Vogt–Koyanagi–Harada Disease

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Abstract

Vogt–Koyanagi–Harada disease is rare granulomatous inflammatory disease that affects pigmented structures, such as choroid, inner ear, meninges, hair, and skin. Ocular involvement is characterized by bilateral, diffuse, granulomatous panuveitis and exudative retinal detachment. Vogt–Koyanagi–Harada disease has usually a benign course if diagnosed early and adequately treated. Imaging remains an integral part of diagnosis of Vogt–Koyanagi–Harada disease and plays an important role in diagnosis, quantification of inflammation, and disease monitorization.

Vogt–Koyanagi–Harada (VKH) disease is an idiopathic bilateral chronic granulomatous panuveitis that may be associated with central nervous system (CNS), auditory, and integumentary manifestations.

Three researchers described separately the different spectrum of this single systemic inflammatory condition and hence the disease named so. Vogt [1] and Koyanagi [2] described bilateral anterior uveitis associated with vitiligo, alopecia, and poliosis and Harada [3] described five patients with posterior uveitis with exudative retinal detachment and cerebrospinal fluid (CSF) pleocytosis.

The prevalence of VKH disease is variable among different populations. In Japan, VKH disease represents 10.1% of all uveitis cases [4] whereas the disease

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J. Chhablani et al. (eds.), *Retinal and Choroidal Imaging in Systemic Diseases*,
https://doi.org/10.1007/978-981-10-5461-7_12

accounts only for 2% of all uveitis cases in India [5]. VKH disease is believed to affect people with certain genetic predispositions and pigmented races like Asians, Hispanics, Native Americans, and Asian Indians. However, the disease is less common in blacks from sub-Saharan countries [6]. The disease usually occurs in patients between the ages of 20 and 50 years, but any age group can be affected. Women are affected slightly more frequently than men. The etiology of VKH disease remains largely idiopathic. It is thought to be an autoimmune process directed against proteins related to stromal choroidal melanocytes [7].

VKH disease typically consists of four distinguished consecutive phases—prodromal, uveitic, convalescent, and chronic recurrent. The prodromal phase usually lasts 3–5 days and is characterized by neurologic and auditory manifestations, including headaches, tinnitus, neck stiffness, and hearing loss. In this stage, cerebrospinal fluid may reveal pleocytosis. Acute uveitis stage lasts for several weeks and is characterized bilateral posterior granulomatous uveitis. The underlying pathologic process primarily manifests as diffuse stromal choroiditis and exudative detachment of the neurosensory retina secondary to diffuse choroidal inflammation is common. As the inflammation extends anteriorly patients develop acute bilateral granulomatous iridocyclitis and often shallow anterior chamber secondary to ciliary body edema and suprachoroidal fluid collection. Convalescent stage is characterized by depigmentation of the integument and choroid and can manifest as depigmented fundus, vitiligo, alopecia, and poliosis. Approximately 17–73% of patients may progress to recurrence or chronicity, which is characterized by recurrent episodes of anterior uveitis. Ocular complications are common in convalescent and chronic stages (Table 12.1).

The diagnosis of VKH disease is usually clinical. Revised diagnostic criteria for VKH, created by a panel of experts convened at an international workshop in 1999, classifies the disease into three categories: complete, incomplete, and probable VKH [6] (Table 12.2).

Table 12.1 Ophthalmic manifestations of VKH

Clinical phase	Ophthalmic manifestations
Prodromal phase	Uncommon
	Optic nerve involvement can occur [8]
Acute uveitis phase	• Bilateral granulomatous uveitis, can be asymmetrical • Diffuse stromal choroiditis • Ciliochoroidal detachment, ciliary body edema • Serous retinal detachment • Optic disc edema
Chronic (convalescent) stage	• Depigmentation of choroid: “sunset glow fundus” • Dalen-Fuchs nodules • Sugiura sign: perilimbal vitiligo
Chronic recurrent stage	High chances of developing complications • Cataract • Glaucoma • Choroidal neovascular membranes (CNVM), and • Subretinal fibrosis

Table 12.2 Revised diagnostic criteria of Vogt–Koyanagi–Harada disease proposed by the International Nomenclature Committee [6]

