Risk Factors for Secondary Glaucoma in Patients with Vogt-Koyanagi-Harada Disease

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Research Article

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Abstract

Background: To identify the prevalence and risk factors for secondary glaucoma among Mexican-mestizo patients with Vogt-Koyanagi-Harada Disease (VKH). A retrospective cohort study was conducted to identify the risk factors for developing secondary glaucoma based on demographic, clinical, and epidemiological variables of VKH Mexican-mestizo patients. Risk estimates were calculated using a Cox proportional hazards regression model.

Main text: One hundred eyes of 50 patients, 44 (88%) women and 6 men (12%) with a median age of 35.5 years (IQR 29 – 46), and a median follow-up time of 72 months (IQR 13.7 – 126.7) were included for analysis. The prevalence of glaucoma was 20%, with angle-closure glaucoma accounting for 70% of all cases. Significant clinical risk factors for glaucoma development were a chronic recurrent stage at presentation (RR 2.88 95% CI 1.11 – 12.63, p=0.037), more than two episodes of recurrent anterior uveitis (RR 8.52 95% CI 2.02 – 35.92, p<0.001), angle-closure disease (ACD, RR 7.08 95% CI 2.44 – 20.48, p<0.001), iris bombé (RR 5.0 95% CI 2.10 – 11.90, p<0.001), and peripapillary atrophy (RR 3.56 95% CI 1.43 – 8.85, p<0.001). Exposure to prednisone for more than 24 months (RR 9.33 95% CI 2.21 – 39.28, p<0.001) or topical corticosteroid drops for more than 12 months (RR 3.88 95% CI 1.31 – 11.46, p=0.007) were associated with an increased likelihood for secondary glaucoma development.

Conclusions: Glaucoma is a frequent complication in patients with VKH, often attributed to mixed pathogenic mechanisms. Chronic disease at presentation, recurrent inflammation, angle-closure mechanisms, iris bombé, and peripapillary atrophy represent clinically significant risk factors for secondary glaucoma development. Prompt and aggressive steroid-spearing immunosuppressive therapy for reaching adequate control of inflammation may lower the risk of glaucoma in VKH patients.

Background

Vogt-Koyanagi-Harada disease (VKH) is a primary autoimmune choroiditis characterized by a rapid-onset bilateral granulomatous panuveitis associated with neurologic (headache, meningismus, tinnitus) and integumentary (alopecia, poliosis, vitiligo) findings [1, 2]. Choroidal inflammation manifests as serous retinal detachment, optic disk edema, and depigmentation resulting in a sunset glow fundus (SGF) appearance [3]. The prevalence of VKH in uveitis clinics in Mexico, where most of the population is mestizo, is reported to be 2.4% [4]. The clinical presentation can occur in four distinct phases: prodromal, acute uveitis, convalescent, and chronic recurrent [5]. Early combined corticosteroid and immunosuppressive therapy (IMT) can improve the visual outcome associated with comorbidities, which frequently occur due to longer disease duration and recurrent episodes of inflammation [3]. Among the most frequently reported sight-threatening complications of VKH are band keratopathy, cataract formation, secondary glaucoma, posterior synechiae, and subretinal fibrosis [6].

Secondary glaucoma is a common and potentially blinding complication in VKH eyes, with a prevalence ranging from 2.6% to 45% [7, 8]. Glaucoma was reported as a complication in 24% of eyes in a case

series of 43 VKH Mexican patients, and the majority of them (67%) required glaucoma surgery to control intraocular pressure [9]. Few studies have examined risk factors for glaucoma development in VKH concerning clinical characteristics and treatment modalities. In an Indian study involving 448 VKH eyes, uveal effusion (odds ratio [OR], 9.47) and an increased number of recurrent inflammatory episodes were identified as risk factors for glaucoma development (OR, 1.31) [10]. Other reported risk factors for ocular hypertension (OHT) and glaucoma development in a large Chinese population of 1457 patients with VKH included worse visual acuity (VA) at first (OR, 4.8) and last (OR, 4.2) visits, longer interval between the onset of uveitis and referral (OR, 3.3), more than three recurrent episodes of inflammation (OR, 4.17), and posterior synechiae development (OR, 1.78) [11].

