Chapter

Vogt-Koyanagi-Harada Disease: Current Diagnosis and Management

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Abstract

Vogt-Koyanagi-Harada (VKH) disease is a rare granulomatous inflammatory disease that affects pigmented structures, such as eye, inner ear, meninges, skin, and hair. This disease is mainly a T1 lymphocyte-mediated aggression to melanocytes. The availability of new investigational methods has improved our knowledge of the pathogenesis, clinical approach, diagnosis, and management of VKH disease. The disease has an acute onset of bilateral blurred vision with hyperemia in the absence of prior ocular trauma or any previous intraocular surgery. The chronic phase comprises of ocular and integumentary system pigmentary changes. Ocular findings may be accompanied by meningismus, hearing impairment, and skin lesions in a variable proportion of patients. Prompt diagnosis with early, aggressive, and long-term treatment of high-dose corticosteroids ensures good visual outcomes. The aim of this chapter is to present the clinicopathology, classification, recent imaging, investigations, and management of VKH disease.

Keywords: Vogt-Koyanagi-Harada disease, granulomatous uveitis, imaging, immunomodulatory therapy, optical coherence tomography, corticosteroids, immunosuppressant

1. Introduction

Vogt-Koyanagi-Harada (VKH) disease, formerly called as uveo-meningitic syndrome, is a systemic autoimmune disorder involving multiple organ systems, including the ocular, auditory, nervous, and integumentary. Severe bilateral panuveitis along with exudative retinal detachment is characteristic for this disease [1]. Fluorescein angiography and optical coherence tomography (OCT) have helped diagnose the condition through the analysis of changes in the retina and, recently, the choroid. Corticosteroids and, more recently, steroid-sparing immunomodulators have been the mainstay of treatment [2].

2. History

VKH disease was first described by Ali-ibn-Isa (940-1010 AD) who described inflammation of the eyes and whitening of the eyelashes, eyebrows, and hair (poliosis) [3]. In 1873, this association was reported again by Schenkl followed by Hutchinson in 1892 and Vogt in 1906 [4–6]. In 1962, the Japanese physician Einosuke Harada described a posterior uveitis accompanied by exudative retinal detachment and cerebrospinal fluid (CSF) pleocytosis [7]. In 1929, bilateral iridocyclitis associated with vitiligo, alopecia, and poliosis along with tinnitus and deafness was described by Koyanagi [8]. Babel in 1932 and later Bruno and McPherson in 1949 combined the descriptions of Vogt, Koyanagi, and Harada and proposed that these signs and symptoms were a series of manifestations of the same underlying disease process, differing only in intensity and the distribution from one patient to another [9, 10]. A common alternative to uveomeningoencephalitic syndrome is VKH disease, which has existed since then.

3. Epidemiology

While population-based epidemiological studies are relatively rare, epidemiological data from tertiary referral centers indicate a wide variation in the incidence of VKH disease. A predilection for this disease occurs among those with dark pigments, in particular Asians, Hispanics, Middle Easterners, and Native Americans [1]. Geographically, VKH syndrome accounts for an estimated 4% of all uveitis referrals in the United States and 8% in Japan [10]. These patients appear to vary globally in their gender predilection, but most studies suggest that women are affected somewhat more often than men [11–17]. Most patients are in the second to fifth decades of life at the onset of the disease and while uncommon, it has been well recognized in children [11–14, 17–22].

The most common cause of panuveitis in India is VKH, with a prevalence of 21.08% [2]. Martin and colleagues studied new cases of uveitis in South India and found that 1.2% were diagnosed with VKH, of which 8.2% were children [2]. An average age of 13.5 years was observed among patients between the ages of 8 and 16. In 75% of the cases, the final vision of the child was better than 20/40 [2].

4. Etiology and pathogenesis

There is no definitive etiology or pathogenesis for VKH syndrome, but it is believed that it is primarily the result of an autoimmune inflammatory reaction that targets melanin-containing cells or a common antigen present in the skin, eye, meninges, and ear. Following viral infection-induced challenge, an autoimmune attack against melanocyte-associated antigens is considered the most likely mechanism in genetically susceptible individuals (**Figure 1**). According to some studies, individuals who are genetically susceptible develop an autoimmune response mediated by T lymphocytes against self-antigens associated with melanocytes across all organ systems [24, 25]. Research suggests that HLA-DR4 is associated with the disease among Japanese, and HLA-DR1 or HLA-DR4 with Hispanic patients from southern California, further supporting the genetic predisposition [26, 27].

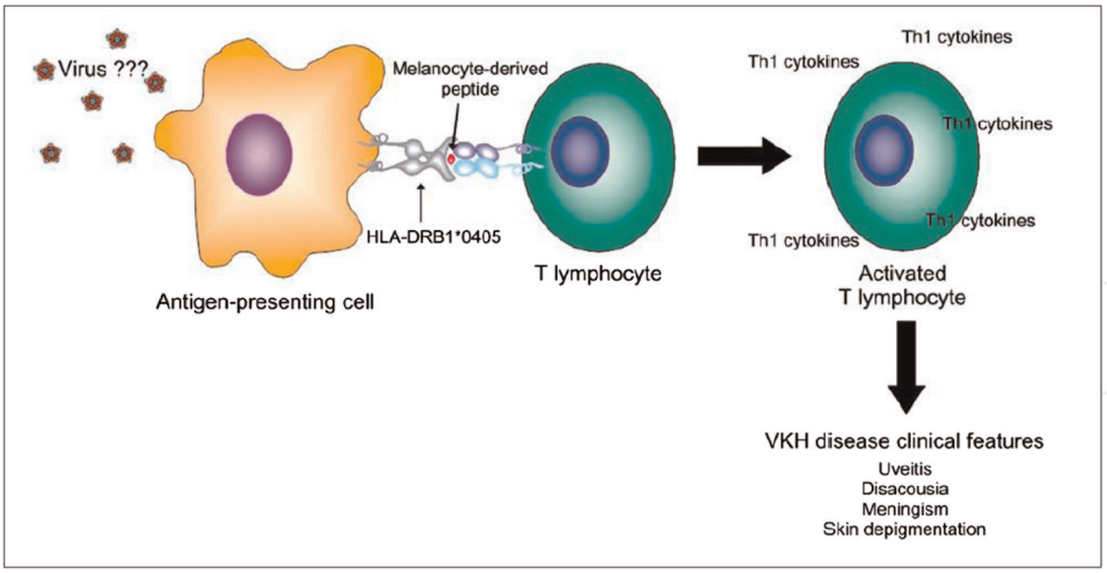

Figure 1.
Pathogenesis of VKH [23].

Studies have shown that tyrosinase protein antigens are reactive with lymphocytes of VKH patients, suggesting that these proteins are the target antigens of immune reactions in this disease. Patients with VKH disease have helper CD4+ lymphocytes in vitiligo lesions, as well as an altered ratio of CD4+/CD8+ cells (3:1). Other studies related to dermal lesions have shown that melanin-rich cells in the epidermis are eliminated and connective tissue is infiltrated by T cells, suggesting that cell-mediated immune responses are a major pillar of pathogenesis [28].

5. Histopathological features

The histopathological features of VKH vary according to the stage of the disease. Diffuse thickening of the uveal ducts (mainly in the peripapillary choroid) is the main pathologic feature of VKH [29, 30].