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:* I. Evidence of diffuse choroiditis (with or without anterior uveitis, vitreous inflammatory reaction, or optic disc hyperemia), which may manifest as (A) focal areas of subretinal fluid, or (B) bullous exudative retinal detachments. II. If equivocal fundus findings, then both: A. Fluorescein angiography showing focal delayed choroidal perfusion, multiple areas of pinpoint leakage, large placoid areas of hyperfluorescence, pooling within subretinal fluid, and optic nerve staining; B. Ultrasonography showing diffuse choroidal thickening without evidence of posterior scleritis. B. *Late manifestations of disease:* I. History suggestive of prior presence of early findings noted in 3A and either (II) or (III) below, or multiple signs from (III) below: II. Ocular depigmentation: either (A) sunset glow fundus or (B) Sugiura sign. III. Other ocular signs including (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 resolve by time of evaluation):* a. Meningismus (malaise, fever, headache, nausea, abdominal pain, stiffness of the neck and back, or a combination of these factors); note that headache alone is not sufficient to meet definition of meningismus. b. Tinnitus c. Cerebrospinal fluid pleocytosis
5. *Integumentary findings (not preceding onset of central nervous system or ocular disease):* a. Alopecia, or b. Poliosis, or c. Vitiligo.

Complete VKH: criteria 1–5 must be present
Incomplete VKH: criteria 1–3 and either 4 or 5 must be present
Probable VKHD (isolated ocular disease): criteria 1–3 must be present

12.1 Fundus Autofluorescence (FAF)

Fundus autofluorescence (FAF), based on excitation of inherent fluorophores like lipofuscin, which accumulate in retinal pigment epithelium (RPE) is a good indicator of RPE activity and metabolic stress. Being a non-invasive and rapid method, it has become very popular over the last decade.

RPE is extensively damaged in VKH, the posterior pole being involved in the acute phase and the periphery also involved in the convalescent and the chronic recurrent phase. FAF features in acute VKH were described by Koizumi et al. [9]. They described two distinct patterns; the first pattern was of mild hyperautofluorescence in patients who received early intense immunosuppression and the second pattern of widespread and more hyperautofluorescence seen in patients who did not

receive treatment or received too late. Thus, FAF can help in monitoring and prognosticating acute phase of VKH.

In chronic VKH, hypoautofluorescence is mainly seen in areas of atrophy and scars, while hyperautofluorescence is mainly seen in areas of subretinal fluid in cases of recurrences [10, 11]. Vasconcelos-Santos et al. [10] have demonstrated the combined use of FAF and SD-OCT for evaluation of RPE and outer retinal changes and detecting subclinical recurrences in chronic VKH patients. Heussen et al. [11] have used wide field FAF to describe peripheral lesions in chronic VKH patients and includes multifocal hypofluorescent spots, focal hyperfluorescent spots, and a unique lattice-like hyperfluorescent streak. These changes may correlate with the proliferation of RPE leading to an increase in the total amount of fluorophores or their accumulation in the outer retina. Thus, FAF may be used as a supplement in monitoring RPE changes during the chronic phase as it is noninvasive and therefore can be repeated at closer intervals (Fig. 12.1).

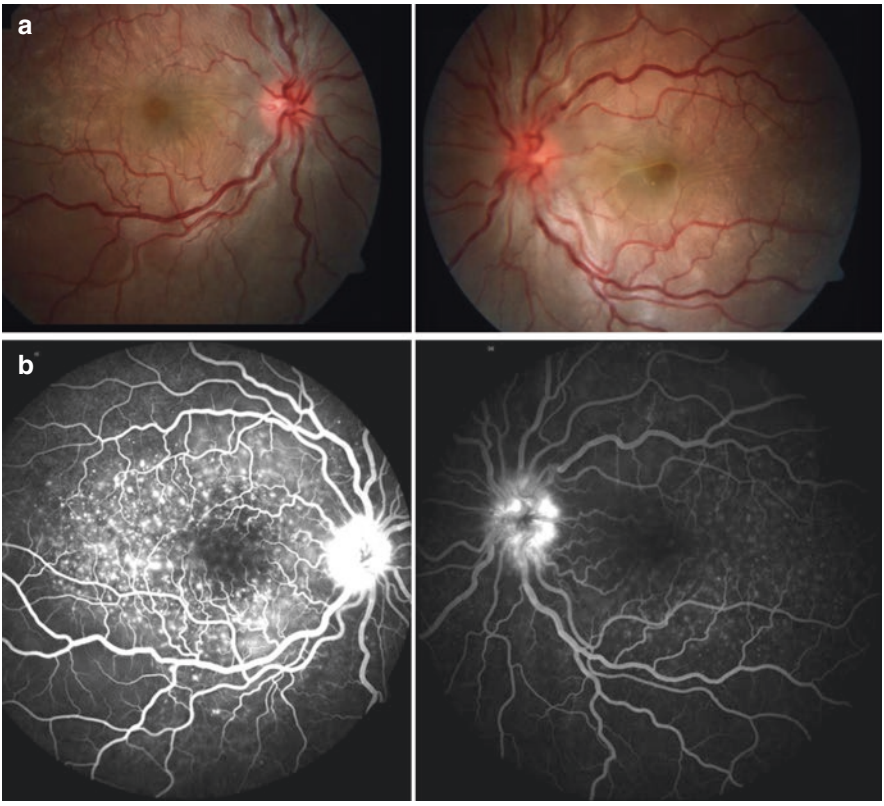

Fig. 12.1 This patient illustrates the classic findings of VKH. (**a**) Note the bilateral multiple serous detachments of the neurosensory retina. Also note the erythematous discs. (**b**) Fundus fluorescein angiography showed pinhead hyperfluorescent spots in early phase and (**c**) placoid pooling of the dye in late phase