There is convincing evidence that long-term corticosteroid treatment in patients with uveitis is associated with an increased risk of OHT and glaucoma development. According to a study of uveitic eyes, a prednisone dose higher than 7.5mg/day (adjusted hazard ratio [aHR], 1.86), periocular steroids in the last three months (aHR, 2.23), more than eight drops per day of topical corticosteroid (aHR, 2.58), and prior use of fluocinolone implants (aHR, 9.75) were major risk factors for glaucoma development [12].

The purpose of this study was to determine the prevalence of glaucoma associated with VKH disease and identify its clinical and therapeutic risk factors in a cohort of Mexican patients.

Methods

Design and setting

We conducted a retrospective cohort study on VKH Mexican-mestizo patients at a tertiary eye-care center. The clinical records from our institution's Ocular Immunology and Uveitis Service were reviewed between January 2002 and October 2020. The study was previously approved by our institution's Ethics and Research Committees (License No. P000367-FRGVKH-CEIC CR002) in adherence to the tenets of the Declaration of Helsinki.

Study population

Patients included had a minimum follow-up of 12 months. They were diagnosed according to the revised diagnostic criteria for VKH published by an International Committee on Nomenclature in 2001 [13]. Other forms of uveitis resembling VKH were excluded based on the clinical history, laboratory investigation for infectious diseases, physical and ophthalmologic examinations. Patients were classified into two groups based on the presence of glaucoma or not at the last visit.

Clinical data collected included: age, gender, age at diagnosis, extraocular manifestations, symptoms onset, and VKH stage at the time of diagnosis. The total exposure time to oral and topical corticosteroids was calculated for the first 24 months of follow-up. Early IMT was defined as nonsteroidal anti-inflammatory medication within 6 weeks of symptom onset of the uveitic phase. Glaucoma was defined

as a cup-to-disc ratio larger than 0.7, asymmetry between the two eyes larger than 0.2, or the presence of a nerve fiber layer defect on fundus examination.

Statistical analysis

Statistical analysis was performed using the IBM Statistical Package for Social Sciences (SPSS) v.21 (IBM Inc., Armonk, NY, USA). We first assessed normality using the Kolmogorov-Smirnov test. The demographic characteristics were summarized using means and standard deviations for normally distributed data, whereas medians and interquartile ranges were used to summarize non-normally distributed data. For comparisons, normally distributed data were analyzed using the parametric T-student test, whereas non-normally distributed data were analyzed using the Mann-Whitney test. Multivariate logistic regression analysis was performed to identify risk factors for developing secondary glaucoma in non-glaucomatous eyes. The Kaplan-Meier survival curve was plotted for glaucoma occurrence in VKH eyes without glaucoma at the first visit. A p-value <0.05 was considered statistically significant.

Results

A total of 50 patients (100 eyes) with VKH disease were divided into two groups: 10 with glaucoma (20 eyes) *vs*. 40 without glaucoma (80 eyes). The clinical and demographic characteristics of the cohort are described in Table 1.

1 Demographic data and clinical features of VKH eyes with and without glaucoma.

	Total eyes (*n* = 100, 100%)	Non-glaucoma (*n* = 80, 100%)	Glaucoma (*n* = 20, 100%)	*P*
r				
nale	88 (88)	68 (85)	20 (100)	
le	12 (12)	12 (15)	0 (0)	0.327
diagnosis, years[a]	35.5 (29-46)	35 (26.7-45.7)	37 (29-54)	0.304
-up, months[a]	72 (13.7-126.7)	39 (11-95)	116.5 (90-175)	0.001
om onset, months[a]	1 (1-22)	1 (1-7)	23 (1-96)	0.009
cular findings[b]				
iosis	8 (8)	4 (5)	4 (20)	0.049
iligo	14 (14)	8 (10)	6 (30)	0.021
-like	35 (35)	27 (33.8)	8 (40)	0.60
adache	76 (76)	60 (75)	16 (80)	0.64
nitus	60 (60)	50 (62.5)	10 (50)	0.307
tage at diagnosis				
eitic	69 (69)	62 (77.5)	7 (35)	
ronic-recurrent	27 (27)	14 (17.5)	13 (65)	
ıvalescent	4 (4)	4 (5)	0 (0)	<0.001

terquartile range, *VKH* Vogt-Koyanagi-Harada.
ian (IQR).
eral patients reported ≥ 1 extraocular finding.

