Rubella Virus-associated Uveitis: The Essentiality of Aqueous Humor Virological Analysis

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Abstract

Aims / background: Rubella virus-associated uveitis (RVAU) classically presents with the clinical features of Fuchs uveitis syndrome (FUS). We report a series of RVAU, and discuss the relevance of available diagnostic strategies, and vaccination to prevent disease.

Methods: We retrospectively included patients with RV-positive aqueous humor (AH) with RT-PCR and/or intraocular RV-IgG production, between January 2014 and December 2019. RV-IgG titers from AH and serum were compared with other virus-specific IgG titers (VZV and/or CMV and/or HSV-1), to determine the derived Goldmann-Witmer coefficient (GWC). Clinical findings at presentation and during follow-up are reported, as well as the anti-RV vaccination status.

Results: All 13 included patients demonstrated intraocular synthesis of RV-IgG (median GWC: 9.5; 3.2-100). RV-RNA was detected in one patient while PCR results were negative for other HSV1, VZV and CMV. The mean delay in diagnosis was 13 ± 12.6 years, with an initial presentation of FUS in only 3 patients (23%). Only four patients had been vaccinated, but all after the recommended age.

Conclusion: As RVAU is a pleiomorphic entity, virological analysis (RV RT-PCR and GWC) of aqueous humor is essential to improve the diagnosis and management of this entity. Improper vaccination against RV appears to be implicated in RVAU.

Introduction

Rubella virus (RV) is a strictly human pathogen transmitted via aerosols to infect the respiratory tract.¹ RV infections of unimmunized children or adults are usually benign but when it occurs during embryogenesis it can cause congenital rubella syndrome (CRS),² which typically includes cataracts, cardiac abnormalities and sensorineural deafness.^{3,4} Rubella and CRS are close to being eliminated in many countries due to implemented immunization programs. However, since the early 2000's, RV has been associated with the occurrence of chronic uveitis.⁵⁻⁷ The clinical picture of RV-associated uveitis (RVAU) is somewhat comparable with the so-called Fuchs uveitis syndrome (FUS) in a significant proportion of cases. This clinical entity is characterized by low grade, typically unilateral inflammation of the anterior segment associated with peculiar iris heterochromia and nodules, diffuse keratic precipitates (KPs), a predisposition to develop cataracts and glaucoma and a mild vitritis.⁸ FUS has been linked to infection with RV, Herpes simplex virus type 1 (HSV-1) and cytomegalovirus (CMV).^{7,9-11} The latter is common in Asian patients, with an onset of disease between the third to fifth decade, while RV predominates in Europeans and occur usually in the second to third decade of life.^{7,10,12} Groen-Hakan recently reported a large series of RVAU with none of the patients being vaccinated against RV, which was compelling for the still-debated role of RV in causing uveitis.⁷

Visual prognosis associated with FUS and more generally with RVAU, is considered good.^{7,13} However, diagnosis can be very challenging in various situations. In children, the disease may present initially with an incomplete clinical picture.¹⁴ Whereas clinical FUS landmarks (heterochromia) can be missed in adult, especially those with dark irides,^{15,16} or with bilateral diseases.¹⁷ Furthermore, corticosteroids are ineffective and deleterious, hastening the occurrence of cataract and glaucoma.⁸ Thus, FUS and RVAU misdiagnoses lead to inappropriate management and iatrogenic complications.

Virological analysis of AH is of major importance,⁷ by influencing the prevention of useless corticosteroids or antiviral therapy and ultimate iatrogenic complications¹⁸. However, virological diagnosis is not yet standardized.¹⁹ Two virological techniques are currently available: reverse transcriptase (RT)-PCR to detect RV RNA in AH, or an immunoassay to detect intraocular anti-RV IgG.²⁰

In this study, we report a series of proven RVAU and discuss the relevance of available diagnostic strategies, to improve patient management and vaccination to prevent disease.

Patients And Methods

Patients with RT-PCR confirmed RV-positive AH and/or intraocular RV-IgG production, between January 2014 and December 2019 in the Department of Virology, Paul Brousse hospital were considered for inclusion. Patients for whom clinical data were missing were excluded from analysis.