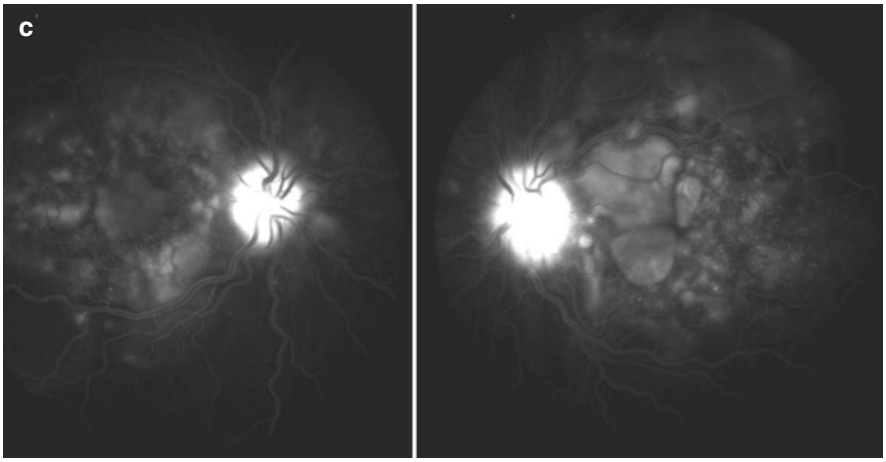

Fig. 12.1 (continued)

12.2 Fundus Fluorescein Angiography (FFA)

Fluorescein angiography is the most widely used ancillary investigation and helps to rule out similarly presenting conditions like central serous chorioretinopathy (CSCR), which is very important as the management of both the conditions is paradoxical.

In VKH, severe primary choroidal inflammation leads to spilling over of subretinal fluid to the retina, which in turn leaks profusely through the RPE causing an exudative retinal detachment. During the acute phase of VKH, the inflamed choroidal vessels become dilated and leak fluid, especially around the posterior pole. The choroidal inflammation usually spares the choriocapillaries but involves medium sized vessel. In majority of the patients, there is a delay in the choroidal filling, which is seen as spotted choroidal hyperfluorescence [12]. The RPE cells around the peripapillary region and macula are also inflamed during the acute phase of the disease. This is manifested as characteristic multiple punctate hyperfluorescent dots at the level of the RPE, often called as "stars at night" appearance. In subsequent phases of angiogram, the inflamed RPE allows the dye to leak and accumulate in the subretinal space over the posterior pole. This is manifested as placoid pooling of the dye and highlights the extent of exudative retinal detachment in the late phase of the angiogram. Optic disc hyperfluorescence is another important finding in angiogram and is seen in about 70% of patients in acute phase of the disease [13] (Fig. 12.2).

In the chronic recurrent stage, there are multiple hyperfluorescent RPE window defects and blocked fluorescence due to RPE hyperplasia. There can be alternating hyper- and hypofluorescence from RPE alterations, sometimes referred to as "moth-eaten" scars and "salt and pepper" pattern [14] (Fig. 12.3).