The median age was 35.5 years (IQR 29-46), and most patients were women (88%, n=44). The median follow-up time was 72 months (IQR 13.7-126.7).

Secondary glaucoma was identified in 20 eyes of 10 patients (prevalence of 20%). Of those, 4 eyes already had glaucoma at the first visit. Angle-closure disease (ACD) was found in 10 of 16 eyes (71%) that developed glaucoma, but only in 14 eyes (19%) in the non-glaucoma group (p<0.001).

The median time elapsed between the disease onset and the first visit to our clinic was significantly longer in patients with glaucoma (23 *vs*. one month, p=0.009). Additionally, the glaucoma group had a longer follow-up period (116.5 *vs.* 39 months, p=0.001). There was a difference in the extraocular findings between groups, where 6 eyes with glaucoma (30%) developed vitiligo compared to only 8 (10%) eyes without glaucoma (p=0.021). While 13 eyes (65%) of the glaucoma group presented in the chronic recurrent phase of VKH disease, only 14 eyes (17.5%) did from the non-glaucoma group (p<0.001). In glaucoma-affected eyes, the time required to achieve inflammatory control (p=0.026) and the time elapsed to the first VKH disease recurrence (p<0.001) was significantly longer (Table 2).

Recurrences and inflammatory control of VKH eyes with and without glaucoma.

	Total eyes *n* (%)	n	Non-glaucoma *n* (%)	n	Glaucoma *n* (%)	n	*P*
ecurrences[a]	59 (60.2)	98	44 (56.4)	78	15 (75)	20	0.13
1st recurrence, months[a]	5 (2-10)	67	5 (2-8)	45	18 (8-48)	16	<0.001
inflammatory control, a	2 (1-3)	90	2 (1-3)	74	3 (2-3)	16	0.026
nflammation at last visit[a]	76 (76.8)	99	20 (25.3)	79	3 (15)	20	0.392

erquartile range, *VKH* Vogt-Koyanagi-Harada.
an (IQR).

At the initial visit, VKH patients in the uveitic or chronic recurrent phase of the disease with active inflammation were treated with oral prednisone (1mg/kg/day) and topical corticosteroids as a standard management protocol. Simultaneously, IMT was initiated if there were no systemic contraindications or laboratory abnormalities, with azathioprine (2-2.5mg/kg/day), the first-line treatment in all patients. Table 3 summarizes the anti-inflammatory treatment used during a 24-month interval in eyes with and without glaucoma.

Table 3 Anti-inflammatory therapy for eyes with VKH disease.					
	Glaucoma ***n* (%)**	**n**	**Non-glaucoma** ***n* (%)**	**n**	***P***
Immunosuppressive therapy					
Baseline	20 (100)	20	74 (92.5)	80	0.597
6 months	16 (88.9)	18	64 (89)	72	0.999
12 months	16 (88.9)	18	48 (77.4)	62	0.503
24 months	14 (77.8)	18	31 (51.6)	60	0.049
Topical steroid					
Baseline	17 (85)	20	65 (81.3)	80	0.696
6 months	15 (83.3)	18	44 (59.5)	74	0.058
12 months	15 (83.3)	18	28 (42.4)	66	0.002
Oral prednisone (mg)[a]					
Baseline	40 (30-52.5)	18	50 (20-60)	70	0.352
6 months	7.5 (6.8-11.2)	18	10 (5-15)	60	0.563
12 months	8.7 (5.6-13.7)	8	6.2 (5-7.5)	36	0.151
Total steroid exposure[a]					
Months of Oral Prednisone	62 (39-104)	18	11.5 (7-26.7)	80	<0.001
Months of Topical Steroid	25 (14-54)		8.5 (2.2-24)		0.008
IQR interquartile range, *VKH* Vogt-Koyanagi-Harada. [a]Median (IQR)					

As shown, a significant number of eyes (n=15, 83.3%) were using topical corticosteroids after 12 months of therapy (p=0.002). There was no difference in the dose regime of oral prednisone between groups during the entire follow-up time; however, the total time of systemic corticosteroid exposure was significantly different between groups. While in the glaucoma group, the total time of exposure to oral prednisone was 62 months (IQR 39-104), in the non-glaucoma group, it was only 11.5 months (IQR 7-26.7, p<0.001).

