An Eye for an Eye, An Ear for an Ear: A Midwestern Case Report of Vogt-Koyanagi-Harada Disease

Neil Dixit, MD; Emily Koller, MD; Nicole Avendaño, MD; Pinky Jha, MD

ABSTRACT

Introduction: Vogt-Koyanagi-Harada (VKH) disease is an autoimmune condition affecting both ocular and extraocular systems. This case highlights the need for research into the epidemiology and pathophysiology of VKH.

Case Presentation: A 23-year-old cisgender Hispanic female presented to our tertiary care center with severe headache, eye pain, vision changes, photophobia, hearing loss with tinnitus, phonophobia, nausea, vomiting, and vertigo. She was diagnosed with VKH disease.

Discussion: This report shares a case of VKH disease in the Midwestern United States. A 2023 Northwestern University study highlights the orphan nature of the disease; even with a small sample size, that study proved to be a larger cohort in studies of VKH.

Conclusions: This report contributes to the growing literature documenting VKH disease. Especially in diagnoses associated with certain racial groups, a broad differential diagnosis is essential, as delay in diagnosis may result in irreversible sequelae. Prompt coordination with colleagues may reduce subsequent morbidity and mortality.

INTRODUCTION

Vogt-Koyanagi-Harada (VKH) disease is an autoimmune, inflammatory condition characterized by a constellation of symptoms affecting the eyes, ears, integument, and meninges, classically associated with bilateral granulomatous uveitis.[1] Since the first cases of what would be eventually known as VKH were described in the early 1900s, much progress has been made in understanding its pathophysiology, course, and treatment.[1] The current understanding of VKH disease posits that a T-cell mediated autoimmune response to antigens present on melanocytes plays an integral role in the disease.[1] Early identification and treatment of VKH with combined steroidal and nonsteroidal immunosuppression is imperative to prevent chronic evolution of the disease, including permanent vision loss.[2,3] This report of a Wisconsin-based case of VKH disease highlights the need for continued research on its epidemiology and management, as well as the importance of maintaining suspicion for this disease in all patients presenting with unexplained uveitis.

CASE PRESENTATION

A 23-year-old cisgender, Hispanic female with no significant past medical history presented from an outpatient ophthalmology clinic to a tertiary care center in the northern Midwest during the late winter months. She reported 3 weeks of severe headache described as the worst of her life, eye pain, vision changes, photophobia, hearing loss with tinnitus, phonophobia, and vertigo when supine, as well as nausea and vomiting. She had presented previously to an outside hospital and initially received erythromycin ointment, followed by reevaluation and treatment with trimethoprim-polymyxin B drops. Despite these treatments, she said that her symptoms continued and only her pain improved with ibuprofen.

Admission vitals were unremarkable except for low blood pressure, which was found to be her baseline. Initial laboratory studies revealed no electrolyte or metabolic derangements, though platelet count was elevated to the mid-500 000 range (laboratory range: 165 000-366 000). Infectious workup with QuantiFERON-Tb Gold+ testing, HIV 1/2 antibody and antigen, and treponemal serology were overall reassuring. A treponemal antibody screen as well as rapid plasma reagin (RPR) were obtained to rule out ocular syphilis, as it was noted that the RPR

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Author Affiliations: Medical College of Wisconsin, Milwaukee, Wisconsin (Dixit, Koller, Avendaño, Jha).

Corresponding Author: Neil Dixit, email neildixi@med.umich.edu; ORCID ID 0009-0005-6580-7416

test cannot safely rule out ocular syphilis, which is in line with expert opinion that suggests performing antibody testing as the initial screen for ocular syphilis.[4] Chest x-ray showed no sign of an acute cardiopulmonary process. Magnetic resonance imaging (MRI) was not performed, though computed tomography (CT) head without contrast from the month prior to admission showed no intracranial abnormality.

