Characteristics, Upon Presentation, of a Cohort of Patients with Vogt-Koyanagi-Harada Disease in Puerto Rico

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Objective: To describe the clinical features, upon initial presentation, of a cohort of patients with Vogt-Koyanagi-Harada (VKH) disease who live in Puerto Rico.

Methods: A retrospective medical record review of patients with VKH was performed. The demographic and clinical characteristics were analyzed.

Results: Twenty-two patients who met the diagnostic criteria for VKH were identified and included in the analysis. The median age at presentation was 41 years; 68.2% were female, and all patients were Hispanics. Bilateral disease was present in 90.9% of patients, and 59.1% of patients were categorized as having probable VKH. A headache was reported in 54.5% of patients and was the most common complaint at the time of presentation; the second most common complaint was tinnitus, which was present in 22.7% of patients. Vitiligo, alopecia, and meningismus were each preset in 9.1% of patients while hearing loss and aseptic meningitis were each reported in 4.5% of patients. Seventy-seven percent of patients had either topical or systemic corticosteroid use prior to the initial encounter.

Conclusions: Our study suggests that in Puerto Rico, patients with Vogt-Koyanagi-Harada disease may have a distinctive prevalence of characteristics at the presentation when compared to other ethnic groups, including other Hispanic cohorts. [*P R Health Sci J 2021;40:168-173*]

Key words: Vogt-Koyanagi-Harada, Panuveitis, Puerto Rico, Hispanics

Vogt-Koyanagi-Harada (VKH) disease is a multisystem autoimmune bilateral granulomatous panuveitis that has been described since the early 20th Century (1,2). The disease primarily affects pigmented tissues and has ocular, auditory, central nervous system, and integumentary manifestations (1–3). Studies have shown that 55%-78.3% of VKH patients are female and that people are primarily affected between the ages of 20-50, although pediatric cases have been reported (1,3).

The pathogenesis of VKH is thought to be a T-cell-mediated autoimmune response directed against antigens on melanocytes, pigment cells that are present in the systems affected by the disease (1,4). There are environmental as well as genetic factors thought to be at play in the development of VKH, which occurs most frequently among Asians, Native Americans, Hispanics, Asian Indians, and Middle Easterners (1,3,4). These pigmented ethnic groups often have a genetic predisposition for VKH due to the presence of particular Human Leukocyte Antigen (HLA) genes, including HLA-DQ and HLA-DR genotypes, which have strong associations with the disease (3,4). VKH is associated with HLA-DRB1*04 subtypes in Hispanic patients (5,6). However, despite the predominance of VKH among pigmented races, the expected incidence among black patients in Africa would be high, when in fact, they are seldom affected, suggesting differences in pigment genetics as well as an environmental component to affliction (3,4,6).

The diagnostic criteria for Vogt-Koyanagi-Harada disease have varied through the years, with the most recent guidelines proposed in 2001, the Revised Diagnostic Criteria (RDC) for VKH, which are illustrated in Table 1 (1,3,7). These criteria categorize patients as presenting with complete, incomplete, or probable VKH depending on the extent of neurological, auditory, and integumentary manifestations (1,7). There are four clinical stages of VKH; prodromal stage, acute stage, convalescent stage, chronic recurrent stage (1,3). Flu-like symptoms characterize the prodromal phase, which usually

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lasts for 1 to 2 weeks (3). However, prodromal symptoms are nonspecific and include headaches, periorbital pain, nausea, tinnitus, dysacusis, and neck and back stiffness, resembling aseptic meningitis (3). The acute stage, during which most patients present, is characterized by the onset of acute bilateral panuveitis (3). The most frequent complaint at this stage is vision loss, which commonly occurs secondary to posterior segment involvement, such as exudative retinal detachment and optic disk swelling (1,3,4). Depigmentation in the integumentary system, as well as uveal tissue, is characteristic of the third, convalescent stage, with findings such as sunset glow fundus, Sugiura sign (depigmented limbus), retinal pigmented epithelium clumping/migration, poliosis, alopecia, and vitiligo (1,3). The chronic recurrent stage has mild panuveitis with recurrent episodes of anterior uveitis, usually resulting from inadequate treatment, with mutton fat keratic precipitates on the cornea as a typical finding (1,3).