Kaplan-Maier survival analysis was done for the development of glaucoma based on the VKH phase at presentation. Figure 1 shows the cumulative probabilities for developing glaucoma. None of the eyes within the acute uveitic phase or convalescence at presentation developed glaucoma in the first and second years, whereas only 22.1% developed glaucoma in the fifth year. On the other hand, the eyes in the chronic recurrent phase of the disease at the initial visit developed glaucoma at 21.1% in the first year and 31.6% in the second year.

A multivariate logistic regression analysis was performed to determine the effect of oral and topical corticosteroids, early IMT, the stage of VKH disease at diagnosis, and clinical characteristics on the likelihood of developing secondary glaucoma as depicted in Table 4.

Table 4 Multivariate analysis of risk factors for secondary glaucoma in eyes with VKH disease.

Risk Factor	Glaucoma eyes (n = 16, 100%)[a]	Controls (n = 78, 100%)[b]	Relative Risk (95% CI)	*P*
Oral prednisone > 24 months	12 (85.7)	24 (30.8)	9.33 (2.21-39.28)	<0.001
Topical steroids > 12 months	10 (71.4)	26 (33.3)	3.88 (1.31-11.46)	0.007
Anterior chamber cells ≥ 2+	11 (78.6)	37 (47.4)	3.36 (1.003-11.26)	0.032
≥2 recurrences	12 (85.7)	26 (33.3)	8.52 (2.02-35.92)	<0.001
Chronic-recurrent stage	6 (42.9)	13 (16.7)	2.88 (1.11-12.63)	0.037
Angle closure	10 (71.4)	14 (18.9)	7.08 (2.44-20.48)	<0.001
Iris bombé	6 (42.9)	6 (7.7)	5.00 (2.10-11.90)	0.002
Peripapillary atrophy	6 (42.9)	10 (12.8)	3.56 (1.43-8.85)	0.014

[a]Four eyes with glaucoma at first visit were excluded.
[b]Two eyes without management with oral prednisone (convalescent stage) were excluded.

Exposure to topical corticosteroids for more than 12 months (RR 3.88 95% CI 1.31 – 11.46, p=0.007) or oral prednisone for more than 24 months (RR 9.33 95% CI 2.21 – 39.28, p<0.001) were major treatment risk factors. Reduced risk for glaucoma was not found in our population when early IMT was started within 6 weeks of the symptom onset (RR 0.40, 95% CI 0.12-1.30, p=0.183). Table 5 compares the clinical characteristics of VKH eyes with and without glaucoma at initial and final visits.

Table 5 Comparison of clinical characteristics of VKH eyes at presentation and final evaluation.

	Presentation				*P*	Last visit				*P*
	Eyes with glaucoma *n* (%)	**n**	**Eyes without glaucoma *n* (%)**	**n**		**Eyes with glaucoma *n* (%)**	**n**	**Eyes without glaucoma *n* (%)**	**n**	
BCVA[a]	1.55 (0.75-2.8)	20	1 (0.4-1.3)	80	0.001	0.55 (0.22-2.3)	20	0.2 (0-0.6)	80	0.003
Iris nodules	14 (70)	20	38 (47.5)	80	0.072	9 (45)	20	9 (11.3)	80	<0.001
Angle configuration										
Open angle Closed angle	5 (25) 15 (75)	20	62 (79.5) 16 (20.5)	80	<0.001	6 (30) 14 (70)	20	14 (17.5) 66 (82.5)	80	0.223
IOP[a]	17 (14-23.5)	20	14 (11-16)	80	<0.001	13.5 (12-15.7)	20	14 (12-16)	80	0.855
SGF	10 (55.6)	18	16 (20)	80	0.002	16 (88.9)	18	50 (62.5)	80	0.031
DF Nodules	12 (66.7)	18	25 (31.3)	80	0.005	18 (100)	18	58 (60)	80	0.001
SRD	7 (38.9)	18	40 (50)	80	0.394	1 (5.6)	18	2 (2.5)	80	0.46
PPA	10 (55.6)	18	10 (12.5)	80	<0.001	14 (77.8)	18	39 (37.5)	80	0.002
OD swelling	4 (22.2)	18	44 (55)	80	0.012	0 (0)	18	2 (2.5)	80	<0.001
C/D ratio[a]	0.6 (0.35-0.85)	8	0.4 (0.3-0.5)	27	0.022	0.8 (0.55-0.9)	8	0.4 (0.3-0.4)	27	<0.001