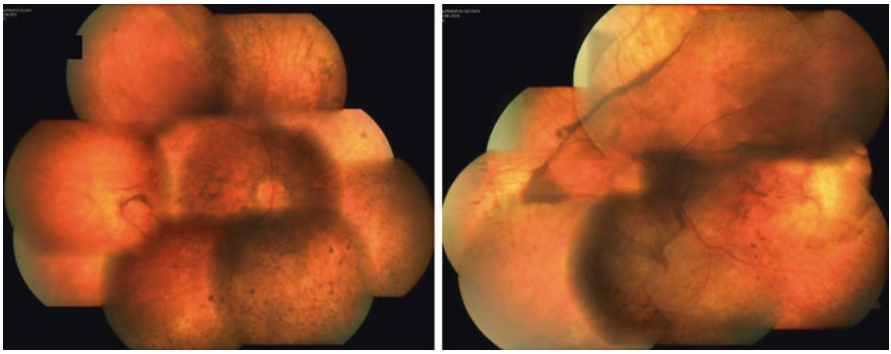

Fig. 12.2 Sunset glow fundus in VKH

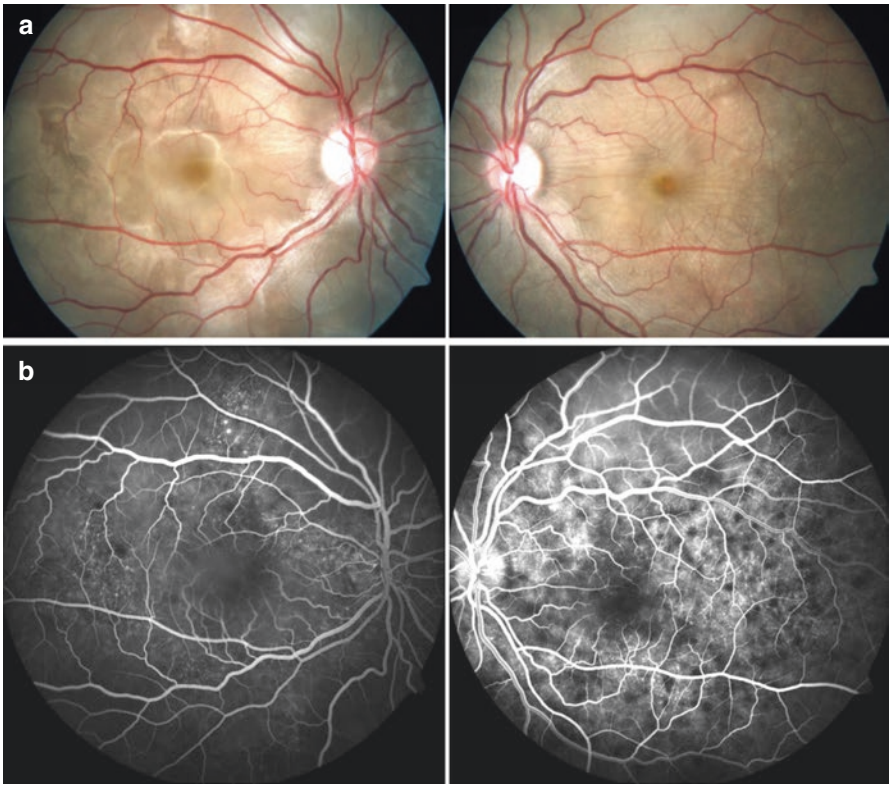

Fig. 12.3 This 54-year-old lady presented with headache, neck pain, and loss of vision in both eyes. Clinical examination revealed pockets of subretinal fluid and choroidal folds in both eyes (**a**). Early phase of the angiogram showed pin-head hyperfluorescent leaks (**b**) which increased and manifested as placoid pooling of the dye in late phase (**c**)

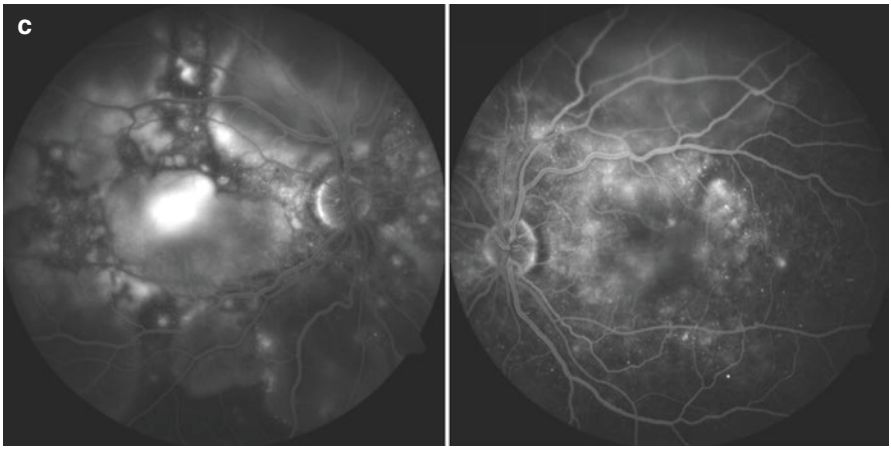

Fig. 12.3 (continued)

Table 12.3 FFA features in VKH and their clinical correlation

FFA features	Clinical correlation
Spotted choroidal hyperfluorescence	Choroidal inflammation
Early pinpoint hyperfluorescence	Breakdown of blood ocular barrier due to inflammation
Disc hyperfluorescence	Inflammation of the optic disc
Late placoid pooling of the dye	Subretinal fluid or exudative detachment
Spotted hyper and hypofluorescence (salt and pepper pattern)	RPE damage
Choroidal hypofluorescence	Delayed choroidal filling
Mixed band of hyper and hypofluorescence	Choroidal folds

