Clinical Manifestations, Prognosis, and Vaccination Status of Patients With Rubella Virus–Associated Uveitis

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• PURPOSE: To assess the clinical and laboratory manifestations and vaccination status of uveitis patients positive for rubella virus (RV) in aqueous humor and investigate its relationship to Fuchs uveitis syndrome (FUS).

• METHODS: Retrospective study of all uveitis patients, positive for RV in aqueous humor analysis (polymerase chain reaction [PCR] and/or Goldmann-Witmer coefficient [GWC]) between January 2010 and October 2016 at the ophthalmology departments in the Erasmus Medical Center (Rotterdam) and University Medical Center Utrecht. Outcomes of aqueous analyses of FUS patients during this period were assessed.

• RESULTS: We included 127 patients (144 eyes) positive for RV in aqueous fluid: 23 (20%) by PCR, 120 (97%) by GWC, and 16 (13%) by both. The average age at first presentation was 37 years. Patients typically complained of blurred vision and exhibited a combination of unilateral anterior uveitis, keratic precipitates, vitritis, and absence of posterior synechiae, but the classical FUS was observed in a minority. The main cause of untreatable visual loss was glaucoma. Cystoid macular edema (CME) before intraocular surgery was not encountered. None of the unilateral cases developed involvement of the other eye. None of the patients was vaccinated against RV. All FUS patients, except 2 (5%), were positive for RV.

• CONCLUSION: RV-associated uveitis and FUS are not exchangeable. Chronic anterior uveitis, vitritis, early development of cataract, and the absence of posterior synechiae and CME characterize RV-associated uveitis. Almost all FUS cases had documented intraocular RV infection, but only some of the patients with RV-associated uveitis presented with FUS. (Am J Ophthalmol 2019;202:37–46. © 2019 Elsevier Inc. All rights reserved.)

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RUBELLA VIRUS (RV), WHICH BELONGS TO THE FAMily *Togaviridae*, is a cause of severe congenital rubella syndrome and is characterized by a classical triad consisting of deafness, eye abnormalities (cataract, retinopathy), and heart disease. In addition, microcephaly, intellectual disability, and hepatosplenomegaly may also occur.[1–3] This syndrome has almost disappeared in the western world after the introduction of the rubella vaccination programs.[4]

Surprisingly however, in 2006 RV was associated with an enigmatic uveitis entity, known as Fuchs uveitis syndrome (FUS), by anterior chamber fluid analysis for RV by polymerase chain reaction (PCR) and/or Goldmann-Witmer coefficient (GWC).[5–7] Based on this association, RV is likely to be 1 of the causes of this syndrome. Two studies described RV-associated uveitis and reported that a majority of patients with RV-associated uveitis, but not all, have clinical features typical of FUS, and vice versa.[8,9] Other studies also reported on other possible causes of FUS.[10] One study compared the clinical manifestations of RV-associated uveitis with herpes simplex virus (HSV)-associated or varicella-zoster virus (VZV)-associated anterior uveitis and identified younger age at onset, a more chronic course of disease, and more often cataract at presentation in RV-associated uveitis.[9]

To date, many clinicians have assumed that RV-associated uveitis always presents with the FUS phenotype. In the present study, we further investigate the ocular manifestations and complications of RV-associated uveitis and demonstrate its relation to FUS and rubella vaccination. Our main purpose is to expand the knowledge on RV-associated uveitis in a large series and elaborate on the relationship between FUS and RV-associated uveitis.

METHODS

• PARTICIPANTS: All consecutive patients who had positive PCR of GWC for RV in aqueous humor analysis between January 2010 and October 2016 at the ophthalmology

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TABLE 1. Basic Characteristics of Patients With Positive Aqueous Humor Analysis for Rubella Virus

Characteristics	Results
Total no. of patients	127
Total no. of affected eyes	144
Total follow-up time[a]	
Mean (years ± SD)	7.2 (±9.7)
Median (IQR)	3.1 (7.7)
Bilateral involvement	17/127 (13%)
Mean age at onset of ocular complaints (years ± SD)[b]	37.1 (±11.4)
Mean age at first presentation ophthalmologist (years ± SD)[b]	39.3 (±12.0)
Mean age at presentation to the university center (years ± SD)	44.0 (±11.0)
Male-to-female ratio	1:1.1
Race	
White	98/127 (77%)
Asian	14/127 (11%)
African	15/127 (12%)
Aqueous examination for RV infection	
PCR+, GWC+	16/127 (13%)
PCR+, GWC-	4/127 (3%)
PCR-, GWC+	94/127 (74%)
Other[c]	13/127 (10%)

GWC = Goldmann-Witmer coefficient; IQR = interquartile range; PCR = polymerase chain reaction; RV = rubella virus; SD = standard deviation.

[a]The time between first contact to an ophthalmologist and the last visit at the university center.

[b]No information could be extracted on the date of onset of ocular complaints in 53 (42%) and of the first presentation to an ophthalmologist in 21 (17%).

