Vogt–Koyanagi–Harada Disease

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Peizeng Yang and Zi Ye

Introduction

Vogt–Koyanagi–Harada (VKH) disease is an autoimmune disorder characterized by bilateral granulomatous panuveitis frequently associated with multiple extraocular findings such as vitiligo, poliosis, dysacusis, alopecia, and neurological involvement. In 1906, Vogt reported a patient with nontraumatic uveitis associated with poliosis. Bilateral idiopathic uveitis patients with poliosis, vitiligo, dysacousia, and alopecia were subsequently reported by Koyanagi in 1929. Because of the uniformity of these findings, disease reported by Vogt and Koyanagi was identified as one uveitis entity and named as Vogt–Koyanagi syndrome. In 1926, a disease characterized by cerebrospinal fluid (CSF) change and retinal detachment was reported by Harada as a separate uveitis entity. Subsequently, more and more studies suggested that Vogt–Koyanagi syndrome and Harada disease are the different manifestations in different stages of the same disease. In a study on 410 Chinese VKH patients, we revealed that Harada disease is the early manifestation, whereas Vogt–Koyanagi syndrome is the feature in recurrent stage (Yang et al. 2007).

VKH disease commonly affects young and middle-age adults, and the predominant age of disease onset is 20–50 years. It has no gender predilection, although several studies show that female is more likely to be affected. VKH disease primarily occurred in pigmented races, such as Asians and native Americans. It has rarely been reported in European populations (Du et al. 2016).

P. Yang (✉) · Z. Ye
The First Affiliated Hospital of Chongqing Medical University, Chongqing Key Lab of Ophthalmology, Chongqing Eye Institute, Chongqing, People's Republic of China

Etiopathogenesis

Although exact pathogenesis of VKH disease remains uncertain, microbial infection, autoimmune response, and genetic susceptibility have been thought to play a role in the development of this disease. As the meningeal manifestations such as headache, fever, and meningismus are observed prior to the uveitis attack, microbial infection is considered as a triggering factor in VKH disease. Earlier studies have detected the Epstein–Barr virus (EBV) DNA in CSF and vitreous from patients with VKH disease. However, these findings are not confirmed by subsequent studies. Sugita et al. find that peptides derived from cytomegalovirus envelope glycoprotein H (CMV-egH$_{290\text{-}302}$) and from tyrosinase have a high homology of amino acid sequence and that the T-cell clones established from VKH patients can recognize CMV-egH$_{290\text{-}302}$ as well as tyrosinase peptides (Sugita et al. 2007). A hypothesis that immune cells may recognize and attack the host proteins as exogenous antigens because of the similarity of genome sequence has been proposed. Other evidences supporting this hypothesis are that the expression of some pattern recognition receptors (PRRs, which could recognize microbial products and then trigger the immune response), TLR3, TLR4, NOD1, and NOD2, is significantly increased in active VKH patients.

An autoimmune response directed against melanin-associated antigen, interphotoreceptor retinoid binding protein, and retinal S-antigen has been observed in VKH disease. Increasing number of studies provide evidences that T-cell subsets, including Th17, Th1, and Treg cells, together with their functional cytokines IL-17, IFN-γ, IL-10, and TGF-β play an important role in the initiation and maintenance of the autoimmune response (Chi et al. 2007; Du et al. 2016). Significantly higher expression of IL-17 and IFN-γ and increased percentage of Th17 and Th1 cells are observed in active VKH patients. Treg cells, which possess immune regulatory properties, show functional impairment and

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quantitative reduction in active VKH patients. Other immune cells such as macrophage and dendritic cells (DCs) also contribute to the development of VKH disease. They can produce IL-23 and IL-12, which in turn stimulate Th17 and Th1 cell polarization and promote IL-17 and IFN-γ production. In addition, a network of cytokines, chemokines, cell receptors, as well as other factors also contribute to the development of VKH disease through modulating IL-23/IL-17 pathway. Higher expression of leptin, osteopontin (OPN), IL-7, and IL-21 and lower expression of 1,25-dihydroxyvitamin D3, liver X receptor, IL-27, IL-25, and IL-37 are detected in active VKH patients. This disturbed expression of these molecules may collectively result in the activation of IL-23/IL-17 pathway and in turn lead to the development of VKH disease.

Human leukocyte antigens DR4 (HLA-DR4) and DRw53 (HLA-DRw53) have been shown to be strongly associated with VKH disease in different ethnic populations. Other HLA antigens including DQw3, B54, DQ4, DR1, DRB1∗0405, DQA1∗0301, and DQB1∗0401 are also identified as susceptible genetic factors for this disease. Genome-wide association studies (GWAS) on Chinese VKH patients confirm the strong association of HLA-DRB1/DQA1 loci with this disease. Additionally, two new non-HLA loci including IL23R-C1orf141 and ADO-ZNF365-C1orf141 are identified as VKH disease-susceptibility loci (Hou et al. 2014). Studies in different populations identified that single-nucleotide polymorphisms of CTLA-4, SUMO4, PTPN22, IFN-γ, IL-17, IL-12B, TLR9, TNIP1, NLRP1, OPN, miR-146a, and DHCR7 confer susceptibility to this disease. In addition, copy number variations (CNVs) of some immune-related genes including complement 4 (C4), C3, IL-17F, IL-23A, and FAS are also found to be associated with VKH disease.