Choroidal folds, undulations in the retinal pigment epithelium (RPE), the Bruch membrane, and inner aspects of the choroids are usually indiscernible on routine ophthalmoscopy in VKH. Recently this clinical manifestation was reported by several groups and thought to be a sign of severe choroidal inflammation. Wu et al. [15] observed choroidal folds in VKH to show hypofluorescence on FFA instead of alternating hypofluorescent and hyperfluorescent bands seen in choroidal folds in other clinical entities [16]. They postulated that compaction of RPE in the troughs decreases transmission of choroidal fluorescence and causes hypofluorescence, whereas the RPE in the peaks being normal do not show hyperfluorescence.

Chee et al. [17] have described the prognostic importance of FFA in VKH. They found that the absence of early pinpoint peripapillary hyperfluorescence on FA is a poor prognostic factor as it suggests that the disease is no longer in the hyperacute phase, and hence it may possibly need to be treated more aggressively and with a more prolonged course of immunosuppressive therapy (Table 12.3).

12.3 Indocyanine Green Angiography (ICG)

Indocyanine green (ICG) angiography is a very sensitive tool to show minimal and subclinical changes within the choroid and found to be an ideal ancillary test to investigate choroidal disorders. ICG can highlight the presence of small choroidal inflammatory foci and provide information on the choriocapillaris and choroidal stromal vessels (Fig. 12.4).

During acute phase, severe choroidal stromal inflammatory vasculopathy is manifested as early choroidal stromal vessel hyperfluorescence and leakage. Hypofluorescent dark spots, corresponding to choroidal foci or granuloma, are one of the most useful ICG sign for diagnosis and monitoring the activity of the

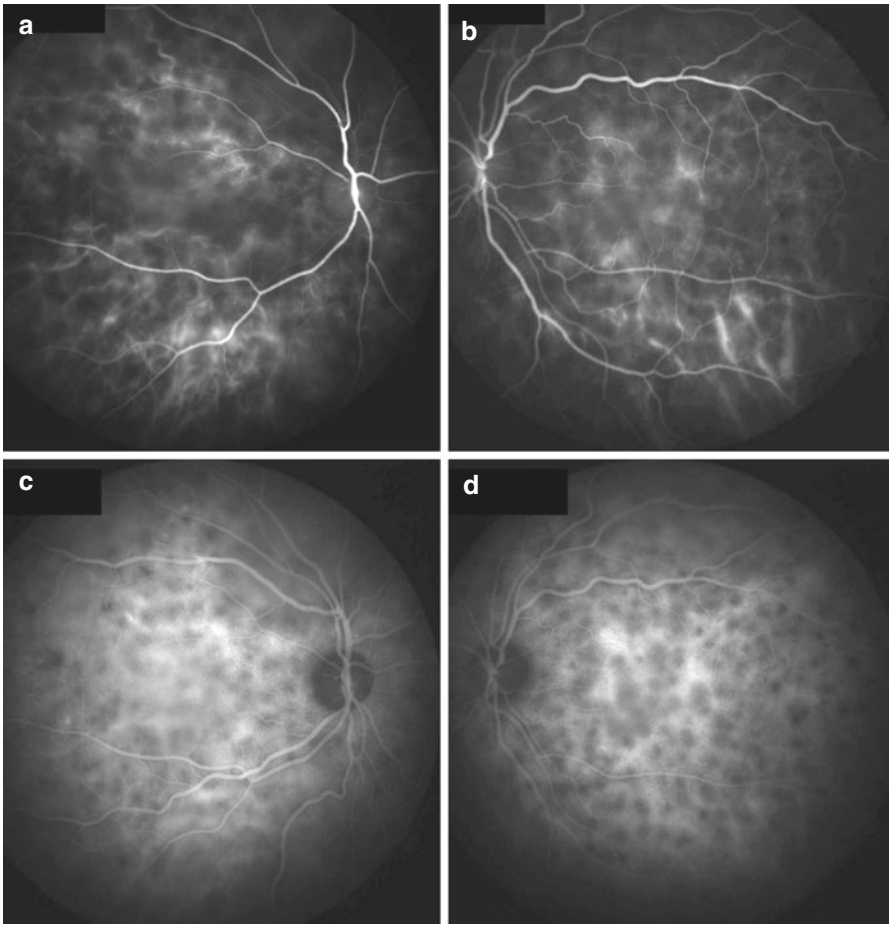

Fig. 12.4 ICG of a patient with VKH disease demonstrating choroidal stromal inflammatory vasculopathy as early choroidal stromal vessel hyperfluorescence and leakage (**a**, **b**). Note the hypofluorescent dark spots, corresponding to choroidal foci or granuloma (**c**, **d**)

