Vogt–Koyanagi–Harada syndrome: a rheumatologic perspective

Vogt–Koyanagi–Harada (VKH) syndrome is an idiopathic systemic inflammatory disorder that affects various melanocyte-containing structures, including the eyes, meninges, inner ear and skin. It classically leads to bilateral chronic granulomatous diffuse uveitis, and its extraocular manifestation can include sensorineural hearing loss, meningitis, and cutaneous findings of vitiligo, poliosis (loss of hair pigment) and alopecia. Ethnicity/racial background and HLA genotype play a strong role in the pathogenesis of VKH syndrome. The inflammatory process is not completely understood, but recent studies have pointed to several potential autoantigen targets, and have also demonstrated the role IL-23 plays in inducing the differentiation of Th17 cells and the subsequent production of IL-17. The success in preserving the vision of VKH syndrome patients hinges on early diagnosis and aggressive treatment that includes immunomodulatory therapy, and as a result ophthalmologists are increasingly referring such patients to rheumatologists for management. It is therefore necessary for the rheumatologists to be familiar with VKH syndrome and its clinical aspects and management. Although the role of biologics in the treatment of VKH syndrome has yet to be investigated, it is possible that such treatments may prove beneficial, given what is currently known about the pathogenesis of the disease.

KEYWORDS: ankylosing spondylitis  chorioretinitis  HLA-DRB1*04  IL-23  immunomodulatory therapy  poliosis  sensorineural hearing  Th17 lymphocytes  uveitis  vitiligo  Vogt–Koyanagi–Harada syndrome
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Prevalence nationwide

For example, a report indicates 7% prevalence regions with higher percentages of Hispanic and indicating that more is involved in the pathogenesis of the disease than just the skin pigmentation. The changing population demographics are resulting in increasing incidence of VKH syndrome in regions with higher percentages of Hispanic and Asian (including Middle Eastern) populations. For example, a report indicates 7% prevalence of VKH syndrome at a uveitis tertiary referral center in southern California versus 1–4% of VKH syndrome nationwide [15]. The disease usually strikes between the third and fifth decades of life, although there are also rare reports of its occurrence in children [16]. Familial cases are rare [17]. It is two-times more common in women than men, although this trend does not appear to hold true in Japan [4,18,19].

Pathogenesis

Etiopathogenesis of VKH syndrome is not well understood; it tends to occur in genetically susceptible individuals, but a trigger, which is as yet unknown, is needed to initiate a CD4+ T cell-mediated autoimmune process against an unidentified autoantigen expressed in melanocytes [8,9,19–23]. A systemic inflammatory cascade follows, affecting the meninges, uvea tract, inner ear and epidermis. There is a strong association with HLA-DR4 [24], and in particular the allele HLA-DRB1*0405 [14,25]. This allele codes for amino acid substitutions in the antigen-binding groove, presumably affecting the immune function of the antigen-presenting cells and their interaction with the cytotoxic CD4+ T cells. The association with HLA-DR4 holds true for multiple ethnic/racial groups [14,18,25]; however, there is also a secondary association with other MHC class II alleles – most notably HLA-DR1 [14,24].

Perhaps the most successful research into the etiology of VKH syndrome to date is the work carried out in identifying an autoantigen target. Logically, the identification of melanocytes as a potential target in VKH syndrome is consistent with both the cutaneous findings of vitiligo/poliosis in VKH syndrome patients and the increased prevalence of the disease in more heavily pigmented groups. Melanocyte differentiation proteins, such as tyrosinase-related peptide (TRP)-1, TRP-2, gp100/PMel-17 and MART-1/MelanA, are some of the most studied in VKH syndrome pathogenesis [8,20–23]. Along with tyrosinase, which catalyzes the oxidation of tyrosine in the process of melanization, this protein family may be the leading candidate for autoantigen target in VKH syndrome. Studies have demonstrated that T lymphocytes isolated from the peripheral blood of VKH syndrome patients show significant proliferation when compared with those of healthy control subjects upon in vitro exposure to tyrosinase family proteins [19]. Furthermore, Yamaki et al. have demonstrated that rats immunized with TRP-1 and TRP-2 show both ocular inflammation similar to that of humans afflicted with VKH syndrome, as well as histological changes in the skin and meninges [20]. However, a subsequent analysis of microsatellite polymorphisms in the tyrosinase gene family in 87 Japanese VKH syndrome patients and 122 healthy controls failed to show any increased risk attributed to the gene family [21]. Other autoantigens, such as KU-MEL-1 [12] and Lens epithelium-derived growth factor [23], have also been identified as possibly being involved in the pathogenesis of VKH syndrome via an IgG-mediated process.