Data collected from patient files included: sex, ethnicity, age at onset of symptoms, age at diagnosis of RVAU (date of positive AH analysis and considered as the date of inclusion) and rubella vaccination history. In France, 2 rubella immunizations are recommended for all children from 12 months, since 1986. Rubella vaccination history was available for all patients born after 1986. Patients born before 1986 or born in a country lacking a national rubella vaccination program, were considered unimmunized unless proven otherwise. The diagnostic delay defined time between first ophthalmic symptoms and a positive AH rubella test.

Virological analysis

RV RT-PCR and anti-RV IgG testing was performed on the AH of all patients. One eye only was tested in cases of bilateral disease.

RNA extraction and RV RT-PCR

Viral RNA was extracted from 200 μ L AH using NucliSENS® easyMag® (bioMérieux, Craaponne, France), and eluted in 50 μ L. For RV, real-time PCR was performed using RV98F/RV251R primers (5' GGC AGT TGG GTA AGA GAC CA 3'/5' CGT GGA GTG CTG GGT GAT 3') and NSP-probe (5' FAM-ACA TCG CGC ACT TCC CAC G- BHQ1 3'), targeting the RV E1 gene region. All assays included a heterologous amplification system (internal positive control) to identify possible RT-PCR inhibition and to confirm assay integrity. Positive controls were provided by CDC, USA. One-step PCR cycling commenced at 50 °C for 15 min followed by 95 °C for 2 min and 50 cycles of 95 °C for 15 s, 60 °C for 40 s were performed using an Applied Biosystems ViiA7 instrument (Applied Biosystems,

ThermoFisher, Waltham – MA, USA). For HSV-1, VZV and CMV, real-time PCR were performed using Argene® HSV1-2 VZV R-gene and Argene® CMV R-gene (bioMérieux, Craponne, France) following manufacturer's instructions. PCR cycling commenced at 95 °C for 15 min, and 45 cycles of 95 °C for 10 s, 60 °C for 40 s were performed using an Applied Biosystems ViiA7 instrument (Applied Biosystems, ThermoFisher, Waltham – MA, USA). The lower limit of detection for the RV RT-PCR was 20 copies/ml.

Antibody detection and derived Goldmann-Witmer coefficient calculation

IgG antibody titres were determined using Enzygnost specific IgG enzyme-linked immunosorbent assay kits (Siemens, Marburg, Germany) for RV, HSV-1, VZV and CMV, according to manufacturer's instructions. AH and blood serum were paired for analysis in the same analytical run. Optical density was evaluated as arbitrary concentration units (AU), by reference to a standard curve. RV-IgG titers from AH and serum were compared with other virus-specific IgG titers (VZV and/or CMV and/or HSV-1), to determine the Goldmann-Witmer coefficient²¹ (GWC'): $GWC' = (AH\ RV-IgG \times serum\ other\ virus-IgG) / (serum\ RV-IgG \times AH\ other\ virus-IgG)$. GWC' of greater than 3 indicated RV-IgG-positive AH. Ratios were calculated with at least 2 other virus-specific IgG, as some patients may be seronegative for HSV-1, CMV or VZV. Patients seronegative for two other viruses were not considered for inclusion in the study.

Ophthalmological data and clinical presentation

Ophthalmological data included best-corrected visual acuity (BCVA) and slit-lamp findings. Patients were categorized into two groups based on the clinical presentation. Group 1 included typical FUS patients,⁷ with all criteria required for diagnosis (including: i) chronic low-grade anterior segment inflammation, ii) diffuse stellate KPs, iii) iris heterochromia, iv) lack of posterior synechia and v) cataract (**Figure 1**)). Group 2 included patients not fulfilling typical FUS criteria, or with additional clinical presentations such as: predominant posterior segment involvement, or retinal vasculitis. Complications experienced were also collected at virological diagnosis and during the follow-up and included: i) ocular hypertension (OHT) (defined by intraocular pressure > 21mmHg without glaucomatous optic neuropathy), ii) glaucoma (i.e. typical glaucomatous optic nerve head and visual field alterations) and iii) surgical procedures.

The study adhered to the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of the French Society of Ophthalmology (IRB 00008855 Société Française d'Ophtalmologie IRB#1). Informed consent was obtained for all the participants (or from a parent for participants under 18).