Table 12.4 ICG features in VKH and their clinical correlation

ICG features	Clinical correlation
Early hyperfluorescence	Choroidal stromal inflammatory vasculopathy
Hypofluorescent dark spots	Choroidal granuloma
Disc hyperfluorescence	Severe disease
Small, irregular hyperfluorescent dots in periphery in chronic VKH	Dalen-Fuchs nodules

inflammation in VKH disease [18]. Serous retinal detachment usually appears hypofluorescence inside and around the detachment as highly protein-bound ICG molecule does not readily leak into the subneurosensory retinal space (Table 12.4).

12.4 Optical Coherence Tomography (OCT)

Optical coherence tomography is a non-invasive and a fast imaging modality which can pick up various features of vitreoretinal interface, retina and with newer machines the choroid in various phases of VKH.

OCT has been proven to be a better tool to visualize and understand the morphologic changes of the choroid in VKH patients. Cross-sectional images of multilobular serous retinal detachment in VKH disease have been studied in detail using OCT by various authors. Yamaguchi et al. observed that the subretinal fluid seen during the acute stage appeared to be divided into multiple compartments by inflammation-induced fibrous septa, creating the multilobular configuration of dye pooling sometimes demonstrated on FA in this disease [13].

Using a sequence of sectional images of the posterior pole obtained by OCT, cystoid structure within the retina in acute phase of VKH has been proposed by various authors [14, 19, 20]. Intraretinal fluid accumulation in the form of a cyst between the photoreceptor inner segment layers and the outer segment layers resolves earlier than subretinal fluid following treatment [20].

Choroid became significantly thicker during the active phase of VKH disease and choroidal thickness can be used as surrogate bio-marker to quantitatively evaluate the disease activity. EDI-OCT is an excellent method to directly visualize the choroid. It allows clear detection of the choroidal/retinal and choroidal/scleral interfaces, in vivo measurement of the total choroidal thickness. Choroidal thickness in active VKH disease is reported to exceed 800 μm compared with the normal choroid (379 μm) [21, 22]. The boundaries between the retina and the RPE and in turn between the RPE and the choroid are readily visible with the help of EDI-OCT. However, in case of choroidal thickening exceeding 1,000 μm, delineating the boundary between the choroid and the inner sclera may be difficult. EDI-OCT reveals a focal hyperreflectivity in the inner choroid, representing cross-sectional views of pericapillary arterioles and venules [23]. Reduction of focal hyperreflectivity in inner choroid is seen in both acute and convalescent stages of VKH. Fong et al. [23] attributed this feature due to compression and nonperfusion of small

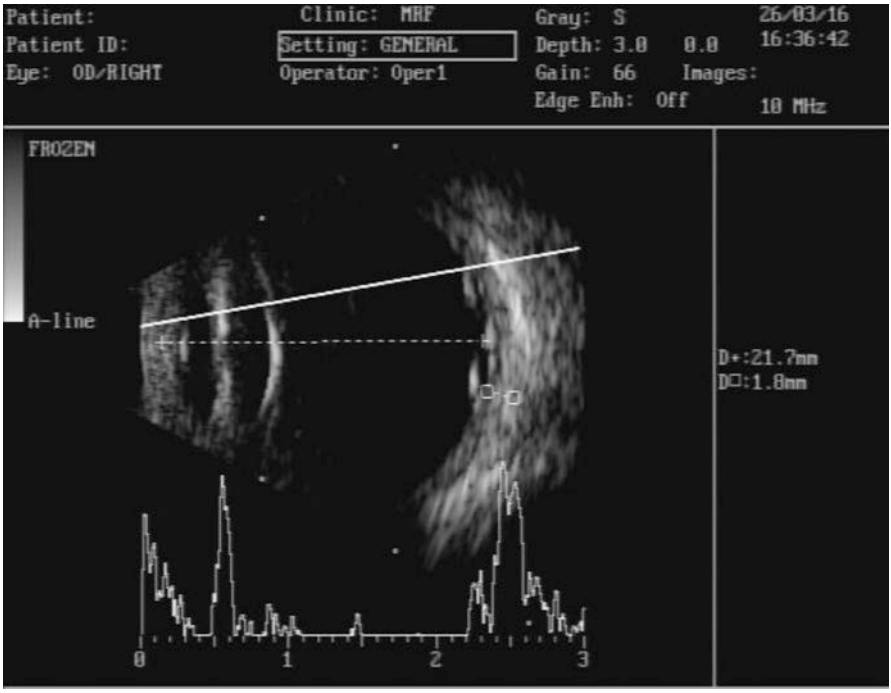

Fig. 12.5 Ultrasound B-scan of right eye of a patient with VKH showing multiple pockets of subretinal fluid with diffuse choroidal thickening

choroidal vessels from massive infiltration of inflammatory cells and granuloma in acute phase and shrinkage and dropout of small choroidal vessels caused by stromal scarring in convalescent stage of the disease (Fig. 12.5).

