Major review

Vogt-Koyanagi-Harada disease

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**Abstract**

Vogt-Koyanagi-Harada disease, a severe bilateral granulomatous intraocular inflammation associated with serous retinal detachments, disk edema, and vitritis, with eventual development of a sunset glow fundus, is an autoimmune inflammatory condition mediated by T cells that target melanocytes in individuals susceptible to the disease. Vogt-Koyanagi-Harada disease presents clinically in 4 different phases: prodromal, uveitic, convalescent, and recurrent, with extraocular manifestations including headache, meningismus, hearing loss, poliosis, and vitiligo, to varying degrees. There have been considerable advances in imaging modalities resulting in earlier diagnosis and improved understanding of this disease. Ocular coherence tomography has replaced other imaging modalities in the diagnosis of acute and chronic Vogt-Koyanagi-Harada disease by revealing exudative detachments of the retina in the acute stage, along with choroidal thickening and demonstrating choroidal thinning in the chronic stage. Treatment of this disease is initially with corticosteroids, with a transition to immunomodulatory drugs for long-term control. Patients with Vogt-Koyanagi-Harada disease can have good final outcomes if treated promptly and aggressively and thus avoid complications such as sunset glow fundus, cataracts, glaucoma, subretinal fibrosis, and choroidal neovascularization.

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1. Introduction

Vogt-Koyanagi-Harada (VKH) disease is a severe bilateral granulomatous posterior or panuveitis associated with serous retinal detachments, disk edema, and vitritis, with eventual development of a sunset glow fundus. Systemically, it may be associated with tinnitus, hearing loss, vertigo, meningismus, poliosis, and vitiligo, although not all patients present with the complete constellation of these extraocular findings. Diagnosis has been aided by fluorescein angiography of the retina and recent advances in imaging, especially optical coherence tomography (OCT) that can evaluate changes in the retina and, recently, in the choroid. The mainstay of treatment has been corticosteroids and, more recently, steroid-sparing immunomodulators.

We examine VKH and analyze the current treatments, including newer immunomodulators, and evaluate in detail the different imaging modalities and their use in the diagnosis and management of this entity.

2. Historical perspective and description

Although cases of poliosis associated with neuralgias and hearing disorders were reported as early as the 12th century,\textsuperscript{162} the first case of Vogt-Koyanagi-Harada disease was
described in a patient with anterior segment inflammation along with poliosis and vitiligo by Vogt in 1906 when he was a 27-year-old medical resident at Basel University Hospital. The first Japanese author credited with describing the disease was Komoto in 1911, but it was Y. Koyanagi who published a review in 1929 of 16 cases illustrating the natural course of the disease. He noted findings of idiopathic bilateral anterior uveitis, dysacusis, vitiligo, poliosis, and alopecia, as well as a prodromal phase of headache, fever, and confusion. Furthermore, he hypothesized that the disease was caused by an “anaphylactoid” reaction against pigment. Harada, in 1926, described a syndrome that included a prodromal phase of malaise and meningeal irritation, bilateral uveitis, and bilateral retinal detachments that spontaneously resolved, lymphocytosis of the cerebrospinal fluid, and dysacusia. Babel of the Department of Ophthalmology at Geneva University Hospital proposed naming the entity Vogt-Koyanagi syndrome and acknowledged that it was similar to that described by Harada. For decades, the terms Vogt-Koyanagi syndrome and Harada disease were used interchangeably, and it was not till the late 1950s that Vogt-Koyanagi-Harada disease was coined to describe the constellation of symptoms.\(^7\) The use of the term “disease” versus “syndrome” was cemented in 2001 by the International Committee on Nomenclature of VKH.\(^173\)

3. Epidemiology and geographic distribution

The prevalence of VKH varies in different populations in the world, being more common in Asia, Latin America, and the Middle East. VKH is not common in the United States and makes up only about 3%–4% of referrals to tertiary care centers.\(^101\) A series of 48 patients in Southern California diagnosed with VKH were predominantly female (69%) and Hispanic (75%), with a mean age of 33.4 years (range 15–78 years).\(^102\) Only 10% were white, 10% were Asian, and 4% were black. Of 26 patients who presented to the Bascom Palmer Eye Institute between March 1969 and February 1990, again the majority were female (77%) and Hispanic (54%). The average age at presentation was 35 years (range 13–73 years). In this series, 23% were black, 14% were white, and 9% were Asian. All were darkly pigmented.\(^175\) When Moorthy and colleagues evaluated 65 patients with VKH disease, 74% were female, 78% were Hispanic, and the average age at presentation was 32 years (range 7–71 years). Ten percent of patients were Asian, 6% were black, and 3% were white. VKH appears to be more common in pigmented individuals and is relatively rare in whites.

VKH was the most common cause of panuveitis in India, with a prevalence of 21.08%.\(^10\) In Thailand, VKH was the most common cause of noninfectious uveitis (16%), followed by HLA B27-associated anterior uveitis.\(^161\) In Saudi Arabia, the prevalence of VKH was 19.4%,\(^3\) and of new cases, VKH comprised 2.5%.\(^86\) In China, the prevalence varies from 15.9% to 16.3%.\(^36,229\) In Tunisia, VKH was the second most common cause of panuveitis at 15%, behind Behçet disease, and the fourth most common type of uveitis at 4.4%.\(^37\) In Iran, similarly, VKH is behind Behçet disease and idiopathic uveitis and accounts for 15.2% of patients with panuveitis.\(^195\) In Japan, VKH has a prevalence of 6.7% to 11%.\(^66,96,105,150,211\) Conversely, a single study out of Bogota, Colombia, suggests that VKH is less common there (1.2% prevalence), although it is frequently seen in Hispanic populations in the United States.\(^49,135\) The prevalence was slightly higher in Brazil at 2.5% in a study that looked at cases at a uveitis referral clinic in Sao Paulo.\(^15\) The prevalence in Mexico, similarly, is 2.4%.\(^40\) VKH is a rare disease in Turkey, representing only 1.2% of all uveitis cases as reported by Tugal-Tutkun.\(^206\)

Finally, VKH appears to be rare in indigenous populations in central Australia.\(^120\) Thus, VKH appears to have a predilection for pigmented races with significant regional and global variation.

Martin and colleagues studied new cases of uveitis in South India and noted 1.2% of patients with a diagnosis of VKH of which 8.2% were children. Age of presentation was 8 to 16 years, and median age was 13.5 years. Most children ultimately did well, with a final vision of better than 20/40 in 75%.\(^126\) In Saudi Arabia, the prevalence of VKH in children younger than 16 years of age was as high as 16%, behind acute anterior nongranulomatous uveitis and intermediate uveitis.\(^50\) This study found that 54% of children with VKH had vision better than or equal to 20/40. Furthermore, these young patients with VKH had the highest rate of complications; that is, glaucoma in 50%, papillitis in 53%, epiretinal membrane in 16%, and retinal detachment in 4%. Children are at risk of amblyopia secondary to VKH; thus, appropriate diagnosis and management is of vital importance in this population.

Patients over age 60 years appear to have a lower prevalence of VKH\(^85\) compared to younger patients. Ikeda and colleagues also noted that the prevalence of VKH in the elderly (age range 60–86 years) was possibly higher in Japanese patients compared to populations in England (Moorfields Eye Hospital, London, UK) and North America (Massachusetts Eye and Ear Infirmary, Boston, Massachusetts, USA) in a comparison across these 3 institutions.\(^60\) Patients above age 65 years had a higher incidence of optic disk hyperemia, choroidal detachment, and cataract compared to younger patients. They were also more likely to need a higher dose of corticosteroids and often maintained good vision despite low-grade smoldering inflammation.\(^107\)

4. Etiology and pathogenesis

Immunological and histopathological studies suggest that VKH is an autoimmune inflammatory condition mediated by CD4+ T cells that target melanocytes.\(^150,194\) These activated T cells likely initiate the inflammatory process through generation of cytokines, IL-17 and IL-23,\(^85\) in individuals with altered tolerance to melanocytes from deficient T regulatory cells.\(^33\) The trigger that induces altered tolerance to melanocytes is still not known. Genetic susceptibility of persons expressing HLA DRB1*0405, combined with viral infection, may play a role in initiating the autoimmune process.\(^43\)

4.1. Autoimmunity against melanocytes

There is evidence implicating autoimmunity to melanocytes as the underlying mechanism supported by clinical,
histopathological, and immunological studies. Clinically, VKH presents with vitiligo and sunset glow fundus that are shown to be from loss of melanocytes at the site of inflammatory cell infiltration.\textsuperscript{82,153,182} The histopathology of chronic VKH showed a loss of choroidal melanocytes and the presence of both T and B lymphocytes in the choroid, with predominance of CD4+ lymphocytes.\textsuperscript{113,124,152,153,224} Interestingly, immunohistochemical analysis of patches of vitiligo revealed loss of skin melanocytes, presence of melanin-laden macrophages, and infiltration of mononuclear cells that were primarily T lymphocytes with expression of HLA DR.\textsuperscript{155} Moreover, electron microscopy of the choroid in rat experimental models of VKH demonstrated thickening from infiltration by lymphocytes and epithelioid cells surrounding melanocytes,\textsuperscript{72} suggesting that the melanocytes were the targets of the inflammatory process. In support of the melanocyte as the target cells, Kobayashi and colleagues showed that in VKH patients, their autologous T cells responded to tyrosinase peptide of melanocytes, and such response took place by recognition of HLA DRB1*0405 expression by the melanocytes.\textsuperscript{108} This melanocyte target was further supported by a study that showed that the patients with HLA DRB1*0405 recognized a broader array of melanocyte-derived peptides compared to controls.\textsuperscript{43}

It is now generally accepted that the tyrosinase peptide antigen is the target of autoimmunity by T lymphocytes.\textsuperscript{108,188} Yamaki and colleagues synthesized peptides based on the sequence of the tyrosinase family of peptides and found that, when lymphocytes from VKH patients were challenged by these peptides, they proliferated significantly.\textsuperscript{215} Furthermore, an animal model using tyrosinase peptide as the antigen was developed and tested in Lewis rats, Akita dogs, and Rhesus monkeys, and all developed a VKH-like disease similar to that seen in humans.\textsuperscript{221} Moreover, it was shown that tyrosinase peptide-specific T cells can mediate an inflammatory response.\textsuperscript{176}

4.2. Genetic factors in the development of VKH

The role of genetic factors in the development of VKH, such as HLA alleles, was first considered in 1976, and this was supported by the development of VKH simultaneously in monozygotic twins.\textsuperscript{180,200} Subsequent studies revealed the alleles that were associated with VKH, particularly HLA DR1, DR4, DRB1 with susceptibility varying from 11.76 to 45.1. Studies on Mestizo patients in Southern California found associations between HLA DR1 and HLA DR4 and VKH.\textsuperscript{215} A study of 29 individuals in Southern California revealed HLA DRB1*0404/0102/0410 to be more associated with VKH compared to controls.\textsuperscript{150} This finding in Mexico Mestizo patients was echoed as the DR locus carried the primary susceptibility gene in that population.\textsuperscript{17} There was a relative risk of 11.76 of developing VKH in Brazilian patients with the DRB1*0405 allele compared to the general population.\textsuperscript{65} HLA DRB1*0405 and DR4 are also found in Chinese patients,\textsuperscript{84,145,233} In Chinese patients, HLA DR4 was found to be associated with VKH.\textsuperscript{233} In white European patients, specifically of Italian heritage, the HLA DR4 allele was noted to be associated with VKH.\textsuperscript{150} A study of Korean patients found that the HLA DRB1*0405 allele conferred a relative risk of 45.1 of developing VKH compared to the general population but also noted that the haplotype HLA DRB1*0405-DQA1*0302-DQB1*0401 was associated with a decrease in visual and ocular complications.\textsuperscript{100} Further studies are required to validate the protective role of the later haplotype.