Taken together, a hypothesis can be that environmental factor such as a virus infection may induce an immune response to the antigens as stated above in a currently unknown way in the individuals with a constellation of risk genetic factors, therefore subsequently leading to the development of VKH disease.

Clinical Features

Various manifestations can be observed in different stages of VKH disease. Moorthy et al. classified this disease into four stages according to the manifestations during the course of the disease: prodromal stage, acute uveitis stage, chronic convalescent stage, and chronic recurrent stage (Moorthy et al. 1995) (Table 9.1). Another phasing system is also proposed based on our study on 410 Chinese VKH patients (Yang et al. 2007). This system also consists of four stages: prodromal stage, posterior uveitis stage, anterior uveal involvement stage, and recurrent granulomatous anterior uveitis stage (Table 9.2). Both systems are generally similar, but our system more highlights the evolutionary process during the course. For instance, the disease begins with diffuse choroiditis, progresses to a non-granulomatous anterior uveitis, and finally becomes a granulomatous panuveitis with striking anterior segment involvement unless appropriate treatments are instituted.

Table 9.1 Classification systems developed for VKH disease by Moorthy et al. (1995)

Stages	Clinical features
Prodromal stage	Headache, fever, meningismus, hearing loss, tinnitus, stiffness of neck and back
Acute uveitis stage	Sudden bilateral blurring and decrease of vision, choroiditis, multiple neuroepithelium detachment, exudative retinal detachment, optic disc edema or hyperemia, acute intraocular pressure (IOP) (occasionally), granulomatous anterior uveitis (occasionally)
Chronic convalescent stage	"Sunset glow" fundus, Dalen-Fuchs nodules, Sugiura's sign, vitiligo
Chronic recurrent stage	Recurrent granulomatous anterior uveitis, Koeppe and Busacca nodules, rare active posterior uveitis, poor response to corticosteroid, intraocular complications

Table 9.2 Classification systems developed for VKH disease by Yang et al. (2007)

Stages	Clinical features
Prodromal stage (about 1 or 2 week before uveitis attack)	Headache, fever, meningismus, hearing loss, tinnitus, stiffness of neck and back
Posterior uveitis stage (about 2 weeks after uveitis attack)	Choroiditis, exudative retinal detachment, optic disc edema or hyperemia, acute IOP (occasionally)
Anterior uveal involvement stage (from 2 weeks to 2 months after uveitis attack)	Active posterior uveitis, non-granulomatous anterior uveitis
Recurrent granulomatous anterior uveitis stage (more than 2 months after uveitis attack)	"Sunset glow" fundus, Dalen-Fuchs nodules, migration of RPE, recurrent granulomatous, Koeppe and Busacca nodules, intraocular complications

Prodromal Stage

The prodromal stage refers to 1 or 2 weeks before uveitis attack and is characterized by meningismus, hearing loss, tinnitus, and abnormal sensitivity to touch of the hair. CSF pleocytosis can be observed in this stage.

Posterior Uveitis Stage

The posterior uveitis stage refers to within 2 weeks after uveitis attack. Sudden bilateral blurring and decrease of vision

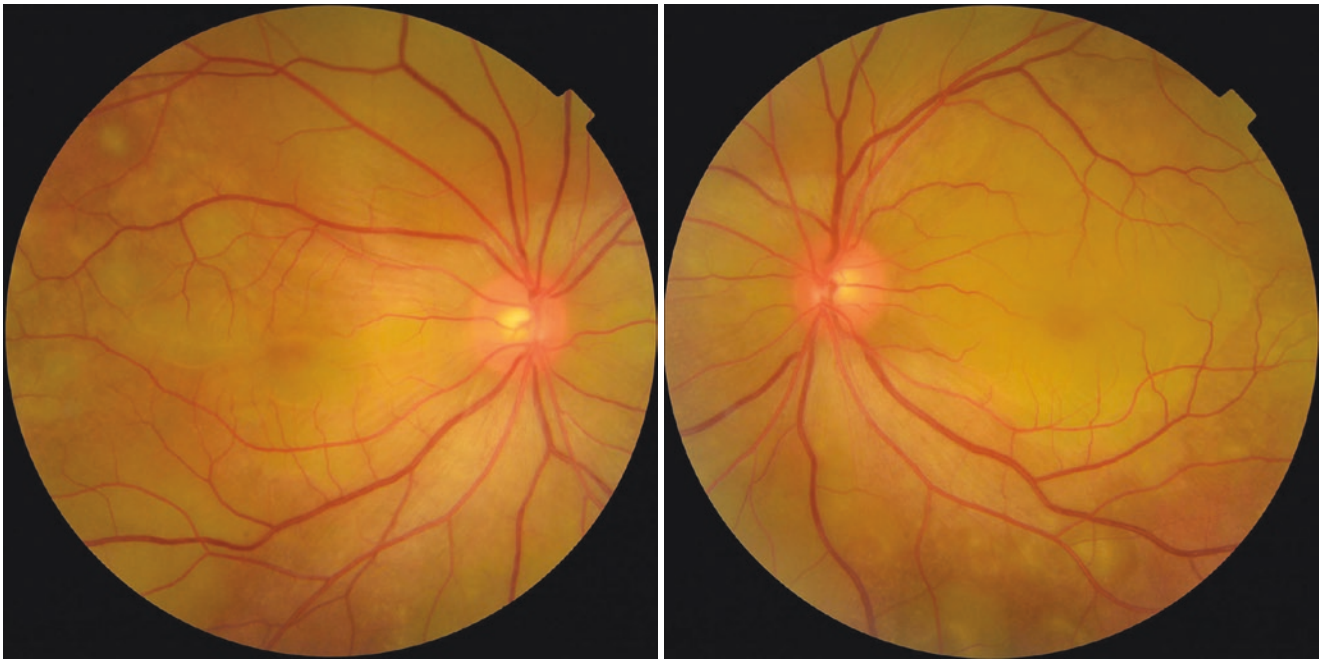

Fig. 9.1 Multiple exudative retinal detachment and optic disc swelling in a patient with VKH disease at posterior uveitis stage