Results

Demographics and rubella vaccination status

Between January 2014 and December 2019, 38 patients tested positive for rubella by either RV RT-PCR and/or GWC'. The complete medical files of 13 patients was retrieved (6 women, 7 men), aged 49.6 ± 22.2 (7-86) years at inclusion (Table 1). The delay in diagnosis was 13 ± 12.6 years (0-42). Most patients (9/13) were not immunized against rubella, while the remaining (4/13) were immunized after the recommended age (between 6 and 28 years) (**Table 1**). Most patients were Caucasian and born in France (10/13), while 2 originated from Asia, where they were born (case #10 from India and case #13 from Vietnam) and one was born in Africa (from African descent) (case #11).

Virological data

RV RT-PCR as well as HSV-1, VZV and CMV PCR were performed in 11 cases and RV-RNA was detected in the AH of one patient (case #12). PCR results for other viruses were all negative.

All patients were seropositive for RV, HSV-1 and VZV. Additionally, ten patients were also seropositive for CMV. Therefore, GWC' could be calculated for all patients using two other viruses, and for ten patients, three other viruses. AH anti-RV-IgG was demonstrated in all cases, with a median GWC' of 9.5 (range 3.2 - 100) (**Table 2**). GWC' was negative for all other viruses in all patients.

Ophthalmological data and clinical presentation

Three patients were classified into Group 1, fulfilling all FUS criteria, and 10 were classified in Group 2. Patient's initial complaints were vision loss ($n = 11$, 85%) and floaters ($n = 3$, 23%). At presentation, mean BCVA of the affected eyes was 0.6. Ten patients had cataract in the affected eyes (3 in group 1 and 7 in group 2) and 7 patients had either OHT or glaucoma (1 in group 1 and 6 in group 2). Low grade inflammation of the anterior segment was present diffuse KPs were present in 8 patients (3 in group 1 and 5 in group 2 for both). Iris atrophy, heterochromia, or nodules were noted in 6, 3 and 3 patients, respectively (**Table 3**). Vitreous involvement was present in 10 eyes (9 patients) and retinal vasculitis in 5 eyes (4 patients). One patient (case #10) had bilateral disease.

At follow-up of 96 ± 103 months (2-306), BCVA was similar (0.6) ($p = 0.61$). Cataract was detected in one additional eye, surgery was required in 10 eyes (9 patients). Glaucoma occurred in 3 additional eyes and surgical procedures were required in 6 eyes of 6 patients. The mean delays between onset of symptoms and virological diagnosis was 157.6 ± 153 months.

Discussion

The clinical spectrum of RVAU

RVAU appears to be a pleiomorphic entity. As in previous studies,⁷ our cohort had a minority of patients fulfilling FUS criteria (3/13 patients). In group 2, some patients had completely atypical pictures where retinal vasculitis and posterior segment features were predominant, while other had "incomplete" FUS that could be explained by individual particularities or the moment in the course of the disease where clinical examination was performed. Diagnosis of heterochromia depends on the initial amount of iris pigment and the degree of atrophy. Therefore, it is often absent in dark-colored irides and during the first

years of diseases,^{12,14} and present in approximately 1/4 of RVAU patients.²² The common clinical denominator of RVAU in the previous series and in our study, however, was the absence of posterior synechiae and macular edema.⁷ These clinical findings are not specific for RVAU, and overlap with CMV anterior uveitis²³ and some HSV-1- and VZV-related uveitis.⁹⁻¹¹

The essential role of virological AH analysis

Altogether, there is weakness in clinical diagnosis alone, while virological assays contribute significantly in correctly managing patients with uveitis. Accurate diagnosis can improve management, by avoiding unnecessary corticosteroids or antiviral treatments if Herpesviridae is suspected. In contrast, some FUS may be caused by CMV or HSV-1 and thus require specific antiviral treatments.^{10,24} Furthermore, some patients may be co-infected with RV and HSV-1.¹¹