[c]PCR positive and GWC not determined (n = 3), PCR not determined and GWC positive (n = 10).

departments of the Erasmus Medical Center (EMC, Rotterdam, Netherlands) and of the University Medical Center Utrecht (UMCU, Utrecht, Netherlands) were included. In addition, we subsequently reviewed the medical records of all patients who presented with complete FUS in the same period of time and assessed their outcomes for RV in the aqueous humor samples. The medical ethical committee in both institutions approved the present study with the bio banking protocol and the associated procedures.

• **AQUEOUS HUMOR TAP:** The decision to perform diagnostic aqueous tap in the Netherlands depends on the suspicion of infection; it is also performed before initiating systemic immunosuppressive treatment in patients with uveitis of unknown cause despite an initial examination. Suspicion of infectious anterior uveitis was defined as the presence of unilateral uveitis with or without small-to-medium-sized keratic precipitates (KPs), some form of iris abnormalities, high intraocular pressure (IOP), and resistance to steroids. In patients with posterior segment involvement, infections were suspected in unilateral cases and in cases with focal retinal lesions and/or retinal necrosis. Either the initial diagnostic screening in these patients was negative before performing an aqueous humor tap or the suspicion of infection was very high, directly requiring an aqueous humor tap. A panel of PCRs and GWCs for viruses is being determined in all diagnostic taps, which includes assessment for HSV, VZV, cytomegalovirus (CMV), and RV. However, the results for all viruses are not always available, as the limited volume sometimes does not always allow assessment for all specific agents. In total, 1460 aqueous humor taps were performed during the study period and approximately 65% were tested for RV. The GWC (specific IgG eye/specific IgG serum) *(IgG1 serum/IgG1 eye) was defined as positive if above 3.0 and highest for RV.[11]

• **SAMPLE COLLECTION AND PROCESSING:** The ocular fluid samples were stored at −80 C until processing. Serum samples were obtained at time of aqueous humor tap and stored at +4 C until processing. PCR assay was performed as described previously.[10,11] Specific immunoglobulin G (IgG) titers against RV, HSV, VZV, and CMV in serum and aqueous humor were either performed as previously reported or determined with the Euroimmun indirect immunofluorescence test kit (Euroimmun, Luebeck, Germany).[11] Further information is specified in the Supplemental Appendix (Supplemental Material available at AJO.com).

• **ASSESSMENT OF CLINICAL CHARACTERISTICS:** The following data were collected from the patient files: sex, race, age at onset of symptoms, age at first presentation to an ophthalmologist, and age at diagnosis of RV-associated uveitis (defined as the date of positive anterior chamber fluid analysis), as well as the vaccination history.

We also reviewed the referral letter for the initial anatomic classification, the presence of vitritis, and whether or not the ophthalmologist considered FUS in the differential diagnosis. Further, visual complaints and their causes at first consultation at the university center and follow-up were recorded, as well as visual acuity and prior ocular surgeries. All ocular manifestations of RV-associated uveitis were noted, including the presence of retinal scars.[12] Anatomic classifications determined by the referring ophthalmologist and by the ophthalmologist in the university center were also registered.

The presence of ocular hypertension, glaucoma, and cataract was also registered. Ocular hypertension was defined as IOP ≥21 mm Hg measured at least 2 times. Glaucoma was defined as ocular hypertension combined with glaucomatous visual field defects and/or glaucomatous opticopathy. Also, IOP of ≥35 mm Hg without visible

