Predictive Factors of Intraocular Pressure Level Evolution Over Time and Glaucoma Severity in Fuchs' Heterochromic Iridocyclitis

Sara Touhami,[1] Antoine Vanier,[2] Alessandra Rosati,[3] Magdalena Bojanova,[4] Bouchra Benromdhane,[1] Phuc Lehoang,[1] Flore Rozenberg,[4] and Bahram Bodaghi[1]

[1]Ophthalmology Department, Reference Center in Rare Diseases, Département Hospitalo Universitaire Sight Restore, Hôpital Pitié Salpêtrière, University Paris VI, Paris, France
[2]Inserm, University Bretagne Loire, University of Nantes, University of Tours, Unité Mixte de Recherche, U1246 Sciences Philosophie Histoire, Nantes, France
[3]Ophthalmology Unit, Dipartimento di Neuroscienze Salute Mentale e Organi di Senso, S. Andrea Hospital, Faculty of Medicine and Psychology, Sapienza University, Rome, Italy
[4]Virology Department, Hôpital Cochin, Paris Descartes University, Paris, France

Correspondence: Sara Touhami, Ophthalmology Department, Reference Center in Rare Diseases, Département Hospitalo Universitaire Sight Restore, Hopital Pitié Salpêtrière, University Paris VI, 47-83 Boulevard de l'Hôpital, 75013, Paris 75013, France; saratouhami@gmail.com.

ST and AV contributed equally to the work presented here and should therefore be regarded as equivalent authors.

Submitted: April 19, 2018
Accepted: April 21, 2019

Citation: Touhami S, Vanier A, Rosati A, et al. Predictive factors of intraocular pressure level evolution over time and glaucoma severity in Fuchs' heterochromic iridocyclitis. *Invest Ophthalmol Vis Sci*. 2019;60:2399–2405. https://doi.org/10.1167/iovs.18-24597

Purpose. To investigate the clinical and virologic-associated and predictive factors of intraocular pressure (IOP) evolution over time and its severity in Fuchs' heterochromic iridocyclitis (FHC).

Methods. Consecutive patients with both clinical FHC and intraocular synthesis of rubella virus (RV)-specific antibodies were included in this study. Specific ocular production of RV antibodies was confirmed using the quotient of serum/aqueous humor ratio of RV IgGs (Crv) and control antiviral IgGs (Cctl), using quantitative serology methods. Epidemiologic, clinical, biological, and virologic data at referral were collected and correlated with IOP values over time, occurrence, and severity of glaucoma.

Results. Sixty-eight eyes of 68 patients were included. Mean age at diagnosis was 40.7 ± 11.1 years. Mean follow-up was 4.3 ± 4.3 years. Mean baseline Crv and Cctl values were 12.34 ± 14.67 and 216.70 ± 98.4, respectively. Mean baseline IOP was 17.2 ± 7.2 mm Hg (range, 9–40) and 15.6 ± 5.6 (range, 3–30) 5 years after referral. The predictive factors for pejorative IOP evolution over time and glaucoma severity were male sex ($P = 0.03$) and decreased Crv ($P = 0.04$) and presence of iris nodules ($P < 0.001$) and decreased Cctl ($P = 0.02$), respectively. Diagnostic delay was associated with increased likelihood of undergoing glaucoma surgery ($P = 0.02$).

Conclusions. Time to diagnosis, male sex, presence of iris nodules at baseline, and decreased Crv and Cctl ratios were associated with increased likelihood of pejorative IOP evolution over time. Given the aggressiveness of glaucoma in FHC, these results provide interesting insight into what category of patients should need the closest screening.

Keywords: Fuchs' heterochromic iridocyclitis, uveitis, ocular hypertension, glaucoma, rubella, flare, prognosis, predictive factors

Fuchs' syndrome (FHC), also referred to as Fuchs' heterochromic iridocyclitis, is a rare form of nongranulomatous uveitis that accounts for 2% to 3% of uveitis cases.[1–3] First described in the early 1900s,[4] this syndrome affects both sexes[5] in their third or fourth decade and is defined by the presence of typical features including stellate keratic precipitates, iris heterochromia, low-grade iridocyclitis, cataract, and absence of posterior synechiae.[6–9] Although clinical diagnosis can be straightforward in the presence of these characteristics, less well-recognized or frequently overlooked signs can be misleading. These include bilateral presentation, chorioretinal scars, and presence of vitreous opacities, for instance. Similarly, diagnosis of FHC in dark-eyes irises can be challenging because heterochromia is rarely obvious.[10] Overall, all these aforementioned situations explain why FHC is still one of the most under- or misdiagnosed entities.[11,12] A study by Brancaleoni et al. reported a diagnostic delay of 3.67 ± 4.34 years in FHC (Brancaleoni A, et al. *IOVS* 2003;44:ARVO E-Abstract-2381), and others reported delays of up to 26 years.[13] This can have disastrous consequences, given that disease progression can lead to glaucoma in 20% to 60% of cases.[3,9,11]

Many different etiologies have been proposed over the past century,[13–17] and the latest theory strongly supports the role of the rubella virus.[15,17,18] Identification of rubella antibodies in the aqueous humor of FHC-suspect patients has in fact become an important confirmatory tool, especially in atypical cases.[15]

The purpose of this study was to investigate the clinical and virologic-associated or predictive factors of intraocular pressure (IOP) evolution over time and glaucoma severity in FHC patients in order to provide better follow-up recommendations

for the patients that are at higher risk of developing ocular hypertension over the course of FHC disease.