Ophthalmology and otolaryngology were consulted given vision and hearing impairment. Ophthalmology exam also revealed keratic precipitates and vitritis bilaterally. On the initial ophthalmology exam, visual acuity was 20/200 in the right eye (OD) and only for hand motion in the left eye (OS), with pinhole visual acuity as follows: OD 20/70-1, OS 20/400. Maximum noted intraocular pressure (IOP) on admission was OD 20 mmHg and OS 28 mmHg, both of which are elevated. Over the admission, IOP ranged from OD 13 to 22 and OS 15 to 28. Further ocular study showed choroidal thickening on B-scan ocular ultrasound, hyperreflective vitreous opacities and paracentral acute middle maculopathy (PAMM) lesions on optic coherence tomography (OCT) and optic nerve leakage on fluorescein angiography. Serous retinal detachments were not commented on by ophthalmology in this case, though these findings are commonly found on OCT in VKH disease.[5] Otolaryngology, on exam, found Weber test lateralized to the left, and Rinne test with air conduction favored over bone conduction bilaterally, consistent with sensorineural hearing loss.

Based on the patient's clinical presentation and negative workup for alternative etiologies adequately explaining her constellation of symptoms, the diagnosis of VKH disease was made, though the differential diagnosis included infectious conditions and other autoimmune conditions such as sarcoidosis, Cogan syndrome, and Susac syndrome.

The patient was started on intravenous (IV) methylprednisolone with improvement of ocular and meningismus symptoms by day 4, followed by a 24-hour trial period of oral prednisone prior to discharge. For the ocular manifestations of VKH disease, she was started on several bilateral eye drops: prednisolone every 2 hours, dorzolamide hydrochloride-timolol hydrochloride twice daily, and cyclopentolate twice daily. There was improvement in the visual acuity to 20/20 in each eye and in her IOP to OD 13 and OS 15. Auditory symptoms had improved somewhat, though outpatient follow-up with otolaryngology was necessary to monitor for ongoing hearing loss.

On outpatient follow-up with ophthalmology 5 days after discharge, elevated IOP and PAMM lesions noted on OCT were both observed to have improved. The patient began a prednisone taper and started difluprednate eye drops to alleviate the improved, though ongoing uveitis. At this follow-up visit, ophthalmology planned to start the patient on immunomodulatory therapy if ocular inflammation recurs, which is of high likelihood in VKH. Otolaryngology follow-up was significant for ongoing tinnitus, torsional nystagmus with left-sided Dix-Hallpike maneuver, and left benign paroxysmal positional vertigo. The Epley maneuver was performed twice and a referral for a vestibular evaluation was placed. MRI of the head was ordered to rule out intracranial pathology for her otolaryngological findings.

DISCUSSION

We describe the case of incomplete VKH disease in a patient who presented with vision loss, hearing loss, and symptoms of meningismus.

The first probable descriptions of VKH date to the early 20th century.[1] In 1906, Swiss ophthalmologist Alfred Vogt described a case in which his patient was noted to have eyelash whitening (poliosis), as well as concomitant intraocular inflammation.[1] Several years later in Japan, ophthalmologists Jujiro Komoto and Yoshizo Koyanagi both noted a similar presentation in a handful of their patients, publishing their findings in a German and Japanese medical journal, respectively.[1] In 1929, Koyanagi published a report detailing 16 additional cases where he described the natural course of what would eventually be termed Vogt-Koyanagi-Harada disease.[1] Koyanagi noted that there was no current treatment.[1] Japanese ophthalmologist Einosuke Harada observed a similar constellation of symptoms in several of his patients, which he described in the mid-1920s and referred to as Harada's disease.[1] Recognizing the similarities among cases reported in Switzerland and Japan, Professor Jean Babel of Geneva proposed the name Vogt-Koyanagi syndrome.[1] In 2001, the disease became formally known as Vogt-Koyanagi-Harada disease.[3]

Vogt-Koyanagi-Harada disease affects individuals during the second to fifth decade, especially females with high melanin pigments in their skin.[6] The prevalence of the disease varies widely across the world, and it is considered rare in the United States.[3] In India, VKH disease is the most common cause of panuveitis, with prevalence 21.08%; in Japan, its prevalence is 6.7% to 11%, with an incidence of approximately 800 new cases each year.[7] VKH is reported at higher rates among those of Asian, Hispanic, Middle-Eastern, First Nation, Metis, and Inuit origin.[8] In a recent study on demographics of patients diagnosed with VKH disease at Northwestern University, more than 50% of patients self-reported as non-Hispanic White or Black/African-American.[8]