In the acute stage, it is important to note that there is diffuse lymphocytic infiltration with aggregates of epithelioid cells and multinucleated giant cells without any obvious choroidal necrosis. The choroidal infiltrate consists of T lymphocytes and melanocytes expressing molecules of the class II major histocompatibility complex. During acute uveitis, the subretinal fluid is made up of eosinophilic proteinaceous material. There is diffuse infiltration of lymphocytes, epithelioid histiocytes, and multinucleated giant cells, similar to features of the choroidal stromal disease [31]. Dalen-Fuchs nodules can be formed by the accumulation of hyperplastic retinal pigment epithelium (RPE), macrophages, epithelioid cells, and lymphocytes between the RPE and Bruch's membrane [32, 33]. Histopathology during convalescent stage showed non-granulomatous inflammatory cellular infiltrate with focal lymphocyte aggregates and occasional macrophages. The loss of choroidal melanocytes results in a pale and depigmented appearance of the choroid. As a result, images like "sunset glow fundus" can be enjoyed [32, 33]. In the chronic recurrent stage, granulomatous choroiditis with choriocapillary damage can be observed. In addition, a granulomatous infiltrate can be observed, with less pronounced diffuse thickening of the uvea in

comparison with the acute phase. Atrophy or proliferation of RPE is often accompanied by chorioretinal adhesions. Hyperpigmented areas in atrophic patch are due to the proliferation of RPE, rarely associated with subretinal neovascularization [33]. Immunological markers like CD3 and CD20 with increased T cell involvement have been found in cases of VKH syndrome [34].

6. Clinical manifestations

VKH disease presents in four clinically distinct phases: prodromal, uveitic, convalescent, and chronic recurrent.

6.1 Prodromal stage

The prodromal period is characterized by flu-like symptoms. Systemic associations like headache, nausea, meningeal irritation, impaired hearing, tinnitus, fever, orbital pain, photophobia, and sensitivity to touch may precede ocular symptoms. Focal neurological signs, although rare, may include multiple cranial neuropathies, hemiparesis, aphasia, transverse myelitis, and ganglionitis. CSF analysis revealed lymphocytosis and normal glucose in more than 80% of patients; this observation may persist for up to 8 weeks [1, 2, 35]. Central hearing loss occurs early in the disease course in approximately 30% of patients, usually with high frequency, and usually improves within 2–3 months; however, persistent deficits may persist.

6.2 Acute uveitic stage

The acute uveitis phase begins with persistent visual impairment in both eyes 1 to 2 days after the onset of central nervous system symptoms. It is marked by bilateral granulomatous anterior uveitis, a variable degree of vitritis, thickening of the posterior choroid, edema of the optic nerve, and multiple serous retinal detachments. There are often small, cloverleaf-shaped focal serous retinal detachments around the posterior pole. However, these can coalesce into large, bullous detachments and become exudative. Fluorescein angiogram in acute uveitic stage typically shows multiple hyperfluorescent pinpoint spots merging into pools of fluorescein in the subretinal space. Profound vision loss may be seen in this stage [22]. Less commonly, mutton fat Keratic precipitates (KPs) and inflammatory iris nodules can be seen at the pupillary margin. Secondary IOP rise, anterior chamber shallowing due to ciliary edema, and/or annular choroidal detachment resulting in anterior displacement of the lens-iris septum can be rarely seen in this stage. Alternatively, IOP may be low, possibly due to ciliary shutdown. Recent confocal scans of corneal deposits have shown that non-infectious causes of uveitis (such as VKH) appear as smooth, round deposits, while infectious uveitis appears as dendritic deposits.

6.3 Convalescent stage

The recovery phase occurs after a few weeks and is characterized by the resolution of exudative retinal detachment and progressive depigmentation of the choroid, resulting in classic orange-red discoloration or twilight fundus. Small, round, inconspicuous lesions were also present in the lower peripheral fundus. Pericapillary hyperpigmentation may also be observed. The sunset-glow fundus may show focal

areas of retinal hyper- or hypopigmentation. In up to 85% of Japanese patients, perilimbal vitiligo (Sugiura sign) is present, but rarely in white patients [1]. Skin changes, including vitiligo, alopecia, and graying, usually occur during the recovery phase in approximately 30% of patients and coincide with the development of fundus hypopigmentation. Usually, skin and hair changes occur late the onset of ocular inflammation, but in some cases, they can occur at the same time. Vitiligo occurs in 10 to 63% of patients, depending on ethnicity; cutaneous manifestations and other extraocular manifestations are relatively uncommon in Hispanic patients.

7. Chronic recurrent stage

The chronic relapsing phase is characterized by recurrent episodes of granulomatous anterior uveitis with keratic precipitates, posterior synechiae, iris nodules, iris depigmentation, and stromal atrophy. Recurrent posterior segment inflammation can occur but is uncommon during this stage. It is at this stage that the vision-impairing effects of chronic inflammation appear, such as posterior subcapsular cataracts, glaucoma, choroidal neovascularization (CNV), and subretinal fibrosis.

8. Extraordinary manifestations

8.1 Integumentary system

Integumentary system manifestations are seen at various stages of the disease and these vary markedly among reported series. Seventy-two percent of patients reported sensitivity to touch of the hair and skin in the prodromal stage [18]. Alopecia, poliosis, and vitiligo are all well recognized in VKH, although their reported prevalence varies from just over 10% to over 60% in published studies [13, 14]. One report suggested that Hispanic people may have a lower dermatologic involvement incidence than Asian patients [13].

8.2 Neurologic manifestations

Headache, confusion, orbital pain, and stiff neck are common symptoms of prodromal stage. In a study published by Beniz and colleagues, headaches were by far the most common neurological complaint [13]. CSF pleocytosis with predominance of lymphocytes and monocytes with normal glucose level has been found in 80% of VKH patients [11, 18]. A rare case of polymorphonuclear pleocytosis resembling infectious meningitis in VKH has also been reported earlier. Rarely, focal neurological signs such as cranial neuropathies, hemiplegia, aphasia, transverse myelitis, and ganglionitis are also associated [36–38].

8.3 Auditory manifestations

Hearing problems such as tinnitus occur in 75% of patients, often associated with active eye disease [39]. Hearing loss is usually for higher frequencies but rarely can affect all frequencies [40]. Improvement is usually seen within 2–3 months, but persistent changes may occur [18].

9. Unilateral VKH

Although bilateral involvement is required for the diagnosis of VKH according to the current revised diagnostic criteria, there have been a few reports of monocular or asymmetrical ocular involvement [41–44]. VKH may present with atypical features, such as unilateral or asymmetric signs and symptoms. Forster et al., Roe et al., and Usui et al. have reported cases of unilateral VKH or cases in which the fellow eye was involved late [41, 43, 44].

10. Diagnostic criteria

Several sets of criteria have been proposed for the diagnosis of VKH disease, since it was initially considered as a single clinical uveitis entity. The evolution of the criteria reflects our growing understanding of the disease. Diagnosis of VKH disease is straightforward and is based on suspicion of bilateral acute diffuse uveitis and various extraocular features. However, this condition may bear considerable similarity to sympathetic ophthalmia, which is also characterized by bilateral acute diffuse uveitis with alopecia, vitiligo, whitening of hair, and hearing loss. However, the latter usually occurs after ocular trauma or intraocular surgery and rarely has extraocular manifestations.

Diagnosis of VKH is primarily based on clinical features. Several criteria have been proposed to specify the diagnostic approach, including the American Uveitis Society (AUS) in 1978 (**Table 1**) and the Sugiura criteria in 1976 (**Table 2**). The AUS adopted the following diagnostic criteria [12, 29].

1. No previous ocular trauma and/or surgery;

2. At least three of the following four signs are present;

3. Bilateral chronic iridocyclitis;

4. Posterior uveitis (multifocal exudative retinal or RPE detachments; disc hyperemia or edema; or "sunset glow fundus," which is a yellow-orange appearance of the fundus due to depigmentation of the RPE and choroid);

5. Neurologic signs (tinnitus, neck stiffness, cranial nerve or central nervous system symptoms, or cerebral spinal fluid pleocytosis);

6. Cutaneous signs (alopecia, poliosis, or vitiligo).

1. Patient should have no history of ocular trauma or surgery
2. At least three of the following four signs should be present: a. Bilateral chronic iridocyclitis, b. Posterior uveitis, including exudative retinal detachment, forme fruste of exudative retinal detachment, disk hyperemia or edema, and "sunset glow" fundus, c. Neurologic signs of tinnitus, neck stiffness, cranial nerve or central nervous system problems, or CSF pleocytosis d. Cutaneous findings of alopecia, poliosis, or vitiligo.
[a] *From Snyder and Tessler, 1980.*

Table 1.
Criteria proposed by the American Uveitis Society for diagnosis of VKH disease.