Methods

Institutional review board approvals for retrospective chart reviews were obtained commensurate with the respective institutional requirements prior to the beginning of the study. Described research was approved by the Ethics Committee of the French Society of Ophthalmology and adhered to the tenets of the Declaration of Helsinki. Fully informed consent was obtained from all patients. In the ophthalmology department of the Pitié-salpétrière hospital (Paris, France), consecutive patients with both clinical FHC and rubella-specific intraocular antibody synthesis were identified in the database and included in this study. Diagnosis of FHC was based upon clinical grounds[3] and after ruling out the main differential diagnoses. Investigations including clinical examination by an internal medicine specialist, Quantiferon Gold/Mantoux reaction, TPHA-VDRL, serum antibodies against toxoplasmosis, cytomegalovirus (CMV), herpes virus 1 and 2 (HSV), and varicella zoster virus (VZV), as well as chest X-ray, serum angiotensin-converting enzyme levels, and other targeted ancillary tests were performed when deemed necessary.

Diagnosis of Ocular Production of Rubella Antibodies

Paired aqueous humor (AH) and serum samples of all FHC suspected patients were collected and tested for antibody production against rubella virus (RV) as previously described.[19] Briefly, titers of specific antibodies (anti-RV IgGs and anti-HSV, anti-VZV, and anti-CMV IgGs as control antibodies) were determined via the quantitative Enzygnost ELISA technique (Siemens Healthcare GmbH, Erlangen, Germany) using the α-method, by testing three serial dilutions for serum (1/231, 1/1155, 1/2310) and ocular fluids (1/23, 1/46, 1/92) in the same analytical run.[19] These control IgGs were chosen because of the high seroprevalence of herpes viruses in human populations and because of their implication in human uveitis. More specifically, the choice of the control antibody depended on the patient's immunization status. In other words, CMV titers were used as control antibodies in all patients except those with absence of anti-CMV IgGs in the blood. In such cases, either VZV (95% of the population is immunized against VZV) or HSV titers were used. Titers were taken into account if they corresponded to optical density (OD) values in the intervals $0.195 < \text{OD} < 2.195$, and if the r^2 linearity values were below 0.9. Serum/AH ratios of RV IgGs (Crv) and either CMV, VZV, or HSV as control IgGs (Cctl) were then calculated. For undetectable AH control IgGs, the ratio was assigned the value (300) of the physiological blood–aqueous barrier. The C' quotient of Cctl and Crv ratios (C' = Cctl/Crv) differentiates passive serum–AH diffusion or nonspecific AH IgG production from specific antibody production. Specific ocular antibody production against RV was previously defined by $\text{Crv} < 80$ and $\text{C}' \geq 3$.[19]

Data Collection and Outcome Measures

For each patient, demographic data and medical and treatment history were recorded. Clinical parameters were collected at baseline (i.e., the day on which an anterior chamber tap was performed at first presentation to our clinic), during the follow-up (whenever available) and at the last visit and included the following: best-corrected visual acuity (BCVA) (decimal scale), analysis of anterior chamber and fundus features, anterior chamber cell number (on a scale of 0 to 4+), and vitreous inflammatory reaction according to the SUN criteria.[6] Ancillary parameters included quantification of anterior segment flare (Laser cell flaremeter analyser; Kowa FC 1000, Tokyo, Japan) and AH and blood serum analyses. Disease duration was defined as the difference between age at FHC diagnosis and age at the onset of the first symptoms.

The primary outcome measure was IOP, and two secondary outcomes (use of glaucoma medications and need for glaucoma surgery) were analyzed to further ascertain the severity and/or clinical relevance of the pressure rise observed in affected patients. IOP was collected at baseline (at the time of diagnosis and anterior chamber tap) and over time depending on the available follow-ups for each patient since the referral. All these outcomes were collected at these possible time points after diagnosis: month 3, 6, 12, 24, 36, 48, 60, 120, 180, and 240.

Epidemiologic, clinical, biological, and virologic data at baseline were considered as associated variables or potential predictors of the aforementioned outcomes.

Statistical Analyses

Baseline statistics were described using relevant position and dispersion parameters.

Main Outcome: Factors Associated With, or Predicting, the Evolution of IOP Over Time. The model included the following variables: sex, age at first symptoms, disease duration, presence of keratic precipitates, iris nodules, flare values, Crv, and Cctl.