are the most common symptoms. The majority of patients present with decreased vision simultaneously in both eyes. In the remaining patients, the interval between uveitis onsets of both eyes is usually from 1 to 2 weeks. Diffuse choroiditis is the characteristic finding. Most patients present with exudative retinal detachment and optic disc swelling (Fig. 9.1). No anterior reaction is observed in this stage. Fundus fluorescein angiography (FFA) shows numerous punctate hyperfluorescent dots in the early phase and subretinal dye pooling in the late phase (Fig. 9.2a). Optic disc staining is also a common finding. Indocyanine green angiography (ICGA) typically shows multiple hypofluorescent dots and dark areas corresponding to serous retinal detachment (Fig. 9.2b). Exudative retinal detachment disclosed with optical coherence tomography (OCT) is a rule in this stage (Fig. 9.2c). Tinnitus, hearing loss, and meningismus may be still present in this stage.

Anterior Uveal Involvement Stage

The anterior uveal involvement stage usually begins from 2 weeks after the uveitis attack. This stage usually lasts for 1.5 months. In this stage, choroiditis is still observed in most patients. A mild to moderate anterior uveitis characterized by flare and cells in the anterior chamber and dust-keratic precipitates (KP) is the prominent manifestation. Granulomatous anterior uveitis is very rarely seen in this stage. Mild vitreous inflammatory reaction and optic disc swelling are also noted. Tinnitus and hearing loss are the most common extraocular symptoms, and integumentary changes including poliosis, alopecia, and vitiligo are observed in some patients in this stage (Fig. 9.3).

Recurrent Granulomatous Anterior Uveitis Stage

Without appropriate and prompt treatment, VKH patients may eventually develop recurrent chronic granulomatous anterior uveitis. During this stage, active choroiditis normally resolves and "sunset glow" fundus ensues as a result of depigmentation of the retinal pigment epithelium (RPE) cells and the choroid (Fig. 9.4). In some patients, the sclera tissue can be observed because of severe depigmentation of the choroid (Fig. 9.5). Dalen-Fuchs nodules, which manifest as small, round to oval active lesions in the midperiphery of the fundus, chorioretinal atrophy, and migration of RPE cells are the other common findings in the posterior segment (Fig. 9.4). Anterior uveitis is a very striking feature and typically presents with mutton fat KP, Koeppe nodules, Busacca nodules, and significant anterior chamber reaction (Fig. 9.6). Window defects due to RPE cell damages and blockade of fluorescence arising from migration of retinal RPE cells are common FFA findings. Ultrasound biomicroscopy may show the cells in the anterior chamber as thickened and swollen ciliary body as well as ciliochoroidal detachment in patients in this stage (Fig. 9.7). Ocular complications including cataract, secondary glaucoma, subretinal fibrosis, and choroidal neovascularization are observed in this stage. Poliosis, alopecia, and vitiligo are common extraocular findings.