Major Symptoms
1. Acute bilateral uveitis with simultaneous involvement of both eyes. Symptoms may not be noted for 1–10 days in the second eye. 2. Circumscribed retinal edema most markedly at the posterior pole. Fluorescein angiography reveals characteristic leakage of dye through the retinal pigment epithelium into the subretinal spaces. 3. Pleocytosis of the cerebrospinal fluid is noted in the early stages of the disease. Dysacousia, vertigo, and scalp sensitivity when touching the hair are of value in early diagnosis, if present.
Minor symptoms
1. Floating cells in the anterior chamber, granulomatous keratic precipitates, and iris nodules are important signs that may be absent in early stages. 2. Hair loss and depigmentation of the eye, skin, and hair are also important signs in the convalescent stage. Depigmentation of the corneal limbus (Sugiura's sign) appears earliest (Friedman and Deutsch-Sokol, 1981), roughly 1 month after onset, and is also of value for confirming the early diagnosis if present.

Table 2.
Diagnostic criteria proposed by Sugiura for VKH disease (Sugiura, 1978).

The AUS criteria fail to distinguish acute from chronic cases. Another limitation consists of the inadequate compilation of acute cases, as two of the four cardinal signs characteristically occur in the convalescent/chronic stages of the disease. AUS criteria failed to consider fluorescein (FA), indocyanine angiography (ICGA), and ultrasonographic findings. Therefore, neither chronological examinations nor extra examinations were taken into account.

Sugiura et al. proposed another set of diagnostic criteria for VHK (**Table 2**). This system is seldom used outside Japan, where CSF analysis is mandatory [12, 22]. Sugiura's criteria included 3 main symptoms: simultaneous bilateral uveitis, localized retinal edema at the posterior pole with characteristic fluorescent dye leakage, and pleocytosis of CSF in acute phase. According to Sugiura's criteria, CSF pleocytosis is also an important sign necessary for the diagnosis of the disease [2]. The International Nomenclature Committee defined more comprehensive criteria, the Revised Diagnostic Criteria (RDC) in 2001 [30]. RDC divides the disease into three categories based on the presence of extraocular findings: complete, incomplete, and probable VKH (**Table 3**) [30]. By considering both early and late ocular manifestations, patients can be diagnosed regardless of time since presentation. Additional examinations (i.e., ICGA and optical coherence tomography (OCT) were not considered. RDC also did not consider follow-up period and treatment; these two parameters can interfere with the occurrence of extraocular manifestations.

More recently, a correlation between fundus changes and full-field electroretinogram (ffERG) with advanced VKH (more than 6 months after onset) was shown by da Silva et al. Fundus parameters were used to provide a framework for analyzing fundus changes in advanced stages of VKH, namely: diffuse pigmentary changes; nummular lesions; pigmented masses; and subretinal fibrosis [45]. Correlations of severity in fundus with ffERG parameters suggest that fundus changes may reflect functional abnormalities. Lumbar puncture is helpful only for diagnosing acute VKH. Given the large number of patients with hearing problems, audiometry is recommended in patients with VKH [35].

11. Diagnosis

The diagnosis of VKH is clinical (as no laboratory marker identifies the presence thereof) and is based on the RDC to date (**Table 3**) [30]. It is common trend in the United States and several other countries for most patients to undergo retinal fluorescein angiography if VKH has been suspected. Japanese and European doctors perform lumbar punctures to detect pleocytosis in cerebrospinal fluid. A variety of other investigations may be useful in identifying VKH, including indocyanine green (ICG)

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): a. Early manifestations of disease 1. Diffuse choroiditis (with or without anterior uveitis, vitreous reaction, or optic disk hyperemia), as manifested by either: 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 area 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 IIIA, 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. Sugiura signs 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 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
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, and, either 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. Bilateral ocular involvement as defined for complete Vogt-Koyanagi-Harada disease above. Isolated ocular disease.
[a] *From Am J Ophthalmol 2001:131, 647-652.*

Table 3.
Revised diagnostic criteria for Vogt-Koyanagi-Harada Disease.

angiography and ultrasonography, which measure choroidal thickness. However, although electroretinograms and electroencephalograms have been used in the past, these procedures are rarely conducted and may not be necessary for diagnosing VKH in the vast majority of cases. Recent advances in imaging technology have made it possible not only to analyze but also to objectively evaluate disease progression and treatment efficacy in VKH patients (**Table 4**). Advances in OCT in the measurement of choroidal thickness, along with other imaging modalities, have enabled the non-invasive delineation of changes in the retina, retinal pigment epithelium, and choroid that were previously not apparent on clinical examination [2].

11.1 Fluorescein angiography (FA)

Changes in FA during the acute uveitic stage are characteristic and can help differentiate VKH from other conditions. Initially, in the setting of active inflammation, FA showed delayed choroidal perfusion, resulting in hypofluorescence in poorly perfused areas. There are numerous consecutive hyperfluorescent pinpoint spots, possibly corresponding to alterations in the RPE. When these hyperfluorescent spots magnify and stain the surrounding subretinal fluid, a pool of stain appears in the subretinal space. The areas of choroiditis correspond to these hyperfluorescent lesions. During the acute phase of the disease, nearly 70% of patients develop disc leaks (**Figures 2–4**) [47]. Some linear areas of hypofluorescence can be observed due to the presence of choroidal ischemia or folds. The presence and extent of the pinpoint leakage can be used to monitor the effectiveness of initial treatment with corticosteroids. During the recovery phase, disc leaks and hyperfluorescent spots were also observed in 29% and 14% of patients, respectively [48, 49].

In the chronic and recurrent stages, FA may exhibit multiple hyperfluorescent window defects, as well as areas of blocked hypofluorescence in areas of damaged RPE, presenting as "moth-eaten" appearance. Choroidal neovascularization (CNV), retinochoroidal anastomosis, and disc neovascularization may be seen rarely [35].

11.2 Indocyanine green angiography (ICGA)

ICGA is commonly used for studying inflammatory pathologies of choroidal vasculature and stroma [50]. Herbert et al. reviewed and described characteristic ICGA signs in VKH disease. Inflammatory damage to choroidal vessels can lead to delayed choroidal perfusion in the early stages of ICGA (2–3 minutes after dye injection) [48, 51, 52]. Even when fundus and FA findings are inconspicuous, hypofluorescent spots may appear in the early stages of ICGA; thus, ICGA can serve as a sensitive marker for the detection and monitoring of subclinical choroidal inflammation (**Figure 4**). The heterogeneous background choroidal fluorescence observed at provisional ICGA is the result of multiple hypofluorescent circular lesions in the choroidal stroma (**Figures 2–4**). Early hyperfluorescence with leakage throughout the choroidal stroma along with loss of large choroidal vessels (dark vessels) in intermediate stages causes diffuse hyperfluorescence. Numerous hypofluorescent and homogeneous lesions (black dots) in the intermediate stage gradually become isofluorescent in the late stage signifies choroidal granulomas (**Figure 2**). Optic disc hyperfluorescence can also be seen in late phase.

Until recently, disease activity parameters in non-acute VKH were primarily clinical; nowadays, there is a trend toward posterior segment imaging to see signs of inflammation, as an indicator for considering systemic therapy [35].