More recently, the focus has transitioned from identifying HLA genes associated with an increased risk of VKH to the identification of alternate genes like Killer Immunoglobulin-like Receptors (KIRs) genes that affect susceptibility to the disease. These KIR genes are known to be associated with HLA in specific interactions, and the genes encode inhibitory and activating receptors on natural killer cells. KIR genes may protect against VKH disease or reduce the severity of disease, but may also increase the risk of VKH disease expression\textsuperscript{45}; KIR2DL2/2DL3+HLA C1 is higher in controls than in VKH patients and KIR genes 3DS1/2DS5 were more frequently found in VKH patients than in control patients.\textsuperscript{119,145,184} Furthermore, an inhibitory KIR gene 3DL1 is decreased in VKH patients compared to controls.\textsuperscript{118,119} Further work needs to be done in the field to elucidate the importance of these findings.

Other studies have focused on polymorphisms of genes that appear to be associated with VKH, including osteopontin,\textsuperscript{37,145} IL 17,\textsuperscript{188} STAT 4,\textsuperscript{185} CTLA 4,\textsuperscript{52} programmed cell death 1,\textsuperscript{130} protein tyrosinase phosphatase nonreceptor 22,\textsuperscript{232} tumor necrosis factor alpha-induced protein 3,\textsuperscript{121} and macrophage migration inhibitory factor,\textsuperscript{231} although the importance of these findings is currently unclear. Although the genetic susceptibility studies were helpful in understanding the pathogenesis of VKH, their role in diagnosis and management of VKH is uncertain. Further studies are required to show importance of the polymorphism in diagnosis, development of extraocular changes, prognosis, and treatment of VKH.

4.3. Viral infection

Hayasaka and colleagues described almost simultaneous onset of VKH in 6 coworkers, friends, and neighbors, suggesting an environmental factor such as a virus.\textsuperscript{73} Sugita and colleagues noted in 2001 that there was a cross-reaction between the tyrosinase peptide and a cytomegalovirus peptide (CMV-egH 290-302), hypothesizing that perhaps VKH developed in patients from molecular mimicry after infection with CMV.\textsuperscript{195} Usui and colleagues also detected the presence of another virus, EBV DNA by PCR, in CSF from patients with VKH.\textsuperscript{209} Another study, however, was only able to detect 1 patient out of 8 with VKH with the EBV genome in the CSF.\textsuperscript{181} Recently, viral dsRNA was shown to stimulate toll-like receptor 3 in human melanocytes, inducing melanocyte death;\textsuperscript{230} however, Ito and colleagues evaluated polymorphisms in TLR9, which recognizes DNA motifs on viruses such as EBV and CMV, and they were not associated with VKH.\textsuperscript{96} Unfortunately, no unifying hypothesis regarding a viral etiology has come forth for VKH.

5. Clinical features in different phases of VKH

VKH presents clinically in 4 different phases: prodromal, acute uveitic, convalescent, and chronic recurrent. Clinical
features differ during these phases and recognition of the differing features is important for proper diagnosis and treatment of VKH.

5.1. Prodromal phase

The prodromal phase may present a viral infection and last anywhere between a few days to a few weeks. In this phase, before ocular involvement, clinical manifestations are predominantly extraocular and include headache (82%), meningismus (55%), fever (18%), nausea (9%), vertigo (9%), orbital pain, and auditory disturbances. One or several symptoms can develop during this phase; however, some patients present with typical clinical features of VKH without the prodromal symptoms. Cerebrospinal fluid may show pleocytosis in more than 80% of patients. A review of Hispanic patients from Southern California found that they often presented initially without extraocular changes, but these developed once the disease evolved into the chronic phase.

5.2. Acute uveitic phase

Following the prodromal phase, blurring of vision develops in patients in both eyes, although involvement of 1 eye may be delayed. Clinically noted is a sudden onset, bilateral granulomatous uveitis in up to 70% of patients, with pockets of subretinal fluid and choroidal thickening, blurring of vision, and conjunctival injection. Signs also include swelling and hyperemia of the optic nerve head and retinal edema. Figure 1A and B shows a patient with acute VKH with bilateral serous retinal detachment and optic nerve head hyperemia.

The initial choroidal thickening develops in multifocal segments of inflammation. Subsequent breakdown of the retinal pigment epithelium results in areas of serous retinal detachments. These can be evaluated on both optical coherence tomography and fluorescein angiography. In this acute stage, these serous retinal detachments have a positive predictive value of 100 of being VKH and a negative predictive value of 89.2.

The initial posterior uveitis, if untreated, spreads to both the vitreous and anterior uvea, although vitritis and anterior uveitis are not necessary for the diagnosis. The anterior segment is significant for a granulomatous reaction with the presence of mutton fat keratic precipitates. Recent confocal scans of keratic precipitates reveal that noninfectious etiologies of uveitis, such as VKH, present with smooth and rounded precipitates, whereas infectious uveitides present with dendritiform precipitates.

Nakao and colleagues described ischemic optic neuropathy associated with VKH in 6 older patients based on disk swelling and visual field loss. Recent studies have shown that disk edema is more likely to develop in patients with a smaller cup-to-disc ratio and in those of older age. Furthermore, as expected, visual field defects from nerve involvement develop in those with disk swelling.

Clinically, patients appreciate deleterious effects on visual fields, color vision, and central visual acuity. After receiving treatment, improvement in visual fields can lag behind improvements in color and central vision, implying subclinical abnormalities in macular function.

Initial findings may also include a moderate increase in intraocular pressure in up to 54% of patients. Figure 2A—D demonstrates a patient with acute uveitis with shallow anterior chambers. VKH presenting with a bilateral increase in intraocular pressure occurs more often in older women. These patients often present with blurring vision that is out of proportion to the measured increase in intraocular pressure. The increase in pressure responds better to steroids than to antiglaucoma medications. This presentation is thought to be the result of a transient swelling of the ciliary body, as well as a forward displacement of the lens-iris diaphragm; however, patients can also present with relative hypotony because of inflammation of the anterior uvea and ciliary body shutdown.

5.3. Convalescent phase

Several weeks to months after the acute uveitic phase, depigmentation of the choroid, vitiligo, and poliosis occurs. This convalescent phase usually lasts for months. Signs of depigmentation occur in the limbal area (Sugiura sign) as early as a month after the onset of uveitis are often reported in Japanese patients. Depigmentation of the choroid usually takes 2 to 3 months, resulting in the “sunset glow”—a bright orange-red appearance of the fundus (Fig. 3A and B). The presence of a
sunset glow fundus in patients with uveitis carries a positive predictive value of 94.5 and a negative predictive value of 89.2 for the diagnosis of VKH. The duration from disease onset to appearance of sunset glow fundus is shorter in those with chronic inflammation than in those without. Furthermore, Keino and colleagues noted that the frequency of CSF pleocytosis and the number of cells in the CSF were higher in patients in whom a sunset glow fundus eventually developed. Mizuuchi and colleagues evaluated trabecular meshwork and limbal depigmentation and found that the meshwork pigmentation was lighter in those with sunset glow fundus than in those without it (P = 0.022) but was not related to either limbal depigmentation or vitiligo skin lesions.

5.4. Chronic recurrent phase

Chronic recurrent intraocular inflammation develops in some of the patients and is characterized by exacerbations of granulomatous anterior uveitis that is usually resistant to systemic steroid therapy. This chronic recurrent phase usually develops 6 to 9 months after initial presentation and is also marked by complications such as retinal pigment epithelium (RPE) proliferation, subretinal fibrosis (Fig. 4A and B), subretinal neovascular membranes, posterior subcapsular cataract, posterior synechiae, open-angle glaucoma and, occasionally, angle-closure glaucoma, as well as band keratopathy. Recurrent VKH may be associated with a longer
lasting breakdown in the blood aqueous barrier and thus, more inflammation than at initial disease onset.56 The presence of choroidal folds in patients with a history of VKH and a short axial length may be an early sign of recurrence.202 Subretinal fibrosis may also be seen as a sequela of chronic recurrent disease. This appears to develop faster in Hispanic patients (approximately 6.5 months) compared to non-Hispanic patients (6.5 years).111 The subretinal fibrosis and choroidal neovascularization could develop in patients with severe intraocular inflammation and a chronic and recurrent disease course.117 The relapses in choroiditis may be associated with exudative retinal detachments.55

5.5. Extraocular manifestations

Extraocular manifestations are varied, both during the course of the disease and among patients.