Though our patient identified with an ethnic group classically associated with VKH disease in the literature, it is essential to assess the clinical picture and not discount the diagnosis of VKH based on a patient's race or ethnicity, as doing so may lead to delayed diagnosis and treatment.[8] The authors suggest that the low prevalence of VKH may be attributed to this condition being underrecognized and underreported.[8]

The underlying mechanism of this disease is thought to be the result of autoimmune processes. Specifically, CD4+ and Th17 T cell-directed responses toward melanocyte-specific antigens

derived from tyrosinase peptides and melanocyte-specific antigens are thought to play a major role in its pathophysiology.[3,9] This autoimmune mechanism raises concern for viral triggers of the disease. VKH disease following both infection and vaccination has been reported for multiple infectious agents, including COVID-19, tuberculosis, and influenza A, among others.[9] The relationship between VKH and viral triggers is of particular interest in the wake of the COVID-19 pandemic caused by the SARS-CoV-2 virus and related vaccination.[9] Though reports of VKH disease following COVID-19 infection and vaccination exist, there has not been an identifiable change in VKH epidemiology following the pandemic.[9] For VKH following either COVID-19 vaccination or infection, there may be a relationship with the HLA class II antigen, namely HLA-DR4, though the exact nature of this possible genetic susceptibility to VKH remains to be fully elucidated.[9] Molecular mimicry, as well as adjuvants and additives in the vaccine formulations, also have been posited to play a role in precipitating VKH following vaccination.[9] Though it remains one of the most common causes of uveitis following infection, the unlikely possibility of VKH disease following vaccination against SARS-CoV-2 should not preclude vaccination.[9]

Multiple attempts to classify the signs and symptoms into standardized diagnostic criteria have been made.[3,6] The Revised Diagnostic Criteria developed in 2001 stratify the disease into "incomplete," "complete," and "probable" VKH.[3] Incomplete VKH disease requires the lack of ocular trauma, no findings suggestive of other ocular disease, and bilateral ocular involvement, with either neurological and auditory findings or integumentary involvement.[3] Complete VKH requires all of the previous criteria to be met.[3] Probable VKH does not require neurological, auditory, or integumentary involvement.[3]

There is no definitive laboratory test for diagnosing VKH disease.[3] As a result, the diagnosis is based on the clinical presentation and exclusion of history of ocular trauma or surgery, followed by ophthalmological examination and evaluation to rule out any infectious or other causes of ocular pathology.[3] Though not routinely performed in the United States for this indication, cerebrospinal fluid may be collected via lumbar puncture to assess for pleocytosis—namely in Japan and Europe—though this remains a controversial component of evaluation.[3]

The ocular and integumentary findings in VKH will vary depending on the stage of disease at presentation. VKH may present in 1 of 4 phases: prodromal, uveitic, convalescent, and recurrent.[3,6] In its earlier phases, typical optical findings include optic disk hyperemia, bilateral granulomatous panuveitis, and serous retinal detachments.[8,10] Meningismus signs, such as the headache, nausea, vomiting, and photophobia seen in our case, present in the prodromal phase of VKH.[1] As the disease progresses to the convalescent phase, ocular findings include depigmentation of the retina (ie, the classically associated "sunset glow fundus") and chronic anterior uveitis, while integumentary findings include vitiligo and poliosis.[8,11]

Several imaging modalities—namely optical coherence tomography (OCT) and fluorescein angiography (FA)—are used to diagnose VKH. Indocyanine green angiography also has been used.[5] Optic coherence tomography (OCT) has been studied as an optic imaging tool to assist in VHK diagnosis.[5] OCT can show subretinal hyperreflective opacities as well as choroidal thickening in the acute phase of VKH.[5] Fluorescein angiography shows leakage in VKH, which correlates with the subretinal and intraretinal fluid collection noted on OCT.[5] Other long-term, extraocular findings include pigmentary changes of the integument, such as poliosis, alopecia, or vitiligo, that occur after the onset of uveitis.[12]