Imaging	Initial phase	Convalescent phase	Prognosis	Role of differential diagnosis
Optical Coherence Tomography	• Exudative retinal detachment • Presence of typical fibrinous septa dividing the subretinal space into several compartments • Folds of the RPE without retinal pigment epithelial detachments • Undulations of the inner retinal layers • Markedly thickened choroid	• Progressive subfoveal choroidal thinning • Loss of small choroidal vessels with stromal scarring • Thinning of RPE layers and disruption of outer retinal layers in the area of RPE atrophy • Progressive posterior bowing on OCT during the follow-up period	• The eyes with RPE undulations were more likely to develop posterior recurrences and have worse vision at 12 months	• Differential diagnosis with acute bilateral central serous chorioretinopathy with multiple retinal pigment epithelial detachments
Fundus Autofluorescence	• Hyperautofluorescence in the macula mixed with hypoautofluorescence in the areas of serous retinal detachment • (mild and uniform pattern if presented within 1 week after onset, diffuse and mottled pattern for delayed presentation) [46]	• Scattered and widespread hyperautofluorescence, which gradually became evident and concentrated in the macula, partially resulting in some hypoautofluorescent dots at 6 months	• Non-invasive imaging helps accessing granular hyperautofluorescence in eyes with acute and/or persistent inflammation.	NA
Fundus Fluorescein Angiography	• Focal areas of delay in choroidal perfusion • Multifocal punctuate hyperfluorescent at the level of RPE • Pooling of dye within subretinal space in areas of neurosensory detachment, and • Optic disc head staining	• Multiple hyperfluorescent window defects without progressive staining in areas of focal RPE loss and atrophy. • Absent optic disc fluorescence	• The absence of early pinpoint peripapillary hyperfluorescence on pretreatment FFA is a poor prognostic factor for developing chronic VKH	• For atypical cases without clinically evident exudative retinal detachment, FFA revealed optic disc hyperfluorescence corresponding to bilateral optic disc swelling in 97% of eyes.
Indocyanine Green Angiography	• Delayed choroidal perfusion • Early choroidal stromal vessel hyperfluorescence and leakage	• Decreased choroidal stromal hyperfluorescence and disc hyperfluorescence	• Hypofluorescent dark dots and fuzziness of stromal vessel is sign of persisting activity • Early hyperfluorescent choroidal vessels and disc hyperfluorescence	• For atypical cases without clinically evident exudative retinal detachment, ICGA disclosed decreases in the number of large choroidal vessels and fuzzy

Imaging	Initial phase	Convalescent phase	Prognosis	Role of differential diagnosis
	• Hypofluorescent dark dots (HDD) during the intermediate phase, • Intermediate to late fuzzy vascular pattern and, • Optic disc hyperfluorescence		are indicative of more acute disease. • Thus, ICGA can be a sensitive marker of monitoring subclinical inflammation	choroidal vessels in more than 97% of eyes
Ultrasound Biomicroscopy	• Ciliary body edema with ciliochoroidal detachment • Shallow anterior chamber • Acute angle closure	• Ciliary thickness and area significantly increased in the recurrent group compared with the initial-onset group • Absence of ciliochoroidal detachment	NA	• Distinguish between angle closure in these eyes arising from ciliary edema rather from a primary angle-closure mechanism
B-scan Ultrasonography	• Diffuse, low- to medium-reflective choroidal thickening, predominating around optic nerve head • Serous retinal detachment, located inferiorly or in the • Posterior pole • Mild vitreous opacities • Thickening of the sclera and/or episclera posteriorly	• The amount of choroidal and scleral thickening, as well as the degree of serous elevation of the retina, decreased significantly after several weeks of therapy	NA	• Indicated for a typical presentation or with poor fundus visualization. • Differential diagnosis with posterior scleritis, where the scleral thickening has high reflectivity and is frequently accompanied by "I" sign—some of the characteristic features may be either absent or difficult to visualize in the presence of opaque media

Table 4.
Multimodal imaging in VKH, clinical findings, prognostic signs, and role of differential diagnosis.

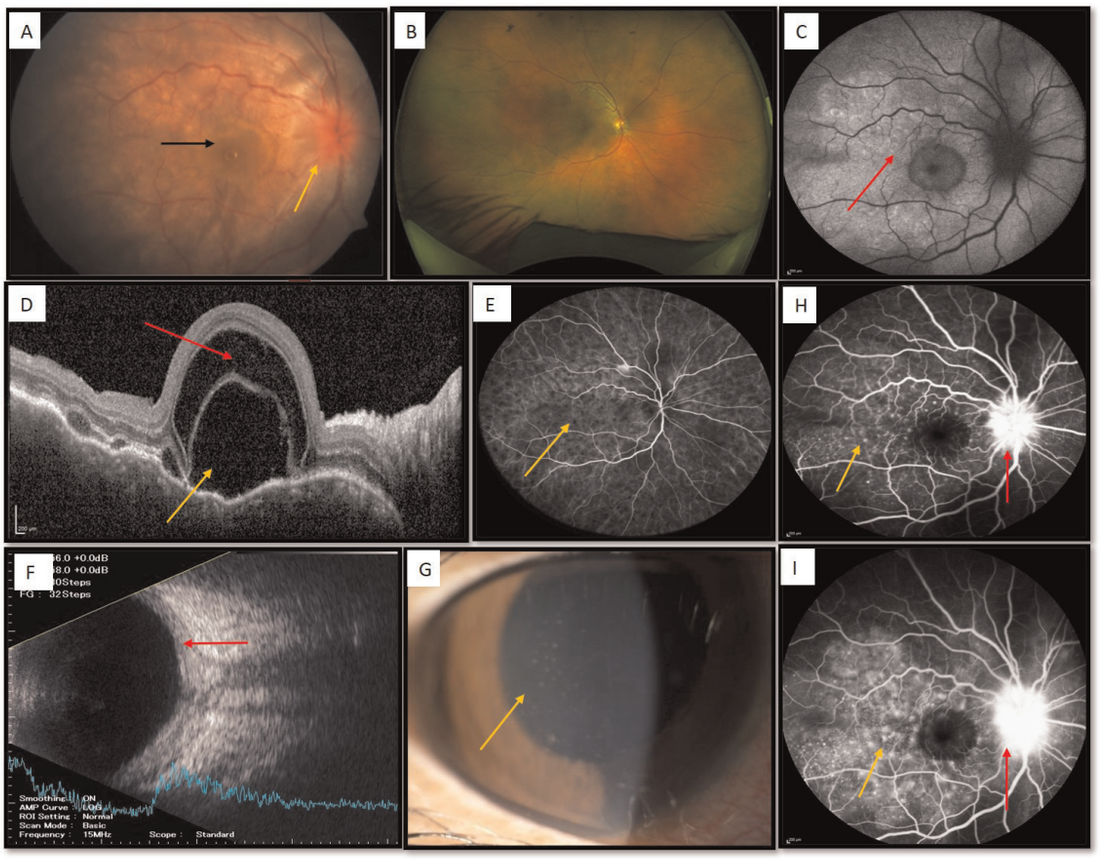

Figure 2.
Multimodal Imaging in VKH. (A) - Colour Fundus Photo shows SRF pocket (black arrow) with hyperemic disc (yellow arrow), (B) - Ultra widefield Optos Imaging showing "Sunset Glow Fundus", (C) - Fundus autofluorescence shows puntate hyperautofluorescence (red arrow), (D) - OCT shows SRF(yellow arrow) with bacillary layer detachment (red arrow) and choroidal undulations with increased choroidal thickness and obscured choroidal vessel details, (E) - ICGA showing hypofluorescence dots (yellow arrow), (F) - B scan ultrasonography showing increase in Retinal-Choroidal Scleral Complex (red arrow), (G) - Slit lamp photo showing granulomatous KPs (yellow arrow), (H & I) - Sequential fundus fluorescein angiogram (FFA) showing pinpoint hyperfluorescence (yellow arrow) increasing in late phases with pooling of dye in late phase (I) - with disc leakage (red arrow).

11.3 Fundus autofluorescence (FAF)

FAF reflects functional changes in RPE by visualizing lipofuscin or melanin or its compounds. Acute VKH shows hypoautofluorescence in areas corresponding to serous macular detachment. After subretinal fluid resolution, FAF showed hyperautofluorescence in the macular and peripapillary area corresponding to hypofluorescence on ICGA [53]. In patients treated with a first pulse of corticosteroids, areas of hyperautofluorescence disappear, whereas in patients who received delayed treatment, hyperautofluorescence persists, signifying changes in melanin distribution and lipofuscin [53]. In a retrospective study of 10 patients with chronic VKH using an ultra-wide-angle FAF, Heussen et al. demonstrated that peripheral changes in FAF images were inconsistent with color images [54]. VKH affects both the choroid and the RPE, so different FAF patterns are common.