5.5.1. Neurologic findings

Neurologic signs, including headache, meningismus, or cerebrospinal fluid pleocytosis, occur more commonly during the prodromal phase. Integumentary manifestations, including sensitivity of the scalp and of the skin to touch, also occur during the prodromal phase.197 VKH has also presented as meningitis189 and should be on the differential for patients presenting with meningismus. Patients may also present with focal neurologic signs including cranial neuropathies, transverse myelitis, hemiparesis, and aphasia.123

5.5.2. Auditory findings

Eighteen to 50 percent of patients have some form of sensory hearing loss, most often at higher frequencies such as 4, 6, and 8 kHz.154,203 Tinnitus is present in 42%.51 These auditory manifestations respond to treatment variably, and those with profound bilateral hearing loss may benefit from cochlear implantation. Given the large percentage of patients found to have auditory symptoms, audiological testing is recommended for those with a positive review of systems for hearing or vestibular abnormalities.51

5.5.3. Integumentary findings

During the convalescent phase, when depigmentation of the choroid occurs, the eyebrows, eyelashes, hair, and skin also lose pigment, resulting in poliosis and vitiligo.16,67 Although different races will have a different incidence of skin and hair changes, a recent study documented that integumentary changes associated with VKH developed in 30% of patients.226 Although these changes are developed before ocular involvement in a few patients, these changes develop after the onset of uveitis in the vast majority.

6. Diagnostic criteria

Diagnostic criteria for multiple systemic and ocular diseases can be used in a clinical research setting for standardization. This is most useful in situations where the disease is complex and involves multiple organ systems but also requires the use of ancillary testing and imaging. VKH has been described in the literature for many years; however, there is no single laboratory test that can be relied on to make the diagnosis, and no single manifestation of the disease is specific to VKH. Ocular manifestations of VKH can be shared with other forms of uveitis, including sympathetic ophthalmia, posterior scleritis.
intraocular lymphoma, and so forth (see Section 8). Similarly, the systemic findings can be seen in disease states that result in hearing loss, idiopathic vitiligo, aseptic meningitis, transverse myelitis, and so forth. Because of this, a diagnostic criterion to standardize the diagnosis of this disease was developed by the American Uveitis Society (AUS) in 1978 (Table 1). Sugiura also released diagnostic criteria in 1978. The AUS criteria required a lack of prior ocular trauma to diagnose VKH as opposed to sympathetic ophthalmia. One of the following group of signs was also required to be present: chronic bilateral iridocyclitis, posterior uveitis including exudate retinal detachments or forme fruste exudative retinal detachments (optic disk hyperemia or edema or subretinal macular edema) or sunset glow fundus, neurologic symptoms or signs of tinnitus, neck stiffness, cranial nerve or other central nervous system problems or CSF pleocytosis, and cutaneous findings such as alopecia, poliosis, or vitiligo. Sugiura’s criteria include 3 major symptoms: bilateral simultaneous uveitis, circumscribed retinal edema in the posterior pole with characteristic leakage of fluorescein dye, and pleocytosis in the cerebrospinal fluid in the acute stage. Pleocytosis of the cerebrospinal fluid as a major sign was necessary for the diagnosis of the disease based on Sugiura’s criteria, along with either uveitis or retinal edema. Manifestations in the other organ systems, active uveitis, systemic findings compared with complete VKH. Finally, "probable" VKH is the presence of ocular disease only. This only requires the presence of criteria 1–3.

Table 2 – Revised diagnostic criteria for Vogt-Koyanagi-Harada syndrome

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<td>4. Neurological findings (may have resolved): meningismus, tinnitus, or CSF pleocytosis (Note: headache alone is not sufficient.)</td>
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Tokyo Medical University and culminated in the first international workshop on VKH disease. Criteria developed during this workshop were henceforth described as the Revised Diagnostic Criteria for Vogt-Koyanagi-Harada Disease. These criteria were developed for the purpose of conducting multicenter, national, or international studies on this entity. The criteria proposed were different from the criteria put forth by the AUS in that the Revised Diagnostic Criteria recognized the varied presentations of the disease in its different stages and excluded patients with prior intraocular surgery. CSF pleocytosis was not a diagnostic requirement except in the absence of meningismus or tinnitus. CSF pleocytosis, on the other hand, was considered an absolute in the criteria proposed by Sugiura. In the Revised Diagnostic Criteria, the presentations of VKH were described as complete, incomplete, and probable, depending on how many of the diagnostic criteria they fulfilled. The “complete” presentation of VKH required the presence of the following 5 criteria: (1) no prior history of trauma or intraocular surgery; (2) no clinical or laboratory evidence of other ocular disease entities; (3) bilateral ocular involvement (either early or late manifestations); (4) neurological or auditory signs; (5) integumentary findings. "Incomplete" VKH is considered to be the presence of criteria 1–3, and either criteria 4 or 5. Incomplete VKH is ocular involvement with only a few of the systemic findings compared with complete VKH. Finally, "probable" VKH is the presence of ocular disease only. This only requires the presence of criteria 1–3.

Yamaki and colleagues evaluated the Revised Diagnostic Criteria in a group of 49 patients and found that patients evaluated in the first 2 weeks, 3/49 (6%) would not have received the diagnosis of VKH; however, at the final visit, all patients would have had some form of the diagnosis. They did not, however, use the third category of disease, “probable VKH”, to evaluate the remaining patients. Kitamura and colleagues also assessed the Revised Diagnostic Criteria and noted that 155/169 (91.7%) patients diagnosed by the Sugiura criteria would have been diagnosed correctly, whereas 14/169 patients would have had some form of the diagnosis.220

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(8.3%) patients would have been excluded. A response to this article by Tsai and colleagues, stated that of the 14 excluded, 2 patients should have been diagnosed with incomplete VKH and 9 with probable VKH. The Revised Diagnostic Criteria were 100% specific and had a higher diagnostic sensitivity than the Sugiura system. Rao and colleagues, in 2007, evaluated 28 patients in the early phase of VKH and 88 patients in the late phase of VKH and noted that there was 100% concurrence with the Revised Diagnostic Criteria. Cardoso and da Silva also found the Revised Diagnostic Criteria to have good applicability to their population of Brazilian patients. Based on these evaluations of the Revised Diagnostic Criteria, it appears that complete VKH is the least common presentation of this disease (Table 3). This finding is clinically important because patients who present with ocular disease with or without the involvement of auditory, neurological, or integumentary system must still be diagnosed in a timely fashion and started on immunomodulatory therapy to have the best outcomes. These criteria appear to be most useful for standardization of the diagnosis of VKH for multicenter research studies.

For clinical and routine diagnosis of VKH, a multinational study was recently reported that attempted to distinguish clinical features in patients with VKH and non-VKH uveitis. It found that the presence of bilateral intraocular inflammation associated with exudative retinal detachments carried a positive predictive value of 100 in patients in the acute phase and a negative predictive value of 88.4. This implies that bilateral exudative retinal detachments in the presence of intraocular inflammation is highly suggestive of VKH. Furthermore, in patients with chronic intraocular inflammation, a sunset glow fundus carried a positive predictive value of 94.5, again indicating that a sunset glow fundus is highly suggestive of VKH uveitis. This study, however, was performed at uveitis centers around the country. Positive predictive value and negative predictive value are influenced by the population being studied. This data can, thus, be extrapolated to major uveitis centers, but the ratios would certainly be different in the community setting. In addition, the clinical finding of a sunset glow fundus seen primarily in patients with pigmented irides and uveitis can also be seen in lightly pigmented white patients without uveitis, so care must be taken in confirming this finding. The blond fundus seen in whites is devoid of nummular choriretinal scars that are frequently seen in patients with VKH with a sunset glow fundus. Extracocular findings—including poliosis, vitiligo, alopecia, and hearing loss—although present over the course of the disease, did not improve the likelihood ratio/positive predictive value/negative predictive value when compared to the presence of sunset glow fundus alone. Finally, fluorescein angiography appeared to be a superior ancillary test compared with cerebrospinal fluid analysis in supporting the diagnosis of VKH, with 83% of patients with a positive finding on fluorescein angiography, compared with 77% of patients with pleocytosis on cerebrospinal fluid analysis. In this multicenter study, VKH disease was classified into 2 groups (acute and chronic), based on the standardized uveitis nomenclature classification; however, prior studies have revealed 4 phases of disease progression as described in the following.

### Ancillary diagnostic tools

Clinically, most patients in the United States and several other countries with the diagnosis of VKH undergo retinal fluorescein angiography. In Japan and Europe, lumbar puncture is performed to detect pleocytosis in cerebrospinal fluid. Other investigations found useful in supporting the diagnosis of VKH include indocyanine green (ICG) angiography to detect choroidal changes and ultrasonography to measure choroidal thickness. Although electroretinogram and electroencephalogram have been used, these procedures are rarely conducted and may not be required for supporting diagnosis of VKH in vast majority of patients. Interestingly, recent advances in imaging technology have enhanced not only the diagnosis but also provide objective evaluation of disease progression and efficacy of treatment in VKH patients. Advances in OCT in measuring choroidal thickness, along with other imaging modalities such as fundus autofluorescence, have allowed for noninvasive delineation of changes to the retina, retinal pigment epithelium, and choroid not previously evident on clinical examination. In the acute phase of the disease, OCT is most useful in evaluating the increased thickness of the choroid, as well as the presence of subretinal fluid and exudative retinal detachments. See Table 4 for imaging findings in acute VKH using various modalities.