Treatment for VKH includes rapid and aggressive therapy with systemic corticosteroids, as well as immunomodulatory therapy (IMT) (1,3,4). Typically, patients are initially treated with 1mg/kg/day of oral prednisone; alternatively, pulsed IV methylprednisolone (1g/day) for 3 days may be used for the most severe cases (1,3,4). Mounting evidence suggests that the concomitant use of IMT for the treatment of VKH is associated with improved visual outcomes compared with systemic corticosteroid monotherapy (1,3,8–10). In general, once the acute inflammation subsides, the systemic corticosteroids are slowly tapered, over a period of 3 to 4 months to an initial target dose of 7.5 mg, at which point steroids may be further tapered at rates as slow as 1 mg per month (11,12).

We analyzed data from patients with Vogt-Koyanagi-Harada disease living in Puerto Rico with the purpose of identifying the ocular and systemic characteristics at the time of presentation in order to assess the severity and spectrum of disease in this subset of Hispanics in comparison to other ethnic groups.

Methods

Medical records covering from July 2006 through May 2020 were reviewed. The records were located in the medical records databases of the Medical Services Administration of Puerto Rico, outpatient clinics of the University of Puerto Rico Medical Sciences Campus Department of Ophthalmology, and 2 private uveitis practices. Charts of patients with a diagnosis of VKH were selected for analysis.

The inclusion criteria for the study included a clinical diagnosis of VKH, as determined by two well-experienced uveitis specialists using the RDC for VKH. Those patients who presented after 3 months from the initial onset of symptoms were excluded from this analysis. The demographic and clinical data were collected for those meeting the inclusion and exclusion criteria. The clinical data included measurements obtained at the time of presentation, such as visual acuity, tonometry, and other ocular and systemic manifestations of the disease, such as anterior uveitis, vitritis, serous retinal detachment, poliosis, and vitiligo. Anterior uveitis was defined as the presence of a 0.5 or higher grade of white blood cells in the anterior chamber, as defined by the standardization of uveitis nomenclature (SUN) working group criteria (13). Vitritis was defined as any evidence of vitreous cells on a slit lamp examination.

Descriptive analysis of the ocular and systemic characteristics at the time of presentation was used to evaluate variables and compare them to existing literature. The University of Puerto Rico, Medical Sciences Campus Internal Review Board reviewed and approved this protocol.

Results

The medical records for 25 patients with a diagnosis of VKH were identified. Of these, one patient was excluded after being determined as not to having VKH by one of the senior authors. Two other patients were excluded as they had presented after 3 months since the initiation of symptoms, after having received their initial treatment at institutions other than those pertaining to our study.

The study population characteristics at the time of presentation are summarized in Table 2. The age of presentation was between 11 and 60, with a median of 41. The majority of patients were women (68.2%), and all of the study participants were Hispanic. The median duration of symptoms prior to presentation was 3 weeks, ranging from 1 to 10 weeks. Twenty patients (91%) had bilateral disease, and all patients reported blurry vision at the time of presentation. Metrics taken during the initial encounter were remarkable for visual acuity (VA) in the better-seeing eye as 20/50 or worse in 81.8%, and 20/200 or worse in 63.6% of the patients. One patient had a VA of 20/25 in the better-seeing eye.

The majority of patients reported a headache (54.5%), followed by tinnitus (22.7%). Other neurological complaints included meningismus (9.1%), hearing loss (4.5%), and a finding of aseptic meningitis in 4.5% of patients. Integumentary findings such as alopecia and vitiligo were present in 9.1% of patients each, while poliosis was not found in any study participants at the time of the initial evaluation.

