Vogt-Koyanagi-Harada Disease

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INTRODUCTION

The present search was conducted with severe parameters towards the theme of this review. The information that are being exposed to that review are confirmed. It has been used Pubmed and Cochrane library for the data collection. The search was focused in Vogt-Koyanagi-Harada disease and reveals the latest data towards etiology-pathogenesis, epidemiology, genotype correlation, pathology, diagnosis, prognosis, complications and treatment. Also there is a clinical approach of the disease. There were used systematic reviews and clinical researches, which were evidence based. It was made an effort of creating a comprehensive and scientific proven review towards the Vogt-Koyanagi-Harada disease and its aspects.

Vogt-Koyanagi-Harada Disease

Vogt-Koyanagi-Harada (VKH) disease, also known as uveomeningitic or uveomeningoencephalitic syndrome, is an idiopathic multisystem autoimmune disease featuring inflammation of melanocyte-containing tissues such as the uvea, ear, and meninges (1). VKH disease is characterized by a severe bilateral granulomatous panuveitis associated with serious retinal detachment, and a varying constellation of neurological, auditory, and cutaneous manifestations. The associated extraocular signs and symptoms of VKH disease can include dizziness, tinnitus, dysacusis, headache, and meningismus in the prodromal stage and poliosis, vitiligo, and alopecia in the convalescent stage. However, these are not always present, and this may lead to diagnostic controversy (3, 6, 7). The varied clinical appearance and the interpretation of these features led to the formation of criteria for the diagnosis of VKH disease in 1978, and subsequently to their revision in 1999 (12). The first descriptions of this disease (poliosis associated with ocular inflammation) were written in the 12th century by an Arab physician, Ali-ibn-Issa and in the 19th century Jacobi, Nettelship, and Tay also described it. Many of these cases were actually different diseases, but many of them were clearly VKHS cases. Vogt has reported also in 1906 the association of poliosis with ocular inflammation. Harada described a primary posterior uveitis with exudative retinal detachments in association with cerebrospinal fluid pleocytosis. Three years later, in 1929, Koyanagi described 6 patients with bilateral chronic iridocyclitis, patchy depigmentation of the skin, patchy hair loss, and whitening of the hair, especially the eye lashes. This constellation of findings was termed “uveitis with poliosis, vitiligo, alopecia, and dysacusis.” Babel in 1932 and Bruno and McPherson in 1949 combined the findings of Vogt, Koyanagi, and Harada and suggested that these processes represent a continuum of the same disease, thereafter recognized as VKH syndrome (1, 6).

EPIDEMIOLOGY
VKH disease occurs more frequently among races with genetic predisposition and pigmented skin. Asians, Asian Indians, Hispanics, Native Americans, and Middle Easterners are more commonly affected than whites and black people of sub-Saharan Africa. It has been suggested that these populations have a common Asian ancestry and that genetic predisposition spread with the migration across the Bering Strait land bridge into the Americas. Women seem to be affected more frequently than men, although this sex predilection is not so clear in the Japanese population, and VKH disease predominantly affects those in their third to fourth decades of life, although children as young as 4 years of age have been diagnosed with VKH disease. The prevalence of this VKH disease varies and is different among different populations. Japan is the most affected country where VKH disease represents 10% of all uveitis cases. In Brazil VKH represents the 2.5% cause of noninfectious uveitis. In the U.S.A, VKH disease accounts for 7% of uveitis referrals and it has been reported that a large proportion of these patients have native American ancestry. In India VKH disease accounts for 2% and 5.8% of uveitis in Mexico. In Chinese patients, VKH disease had an incidence of 32.8% over a 5 years period. In a study conducted by Yang et al in Singapore, from a total of 1752 patients in the uveitis department 15.9% had VKH disease, and it was considered the second leading cause of panuveitis after Adamantiades-Bechets disease. In Iran, only 3.9% uveitis patients were diagnosed with VKH disease, and in Saudi Arabia from 20,191 new uveitis cases, 2.5% had VKH disease. There are not epidemiologic data published on VKH in disease in children, although there are 3 series of cases reported in the literature. Tabbara and associates in Saudi Arabia described among 97 patients with VKH disease 13 patients were diagnosed by 14 years old age that would be 16.5%. Rathinam and colleagues described 3 children, less than 16 years old age with VKH disease from a cohort of 98 patients in South India. Recently El-Asrar and associates described VKH patients 16 years old or younger at diagnosis seen over a 7 year period, also in Saudi Arabia. In 1984, Kanski and Shun-Shin analyzed 340 cases of systemic uveitis syndromes in childhood and found only one 6 years old Arabian child with VKH disease, that stands for 0.29%.

