VOGT-KOYANAGI-HARADA SYNDROME IN A GROUP OF PATIENTS IN TWO OPHTHALMOLOGY REFERRAL CENTERS IN BOGOTA, COLOMBIA

Running Title: VKH syndrome in Colombia

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ABSTRACT

Purpose*:* To describe the clinical presentation of Vogt-Koyanagi-Harada syndrome in a group of patients in Colombia.

Methods: Retrospective-review of 2638 medical-records of patients with uveitis in two centers during 17 years.

Results: Twenty-five patients with uveitis were diagnosed with Vogt-Koyanagi-Harada syndrome (0.95%), 23 patients were included in the data analysis (0.87%), 78.3% females, mean age of diagnosis 37 years old (SD ±29). Main complaints: blurred vision (87%), headaches (47.8%), tinnitus (26.1%) and hearing impairments (21.7%). Ophthalmic findings: bilateral serous retinal-detachment (73.9%), non-granulomatous uveitis (52.3%). Most of the patients were diagnosed with *probable disease (*56.5%). Mean duration of follow-up was fourteen months; disease relapse was encountered in 26% of patients despite treatment.

Conclusion: Patients in Colombia with Vogt-Koyanagi-Harada had clinical features similar to those reported in other Hispanic populations, except for the non-granulomatous uveitis. This disease may be considered as having variation of clinical manifestations across population groups.

Key words**:** Clinical characteristics; Colombia; epidemiology; serous retinal detachment; uveitis; Vogt-Koyanagi-Harada.

INTRODUCTION

Vogt-Koyanagi-Harada (VKH) syndrome, also known as uveo-meningeal syndrome, is an autoimmune inflammatory disease characterized by bilateral uveitis with systemic symptoms, which may include neurological, hearing and integumentary manifestations[1,2]. Its cause is unknown, but an autoimmune mechanism against melanocytic pigment has been described.[1,3] Dark pigmented races such as Asiatic and Hispanic are more susceptible to developing the disease, but it is unclear whether or not race is an isolated risk factor.[1] Alfred Vogt, a Swiss ophthalmologist, first described the

syndrome in 1906. In subsequent years, Einosuke Harada and Yoshizo Koyanagi defined it more precisely when reporting serial cases of Japanese patients with VKH syndrome in 1926 and 1929, respectively.[4]

The prevalence of VKH syndrome is variable worldwide.[5,6] Japanese and Chinese populations have the highest incidence of the disease, accounting for 6.8% to 9.2% of all uveitis consultations. In comparison, the United States accounts for 1% to 4% of all uveitis referrals.[6] Other countries such as Brazil and Colombia report a lower incidence of the disease, accounting for 6% and 1.2%, respectively, of all patients with a uveitis diagnosis.[7,8]

Diagnosis of VKH syndrome is based on clinical findings and by exclusion of other diseases.[2,9] There are different criteria to diagnose the entity. The *First International Consensus for the Diagnosis of VKH Disease* attempted to unify criteria for the syndrome. Different studies have been conducted to evaluate its applicability in diagnosing the disease, which have found the Consensus to be useful in such diagnosis. The criteria, however, lack prospective studies to determine the positive and negative predictive values when diagnosing the disease.[10] The Consensus classifies the disease into three clinical stages: complete, incomplete and probable.[2]

Patients diagnosed with VKH syndrome usually complain of unilateral or bilateral sudden or progressive blurred vision, ocular pain, and hearing impairment.[11] Neurological manifestations that occur in the prodromal phase of the disease are headache, nausea, photophobia, vertigo, stiff neck and fever.[12] The early phase of the syndrome may be characterized by focal neurological signs like nerve palsies and optic

neuritis, in addition to pleocitosis in the cerebral spinal fluid (CSF). Eye examination often shows diffuse choroiditis, an optic disc swelling and an exudative retinal detachment. Furthermore, systemic manifestations in the late phase of the disease include vitiligo, poliosis and inner ear problems.[13] However, there are variations in systemic manifestations among populations, e.g. higher prevalence among Asiatic people.[1,7]

Early and aggressive treatment with systemic corticosteroids is the cornerstone of therapeutic management in VKH syndrome.[12] There are adjuvant therapies to prevent relapses, including methotrexate and immunomodulatory drugs (IMD) such as cyclosporine, cyclophosphamide and azathioprine. Additionally, biologic agents are also described as an alternative treatment, as well as anti-Tumor Necrosis Factor (infliximab) and anti-endothelial growth factor agents (bevacizumab).[13,14]

This study aims to describe the demographic profile and clinical presentation of Vogt-Koyanagi-Harada (VKH) syndrome in a group of patients in Bogota, Colombia.

