Review Article

Update on the diagnosis and treatment of Vogt-Koyanagi-Harada syndrome

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Abstract: Vogt-Koyanagi-Harada syndrome (VKH) is a bilateral granulomatous panuveitis associated with serous retinal detachments and vitritis, and can be associated with extraocular manifestations of meningismus, poliosis, vitiligo, hearing loss, and headaches. It is mediated by CD4+ T cells that target melanocytes in the eye, ear, meninges, and skin. It classically presents in 4 different phases: prodromal, uveitic, convalescent, and recurrent. There have been considerable advances in our understanding of the disease in recent years, and options for treatment have also expanded beyond systemic corticosteroids though these remain the mainstay of therapy in patients with VKH. This brief review will focus on updates in the diagnosis and treatment of VKH, specifically advances in imaging techniques including the use of optical coherence tomography angiography (OCTA) and enhanced depth imaging (EDI) optical coherence tomography (OCT). OCT parameters that are diagnostically predictive of acute VKH compared to other exudative maculopathies include the presence of subretinal membranous structures, a high retinal detachment, subretinal hyperreflective dots, and RPE folds. Evaluations of choroidal thickness using EDI-OCT demonstrate predominant involvement of the outer choroid in the acute inflammatory phase of VKH, consistent with histopathological analysis. OCTA may emerge as an alternative to fluorescein angiography (FA) and indocyanine angiography (ICGA) but is limited at this time due to its small field of view. While the mainstay of treatment of acute VKH continues to be systemic corticosteroids, biological response modifiers (BRMs) such as adalimumab and infliximab have been shown to be effective in the management of adult and pediatric VKH with one benefit being a faster onset of action compared to conventional immunosuppression. Literature Search: A literature search was done in PubMed using the words "Vogt Koyanagi Harada" "imaging" "diagnosis" "treatment" "therapy "posterior uveitis".

Keywords: Vogt-Koyanagi Harada; posterior uveitis; imaging; immunomodulatory therapy; optical coherence tomography

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Introduction

Vogt-Koyanagi-Harada syndrome (VKH) is a bilateral granulomatous panuveitis associated with serous retinal detachments and vitritis, and can be associated with extraocular manifestations of meningismus, poliosis, vitiligo, hearing loss, and headaches. It is mediated by CD4+ T cells that target melanocytes in the eye, ear, meninges, and skin. It classically presents in 4 different phases: prodromal, uveitic, convalescent, and recurrent. There have been considerable advances in our understanding of the disease in recent years, and options for treatment have also expanded beyond systemic corticosteroids though these remain the mainstay of therapy in patients with VKH.

This brief review will focus on updates in the diagnosis and treatment of VKH, specifically advances in imaging

techniques including the use of optical coherence tomography angiography (OCTA) and enhanced depth imaging (EDI) optical coherence tomography (OCT) to further understand this disease. While the mainstay of treatment of acute VKH continues to be systemic corticosteroids, we will also discuss updates in treatment options for this vision-threatening disease.

Updates in imaging

Due to the presence of serous retinal detachments, optical coherence tomography (OCT) has been extensively evaluated in VKH, with specific descriptions of changes seen in the retina and retinal pigment epithelium that were otherwise less evident on clinical examinations. Findings on OCT include intraretinal edema, subretinal fluid, subretinal septae, and subretinal hyperreflective dots, along with retinal pigment epithelium (RPE) folds, as well as choroidal thickening in the acute stage and thinning in the convalescent stage (1). Liu *et al.* evaluated OCT parameters that were diagnostically predictive of acute VKH and noted that the presence of subretinal membranous structures, a high retinal detachment, subretinal hyperreflective dots, and RPE folds had a high diagnostic value for acute VKH compared to other exudative maculopathies (2).

Intraretinal and subretinal fluid noted on OCT correlates with dye leakage seen on fluorescein angiography (FA) (3). This is a classic finding in VKH. Lin *et al.* further evaluated the submembranous space in VKH and in central serous chorioretinopathy (CSR) and found that the optical intensity of the fluid was similar between the two. This implies both are similar in composition and likely caused by exudates from the choroidal vasculature (4). Ishihara further evaluated the septae seen in acute VKH noting they appeared continuous with a band representing the ellipsoid zone in the areas of attached retina. They concluded the septae are a separation of the inner and outer segments of the photoreceptors in the acute phase that then reattach once the initial inflammation resolves (5). These subretinal septae are thought to be comprised of inflammatory products (6) versus increased cell debris from outer segment photoreceptors (3).