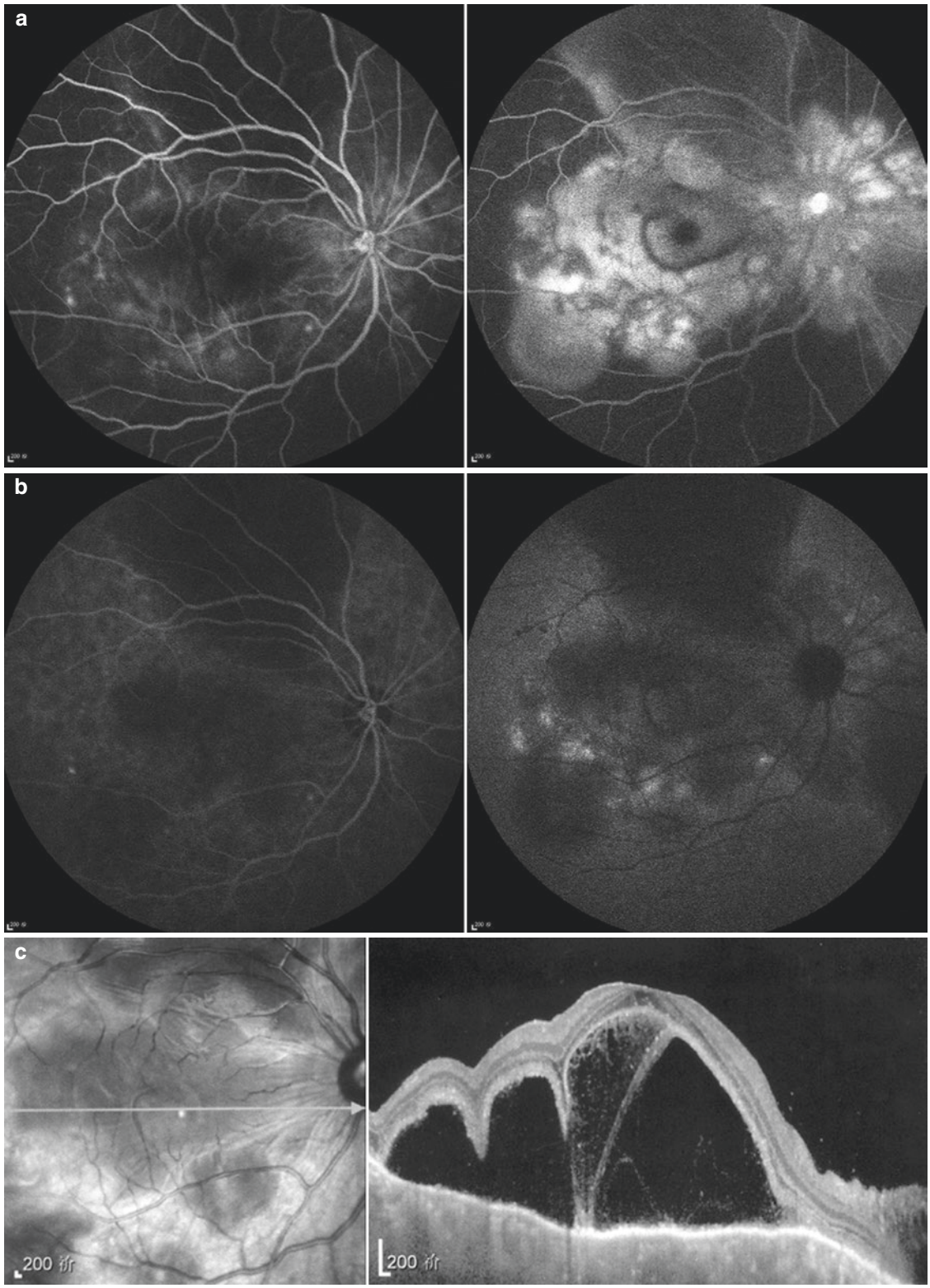

Fig. 9.2 FFA, ICGA, and OCT examination of a patient with VKH disease at posterior uveitis stage. (**a**) FFA shows punctate hyperfluorescent dots in the early stage and subretinal dye pooling in the late stage. (**b**) ICGA shows multiple hypofluorescent dots and dark areas corresponding to serous retinal detachment. (**c**) OCT shows serous retinal detachment. (**d**–**f**) The aforementioned alterations resolved at 1 month following treatment