VKH Vogt-Koyanagi-Harada, *BCVA* best corrected visual acuity, *IOP* intraocular pressure, *SGF* sunset glow fundus, *DF* Dalen Fuchs, *SRD* serous retinal detachment, *PPA* peripapillary atrophy, *OD* optic disc, *C/D* cup-to-disc ratio.
[a]Median (IQR)

Discussion

Secondary glaucoma is one of the most feared complications of VKH disease. The prevalence of secondary glaucoma in VKH disease ranges from 2.6% to 45% [10, 14-16]. The chronic recurrent form of VKH disease [15, 17], significant anterior chamber reaction (≥ 2+) [16, 17], three or more VKH recurrences, and the presence of posterior synechiae, extraocular manifestations, and a worse VA at disease onset [16], are deemed as significant risk factors for secondary glaucoma development. As expected, patients who develop OHT or glaucoma have the worst visual prognosis [10, 11].

The present study findings suggest that the chronic recurrent stage, recurrent episodes of inflammation, ACD, and peripapillary atrophy are all significant risk factors for the development of glaucoma in eyes with VKH. In this cohort of 50 patients, we found a 20% prevalence of glaucoma, which is consistent with previous reports [6, 10].

Numerous mechanisms have been implicated in the development of glaucoma in VKH eyes. Traditionally, open-angle mechanisms associated with corticosteroid-induced OHT and inflammatory trabecular meshwork dysfunction have been considered the leading causes of glaucoma in VKH [14]. However, the role of angle-closure mechanisms has gained considerable interest in uveitic glaucoma [18]. Clinical

signs of ACD are the development of peripheral anterior synechiae, complete pupillary block associated with posterior synechiae (secclusio pupillae), iris bombé configuration, and ciliary body detachment with anterior rotation of ciliary processes [11]. In our VKH population, angle-closure was an important pathogenic mechanism in most eyes that developed glaucoma (71.4%). Chronic recurrent episodes of anterior segment inflammation are certainly a significant factor in the high prevalence of ACD. A retrospective case series of 48 VKH patients in Thailand reported glaucoma in 29% of the eyes. The authors, however, reported no association between the development of ocular complications, including glaucoma, and the stage of VKH disease at presentation and treatment modalities [19].

In their study, only 6/45 patients (13%) had VKH disease recurrences, all of them associated with early corticosteroid therapy withdrawal. Thus, the authors suggest that the lack of associated risk factors (i.e., chronic recurrent VKH disease) and glaucoma development might be related to long-term use of corticosteroids and/or IMT [19]. These findings are supported by Al-Kharashi et al., who reported that rapid corticosteroid tapering, defined as 1 mg/kg of oral prednisone for less than 2 months or tapering to 10 mg in less than two months, was associated with $\geq$ 3 recurrences. Moreover, the authors reported that multiple recurrences were significantly associated with a higher incidence of glaucoma development [16].

The optimal management of acute VKH with a combination of a corticosteroid and a nonsteroidal immunosuppressive agent is critical for avoiding disease progression to the chronic recurrent phase, which may occur in up to two-thirds of patients [20]. Impending disease progression can only be possible if prompt and adequate treatment is started within three weeks of symptoms onset [3]. In the present study, the time interval between symptoms onset and the first consultation was longer (23 months) in the glaucoma group than in eyes without glaucoma (one month). This finding demonstrates that glaucoma development is related to chronic disease progression, which is more refractory to treatment and requires prolonged anti-inflammatory treatment. The high prevalence of vitiligo in the glaucoma group could be related to the chronic recurrent phase at presentation. VKH Hispanic patients usually present without extraocular changes, developing once they evolve into a chronic disease [21]. The survival analysis shows a clear difference between VKH phases, where none of the eyes developed glaucoma in the first and second year of follow up probably related to adequate anti-inflammatory treatment. The survival analysis highlights the importance of the VKH phase at presentation. In eyes presented in the uveitic stage, only 22.1% developed glaucoma in a 5-year follow-up. In contrast, in the eyes in the chronic recurrent stage, the same incidence of glaucoma was found in the first year of follow-up.