The most common ocular findings were exudative retinal detachment (86.4%), active anterior uveitis (68.2%), and active vitritis (59.1%). Cataracts were present in 31.8% of participants. Posterior synechiae were found in 22.7% of patients, while cystoid macular edema was found in 18.2%. One patient (4.5%) had epiretinal membrane formation, and four patients (18.2%) had optic disk edema, which was present in seven eyes. There were no patients with sub-retinal neovascularization or fibrosis, or phthisis at presentation.

Based on the clinical findings and symptoms described above, patients were categorized as having complete VKH, incomplete VKH, or probable VKH according to the diagnostic criteria described in Table 1. As summarized in Table 3, thirteen patients (59.1%) were categorized as probable VKH, seven (31.8%) were

Table 1. Diagnostic criteria for Vogt-Koyanagi-Harada (VKH) disease*

Complete Vogt-Koyanagi-Harada disease (criteria 1 to 5 must be present)
1. No history of penetrating ocular trauma or surgery preceding the initial onset of uveitis
2. No clinical or laboratory evidence suggestive of other ocular disease entities
3. Bilateral ocular involvement (a or b must be met, depending on the stage of disease when the patient is examined)
A. Early manifestations of disease
(1) There must be evidence of a diffuse choroiditis (with or without anterior uveitis, vitreous inflammatory reaction, or optic disk hyperemia), which may manifest as one of the following
(a) Focal areas of subretinal fluid, or
(b) Bullous serous retinal detachments
(2) With equivocal fundus findings; both of the following must be present as well:
(a) Focal areas of delay in choroidal perfusion, multifocal areas of pinpoint leakage, large placoid areas of hyperfluorescence, pooling within subretinal fluid, and optic nerve staining (listed in order of sequential appearance) by fluorescein angiography, and
(b) Diffuse choroidal thickening, without evidence of posterior scleritis by ultrasonography.
B. Late manifestations of disease
(1) History suggestive of prior presence of findings from 3a, and either both (2) and (3) below, or multiple signs from (3)
(2) Ocular depigmentation (either of the following manifestations is sufficient):
(a) Sunset glow fundus, or
(b) Sugiura sign
(3) Other ocular signs
(a) Nummular chorioretinal depigmented scars, or
(b) Retinal pigment epithelium clumping and/or migration, or
(c) Recurrent or chronic anterior uveitis.
4. Neurological/auditory findings (may have resolved by time of examination).
a. Meningismus (malaise, fever, headache, nausea, abdominal pain, stiffness of the neck and back, or a combination of these factors; headache alone is not sufficient to meet definition of meningismus, however), or
b. Tinnitus, or
c. Cerebrospinal fluid pleocytosis
5. Integumentary finding (not preceding onset of central nervous system or ocular disease)
a. Alopecia, or
b. Poliosis, or
c. Vitiligo
Incomplete Vogt-Koyanagi-Harada disease (criteria 1 to 3 and either 4 or 5 must be present)
1. No history of penetrating ocular trauma or surgery preceding the initial onset of uveitis, and
2. No clinical or laboratory evidence suggestive of other ocular disease entities, and
3. Bilateral ocular involvement.
4. Neurologic/auditory findings; as defined for complete Vogt-Koyanagi-Harada disease above, or
5. Integumentary findings; as defined for complete Vogt-Koyanagi-Harada disease above
Probable Vogt-Koyanagi-Harada disease (isolated ocular disease; criteria 1 to 3 must be present)
1. No history of penetrating ocular trauma or surgery preceding the initial onset of uveitis.
2. No clinical or laboratory evidence suggestive of other ocular disease entities.
3. Bilateral ocular involvement as defined for complete Vogt-Koyanagi-Harada disease above.