The presence of retinal pigment epithelium (RPE) folds is diagnostically useful in acute VKH (7-11). Gupta *et al.* demonstrated the relative normal thickness, or sparing, of the retina from the internal limiting membrane to the external limiting membrane in the presence of RPE undulations and bumps in acute VKH (7). Kato *et al.* observed RPE folds in 30/42 eyes (71%) of those with acute VKH but in none of the other 72 eyes with other etiologies of uveitis, pointing to the diagnostic utility of this finding (8). Hosoda *et al.* also noted an increased RPE undulation index in eyes with acute VKH. They found that eyes with a larger RPE undulation index were associated with an increase in choroidal thickness (9). Hashizume found that those with increased RPE undulations were older, more likely to develop recurrences at 12 months and have worse vision (10). However, Nazari and Rao while also noting the presence of RPE folds in a population of patients with acute VKH found that they did not correlate with final visual acuity or response to corticosteroid treatment, though their sample size was smaller than the former study (11).

Hirooka *et al.* further evaluated the choroidal layers in 15 eyes with acute VKH at baseline and post-treatment with systemic corticosteroid therapy given prior studies showing choroidal thickening in the acute phase. The mean whole and outer choroidal layer in patients with acute VKH decreased after systemic treatment at the 1 week and 3-month mark without any significant thinning of the inner layer of the choroid. Importantly, there was a significant positive correlation between the rates of change of the whole and outer layer thickness from 1 week to 3 months ($R = 0.9312$, $P<0.0001$), but not between the rates of whole and inner layer thickness changes. This suggests that the increase in choroidal thickness seen in the acute phases of the disease are correlated with the thickening of the outer choroid (12). From a histopathologic standpoint, lymphocytic infiltration has been noted in the swollen choroidal stroma, but not in the choriocapillaris, consistent with the above finding (13).

Optical coherence tomography angiography is a relatively new technique that allows for non-invasive visualization of retinal and choroidal blood flow, and has many potential applications in understanding the pathophysiology behind retinal and choroidal disease. Aggarwal *et al.* evaluated optical coherence tomography angiography (OCTA) in patients with VKH and CSR and compared the findings to fluorescein angiography (FA), indocyanine green angiography (ICGA) and enhanced depth imaging (EDI) OCT. Thirty four eyes (10 with VKH and 14 with CSR) were evaluated. In CSR, OCTA en face images demonstrated apparent areas of choriocapillaris flow void due to a shadowing effect from overlying subretinal fluid and pigment epithelial detachments (PED) where those with VKH showed a true choriocapillaris flow void on OCTA (14). This flow void was consistent with areas of ischemia on ICGA which could potentially allow for the

use of OCTA as an alternative to ICGA in the diagnosis of VKH, though the smaller field of view provided by OCTA at this time is a limitation to widespread and effective use.

Choroidal granulomas are seen in different conditions that may be clinically similar in appearance, for example, sarcoidosis and VKH. Invernizzi *et al.* evaluated 44 choroidal granulomas from 15 eyes on enhanced depth imaging (EDI)-OCT and compared those seen in VKH (7 granulomas in 2 patients) to sarcoidosis (22 granulomas in 4 patients) and tuberculosis (15 granulomas in 3 patients). Granulomas in VKH were more likely to span the full thickness of the choroid compared to sarcoidosis and tuberculosis. They were also more likely to be round in shape and homogenous in appearance compared with tuberculosis. However, the granulomas were less well defined in VKH than in sarcoidosis (15). Further studies using EDI-OCT may be helpful in differentiating these inflammatory uveitides.

Classically, the recurrent form of VKH is limited to the anterior segment. In an interesting study, Takemoto *et al.* evaluated ICGA findings and laser speckle flowgraphy (LSFG) in 17 eyes of 11 patients with recurrent VKH showing only anterior recurrence on clinical examination. ICGA and LSFG was performed at the time of recurrence and again one month after the initiation of corticosteroid therapy. Hypofluorescent dark dots on ICGA were noted on both exam and counted independently by three physicians and the mean blur rate (MBR) was quantified via LSFG. 13 of 17 eyes (76%) of patients were noted to develop HDD and the number and total area of the HDD significantly decreased on follow up at 1 month. The MBR also significantly increased by 16.3% after treatment. This paper demonstrated that there can be subclinical involvement of the posterior pole during anterior recurrence of VKH (16) and likely needs to be evaluated further. It is unclear whether this involvement of the posterior pole is clinically relevant over a longer duration given the chronic nature of VKH. Electroretinogram studies have shown a decrease in visual function over time (17,18) that is associated with the development of a depigmented fundus, and future studies are needed to correlate the presence of subclinical posterior segment recurrences and longitudinal ERG findings.