Regarding anterior segment inflammation, our findings are consistent with previous reports of severity of anterior chamber reaction ($\geq$ +2 cells) and more than two recurrences of inflammation as risk factors for glaucoma development in VKH [10, 11]. Chronic inflammation requires prolonged and repeated corticosteroid administration. In the present study, patients with VKH who received oral prednisone for more than 24 months and/or topical corticosteroids for more than 12 months had a nine-fold and four-fold increased risk of developing glaucoma during the follow-up time. The correlation of peripapillary atrophy (PPA) as a risk factor for glaucoma in VKH can be related to corticosteroid use. There is evidence that the development of PPA is dependent on exposure to high doses of systemic corticosteroids [22].

Moreover, the development of PPA is significantly associated with an increased risk of either cataract, glaucoma, or subretinal neovascular membrane formation [17]. In our study, PPA has been deemed a significant risk factor for glaucoma development (RR 3.56 95% CI 1.43 – 8.85, p<0.001), and as stated above, glaucoma development was associated with prolonged topical and systemic corticosteroid exposure. Thus, recognizing that oral prednisone exposure might represent a modifiable risk factor for the development of glaucoma emphasizes the critical role of early IMT. Urzua et al. reported that the chronic-recurrent form of VKH disease, a VA ≤ 20/200, tinnitus, and the presence of SGF at presentation were risk factors for poor glucocorticoid response, which the authors defined as (1) persistent retinal detachment and (2) absence of visual and (3) inflammatory improvement [23]. The authors reported no significant differences in VA improvement or reduced risk of ocular complications (i.e., glaucoma, OHT, cataract) in patients with or without early IMT (<6 weeks). However, they found a significant improvement in VA in eyes unresponsive to oral corticosteroids receiving early IMT (p=0.04) [23]. Moreover, authors describe that delaying IMT in patients with initial SGF (4.4 *vs*. 12.3 months, p=0.02) or chronic-recurrent disease (6.5 *vs*. 14.5 months, p=0.01) was associated with a reduced improvement in VA [23]. Similar findings were described by El-Asrar et al., who reported that the use of IMT was significantly associated with a reduced risk of SGF and that SGF was associated with the development of ocular complications, including glaucoma, cataract, and subretinal neovascular membrane formation [17]. However, when analyzing glaucoma alone, the authors found no significant differences in the occurrence of secondary glaucoma in acute (p=0.227) and/or chronic-recurrent (p=0.241) VKH patients receiving IMT [17].

Choroidal depigmentation, the so-called “sunset glow fundus”, is the loss of choroidal melanocytes after inflammatory T-cell infiltration that develops during the convalescent stage of VKH disease, typically 2 to 6 months after onset [5, 7, 24]. SGF was previously considered part of the “natural course” of VKH disease; however, it is currently a marker of ongoing choroidal inflammation [25]. As with glaucoma development, the presence of SGF is highly associated with the chronic-recurrent form of VKH disease [17]. In our study, we found a significantly higher prevalence of SGF in eyes with glaucoma at the initial (p=0.002) and final (p=0.031) visits. However, the presence of SGF failed to reach statistical significance as a risk factor for secondary glaucoma development (RR 2.53 95% CI 0.99 – 6.49, p=0.08). Concerning the development of glaucoma, we also failed to demonstrate a reduced risk of occurrence in patients receiving early IMT (RR 0.40, 95% CI 0.12-1.30, p=0.183). In the present study, three hypotheses could explain why early IMT did not confer a reduced risk of secondary glaucoma development. First, the duration of immunosuppression might have been inadequate. El-Asrar et al. reported a prevalence of glaucoma and SGF of 2.6% and 0%, respectively, in 76 eyes (38 patients) with initial-onset acute VKH disease who were initially managed with aggressive immunosuppression, including mycophenolate mofetil (MMF, 2g daily) and high-dose systemic corticosteroids (1 mg/kg/day). Steroids were maintained for three weeks and subsequently tapered 10 mg every two weeks until a 40 mg daily dose was reached. Next, prednisone was tapered 5 mg until 5-10 mg was reached. The median duration of oral prednisone and MMF was 17.5 (range: 10 – 34) and 20.2 (9 – 34) months, respectively [7]. In our study, the median duration of oral prednisone was 14 months (range: 8 – 45) and, at 12-months follow-up, only 32 patients (80%, 64 eyes) were still under IMT. Moreover, the median dose of oral prednisone at baseline was 50 mg