It is difficult to diagnose RVAU with RV-RNA detection alone and combining immunological and molecular assays may improve the diagnosis of infectious uveitis²⁵⁻²⁷. RVAU diagnosis relies on RV-IgG-positive AH and/or presence of RV-RNA.⁷ While all our patients were GWC' positive, only one was positive by RT-PCR. Thus, RT-PCR diagnosis alone would have missed 90% of cases. Our results are consistent with previous studies, where 10 to 20% of suspected cases were positive by RT-PCR, whereas 97 to 100% of AH samples were RV-IgG-positive.^{6,7,11} Low viral loads and the small volumes of AH fluid contribute to the low sensitivity of RV RT-PCR, which also contain inhibitory compounds.²⁸ In the future, deep sequencing has the potential to detect any foreign genomic sequence in small clinical samples (20 - 50µL) and could greatly improve the diagnosis of infectious uveitis.²⁹

Pathophysiology of ocular infections with RV

Detection of RV-RNA from AH in some patients and anti-RV IgG in all, demonstrates that RVAU can be caused by intraocular infection and possibly persistent viral replication associated with an immune-mediated inflammation triggered by systemic RV infection. Thus, the seric anti-RV IgG indicates a necessity for RV viremia, whether postnatal or *in utero*.³⁰ Winchester *et al.* reported high titre of anti-RV IgG and RV RT-PCR-positive AH in a CRS patient with bilateral FUS in his third decade.³¹ None of patients in our series had history or signs of CRS but as we did not conduct in depth investigations, CRS cannot be excluded.

Also consistent with results of previous studies is the absence of Rubella vaccination in RVAU patients.^{7,32} Meanwhile, recent epidemiological studies demonstrate a decline in FUS incidence since the introduction of mass rubella vaccination and this trend was not observed in an unimmunized control group.³³

Why RV still occurs in immunized patients?

In France, vaccination against rubella is recommended since 1986, and the double-dose regime given between 12 and 18 months of age is mandatory since 2018.³⁴ Stunf *et al.* reported that 4/11 anti-RV-positive AH RVAU patients were immunized.³⁵ However, RV infection occurring before vaccination cannot be ruled out. Indeed, in our study, 4/13 RVAU patients reported incomplete vaccination. Three were immunized late during childhood, between ages 6 and 7, leaving them exposed to rubella prior to vaccination, in the early 80's, a period where RV was highly prevalent in France. Our third 'partially immunized' case was born in Vietnam when rubella vaccination were unavailable, and was subsequently immunized at the age of 28, in France, after the birth of a child upon negative RV-IgG in the early 80's. However, a serologic control performed after vaccination was still negative and there were no ocular complaints. In contrast, the patient had seroconverted to RV-IgG- performed with ELISA assay in our study was positive by the time of our study. It is still possible that her initial test was false negative due to the poor sensitivity of serologic assays (inhibition hemagglutination assay) performed at this time.³⁶

The rubella immunogen is a live-attenuated virus, and so it cannot be completely ruled out that vaccination could be involved in some rare cases of RVAU, as it is the case for live attenuated VZV vaccination.³⁷ However, to date this has never been demonstrated. Sequencing and phylogenetic analysis could help to confirming or excluding this possibility. However, RV-RNA sequencing in the AH is extremely challenging,³⁸ and it failed in our only RV-PCR-positive patient, due to insufficient sample volume.

In summary, RVAU is a pleiomorphic entity for which clinical diagnosis can be easily undermined. AH analysis combining RV RT-PCR and detection of intraocular specific anti-RV IgG are essential in the management of patients with compatible clinical findings. Detection of other pathogens should also be performed. Overall, it seems that improper vaccination against RV is implicated in RVAU.

Declarations

Author's contributions:

J.P., M.L., C.V.F., A.R. designed the study, analyzed the data and drafted the manuscript.

E.B., O.H., I.L., A.K., F.M., E.B. analyzed the data and drafted the manuscript.

All authors reviewed the manuscript.

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Tables

Table 1: Demographics and rubella vaccination status. M = male, F = Female, C = Caucasian, Af = African descent, A = Asiatic descent, NA = not applicable.