Developments in treatment

Systemic corticosteroids are still the mainstay of treatment of acute VKH with the principle of treatment being to halt the inflammation quickly, and then once the eye is quiet, slowly taper the corticosteroids over months. Immunomodulatory therapy (IMT) can be started concurrently in patients as it can take weeks to months to achieve a full effect, thus allowing withdrawal of the corticosteroids (19-21), and dexamethasone implants have recently also been used for this purpose (22,23).

Hosoda *et al.* evaluated the use of subtenon triamcinolone injections (STI) as the primary treatment for acute VKH. Twenty-seven eyes of 14 patients were treated with isolated STI for acute VKH, of which 6 eyes in 3 patients recurred, all of whom had headaches at the initial visit. Thus, treatment with STI alone resulted in disease resolution without a recurrence in 77.8% of the patients as long as systemic symptoms were not present (24). There may be a role for local corticosteroid injections, as a primary treatment, in patients without systemic signs of VKH, though, data for this is limited and needs to be further evaluated.

Paredes and colleagues recommend using immunomodulatory therapy as a first-line treatment for VKH with or without the addition of corticosteroids based on results from a study between 2 groups of patients, the first receiving prolonged systemic corticosteroid treatment with or without the delayed addition of immunomodulatory therapy (5 patients) and the second receiving relatively prompt immunomodulatory therapy with or without corticosteroids (8 patients). They demonstrated a superior visual outcome of prompt immunomodulatory therapy when compared with steroid as monotherapy or delayed addition of IMT (20). Recently, Urzua *et al.*, while noting that there was no significant difference in visual outcomes in patients treated with first line IMT and prednisone or late IMT, noted a specific subgroup of patients had a superior visual outcome with early IMT initiation. These patients had earlier initiation of IMT while on corticosteroids but had demonstrated a poor response to corticosteroid therapy (21). The study was retrospective and more work needs to be done to determine how quickly IMT should be started, or in which population it provides the most benefit while limiting systemic side-effects.

Abu El-Asrar and colleagues demonstrated the utility of mycophenolate mofetil as a first line IMT agent in 38 patients (76 eyes) with VKH in a prospective study in which 93.4% of eyes attained vision of 20/20, two eyes (2.6%) developed glaucoma, and five eyes (6.6%) developed cataract, but most importantly, none developed a sunset glow fundus appearance (25). Azathioprine and methotrexate have also been shown to be effective in patients as has cyclosporine A (26-30). Haruta *et al.* evaluated the use of low dose (100 mg daily) cyclosporine

in 23 eyes of 13 patients with VKH resistant to systemic corticosteroids. 92.8% eyes with anterior inflammation had resolution of inflammation at 3 months and 76.9% of eyes with posterior inflammation had resolution at 3 months after CsA treatment (30).

Biological response modifiers (BRMs) have been shown to be effective in the management of uveitis refractory to treatment with conventional immunosuppression and their use is becoming increasingly frequent. Adalimumab and rituximab have both demonstrated efficacy in the pediatric and adult population in the control of VKH (31-36) though these reports are limited. Couto *et al.* evaluated 14 patients with VKH who were able to transition from 20 mg of oral prednisone to 4 mg at 6 months after initiation of adalimumab (34). Infliximab demonstrated efficacy in refractory cases of VKH with clinical remission being observed within a month or two of onset of treatment (37-39). Budmann recently reported a case of pediatric VKH that has been controlled with 6 mg/kg/pulse infliximab every 60 days along with methotrexate at 15 mg/week for 10 years (40). One of the main benefits of biologic response modifiers may be their faster onset of action compared to more traditional immunomodulatory agents, but needs further assessment. Since VKH is primarily a T-cell mediated immune response against melanocytes, the efficacy of cyclosporine A (CsA) which targets T cells is consistent with this pathogenic mechanism. It is thus notable that rituximab, a monoclonal antibody targeting CD-20, has also demonstrated efficacy in limited case reports. Further research needs to be performed on the role of B cells in VKH and on the use of biological response modifiers in this disease.

Conclusions

VKH is a severe vision-threatening illness and inadequate control of the disease can result in permanent defects in visual function. OCT, OCT-A, and EDI-OCT have emerged as useful tools in distinguishing this condition from other uveitides in a non-invasive manner, though FA and ICGA remain the primary diagnostic modalities. Oral corticosteroid therapy is still the mainstay of treatment for patients with acute VKH, but most patients have a need for long-term immunosuppression, and treatment options have expanded significantly over the last decade to allow for improved control of inflammation and better visual outcomes. Understanding treatment response may allow us to better understand the pathophysiology of this disease.

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