(range: 5 – 120), at one month 30 mg (range: 5 – 100), and at 3 months 10 mg (range: 0 – 60). Although all patients received IMT at the first visit, dosing of systemic steroids might have been insufficient. Aggressive and sustained immunosuppression at the acute phase of VKH disease might result in a reduced progression to chronic-recurrent VKH, thus, a lower risk of developing ocular complications, including SGF and glaucoma [3].

Second, a significant number of eyes within our cohort were at the chronic-recurrent stage of VKH disease. In our study, all eyes were initially managed with IMT. Despite the latter, and after excluding 4 eyes with a previous diagnosis of glaucoma, 16 eyes developed glaucoma during follow-up. Of those, 43% *vs*. 17% non-glaucoma eyes were at the chronic-recurrent phase of the disease (RR 2.88 95% CI 1.11 – 12.63, p=0.037). Our results are consistent with other studies reporting an increased risk of secondary glaucoma in patients with chronic-recurrent VKH disease [15, 17].

Finally, the retrospective nature of the study design, the number of patients included, along the fact that not all clinical and therapeutic risk factors for glaucoma were considered for analysis precluded us from drawing definitive conclusions about our findings. Also, the selection bias of Hispanic patients with a usually larger proportion of severe and advanced disease referred to tertiary referral centers may not represent the general population of VKH disease in Mexico. Nevertheless, our findings are valuable, showing related to ethnic and environmental factors that can further influence the response to anti-inflammatory treatment and the development of glaucoma.

The main risk factors for glaucoma development in the present study were the chronic recurrent stage of the disease at presentation, more than two recurrences of inflammation during the follow-up time, ACD, and prolonged exposure to oral and topical corticosteroids. These findings have important implications for the clinical management of VKH patients. Prompt and combined systemic corticosteroid and IMT for active disease, detecting early manifestations of angle-closure, and limiting topical and oral corticosteroid exposure are crucial to reducing ocular complications and secondary glaucoma development in patients with VKH disease. The recognition of glaucoma as a prominent complication of chronic progressive disease could eventually encourage adequate inflammatory control to prevent a poor visual outcome.

Abbreviations

ACD: angle-closure disease; aHR: adjusted hazard ratio; IMT: immunosuppressive therapy; IQR: interquartile range; MMF: mycophenolate mofetil; OHT: ocular hypertension; OR: odds ratio; PPA: peripapillary atrophy; SGF: sunset glow fundus; VA: visual acuity; VKH: Vogt-Koyanagi-Harada.

Declarations

Ethics approval and consent to participate: The study was approved, prior to initiation, by the Institutional Review Board and Ethics Committee following the tenets of the Declaration of Helsinki and approved by

the Ethics (Registration No. P000367-FRGVKH-CEIC-CR002) and Research (Registration No. P000367-FRGVKH-CI-CR002) Committees of our institution (License No. CONBIOETICA 19 CEI 011-2016-10-17 and COFEPRIS 20 CI 19 039 002, respectively). Written informed consent was obtained from each study participant, and from the guardian of underage (< 18 years) participants prior to clinical examination and data collection. Information was kept confidential throughout the study.

Consent for publication: Not applicable

Availability of data and materials: Results obtained in this study were generated from data collected and analyzed based on the stated methods section. Since all data is already found in the manuscript, there are no supplementary files.