Indocyanine green angiography is also useful in the acute stage as it demonstrates changes in choroidal perfusion. Similarly, fluorescein angiography allows evaluation of changes to choroidal perfusion, as well as pinpoint areas of hyperfluorescence and subsequent leakage into the subretinal space. Fundus autofluorescence is also useful in evaluating

<table>
<thead>
<tr>
<th>Study</th>
<th>Stage</th>
<th>No. of patients</th>
<th>Complete VKH</th>
<th>Incomplete VKH</th>
<th>Probable VKH</th>
<th>Not VKH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yamaki et al a</td>
<td>Early</td>
<td>41</td>
<td>39</td>
<td>2</td>
<td></td>
<td></td>
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<tr>
<td>Yamaki et al a</td>
<td>Late</td>
<td>8</td>
<td>7</td>
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<tr>
<td>Kitamura et al</td>
<td>Late</td>
<td>169</td>
<td>20</td>
<td>120</td>
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<td>14</td>
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<tr>
<td>Tsai et al b</td>
<td>Early</td>
<td>14</td>
<td>2</td>
<td>9</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Rao et al</td>
<td>Early</td>
<td>28</td>
<td>13</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rao et al</td>
<td>Late</td>
<td>88</td>
<td>19</td>
<td>33</td>
<td>36</td>
<td></td>
</tr>
</tbody>
</table>

VKH, Vogt-Koyanagi-Harada.

a The authors did not use the third category “probable VKH” in their assessment.

b The authors specifically evaluated the 14 patients that Kitamura et al deemed “not VKH.”
changes to the retinal pigment epithelium before changes evident on clinical examination. In the convalescent phase of disease, thinning of the choroid is apparent on OCT, as is blocked choroidal fluorescence on fluorescein angiography. ICG angiography and OCT enhanced imaging is helpful in the chronic recurrent stage and during treatment as they demonstrate subclinical disease in the choroid that can help tailor treatment with corticosteroids and immunomodulatory agents. Imaging of subretinal fluid height measurement and choroidal thickness at subfovea with OCT is found useful in objectively determining response to corticosteroids; with systemic corticosteroids, the subretinal fluid height is reduced to 50 percent in a week, and all fluid subsides within 2–4 weeks. Similarly, choroidal thickness reduction is seen at 2 weeks and can return to normal thickness by 4 weeks.\(^{127,142,144}\) The sub-retinal fluid resolution and choroidal thickness measurement reduction to normal level correlates well with improvement of visual acuity, suggesting that image-based follow-up examinations could help in determining gradual tapering of systemic corticosteroids. Although such imaging modalities have helped in diagnosis and monitoring response to treatment, it is not clear how often and which imaging modalities should be used in acute, convalescent, and chronic recurrent phases of the intraocular inflammation. Most uveitis clinics currently use OCT and autofluorescence imaging during follow-up examinations, but further studies are required to determine usefulness of OCT and other imaging modalities during treatment and how often they should be performed.

Although the revised criteria advocate for the use of fluorescein angiography and ultrasound to aid in diagnosis, with recent advances in OCT, the criteria should be revised to include the use of OCT to diagnose thickening of the choroid and the presence of exudative retinal detachments\(^{128,158}\) in the acute stage and subsequent thinning in the convalescent stage.\(^{59,127,138,187}\)

### 7.1. Fluorescein angiography and indocyanine green angiography

Fluorescein angiography and ICG angiography have allowed minimally invasive delineation of changes to the retina, RPE, and choroid. Fluorescein angiography is helpful in evaluating retinal and choroidal changes during the different stages of the disease. Figure 5A–F depict fluorescein angiography from a patient with acute VKH with characteristic hyperfluorescent spots and late leakage. A similar angiographic pattern is seen in wide-field angiography (Fig. 6). Arellanes-Garcia and colleagues evaluated fundus fluorescein angiography in 60 patients divided into 4 groups based on disease stage at the time of the study.\(^{120}\) The acute stage is marked by optic disk hyperfluorescence and disseminated spotted choroidal hyperfluorescence in 94.4% and choroidal hypofluorescence (delayed choroidal filling) in 83.3%. In the chronic uveitic stage, the most common findings were hyperfluorescence and hypofluorescence (72.7%) and optic disk hyperfluorescence (72.7%). Retinal vascular hyperfluorescence was also present at this stage in 18.2%. The convalescent stage was marked by spotted hyperfluorescence and hypofluorescence (73.3%) and blockage of choroidal fluorescence from retinal pigment epithelial migration (56.7%), as well as dot-like hyperfluorescence at the equator in 43.3% that had a clinical correlation with nummular white scars. Chee and colleagues noted early pinpoint peripapillary hyperfluorescence on fluorescein angiography in patients in the hyperacute phase (those who were imaged less than 14 days after onset of symptoms). Patients with this finding had resolution of the disease compared to those patients without it. This may be a valuable prognostic sign in that the disease is still in the hyperacute phase; thus, patients without this finding require longer and more aggressive courses of treatment as their treatment has started later in their disease course.\(^{11}\)

ICG angiography has been useful in assessing angiographic findings in early stages of the disease, including a diffuse delayed perfusion of the choroid.\(^{56}\) Harada and colleagues noted leakage, segmental hyperfluorescence, and hypofluorescent areas, all of which are not noted on fluorescein angiography.\(^{71}\) These changes have been noted in other studies as well.\(^{155,163}\) Bouchenaki and colleagues evaluated the choroid in VKH, ocular sarcoidosis, tuberculosis, and birdshot chorioretinopathy and found stromal inflammatory

### Table 5 – Differential diagnosis of Vogt-Koyanagi-Harada syndrome

<table>
<thead>
<tr>
<th>Prior trauma</th>
<th>Infectious etiologies</th>
<th>Malignancies</th>
<th>Inflammatory diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sympathetic ophthalmia</td>
<td>Bacterial infection</td>
<td>Intraocular lymphoma</td>
<td>Bilateral posterior scleritis</td>
</tr>
<tr>
<td></td>
<td>Fungal infection</td>
<td>Diffuse uveal lymphoid hyperplasia</td>
<td>Sarcoidosis</td>
</tr>
<tr>
<td></td>
<td>Tuberculosis</td>
<td>Bilateral diffuse uveal melanocytic hyperplasia</td>
<td>Acute posterior multifocal placoid pigment epitheliopathy</td>
</tr>
<tr>
<td></td>
<td>Syphilis</td>
<td>Monoclonal gammapathies</td>
<td>Multiple evanescent white dot syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Systemic lymphoma or leukemia</td>
<td>Lupus chorioidopathy</td>
</tr>
</tbody>
</table>
vasculopathy, fuzzy indistinct vessels, and diffuse choroidal hyperfluorescence, implying an inflammatory vasculopathy. The findings of hyperfluorescent areas, hypofluorescent dark dots and disk hyperfluorescence, especially in severe disease, have been noted by others.

Subclinical disease during tapering of treatment, and relapses is also visible on ICG angiography imaging. Visualizing subclinical disease during tapering can make the duration of immunosuppression longer but results in lower long-term sequelae such as sunset glow fundus. Although ICG angiography may provide details on persistent choroidal inflammation that is not clinically apparent, recent advances in OCT imaging modalities through measurement of choroidal thickness could provide a similar clinically relevant finding.

7.2. Optical coherence tomography

OCT has allowed for specific delineations of changes to the retina and retinal pigment epithelium that were otherwise less evident on clinical examinations. Patients in the acute phase have exudative retinal detachments (Fig. 7), with subretinal septae likely made up of inflammatory products that can be demonstrated on OCT. There is considerable intraretinal fluid accumulation, as noted by Maruyama and Kishi in 2004, wherein 40% of consecutive eyes had fluid in the outer retina. This intraretinal fluid appears to be associated with severe dye leakage from the retinal pigment epithelium. Yamaguchi and colleagues demonstrated that the serous retinal detachments contain structures that could be subretinal septae and hypothesized these were comprised of inflammatory products. Ishihara and colleagues thought that the septae were actually a separation of the inner and outer segments of the photoreceptors and presence of fibrin among the outer segments secondary to inflammation. It has also been demonstrated that previously noted striations of the choroid are actually undulations of the retinal pigment epithelium. Nazari and colleagues reviewed OCTs from 12 eyes (6 patients) and noted that the height of subretinal fluid on OCT correlated with visual acuity. Height of subretinal fluid on initial presentation did not correlate with resolution.

Fig. 5 – Fluorescein angiography of acute VKH demonstrating early blockage of dye (A-D) and late leakage and pooling (E and F).

Fig. 6 – Widefield late-phase fluorescein angiography of acute VKH.
Presence of choroidal folds and multifocal retinal detachment correlated with initial visual acuity, but not with vision at the 3-month follow-up or time to resolution of subretinal fluid.144 There has been considerable advancement in technology in the field of OCT since its inception; however, there have been few direct comparisons between OCT technologies. Branchini and colleagues assessed the reproducibility of measurements of the choroidal thickness across 3 spectral domain OCT (SD-OCT) instruments (Cirrus, Spectralis, and RTVue) and found good reproducibility among these instruments.23 Park and colleagues evaluated conventional OCT raster scans and enhanced depth imaging raster scan protocol and found a high agreement between them when measuring retinal thickness and volume.160 There do not appear to be enough data at this time to support a significant difference between enhanced depth imaging over conventional OCT imaging. There have, however, been reports of improved visualization of the ellipsoid zone and external limiting membrane in acute VKH disease with enhanced SD-OCT imaging compared to prior modalities (OCT 2000 and Stratus OCT, specifically).82 Based on the literature, enhanced SD-OCT technology provides a good view of the pertinent retinal structures involved in the disease process.

Enhanced depth imaging of spectral domain OCT shows thickening of the choroid in the acute phase of VKH.59,127,138 Fong and colleagues found that the mean choroidal thickness of patients with acute VKH was 424 ± 50.1 μm, convalescent VKH was 273 ± 71.3 μm, and control subjects was 287 ± 77.2 μm.59 Maruko and colleagues found that the mean choroidal thickness in patients presenting with acute VKH decreased from 805 ± 173 μm at the first visit to 524 ± 151 μm at 3 days (P < 0.001) and 341 ± 70 μm by 2 weeks (P < 0.001) after the initiation of corticosteroid treatment.127 Nakai and colleagues had similar findings using high penetration OCT that uses a longer wavelength than conventional OCT:138 OCT, thus, can be used to evaluate the stage of disease, as well as monitor the efficacy of treatment. The thickness of the choroid can also be used as an indicator of disease recurrence, that is, the presence of choroidal folds at time of recurrence187 or an increase in choroidal thickness during recurrence of disease.138 The choroid is thinner in patients in the convalescent phase and in those with the clinical findings of a sunset glow fundus and in those with longstanding disease.48,59,138,187 Takahashi found that subfoveal choroidal thickness was approximately 144 ± 72 microns in those with fundus depigmentation compared with those without depigmentation.205 Silva and colleagues found that the subfoveal choroidal thickness was about 250 ± 93 microns in those with longstanding disease but not necessarily with fundus depigmentation.156 Histopathological studies revealed loss of choroidal melanocytes and choroidal atrophy during the convalescent and chronic recurrent phases of VKH particularly in eyes with a sunset glow fundus. Moreover, during the convalescent phase, there is a loss of choriocapillaris.82,182 The thinning of the choroid as measured by OCT may reflect either choroidal melanocyte loss and or loss of choriocapillaris.143

OCT, thus, continues to be an impressive technology allowing us to understand more about the disease process of VKH and has been valuable in visualizing improvement in subretinal fluid, retinal thickness, and choroidal thickness with successful therapy as well as visualizing disease recurrence.

