



Uveitis Society (India)

EDITION-05

# NEWSLETTER

VOLUME - 1 | FEBRUARY 2023

## VOGT KOYANAGI HARADA'S DISEASE



## From the Desk of **PRESIDENT**



Dear friends,

Wish you all a very happy and prosperous new year 2023.

It is with great pleasure we bring to you the 5<sup>th</sup> edition of the USI newsletter. This edition features Vogt koyanagi Harada disease (VKH), a disease if not diagnosed early or treated aggressively, is known to be associated with poor visual outcomes. Our editorial team has compiled some interesting topics in this newsletter. I am sure the panel discussions by our national and international faculty will address many queries on this disease, which will be useful in our clinical practice.

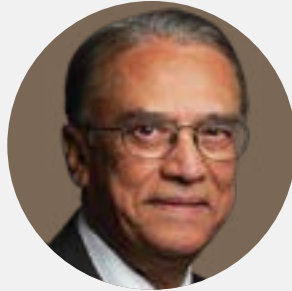
I thank all the authors, our national and international panel for this edition and the editorial team led by Dr. Balamurugan for their coordinated efforts in bringing this interesting issue on VKH.

### **Dr. Kalpana Babu**

Prabha Eye Clinic and Research Centre  
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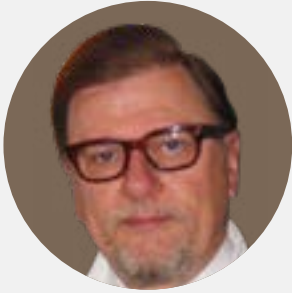


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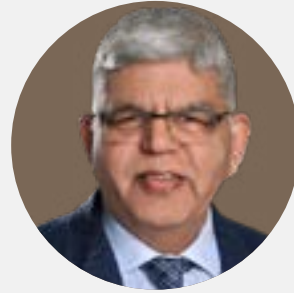


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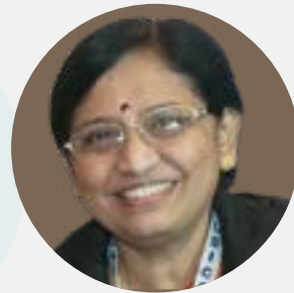
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## From the USI EDITORIAL DESK...



Pleasure is mine to be the part of the elegant editorial team in the field of uveitis who have actively contributed for this wonderful edition of USI Newsletter on Vogt Koyanagi Harada's uveitis. This is a highly intriguing topic which has grown in leaps and bounds due to the proimaging strategies, advances in molecular biologies and histopathologies

The challenging era of COVID-19 is far behind us and we need to focus single mindedly at the modifiable risk factors in our life to make it an useful energetic voyage of life. We strongly believe that collective human endeavors shall bear triumphant fruits for sure like in this journey of USI newsletter. I sincerely thank all the motivating leaders, contributors, readers, critics for propelling us to improve and refine our sincere efforts. All the bouquets pertaining this newsletter are surrendered to the almighty. All the brickbats concerning this newsletter are valuable pearls for us to refine and define our selves in the future. Understand that you ask me why....It's because otherwise it would have been a lucid garland in the lotus feet of Almighty and make you smile....

### **Dr. S Bala Murugan**

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# CONTENTS

Click on the icon to view the article...



## History of Vogt- Koyanagi- Harada Disease

*Dr. S Bala Murugan, Dr Yuvraj Madhav, Dr. Aditya Anand*

10



## Immunopathogenesis of Vogt Koyanagi Syndrome

*Dr. Eliza Antony, Dr. Vedhanayagi R, Dr. S Bala Murugan*

15



## Expert's Opinion

*Dr. Jyotirmay Biswas, Prof. Shwu-Jiuan Sheu, Dr. Annabelle A Okada*

19



## Crossword Puzzle

*Dr. Gazal Patnaik*

27



## INVESTIGATIONS IN UVEITIS

**A**

### Ultrasound and fundus autofluorescence in Vogt-Koyanagi-Harada disease

*Dr. Kalpana Babu, Dr. Satabdi Nanda, Dr. Vidya Mooss  
Dr. Preethi S Shetty, Dr. Vinaya Kumar Konana*

30

**B**

### Optical coherence tomography in Vogt Koyanagi Harada disease(VKH)

*Dr. Jyotirmay Biswas, Dr. Vishnu Deepthi N*

38

**C**

### Optical Coherence Tomography Angiography in Vogt-Koyanagi- Harada disease

*Dr. Aniruddha Agarwal*

50

**D**

### Fundus Fluorescein Angiography and Indocyanine Green Angiography in Vogt-Koyanagi- Harada Disease

*Dr. Aditya Patil, Dr. Ankush Kawali, Dr. Srinivasan Sanjay  
Dr. Sai Bhakti Mishra, Dr. Padmamalini Mahendradas*

58



# CONTENTS

Click on the icon to view the article...