Choroidal folds are undulations or wrinkles in the retinal pigment epithelium (RPE), Bruch's membrane, and inner aspects choroid, and can be seen in various conditions like hypermetropia, hypotony, orbital diseases, choroidal tumors, ocular hypotony, scleritis, papilledema, choroidal detachment, etc. Choroidal folds are also observed in acute phase of VKH and are believed to be due to marked congestion and thickness of choroids which cause these folds to adapt the unchanged intraocular volume [24]. In VKH, choroidal folds are seen radiating from the optic disc to the periphery [15, 24].

Zhao et al. [24] concluded that the hypofluorescent lines on FFA are not always due to choroidal folds, but can be choroidal veins. According to them, choroidal veins can be differentiated from choroidal folds by discernibility on fundus photography, not straightly radiating from optic disc, irregular arrangement [24]. Gupta et al. [25] reported that changes in acute phase of the disease are seen mainly in the outer retinal segment like thickening or irregularity of the photoreceptor inner segment/outer segment (IS/OS) junction, with undulations and bumps on the surface of RPE on spectral domain OCT which resolved after systemic corticosteroids therapy.

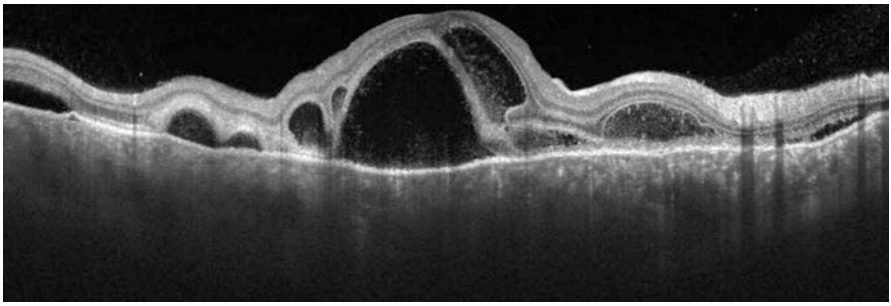

Fig. 12.6 Swept Source-OCT of right eye of the same patient showed multilobular serous retinal detachment

In a quantitative analysis for evaluating choroidal folds, Hosoda et al. [26] used RPE undulation index as a marker for choroidal folds in grading the disease severity of VKH. The RPE undulation index had a high value before steroid therapy, which was reduced after treatment and was strongly correlated with both retinal and choroidal thickness. Chee et al. [27] compared Swept Source-OCT and EDI-OCT in VKH patients and concluded that SS-OCT provides much better resolution images of the choroid than EDI-OCT resulting in accurate measurement of subfoveal choroidal thickness (Fig. 12.6).

12.5 Ultrasonography

Ultrasonography (USG) B scan is an important tool in diagnosis of VKH especially in cases where view of fundus is obscured by media opacity (e.g., extensive posterior synechiae preventing pupillary dilatation, cataract, or dense vitritis). It is also helpful in eyes where the amount of subretinal fluid is too extensive to be imaged by an OCT. USG B scan have been found to be useful in differentiating from posterior scleritis. In VKH, where sclera is secondarily involved, USG B scan shows diffuse, low to medium reflective choroidal thickening whereas in posterior scleritis the scleral thickening has high reflectivity and is frequently accompanied by retrobulbar edema in the peripapillary region resulting in the "T" sign [28]. USG B scan is also helpful in evaluation of choroidal detachment in VKH which, though rare, can occur in absence of prominent retinal detachment [29] (Fig. 12.7).

Various features seen on Ultrasonography B scan in VKH:
- Low to medium reflective thickening of the choroid
- Serous retinal detachments with shifting fluid
- Mild thickening of the sclera and/or episclera adjacent to areas of choroidal thickening
- Vitreous opacities.
- Extensive subretinal fibrosis in chronic cases.