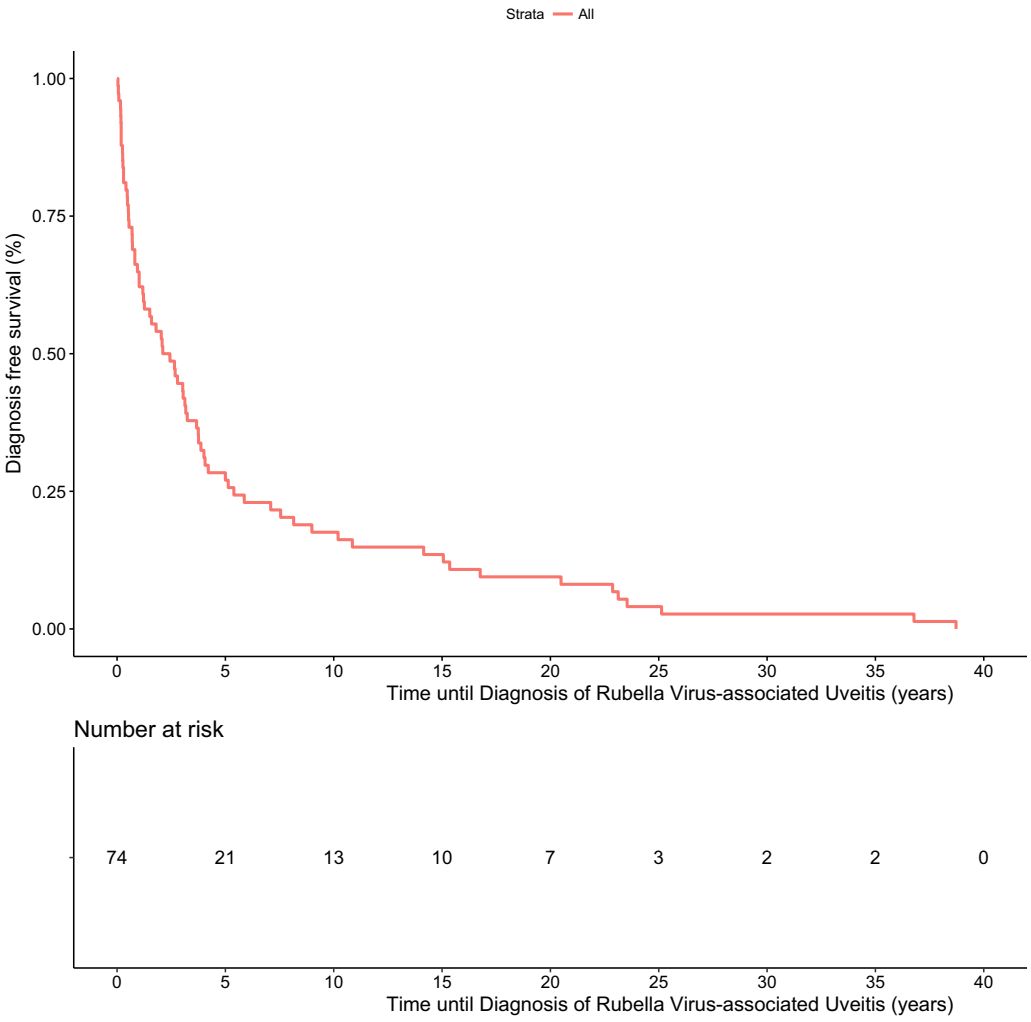

FIGURE 1. Estimated risk of confirmation of rubella virus–associated uveitis by aqueous humor analysis. Kaplan-Meier curve shows percentage of patients without confirmation of rubella virus by aqueous humor analysis.

damage of the optic disc and/or without visual field defects was classified as glaucoma.

• **DEFINITION OF FUCHS UVEITIS SYNDROME:** Since Ernst Fuchs's publication in 1906, diverse clinical features were attributed to FUS. So far, no standardized diagnostic criteria exist and diverse combinations of clinical features are being used for the diagnosis of FUS.[13–17] For the purpose of this study we have chosen the original criteria and all of the following were required for the diagnosis of complete FUS: (1) heterochromia and/or diffuse iris atrophy, (2) chronic iritis/iridocyclitis, (3) KPs scattered over the whole corneal endothelium, (4) absence of posterior synechiae, and (5) cataract.

• **VACCINATION STATUS:** In the Netherlands, the RV vaccination program was offered to 11-year-old girls from 1974 to 1987 and to all children from 1987 in the combined measles, mumps, and rubella vaccination given at the age of 14 months and 9 years.[18] Therefore, all patients born in the Netherlands after 1987 who complied with the national vaccination program were considered as vaccinated and patients born before 1987 were considered as not vaccinated. The patients born outside the Netherlands who were not subjected to RV vaccination were considered not vaccinated.

• **STATISTICAL ANALYSIS:** The characteristics of patients were summarized using descriptive statistics, such as means and percentages. Appropriate (non)parametric tests were used to compare characteristics between the groups. Survival analysis was performed for the interval from the first presentation to an ophthalmologist until diagnosis, date of cataract extraction, and glaucoma surgery, using R (Package for Survival Analysis).[19–21]

TABLE 2. Anatomic Classification of Patients With Positive Aqueous Humor Analysis for Rubella Virus

Anatomic Classification	Referring Ophthalmologist	University Center Ophthalmologist
Anterior	33/127 (26%)	48/127 (38%)
Anterior + intermediate	3/127 (2%)	4/127 (3%)
Intermediate	23/127 (18%)	18/127 (14%)
Posterior	8/127 (6%)	3/127 (2%)
Panuveitis	13/127 (10%)	27/127 (21%)
Combination of localizations, not according to the SUN classification	5/127 (4%)[a]	4/127 (3%)[b]
Not specified or no information available	42/127 (33%)	23/127 (18%)

SUN = Standardization of Uveitis Nomenclature.

[a]Including patients who were categorized as anterior + posterior (n = 2), intermediate uveitis or panuveitis (n = 2), and intermediate or posterior uveitis (n = 1).

[b]Including patients who were categorized as keratouveitis (n = 1), intermediate or posterior uveitis (n = 1), intermediate or panuveitis (n = 1), and anterior or intermediate or posterior uveitis (n = 1).

