diagnostic tools can be of great benefit. For example, iris changes in dark color iris or bilateral cases can be subtle and difficult to visualize at the beginning of the disease; therefore, anterior segment optical coherence tomography (AS-OCT) can be helpful in detecting this changes. Other features that AS-OCT evaluates are iris thickness, AC depth, and iridocorneal angle measurements, parameters that have been studied in FUS patients. Basarir et al. evaluated unilateral cases of FUS and found a deeper AC, a larger angle in the temporal quadrant, a thinner iris, and a decreased convexity or flattening of the iris in the affected eye compared to the healthy one [20]. Another available tool is laser flare photometry that is a noninvasive quantitative method to determine AC activity [50].

Angiography is an additional diagnostic tool to evaluate iris vessels, which can detect neovascularization of the iris and AC angle in cases of chronic uveitis. Laatikainen et al. described the leakage of the peripupillary capillaries and neovascularization of the angle; however, this findings are not specific to FUS and can be present in other entities with chronic inflammation [51]; these observations were confirmed by Verma and Arora, who were the first to describe hyperfluorescent areas in the nasal iris accompanied by peripupillary leakage in a patient with dark-colored iris, concluding that there is a vascular insult in FUS patients [21].

Confocal microscopy is a rarely used ancillary test that can be used to study KP's configuration in vivo as was shown by Labbé et al. [52].

Ciliary body involvement is not considered a classical finding in FUS; however, a large series described by Yang et al. reported a 75% incidence of exudates adjacent to the ciliary body that were only detected by high-resolution ultrabiomicroscopy [53].

Other authors have found late staining of the optic nerve in 22–66% of patients with fluorescein angiography [22,53].

In order to rule out infectious or autoimmune entities, an AC tap with aqueous humor analysis with PCR or Ig analysis can be of help [34,37,38].
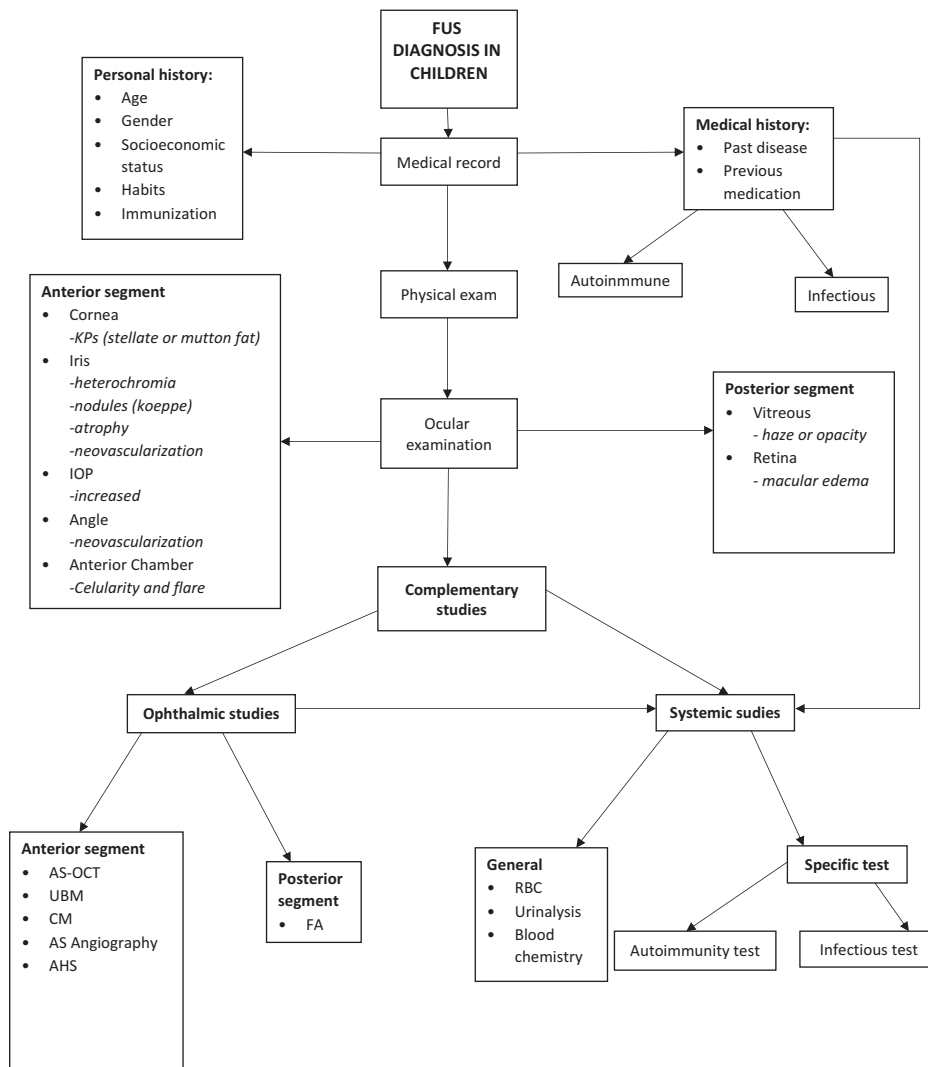
Figure 1. IOP: Intraocular pressure, AS-OC:T Anterior Segment Optic Coherence Tomography, UBM: ultrabiomicorscopy, CM:Confocal Microscopy, FA: Fluorescein Angiography, RBC: Red blood cell count, AHS: Aqueous Humor Sample.