IMMUNOPATHOGENESIS

The exact cause of VKH disease is not known, however various investigators have suggested an underlying autoimmune or infectious process. Some studies strongly suggest an autoimmune T-cell-mediated reaction against some melanocyte-related antigens, perhaps a member of the tyrosinase family of proteins. An association with HLA-DR1 and –DR4 has been found among 84% of Southern Californian Hispanic patients with VKH disease, where HLA-DR1 was associated with a relative risk of 4.11 compared with 1.96 for HLA-DR4. HLA-DR4 is associated in Japanese patients with VKH disease, and these patients and individuals from Korea show significant association with DRB1*0405. T-cell clones specific to the tyrosinase family of proteins were isolated from VKH patients and some of those clones showed a proliferative response to peptides that matched the motif of the strong binding site for HLA DRB1*0405. Moreover animal studies have shown that immunization of rats with tyrosinase, TRP1 or TRP2, which are tyrosinase-related protein 1 or 2, can induce autoimmune disease. Also recent human studies have shown that lymphocytes of VKH patients are reactive to tyrosinase family proteins and suggest that tyrosinase family proteins are the target antigens of immune reactions incited by VKH disease. It has been reported that vitiligo lesions of patients with VKH disease showed helper/inducer CD4+ lymphocytes and an altered ratio of CD4+/CD8+(3:1) cells. The melanin-laden cells of the epidermis were partially lost and the presence of infiltrates, composed mainly by T cells, suggested that a cell mediated immune response plays a central role in the pathogenesis of dermal lesions. Choroidal infiltrates in active VKH patients also showed predominantly CD4+ T lymphocytes that express a transmembrane protein CD-
25: this molecule is an alpha chain of the receptor for the interleukin-2 (IL-2). CD25 is expressed by conventional T cells after stimulation. Furthermore, other cells express CD26 that is a T cell activation antigen and potentiates T cell activation leading to subsequent exertion of T cell effector function. So CD26 is considered a marker for late activation. Pathologic analysis demonstrates a diffuse non-necrotizing granulomatous infiltration of the uvea that spares the choriocapillaris. (2) Lymphocytes predominate, but epithelioid cells, plasm cells, and multinucleated cells are also present. The epithelioid and giant cells contain melanin. Dalen-Fuchs nodules consisting of macrophages, epithelioid cells, and lymphocytes with an alteration in the RPE can be seen in the chronic phase. As it was mentioned is unclear what triggers the immune system of a patient with the genetic predisposition to mount an autoimmune response against the target cells and antigens. Epstein-Barr virus is very likely that is a viral trigger. Vkh has been reported after cutaneous injury, supposing a theory that it may result from systemic sensitization to shared melanocytic antigens. (6, 7)

**CLINICAL FEATURES**

Vogt-Koyanagi-Harada disease is a chronic, bilateral, granulomatous uveitis with extraocular manifestations in the central nervous system such as cerebrospinal fluid pleocytosis (CSF), dysacusis, tinnitus, vertigo, and in some cases, integumentary system vitiligo, poliosis, and alopecia. The ocular components of the disease are fairly constant and are characterized by multifocal serous retinal detachment, choroidal swelling, and optic disk hyperemia in the acute stage. (1, 5) Although classic cases of VKH disease show all of the ocular and extraocular manifestations, such cases are unusual, and the incidence of extraocular manifestations varies according to different studies. For the diagnosis of VKH disease we use the revised diagnostic criteria of the First International Workshop on VKH during the year 1999. The revised criteria for the diagnosis of VKH disease included the concepts of definite diagnosis (complete and incomplete) and probable diagnosis of VKH disease (6, 12). (Table 1)