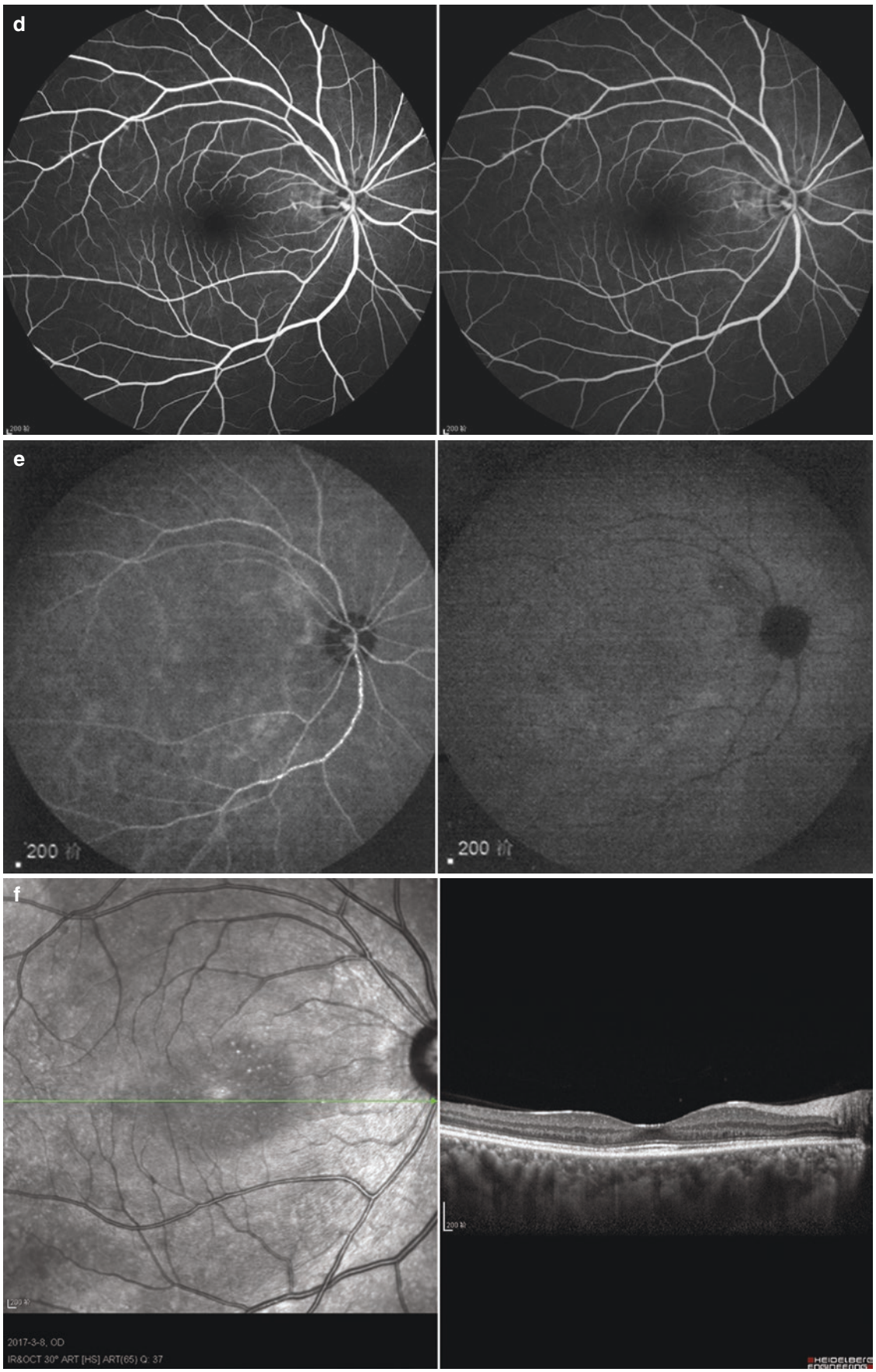

Fig. 9.2 (continued)

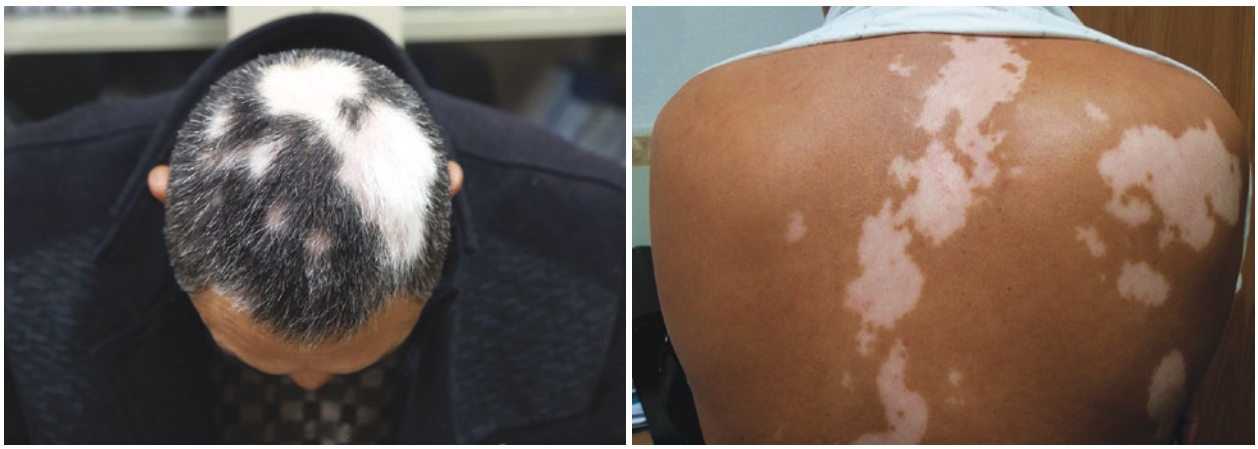

Fig. 9.3 Poliosis, alopecia, and vitiligo observed in VKH patients

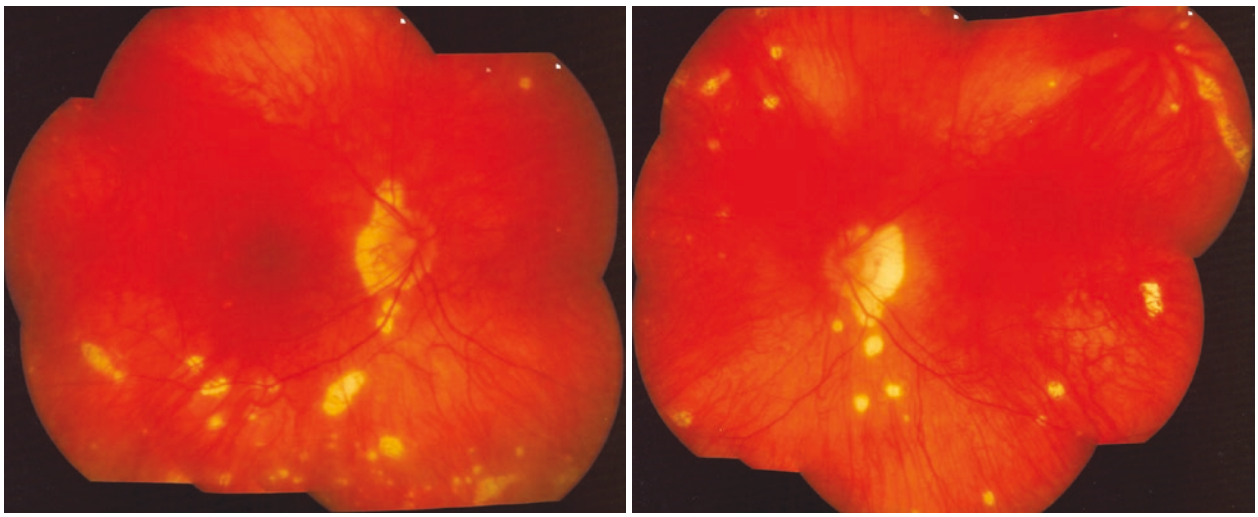

Fig. 9.4 Sunset glow fundus and multiple Dalen-Fuchs nodules observed in a patient with VKH disease at recurrent granulomatous anterior uveitis stage