11.4 Optical coherence tomography (OCT)

OCT has revealed the special feature of multifocal serous retinal detachments in acute VKH, with cystic spaces and membranous structures continuous to the ellipsoid

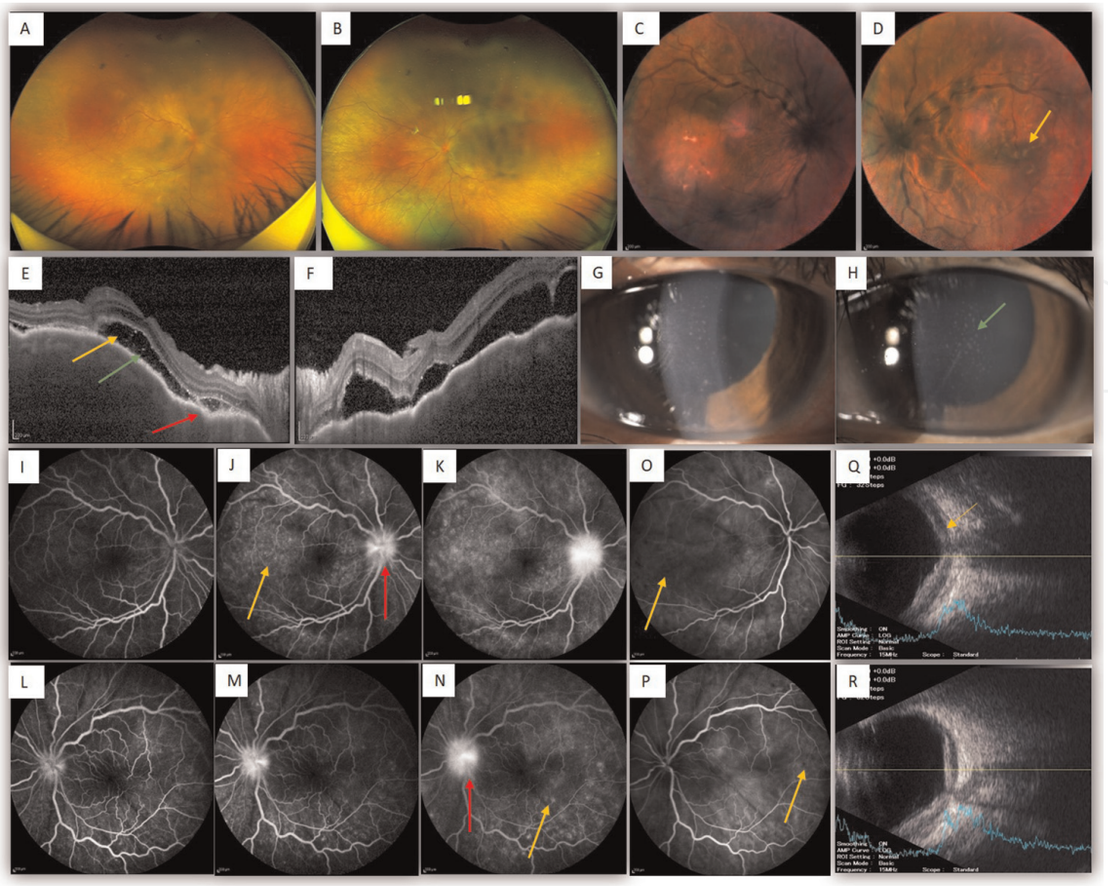

Figure 3.
Imaging in a case of bilateral VKH in a young 34 years old female. (A and B) – Ultra-wide-field Optos coloured fundus photo showing multiple SRF pockets with disc edema in right eye (A) and left eye (B), (C and D) - Multicolour image showing multiple SRF pockets with disc edema in both eyes (green arrow), (E and F) - Enhanced depth imaging EDI OCT showing subretinal fluid (yellow arrow), hyperreflective dots (green arrow), choroidal undulation with increased choroidal thickness with obscured choroidal details (red arrow) in both eyes. (G and H) – Slitlamp photo showing diffuse granulomatous KP (green arrow) in both eyes. (I,J,K,L,M,N) Fundus fluorescein angiogram (FFA) showing multiple pinpoint hyper fluorescence (yellow arrow) with disc leakage (red arrow) increasing over time from early to late phase (I- K – right eye, L-N – left eye), (O and P) Indocyanine green angiogram (ICGA) showing diffuse hypo fluorescence due to blockage of choroidal fluorescence (yellow arrow), (Q and R) B scan Ultrasound of right eye (Q) and left eye (R) showing increase in retinal–choroidal–scleral complex with subretinal exudation yellow (arrow).

zone (junction of the internal and external segments of the photoreceptors). About 45% of the examined eyes showed a splitting of retinal layers along the IS/OS line near cystoid spaces involving the fovea. All of these abnormal features were seen below the external limiting membrane, that is, in the outer photoreceptor layer [55]. Several authors hypothesized that these threads are formed by fibrin and disrupted outer segments of the photoreceptors. Many studies have also shown the presence of "bacillary layer detachment" which is defined as a separation of the retinal photoreceptor layer into the myoid inner layer and ellipsoid outer layer, as a feature of acute VKH (**Figures 2** and **4**). Other OCT findings in the acute stage are intraretinal edema, multiple subretinal fluid pockets, choroidal folds (RPE undulations), and choroidal hyperreflective dots among others (**Figures 2–4**) [55]. Rapid resolution is observed in OCT after high-dose systemic corticosteroids [56]. Several OCT parameters were associated with a worse prognosis, such as "separation" of the outer segment and inner segment of the photoreceptors, the height of the serous retinal detachment, and RPE undulation [57].