IOP was modeled using a linear mixed model with one random effect (random intercept for each patient), a fixed time effect, relevant baseline variables as fixed effects, and relevant first-order interactions as fixed effects. To select the most parsimonious model including only potentially interesting effects, models with random intercept, time effect, one baseline variable, and its interaction with time were first fitted separately ("univariate" analyses). At this stage, the threshold to select a potentially relevant baseline variable was a P value under 0.10 for its main effect or interaction with time. Then, a first multivariate model with random intercept, time effect, selected baseline variables, and first-order interactions was fitted. A backward selection procedure was applied in order to remove interactions and main effect terms that did not contribute to explaining the IOP. The final selected model was based on iterative likelihood ratio test (LRT): Terms were removed until a nonsignificant LRT was obtained. Type 1 error rate for this multivariate procedure of selection was 5%.

Secondary Outcomes: Factors Associated With, or Predicting, the Evolution of the Number of Antiglaucoma Medications and Occurrence of Glaucoma Surgery Over Time. The number of antiglaucoma medications over time was modeled using a generalized linear mixed model with a Poisson link function. The model included a random intercept for each patient, a fixed time effect, relevant baseline variables as fixed effects, and relevant first-order interactions as fixed effects. Model selection procedure was as described in the previous paragraph for IOP modeling over time.

The probability of not undergoing glaucoma surgery over time was modeled using a Kaplan-Meier estimate curve. Predictive factors of glaucoma surgery at baseline were tested one by one using a univariate Cox model. The relevant predictors with a P value under 0.10 were retained. Finally, a

Table 1. Baseline Demographics and Clinical Characteristics of FHC Patients

Characteristics	Estimate*
Demographic characteristics and medical history	
Age at diagnosis, y	40.7 ± 11.1 [21–68]
Age at first symptoms, y	35.9 ± 12.6 [10–66]
Disease duration	5.2 ± 7.7 [0.01–32.6]
Follow-up, y	4.3 ± 4.3 [0.02–20]
Females	40 (58.8)
Ocular symptoms	
Blurry vision	51 (75.0)
Floaters	14 (20.6)
Clinical findings	
Bilateral presentation	3 (4.4)
BCVA, decimals	0.6 ± 0.4 [0–1]
Intraocular pressure, mm Hg	17.2 ± 7.2 [9–40]
Keratic precipitates	65 (95.6)
Stellate, diffuse	49 (72.1)
Iris findings	
Heterochromia	21 (30.9)
Nodules	27 (39.7)
Pigment epithelium atrophy	31 (45.6)
Anterior chamber cells (+)†	0.5 ± 0.5 [0–2]
Vitreous inflammatory reactions (+)†	1.1 ± 0.9 [0–4]
Ancillary parameters	
Anterior chamber flare, ph/ms	16.2 ± 19.0 [3–85]
Crv‡	12.34 ± 14.67 [1–80]
Cctl‡	216.70 ± 98.4 [10–300]
C' ratio‡	45.74 ± 58.65 [3.6–300]

* Estimates are mean ± standard deviation [range] for quantitative variables and number (%) for qualitative variables. Visual acuity was measured on a decimal scale.

† Anterior chamber cells and vitreous inflammatory reactions were clinically determined based on the SUN criteria.[6]

‡ Crv, Cctl, and C' ratios were calculated as defined by Bojanova et al.[19]

multivariate Cox model was fitted with a type 1 error rate fixed at 5%.

All analyses were performed using R3.5.1, 2018 (R Development Core Team, Vienna, Austria).

Results

Demographic Characteristics (Table 1)

Sixty-eight eyes of 68 consecutive patients that were clinically suspected to have FHC and had a positive anti-RV serology and a positive antirubella antibody synthesis in the AH were included in this study. Mean age at diagnosis was 40.7 ± 11.1 years (range, 21–68). Mean disease duration was 5.2 ± 7.7 years (range, 0.01–32.6). Mean follow-up was 4.3 ± 4.3 years (range, 0.02–20).

Fuchs Diagnosis (Table 1)

Clinical diagnosis of FHC was made at referral and confirmed by intraocular antirubella antibody production as defined by Crv < 80 and C' ≥ 3. Mean values of Crv and Cctl ratios were, respectively, 12.34 ± 14.67 and 216.70 ± 98.4.

Ophthalmologic Findings (Table 1)

Symptoms: Percentage of patients reporting visual symptoms was 92.6% (75% reported intermittent blurry vision and 21% symptomatic floaters).