METHODOLOGY

2,638 medical charts of patients diagnosed with uveitis were retrospectively reviewed in two ophthalmology referral centers during a period of 17 years in Bogotá, Colombia from January 1996 to December 2013. Patient follow-up was at the Uvea and Retina Unit of ‘Fundación Oftalmológica Nacional’ (FUNDONAL), a tertiary eye care hospital, and de-la-Torre’s private practice office. All patients were diagnosed by ophthalmologists specializing in uveal diseases. This study was conducted after approval by the ethics committee of FUNDONAL.

Patient information, including age, gender, age at disease onset, chief complaints, physical exam findings, diagnosis, relapses, treatment and complications, was gathered from medical records. Patients were classified according to *The First International Consensus for VKH Diagnosis*. All Colombian patients who satisfied this diagnostic criterion were included in this study.

Data were collected for analysis using Excel 2013 and SOSS version 20. Patient identification was coded to maintain patient confidentiality.

RESULTS

A total of 2,638 charts were reviewed, of which 25 patients were diagnosed with VKH syndrome (0.95%). 23 patients were included in the data analysis (0.87%). Two patients were excluded due to having only one physician encounter and insufficient medical records to support the diagnosis. All patients were Colombian and predominantly females (n=18, 78.3%). The mean age of disease onset was 37 years with a range from 9 to 66 years old. Most of the patients came from central Colombia (n= 17, 73.8%), the area in which the referral centers are located. Patient follow-up occurred between 1 and 70 months (mean of 14 months), only 30% of whom were seen in the acute phase of the disease.

Main complaints at first consultation were blurred vision (n=23, 87%), headache (n=12, 47.8%), tinnitus (n=7, 26.1%) and hearing loss (n=6, 21.7%), followed by nausea and fever with much less frequency (n=1, 4.3%). There were no reports of abdominal pain or meningeal symptoms like neck stiffness or confusion. First ophthalmology examination showed serous retinal detachment (SRD) (n=17, 73.9%), anterior uveitis (n=14, 52.2%)

and panuveitis (n=10, 37%). Anterior and posterior uveitis were found during the disease's early stages (n=14, 52.2% vs. n=10, 37.4%) and late stages (n=3, 10.8% vs. n=1, 4.8%). Additionally, despite treatment, inflammatory involvement of the posterior pole of the eye and SRD were seen in patients (n=10, 42.8%). No associations with chronic systemic pathology, autoimmune diseases, refractive defects or eye disease were seen in the patients. During the follow-up visits with the ophthalmologist (mean= 14 months) after treatment was initiated, visual acuity improved in 78.23% of patients (n=18) (Table 1).

Most of the patients were classified as having a *probable* disease (n= 13, 56.5%), followed by *incomplete* (n=8, 34.8%) and *complete* (n=2, 8.7%) (Table 2 and Table 3)). Systemic manifestations, including vitiligo (n=3, 13%), poliosis (n=3, 13%), and alopecia (n=2, 8.7%), were present in only five patients (21.7%) and only during the late phase of the disease. Both vitiligo and poliosis were present at the same time. Complications were cataract (n=4, 17.4%) and synechiae (n=3, 13%); followed less frequently by pupillary seclusion, band keratopathy, epiretinal membrane, and choroidal folds (n=1, 1.8% each one).

Patients were mainly treated with systemic corticosteroids (n=24, 91.3%) and methotrexate (n=6, 22.7%). No adverse drug side effects were reported. The dosage for corticosteroids ranged from 25 to 75 mg/day (1mg/kg/day); lower or higher doses were used less frequently (n=3, 13%). Methotrexate was administered in doses ranging from 5 to 10 mg/week; only four patients responded to this treatment. Two patients required the use of immunosuppressive agents like Azathioprine or Micophenolate Mofetil. Despite treatment, 6 patients experienced relapses (26%) as follows: 3 cases had one

relapse, 2 cases had three relapses and 1 case had two relapses. Eye examination was characterized by serous retinal detachment (SRD) (n=5, 18.3%), non-granulomatous anterior uveitis (n=2, 7.1%) and posterior uveitis (n=1, 4.8%).

DISCUSSION

VKH syndrome accounts for a minority of ophthalmology referrals in the hospital setting.[1,15–17] A previous study in Colombia reported uveitis with a point prevalence of 600 per 100,000 consultations (0.0060%). There, of 693 patients diagnosed with uveitis, only 8 patients were diagnosed with VKH syndrome (1.2%).[8] Similar prevalence was found in this study (0.95%). The United States and Brazil, however, report a higher prevalence of 6% and 4%, respectively.[7,8] The majority of patients was middle-aged females at disease onset, findings that were previously described in the literature.