Ocular outcomes may improve with rapid initiation of treatment in the acute phase of VKH, though more research is needed to elucidate the role of treatment timing and stage of disease at presentation in preventing ocular and extraocular manifestations of the disease.[13] Our case of VKH disease demonstrates the importance of multidisciplinary approach, where the primary care team coordinates care with colleagues in otolaryngology, neurology, ophthalmology, and dermatology to ensure prompt diagnosis and treatment.

High-dose, systemic corticosteroid therapy with eventual transition to nonsteroidal immunosuppression, such as mycophenolate mofetil, and steroid taper, is the mainstay of treatment for patients with acute VKH disease.[3] Treatment with both prolonged oral corticosteroids and IV methylprednisolone bolus for 3 to 5 days has been shown to provide similar visual recovery and final visual acuity in patients who experienced vision loss; however, Accorinti et al found in patients initially treated with IV corticosteroids, long-term recurrence of the disease and risk of requiring further intervention was lower when compared to patients initially treated with oral corticosteroids, possibly due to a longer follow-up period in their study.[14] While early treatment is essential in the proper management of VKH disease, patients may require long-term immunosuppression with immunomodulators.[5] There is evidence that both mycophenolate mofetil and corticosteroids may be efficacious in the treatment of acute VKH with reduction in recurrent inflammation compared to treatment with only corticosteroids.[3] There is ongoing research examining the possible role of biological response modifiers in long-term treatment for VKH, with case reports suggesting response in immunosuppression-resistant cases.[3,5]

The prognosis and complications associated with VKH depend largely on when the diagnosis is made and treatment is initiated.[3] There has been suspicion that VKH has a window of opportunity to initiate treatment following disease onset for best outcomes.[14,15] Other factors that affect prognosis include age at onset of disease, duration of disease, number of recur-

rent episodes of inflammation, and number of complications associated with disease.[12] One study showed that treatment with high-dose corticosteroid combined with immunomodulators initiated within 3 months caused a significant reduction in risk of progression to chronic recurrent uveitis.[16] Another study showed that if treatment with mycophenolate mofetil and systemic corticosteroids is initiated within 2 to 3 weeks from symptom onset, progression to chronic recurrent granulomatous inflammation and development of "sunset glow fundus" can be prevented.[17] Herbort et al suggested that aiming for adequate treatment with both steroidal and nonsteroidal immunosuppression within 2 to 3 weeks of symptom onset and monitoring for findings of subclinical choroiditis via indocyanine green angiography with the intention to increase therapy if necessary can induce cure prior to depigmentation of the retina.[15] If VKH disease is left untreated, recurring granulomatous anterior uveitis, stromal iris atrophy, posterior synechiae, and Busacca nodules may occur.[6,18] Additionally, the development of posterior subcapsular cataracts, glaucoma, and subretinal fibrosis can occur, leading to permanent and complete vision loss.[6,18]

This case highlights the importance of considering a broad differential, especially with regard to diagnoses typically seen in specific racial or ethnic groups, as delay in diagnosis and treatment may result in irreversible disease progression. This case also emphasizes the importance of the primary medicine team acting as a facilitator of communication between consulting subspecialties, ensuring prompt diagnosis and adequate management to improve outcomes. Given the rarity of this condition, the majority of studies on VKH necessarily draw from small sample sizes, which hampers the generalizability of the research findings. Finally, this report illustrates the necessity of both continued research to help better understand the epidemiology and demographic patterns of this disease and a multidisciplinary approach to management.

CONCLUSIONS

We present a clinical case of Vogt-Koyanagi-Harada disease–a rare, inflammatory, autoimmune disorder–to increase awareness of this condition among health care professionals. Early recognition and treatment can prevent long-term morbidity, including permanent vision loss. This report aims to encourage further research by adding to the existing literature on VKH disease.

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