Table 2. Predictive Factors of IOP Over Time

Linear Mixed Model Test of Effects			
Variable	**Estimate, β**	**Standard Error**	***P***
Multivariate final model			
Intercept	16.954	1.12	<0.001
Time	0.060	0.18	0.75
Sex, female	−2.322	1.05	**0.03**
Disease duration	0.132	0.06	**0.04**
Interaction between time and Crv ratio	−0.032	0.02	**0.04**
Test of main effect one by one			
Time	−0.197	0.13	0.16
Sex, female	−1.969	0.98	**0.04**
Age at onset	−0.011	0.04	0.76
Disease duration	0.144	0.06	**0.03**
Iris nodules	−1.310	1.01	0.20
AH flare	0.067	0.07	0.35
Crv ratio	−0.010	0.03	0.77
Cctl ratio	−0.006	0.01	0.27
Test of each interaction with time one by one			
Age at onset	−0.002	0.01	0.77
Disease duration	−0.026	0.02	0.12
Iris nodules	0.378	0.27	0.16
AH flare	−0.001	0.02	0.99
Crv ratio	−0.029	0.01	0.04
Cctl ratio	0.001	0.00	0.69

Ocular signs: Disease was bilateral in three cases. The mean BCVA (decimal scale) was 0.6 ± 0.4 at baseline (N = 68) and 0.7 ± 0.3 at 5 years after referral (N = 19). At baseline, keratic precipitates were identified in 65 cases. They were stellate and diffusely distributed in 49 cases (75.4%) while the remainder were mostly inferior. The mean cell number in the anterior chamber was 0.5 ± 0.5 (range, 0–2) based on the SUN criteria,[6] the mean vitreous inflammatory reaction was 1.1 ± 0.9 (range, 0–4), and the mean automated flare value was 16.2 ± 19.0 photons/milliseconds (ph/ms) (range, 3–85) at referral. Iris nodules were identified in 27 cases (39.7%) initially. Thirty-one eyes (45.6%) demonstrated focal or diffuse iris pigment epithelium atrophy, while heterochromia was seen in only 21 patients (30.9%). Cataract was diagnosed in 90.9% of included eyes over the follow-up. No toxoplasmosis-like chorioretinal scars were found. Topical steroids were used (<15 days) in 54.4% of cases (37 patients).

IOP: Baseline, Evolution, Associated and Predictive Factors

At baseline, mean IOP was 17.2 ± 7.2 mm Hg (range, 9–40) (N = 68) (Table 1), and it was 15.6 ± 5.6 (range, 3–30) 5 years after referral (N = 20). Twenty-one percent of patients had increased IOP at referral (>21 mm Hg).

After univariate analyses, potential factors associated with increased ($\beta > 0$) or decreased IOP ($\beta < 0$) (P value under 0.10) are depicted in Table 2 (Test of main effect, Test of each interaction). The final multivariate model (Table 2) retained three statistically significant independent effects (P value under 0.05) associated with increased ($\beta > 0$) or decreased IOP ($\beta < 0$). Irrespective of time, women had on average lower IOP than men ($\beta = -2.322$, $P = 0.03$), and longer disease duration before diagnosis was associated with increased IOP values ($\beta = 0.132$, $P = 0.04$). If time was not found as having

Table 3. Predictive Factors of the Number of Antiglaucoma Treatments Over Time

Generalized Linear Mixed Model (Poisson) Tests of Effects			
Variable	**Estimate, β**	**Standard Error**	***P***
Multivariate final model			
Intercept	−0.872	0.33	0.008
Time	0.024	0.04	0.55
Disease duration	0.446	0.20	0.03
Iris nodules	−2.075	0.57	<0.001
Cctl ratio	−0.543	0.23	0.02
Interaction time and iris nodules	0.271	0.07	<0.001
Test of main effect one by one			
Time	0.117	0.03	<0.001
Sex, female	−0.441	0.55	0.42
Age at onset	0.244	0.25	0.33
Disease duration	0.513	0.23	0.03
Iris nodules	−0.889	0.54	0.09
AH flare	−0.254	0.70	0.72
Crv ratio	−0.268	0.28	0.34
Cctl ratio	−0.614	0.28	0.03
Test of each interaction with time one by one			
Age at onset	−0.042	0.04	0.26
Disease duration	0.017	0.03	0.50
Iris nodules	0.273	0.07	<0.001
AH flare	0.140	0.15	0.36
Crv ratio	−0.122	0.07	0.08
Cctl ratio	−0.072	0.03	0.03

an effect on IOP ($\beta = 0.06$, $P = 0.75$), a significant interaction between time and Crv ratio was observed ($\beta = -0.029$, $P = 0.04$). In other words, higher Crv ratio figures at baseline were associated with decreased IOP values over time ($\beta = -0.032$, $P = 0.04$), which means that patients with a low Crv ratio at baseline are at higher risk of increasing their IOP over time.

Associated and Predictive Factors of IOP Severity Based on the Number of Antiglaucoma Treatments

At baseline, the mean number of antiglaucoma treatments was 0.7 ± 0.4 (range, 0–5) ($N = 68$) (Table 1), and it was 1.0 ± 1.3 (range, 0–5) 5 years after referral ($N = 23$). At baseline, 46 (73%) patients had no antiglaucoma medications, 6 (9.5%) had one, and 11 (17.4%) had had two to five types of glaucoma treatment.