Chief complaints were blurred vision and headaches; but hearing impairment and meningismus were not found in higher proportion. Furthermore, systemic manifestations occurred less frequently, and were present only in the late phase of the disease. Different studies involving Hispanic populations report similar findings, showing less neurological and systemic symptoms.[7,18]

A Chinese study identified four clinical stages of VKH syndrome when it retrospectively characterized the clinical symptoms in 430 Chinese patients during the development of the disease. It found posterior uveitis during eye examination in the early stages, followed by anterior uveitis in later stages.[11] Other studies also report a higher prevalence of granulomatous uveitis in Asians.[1,2] In contrast, most Colombian patients had non-granulomatous and anterior uveitis in early stages of the disease, although

only 30% of them were seen in the acute phase. Similarly, a study in India found anterior uveitis to be the most common finding during eye examination of South Asians at disease onset.[17,19] One study from Saudi Arabia reported granulomatous uveitis with the presence of mutton-fat keratic precipitates in 78 out of 174 eyes (44.8%), and non-granulomatous uveitis in 96 out of 174 eyes (55.2%).[20] The presence of iris nodules was registered in only 16 out of 174 eyes (9.2%). Similarly, we found that the presence of mutton-fat keratic precipitates and iris nodules were not the most common findings in our patients. The features of uveitis among complete and incomplete VKH cases are presented in Table 3a-b.

Thus, it is unclear whether an anterior uveitis finding at disease onset in Colombian patients is due to late diagnosis or a clinical manifestation occurring in Hispanic populations. There is a lack of studies that characterize this disease among different ethnic groups.

Our study had a very homogenous demographic profile since all were Hispanics. The follow-up, however, was short and the patient sample small. There was a low rate of relapse but our follow-up averaged 14 months.[21] No patient underwent complementary testing, such as genetic testing and lumbar puncture, in order to compare to other populations.

CONCLUSION

In conclusion, although patients in Colombia with VKH syndrome had clinical features similar to those reported for other populations, there are some particular features that differed from the classical described findings, such us the predominance of non-

granulomatous presentation and the incomplete form of the disease in our cases. The clinical manifestations were predominantly characterized by bilateral anterior and posterior uveitis and, although less common, neurological and integumentary manifestations. These findings were previously described in Hispanic. Most of the cases were diagnosed with probable disease. Few cases presented hearing impairment. Non-granulomatous and anterior uveitis were often seen on eye examination despite the clinical stage of the disease.

VKH syndrome is currently diagnosed only by clinical findings and exclusion of other diseases. A diagnostic tool is not available to confirm the diagnosis in the clinical setting. Enhanced awareness of this entity is necessary to promptly detect the disease, as treatment initiation improves visual acuity outcomes. Prospective studies should be conducted to identify risk factors to diagnose this syndrome as soon as possible. Reported clinical symptoms of the disease in the literature may vary by ethnic groups. Indeed, observational studies suggest that there may be a different clinical presentation across population groups.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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January(Published online).

Table 1 Presenting best corrected visual acuities of 46 eyes after treatment. BCVA= Best corrected visual acuity

BCVA	***Number of eyes n= 46***	***Percentage***
≥20/40	25	54.4%
20/50 - 20/80	7	15.2%
20/80 - 20/400	8	17.4%
<20/400	6	13%

Table 2 Distribution of VKH patients according to the revised diagnostic criteria. VKH=Vogt-Koyanagi-Harada Syndrome.

CLINICAL MANIFESTATIONS	**PATIENTS (n= 23)**
1) No history of penetrating ocular trauma or surgery preceding the initial onset of uveitis	n= 23 (100%)
2) No clinical or laboratory evidence suggestive of other ocular disease entities.	n= 23 (100%)
3) Bilateral ocular involvement a) Early manifestations of disease. 1. Anterior uveitis 2. Bullous serous retinal detachment 3. Characteristics fluorescein angiography findings b) Late manifestations of disease. 1. Ocular depigmentation (sunset glow fundus) - Nummular chorioretinal depigmented scars - Retinal pigment epithelium migration - Recurrent or chronic anterior uveitis	n= 23 (100%) **EYES: n= 46 (%)** n= 24 (52.2%) n= 34 (73.9%) n= 7 (15.2%) n= 14 (30.43%) n= 14 (30.43%) n= 6 (13%) n= 5 (10.8%)
4) Neurological/auditory findings. *1.* Tinnitus	**PATIENTS (%)** n= 6 (26.1%)
5) Integumentary findings. a. Alopecia b. Poliosis c. Vitiligo	 n= 2 (8.7%) n= 3 (13%) n= 3 (13%)
Complete VKH: criteria 1 to 5 must be present	**n= 2 (8.7%)**
Incomplete VKH: criteria 1 to 3 and either 4 or 5 must be present	**n= 8 (34.8%)**
Probable VKH: (isolated ocular disease) criteria 1 to 3 must be present	**n= 13 (56.5 %)**