Less is known about the trigger that leads to dysregulation of the immune system in the development of the disease. The leading hypothesis is that exposure to a virus causes a T-cell response against autoantigens by molecular mimicry. The idea that VKH syndrome may have a viral trigger is not new, as it has long been noted that the first phase of VKH syndrome is often marked by a prodromal period suggestive of an acute viral infection. Epstein–Barr virus DNA has previously been isolated from the vitreous humor of patients with VKH syndrome [26,27], and a more recent study by Sugita et al. showed that a cytomegalovirus infection could produce T cells that cross-react with tyrosinase [28]. Also supporting the virus-as-trigger hypothesis are case reports of simultaneous onset of the disease in coworkers, friends and neighbors, all of whom reported a flu-like prodromal phase [29].

The inflammatory cascade in VKH syndrome has been described as being a CD4+ T cell-dependent process within the environment of a T helper (Th)1 cytokine profile. Sakaguchi et al. demonstrated that T-cell clones isolated from the aqueous humor of VKH syndrome patients produced greater amounts of IL-6, IL-8 and IFN-γ when compared with T-cell clones from healthy
donor peripheral blood mononuclear cells [30]. Of major interest is the recent finding that IL-23, through its induction of the formation of IL-17-producing CD4+ T cells, is responsible for the autoimmune inflammatory response in VKH syndrome [33]. The IL-23/IL-17 axis has already been recognized for playing a role in the inflammatory reactions of other autoimmune diseases, such as psoriasis, rheumatoid arthritis (RA), inflammatory bowel disease and multiple sclerosis [31,32]. Novel therapeutics being used to target the inflammatory cascade in these other diseases may also prove helpful in treating VKH syndrome.

The dysregulation of normal lymphocyte apoptosis also appears to play a role. Yang et al. demonstrated that T lymphocytes in both VKH syndrome and Bechet’s disease are more resistant to Fas-mediated apoptosis when compared with healthy controls [33]. They have hypothesized that this inability to self-regulate may in turn lead to the chronic, recurrent uveitis, which is often the final stage of the disease.

Finally, a recent study by Du et al. demonstrated that ethnic Han Chinese patients with VKH syndrome have a higher number of single nucleotide polymorphisms in the gene that codes for cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) compared with healthy controls [34]. CTLA-4, which is expressed on activated and regulatory T cells, acts as a negative regulator of the T cell-mediated immune response by competitively binding CD-28. By doing so, CTLA-4 prevents activation of the T cells by blocking costimulation by B7 ligands CD80 and CD86 on the antigen-presenting cell. Single nucleotide polymorphisms in CTLA-4 are already known to be associated with some of the other autoimmune diseases, and may also contribute to an element of VKH genetic susceptibility that is not completely accounted for by HLA-type and ethnic/racial background. This finding may also have important implications in the treatment of VKH syndrome, as costimulation blockers have proven effective in the treatment of RA and juvenile idiopathic arthritis [35].

**Clinical presentation**

Vogt–Koyanagi–Harada syndrome course is classically divided into four stages. The first of these stages, the prodromal stage, typically lasts days to weeks and precedes ocular involvement. This stage is suggestive of an acute viral illness or aseptic meningitis. Headache, nuchal rigidity, nausea, low-grade fevers, photophobia, dysacusia, vertigo and tinnitus are all typical findings [4,5,36–42]. Meningismus is the most common of the extraocular signs, but individual presentations of VKH syndrome vary greatly among individuals and ethnic groups. Specifically, it appears that the extraocular manifestations are less common in Hispanics when compared with Asians [14]. More than 80% of VKH syndrome patients in this first stage will have a lymphocytic pleocytosis on CSF analysis [42]. Hypersensitivity of the hair and scalp to touch is also not uncommon.