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Table 2. Demographic and Clinical characteristics of patients with VKH

Number of patients (n)	22
Median age (y)	41 (range, 11-60)
Gender (%)	
Female	68.2%
Male	31.8%
Race (%)	
Hispanic	100
Bilateral disease (%)	90.9
Corticosteroid use prior to the 1st encounter (%)	77.3
Topical	63.6
Systemic	59.1
Immunomodulator therapy prior to the 1st Encounter (%)	13.6
Systemic complications (%)	
Vitiligo	9.1
Poliosis	0
Tinnitus	22.7
Hearing loss	4.5
Headache	54.5
Meningismus	9.1
Aseptic meningitis	4.5
Alopecia	9.1
Visual acuity, Better seeing eye (%)	
20/50 or worse	81.8
20/200 or worse	63.6
Ocular findings (%)	
Anterior Uveitis	68.2
Posterior Synechiae	22.7
AVitritis	59.1
Cataract	31.8
Cystoid Macular Edema	18.2
Epiretinal Membrane	4.5
Subretinal Neovascularization or Fibrosis	0
Exudative Retinal Detachment	86.4
Optic Disk Edema	18.2
Phthisis	0

incomplete VKH, and only two patients (9.1%) met the criteria for complete VKH at the time of presentation. Of those patients meeting clinical criteria for incomplete VKH, five (27.3%) had neurological manifestations, while only one (4.5%) had integumentary manifestations.

At the time of evaluation, treatment with corticosteroid therapy or immunomodulatory therapy was documented for each patient. Of the 17 (77.3%) patients on corticosteroid therapy prior to presentation, 14 (63.6%) had started topical corticosteroid therapy, and thirteen (59.1%) had started systemic treatment. Three (13.6%) of patients had been started on IMT, all of which were also on systemic corticosteroid therapy. Of the 13 patients on systemic corticosteroid therapy, two met clinical criteria for complete VKH, five patients met criteria for incomplete, and six for probable VKH.

Table 3. Diagnostic criteria profile for patients at presentation

Complete	2 (9.1%)
Incomplete	7 (31.8%)
Probable	13 (59.1%)

Discussion

At the time of presentation, most of our study participants were diagnosed as probable VKH (59.1%) according to the established clinical criteria (7). Only two patients were categorized as complete VKH and seven as incomplete VKH, suggesting that patients in Puerto Rico have a tendency towards an incomplete spectrum of disease, in which systemic manifestations are not as common in the early phase of the disease as compared to other races or ethnic groups (5,14). In our population, females were more likely than males to be affected (68.2%), which is similar to other reports revealing a range of 55%-77% for female involvement (3,14). The median age at presentation was 41, with a range from 11 to 60, which was consistent with previous reports (2,3,5,14,15).

Our study population was comparable to those of Moorthy, Beniz, and Sukavatcharin, who also assessed Hispanic subjects, and showed variations in the systemic manifestations at the time of presentation in comparison to non-Hispanics, as shown in Table 4 (5,14,15). In this series, subjects presented with a visual acuity of 20/200 or worse more frequently (63.6%) compared to other studies, which reported a range of 41-46% (5,14,15). The most common neurological manifestation of VKH is meningismus, with a prevalence of 55%-69%, while in our study, 54.5% of patients described experiencing headache; however, only 9.1% fulfilled the criteria for meningismus, distinctly less in comparison (5,14,15). A study of patients in Bogota, Colombia, reported meningismus in 21.7% of patients, which also deviates from previous studies (16). There was also a higher prevalence of tinnitus within our population, with 22.7% affected, compared to 10%-18% in the literature; however, dysacusia showed a lower prevalence with only 4.5% affected, compared to 8%-11% in other studies (5,14,15). Guayacán et al. reported tinnitus in 26.1% of patients, a notable similarity. The prevalence of vitiligo was similar to other studies, which range from 0%-8%, with 9.1% of our patients affected (5,14,15). Alopecia and poliosis had a lower prevalence in our population, as described in Table 4 (5,14–16). Comparison of these studies, whose patient populations are located in Southern California, Colombia, and Puerto Rico, demonstrates the varying clinical presentation of VKH among Hispanics across different population groups (5,14–16).

Vogt-Koyanagi-Harada disease has varied manifestations according to ethnicity (15). Clinical manifestations in Japanese patients include auditory abnormalities in up to 80% of patients (5,14,15). At the same time, studies show these are less common in Hispanics, who also have lower rates of meningismus compared to Japanese, who may have the symptom in up to 97% of patients (5,14,15,17).