## **Treatment in VKH**

*Dr. Sabia Handa, Dr. Reema Bansal*

69



## **Vogt Koyanagi Harada disease in a pregnant woman – Challenges in treatment**

*Dr. Jyotirmay Biswas*

75



## **Literature Review**

*Dr. Gazal Patnaik*

80



## **Awards and Recognitions**

91

## **CME Conducted Under the Aegis of Uveitis Society (India)**



## **Bengal Uveitis Summit 2022**

99



## **IGNITE 2023**

100



## **Crossword Answers**

101

# History of Vogt-Koyanagi- Harada Disease



**Dr. Yuvraj Madhav**  
**Dr. Aditya Anand**



**Dr. S Bala Murugan**  
*Aravind Eye Hospital, Pondicherry*

Vogt- Koyanagi- Harada disease described for the first time by Alfred Vogt in 1906 in a case description that primarily focused on poliosis. The 14 page long article dedicated only 5 lines to intra ocular inflammation. Alfred Vogt was a Swiss Ophthalmologist, who developed the techniques for retinoscopy and the surgical management of retinal detachment. Vogt was a pioneer of specular microscopy. Using a slit lamp with a corneal microscope to investigate the structures of the anterior areas of the eye, in 1918 he became the first to perform direct examination of the corneal endothelium.



After the article written by Alfred Vogt in 1906, several patients with VKH were described in Japan. The first was published by Professor Jujiro Komoto in 1911. In 1914, Yoshizo Koyanagi described 2 cases published in the Japanese journal, named Nippon "Ganka Gakkai Zashii". Yoshizo Koyanagi was the first Professor of Ophthalmology of Tohoku Imperial University in Sendai, 300 km north of Tokyo. In 1929 he published a ground-breaking article in the German journal, named "Klinische Monatsblätter für Augenheilkunde", describing 16 cases of VKH. The importance of that article lay in the fact that for the first time it described the precise natural course of VKH, although no treatment was available back then. At the time, to gain international exposure, Japanese authors mostly published in German journals, because the medical doctrine and structure were built on the German system; many professors and numerous doctors completed their training in Germany. Koyanagi passed away in 1954 and was buried in Sendai, after having been dissuaded from his wish to have his ashes spread in the Bay of Matsushima, off Sendai.

In parallel, Einosuke Harada described one case in 1923, published in German, and 5 cases in 1926, published in Nippon Ganka Gakkai Zashii, of a novel condition. The latter article described the posterior involvement of VKH disease, which he called acute diffuse choroiditis (choroiditis diffusa acuta). Einosuke Harada was born in 1892 in Amakusa, on Kyushu Island, in Southern Japan. After training as an internist, and working for the army, Harada then reoriented his training towards ophthalmology. In 1923, he published the first “Harada” case, described as “acute diffuse choroiditis”. In 1926, he wrote his main article on five cases, which included the previously described case, and thus, contributed his name to the present eponym of the disease. Essentially, he described the posterior features of VKH disease. He worked in the Hara Eye Clinic in Nagasaki until 1943, when he was drafted by the army to the battlefield in the Philippines. From there, he was sent home, due to illness. His clinic was destroyed by the atomic bomb. He was planning to rebuild it but succumbed to illness in December 1946. He is buried in his hometown of Amakusa, south of Nagasaki.

The final eponym was coined by Professor Jean Babel of Geneva, who joined the names Vogt and Koyanagi in a proposal to call the disease Vogt-Koyanagi syndrome (disease). At that time, it was known that Harada’s disease and Vogt-Koyanagi syndrome were nearly identical. By 1970, the majority of articles published used the term Vogt-Koyanagi-Harada disease (syndrome), and by 2003, most authors had adopted the term Vogt-Koyanagi-Harada disease.

## **The revised diagnostic criteria proposed by the First International Workshop on Vogt Koyanagi Harada Disease:**

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

- 1. No history of penetrating ocular trauma or surgery preceding the initial onset of uveitis**
- 2. No clinical or laboratory evidence suggestive of other ocular disease entities**
- 3. Bilateral ocular involvement (a or b must be met, depending on the stage of disease when the patient is examined)**

#### **a) Early manifestations of disease**

**There must be evidence of a diffuse choroiditis (with or without anterior uveitis, vitreous inflammatory reaction, or optic disc hyperemia), which may manifest as one of the following:**

- Focal areas of subretinal fluid, or
- Bullous serous retinal detachments.

**With equivocal fundus findings; both of the following must be present as well:**

- 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
- Diffuse choroidal thickening, without evidence of posterior scleritis by ultrasonography.

**b) Late manifestations of disease:**

- History suggestive of prior presence of findings from 3a, and either both (4) and (5) below or multiple signs from (5)
- Ocular depigmentation (either of the following manifestations is sufficient)
- Sunset glow fundus, or
- Sugiura sign

**Other ocular signs:**

- Nummular chorioretinal depigmented scars, or
- Retinal pigment epithelium clumping and/or migration, or
- Recurrent or chronic anterior uveitis.