7.3. Fundus autofluorescence

Fundus autofluorescence primarily visualizes lipofuscin that accumulates in the RPE and has been instrumental in evaluating abnormalities in VKH that are not visible on clinical examination. In addition, wide-field scans are useful in documenting the extent of disease.77 Autofluorescence signals correlate to the health of RPE and retina18 and are useful in evaluating early damage to the RPE.59 In the acute phase, fundus autofluorescence shows a
diffuse increased signal, as well as blocked signal, correlated to the presence of exudative retinal detachments if seen at onset of initial symptoms. These resolve in 6 months after treatment with high-dose intravenous steroids; however, in patients presenting weeks after initial onset of symptoms, autofluorescence shows diffuse and mottled hyperautofluorescence mixed with hypoautofluorescence in areas of exudative retinal detachments and demonstrated hypoautofluorescent dots at 6 months after treatment. See Figure 8 for an example of autofluorescence abnormalities in the acute phase of VKH.

Patients who present in the late acute phase without prior treatment can also present with hyperautofluorescence and hypoautofluorescence as well as lattice-like patterns. In the chronic phase, fundus autofluorescence images show both an increased autofluorescence pattern and a decreased autofluorescence pattern. The decreased autofluorescence pattern is related to the loss of RPE and involvement of the outer retina in the disease process. Peripapillary atrophy manifests as decreased autofluorescence, as do nummular chorioretinal scars. An increased pattern is related to the development of cystoid macular edema, subretinal fibrosis, and areas of RPE proliferation. Interestingly, the appearance of a sunset glow fundus did not correlate with abnormalities on fundus autofluorescence. Because autofluorescence correlates to the health of the RPE, recurrent bouts of inflammation and subclinical inflammation can be evaluated well on fundus autofluorescence and wide-field imaging (Fig. 9). This along with OCT evaluation can help evaluate disease severity, which can have prognostic implications.

7.4. Retinal electrophysiologic tests

Electroretinography has been useful to assess macular function in acute and chronic VKH. Da Silva and colleagues noted that ERGs had diffusely diminished amplitudes and preserved implicit times, and they were able to stratify late-stage VKH based on retinal function. Yan and colleagues used the multifocal electroretinogram to evaluate improvements in visual function before treatment and after treatment. They noted that macular function recovered (i.e., an improvement in latency and amplitude); however, macular function was still significantly decreased compared to normal controls. Visual acuity improved faster than macular function on multifocal electroretinogram. Chee found evidence of markedly reduced amplitudes and implicit times in eyes with large peripapillary atrophy compared to those without; however, peripapillary atrophy is not specific to VKH. Further studies should be done evaluating multifocal electroretinography in those with PPA and different types of uveitis. Although ERGs may be more useful in assessing retinal function over measurement of visual acuity, there are no data on basing treatment duration on normalization of ERG instead of retinal imaging modalities.

7.5. Lumbar puncture

The role of lumbar puncture in the diagnosis of VKH has been controversial. Cerebrospinal fluid pleocytosis, a finding obtained only by lumbar puncture, was included as a major criterion required to make the diagnosis of VKH by Sugiyama. The Revised Diagnostic Criteria put forth in 2001 requires a finding of CSF pleocytosis only in the absence of neurological or auditory findings. Kitamura and colleagues, in a review of 169 VKH patients, found that 71.6% had CSF pleocytosis. Tsai and colleagues evaluated 10 patients with a diagnosis of VKH who underwent lumbar puncture, and 2 of these patients did not have pleocytosis of CSF at presentation in the acute uveitic stage. Both of the patients without CSF pleocytosis had both neurological symptoms (headaches) and anterior and posterior uveitis. Both patients also had disk edema, but one did not have a retinal detachment. In both of these articles, 20%–30% of patients would not have received the diagnosis of VKH if CSF pleocytosis was required. The presence of clinical features consisted with VKH, especially as highlighted on fluorescein angiography (disk edema, pinpoint hyperfluorescence, and characteristic dye leakage) suggest that lumbar puncture is not necessary for the diagnosis of acute VKH, but may be reserved for atypical presentations without the angiographic features. Finally, CSF pleocytosis cannot differentiate between VKH, Lyme disease, neurosyphilis, multiple sclerosis, neuroarospondosis, or Behçet’s disease, making it difficult to incorporate it in major diagnostic criteria. The presence, however, of melanin-laden macrophages in the CSF is a feature of acute VKH. Kim and colleagues described a case of a 51-year-old Hispanic woman who presented with bilateral intraocular inflammation, serous retinal detachments with angiographic features as seen in VKH, in the setting of an elevated serum rapid plasma reagin titer of 1:32, positive treponemal antibody test and pleocytosis of the CSF that led to her initial treatment for neurosyphilis with IV penicillin G, followed by intramuscular injection of penicillin for 3 weeks. Cerebrospinal fluid analysis was negative for Venereal Disease Research Laboratory and fluorescent treponemal antibody tests; however, the CSF showed the presence of melanin-laden macrophages that led to the diagnosis of VKH, and she improved after treatment with immunomodulatory therapy. The importance of the presence of melanophages in CSF in the diagnosis of VKH was also commented on by others previously.

![Fig. 9 – Widefield autofluorescence imaging demonstrating hypoautofluorescent spots in the retina.](image-url)
Although the vast majority of VKH is diagnosed on direct clinical examination, occasionally, the view to the posterior chamber is obscured because of dense vitritis, posterior syn-echiae, or the presence of a cataract. In such cases, ultrasonography can be used to make the diagnosis. The following are features noted on ultrasound to be consistent with the diagnosis of VKH: (1) diffuse, low to medium reflective thickening of the choroid posteriorly; (2) serous retinal detachment located inferiorly or in the posterior pole; (3) mild vitreous opacities with no posterior vitreous detachment; (4) thickening of the sclera and/or episclera posteriorly. Furthermore, ultrasonography can also be used to follow response to treatment in the absence of a direct view, as resolution of these findings occurs with appropriate steroid and immunomodulatory treatment.

Ultrasonography, however, must be used carefully to distinguish between several different entities such as posterior scleritis, benign reactive lymphoid hyperplasia of the uvea, and diffuse melanoma of the choroid. Ultrasonographic features of VKH and sympathetic ophthalmia are the same with the distinguishing feature being the absence of prior intraocular surgery or ocular trauma in the former.

VKH may also present uncommonly with elevated intraocular pressure and a shallow anterior chamber. Yang and colleagues performed a retrospective review of 486 VKH patients of whom 8 (16 eyes) were misdiagnosed as acute angle-closure glaucoma. Six patients were male and 2 were female. The mean age at onset of disease was 55.6 years. All 8 patients presented with headache, sudden onset of blurry vision, and the fundus examination is significant for the presence of a cataract. The mean IOP was 32.9 ± 4.2 (range 27–40 mm Hg). Ultrasound biomicroscopy demonstrated a shallow anterior chamber, narrow angles, detachment of the ciliary, and peripheral choroidals. These findings resolved with treatment. This presentation is thought to be secondary to swelling of the ciliary body and anterior rotation of the ciliary processes. This study supports the use of ultrasound biomicroscopy in differentiating acute angle-closure glaucoma from glaucoma secondary to VKH.

The differential diagnosis of VKH is broad (Table 5), and the first step is to determine whether there is a history of trauma. If so, sympathetic ophthalmia should be on the differential. If there is no prior trauma, then infectious causes such as bacterial, fungal, tuberculosis, and syphilis should be ruled out. Once infectious causes are ruled out, malignancies such as intraocular lymphoma, diffuse uveal lymphoid hyperplasia, bilateral diffuse uveal melanocytic hyperplasia, and monoclonal gammapathies should be considered. Finally, inflammatory diseases such as bilateral posterior scleritis, sarcoidosis, acute posterior multifocal placoid pigment epitheliopathy (APMPPE), lupus choroidopathy, and multiple evanescent white dot syndrome should be excluded.

**8. Differential diagnosis**

Sympathetic ophthalmia is an important consideration in the differential diagnosis. In fact, whenever Vogt-Koyanagi-Harada disease is in the differential for a disorder, sympathetic ophthalmia must be included as well, and vice versa. This is because these entities present with an almost identical clinical picture. The distinguishing feature of sympathetic ophthalmia is prior penetrating ocular trauma or surgery. Although the presence of alopecia, vitiligo, and poliosis is recognized more in VKH, sympathetic ophthalmia (SO) can also present with such findings. Furthermore, in certain populations, such as Hispanic patients, intregumentary symptoms in VKH do not present until later in the disease, so information regarding the presence or absence of intregumentary symptoms should be handled with caution.

**8.1. Sympathetic ophthalmia**

Intraocular inflammation secondary to an infectious process must be ruled out before initiating treatment for VKH. The mainstay of therapy for acute VKH is immune suppression with corticosteroids that can have devastating consequences in an eye that has inflammation from infection. The presentation of infectious intraocular inflammation is wide and varied. The clinical history is of utmost importance, with a focus on previous surgery or ocular trauma, as well as exposure to animals, to sexually transmitted diseases, or time spent in countries with endemic diseases such as tuberculosis. Intraocular inflammation following or ocular trauma may make a bacterial or fungal infection more likely. These usually present with intense inflammation. Retinal examination may reveal creamy white lesions characteristic of fungal infection. Intraocular tuberculosis must be ruled out with a tuberculin skin test, gamma interferon release assay, chest X-ray, and inquiry regarding travel to countries with a high rate of tuberculosis. Although PCR can be performed to evaluate for intraocular tuberculosis, patients with a positive tuberculin skin test should be evaluated for treatment with antituberculosis agents, given that systemic immunosuppression may cause reactivation of the disease. Infectious etiologies should be ruled out with appropriate serologic testing before the initiation of corticosteroids for VKH; however, the presence of subretinal fluid and bilateral intraocular inflammation has a high positive predictive value for VKH (100%). Infectious inflammation is unlikely to present with a serous retinal detachments, as well as angiographic findings of early pinpoint hyperfluorescence with late leakage.