TABLE 3. Clinical Characteristics and Complications of Patients With Rubella Virus–Associated Uveitis

Presence	At Presentation in University Center	Anytime During Whole Follow-up Period[a]
Keratic precipitates	83/127 (65%)	114/127 (90%)
Posterior synechiae[b]	7/127 (6%)	12/127 (9%)
Iris atrophy	33/127 (26%)	58/127 (46%)
Heterochromia	10/33 (30%)	18/58 (31%)
Diaphany/atrophy	23/33 (70%)	40/58 (69%)
Iris nodules[c]	3/127 (2%)	6/127 (5%)
Cataract	85/127 (67%)	101/127 (80%)
Vitritis	103/127 (81%)	113/127 (89%)
Retinal abnormalities		
Scars[d]	10/127 (8%)	13/127 (10%)
Optic disc edema/ hyperemia	11/127 (9%)	13/127 (10%)
Retinal detachment	4/127 (3%)	4/127 (3%)
Glaucoma	22/127 (17%)	36/127 (28%)
Ocular hypertension	23/127 (18%)	28/127 (22%)

[a]Median follow-up time 3.1 years (interquartile range 7.7).

[b]Out of 12 patients with synechiae, 7 did not have any precipitating trauma or intraocular surgery.

[c]Four out of 6 patients with iris nodules had Koeppe nodules and 2 patients had Busacca nodules (1 patient had both and in 1 patient type was not described).

[d]Atrophic areas, vasculitis, hypo- or hyperpigmentation, and retinal pigment epithelium were not taken into account. No new active retinal lesions during the follow-up were noted. The 3 lesions noticed during follow-up were probably not noted earlier. The location of the unilateral retinal scars was as follows: zone 1 (n = 5), zone 2 (n = 1), zone 3 (n = 1). The remaining patients had scars in both eyes: 3 patients with scars in zone 1 in both eyes, 3 patients with a scar in the contralateral nonuveitis eye (zone 2, n = 1; zone 3, n = 2, of which in 1 patient the size was not described). The majority of scars had size of less than 1 disc diameter in 6 (46%). In 4 patients, no funduscopic photographs were taken; size of the scar could be determined.

RESULTS

• **CHARACTERISTICS OF THE STUDY POPULATION:** Table 1 shows the general characteristics of our RV-positive population. Our study included 127 consecutive patients who had either positive PCR or GWC for RV. Bilateral involvement was present in 17 (13%) patients, resulting in 144 affected eyes. Out of all 127 patients, 60 (47%) were male and 98 patients were of white origin (77%). None of the patients with unilateral manifestations at onset developed involvement of the other eye during the course of the disease. The mean duration between onset of symptoms and diagnosis of RV-associated uveitis is depicted in Figure 1.

• **VACCINATION STATUS:** None of the patients underwent early childhood vaccination against RV. All patients were born before the vaccination program was introduced, except 3 patients. Of these 3 patients, 2 were born outside the Netherlands (Poland, n = 1; and Somalia, n = 1) and the 1 patient born in the Netherlands after 1987 was not vaccinated on religious grounds. Patients born outside the Netherlands (n = 34) were younger at onset of uveitis compared to patients born in the Netherlands (33.7 vs 41.5, $P < .05$).

• **AQUEOUS HUMOR ANALYSIS:** The results of aqueous humor analysis are depicted in Table 1. Both GWC and PCR were positive for RV in 16 (13%) patients. Out of all patients in whom PCR was determined (n = 117), PCR was positive for RV in 23 (20%) patients (PCR was not determined in 10 patients). Comparison of RV PCR-positive and RV PCR-negative patients resulted in no differences considering sex, race, place of birth, laterality, presence of iris atrophy, iris nodules, presence of vitritis at presentation to the first ophthalmologist or anytime during the whole follow-up, KPs, retinal scars, glaucoma, or cataract (all $P > .05$, Supplemental Table 1; Supplemental Material available at AJO.com). However, the PCR positivity was predictive of developing glaucoma during follow-up among patients who were at risk on referral (odds ratio [OR] 6.0; 95% confidence interval [CI] 1.6–22.4, $P = .01$); PCR positivity was not predictive of developing cataract among patients who were at risk on referral (OR 3.7; 95% CI 0.72–19.0, $P = .22$). In addition, RV PCR-positive patients were younger at the onset of symptoms than PCR-negative patients (29.6 vs 38.5, $P = .01$).

TABLE 4. Prevalence of Diverse Clinical Signs and Their Combinations in Patients With Rubella Virus–Associated Uveitis

Clinical Manifestations[a]	At Presentation in University Center	During Whole Follow-up Period
1	23/127 (18%)	46/127 (36%)
Iris atrophy		
Keratic precipitates		
Absence of posterior synechiae		
2[b]	18/127 (14%)	37/127 (29%)
Iris atrophy		
Keratic precipitates		
Absence of posterior synechiae		
Cataract		
3	17/127 (13%)	38/127 (30%)
Iris atrophy		
Keratic precipitates		
Absence of posterior synechiae		
Vitritis		
4	13/127 (10%)	31/127 (24%)
Iris atrophy		
Keratic precipitates		
Absence of posterior synechiae		
Cataract		
Vitritis		
5	58/127 (46%)	82/127 (65%)
Unilateral inflammation		
Keratic precipitates		
Absence of posterior synechiae		
Vitritis		
6	47/127 (37%)	72/127 (57%)
Unilateral inflammation		
Keratic precipitates		
Absence of posterior synechiae		
Cataract		
7	34/127 (27%)	62/127 (49%)
Unilateral inflammation		
Keratic precipitates		
Absence of posterior synechiae		
Vitritis and cataract		

[a]All patients exhibited anterior uveitis.
[b]This combination represented our definition of complete Fuchs uveitis syndrome.