After univariate analyses, potential factors associated with the number of antiglaucoma treatments (*P* value under 0.10) are depicted in Table 3 (Test of main effect, Test of each interaction).

The final multivariate model (Table 3) retained five statistically significant independent effects (*P* value under 0.05) associated with the number of antiglaucoma treatments. Irrespective of time, longer disease duration before diagnosis was associated with greater number of glaucoma treatments ($\beta = 0.446$, $P = 0.03$). On the other hand, increased Cctl ratio was correlated with a lower number of glaucoma medications ($\beta = -0.543$, $P = 0.02$). If, irrespective of time, presence of iris nodules at baseline was found to be associated with a lower number of treatments ($\beta = -2.075$, $P < 0.001$), there was a pejorative interaction with time: Patients with iris nodules at baseline had a higher risk of increasing their number of antiglaucoma treatments over time ($\beta = 0.271$, $P < 0.001$).

Table 4. Baseline Factors Associated With an Instantaneous Risk of Undergoing Glaucoma Surgery

Cox Model for Proportional Hazard Ratio Analysis			
Variable	**Hazard Ratio**	**CI 95%**	***P***
Multivariate final analysis			
Disease duration	1.06	1.01–1.11	0.02
Univariate analyses			
Sex, female	0.56	0.20–1.60	0.28
Age at onset	0.99	0.96–1.04	0.99
Disease duration	1.06	1.01–1.12	0.02
Iris nodules	0.15	0.03–0.69	0.01
AH flare	1.03	0.98–1.09	0.25
Crv ratio	0.98	0.92–1.04	0.48
Cctl ratio	0.99	0.99–1.01	0.19

Factors Associated With the Occurrence of Glaucoma Surgery

The Figure depicts the estimated probability of not undergoing glaucoma surgery over the follow-up in this cohort. The median time without undergoing glaucoma surgery was between 118 and 218 months after diagnosis of FHC.

After Cox univariate analyses, the potential factors associated with an instantaneous risk of glaucoma surgery (*P* value under 0.10) are depicted in Table 4 (Univariate analyses).The final Cox multivariate model showed that longer disease duration before diagnosis increased the risk of surgery (hazard ratio = 1.06, confidence interval [CI] at 95% = [1.01–1.11], $P = 0.02$) (Table 4).

Discussion

Despite its apparently benign nature,[1,3] ocular complications are possible in Fuchs uveitis syndrome. Because of its mildly symptomatic nature and the possible atypical signs, diagnosis can be overlooked or delayed for years and even decades (Brancaleoni A, et al. *IOVS* 2003;44:ARVO E-Abstract 2381), increasing the risk of developing sight-threatening complications. Toniolo et al.[20] recently reported that 39% of FHC patients eventually develop intraocular hypertension (IOH) or glaucoma.[20] In this pathology, the severity of glaucoma resides in its poor responsiveness to maximal medical therapy but also to surgery.[8,9,21] If follow-up is recommended for all FHC patients, there are still no evidence-based guidelines regarding what subpopulation is at higher risk of complications. The purpose of this study was to identify the risk factors of IOH/glaucoma in order to suggest what subgroups of patients might need the closest monitoring.

Today, strong evidence supports the major role of RV in the pathogenesis of FHC.[15,17,18,22,23] Detection of rubella-specific antibodies in the anterior chamber is strongly associated with FHC,[24] whereas the detection of rubella genome is inconstant because limited amounts are detectable and sequences may vary.[25–27] Ocular rubella serology has therefore been included in the routine investigation of uveitis in our practice. Collection of paired aqueous and serum samples for antibody production is a standard of care in our institution and was systematically performed when FHC was suspected. In our clinic, all patients that were clinically suspected of having FHC and were virologically tested were found to be rubella+. On the other hand, and because of the screening modalities of this study, no further information could be collected regarding the patients that did not undergo virologic testing. As a consequence and for the sake of this study and its homogeneity, we