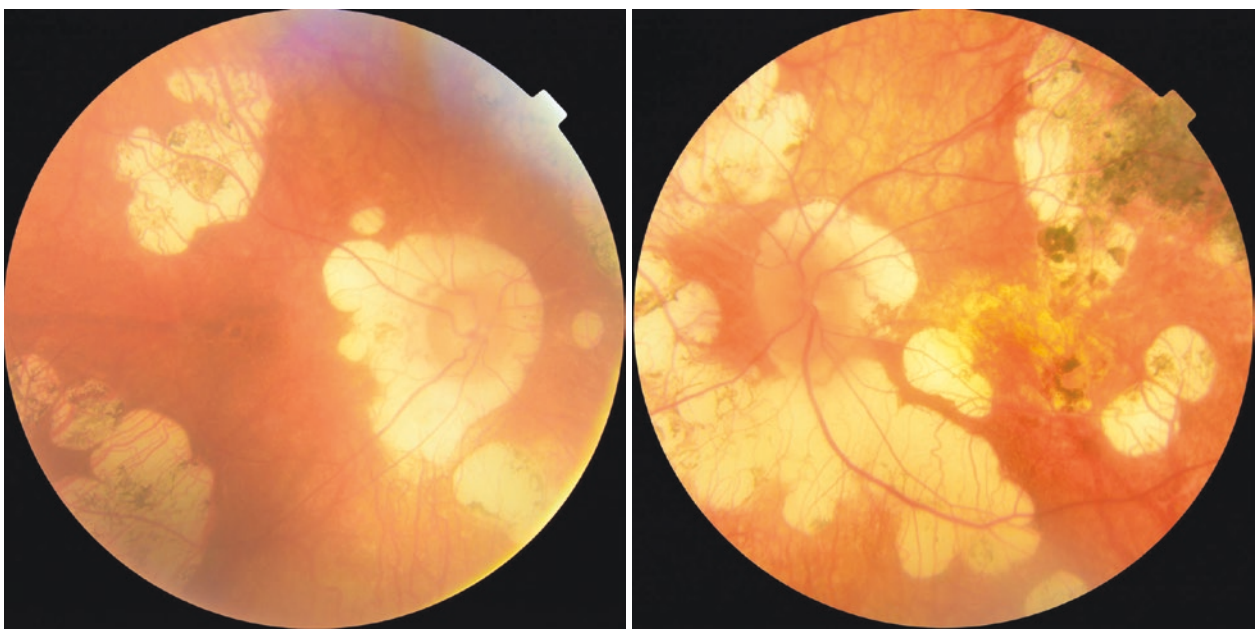

Fig. 9.5 Confluent chorioretinal atrophies and irregular hyperpigmentation observed in a patient with VKH disease at recurrent granulomatous anterior uveitis stage

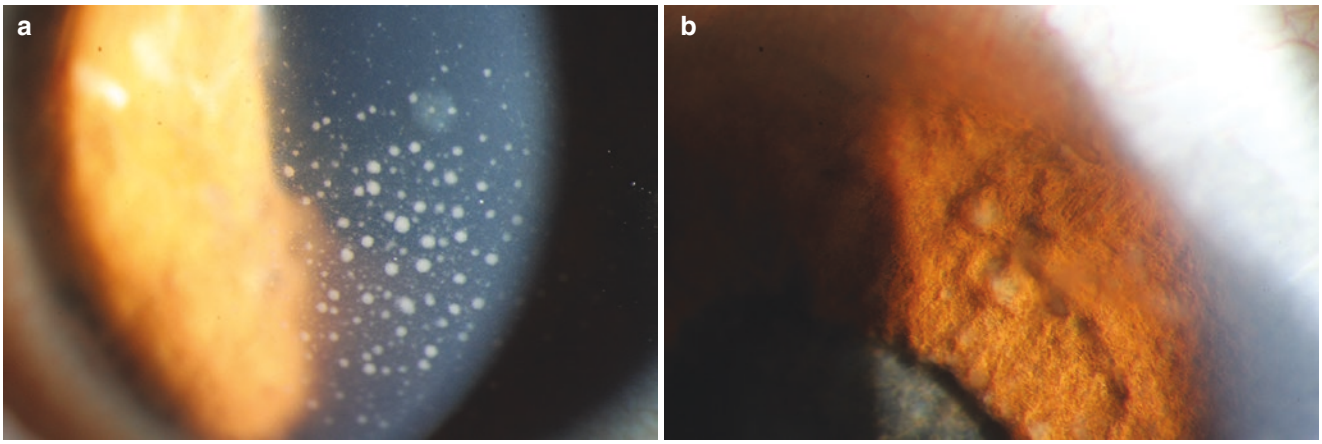

Fig. 9.6 Mutton fat keratic precipitate (**a**) and Busacca nodules (**b**) observed in a patient with VKH disease at recurrent granulomatous anterior uveitis stage