The duration from onset of symptoms until the diagnosis was similar for PCR-positive and PCR-negative patients ($P = .15$). Out of all 127 PCR- and/or GWC-positive patients for RV, the final diagnosis of uveitis was considered not to be related to RV in 4 patients (Supplemental Table 2; Supplemental Material available at AJO.com), but as these patients complied with the inclusion criteria, they were included in all analyses. Five of the GWC-positive patients also had another positive GWC (2 for VZV, 2 for *Toxoplasma gondii*, and 1 for HSV), but in all cases it was lower than the GWC for RV. These 5 patients were negative in PCR for all investigated agents. None of the remaining RV PCR-positive patients had another infectious agent positive in PCR or GWC.

• **CLINICAL CHARACTERISTICS:** The referring ophthalmologist classified uveitis mainly as anterior despite the presence of vitritis in 86 patients (68%, Table 2). FUS was mentioned as a differential diagnosis in the referral letter in 25%.

The most common patient complaint at referral was blurred vision (55/127; 43%), mostly caused by cataract (25/55; 45%). Seeing floaters was also common (36/127; 28%), sometimes in combination with other complaints such as decreased vision. In total, 5 patients (4%) had some complaints of photophobia, either with or without blurred vision and/or floaters.

The ophthalmologist at the University Center classified uveitis mainly as anterior uveitis or panuveitis

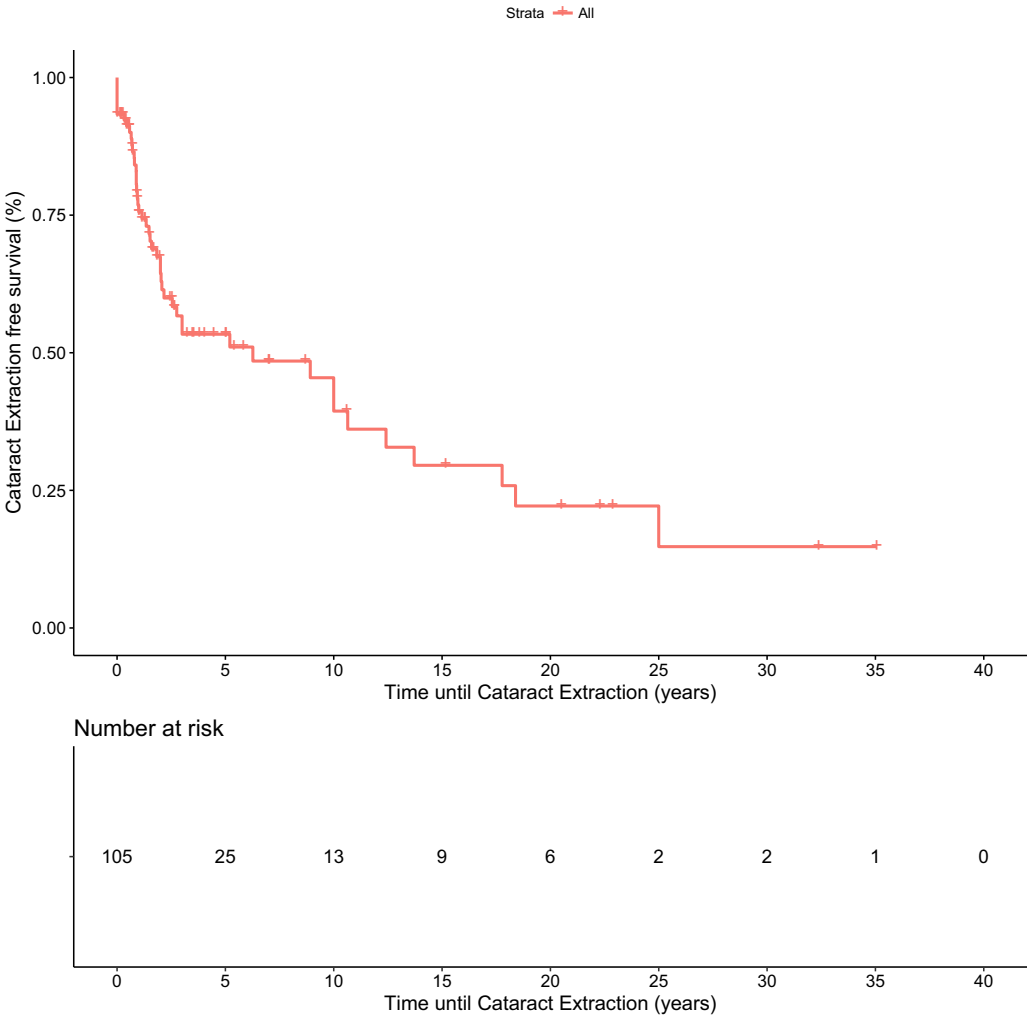

FIGURE 2. Estimated risk of undergoing a cataract extraction in patients with rubella virus–associated uveitis. Kaplan-Meier curve shows percentage of patients without cataract extraction.