All these ancillary tests have proven useful in the study of FUS patients; however, it is important to mention that none of them have been used extensively in children.

FUS diagnosis is based on clinical findings; nevertheless, it is important to rule out other causes of infectious and noninfectious uveitis. Urinalysis, blood chemistry, and a complete blood count are the basic tests that should be requested; while additional specific tests such as chest x-ray, angiotensin-converting enzyme assay, erythrocyte sedimentation rate, anti-DNA antibodies, antinuclear antibodies, anti-streptolysin O, erythrocyte sedimentation rate, tuberculin test, C-reactive protein, or syphilis serology should be performed when it is clinically suggested.

6. Complications and treatment

It is rare to observe complications of FUS in children due to its low-grade chronic intraocular inflammation; complications are more commonly seen in young adults.

Tappeiner et al. reported in their pediatric series an incidence of cataract formation of 73.1%, while ocular hypertension and glaucomatous optic neuropathy were present in 11.5% and 7.7% of patients 10 years after the initial diagnosis of uveitis [12]. Chronic inflammation leads to complications developing years after the beginning of the disease; therefore, in most cases, treatment is not required until complications appear (cataract and glaucoma).

Ocular hypotensors are used to prevent optic nerve damage when intraocular pressure is high. Phacoemulsification with intraocular lens implantation is recommended when a cataract is causing visual impairment [54,55].

7. Expert commentary

FUS is rarely diagnosed in children; therefore, we assume the prevalence is higher due to the difficulty diagnosing this entity. Furthermore, the lack of suspicion among many ophthalmologist delays the diagnosis until complications are already present.

Regarding the etiology, many theories have been proposed; however, we believe the cause may be secondary to a virus, parasite, or even an unidentified microorganism that promotes low intraocular chronic inflammation in susceptible patients that

may have a genetic or immunological predisposition to develop this inflammatory response, a type of two-hit hypothesis.

Clinical findings are mostly present in the AC; however, changes in the posterior segment are also observed; hence, we recommend a thorough slit-lamp examination, which includes a dilated fundus examination. Ancillary tests may be helpful to further support the diagnosis.

In spite of the challenging diagnosis in children, we believe that a complete history with diligent ophthalmic examination and complementary studies should give the clinician the evidence needed to reach the diagnosis.

8. Five-year section

Since FUS is a rare entity, it is difficult to imagine big changes in the near future regarding its diagnosis or management. The etiology of FUS is still unknown; we may have a better understanding of the disease in a few years by gathering data from newer diagnostic tools such as Ig analysis and PCR, being able to identify a common pathway where the different proposed insults (infectious, autoimmune, and genetic) converge and lead to this stereotypical immune response.

Key issues

- FUS is under diagnosed in children.
- Not all cases will present or develop classic iris heterochromia.
- There is no specific etiology that explains all the clinical findings.
- FUS presents with minimal and subtle manifestations in children and is many times diagnosed once complications appear.
- The clinical features are still the cornerstone for diagnosis.
- An Infectious etiology has been gaining support.
- Complication usually appear later in life.
- Posterior segment involvement can be present and should be considered.

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Declaration of interest

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ORCID

Alexandra Abdala-Figuerola http://orcid.org/0000-0001-9004-0767

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