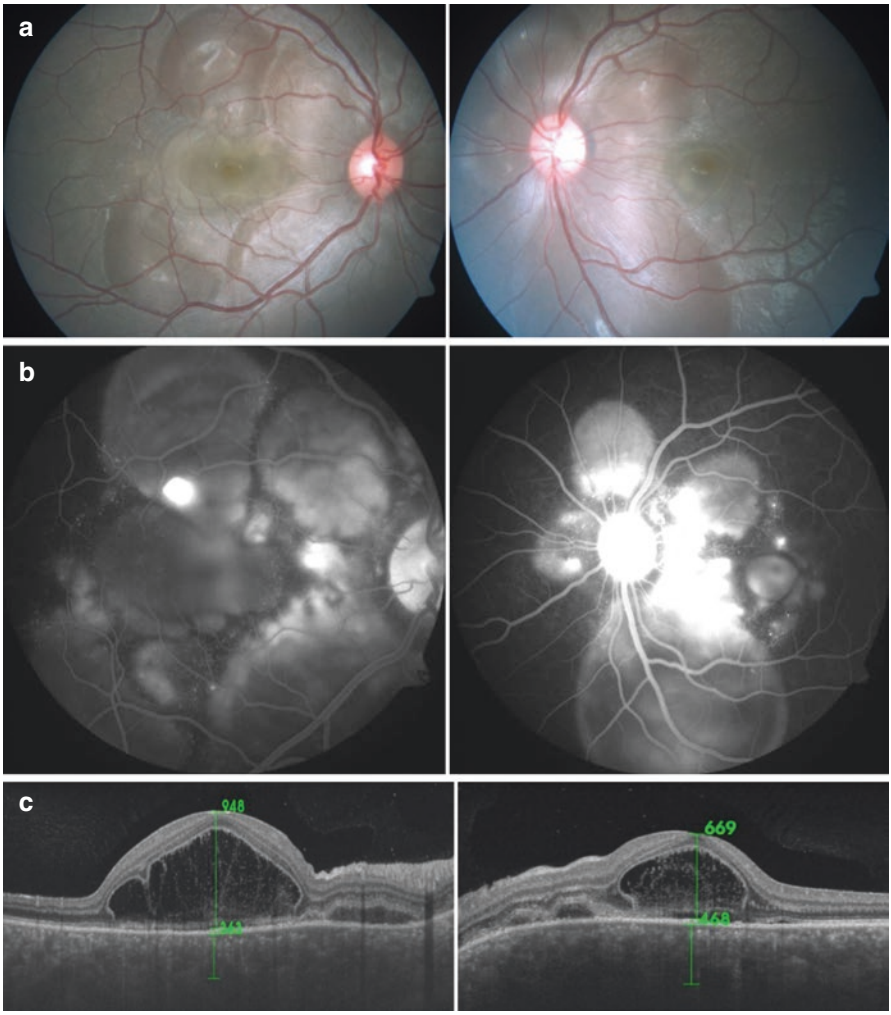

Fig. 12.7 A 14-year-old-girl presented with history of headache, ocular pain, redness followed by diminution of vision in both eyes. (**a**) Fundus examination of both eyes showed OU SRF pockets at posterior pole of both fundus. (**b**) Placoid pooling of the dye observed in late phases of angiogram. (**c**) OCT of the eyes showing multilobular serous retinal detachment with choroidal thickening

Ultrasound biomicroscopic (UBM) examination have demonstrated that ciliochoroidal detachment is a frequent finding in the acute stage of VKH disease and may be responsible for shallow anterior chamber encountered in the early stage of disease. The ciliary body is considered to be the most susceptible site for accumulation of suprachoroidal fluid. Ciliochoroidal detachment in VKH is usually depends on the severity and duration of insult to the choroidal vascular barrier by the inflammatory process. Acute angle closure can be the presenting sign of the disease and can complicate the diagnosis [30–33]. Using UBM, swollen ciliary bodies with

anterior rotation of the ciliary processes were found to be responsible for anterior displacement of the peripheral iris and subsequent appositional closure of the anterior chamber angle [34]. Most of the published literature have shown resolution of ciliochoroidal detachment, ciliary body swelling, and deepening of anterior chamber depth significantly following steroid or immunosuppressive therapy.

12.6 Therapeutic Considerations

The aim of treatment in VKH is to suppress the active intraocular inflammation and prevent potential visual impairment. Early and aggressive treatment with systemic corticosteroids remains the mainstay of the initial therapy. Systemic steroid is administered either orally (1–1.5 mg/kg/day) or through a short course of intravenous methylprednisolone 1000 mg/day, for 3 days and slow tapering of oral corticosteroid. Rapid tapering or discontinuation of corticosteroid may incur in recurrences and the treatment should be continued for at least 6–9 months [35, 36]. Immunosuppressive agents are usually required to achieve long-term remission of the disease. However, these agents are also indicated in conditions inadequately controlled with corticosteroid alone or disease that warrants unacceptably high amount of corticosteroid. Use of immunosuppressive agents in VKH has been reported to have beneficiary effect and associated with reduced risk of vision loss [37].

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