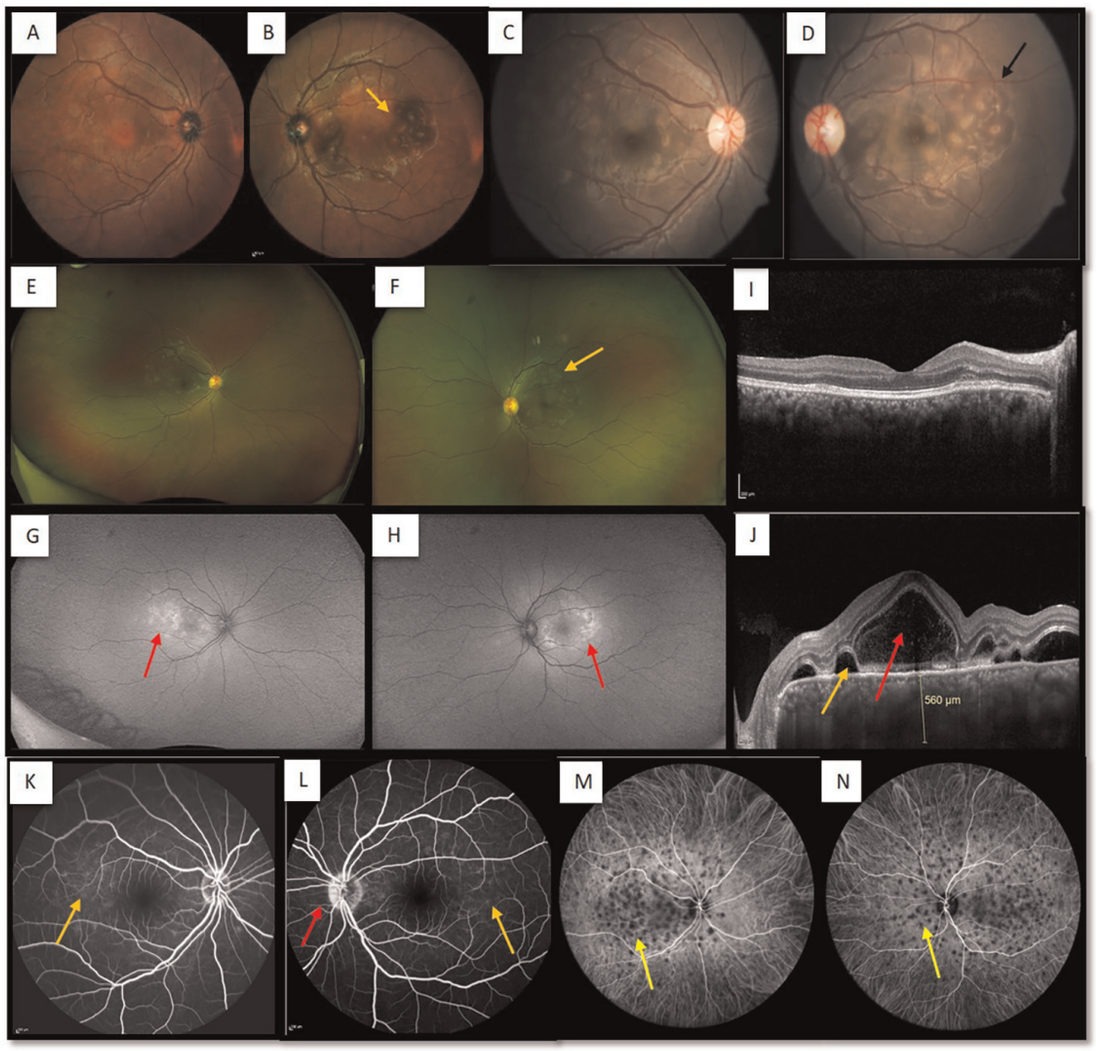

Figure 4.
Imaging of Unilateral (left eye) VKH. (A and B) Multicolour Imaging showing SRF pockets (yellow arrow) in Left Eye, (C and D) Fundus Photo showing multiple orangish lesions and SRF pockets (black arrow) in left eye, (E and F) Ultra widefield optos image showing multiple altered pigmented dots in macula of left eye (yellow arrow). (G and H) – Fundus Auto Fluorescence (FAF) showing hyperautofluorescence in both eyes (red arrow) documenting the importance of FAF in detecting changes even in very early phase of disease like in the right eye. (I and J) OCT image showing bacillary layer detachment (red arrow) and SRF pockets (yellow arrows) in left eye with increased choroidal thickness and normal retinal layers in right eye, (K and L) Fundus fluorescein angiogram (FFA) images showing disc hyperfluorescence (yellow arrow) with pin point hyper fluorescence (red arrow) in left eye, (M and N) Indocyanine green angiogram (ICGA) shows multiple hypo-fluorescent dots (yellow arrows) in both eyes documenting importance of ICGA in detecting changes even in very early phase of disease like in right eye.

OCT imaging of chronic VKH shows RPE cell clumping and damage to inner and outer photoreceptor-segment junctions. Patients with chronic VKH and "sunset glow" fundus have been studied by Vasconcelos-Santos et al. who revealed normal retinal architecture in the "sunset fundus" region, thinning of the RPE/Bruch membrane in the atrophic regions, and thickening of the RPE/Bruch membrane covering the pigmented scar regions on spectral-domain OCT [58].

11.5 Enhanced-depth imaging spectral-domain OCT (EDIOCT)

EDI-OCT is a non-invasive quantitative method that can be used to determine the extent of the choroidal inflammatory response during follow-up [58].

This modality has improved our ability to visualize the choroid and its thickness [58]. Choroidal thickening is marked in acute phase with increased inflammatory infiltrates and exudates (**Figures 2** and **4**). Corticosteroid therapy rapidly reduces choroidal thickening. According to Da Silva et al., in patients with long-term VKH, the choroid is thinner than normal counterparts [45, 60]. Additionally, the choroid is thicker in patients with recurrent inflammation compared to individuals with quiescent disease [60]. The thinning of the choroid in the center of the fovea was inversely proportional to the duration of the disease.

11.6 Ocular ultrasonography (US)

Ultrasound can be an important adjunct to diagnosis, as it can differentiate posterior scleritis, diffuse malignant melanoma, leukemia, and lymphoma [61]. It is useful when media opacity obscures fundus view, appearance is abnormal, and/or extraocular signs are absent. High-resolution ocular ultrasound can demonstrate choroidal thickening in subclinical VKH and can also help monitor treatment response. However, due to its image resolution (100 μm versus 7 μm in SD-OCT and 5 μm in EDI-OCT), US imaging does not add much information where subtle changes occur. The following sonographic signs have been described in VKH by Forster et al. [61]:

1. Diffuse choroidal thickening with low to moderate reflectivity;

2. Serous retinal detachments around or below the posterior pole;

3. Vitreous opacities without posterior vitreous detachment (PVD);

4. Scleral or episcleral thickening.

Ultrasound biomicroscopy (UBM) helps in the detailed evaluation of the ciliary body and iris. Anterior chamber shallowing can occur acutely due to ciliochoroidal detachment and ciliary body thickening. This can lead to anterior displacement of the iris-lens diaphragm, simulating acute angle-closure glaucoma [62].

11.7 Electrophysiological testing

It is helpful to monitor the course of the disease as well as demonstrate the extent of functional compromise resulting from inflammatory damage to retinal components using electroretinograms (ERGs) [63, 64]. ERG abnormalities have been described in VKH patients with extensive chorioretinal atrophy. Correlations between fundus changes and ffERG in patients with late stage VKH were nicely demonstrated by DaSilva et al. [45]. Patients with more severe fundus-based disease presented more severe retinal dysfunction [45]. As a result, both scotopic and photopic amplitudes are diffusely diminished, but implicit times remain unchanged [45].

12. Differential diagnosis

12.1 Sympathetic ophthalmia

Sympathetic ophthalmia is an autoimmune condition usually seen after penetrating trauma or surgery to the eye, exposing ocular uveal tissue molecules as antigenic material leading to the immune system-mediated inflammatory response. This condition may cause bilateral non-necrotizing granulomatous uveitis (**Table 5**) [65, 66].

12.2 Choroidal melanoma

Choroidal melanoma may present with serous retinal detachments, and non-pigmented melanomas may appear as subretinal pigmentary loss which is also seen in VKH [65, 67–69].

12.3 Infectious posterior uveitis

Syphilis, tuberculosis, and endogenous endophthalmitis may manifest as subretinal nodules, intraocular inflammation, and serous retinal detachment mimicking VKH [70, 71]. It is necessary to exclude infectious etiologies before starting immunosuppressive therapy to prevent the worsening of the disease.

12.4 Alport and cogan syndromes

Alport syndrome and Cogan syndrome may manifest as bilateral auditory abnormalities and retinal manifestations. Alport syndrome shows choroidal thickening and significant inner retinal changes. Cogan syndrome is characterized by retinal vasculitis without any subretinal changes [72, 73].

Sympathetic ophthalmia	Previous penetrating ocular trauma or intraocular surgery
Non-infectious choroiditis	Acute posterior multifocal placoid pigmentepitheliopathy (APMPPE) Birdshot chorioretinopathy Multifocal choroiditis and panuveitis (MCP) Multiple evanescent white dot syndrome (MEWDS)
Infectious choroiditis	Syphilis Tuberculosis
Other inflammatory disorders	Posterior scleritis Sarcoidosis Lupus choroidopathy
Non-inflammatory disorders	Hypertensive choroidopathy Bilateral diffuse melanocytic hyperplasia Uveal effusion syndrome Specific hypertensive illness of gestation
Masquerade syndrome	Carcinoma Leukemia Lymphoma Metastasis

Table 5.
Differential diagnosis of Vogt-Koyanagi-Harada disease.

12.5 Sarcoidosis

Sarcoidosis is the distinct cause of posterior uveitis, demonstrating periphlebitis and "candle wax dripping" on fluorescein angiography, thus differentiating it from VKH [74].

12.6 Systemic lupus erythematosus chorioretinopathy

Serous retinal detachments may be present in lupus choroidopathy, but the absence of choroidal thickening with specific systemic features helps in differentiating this disease [75].