The disease invariably progresses to its second phase, the acute uveitic phase, characterized by decreased visual acuity, posterior uveitis and orbital pain. Diffuse bilateral choroiditis or chorioretinitis, exudative retinal detachment, papillitis and vitritis are all early findings [4,5,36]. There is generally no anterior chamber involvement at this stage, although there may be some flare noted on examination owing to mild-to-moderate anterior uveitis simulating a non-granulomatous inflammation as evidenced by keratic precipitates. Neurological and audiological findings can precede, occur concurrently or follow the occurrence of uveitis. Tinnitus is the most common inner ear symptom, occurring in approximately 40% of patients [41,43].

The third phase of the disease follows more than 2 months after the onset of uveitis, and is characterized by recurrent and granulomatous uveitis. At this time many of the earlier signs of posterior uveitis will resolve, but focal areas of depigmentation of the choroid will take place in nearly all patients, giving the characteristic ‘sunset glow’ appearance to the fundus (Figure 1) [4,5,36,44,45]. Less than half of all patients have cutaneous findings that appear within the first 3 months after the initial ocular symptoms. Poliosis is the most frequent sign, followed by alopecia and vitiligo. Poliosis and vitiligo lesions are usually symmetrical and most commonly on the eyebrows, eyelashes and scalp (Figure 2) [4,5,44,45]. There may also be focal areas of alopecia.

Patients who are not properly treated at early stages may then progress to the chronic phase, the hallmark of which is recurrent anterior granulomatous uveitis and ocular complications, the most common being complicated cataracts [4,5]. Advancing to this stage portends poorer prognosis. Common signs of anterior granulomatous involvement include large deposits, known as mutton-fat keratic precipitates (Figure 2), on the endothelium of the cornea as well as whitish nodules in the stroma of the iris.
Diagnosis

There is no definitive test for the diagnosis of VKH syndrome. Diagnosis is based on clinical signs and symptoms with the aid of ancillary testing. The revised criteria for the diagnosis of VKH syndrome were established in 1999 (Box 1), and are more inclusive than previous criteria for diagnosing the disease both in its early and late stages [36]. The first three components of the revised criteria are mandatory for diagnosis. The first component specifies that the patient should not have had any history of penetrating ocular trauma or ocular surgery (including nonpenetrating laser photocoagulation; e.g., for retinal breaks) preceding the onset of uveitis. This provision prevents confusing VKH syndrome with sympathetic ophthalmia that follows ocular injury and is very similar to VKH syndrome clinically, aside from the inciting factor [46].

The second mandatory criterion is that there be no clinical or laboratory evidence suggestive of another ocular disease [36]. VKH syndrome not only has clinical similarities with sympathetic ophthalmia, but the differential diagnosis for patients presenting with diffuse bilateral uveitis is quite broad [4,5]. Before diagnosing VKH syndrome, the clinician must rule out infectious causes, such as syphilis, TB and Lyme disease, malignant causes such as intraocular lymphoma and melanoma, and other inflammatory diseases including sarcoidosis, Behcet’s disease and posterior scleritis [36,47,48].

The third criterion is that the ocular involvement has to be bilateral [36]. Cases of unilateral VKH syndrome are rare enough [49] so that bilateral involvement is mandatory for diagnosis in the revised criteria. The nature of the ocular involvement varies depending on whether the patient is early or late in the course of the disease. The hallmark of early involvement is diffuse choroiditis with either focal areas of subretinal fluid or bullous serous retinal detachment. Ancillary tests, such as fluorescein angiography and ocular MRI, are helpful in equivocal cases [50–52]. If the patient is diagnosed in the chronic and recurrent stages of the disease, he or she must have a clinical history suspicious for those findings mentioned previously in addition to bilateral ocular involvement manifested by either chronic anterior uveitis or retinochoroidal degeneration. The latter may take the form of recurrent retinal pigment epithelium clumping, depigmentation of the choroid (Figure 1) and/or nummular chorioretinal scars, which represent damage to or disappearance of retinal pigment epithelial cells [36,44].