(Table 2), despite the fact that vitritis was observed and recorded in 103 (81%) patients. Thirty-two out of 103 patients with vitritis (31%) were classified as solely anterior uveitis.

Ophthalmologic characteristics noted at referral and during the follow-up in the university center are illustrated in Table 3. Some characteristics changed over time and/or were only temporarily present (eg, KPs and iris nodules). None of the combination of clinical signs differed between PCR-positive and PCR-negative patients. Retinal scars were present in 13 patients (10%) at referral (Table 3).

The diverse combinations of clinical features previously associated with FUS present in our RV-positive patients are given in Table 4. The most common combination of clinical signs consisted of unilateral location, presence of KPs, absence of posterior synechiae, and presence of vitritis. The most common missing criterion was the presence of heterochromia and/or iris atrophy (69/127; 54%). However, detailed iris description was uncommon in the medical records (49/127; 39%). Moreover, of the 69 patients without iris atrophy, 22 (32%) were of nonwhite origin and thus probably had brown eyes.

• **VISUAL PROGNOSIS AND COMPLICATIONS:** At presentation to the university center, 20 (14%) eyes had best-corrected visual acuity (BCVA) of <0.1 and 23 (16%) eyes had BCVA between 0.1 and 0.3. The main cause of visual loss at presentation to the university center was cataract.

At the end of follow-up, 14 (10%) affected eyes had BCVA of <0.1 (none bilateral), with glaucoma representing the main cause of visual loss (n = 5 eyes).

Cataract had already developed in 67% of patients (85/127) at presentation to the university center and 34% of these (29/85) did not use topical corticosteroids at time of referral to the university center or only used them for a

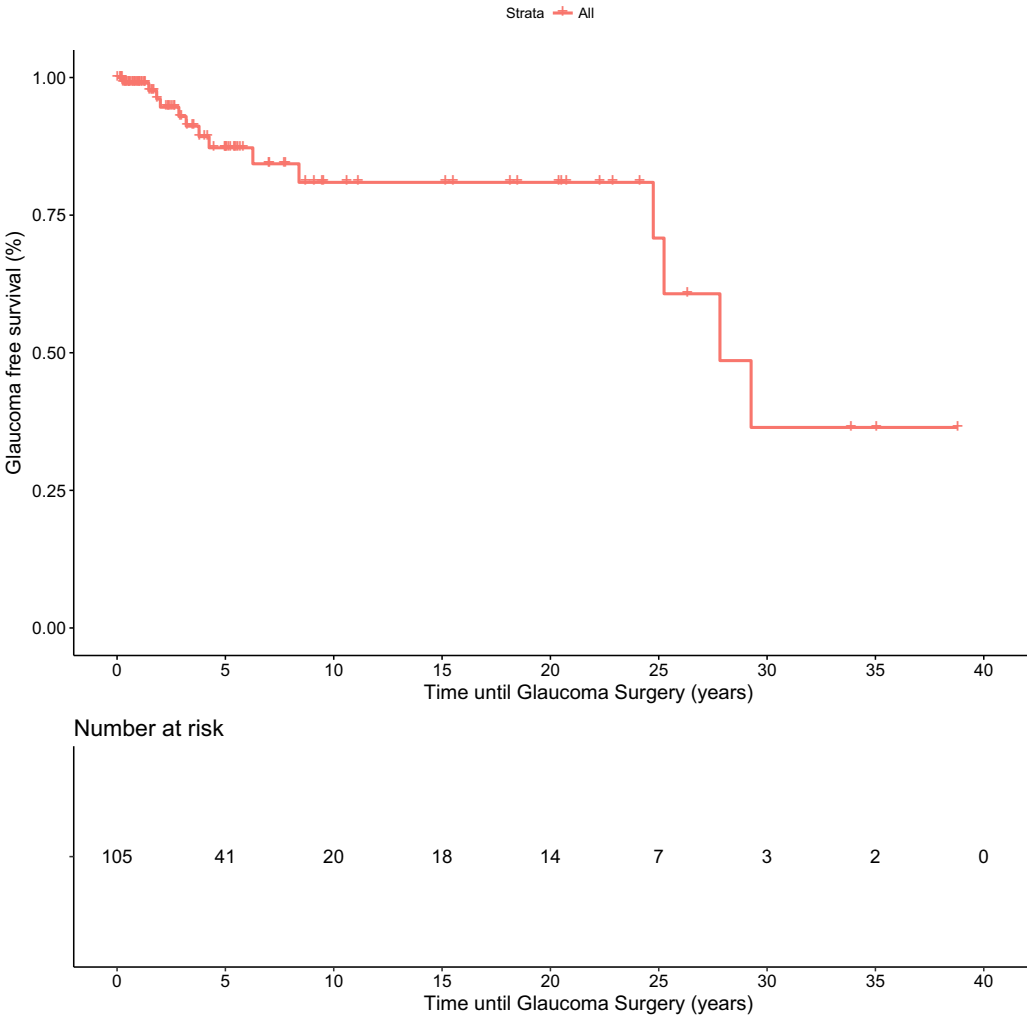

FIGURE 3. Estimated risk of undergoing surgery for the treatment of glaucoma in patients with rubella virus–associated uveitis. Kaplan-Meier curve shows percentage of patients without glaucoma surgery.