**8.2. Infectious intraocular inflammation**

Primary intraocular lymphoma is a variant of primary central nervous system lymphoma and is a variant of non-Hodgkins lymphoma, usually a high-grade B-cell lymphoma, with a median survival of 1–8 years. Patients are usually diagnosed at an older age than with VKH. Patients are usually asymptomatic or present with floaters and painless decreased visual acuity. The fundus examination is significant for the presence...
of multifocal raised yellow infiltrates in the subretinal and sub-RPE space. Lumbar puncture and MRI are useful in the diagnosis of primary central nervous system lymphoma as it requires vitreous and/or chorioretinal biopsy for tissue diagnosis. Fluorescein angiography demonstrates blockage of choroidal fluorescence with staining of the infiltrates in late lesions, whereas in VKH, the early phases show areas of pinpoint hyperfluorescent dots with late leakage.

### 8.4. Bilateral diffuse melanocytic hyperplasia

Bilateral diffuse melanocytic hyperplasia is a paraneoplastic entity associated with varied malignancies, including ovarian, pancreas, lung, uterine, and breast cancers. Patients usually have involvement of both eyes with pigmented and non-pigmented iris and choroidal nodules, cataracts, serous retinal detachments, and diffuse uveal thickening. The patients suffer severe vision loss from the rapidly progressive cataracts and retinal degeneration. Biomicroscopy shows multiple orange spots that appear hyperfluorescent on fluorescein angiography with late staining. These areas of hyperfluorescence tend to be more irregular and widespread instead of the pinpoint hyperfluorescence noted in VKH. Furthermore, there is late staining, whereas in VKH, fluorescein angiography usually shows late leakage corresponding to areas of serous retinal detachments. Diffuse thickening of the choroid can be noted on B-scan ultrasonography. Histopathologic examination of the thickened uvea shows melanocytic hyperplasia. These lesions are believed to be benign, and there have been no cases of metastases. Although the clinical examination is similar to that seen in VKH, the older age of the patients, along with fluorescein angiography, helps to differentiate it clinically.

### 8.5. Diffuse uveal lymphoid hyperplasia

Uveal lymphoid hyperplasia is a low-grade neoplastic lymphoproliferation in the uveal tract that can present bilaterally. Patients have decreased vision, pink fleshy lesions on the episclera, choroidal thickening, hypopigmented choroidal lesions, and serous retinal detachments. Systemic evaluation is important in this disease as lymphoproliferation may be present elsewhere in the body. B-scan ultrasonography can show choroidal thickening with low internal reflectivity, as well as extracranial peripapillary nodules. Fluorescein angiography can show stippling of the choroidal lesions or a mottled hyperfluorescence. Patients initially respond to corticosteroids, but unlike VKH, they can have an incomplete response or stop responding to the treatment, and local radiation may be necessary. Cockerham and colleagues evaluated 10 cases of uveal lymphoid proliferation previously classified as reactive lymphoid hyperplasia. They found that, after performing immunohistochemical and molecular analysis, 8 of the 10 cases were found to be consistent with low-grade B-cell lymphoma.

### 8.6. Bilateral posterior scleritis

Posterior scleritis is more often unilateral, but may occur bilaterally in patients with rheumatological disease. It occurs in women more often than men. Patients can present with pain, redness, photophobia, and decreased vision. The vitreous may contain cells, and the posterior examination may show exudative retinal detachments similar to VKH, as well as choroidal folds, disk edema, and retinal striae. Fluorescein angiography can appear similar to VKH and SO, with a mottled choroidal fluorescence with multiple pinpoint areas of hyperfluorescence in early phases and leakage in late phases. Ultrasonography is useful in differentiating posterior scleritis from VKH. On B-scan ultrasonography, the posterior aspect of the globe appears flattened, retrobulbar edema is present, and the sclera appears thickened with high internal reflectivity. This high internal reflectivity can also be verified by A-scan. Often, in the presence of retrobulbar edema, the “T” sign may also be seen.

### 8.7. Uveal effusion syndrome

Idiopathic uveal effusion is a disease characterized by serous retinal detachments, choroidal elevation, retinal pigment epithelial changes, and a thickened sclera visible on B-scan ultrasonography. The choroidal elevation usually starts peripherally and can appear a brownish color explaining why this can sometimes be confused for uveal melanoma. Although VKH can also present with a thickened sclera and

Fig. 10 — Photo demonstrating hypopigmented scars in sarcoid uveitis (A) compared with widefield imaging showing peripheral nummular scars in VKH (B).
multiple serous retinal detachments, it is usually character- ized by inflammation that is present in the vitreous and the anterior chamber. Ultrasonography reveals a thickened pos- terior choroid in VKH. Uveal effusion syndrome, however, is notable for an absence of inflammation. Vision loss in this syndrome usually occurs from fluid under the macula. Reso- lution of the fluid can leave RPE changes that mimic retinitis pigmentosa. The onset of uveal effusion syndrome is chronic and insidious, unlike the more rapid onset of VKH disease, helping to differentiate it from this disease.

8.8. Sarcoidosis

Sarcoidosis must be included in the differential diagnosis because it causes a granulomatous uveitis. Conjunctival nodules and uveitis are the most common ocular manifesta- tions of sarcoidosis. In blacks, sarcoidosis is more likely to cause an anterior uveitis (70%–75%), whereas in white pa- tients, it is more likely to cause a posterior uveitis (65%– 83%). Sarcoidosis classically presents with a periphlebitis, noted more commonly on fluorescein angiography, along with perivenous exudates named "candlewax drippings." Neither are seen in VKH. Chorioretinal lesions mimicking nummular scars of VKH (Fig. 10A and B) can be present, as well as choroidal granulomas that can appear as a raised white mass. Although Dalen-Fuchs nodules are primarily seen in VKH and sympathetic ophthalmia, such lesions can occur in sarcoidosis, and they tend to be larger than those seen in VKH. Although the involvement of the posterior pole in sarcoidosis is associated with CNS involvement

8.9. Lupus choroidopathy

Lupus choroidopathy is a rare manifestation of systemic lupus erythematosus, with more commonly occurring ophthalmic manifestations being keratoconjunctivitis sicca and lupus retinopathy. The pathogenesis is thought to be immune complex deposition in the choriocapillaris and the presence of an autoantibody with subsequent multifocal disruptions in the RPE and leakage of fluid into the subretinal space. Clinical examination shows a quiet anterior chamber, whereas the posterior pole has multiple areas of serous retinal detachments. Unlike VKH patients, however, patients with lupus choroidopathy do not usually have a thickened choroid. Fluorescein angiography may be notable for delayed choroidal filling, as well areas of leakage corresponding to areas of se- rous retinal detachment seen on biomicroscopy. Although the clinical examination can be similar to that seen in VKH, patients with lupus choroidopathy usually have a history of lupus and are likely to have significant systemic illness. Nguyen and colleagues reviewed cases of lupus choroidopathy and found that associated systemic illness in these pa- tients were nephropathy (64%), hypertension (54%), CNS disease (36%), and coagulopathy (29%). The presence of severe systemic illness in these patients allows for differen- tiation from VKH disease.

8.10. Acute posterior multifocal placoid pigment epitheliopathy

APMPPE is an uncommon, bilateral, self-limited idiopathic condition first described by Gass in 1968 in a 19-year-old woman who was initially thought to have a disseminated embolic choroiditis. APMPPE usually affects young, healthy adults—a similar population to those affected by VKH—and may start unilaterally and then progress to involve the second eye within days to weeks. A viral or flu-like illness may pre- cede the onset of symptoms. Visual complaints usually include blurred vision, scotomas, metamorphopsias, and photopsias. Rarely, a cerebral vasculitis that can be life threatening can occur, either concurrently with eye symp- toms or after disease onset. On initial examination the fundus in APMPPE is marked by creamy gray-white lesions at the level of the RPE. On OCT, these lesions appear hyperreflective in the outer retinal layers. On autofluorescence, these lesions correspond to areas of hypoautofluorescence in the acute phase and in the weeks following increase in auto- fluorescence. On fluorescein angiography, the lesions appear hypofluorescent in early phases and more numerous than evident on clinical examination. In later phases, these active lesions become hyperfluorescent from leakage and staining. Subacute lesions exhibit central hyperfluorescence with late staining. There are multiple overlapping features between VKH and APMPPE as noted by Lee and colleagues in their description of a case of APMPPE mimicking VKH dis- ease. Choroidal thickening can be present, although not described in the initial case by Gass. Furthermore, both en- tities can present with serous retinal detachments that improve with pulse corticosteroid treatment. Fundus autofluorescence in VKH can present as either hyperautofluorescence or hypoautofluorescent dark dots depending on the timing of presentation of the patient. Differ- entiation between these disease entities can be made clini- cally with an absence of significant vitritis and granulomatous uveitis, prompt resolution of retinal detachments with treat- ment, and lack of development of sunset glow fundus in pa- tients with APMPPE.

8.11. Other systemic disorders

Other systemic disorders that can present with serous retinal detachments which mimic VKH include eclampsia, malignant hypertension, systemic lymphoma, leukemia, and para- proteinemias. Eclampsia occurs in pregnant patients who manifest abnormalities of liver enzymes, coagulation factors, platelet counts, and proteinuria as well as elevated blood pressure. Malignant hypertension, again, can be assessed on history and physical by a severely elevated blood pressure along with neurologic or cardiac changes. Serous retinal detachment may be the first manifestation of a para- proteinemia; however, blood tests will show a monoclonal gammopathy, as well as possible abnormalities in serum calcium.
9. Pathology

VKH is classically described as a granulomatous panuveitis. Histopathologic reports by Iiku in 1952 noted diffuse granulomatous inflammation of the uvea.\(^{81}\) Epithelioid cells and giant cells were noted to contain melanin pigment, and the choriocapillaris was relatively spared virtually similar to the histologic findings of sympathetic ophthalmia. In 1982, Croxatto and colleagues examined 100 cases of clinical sympathetic ophthalmia and noted the following pertinent histopathological findings: (1) inflammatory reactions ranged from a focal nongranulomatous reaction to a diffuse non-necrotizing granulomatous reaction; (2) plasma cells were observed in many cases and were associated with the severity of inflammation; and (3) the choriocapillaris was focally obliterated in 40% of cases and was associated with the severity of disease.\(^{41}\) Before this article, VKH was differentiated from sympathetic ophthalmia on the basis of the type of reaction (SO was always associated with a granulomatous reaction), the absence of plasma cells in SO, and the lack of involvement of the choriocapillaris in SO; however, the analysis done by Croxatto and colleagues delineated the lack of histopathological distinguishing features between VKH and SO. Most notably, sympathetic ophthalmia and VKH both featured involvement of the choriocapillaris—indeed severe cases of sympathetic ophthalmia and in chronic stages of VKH. In 1977, Perry and Font emphasized a choroidal inflammation involving the choriocapillaris and the presence of plasma cells, unlike SO;\(^{165}\) however, they compared eyes in the chronic stages of VKH with eyes in the acute stage of sympathetic ophthalmia. As reported by Croxatto and colleagues, during the chronic stage, eyes with VKH and those with SO reveal involvement of the choriocapillaris and chorioretinal adhesions, as well as the presence of plasma cells.