The final two criteria for diagnosis relate to extraocular manifestations of the disease. The fourth criterion involves presence of neurological/auditory findings: meningismus, tinnitus or CSF pleocytosis. Meningismus, tinnitus, sensorineural hearing loss and vertigo are the most common, but occasional cases of encephalitis, transverse myelitis and cranial nerve palsy have also been reported [37–39]. The fifth criterion deals with integumentary findings: alopecia, poliosis or vitiligo, that did not precede ocular or CNS involvement. Occurrences of vitiligo, poliosis and alopecia are highly variable, and manifest in the chronic and recurrent stages of the disease [4,5]. Patients meeting all five criteria are identified as having complete VKH syndrome. Fulfillment of the first three criteria with either neurological/auditory involvement or integumentary findings is diagnostic of VKH syndrome.
incomplete VKH syndrome. Patients meeting only the first three criteria are labeled as having probable VKH syndrome (Box 1) [36].

**Ancillary testing**

A complete medical history and thorough physical examination with special attention paid to dermatological, neurological and visual sequelae are the most important first steps in diagnosing VKH syndrome. Those patients referred by an ophthalmologist to a rheumatologist should already have received a slit lamp and dilated fundus examination with an assessment for decreased visual acuity, retinal edema, disc edema/hyperemia, vitritis and serous retinal detachment – all early signs of VKH syndrome. In addition, intraocular pressure should have been measured by tonometry as edema, and infiltration in the anterior chamber can sometimes lead to acute angle closure glaucoma [50]. Although most VKH syndrome diagnoses can be made by clinical examination, ancillary testing can be helpful both for confirmation of diagnosis when it is not so clear cut and ruling out other disease processes that mimic the signs and symptoms of VKH syndrome [50–52]. These ancillary investigations include fluorescein angiography, indocyanine green angiography, tomography, electroretinogram and electro-oculography [50–52]. Finally, in the case of inner ear involvement, the patient should be referred for audiologic testing with follow-up for evaluation of progression.

While the most recent criteria for diagnosis only require CSF analysis if there is no evidence of meningismus or tinnitus, CSF pleocytosis was formerly a major criterion for diagnosis [36]. CSF analysis is helpful when there are no signs of neurological involvement and also in atypical cases, but the mere presence of pleocytosis is hardly specific for VKH syndrome and is uncommonly needed for diagnosis [42]. The differential for uveitis with CNS involvement is quite broad, and includes infectious causes, such as Lyme disease, syphilis and herpes, as well as other inflammatory conditions, such as Behcet’s disease, neurosarcoidosis and multiple sclerosis [36,40,47]. Intraocular lymphoma masquerading as an autoimmune uveitis is also a possibility [48]. MRI is a helpful tool in differentiating VKH syndrome from lesions characteristic of intraocular lymphoma, multiple sclerosis and neurosarcoidosis [48,52]. It is also useful for differentiating the choroidal thickening of VKH syndrome from the scleral thickening of posterior scleritis. Serum angiotensin-converting enzyme (ACE) and/or lysozyme assays, liver enzymes tests, pulmonary imaging and tissue biopsy are useful adjunctive studies in helping to evaluate for the latter [47]. Ocular ultrasound, another commonly used modality in VKH syndrome diagnosis, demonstrates echographic thickening of the choroid, the patterns of which are distinct from posterior scleritis, sarcoidosis, tuberculosis and lymphoma.

**Prognosis & treatment**

The prognosis for the VKH syndrome patient is fair, with approximately two-thirds of patients maintaining at least 20/40 vision in each eye. However, such success hinges on early diagnosis and aggressive treatment. Patients progressing to the chronic and recurrent stages of the disease are prone to developing ocular complications, including cataract formation, glaucoma, choroidal neovascularization, subretinal fibrosis and optic atrophy. In addition to the duration of disease and number of recurrences, older age of onset, poor initial visual acuity and development of extraocular manifestations are also associated with poorer prognoses [53].