short duration of time. The presentation with cataract to their first ophthalmologist occurred at least in 12% of all patients (15/127) (Table 3). Cataract extraction was performed in 72 of the 144 affected eyes (50%) and the mean time between the first presentation and cataract extraction was 4.2 years (Supplemental Table 3; Supplemental Material available at AJO.com). The time interval from onset of symptoms until cataract surgery is depicted in Figure 2. Glaucoma was the second most common complication (Table 3 and Supplemental Table 3). The mean duration between the first consultation with an ophthalmologist and glaucoma surgery was 9.9 years; the interval from onset of symptoms until glaucoma surgery is depicted in Figure 3. In total, 22 (17%) patients (22 eyes) already had glaucoma at first presentation to the university center. Of these patients, 11 (50%) had not used topical steroids at all, or had only done so for a short duration of time. Presentation with glaucoma/elevated IOP to their first ophthalmologist occurred in at least 7 (6%) patients.

The average time between the first visit to the first ophthalmologist until vitrectomy for disturbing vitreous opacities was 5.3 years. None of the patients with the diagnosis of RV-associated uveitis developed cystoid macular edema (CME) before intraocular surgery.

• **FUCHS UVEITIS SYNDROME PHENOTYPE PATIENTS AND RESULTS FOR RUBELLA VIRUS IN AQUEOUS HUMOR TAP:** During the period of our study, 39 patients presented with complete FUS phenotype. Out of these, 37 tested positive for RV (95%) while negative results were present in 2 (5%) patients (Table 5). No alternative cause of uveitis was found in these 2 RV-negative FUS patients, who had negative results for other potential infectious causes tested.

TABLE 5. Prevalence and Characteristics of Patients With Fuchs Uveitis Syndrome According to Their Rubella Virus Analysis in Aqueous Humor

	Fuchs Uveitis Syndrome[a] (N = 39)
Aqueous humor analysis rubella virus positive	37
Aqueous humor analysis rubella virus negative	2[b]

[a]Defined as presence of iris atrophy, keratic precipitates, absence of posterior synechiae and cataract besides uveitis.

[b]These 2 patients were 50 and 33 years old at presentation to their first ophthalmologist. Both were white women born before 1987 and presented with unilateral anterior uveitis, heterochromia, cataract, and small keratic precipitates and did not develop synechiae during follow-up. Vitritis developed in both patients, but none had retinal scars. One patient had ocular hypertension and the other developed glaucoma. Both were negative for other viruses in their aqueous samples.

DISCUSSION

OUR STUDY SHOWS THAT RV-ASSOCIATED UVEITIS HAS A wider spectrum of clinical signs than the clinical features typical of FUS phenotype. Unilateral chronic anterior uveitis combined with vitritis and the absence of posterior synechiae were often noticed. Early development of cataract and glaucoma were frequent complications, whereas CME was typically absent. One in 4 patients with RV-associated uveitis developed glaucoma and more than half of the patients developed high IOP.

FUS is a clinical syndrome that in Europe is mostly caused by RV.[5,22] Our study supports this finding, since all but 2 patients with FUS were positive for RV in their aqueous samples. However, FUS can also have other causes, including CMV, *T. gondii*, human immunodeficiency virus, and trauma.[4,5,8,22–24] FUS due to CMV infection occurs more frequently in Asian countries.[7,25] The clinical characteristics of CMV-associated anterior uveitis mainly include nummular KPs and endotheliitis, but the clinical presentation with FUS phenotype also occurs.[7,25] Further, not all RV-associated uveitis cases exhibit the classical features of FUS.[8,9] In our series, RV was documented in the aqueous humor of nearly all patients presenting with a clinical syndrome of FUS; however, RV presented as FUS only in a minority of cases (Tables 4 and 5).

The common delay in diagnosis of the recent series might be caused by the lack of awareness of the clinical features characteristic of this disorder.[17,26] One of these characteristics is the frequent presentation with vitritis. In the past, FUS was mainly classified as anterior uveitis and the presence of vitritis was not widely acknowledged.[26] In the presence of vitritis, ophthalmologists usually do not consider FUS (and RV-associated uveitis) in their differential diagnosis, which was also apparent in the present series.[26] Our and previous studies show that vitritis is very common in RV-associated uveitis and might form a prominent clinical feature.[8] Vitritis present in RV-positive patients might be severe, which is also demonstrated by the number of eyes requiring vitrectomy owing to vitreous opacities (21/144; 15% of all affected eyes).