Rao described differences between the pathologic findings of acute VKH and chronic VKH.\(^{169}\) In acute VKH, the uveal tract displays a granulomatous uveitis with an exudative retinal detachment with preservation of the choriocapillaris, whereas the chronic and convalescent stages consist of a nongranulomatous uveitis. The chronic recurrent stage is, again, defined by a granulomatous uveitis with involvement of the choriocapillaris, thus explaining the classic description of VKH as a granulomatous uveitis with preservation of the choriocapillaris in the acute stage and involvement of the choriocapillaris in the chronic stage.\(^{169}\) Furthermore, Rao describes the peripheral depigmented nummular scars in the fundus as a different entity from Dalen-Fuchs nodules.\(^{169}\) The peripheral scars noted in chronic disease are areas of focal chorioretinal atrophy with loss of retinal pigment epithelium. Dalen-Fuchs nodules, however, are mounds of retinal pigment epithelial cells as well as lymphocytes and pigment-laden macrophages situated between the retinal pigment epithelium and Bruch membrane.\(^{169}\) Interestingly, it was noted that the composition of Dalen-Fuchs nodules also changes as the course of the disease progresses with those in the active stage composed of retinal pigment epithelial cells and inflammatory cells and those in the convalescent stage with only a few inflammatory cells and occasional calcification.\(^{82}\)

10. Therapy

10.1. Systemic treatment

Systemic high-dose corticosteroids are still the cornerstone of initial treatment for VKH. Successful initial treatment of VKH with corticosteroids has been shown on many occasions.\(^{16,67,144,179,222}\) Kitaichi and colleagues showed that patients receiving systemic corticosteroids at a dose of 200 mg/day within 13 days of disease onset required a shorter duration of steroid use (10.9 months vs 24.2 months) with an equal final visual acuity in both groups.\(^{104}\) The importance of early treatment has been echoed in a number of other studies that have found early treatment results in fewer recurrences and a decrease in loss of pigmentation.\(^{90,132}\) Jap and colleagues compared 1 mg/kg dosing within 2 weeks of disease onset compared to low-dose corticosteroids (less than 1 mg/kg) and treatment initiation 2–4 weeks after disease onset and determined that patients who received high-dose steroids had a significantly shorter duration of disease compared to the low-dose steroid group (48 months vs 184 months).\(^{88}\) Patients in the low-dose treatment group also had a higher proportion of peripapillary atrophy with increase in recurrences and more frequent episodes.\(^{88}\) Consistent with findings from Kitaichi and colleagues, there was no significant difference in the final visual acuity between the groups.\(^{88,104}\) Treatment with high-dose systemic steroids has also been shown to be associated with a decreased incidence of sunset glow fundus.\(^{93}\)

Regarding duration of treatment, it is imperative to treat VKH with corticosteroids for greater than 6 months based on studies that show a decrease in further ocular symptoms,\(^{54}\) a decrease in recurrence, and an improvement in final visual acuity compared to those treated for shorter times.\(^{112}\) Read and colleagues attempted to determine whether route of administration of initial corticosteroids affecting the development of complications, use of adjuvant immunomodulation, or visual prognosis. They performed a retrospective comparative case series and evaluated 48 patients with acute VKH who were treated with either oral steroids or IV steroids followed by an oral taper. They did not find a difference in the final visual acuity, the development of complications such as cataracts or pigmentary changes in the fundus, or the rate of use of subsequent immunosuppressive therapy in patients.\(^{176}\) Levels of corticosteroids can be decreased during the treatment course of 6 months.

Along with corticosteroids, immunosuppressive agents such as methotrexate, azathioprine, cyclosporine A, mycophenolate mofetil, and alkylating agents have been used successfully to treat VKH.\(^{3,14,24,86}\) The American Uveitis Society and the International Uveitis Study Group, thus, have recommended such immunosuppressive agents as mandatory in the treatment of VKH to prevent recurrences; however, appropriate initial treatment of the disease with high-dose corticosteroids also has an effect on recurrences as outlined previously, so care must be taken to balance the initial treatment with the need for immunosuppressive agents later on.
Azathioprine at a dose of 1–2.5 mg/kg/day has controlled disease progression in VKH in patients that are nonresponsive or poorly responsive to steroids, as well as those who are intolerant to steroids. The median time to corticosteroid-sparing effect was 4 months; however, Cuchacovich and colleagues observed that patients treated with prednisone and azathioprine (at 2–3 mg/kg/day of azathioprine) required higher doses of prednisone compared to those who were treated with prednisone and cyclosporine A (at 3–5 mg/kg/day of cyclosporine A). The mean time to control inflammation with a concurrent dose of prednisone at less than or equal to 10 mg/day was 8.4 ± 4.16 months with azathioprine and 4.5 ± 2.71 months with cyclosporine A. Patients who were treated adjunctly with azathioprine had a significantly higher average dose of prednisone (23.89 ± 9.49 mg/day) compared to those treated with cyclosporine A (14.86 ± 8.89 mg/day). The total cumulative dose of prednisone was 2705.56 ± 1602.84 mg in the azathioprine group compared to 1275 ± 577.96 mg in the cyclosporine A group. No significant differences were noted in complications between the 2 groups. Adverse effects of azathioprine included upper respiratory tract infections, urinary tract infections, Herpes zoster, elevated liver enzymes, gastrointestinal symptoms, and leukopenia. Adverse effects of cyclosporine A included upper respiratory tract infections, low urinary tract infections, mild hypertension, hypertrichosis, and gastrointestinal symptoms. Although both azathioprine and cyclosporine displayed good efficacy, cyclosporine A appeared to have a better steroid-sparing effect.

Paredes and colleagues recommend using immunomodulatory therapy as a first-line treatment for VKH with or without the addition of corticosteroids based on results from a study between 2 groups of patients, the first receiving prolonged systemic corticosteroid treatment with or without the delayed addition of immunomodulatory therapy (5 patients) and the second receiving relatively prompt immunomodulatory therapy with or without corticosteroids (8 patients). Immunomodulatory therapy included mycophenolate mofetil, cyclosporine A, methotrexate, and azathioprine. In this study, however, the patients in the first group were referrals into the clinic that had been unsuccessfully treated elsewhere with corticosteroids; however, there was insufficient information to evaluate whether these patients had been treated with an appropriate dose of corticosteroids at the outside clinics. Kondo and colleagues have demonstrated low-dose systemic methotrexate (6 mg/week) to be an effective steroid-sparing agent in the treatment of VKH. Mycophenolate mofetil was recently evaluated in combined therapy with corticosteroids in acute VKH. The mean interval between starting treatment and tapering prednisone to 10 mg or less was 5.1 ± 2 months (range 3–7 months). Ten of 19 patients (53%) were able to discontinue treatment without relapse. Recurrent inflammation was reduced in the corticosteroid plus MMF group (3%) compared with the corticosteroid only group (18%). Visual acuity improved to 20/20 in 38% of eyes in the corticosteroid group and 74% in the corticosteroid plus mycophenolate mofetil group. None of the eyes in the corticosteroid plus mycophenolate mofetil group developed a sunset glow fundus.

Of the newer biologic agents, both rituximab and infliximab have been effective in cases of poor response to steroids and to other immunomodulatory agents. Effects on the progression of the disease is usually noted rapidly after 1 or 2 infusions and patients were able to be tapered off prednisone as early as 4 weeks after the onset of infusions in 1 case. Infusions, however, have to be given for a number of months, and the number on infusions can vary greatly from patient to patient. In the case outlined by Dolz-Marco, rituximab infusions were administered, whereas in the cases outlined by Nicoli and Wang, 11–14 infusions had to be administered. Furthermore, Wang and colleagues started methotrexate at a dose of 15 mg/week at the same time as the infliximab infusions, making it difficult to separate out the effects of the 2 treatments.

Interferon alpha 2A recently has been used as a treatment for VKH. The medication, however, is not without significant side effects. There have been a number of cases of VKH-like disease in patients being treated with interferon alpha 2A for chronic viral hepatitis. It is unclear at this time why this medication is able to both elicit symptoms and prevent progression of the disease in different subgroups of patients.

Our recommendations, based on the aforementioned publications, are that acute VKH must be treated aggressively with corticosteroids initially, with a minimum treatment duration of 6 months, along with introduction of corticosteroid-sparing agents such as cyclosporine A, methotrexate, or mycophenolate mofetil. In patients who do not respond to corticosteroids combined with corticosteroid-sparing agents, anti-TNF agents and other biologics should be considered.

10.2. Local drug delivery

Topical steroids and cycloplegics are used commonly as first-line agents in iridocyclitis and anterior chamber inflammation in uveitis. Topical mydriatic and cycloplegic agents are used to break and prevent the formation of posterior synechiae and to prevent ciliary spasm. Topical corticosteroid drops are used most often for anterior uveitis, although they are also beneficial for patients with panuveitis who have anterior chamber inflammation. They can be dosed as often as every hour initially when anterior chamber inflammation is aggressive and tapered down to once a day as the inflammation improves. Side effects of topical steroids include ocular hypertension and the development of cataracts. Certain topical preparations like fluorometholone 0.1%, rimexolone 1%, and loteprednol etabonate 0.5%/0.2% have a lower ocular hypertensive effect than prednisolone acetate 1%, dexamethasone 0.1%, and difluprednate 0.05%; however, the latter are more effective in controlling anterior uveitis.