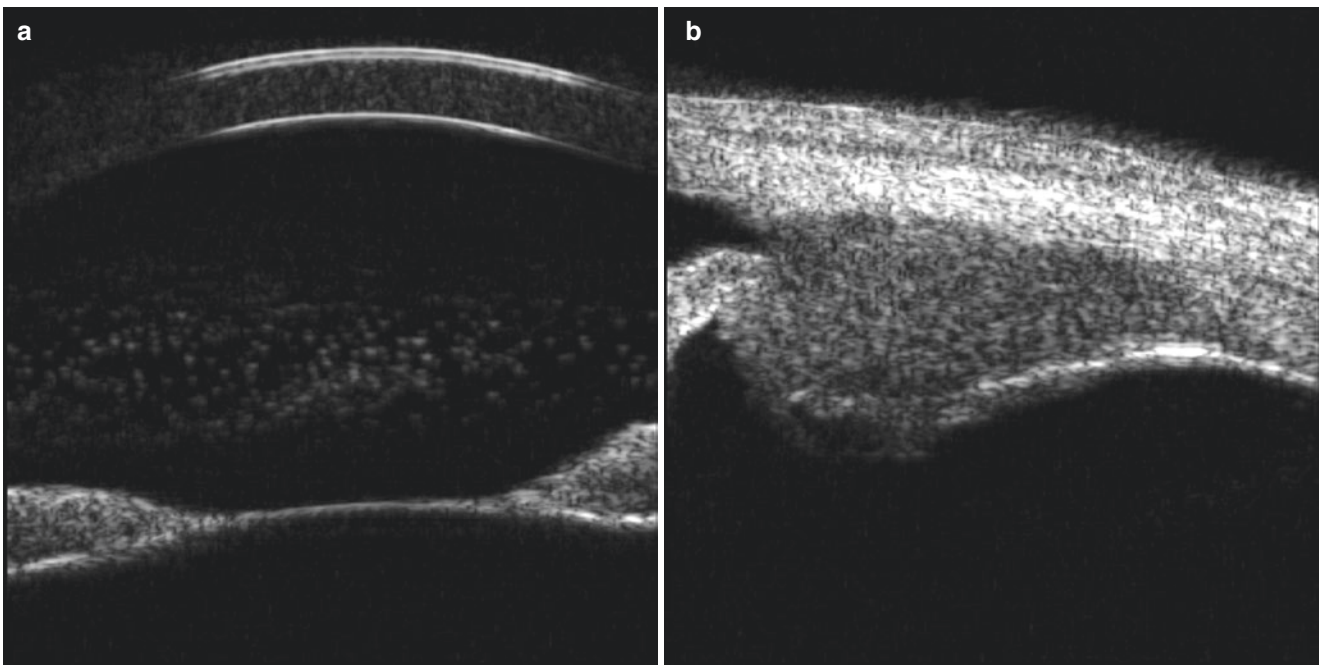

Fig. 9.7 Inflammatory cells in the anterior chamber (**a**) and swollen ciliary body (**b**) disclosed by ultrasound biomicroscopy in a patient with VKH disease at recurrent granulomatous anterior uveitis stage

Diagnostic Criteria

Several diagnostic criteria for VKH disease have been proposed during the last decades. Currently, the most widely used criteria are the revised diagnostic criteria endorsed by the International Nomenclature Committee on nomenclature (Read et al. 2001) (Table 9.3). These criteria include the different manifestations during the disease process and classify VKH disease into three categories: complete VKH disease, incomplete VKH disease, and probable VKH disease. Although the diagnostic criteria are highly sensitive and specific, they define the disease without extraocular manifestations only as "probable VKH disease." It seems not to be scientific enough since some patients present with the typical intraocular signs such as "sunset glow" fundus and Dalen-Fuchs nodules with a typical evolutionary process. Adequate treatment in early stage can influence the long-term clinical manifestations of VKH disease and support the diagnosis. An effort is being made by us to develop novel criteria based on a large number of Chinese VKH patients and is expected to be used clinically in the future.

Table 9.3 Revised diagnostic criteria endorsed by the International Nomenclature Committee on nomenclature (Read et al. 2001)

Complete VKH disease (criteria 1–5 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) Sugiura's 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 the definition of meningismus, however) or
b. Tinnitus or
c. Cerebrospinal fluid pleocytosis
5. Integumentary finding (not preceding the onset of central nervous system or ocular disease)
a. Alopecia or
b. Poliosis or
c. Vitiligo
Incomplete Vogt–Koyanagi–Harada disease (criteria 1–3 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 1–3 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

Management

Prompt and adequate management of VKH disease can halt the disease in early stage and improve the visual prognosis. Systemic treatment with corticosteroids and other immunosuppressive drugs such as cyclosporine A (CsA), cyclophosphamide, methotrexate, azathioprine, and chlorambucil has achieved a good result in most patients. Recently, some biologic agents are employed in the management of recalcitrant VKH disease and show a positive result.