Anatomic classification of patients with combined anterior uveitis and vitritis caused a dilemma (Table 2). The Standardization of Uveitis Nomenclature classification defines anterior uveitis in cases where the focus of inflammation lies in the anterior chamber, and intermediate uveitis is used for patients in whom the focus of inflammation is in the vitreous. RV-associated uveitis, without a clear main focus of inflammation, does not fulfill any of these criteria. Though the classification of the combination of anterior uveitis with intermediate uveitis is permissible, it is not commonly used and included in previous uveitis surveys.[27,28] The anatomic classification becomes even more complicated for patients with associated retinal scars (10% in our current series). Moreover, studies in FUS patients showed that patients who underwent fluorescein angiography exhibited disc hyperfluorescence in 98% of cases; however, it is not clear whether these patients underwent an intraocular surgery before the fluorescein angiography was performed.[29]

The definitive diagnosis of RV-associated uveitis requires the confirmation of RV infection from intraocular fluids. As there is no cure available for RV infection, one could consider that the exact diagnosis is not crucial, as it requires intraocular fluid sampling. However, we believe an exact diagnosis is important in order to improve the management and counseling of patients. With the correct diagnosis of RV-associated uveitis, the patients are not subjected to unnecessary corticosteroids and other immunosuppressive therapies and can get reliable information about possible future complications and the need for follow-up. In unilateral cases, future involvement of the other eye is not likely.

All diagnostic tests have their limitations, and this is also the case for the aqueous fluid assessment. A positive aqueous humor assessment for RV does not always confirm a diagnosis of RV-associated uveitis and needs the critical appraisal of the exact laboratory results and clinical manifestations. In our series, 4 (3%) patients were eventually diagnosed as having other than RV-associated uveitis, despite their positive GWC for RV (Supplemental Table 2). Additionally, a negative test does not rule out RV as a cause of uveitis. The sensitivity of PCR and the limits of GWC laboratory techniques, as well as the leakage through a compromised blood-retina barrier, may have influenced the outcomes of laboratory analyses.[11] One could argue that the PCR-positive cases might have a higher level of evidence for RV infection.[30,31] Our RV

PCR-positive patients were slightly younger and had more chance to develop glaucoma. However, it should be kept in mind that the number of PCR-positive patients, as well as the duration of follow-up, was limited and the moment of diagnosis varied among patients. Thus, the clinical implications of PCR positivity for RV remain to be determined.

The current hypothesis of the pathogenesis of RV-associated uveitis is that the eye becomes infected during a systemic postnatal infection.[32] Although the viremia is cleared by the body's own immune reactions, the intraocular infection is not, and RV might persist in the eye and cause chronic inflammation. Our results strongly support this hypothesis, as none of our patients underwent vaccination at an early age. This is also indirectly supported by earlier investigations reporting a decline of FUS in vaccinated patients.[4] Congenital rubella syndrome usually occurs after a maternal infection during the first 16 weeks of pregnancy. One case report described a development of FUS in a patient with proven congenital RV infection.[33] As heterochromia was documented since birth in a few patients, it might be feasible that occasional cases of RV-associated uveitis may be due to congenital infection (possibly caused by the infection in the later stages of pregnancy).[32]

The retrospective design of this study is characterized by the lack of information on specific clinical characteristics, such as a development of iris involvement throughout the course of the disease. The exact appraisal of uveitis severity and its changes over time could not be analyzed. Another limitation was the selection of the patients suspected for infectious uveitis, which might have brought a selection bias into our study. However, a considerable proportion of all aqueous humor taps was tested for RV, which shows that not only patients with suspected RV were analyzed. Prospective studies could further clarify these shortcomings. Though cataract and glaucoma can be drug induced, our results suggest a limited role of corticosteroids on the development of cataract and glaucoma. Both complications were already present in a portion of patients at the first presentation to an ophthalmologist, before any treatment has been initiated. The role of treatment in the development of cataract and glaucoma cannot be entirely excluded. The clinical syndrome of FUS lacks standard diagnostic criteria. In our series, we have arbitrarily chosen the original criteria. This choice has its limitations and to overcome its restrictions, we include the prevalence of diverse clinical signs commonly associated with FUS in Table 4.

Ophthalmologists often assume that RV-associated uveitis always presents with the FUS phenotype. We demonstrate that patients with RV-associated uveitis show a much wider spectrum of clinical manifestations, commonly consisting of chronic unilateral anterior uveitis as well as vitritis, without posterior synechiae and CME. Cataract developed in nearly all patients, and half of the patients developed intraocular hypertension and/or glaucoma. Our results emphasize the need for long-term monitoring of intraocular pressure. None of the patients with RV-proven uveitis underwent vaccination against RV virus at an early age. Though there is no cure for this disease, the correct diagnosis might highly improve the management of this ocular disease and advance counseling for patients.

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