Use of local steroids in the form of intravitreal or subtenon injections is a useful adjunct to oral and immunosuppressive therapies. Perente and colleagues found that concurrent dosing with subtenon triamcinolone acetonide (40 mg/mL) resulted in improvement in symptoms and allowed for a reduction in systemic corticosteroid dosage. Moreker and colleagues noted that the concurrent use of
in intravitreal triamcinolone (4 mg/0.1 mL) at day 1 of treatment and day 90 of treatment allowed for a shorter duration of systemic corticosteroid treatment.136 Byron and colleagues also found benefit in using intravitreal triamcinolone (4 mg/0.1 mL) in 2 patients in whom rebound inflammation developed after transitioning from intravenous corticosteroids to oral corticosteroid therapy.25 Andrade and colleagues used intravitreal triamcinolone injections in 2 patients presenting with VKH.7 One was initially treated with only intravitreal triamcinolone and, when dysacusia developed a month later, treatment with oral prednisone was started, and the second patient was treated with the injection along with a lower dose of oral corticosteroid (40 mg). Although they did note efficacy of treatment, care should be taken as VKH is a systemic disease that requires systemic treatment. In addition, the patients had large serous retinal detachments, and injections in patients with serous retinal detachments have risks. Both subtenons and intravitreal injections of steroids, however, have been successfully used as adjunctive therapies to intravenous and oral corticosteroid therapy. The ocular side effects of cataract progression and elevated intraocular pressure may also occur in these patients.

Fluocinolone acetonide implants (Retisert) have been used in chronic VKH and appear to decrease the amount of oral corticosteroid required to control ocular inflammation, but the oral corticosteroid could not be completely eliminated.98 Dexamethasone implants (Ozurdex) have been shown in a few patients to be successful in controlling refractory cases of uveitis.38,114,137 Elevated intraocular pressure requiring topical acetazolamide developed in 1 case.114 A second case required systemic corticosteroids in addition to the dexamethasone implant.137

Local treatment alone is not recommended for this disease because it is a multiorgan inflammatory condition. Such treatment will not eliminate the extraocular manifestations, particularly meningesis and tinnitus. Moreover, local treatment will not have an effect on the severity of vitiligo and poliosis. We recommend systemic treatment and, if needed, adjunctive local treatment; however, systemic treatment is necessary to control the extraocular symptoms of VKH.

10.3. Complications of VKH and treatment

Complications in VKH include development of cataract in 15%–45% of eyes, glaucoma in 27%–33% of eyes, posterior synechiae in 23.4% of eyes, choroidal neovascular membranes in 3%–11% of eyes, band keratopathy in 5.2% of eyes, and subretinal fibrosis in 6% of eyes.11,156,175 Patients who had at least 1 complication had a longer duration of disease and larger number of recurrent episodes of inflammation than those who had no complications.175 Final visual acuity was better in eyes that had not developed any complications, and eyes with an increasing number of complications were more likely to have worse visual acuity at final follow-up compared to eyes with fewer or no complications.2,175 Furthermore, acute VKH resulted in better long-term outcomes in visual acuity compared with eyes suffering from recurrent VKH.11 Cataract occurs as a known complication of VKH uveitis in 15%–45% of patients.16,151,175,179,197 Cataract extraction should ideally only be undertaken once the uveitis has been quiescent for at least 3 months. Preoperative recommendations include oral and topical corticosteroids. Postoperative recommendations include slow tapering of steroids and use of topical nonsteroidal anti-inflammatory drops for the control of cystoid macular edema. Mehta performed a meta-analysis of outcomes of cataract surgery in patients with uveitis and found that those patients with posterior uveitis involving the choroid and retina (including VKH) usually had worse visual acuity than in those with anterior or intermediate uveitis. Specifically, 49% of VKH eyes had vision better than or equal to 20/40 (95% CI 0.35–0.59).129 Ram and colleagues published results on 108 eyes of 81 patients with uveitis who underwent cataract extraction, 9 of whom had VKH. Patients who had recurrent inflammation or active inflammation in the 6 months before surgery were given 40 mg of systemic steroids 2 days before surgery as well as topical steroids; however, patients whose eye had been quiescent for 6 months before surgery were only treated with topical steroids. Posterior capsule opacification was the most common complication, in 31 eyes (28.7%), followed by posterior synechiae in 27 eyes (25.0%), cystoid macular edema in 23 eyes (21.3%), and recurrent uveitis in 6 eyes (5.5%). No patients with a history of VKH had recurrences in their study.136 Quiek and colleagues found that in 50 eyes with VKH, 68% had a visual acuity of 20/40 or better and recurrent inflammation was a significant risk factor for poor visual outcome (P = 0.004).187

In the setting of elevated IOP, care should be taken to lower intraocular pressure. This can be achieved by attempting to decrease the oral and topical steroids if inflammation is under control or treating with IOP-lowering medications. Surgery should be undertaken if medical management has failed and intraocular pressure continues to be elevated. Forster and colleagues noted 54% of VKH patients had elevated intraocular pressure at some point during their disease and 38% of patients required medical or surgical intervention. Furthermore, they found Molteno implants were superior to trabeculectomy likely because of scarring during recurrent disease.99 Iwao and colleagues noted that trabeculectomy with mitomycin C was less effective at maintaining a reduction in intraocular pressure in eyes with uveitic glaucoma (including 5 eyes with VKH) compared with primary open-angle glaucoma.87 Shimizu evaluated eyes with uveitis glaucoma treated surgically with trabeculectomy, trabeculotomy, and trabectome and found that despite good surgical success rates with each (82%, 62.5%, and 75%, respectively), males younger than 45 years of age with nongranulomatous uveitis or with postoperative inflammation were more likely to have surgical failure.186 Malone and colleagues found that combined glaucoma shunt surgery with fluocinolone acetonide implant surgery was successful in 7 eyes of 5 patients with uveitic glaucoma, 2 of whom had VKH. In this study, Ahmed S2 and S3 models were implanted.125 Ceballos and colleagues evaluated the success of implantation of Baerveldt drainage device for uveitic glaucoma in 24 eyes of 24 patients with uveitic glaucoma although none of the patients had VKH in this study. The IOP was statistically significantly lowered from a preoperative mean of 30.5 ± 8.96 mm Hg with 3.1 ± 0.99 IOP-lowering medications to a postoperative mean of 13.0 ± 4.6 mm Hg with 0.8 ± 0.8 IOP-lowering medications. The most common complications were choroidal effusions in 4 (16.7%),
hypotony in 3 (12.5%) eyes, cystoid macular edema in 3 (12.5%) eyes, and failure of corneal grafts in 2 (8.3%).

Choroidal neovascularization is a known complication of VKH. Such neovascularization may arise from retinal pigment epithelium alterations such as hypoplasia and hyperplasia and may exhibit a tendency to injure Bruch membrane resulting in type 2 membranes. Active inflammatory CNVs were found, in 1 retrospective study usually to be non-subfoveal but potentially progress toward the fovea as they spread under the neurosensory retina. Before the advent of anti-VEGF therapy, photodynamic therapy was the mainstay of treatment for CNV. PDT was usually successful with improvement in vision after one or more treatments.

Anti-VEGF injections have largely replaced PDT as the main treatment modality for CNV. The mean number of injections required to control CNV was 4.25 injections, with 1 injection required approximately every 12.97 weeks in 1 study. Anti-VEGF injections have also been successfully used in combination with laser photoacoagulation. At this time, a multipronged approach is recommended to treat CNV related to VKH as treatment responses are variable between patients and there is no clear standard of care.

Subretinal fibrosis, an unfortunate complication of VKH, represents hyperplastic RPE with metaplastic changes simulating fibrous tissue. Initially, the changes exhibit pigmentation that gradually disappear and form amelanotic bands of tissue. Usually, overlying retina reveals atrophy of the outer layers. It is a rare complication that occurs in patients with chronic recurrent episodes of uveitis and may be related to development of subretinal fluid. Unfortunately, no interventions are available for this aside from possibly more aggressive treatment of initial disease and recurrences.

Similar to other uveitis entities, surgical interventions are usually reserved for complications of VKH such as posterior subcapsular cataract and elevated intraocular pressure, and care should be taken to make sure the uveitis is quiescent before performing intraocular surgery on these patients.

11. Prognosis

VKH is a severe inflammatory disease, but prompt and aggressive treatment, may lead to better visual outcomes than was possible before the advent of immunomodulatory therapy. Studies suggest final visual acuity can range from 20/20–20/50. Of key importance is initiating treatment early and treating with high-dose corticosteroids for at least 6 months based on our review of the literature. Treating with steroid-sparing agents including methotrexate, cyclosporine A, mycophenolate mofetil, or newer biologic agents allow patients to be tapered down to low doses of steroids while maintaining control of the disease. Care must be coordinated with other specialties, including rheumatology and neurology, as the disease affects multiple organs.

Imaging allows us to evaluate subclinical disease on modalities such as ICG angiography, fundus autofluorescence, and OCT. This can have the consequence of a longer duration of treatment but results in lower occurrences of sunset glow fundus and choroidal thinning.

Our understanding of favorable prognostic factors has also evolved in the last decade. A good initial visual acuity results in a better final visual acuity and treatment of the disease in the acute phase yields better outcomes than initiating treatment in the chronic recurrent phase. Final visual acuity was better in those eyes with fewer complications. Cataract and glaucoma are the most common complications seen in VKH, and surgical management of these is appropriate as long as the uveitis is controlled with medications. Perioperative management of uveitis is key in these situations.

12. Conclusion

In summary, Vogt-Koyanagi-Harada disease is a severe, bilateral, granulomatous panuveitis associated with serous retinal detachments, disk hyperemia, and edema, and vitritis associated with headaches, nausea, meningismus, alopecia, vitiligo, and hearing loss. The extraocular manifestations of the disease are variable, but early detection and treatment are key. OCT, fluorescein angiography, and B-scan ultrasonography aid in the diagnosis of this disorder. The lack of prior inciting trauma differentiates it from sympathetic ophthalmia. The mechanism of disease is thought to be autoimmune to tyrosinase peptides of melanocytes, explaining the presence of depigmentation in the disease. The initial treatment is with high-dose corticosteroids, then steroid-sparing therapy, with a focus on getting the inflammatory response under control to prevent the development of sequelae such as a sunset glow fundus, cataracts, glaucoma, and choroidal neovascularization.

13. Methods of medical literature search

In this review, to summarize developments following the major review that appeared in 1995, we searched English, French, German, Japanese, Chinese, and Spanish literature in Medline for the following keywords: Vogt-Koyanagi-Harada syndrome and Vogt-Koyanagi-Harada disease between the years of 1995 and 2014. A select number of articles have been included before 1995 for historical purposes.

References


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