Table 3a Features of uveitis among *complete* and *incomplete* VKH cases. AU= Anterior uveítis; BFSRF= Bilateral focal areas of subretinal fluid; BRD= Bilateral bullous serous retinal detachment; Com=Complete; Inc= Incomplete; Gr= Granulomatous; H/T=Hypoacusia or Tinnitus; NCRDS= Nummular chorioretinal depigmented scars; Non-Gr= Non-Granulomatous; PS=Prodromic symptoms; RPEM=Retinal pigment epithelium migration; R/C-AU=Recurrent or chronic anterior uveitis; SGF=Ocular depigmentation (sunset glow fundus).

Patient ID – Clasification	PS	Type of Uveitis	AU	BRD	BFSRF	SGF	Papillitis	NCRDS	RPEM	R/C-AU	H/T	Alopecia	Poliosis	Vitiligo
1- Inc	+	Non-Gr	+	+	-	+	-	+	+	+	-	-	+	-
2-Inc	+	Non-Gr	+	+	-	-	+	-	-	-	-	+	+	-
5- Inc	+	Non-Gr	+	+	-	+	-	+	+	+	+	-	-	-
6-Com	+	Non-Gr	+	+	-	+	-	+	-	-	+	-	-	+
9-Inc	+	Gr	+	-	+	+	-	+	+	-	-	-	+	+
10-Inc	-	Gr	+	-	+	+	+	-	-	+	+	-	-	-
13- Inc	-	Non-Gr	-	+		-	-	-	-	-	+	-	-	-
16-Inc	-	Non-Gr	-	+		-	-	+	+	-	+	-	-	-
20-Com	+	Non-Gr	+	+	-	+	-	-	+	-	+	-	-	+
22-Inc	+	Non-Gr	+	+	-	+	-	-	+	+	-	+	-	-
TOTAL	7/10	Gr: 2/10 Non-Gr: 8/10	8/10	8/10	2/10	7/10	2/10	5/10	6/10	4/10	6/10	2/10	3/10	3/10

Table 3b Features of uveitis among *probable* VKH cases. AU= Anterior uveítis; BRD= Bilateral bullous serous retinal detachment; BFSRF= Bilateral focal areas of subretinal fluid; Com= Complete; Inc= Incomplete; Gr= Granulomatous; H/T=Hypoacusia or Tinnitus; NCRDS= Nummular chorioretinal depigmented scars; Non-Gr= Non-Granulomatous; PS= Prodromic symptoms; RPEM=Retinal pigment epithelium migration; R/C-AU= Recurrent or chronic anterior uveitis; SGF= Ocular depigmentation (sunset glow fundus).

Patient ID – Clasification	PS	Type of Uveitis	AU	BRD	BFSRF	SGF	Papilitis	NCRDS	RPEM	R/C-AU	H/T	Alopecia	Poliosis	Vitiligo
3- Prob	+	Gr	+	-	+	-	-	+	-	+	-	-	-	-
4- Prob	+	Non-Gr	-	-	+	-	+	-	-	-	-	-	-	-
7- Prob	+	Non-Gr	-	+	-	-	-	-	-	-	-	-	-	-
8- Prob	+	Gr	-	+	-	-	-	-	-	-	-	-	-	-
11- Prob	+	Gr	-	-	+	-	-	+	-	-	-	-	-	-
12- Prob	-	Gr	+	-	+	-	-	-	-	-	-	-	-	-
14- Prob	-	Non-Gr	-	+	-	-	-	-	-	-	-	-	-	-
15-Prob	-	Non-Gr	-	+	-	-	-	-	-	-	-	-	-	-
17-Prob	+	Gr	+	+	-	-	-	-	-	-	-	-	-	-
18-Prob	+	Gr	+	+	-	-	-	-	-	-	-	-	-	-
19-Prob	-	Non-Gr	-	+	-	-	-	-	-	-	-	-	-	-
21-Prob	-	Non-Gr	-	+	-	-	-	-	-	-	-	-	-	-
23-Prob	-	Gr	-	+	-	-	-	-	-	-	-	-	-	-
TOTAL	7/13	Gr: 6/13 Non-Gr:7/13	4/13	9/13	4/13	0/13	1/13	2/13	0/13	1/13	0/13	0/13	0/13	0/13