13. Treatment

The acute stage of VKH syndrome responds to early and aggressive corticosteroid treatment. Initial dosages of high dose oral or intravenous corticosteroids are standard dosage regime without any significant difference in visual acuity outcomes or the

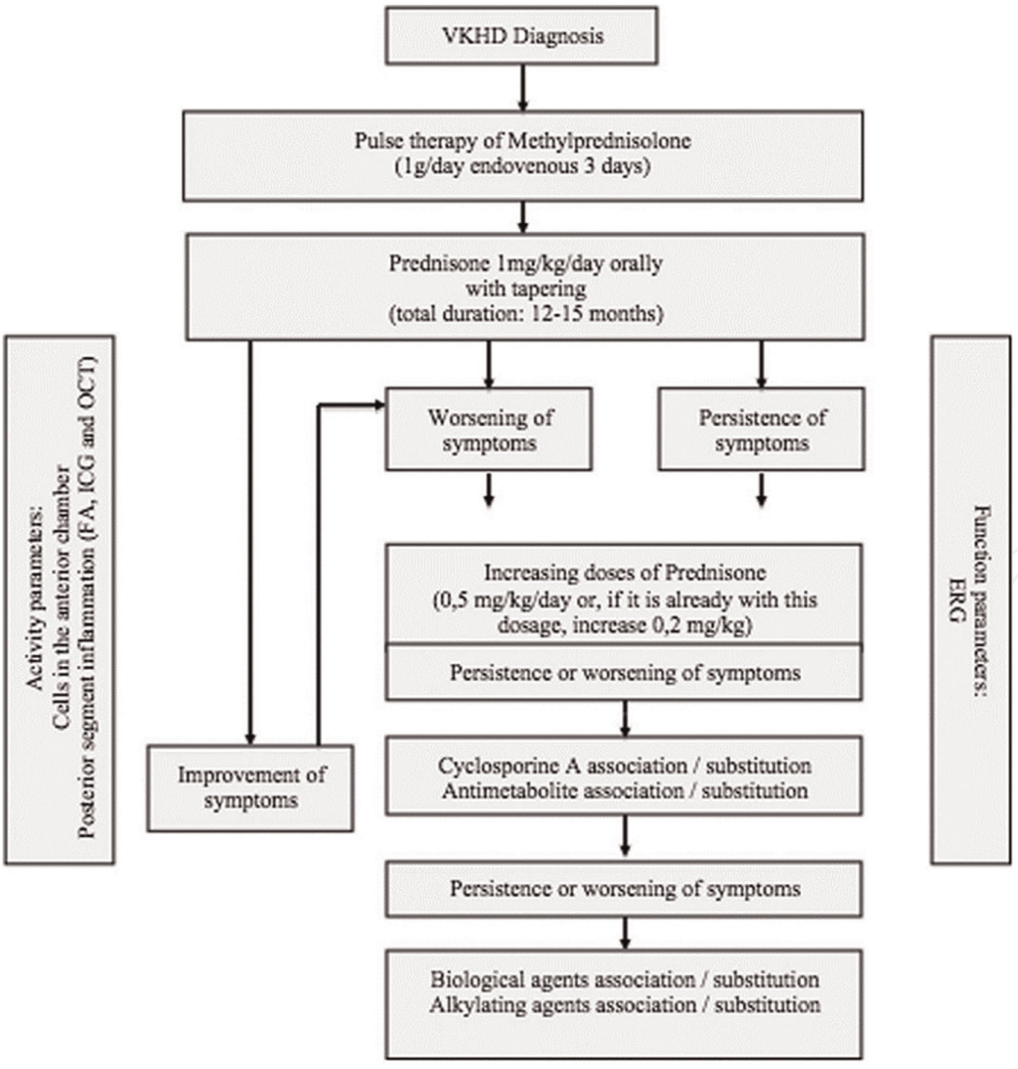

Figure 5.
Schematic flowchart for treatment protocol.

Drug	Dosage	Main side effects
Prednisone or prednisolone	1–1.5 mg/kg/day, gradual tapering along a minimum 6 month-period	Hyperglycemia, hypertension, osteoporosis, Cushingoid appearance, myopathy, cataract, glaucoma
Pulse therapy of methylprednisolone	1 g/day during 3 days, followed by oral prednisone	
Antimetabolites		
Azathioprine	1–2.5 mg/kg/day	Myelosuppression, gastrointestinal disturbances, infection
Methotrexate	7.5–25 mg/week	Nausea, vomiting, abnormalities in liver function tests, infection
Mycophenolate mofetil	1–3 g/day	gastrointestinal disturbances with diarrhea, infection
Calcineurin inhibitors		
Cyclosporine A	Up to 5 mg/kg/day, trough 0.1–0.2 μg/L (whole blood)	Nephrotoxicity, heptatoxicity, hyperglycemia, hypertension, hirsutism, gum hyperplasia, and neurological disorders
Biological agents		
Infliximab (intravenous)	5 mg/kg at 0.2 and 6 weeks, followed by 5 mg/kg every 6–8 weeks	reactivation of latent tuberculosis, lymphoproliferative diseases
Adalimumab (Subq)	40 mg every other week	Headache, infection
Alkylating agents		
Cyclophosphamide	1–2 mg/kg/day	Myelosupression, hair loss, nausea, vomiting, loss of fertility, cancer risk, infection, bladder toxicity

Table 6.
Treatment of Vogt-Koyanagi-Harada disease: drugs, dosage, and main side effects.

development of visually significant complications. Initiating immunosuppressant medication earlier can achieve more prompt inflammatory control (**Figure 5**). Slow tapering of systemic steroid along with immunosuppressants can significantly reduce chance of recurrent episodes (**Table 6**).

13.1 Systemic treatment

13.1.1 Corticosteroids

Systemic high dose corticosteroids are still the cornerstone of initial treatment for VKH. Treatment usually begins with early, high-dose systemic corticosteroids, which has a very good response. These are tapered slowly, usually over 6 months. In severe cases, some have treated with intravenous high-dose pulsed steroid therapy (1 mg of methylprednisolone) followed by oral steroids (1 mg/kg/day). Duration of treatment and rate of drug tapering are case-specific, depending on the clinical response (as shown in flowchart of **Figure 5**). Despite apparent control of clinical signs, suboptimal treatment during the post-acute period is associated with persistent choroidal inflammation. Many studies have suggested that the use of steroids for a longer duration

with slow tapering prevents the reactivation of disease. Associated anterior segment inflammation should also be treated with topical prednisolone 1% and cycloplegic drugs to lessen inflammation and to reduce pain and synechiae. Topical steroids should be tapered according to the response [2].

13.1.2 Immunomodulatory therapy

Despite adequate treatment with systemic corticosteroids, many patients experience recurring episodes of inflammation and structural complications. Likewise, chronic corticosteroid therapy is associated with systemic and ocular complications. As a result, many uveitis specialists prescribe non-steroidal immunomodulatory therapy (IMT) to treat VKH at the onset of the disease, both as steroid sparing therapy and to prevent recurrence of disease. Presumably, early and aggressive immunosuppressive therapy will prevent the autoimmune process, the so-called primary reaction, and will also have a significant effect on refractory uveitis. The use of immunomodulatory therapy is associated with a reduced risk of vision loss in eyes with VKH.

Immunomodulatory therapy used in the management of VKH has been recommended as follows (**Table 6**).

- Cyclophosphamide 1–2 mg/kg/day.
- Chlorambucil 0.1–0.2 mg/kg/day.
- Azathioprine 1–2.5 mg/kg/day.
- Cyclosporine 5 mg/kg/day.
- Tacrolimus (FK 506) 0.1–0.15 mg/kg/day.
- Mycophenolate mofetil 2 mg/day.

This disease may have an immunopathologic basis in T cell-mediated damage to melanocytes as discussed previously. Several studies support the use of cyclosporine in refractory cases, either alone or with low-dose steroids [2].