**Table 1. Revised Diagnostic Criteria for Vogt-Koyanagi-Harada Disease**


**Complete Vogt-Koyanagi-Harada disease (criteria 1 to 5 must be present)**

1. No history of penetrating ocular trauma or surgery preceding the initial onset of uveitis
2. No clinical or laboratory evidence suggestive of other ocular disease entities
3. Bilateral ocular involvement (a or b must be met, depending on the stage of disease when the patient is examined)
   a) Early manifestations of disease
      1. There must be evidence of a diffuse choroiditis (with or without anterior uveitis, vitreous inflammatory reaction, or optic disk hyperemia), which may manifest as one of the following:
         a) Focal areas of subretinal fluid, or
         b) Bullous serous retinal detachments
      2. With equivocal fundus findings; both of the following must be present as well:
         a) Focal areas of delay in choroidal perfusion, multifocal areas of pinpoint leakage, large placoid areas of hyperfluorescence, pooling within subretinal fluid, and optic nerve staining (listed in order of sequential appearance) by fluorescein angiography, and
         b) Diffuse choroidal thickening, without evidence of posterior scleritis by Ultrasonography
b) Late manifestations of disease

(1) History suggestive of prior presence of findings from 3a, and either both (2) and (3) below, or multiple signs from (3)

(2) Ocular depigmentation (either of the following manifestations is sufficient):

(a) Sunset glow fundus, or
(b) Suglura sign

(3) Other ocular signs:

(a) Nummular chorioretinal depigmented scars, or
(b) Retinal pigment epithelium clumping and/or migration, or
(c) Recurrent or chronic anterior uveitis

4. Neurological/auditory findings (may have resolved by time of examination)

a. Meningismus (malaise, fever, headache, nausea, abdominal pain, stiffness of the neck and back, or a combination of these factors; headache alone is not sufficient to meet definition of meningismus, however), or
b. Tinnitus, or
c. Cerebrospinal fluid pleocytosis

5. Integumentary finding (not preceding onset of central nervous system or ocular disease)

a. Alopecia, or
b. Poliosis, or
c. Vitiligo

Table 1. (Continued) Revised Diagnostic Criteria for Vogt-Koyanagi-Harada Disease

**Incomplete Vogt-Koyanagi-Harada disease** (criteria 1 to 3 and either 4 or 5 must be present)

1. No history of penetrating ocular trauma or surgery preceding the initial onset of uveitis, and
2. No clinical or laboratory evidence suggestive of other ocular disease entities, and
3. Bilateral ocular involvement
4. Neurologic/auditory findings; as defined for complete Vogt-Koyanagi-Harada disease above, or
5. Integumentary findings; as defined for complete Vogt-Koyanagi-Harada disease above

**Probable Vogt-Koyanagi-Harada disease** (isolated ocular disease; criteria 1 to 3 must be present)

1. No history of penetrating ocular trauma or surgery preceding the initial onset of uveitis
2. No clinical or laboratory evidence suggestive of other ocular disease entities
3. Bilateral ocular involvement as defined for complete Vogt-Koyanagi-Harada disease above

It is important to make a prompt diagnosis, even when the full set of extraocular criteria are not present. The stages of VKH disease have been well described and include Prodromal, Acute Uveitic, Chronic, and Chronic Recurrent stages.(1,5,6,7)

**Prodromal Stage**

This stage usually lasts for 3 – 5 days and is characterized by a viral-like illness. The symptoms are not specific and include malaise, fever, nausea, headache, dizziness and orbital
pain. Some times may occur in this stage also neurologic manifestations which consist of meningismus and headache. It is rare but it can also occur focal neurologic signs such as cranial nerve palsies, hemiparesis, transverse myelitis and optic neuritis. Eighty percent of patients will show lymphocytic pleocytosis in cerebrospinal fluid for 8 weeks. Moreover ocular symptoms such as photophobia and tearing may occur after the systemic symptoms.(6)

**Acute Uveitic Stage**

This stage may last for several weeks and follows the prodromal stage. The main symptom is diminished visual acuity. 70% of the patients present with bilateral posterior uveitis. In 30% there may be a short delay of 1 to 3 days before the second eye became involved. This is the reason why cases suspected to be VKH disease with unilateral manifestations should be carefully evaluated for subtle signs in the fellow eye, and ultrasound is helpful in these cases to detect choroidal thickening. The uveitis commonly presents with multiple serous retinal detachments, hyperemia and edema of the optic nerve head, and thickening of the posterior choroid with elevation of the peripapillary retinochoroidal layer(Fig.1). Eventually, the inflammation extends to the anterior segment, where mutton fat keratic precipitates, and iris nodules can be found.(1,7)

![Figure 1](image1.png)

A 53-year-old female presented with a 1-week history of decreased vision and headache.

