

# The Clinical Presentation and Diagnosis of Vogt-Koyanagi-Harada Syndrome

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## abstract

Vogt-Koyanagi-Harada syndrome (VKH) is a rare inflammatory disorder diagnosed clinically that presents as panuveitis with serous retinal detachments among other systemic symptoms.<sup>1</sup> Treatment options for this disease vary, but pharmacotherapy with systemic corticosteroids is the mainstay. Ruling out infectious causes prior to initiation of corticosteroids is vital as immunosuppression may worsen disease of an infectious etiology. Herein, we describe an otherwise healthy 34-year-old Métis woman with a three-week history of bilateral uveitis presenting with new onset of tinnitus and skin pigment changes started on high-dose IV corticosteroids with clinical improvement of symptoms.

## introduction

Vogt-Koyanagi-Harada syndrome (VKH) is a rare systemic disease (1.5 people per million) involving melanocyte-containing organs. It is a granulomatous inflammatory disorder that affects the eyes, auditory system, meninges, skin and often presents with neurological findings.<sup>1</sup> VKH occurs in certain ethnic groups that possess darker skin pigmentation such as Native Americans, Asians, Hispanics, and those from the Middle East.<sup>2</sup> Women are usually affected twice as commonly as men and incidence is usually highest in the third or fourth decade of life.<sup>2</sup> VKH is diagnosed clinically, encompassing the patient's signs and symptoms while excluding other possible causes. There are four clinical stages: prodromal stage, acute uveitic stage, convalescent stage, and chronic recurrent stage. These stages of VKH are often indistinct.<sup>3</sup>

Initial manifestations occur with a prodromal stage that consists of headache, nausea, vertigo, fever, and meningismus.<sup>3</sup> Neurological features may also occur but are rare. Tinnitus and hypersensitivity of the skin generally appear early. This stage can last three to five days.<sup>1</sup>

The second stage is the acute uveitic

stage, where bilateral blurry vision presents in 70 % of patients.<sup>3</sup> Most patients present in this stage when they experience ocular pain and red eyes. There can be choroidal inflammation and thickening. Multifocal detachments of the neurosensory retina can be pathognomonic for VKH.<sup>3</sup> Eventually the inflammation and posterior uveitis may extend into the anterior segment.

The third stage, the convalescent stage, follows the second stage gradually. This stage may last several months.<sup>1</sup> This stage includes extra-ocular manifestations such as vitiligo, alopecia and poliosis. Further, there can be a uveal depigmentation within two to six months.

The final stage is the chronic recurrent stage, which interrupts the convalescent stage.

There are recurrence rates of 43 % within the first three months and 52 % within the first six months, often associated with rapid tapering of corticosteroids.<sup>4</sup> Recurrence mainly involves anterior uveitis. In this stage, complications of VKH such as glaucoma, cataract, subretinal neovascular membrane, and subretinal fibrosis may develop.<sup>1</sup>

Herein, we report a patient presentation of VKH in rural northern British Columbia. The patient was treated as an outpatient with a course of systemic corticosteroids.

## case presentation

An otherwise healthy Métis 34-year-old female with a three-week history of severe bilateral uveitis, currently being treated with diclofenac (Voltaren<sup>®</sup>), prednisolone (Pred Forte<sup>®</sup>), and ofloxacin (Ocuflox<sup>®</sup>), presents as an outpatient to an ophthalmologist with new onset of tinnitus and patches of vitiligo in addition to the persistent uveitis. Prior to her initial ocular complaints, the patient had chills and headaches with an acute illness. Family history is significant for ankylosing spondylitis.

Examination on initial consultation revealed best-corrected visual acuity (BCVA) of 20/40 OD and 20/30 OS with intraocular pressures (IOP) of 11 mmHg and 12 mmHg, respectively. Biomicroscopy revealed that the cornea and lens were clear bilaterally. The dilated fundoscopic examination revealed occasional to 1+ cells in the anterior chamber and 2+ cells in the posterior chamber of the right eye. The left eye displayed occasional cells in the anterior chamber. Ophthalmological exam of the right eye showed significant optic nerve edema (360°) with serous retinal detachments superior to the optic nerve and just superior to the fovea. In the left eye,

there was significant macular edema in a serous retinal detachment.