Table 4. Systemic manifestations at time of presentation in Hispanics.

Manifestation	Beniz (n = 36)	Moorthy (n = 51)	Sukavatcharin n (n = 11)	Guayacán (n = 23)	Barquet (n = 22)
Headache	NA	NA	9 (82%)	12 (47.8)	12 (54.5%)
Meningismus	25 (69%)	30 (59%)	6 (55%)	6 (21.7%)	2 (9.1%)
Tinnitus	5 (14%)	5 (10%)	2 (18%)	7 (26.1%)	5 (22.7%)
Dysacusia	4 (11%)	4 (8%)	1 (9%)	6 (21.7%)	1 (4.5%)
Vitiligo	3 (8%)	4 (8%)	0	3 (13%)	2 (9.1%)
Alopecia	6 (17%)	7 (14%)	0	2 (8.7%)	2 (9.1%)
Poliosis	2 (6%)	2 (4%)	0	3 (13%)	0

NA = Not Available

Prior to the initial evaluation at our practices, 77.3% of patients were on corticosteroids, of which 63.6% were topical and 59.1% systemic, while some patients were on both therapies. The prompt initiation of corticosteroid therapy in these patients cannot be overlooked when addressing the question of why these patients lack some of the typical systemic manifestations at the time of presentation, given that is has been proven that aggressive corticosteroid treatment has better visual outcomes for patients (8,10,18).

This study adds evidence to illustrate that not only do Hispanics tend to have fewer systemic manifestations of VKH when compared to other ethnicities, but it also suggests that the Puerto Rican population has different presenting characteristics than the overall Hispanic population; in particular a lower prevalence of alopecia, poliosis, dysacusia, and meningismus, and the greater prevalence of tinnitus (2,5,14,15,17). It would have been beneficial to assess the HLA predominance for these patients for potential identification of a correlation. Further studies are needed with larger patient populations, including Hispanics from different nationalities, to elucidate potential molecular genetics, environmental, or therapeutic causation in presenting symptoms of VKH patients.

As is the case with all retrospective studies, our data must be interpreted with care, as ascertainment bias may have been introduced. Our study is also limited by a small sample size. Referral bias may have been introduced as it is possible that only the most severe cases of VKH were referred to the uveitis practices of the two senior authors. However, as the combined practices of the two senior authors likely receive and manage the majority of patients with VKH in Puerto Rico, it is likely that our sample is representative of the population being studied.

Resumen

Objetivo: Describir las características clínicas, en la presentación inicial, de una cohorte de pacientes que viven en Puerto Rico con la enfermedad de Vogt-Koyanagi-Harada (VKH). Métodos: Se realizó una revisión retrospectiva del historial clínico de pacientes con VKH. Se analizaron las características demográficas y clínicas. Resultados: Veintidós pacientes que cumplieron con los criterios de diagnóstico para VKH fueron identificados e incluidos en el análisis. La edad mediana en la presentación fue de 41 años; el 68.2% eran mujeres y todos los pacientes eran hispanos. La enfermedad fue bilateral en el 90.9% de los pacientes y el 59.1% de los pacientes fueron categorizados como con probable VKH. Dolor de cabeza fue reportado en 54.5% de los pacientes, siendo la queja más común al momento de presentación, seguido por tinnitus, el cual estuvo presente en 22.7% de los pacientes. Vitíligo, alopecia, y meningismo, estaban presentes en 9.1% de los pacientes, cada uno, mientras que la pérdida de audición y meningitis aséptica fueron reportadas en 4.5% de los pacientes, cada uno. Setenta y siete por ciento de los pacientes habían utilizado corticosteroides sistémicos o tópicos antes del encuentro inicial. Conclusiones: Nuestro estudio sugiere que, en Puerto Rico, los pacientes con la enfermedad de Vogt-Koyanagi-Harada podrían tener una prevalencia distintiva de características en la presentación en comparación con otros grupos étnicos; incluyendo otras cohortes hispanas.

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