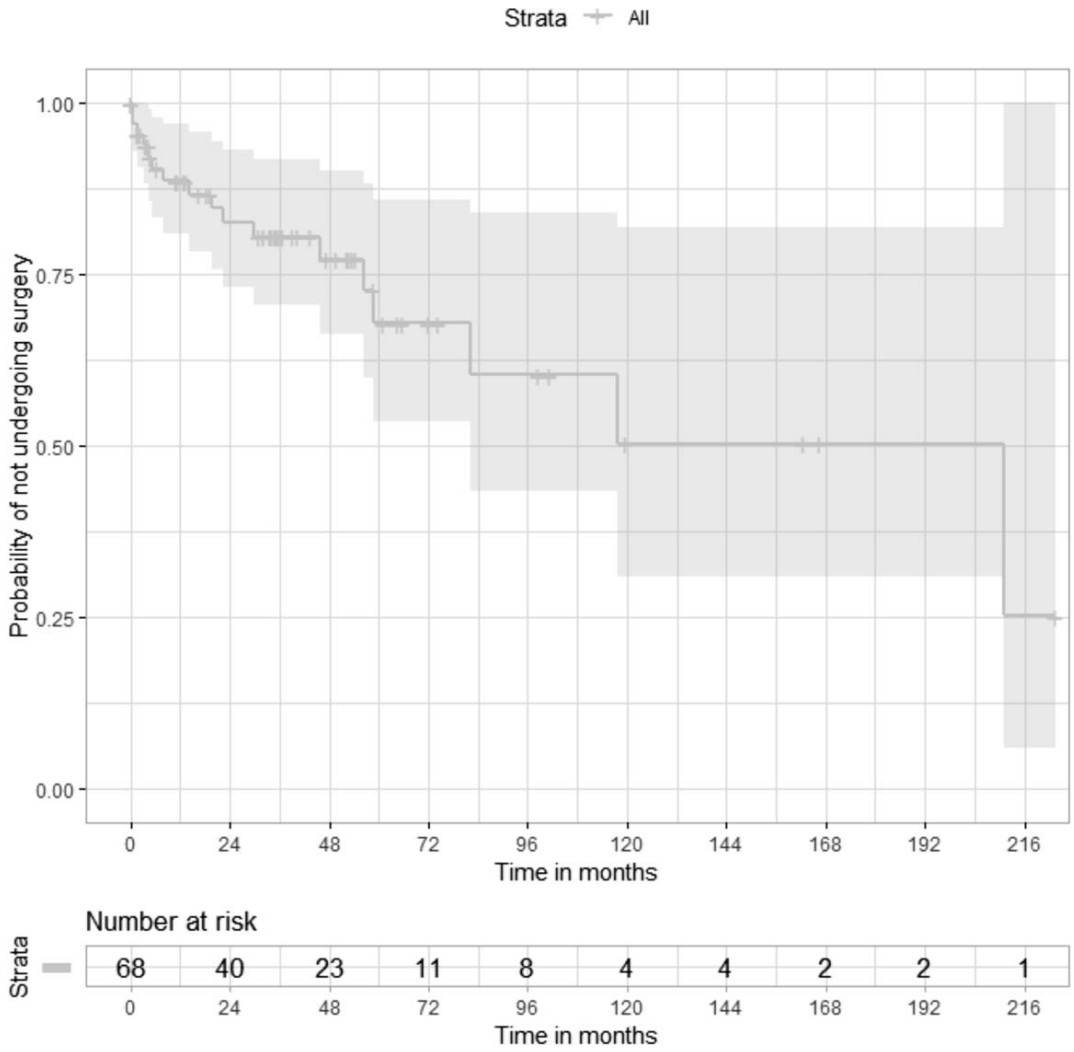

FIGURE. Kaplan-Meier estimate of the probability of not undergoing glaucoma surgery over time.

included patients with both suggestive clinical signs[3] and specific production of ocular rubella antibodies.[19]

Our findings overall were consistent with the literature. Included patients were in their fourth decade and disease was unilateral in the vast majority of cases.[8] Keratic precipitates were present in 95.7% of eyes.[28] With regard to IOH/glaucoma, it has been suggested to occur in 15% to 59% of cases, consistent with our results.[9,20]

Disease duration (i.e., time between onset of symptoms and diagnosis) was found to be positively associated with IOP values, suggesting that early diagnosis is of importance in the management of FHC.

Toniolo and colleagues[20] suggested that age was a risk factor of glaucoma in FHC patients. Here, utilizing specific statistical analyses that take into account multiple variables and their simultaneous variation over time, we were not able to confirm this statement. This makes us believe that other factors probably overweigh the effect of age as an IOH/glaucoma risk factor in Fuchs uveitis. Sex was also correlated with IOP values, and overall, females had lower IOP values ($\beta = -2.322$, $P = 0.03$) and lower instantaneous risk of undergoing glaucoma surgery (hazard ratio = 0.56, although not statistically significant) as compared to males. According to Salvetat et al.,[29] ocular hypertension represents a risk factor of glaucoma based on a conversion rate of 25% after 10 years. To our knowledge, no previous study ever reported a correlation between sex and IOP values, and it would be interesting to pursue the follow-up in a larger cohort in order to provide the actual incidence of IOH and glaucoma according to sex. In all cases and based on our results, it seems legitimate to suggest closer monitoring of IOP in male patients in the context of FHC.

Regarding ocular symptoms, none was associated with, or predictive of, IOP evolution in this cohort. However, this might be biased by the fact that a large majority of patients complained of ocular symptoms, decreasing the probability of pointing out a possible correlation. Regarding objective ocular signs, we found that the presence of iris nodules at baseline was associated with an increased risk of necessitating a high number of antiglaucoma therapies over time. This interesting finding had not been reported so far, and while it is difficult to provide an exact pathophysiogenic explanation for this observation, it seems important to outline it because iris nodules might constitute a predictor of IOP pejorative evolution over time (not statistically significant in this cohort).