Corticosteroids

System corticosteroids are considered as the first choice in the treatment of VKH disease. The reported initial dose of corticosteroids is usually 1–1.5 mg/kg/day followed by gradual tapering (Hayasaka et al. 1982; Moorthy et al. 1995; Rubsamen and Gass 1991; Yang et al. 2007). Higher dose or even intravenous pulse therapy has been recommended by some authors for severe cases. However, high-dose of corticosteroids may virtually cause severe side effects. Recently, we developed the

therapeutic regimens using a relatively lower dose of corticosteroids mostly in conjunction with immunosuppressive agents (see below) for the treatment of VKH disease. The initial dose of corticosteroids is 0.6–0.8 mg/kg/day of prednisone for patients in early stage and 0.4–0.6 mg/kg/day for patients in late stage. Systemic corticosteroid is gradually tapered to a maintenance dose, 15–20 mg/day, over 4–6 months with the subsidence of the intraocular inflammation. Treatment with this maintenance dose usually lasts for another 4–6 months followed by gradual tapering to final cessation. For patients with marked retinal detachment, posterior sub-Tenon's injection of triamcinolone acetonide (20 mg) is used as an adjunct to systemic corticosteroids. For patients with anterior chamber reaction, corticosteroid eye drops and cycloplegic agents are indicated to control the anterior segment inflammation. A study based on 998 Chinese VKH patients shows that these therapeutic regimens can effectively control the intraocular inflammation in 98% of these patients (Fig. 9.2d–f). Up to 80% of these patients achieve a final vision ≥20/40.

Immunosuppressive Agents

Immunosuppressive agents are required for patients who are resistant to corticosteroids or who do not tolerate the side effects of corticosteroids. Furthermore, they are also recommended for patients with recurrent anterior uveitis. CsA is one of the most commonly used immunosuppressive agents. Previous studies show that CsA is a better glucocorticoid-sparing agent as compared to azathioprine (Cuchacovich et al. 2010). In our clinic, we usually commence the treatment with an initial dose of 2–4 mg/kg/day for 5–6 months. If the initial dose is more than 2 mg/kg/day, it is gradually tapered to the maintenance dose of 2 mg/kg/day. Other agents including cyclophosphamide, methotrexate, azathioprine, and chlorambucil are also advocated in the treatment of this disease in the context of the individual conditions. A beneficial result has been observed in most patients treated with various immunosuppressive agents.

Biological Agents

Biological agents such as infliximab, adalimumab, and rituximab have been successfully used in patients with refractory VKH disease. Prospective randomized clinical trials on a large number of patients are needed to optimize the use of these agents in the treatment of VKH disease.

Complication Management

Surgery therapy is necessary for complicated cataract and should be performed after intraocular inflammation is completely controlled (Moorthy et al. 1994). For secondary glaucoma, anti-glaucoma medications show a good result in most patients. Surgery intervention is indicated if complete posterior synechia or widespread anterior synechia is present or the patients fail to respond to medication treatment. Photocoagulation, intravitreal injection of anti-VEGF agents, as well as surgical excision has been used in patients with subretinal fibrosis or choroidal neovascularization.

References

Chi W, Yang P, Li B, Wu C, Jin H, Zhu X, et al. IL-23 promotes CD4+ T cells to produce IL-17 in Vogt-Koyanagi-Harada disease. J Allergy Clin Immunol. 2007;119(5):1218–24. https://doi.org/10.1016/j.jaci.2007.01.010.

Cuchacovich M, Solanes F, Diaz G, Cermenati T, Avila S, Verdaguer J, et al. Comparison of the clinical efficacy of two different immunosuppressive regimens in patients with chronic Vogt-Koyanagi-Harada disease. Ocul Immunol Inflamm. 2010;18(3):200–7. https://doi.org/10.3109/09273941003587541.

Du L, Kijlstra A, Yang P. Vogt-Koyanagi-Harada disease: novel insights into pathophysiology, diagnosis and treatment. Prog Retin Eye Res. 2016;52:84–111. https://doi.org/10.1016/j.preteyeres.2016.02.002.

Hayasaka S, Okabe H, Takahashi J. Systemic corticosteroid treatment in Vogt-Koyanagi-Harada disease. Graefes Arch Clin Exp Ophthalmol. 1982;218(1):9–13.

Hou S, Du L, Lei B, Pang CP, Zhang M, Zhuang W, et al. Genome-wide association analysis of Vogt-Koyanagi-Harada syndrome identifies two new susceptibility loci at 1p31.2 and 10q21.3. Nat Genet. 2014;46(9):1007–11. https://doi.org/10.1038/ng.3061.

Moorthy RS, Rajeev B, Smith RE, Rao NA. Incidence and management of cataracts in Vogt-Koyanagi-Harada syndrome. Am J Ophthalmol. 1994;118(2):197–204.

Moorthy RS, Inomata H, Rao NA. Vogt-Koyanagi-Harada syndrome. Surv Ophthalmol. 1995;39(4):265–92.

Read RW, Holland GN, Rao NA, Tabbara KF, Ohno S, Arellanes-Garcia L, et al. Revised diagnostic criteria for Vogt-Koyanagi-Harada disease: report of an International Committee on Nomenclature. Am J Ophthalmol. 2001;131(5):647–52.

Rubsamen PE, Gass JD. Vogt-Koyanagi-Harada syndrome. Clinical course, therapy, and long-term visual outcome. Arch Ophthalmol. 1991;109(5):682–7.

Sugita S, Takase H, Kawaguchi T, Taguchi C, Mochizuki M. Cross-reaction between tyrosinase peptides and cytomegalovirus antigen by T cells from patients with Vogt-Koyanagi-Harada disease. Int Ophthalmol. 2007;27(2-3):87–95.

Yang P, Ren Y, Li B, Fang W, Meng Q, Kijlstra A. Clinical characteristics of Vogt-Koyanagi-Harada syndrome in Chinese patients. Ophthalmology. 2007;114(3):606–14. https://doi.org/10.1016/j.ophtha.2006.07.040.