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Authors' contributions: CAG, and CHM participated in the study design. CAG and RERL collected the data. CAG participated in the analysis of data. CAG and ARG participated in the clinical management of the patients enrolled in the study. RERL, MEQG, and CAG wrote the main manuscript text. MEQG created the tables. ARG and JEGV edited the manuscript. CHM, ARG, and JEVG supervised the work. All authors read and approved the final manuscript.

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Figures

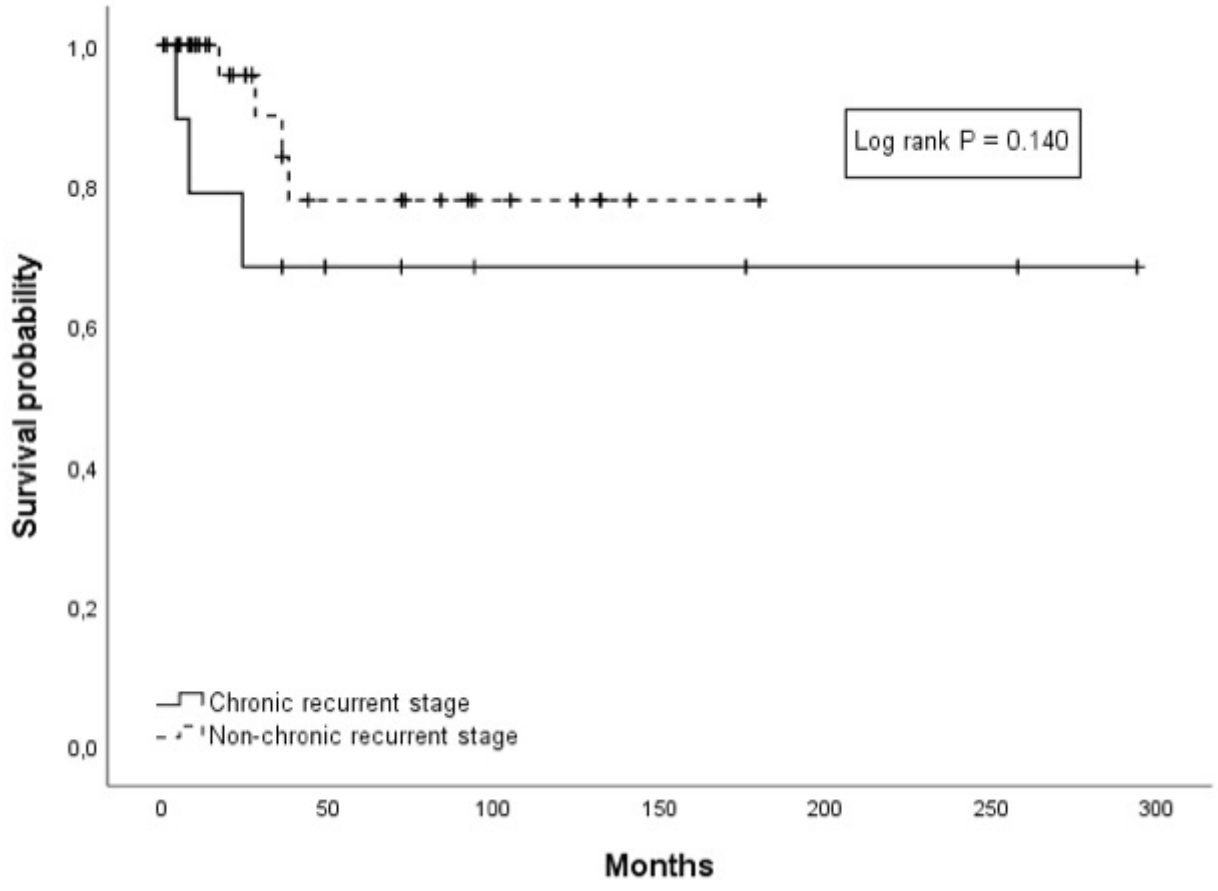

Figure 1

Kaplan-Meier plot of secondary glaucoma development based on the VKH phase at first visit. The incidence of glaucoma in patients with chronic-recurrent VKH disease at one and two years were 22.1% and 31.6%, respectively. Patients with uveitis VKH disease had a risk of secondary glaucoma development of 22.1%. This difference was not significant (p=0.140).