One of the most interesting findings of this study was the correlation that was found between anterior chamber virologic parameters and IOH. The detection of specific ocular antirubella antibodies has proved useful for FHC diagnosis. By coupling Crv and C' ratio analyses, we evidenced a rubella-

specific intraocular immune response in all patients that were clinically suspected of having FHC. More importantly, we showed that decreased Crv was predictive of increased IOP (interaction between time and Crv, $\beta = -0.032$, $P = 0.04$) during the follow-up of FHC patients. This might mean that the intensity of rubella-specific antibody production, as a consequence of persistent viral expression, could play a direct role in the pathophysiology of IOH and glaucoma in this disease. Thorough studies are needed to further investigate the molecular mechanisms behind this interesting finding. In addition to the specific ocular production of anti-RV IgG, and although not statistically significant, a decrease of the Cctl ratio that can witness the breakdown of the serum–AH barrier when < 300 also seemed to be correlated with an increase of IOP (univariate analysis: $\beta = -0.006$). Decreased Cctl at baseline was also associated with the necessity of a higher number of antiglaucoma treatments in FHC patients ($\beta = -0.543$, $P = 0.02$). As reported elsewhere,[19] the Cctl ratio provides objective and direct information regarding the integrity of the blood–ocular barrier and is always available when anterior chamber taps are performed. In cases with serum–AH barrier rupture and Cctl decrease, blood material spills out of the anterior chamber vessels and causes the accumulation of small molecules in the trabecular meshwork, which might eventually induce IOH. The degree of baseline Cctl might provide direct and objective clues regarding the degree of initial intraocular inflammatory reactions and might therefore constitute an interesting tool for the prediction of IOP outcomes in FHC patients and uveitis patients in general. Mechanistically, the measure of total IgG amounts in the anterior chamber is expected to provide the same results. Further studies should be able to prove this hypothesis.

There are limitations to our study that need to be highlighted. First, due to the retrospective nature of this work, corneal thickness values were missing for a large proportion of patients and we were not able to define the severity of glaucoma based on optical coherence tomography or visual field evaluation. In fact, these tests were not performed on the same devices and were not comparable between cases. As a consequence, IOH/glaucoma severity was based upon the number of antiglaucoma drops and the need for surgery. Second, the tertiary characteristics of the inclusion center might have biased the cases toward more severe presentations. Steroids that are an important factor underlying the development of IOH and glaucoma were of very intermittent use and should not be regarded as a confounding factor. Last, although this might have increased the power of the study, we were not able to report all cited parameters for the whole cohort throughout up to 20 years of follow-up.

The objective of this study was to point to potential associated and predictive factors of IOH/glaucoma and their severity in FHC; the validity of this can be confirmed only through further prospective studies that are specifically designed for this purpose. From these results we can, however, postulate that this work proposes novel, valuable, and mainly objective prognostic tools that may help with the screening of the patients that are the likeliest to develop such complications. Overall, time to diagnosis, male sex, presence of iris nodules at baseline, and for the first time decreased Crv and Cctl ratios were associated with increased likelihood of pejorative IOP evolution over time.

In summary, this study focused on a series of clinical and biological parameters that are potential predictive factors of IOH/glaucoma and their severity in FHC. Prospective multicenter studies should be able to confirm these findings. Given the aggressiveness of glaucoma in FHC patients, these results should provide better insight into what category of patients should need more frequent screening.

Acknowledgments

Disclosure: **S. Touhami**, None; **A. Vanier**, None; **A. Rosati**, None; **M. Bojanova**, None; **B. Benromdhane**, None; **P. Lehoang**, None; **F. Rozenberg**, None; **B. Bodaghi**, None