Case #	gender / age at inclusion	Ethnic background	Rubella Vaccination	Age at vaccination (years)	Age at onset of ophthalmic symptoms	Diagnostic delay
1	M / 34	C	+	6	29	5
2	M / 42	C	-	NA	37	5
3	F / 63	C	-	NA	59	4
4	M / 48	C	-	NA	30	17
5	F / 29	C	+	7	29	1
6	F / 86	C	-	NA	75	11
7	M / 7	C	+	6	6	1
8	F / 84	C	-	NA	84	0
9	M / 49	C	-	NA	33	15
10	F / 36	A	-	NA	23	14
11	M / 61	Af	-	NA	18	42
12	M / 40	C	-	NA	18	22
13	F / 66	A	+	28	36	30

Table 2: Virological data. AH = Aqueous humor, P = positive, N = negative, GWC' = derived Goldmann-Witmer coefficient, PCR = Polymerase chain reaction, NA = not available.

Case #	HSV-IgG in serum/AH	VZV-IgG in serum/AH	CMV-IgG in serum/AH	RV-IgG in serum/AH	GWC' RV/HSV	GWC' RV/CMV	GWC' RV/VZV	PCR in AH
1	+	+	+	+	10	5	8.8	-
2	+	+	+	+	100	33	25	NA
3	+	+	+	+	3.2	3.7	3.5	-
4	+	+	-	+	8	NA	10.2	-
5	+	+	-	+	3.5	NA	4	NA
6	+	+	+	+	3.5	5.7	4.8	-
7	+	+	+	+	4.9	6.7	3.3	-
8	+	+	-	+	13.3	NA	14.1	-
9	+	+	+	+	12.8	9.8	10.2	-
10	+	+	+	+	45	68.1	57	-
11	+	+	+	+	7.2	12.3	12.5	-
12	+	+	+	+	11.1	33.3	14.7	+
13	+	+	+	+	5.6	8.4	9.2	-

Table 3: ophthalmological findings. OD = right eye, OS = left, OU = both eyes, BCVA = best corrected visual acuity, KPs = keratic precipitates, OHT = ocular hypertension, NA = not applicable, G = glaucoma. * visual loss secondary to corneal edema caused by pseudophakic endothelial decompensation (not directly linked with RVAU).

Case #	Laterality	Presenting symptoms	BCVA at first visit (dec.)	Diffuse KPs	Low grade anterior segment inflammation / posterior synechiae	Iris atrophy /heterochromia / nodules	Vitritis	Retinal vasculitis	Group	Cataract at presentation / during follow-up	Cataract Surgery / age	OH gla at pre / d foll
1	OD	Floaters + vision loss	0.3	+	-/-	+/-/-	+	-	2	+/+	NA	-/-
2	OD	Vision loss	0.5	+	+/-	+/+/+	+	-	1	+/+	43	-/-
3	OS	Vision loss	0.6	+	+/-	-/-/-	+	-	2	+/+	52	-/-
4	OS	Vision loss	0.1	+	+/-	+/+/+	+	+	1	+/+	33	OH
5	OS	Floaters + Visual Loss + pain	0.7	-	-/-	-/-/-	-	+	2	-/-	NA	G/U
6	OD	None	0.4	+	-/-	-/-/-	+	-	2	+/+	75	OH
7	OS	Vision loss	0.6	-	+/-	-/-/-	+	+	2	-/-	NA	-/-
8	OD	Vision loss	1	-	+/-	+/-/-	+	-	2	-/-	72	G/U
9	OD	Floaters	0.9	+	-/-	+/-/-	-	-	2	+/+	35	G/U
10	OU	Vision loss	1	+	+/-	-/-/+	+	+	2	+/+	OD: 28 OS: 35	-/-
11	OD	Photophobia + Vision loss	0.8	-	+/-	-/-/-	-	-	2	+/+	57	G/U
12	OS	Vision loss	0.9	+	+/-	+/+/-	+	-	1	+/+	NA	-/G
13	OD	Vision loss	1	-	-/-	-/-/-	-	-	2	+/+	59	OH

Figures

Figure 1

Clinical features of Fuchs uveitis syndrome. A & B) Iris heterochromia (patient #4). Left affected eye (B) is clearer and smoother than unaffected right eye (A). C) Iris nodules on the collarette (also known as Koeppé's nodules) (patient #10). D) Diffuse keratic precipitates (patient #12).

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