13.1.3 Biologic agents

In the treatment of VKH, the main biologic agents are anti-TNF-α drugs. Several case series have reported excellent results with infliximab. Adalimumab, a human monoclonal antibody against TNF-α, has been used in refractory cases. Daclizumab, a humanized monoclonal antibody directed against the IL-2 (CD25) receptor, has shown potential in a number of reports for the treatment of non-infectious intermediate and posterior uveitis [2].

13.2 Local drug delivery

The disease is multi-organ inflammatory, so local treatment alone is not recommended. Such treatment will not eliminate the extraocular manifestations, particularly meningismus and tinnitus. Further, local treatment will not affect the severity of vitiligo or polio [2].

Topical steroids and cycloplegics are used commonly as first-line agents. Topical mydriatics and cycloplegics are used to prevent ciliary spasm and also to break and prevent the formation of posterior synechiae. Topical corticosteroid drops are most often used for anterior uveitis, but may also be beneficial in patients with panuveitis. When inflammation is severe, the hourly dosage is advised and tapering down to once a day as the inflammation improves. Topical steroid medication is associated with side effects such as ocular hypertension and the development of cataracts. Some topical preparations, such as fluorometholone 0.1%, rimexolone 1%, and loteprednol etabonate 0.5%/0.2%, have lower side effects than prednisolone acetate 1% and dexamethasone 0.1% and difluprednate 0.05%; however, the latter drugs are more effective in controlling anterior uveitis [2].

Local steroids in the form of intravitreal or subtenon injections are useful adjuncts to oral and immunosuppressive therapy. Fluocinolone acetonide (Retisert) implants have been used in chronic VKH and appear to reduce the amount of oral corticosteroids needed to control ocular inflammation, but effectiveness of oral corticosteroids could not be completely eliminated. Dexamethasone (Ozurdex) implant has also been used as alternative with successful control of refractory uveitis in some patients [2].

14. Complications

VKH complications include cataract in 15–45% of eyes, glaucoma in 27–33% of eyes, posterior synechiae in 23.4% of eyes, choroidal neovascular membrane in 3–11% of eyes. In rare instances, subretinal fibrosis (6%) and band keratopathy (5.2%) can also be seen [1].

14.1 Cataract

Steroid therapy for longer than 6 months and chronic recurrent anterior segment inflammation appeared to be the significant determinants of cataract development [1]. Cataract extraction should only be done after the uveitis has completely been treated and eye has been quiet for at least 3 months. Preoperative oral and topical corticosteroids should be started. Postoperatively, slow tapering of steroids and the use of topical NSAID drops to control cystoid macular edema are recommended [2].

14.2 Glaucoma

Acute angle closure glaucoma has been reported, presumably as a result of ciliary body edema with anterior displacement of the lens-iris diaphragm in the acute stage of the disease. The risk of developing open-angle glaucoma secondary to corticosteroid increases during treatment [1]. When IOP is high, IOP should be lowered as soon as possible. This can be achieved by trying to reduce oral and topical steroids if the inflammation is controlled or treated with antiglaucoma drugs. Surgery should be performed if medical treatment is ineffective and intraocular pressure continues to rise [2]. Laser iridotomy appears to be less successful than surgical iridectomy in patients with angle closure secondary to pupillary block.

When filtering surgery is needed, supplementation with 5-fluorouracil or mitomycin C may increase the success rate of trabeculectomy. In patients with persistent inflammation, implantation drainage device may be the first choice [2].

14.3 Choroidal neovascularization and choroidal neovascular membrane

Choroidal neovascularization (CNV) is an important cause of late visual loss in patients with VKH. The presence of fundus pigmentation, chronic recurrent inflammation, and the recurrence of major anterior segment inflammation appear to be the risk factors for the development of CNV in VKH. CNV tends to develop in the peripapillary, subfoveal, and extrafoveal regions, where foci of inflammation seem to concentrate. Several treatment modalities including laser photocoagulation, photodynamic therapy, surgical excision, intravitreal steroid, and anti-vascular endothelial growth factor (anti-VEGF) therapy have been employed in the treatment of CNV secondary to VKH disease. Anti-VEGF injections have largely replaced PDT as the main treatment modality for CNV in recent years [1].

14.4 Subretinal fibrosis

Subretinal fibrosis is described in 8–40% of VKH cases, but is more common in chronic or recurrent cases. The most common locations are the peripapillary and extrafoveal regions. Histopathological findings show subretinal fibrosis, RPE cell metaplasia, and choroidal inflammatory cells. Fibrosis is induced when RPE cells, Müller cells, and choroidal fibroblasts interact with cytokines, immunoglobulins, and cellular mediators produced by T lymphocytes. The presence of subretinal fibrosis in VKH is associated with poor visual outcome [22].

15. Prognosis

VKH is a serious inflammatory disease, but prompt and aggressive treatment can lead to better visual outcomes. The use of corticosteroids and immunosuppressive agents has greatly improved the visual outcome in VKH patients [1]. Studies suggest final visual acuity can range from 20/20 to 20/50. Review of literature suggests starting treatment early and to treat with high-dose corticosteroids for at least 6 months. Treatment with steroid-sparing agents, including methotrexate, cyclosporine A, mycophenolate mofetil, or newer biologics, allows patients to use low-dose steroids while maintaining control of disease (**Figure 5**). The disease affects multiple organs, thus requiring coordination with other specialties, such as rheumatologist and neurologist. Several imaging modalities can be used to evaluate subclinical disease, including ICG angiography, fundus autofluorescence, and OCT. It can result in a longer treatment duration, but it results in fewer instances of sunset glow fundus and choroidal thinning [2].

Good initial visual acuity leads to better final visual outcomes, and initiating treatment in the acute phase yields more favorable outcomes than treating the disease in the chronic relapsing phase. Final visual outcome is better in eyes with fewer complications. Cataracts and glaucoma are the most common complications of VKH and can be treated surgically as long as the uveitis is controlled with medication. Perioperative management of uveitis is an essential key in VKH.

16. Future

16.1 Optical coherence tomography angiography (OCTA)

More recently, optical coherence tomography (OCTA) angiography has emerged as a useful non-invasive imaging technique that provides in-depth detailed reconstructions of the retinal-choroidal microvasculature using intraluminal blood flow as an intrinsic contrast [46].

OCTA was found to be a sensitive tool for detecting abnormalities such as dynamic changes in the choriocapillary layer, manifesting as multiple dark areas of choriocapillary loss, indicating the presence of "flow voids" in VKH [76]. OCTA has also recently been shown to be an effective tool for identifying changes at choriocapillary level in eyes with acute VKH disease and monitoring disease regression, relapse, and persistence in combination with clinical examination and other imaging modalities [76].

OCTA imaging can aid in diagnosis by identifying features of true choriocapillaris ischemia in eyes with acute VKH disease. Further research is needed to determine the role of OCTA in the management of VKH.

17. Conclusion

In conclusion, Vogt-Koyanagi-Harada disease is a severe bilateral granulomatous panuveitis manifesting as serous retinal detachment, disc hyperemia, and vitritis associated with headaches, nausea, meningeal irritation, alopecia, vitiligo, and hearing disability. The extraocular manifestations of the disease are variable, but early detection and treatment are essential key. SD-OCT, fundus fluorescein angiography, and B-scan ultrasonography are useful in diagnosing this disease. No previous history of trauma helps to distinguish it from sympathetic ophthalmia. The disease is thought to be caused by autoimmunity against the peptide tyrosinase produced by melanocytes, which is also responsible for the depigmentation in this disease. Initial treatment consists of high-dose corticosteroids, followed by steroid-sparing therapy and slow tapering long-term corticosteroids, with focus on controlling the inflammatory response to prevent sequelae like sunset glow fundus, cataract, glaucoma, and rarely choroidal neovascularization, which can limit ultimate visual potential [2]. The overall prognosis is fair, with substantial number of patients achieving a visual acuity of 20/40 or better with early and aggressive corticosteroid treatment.

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The authors declare that they have no financial interests related to the work described in this chapter.

Abbreviations

SD-OCT	spectral-domain optical coherence tomography
ICGA	indocyanine green angiogram
FFA	fundus fluorescein angiogram
FAF	fundus autofluorescence

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