Funduscopys revealed bilateral exudative retinal detachments and hyperemic optic discs.

**Cronic( Convalescent) Stage**

It is during this stage, which lasts for months or even years, that patients develop signs due to depigmentation that may be integumentary and/or uveal. Usually the vitiligo is symmetrical and involves mainly the face, eyelids, and trunk. Depigmentation of the choroid gives the ocular fundus a ‘sunset-glow’ appearance where the choroid appears bright-orange in color and the optic nerve appears pale. Sugiuara’s sign or perilimbal vitiligo is the earliest depigmentation to occur, often within 1 month after disease onset. However this sign is rarely seen in Southern Californian patients and is reported that 85% of Japanese patients do have it. (Fig.2)(6,7)

![Figure 2](image2.png)

Convalescent stage, peripapillary and subretinal fibrosis, and pigment migration.
Chronic Recurrent Stage

Manifests as a recurrent, mainly anterior granulomatous uveitis. Posterior segment inflammation is rare during this phase. Complications such as glaucoma, cataract and subretinal fibrosis, and neovascular membrane formation usually develop at this stage. Factors that are associated with the development of complications are duration of the disease and the number of recurrences.(6)

DIFFERENTIAL DIAGNOSIS

A differential diagnosis of the ocular manifestations which can be seen in VKH should include sympathetic ophthalmia, idiopathic central serous chorioretinopathy, acute leukemia, primary intraocular B-cell lymphoma, metastatic carcinoma, uveal melanocytic proliferation associated with systemic carcinoma, idiopathic uveal effusion syndrome, posterior scleritis, acute posterior multifocal placoid pigment epitheliopathy, multiple evanescent white dot syndrome, Bechet disease, Lyme disease, sarcoidosis, and benign reactive lymphoid hyperplasia of the uveal tract. Systemic blood work and physical exam to rule out systemic disease and malignancy should be performed.(1) Sympathetic ophthalmia may present with a very similar bilateral panuveitis, although anterior segment granulomatous inflammation is more common in sympathetic ophthalmia. Rarely, extraocular manifestations including dysacusis, poliosis, alopecia, and vitiligo can occur, therefore a history of ocular penetration may well be the only differentiating factor between the two entities and must be specifically sought. Sarcoidosis must be considered because 60% of patients with ocular sarcoid have a chronic granulomatous uveitis, although this is usually anterior with posterior uveitis occurring in 6% to 33% of patients. Serous retinal detachment is unusual in sarcoidosis, and the classic retinal vasculitis signs of venous sheathing and candlewax drippings are not seen in VKH disease.(6,7) Uveal effusion syndrome may clinically mimic VKH disease. Angiographically, the effusion syndrome may reveal numerous fluorescent blotches in the subretinal space during the serous detachment phase. The syndrome can involve both eyes, although not simultaneously. Unlike VKH disease, the effusion syndrome lacks intraocular inflammation. Posterior scleritis affects predominantly women and is often bilateral. Patients may present with pain, photophobia, and loss of vision, and the vitreous often reveals cells. Exudative macular detachment and choroidal folds may be noted. Usually, patients with bilateral involvement have a history of rheumatoid disease. Ultrasonography helps in differential diagnosis. Acute posterior multifocal placoid pigment epitheliopathy (APMPPE) may be confused with VKH disease. These patients develop a sudden loss of vision following a viral prodrome, both eyes are usually involved. Multiple white-yellow flat to placoid lesions are seen at the level of the RPE. There is minimal to no vitreous inflammation, which is helpful in differentiating APMPPE from VKH disease.(5,6)