Traditionally, the mainstay of treatment has been several days of high-dose oral prednisone 1–2 mg/kg/day or 200 mg intravenous methylprednisolone followed by high-dose oral corticosteroids for at least 6 months [4]. Topical steroid drops are used in conjunction with systemic therapy to control anterior segment inflammation. IMT was initially used for controlling inflammation in refractory cases and in those patients who could not tolerate the side effects of high-dose corticosteroids. However, in the last several years it has been demonstrated that IMT given as first-line therapy is associated with better visual outcomes when compared with those who either received the treatment later in the disease course or never received it at all [54,55]. Both the American Uveitis Society and the International Uveitis Study Group have since concluded that IMT is mandatory in the treatment of VKH syndrome [53,54]. Examples of IMT that have been employed include

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**Box 1. Diagnostic criteria for Vogt–Koyanagi–Harada syndrome.**

- 1. No history of penetrating ocular trauma/surgery prior to initial onset of uveitis
- 2. Bilateral involvement
- 3. No clinical or laboratory evidence of another ocular disease
- 4. Neurological/auditory findings: meningismus, tinnitus or cerebrospinal fluid pleocytosis
- 5. Integumentary findings: alopecia, poliosis or vitiligo

*All five criteria = complete VKH syndrome; criteria 1–3 plus 4 or 5 = incomplete VKH syndrome; criteria 1–3 only = probable VKH syndrome.*

cyclosporine, mycophenolate mofetil, cyclophosphamide, chlorambucil and azathioprine. While IMT spares the patient from some of the dreaded side effects of long-term, high-dose corticosteroid therapy (including cataract formation and glaucoma), each of these agents also comes with an array of toxicities that may limit their use. There is not enough known about the relative efficacies of each of the steroid-sparing agents in the treatment of VKH syndrome for the formulation of an optimal regimen at this time. With a greater understanding of the pathogenesis of the disease and the inflammatory cascade it is possible that therapies that selectively inhibit or modify these pathways will become useful.

Biologics comprise another branch of therapies that have led to improved outcomes in many autoimmune diseases. These newer treatments, especially those that inhibit TNF-α, such as infliximab, etanercept and adalimumab, have been used successfully in treating chronic uveitis associated with Behchet’s disease and sarcoidosis [56]. Although the role of biologics in the treatment of VKH syndrome has yet to be investigated, it is possible that such treatments will prove beneficial, given what is currently known about the pathogenesis of the disease [54–56]. Recent findings showing a role of IL-23 in the inflammatory cascade of VKH syndrome suggest that new biologics targeted against IL-23 may also have a role in treating this disease [54–56]. IL-23 is thought to induce the formation of Th17 cells and the subsequent production of IL-17. The latter has already been shown to be involved in the pathogenesis of such systemic inflammatory disease as inflammatory dermatosis, systemic lupus erythematosus, RA, Crohn’s disease, ulcerative colitis and Behchet’s disease [54–56]. Ustekinumab is a relatively new human monoclonal antibody against IL-12 and IL-23 that has been demonstrated to be effective in the treatment of plaque psoriasis in Phase III trials and psoriatic arthritis in Phase II trials [59]. It acts by binding to the p40 subunit of IL-12 and IL-23, thereby inhibiting receptor-mediated expression of proinflammatory cytokines.

There may also be a promising role for the biologics that selectively inhibit costimulatory activation of T cells in treating VKH syndrome, as explained earlier in this article. Abatacept, a fusion protein comprising the extracellular domain of human CTLA-4 linked to a modified Fc domain, blocks costimulatory binding of CD28 to the B7 ligands CD80 and CD86 on antigen-presenting cells, and has already been approved by the US FDA for the treatment of moderate-to-severe RA and juvenile idiopathic arthritis [35,60]. As more is learned about the role CD28 costimulation plays in the pathogenesis of other autoimmune diseases, the indications for abatacept and abatacept-like therapies may expand to include autoimmune ocular inflammatory diseases such as VKH syndrome.