Complete VKH Syndrome was diagnosed according to the revised International Diagnostic Criteria outlined by the American Uveitis Society (Figure 1) in which a patient must demonstrate symptoms in five distinct categories.

## investigations

Because mainstay treatment of VKH involves systemic immunosuppression, it was important to exclude other autoimmune or infectious causes associated with bilateral uveitis (e.g. tuberculosis or syphilis)<sup>3</sup> as immunosuppression could further aggravate the condition. Therefore, several tests were ordered, including CSF analysis, Lyme serology, syphilis serology, serum ACE, ESR, CRP, serum protein electrophoresis, serology for cat scratch, and a full 120° visual field test. The patient had slight pleocytosis in the CSF but subsequent culture for bacteria was negative. All other tests were unremarkable.

The CSF analysis was relevant because more than 80 % of patients with VKH disease exhibit a transient CSF pleocytosis within one week and 97 % within three weeks of onset.<sup>5</sup> The pleocytosis resolves within eight weeks of onset in most patients.

Fluorescein angiogram showed diffuse choroiditis with focal delays in choroidal perfusion and multifocal areas of pinpoint leakage, and large placoid areas of hyperfluorescence with pooling within the subretinal fluid and optic nerve staining.

The clinical findings associated with the investigations aided in the diagnosis of VKH while excluding other possible systemic causes.

## treatment

VKH is treated with systemic intravenous or high-dose oral steroids. Possible treatment regimens for VKH are listed in Figure 2. High-dose oral corticosteroids, 80-100 mg per day of prednisone or 200 mg of intravenous methylprednisolone for three days followed by oral administration of high-dose corticosteroids with a slow taper are the mainstay of therapy for VKH.<sup>1</sup> Recurrences

1. There should be no history of ocular trauma or surgery
2. There should be no clinical or laboratory evidence of other ocular disease entities
3. The uveitis must be bilateral exhibiting either A or B A) Early Disease i) Diffuse Choroiditis with either focal or bullous subretinal fluid ii) If fundal appearances are equivocal must have: a) Focal choroidal perfusion delay, pinpoint leakage, placoid fluorescence and optic nerve staining on fluorescein angiography and b) Diffuse choroidal thickening but no scleritis B) Late Disease i) Suggestive history of 3A and either ii or iii ii) Depigmentation, either sunset glow or Sugiura's sign iii) Nummular chorioretinal scars with retinal pigment epithelium (RPE) clumping and migration and recurrent chronic anterior uveitis
4. Active or history of either meningism, tinnitus, cerebrospinal fluid pleocytosis
5. Alopecia, poliosis, or vitiligo
Complete VKH Syndrome requires Criteria 1-5, all inclusive Incomplete VKH Syndrome requires Criteria 1-3 and either 4 or 5 Probable VKH requires Criteria 1-3

**Figure 1:** Revised International Diagnostic Criteria for Vogt-Koyanagi-Harada (VKH)

Corticosteroids
Oral prednisone 100-200 mg initially, followed by gradual taper over 3-6 months
Pulse dose of methylprednisolone 1 g/day for 3 days, followed by gradual tapering of oral prednisone over 3-6 months
Intravenous methylprednisolone 100-200 mg/day for 3 days followed by gradual tapering of oral prednisone over 3-6 months
Cyclosporine 5 mg/kg per day
Azathioprine 1-2.5 mg/kg per day
Biologics
Anti-TNF-alpha monoclonal antibody

**Figure 2:** Treatment options for VKH<sup>1</sup>

may prove to be corticosteroid-resistant so cyclosporine 5 mg/kg per day is instead prescribed.<sup>1</sup>

This patient was treated with IV methylprednisolone 1 g for three days and then oral prednisone 80 mg daily on a tapering dose. The corticosteroid treatment, in addition to her treatment for bilateral uveitis, resulted in reduced optic nerve swelling of the right eye and resolution of serous retinal detachment bilaterally. The patient's oral systemic steroids continued to be tapered over the next six months and the patient's vision continued to improve. As the patient's steroid dose was tapered, the BCVA was 20/40 OD and 20/25 OS with IOPs 15 mmHg and 16 mmHg, respectively (physiological range between 10-21 mmHg).

## discussion

VKH is a rare systemic disease where patients present with bilateral panuveitis associated with cutaneous, neurologic, and auditory findings. Although the etiologic factors in VKH are not exactly known, the clinical course of VKH is usually preceded by an influenza-like episode, which suggests a viral or post-infectious origin. Although a viral cause has been proposed, no virus has been isolated or cultured from patients with VKH syndrome.