TREATMENT

In most cases, early and aggressive treatment with systemic corticosteroids will suppress the acute inflammatory process and minimize the development of complications that are due to uncontrolled inflammation. High dose oral corticosteroids – for example, oral prednisone 1-2 mg/kg/d or 200 mg of intravenous methylprednisolone for 3 days, followed by oral administration of high dose corticosteroids with a gradual tapering of the dose according to clinical response- are the mainstay of therapy in VKH disease. This treatment is usually required from 6 to 9 months. (1,3,5) The use of intravitreal triamcinolone has recently been reported to provide short-term improvement in visual acuity and resolution of serous retinal detachments during the acute stage of VKH disease. The systemic nature of VKH disease, which may not always be clinically apparent, must also be remembered, and the disease should be treated accordingly. A recent multicenter international study on the treatment of VKH disease showed that high dose oral corticosteroids were as effective as intravenous corticosteroid intervention, with similar visual outcomes in the treatment groups. It is well
recognized that the treatment with the corticosteroids should be continued for a minimum of 6 months, as such treatment may prevent recurrences and the complications of chronic inflammation (6,7). Table 2(1) is a list of mechanisms, dose ranges, potential side effects, and necessary monitoring for these immunomodulatory therapies.

Table 2

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Drug Name</th>
<th>Mechanism</th>
<th>Dose</th>
<th>Possible Side Effects</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoral, Sandimmune, SangCyA</td>
<td>Cyclosporine A (CSA)</td>
<td>Reversible T-cell inhibitor</td>
<td>2.5 to 5.0 mg/kg/d IV/PO/Topical</td>
<td>Renal dysfunction, tremor, hirsutism, hypertension, gum hyperplasia, hyperuricemia, hyperglycemia, nausea, and vomiting</td>
<td>Creatine, CBC, LFTs, Mg</td>
</tr>
<tr>
<td>Cytoxan</td>
<td>Cyclophosphamide</td>
<td>Alkylating agent, T- and B-cell lymphotoxic</td>
<td>1 to 3.0 mg/kg/d PO, IV</td>
<td>Myelosuppression, infection, hematuria, hemorrhagic cystitis, malignancy, sterility, and alopecia</td>
<td>CBC, UA</td>
</tr>
<tr>
<td>Imuran</td>
<td>Azathyprine</td>
<td>Purine analog, T- and B-cell lymphotoxic</td>
<td>1 to 3.0 mg/kg/d PO</td>
<td>Leukopenia, GI upset, hepatitis, and infection</td>
<td>CBC, chemistry</td>
</tr>
<tr>
<td>Prograf</td>
<td>Tacrolimus</td>
<td>T-cell inhibitor</td>
<td>0.1 to 0.3 mg/kg/d PO</td>
<td>Nephrotoxicity, hyperkalemia, hypomagnesiumemia, hepatitis, hypertension, diabetes, and possible neutropenia</td>
<td>CBC, chemistry, Mg</td>
</tr>
<tr>
<td>Leukeran</td>
<td>Chlorambucil</td>
<td>Alkylating agent, lymphotoxic</td>
<td>0.1 mg/kg/d PO</td>
<td>Myelosuppression, infection, sterility, malignancy</td>
<td>CBC</td>
</tr>
<tr>
<td>CellCept</td>
<td>M ycophenolate Mol et</td>
<td>IMP dehydrogenase inhibitor, inhibits purine synthesis</td>
<td>500mg–1g PO BID</td>
<td>Diarrhea, nausea, neutropenia, impotence, alopecia, renal, and hepatotoxic infection</td>
<td>CBC, chemistry</td>
</tr>
</tbody>
</table>

Prognosis depends greatly on how early it is diagnosed and correctly treated. Disorders of the auditory system respond well to treatment and are generally completely reversed in 2 to 3 months, whereas the cutaneous lesions are permanent. Prognosis for the vision is extremely variable, although generally favorable. It has been found that the three most important prognostic factors are: good visual acuity 1 month after starting therapy, early high-dose corticosteroids and age at disease onset, with evidence that younger patients suffered a lower rate of ocular complications.(5,6)

Conflicts of interest: none

REFERENCES


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