Conclusion

Vogt–Koyanagi–Harada syndrome is an idiopathic, systemic inflammatory disease caused by an autoimmune T-cell reaction against presumed autoantigens in genetically susceptible individuals. The inflammatory process is probably triggered by a viral infection. The disease selectively involves melanocyte-containing structures, and manifests itself with the distinct presentation of granulomatous diffuse uveitis associated with meningitis, dysacusia and the cutaneous findings of alopecia, vitiligo and poliosis. Ethnicity/racial background and HLA genotype play a strong role in the pathogenesis of VKH syndrome. The inflammatory process is not completely understood, but recent studies have pointed to several autoantigen targets and demonstrated the role IL-23 plays in inducing the differentiation of Th17 cells. While the prognosis of the disease is generally good with early and aggressive treatment, success depends on early detection with a detailed physical examination and ancillary testing. The physician should also make sure to rule out other ocular inflammatory disorders that mimic VKH syndrome. Once a diagnosis is established, early and aggressive use of high-dose oral or intravenous corticosteroids should be given in order to preserve vision. Recent evidence also suggests that patients receiving early treatment with corticosteroid-sparing agents have a better prognosis as well as fewer complications from chronic steroid use. The increasing role of biologic therapies in the treatment of autoimmune diseases may provide rheumatologists and ophthalmologists with another new tool in combating VKH syndrome. Although this disease is relatively rare in individuals of European descent, given its predilection for certain ethnic groups and the changing population demographics in the world, it is reasonable to expect an increasing number of VKH syndrome cases in the coming years in developed western countries. It is therefore important for the rheumatologist to recognize the clinical presentation and be familiar with the treatment options of this disease.
Future perspective

Over the next decade work will focus on understanding the underlying etiopathogenesis of VKH syndrome. Although the role of biologics in the treatment of VKH syndrome has yet to be investigated, it is possible that such treatments will prove beneficial, given what is currently known about the pathogenesis of this disease. Recent findings showing a role of IL-23 in the inflammatory cascade of VKH syndrome suggest that new biologics targeted against IL-23 may also have a therapeutic role. IL-23 is thought to induce the formation of TH17 cells and the subsequent production of IL-17. The latter has already been shown to be involved in the pathogenesis of such systemic inflammatory disease as inflammatory dermatosis, systemic lupus erythematosus, RA, Crohn’s disease, ulcerative colitis and Behcet’s disease. Ustekinumab is a relatively new human monoclonal antibody against IL-12 and IL-23 that has been demonstrated to be effective in the treatment of plaque psoriasis and psoriatic arthritis. It acts by binding to the p40 subunit of IL-12 and IL-23 thereby inhibiting receptor-mediated expression of proinflammatory cytokines.

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Executive summary

- Vogt–Koyanagi–Harada (VKH) syndrome is an idiopathic systemic inflammatory disorder that occurs in genetically susceptible individuals and affects various melanocyte-containing structures, including the eyes, meninges, inner ear and skin.
- VKH syndrome classically leads to bilateral chronic granulomatous diffuse uveitis, and extraocular manifestation can include sensorineural hearing loss, meningitis, and cutaneous findings of vitiligo, poliosis (loss of hair pigment) and alopecia.
- The prognosis for the VKH syndrome patient is fair, with approximately two-thirds of patients maintaining at least 20/40 vision in each eye. However, such success hinges on early diagnosis and aggressive treatment that includes immunomodulatory therapy, and as a result ophthalmologists are increasingly referring such patients to rheumatologists for management of such therapy.
- It is therefore necessary for the rheumatologists to be familiar with VKH syndrome and its clinical aspects and management.

Bibliography

Papers of special note have been highlighted as:

- of interest
- of considerable interest

Identifies possible autoantigen targets in the pathogenesis of VKH syndrome in a mouse model.


* Supports the virus-as-trigger hypothesis for the pathogenesis of VKH syndrome.


** Examines the role of the IL-23/IL-17 axis in the inflammatory cascade of VKH syndrome.


** Important publication describing the most recent criteria for the diagnosis of VKH syndrome.


This study (of a cohort of patients from 1979 to 2007) has demonstrated the efficacy of methotrexate in the treatment of noninfectious ocular inflammatory diseases.


Compares a group of VKH patients treated initially with immunomodulatory therapy to those who were initially treated with corticosteroids.


Profiles the human monoclonal antibody ustekinumab which specifically targets IL-23-mediated inflammation.