VKH is strongly associated with a variety of human leukocyte antigens in patients with different backgrounds. The HLA-DRB1\*0405 allele has been determined as the main susceptibility allele in VKH.<sup>2</sup> The

exact cause of the inflammation directed at the melanocytes is postulated to be driven by T lymphocytes against an unidentified antigen associated with melanocytes.<sup>3</sup>

Different stages of the disease result in different histopathological changes. Initially there is diffuse infiltration of lymphocytes and macrophages. In the convalescent stage, the choroidal melanocytes decrease in number and disappear, which can result in a sunset glow of the fundus.<sup>1</sup> During the chronic stage, the retinal pigment epithelium (RPE) and neural retina may show degenerative changes.<sup>1</sup> The RPE may also reveal hyperplasia and fibrous metaplasia.<sup>1</sup>

## complications

Complications of the VKH are very common, with one retrospective study showing at least one complication occurring in 51 % of eyes.<sup>7</sup> Complications include cataracts (42 %), glaucoma (27 %), choroidal neovascularization (11 %), and subretinal fibrosis (6 %).<sup>7</sup> Patients developing complications are also more likely to have recurrences of VKH.

**Although the etiologic factors in VKH are not exactly known, the clinical course of VKH is usually preceded by an influenza-like episode, which suggests a viral or post-infectious origin.**

## conclusion

VKH is an idiopathic multisystem autoimmune disease against melanocytes causing inflammation of melanocyte-containing tissues in the uvea, ears, skin, and / or meninges. There is no association between mortality and this disease; however, early recognition and prompt treatment is crucial to avoiding loss of visual function.

In general, VKH patients treated with high-dose systemic corticosteroids followed by gradual tapering have a very

### Subjective:

- Previously healthy 34 year old Métis female
- Three week history of pain, redness, blurred vision and increased sensitivity to light in both eyes, previously diagnosed as bilateral uveitis
- Prior to eye complaints, experienced chills and headache with acute illness.
- Significant family history of ankylosing spondylitis
- Recent development of mild ringing of the ears, bilateral, and patches of pale skin appearing in her inguinal area on right side.

### Objective:

- Ophthalmological exam: best corrected visual acuity 20/40 OD and 20/30 OS with intra-ocular pressures of 11 and 12, respectively.
- Dilated fundoscopic exam: Anterior chamber revealed occasional cell and 1+ cells, left and right, respectively. Posterior chamber revealed 2+ cells, bilaterally.
- Significant optic nerve edema 360 degrees with serous retinal detachments in right eye. Significant macular edema with a serous retinal detachment in left eye.
- Fluorescein Angiogram: diffuse choroiditis with focal delays in choroidal perfusion and multifocal areas of pinpoint leakage, bilaterally
- CBC, Lipids, ANA, glucose, Lyme serology, syphilis, serum ACE, ESR, CRP, serum protein electrophoresis, serology for cat scratch and 120 degree Visual Field test were unremarkable.
- CSF revealed pleocytosis but culture was negative for bacteria.

### Assessment:

- VKH, as patient met diagnostic criteria outlined by the American Uveitis Society
- Bilateral anterior uveitis

### Plan:

- Continue treatment for uveitis which includes diclofenac (Voltaren®) drops, prednisolone (Pred Forte®) drops and ofloxacin (Ocuflox®) drops, bilaterally. Cyclopentolate (Cyclogyl®) drops for right eye only.
- Systemic steroid therapy to treat VKH using IV methylprednisolone 1 gram x 3 days and then oral prednisone 80 mg daily on a tapering dose for 3-6 months

Figure 3: SOAP note.

good prognosis, where two thirds maintain visual acuity of 20/40 or better.<sup>1</sup> Hearing is usually restored with control of VKH, although pigment changes are permanent. These changes are treated with mainstay treatments of vitiligo.

It is important to note that causes of bilateral uveitis may not be solely limited to pathologies of the eye and that systemic causes may be the culprit. Therefore, it is important to consider the clinical picture and to inquire for systemic causes of uveitis, as opposed to limiting one's investigations to the affected eye(s) alone. A detailed medical history of this presentation can be observed as a SOAP note in Figure 3.

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