References

1. Mohamed Q, Zamir E. Update on Fuchs' uveitis syndrome. *Curr Opin Ophthalmol*. 2005;16:356–363.
2. Bloch-Michel E, Nussenblatt RB. International Uveitis Study Group recommendations for the evaluation of intraocular inflammatory disease. *Am J Ophthalmol*. 1987;103:234–235.
3. Bonfioli AA, Curi ALL, Orefice F. Fuchs' heterochromic cyclitis. *Semin Ophthalmol*. 2005;20:143–146.
4. Fuchs E. I. Ueber Komplikationen der Heterochromie [in German]. *Ophthalmologica*. 1906;15:191–212.
5. Kimura SJ, Hogan MJ, Thygeson P. Fuchs' syndrome of heterochromic cyclitis. *AMA Arch Ophthalmol*. 1955;54:179–186.
6. Jabs DA, Nussenblatt RB, Rosenbaum JT; Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. *Am J Ophthalmol*. 2005;140:509–516.
7. Norrsell K, Holmér AK, Jacobson H. Aqueous flare in patients with monocular iris atrophy and uveitis. A laser flare and iris angiography study. *Acta Ophthalmol Scand*. 1998;76:405–412.
8. Jones NP. Fuchs' heterochromic uveitis: an update. *Surv Ophthalmol*. 1993;37:253–272.
9. Liesegang TJ. Clinical features and prognosis in Fuchs' uveitis syndrome. *Arch Ophthalmol*. 1982;100:1622–1626.
10. Kimura SJ. Fuchs' syndrome of heterochromic cyclitis in brown-eyed patients. *Trans Am Ophthalmol Soc*. 1978;76:76–89.
11. Fearnley IR, Rosenthal AR. Fuchs' heterochromic iridocyclitis revisited. *Acta Ophthalmol Scand*. 1995;73:166–170.
12. Norrsell K, Sjödell L. Fuchs' heterochromic uveitis: a longitudinal clinical study. *Acta Ophthalmol*. 2008;86:58–64.
13. Hey EL, Jong PT de, Kijlstra A. Fuchs' heterochromic cyclitis: review of the literature on the pathogenetic mechanisms. *Br J Ophthalmol*. 1994;78:307.
14. Teyssot N, Cassoux N, Lehoang P, Bodaghi B. Fuchs heterochromic cyclitis and ocular toxocariasis. *Am J Ophthalmol*. 2005;139:915–916.
15. Quentin CD, Reiber H. Fuchs heterochromic cyclitis: rubella virus antibodies and genome in aqueous humor. *Am J Ophthalmol*. 2004;138:46–54.
16. Schwab IR. The epidemiologic association of Fuchs' heterochromic iridocyclitis and ocular toxoplasmosis. *Am J Ophthalmol*. 1991;111:356–362.
17. de Groot-Mijnes JDF, de Visser L, Rothova A, Schuller M, van Loon AM, Weersink AJL. Rubella virus is associated with Fuchs heterochromic iridocyclitis. *Am J Ophthalmol*. 2006;141:212–214.
18. Stunf S, Petrovec M, Žigon N, et al. High concordance of intraocular antibody synthesis against the rubella virus and Fuchs heterochromic uveitis syndrome in Slovenia. *Mol Vis*. 2012;18:2909–2914.
19. Bojanova M, Bodaghi B, Hannachi N, et al. Measure of herpesvirus-specific ocular antibody production in patients with uveitis. *J Clin Virol*. 2013;58:718–721.
20. Toniolo JT, Hall AJ, Smith JG, Levy J, Lim LL. Risk factors for glaucoma in a cohort of patients with Fuchs heterochromic iridocyclitis. *Ocul Immunol Inflamm*. 2017;25:753–759.

21. Chawla A, Mercieca K, Fenerty C, Jones NP. Outcomes and complications of trabeculectomy enhanced with 5-fluorouracil in adults with glaucoma secondary to uveitis. *J Glaucoma*. 2013;22:663–666.
22. Suzuki J, Goto H, Komase K, et al. Rubella virus as a possible etiological agent of Fuchs heterochromic iridocyclitis. *Graefes Arch Clin Exp Ophthalmol*. 2010;248:1487–1491.
23. Ruokonen PC, Metzner S, Ucer A, Torun N, Hofmann J, Pleyer U. Intraocular antibody synthesis against rubella virus and other microorganisms in Fuchs' heterochromic cyclitis. *Graefes Arch Clin Exp Ophthalmol*. 2010;248:565–571.
24. Kreps EO, Derveaux T, De Keyser F, Kestelyn P. Fuchs' uveitis syndrome: no longer a syndrome? *Ocul Immunol Inflamm*. 2016;24:348–357.
25. Abernathy E, Peairs RR, Chen M, Icenogle J, Namdari H. Genomic characterization of a persistent rubella virus from a case of Fuch' uveitis syndrome in a 73 year old man. *J Clin Virol*. 2015;69:104–109.
26. ten Berge JCEM, van Daele PLA, Rothova A. Rubella virus-associated anterior uveitis in a vaccinated patient: a case report. *Ocul Immunol Inflamm*. 2016;24:113–114.
27. Winchester SA, Varga Z, Parmar D, Brown KE. Persistent intraocular rubella infection in a patient with Fuchs' uveitis and congenital rubella syndrome. *J Clin Microbiol*. 2013;51:1622–1624.
28. Tugal-Tutkun I, Güney-Tefekli E, Kamaci-Duman F, Corum I. A cross-sectional and longitudinal study of Fuchs uveitis syndrome in Turkish patients. *Am J Ophthalmol*. 2009;148:510–515, e1.
29. Salvetat ML, Zeppieri M, Tosoni C, Brusini P. Baseline factors predicting the risk of conversion from ocular hypertension to primary open-angle glaucoma during a 10-year follow-up. *Eye (Lond)*. 2016;30:784–795.

Investigative Ophthalmology & Visual Science