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

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

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

- Alopecia, or
- Poliosis, or
- 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
4. Neurologic/auditory findings: as defined for complete Vogt-Koyanagi-Harada disease above,  
or
5. Integumentary findings: as defined for complete Vogt-Koyanagi-Harada disease above

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

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



# Immunopathogenesis of Vogt Koyanagi Syndrome



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**Dr. S Bala Murugan**  
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## Immunopathogenesis of Vogt Koyanagi Syndrome

Vogt Koyanagi Harada disease (VKH) is a systemic autoimmune disease, characterized by bilateral granulomatous panuveitis. Etiology is unclear and multifactorial with a complex autoimmune response, directed against the melanocyte rich tissue like eyes, ears, meninges and skin. Innate, humoral and cellular immunity along with genetic predisposition and environmental factors, have been implicated in pathogenesis of VKH.<sup>(1)</sup>

VKH involves a T-cell mediated autoimmune response directed against the melanocyte specific peptide autoantigens tyrosinase along with tyrosinase related protein -1 (TRP-1) and tyrosinase related protein - 2 (TRP-2).<sup>(1)</sup> Various infective triggers have been established in pathogenesis of VKH like hepatitis B, hepatitis C, Epstein-Barr virus, cytomegalovirus, influenza A, mycoplasma pneumonia and severe acute respiratory syndrome coronavirus-2 virus (SARS-CoV-2).<sup>(1),(2)</sup> Various reports have described the molecular mimicry exhibited by these infective triggers, which cross reacts with tyrosinase peptidase antigens. Second proposed mechanism is by generation of remnant epitopes, due to breakdown of melanocyte peptide, secondary to extracellular proteolysis following bacterial or viral triggers. These tyrosinase peptidase antigens and remnant epitopes act as autoantigens which initiate reactivation of T cell and B cell mediated immune response and thereby the pathogenesis of VKH. On one hand molecular mimicry is adaptive response and on the other hand remnant epitope is manifest of innate immunity.<sup>(1),(3)</sup>

B cells also play important role in pathogenesis of VKH. Among the four subtypes of CD19+ B cells, there is marked elevation of the unswitched memory B cells population in VKH, as compared to the other three subtypes - the naive B cells, switched memory B cells and the double negative memory B cells, which are also elevated but not significantly.<sup>(4)</sup> Increased levels of B cells chemoattractant, CXCL3 have been reported in aqueous humour of VKH patients. Other biomarkers like Tumour necrosis factor (TNF) like weak inducer of apoptosis (TWEAK), a B cell activating factor of the TNF family (BAFF) and a proinflammatory inducing ligand (APRIL) are involved in B cell mediated immune response and all are found to be elevated in aqueous humour of VKH patients, thus establishing pathogenetic role of B cells in VKH.<sup>(1)</sup>

Peripheral blood of VKH patients also demonstrates increase in monocytes population and in the levels of interleukin- 8 which is produced by these monocytes, thus indicating their role in pathogenesis of disease.<sup>(4)</sup>

Role of genetic predisposition and environmental factors in pathogenesis of VKH has been well exemplified by various reports in literature. Variable distribution and differences in HLA and genetic makeup in different ethnic groups establish the multifactorial pathogenesis of VKH. (Table 1) <sup>(5)</sup> Studying various causative and predisposing factors is very crucial, not only in unveiling the disease pathogenesis but also in developing a more efficient and targeted approach for managing VKH.

**Table 1- Various genetic factors associated with pathogenesis of VKH<sup>(5)</sup>**

HLA serotypes associated VKH	HLA-DQ4 HLA-DQw7 HLA-DR1 HLA-DR4 HLA-DR53
HLA genotypes associated VKH	HLA-DQA1*0301 HLA-DQB1*0604 HLA-DRB1*0404 HLA-DRB1*0405
Interleukins genes associated with VKH	IL-12B, IL-17F, IL-23R,IL-27
	Cytotoxic T-lymphocyte antigen 4 (CTLA-4) Interleukin (IL) genes Killer cell immunoglobulin-like receptors (KIR) gene cluster Programmed cell death 1 (PDCD1) Protein tyrosine phosphatase non-receptor 22 (PTPN22) Osteopontin (OPN) Tumor necrosis factor, alpha-induced protein 3 (TNFAIP3) Macrophage migration inhibitory factor (MIF) Fibroblast growth factor receptor 1 oncogene partner (FGFR1OP)

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# Expert's Opinion



## Dr. Jyotirmay Biswas



Director of uveitis and ophthalmic pathology

Sankara Nethralaya, Chennai

He has published 508 articles in pubmed indexed journals, 62 chapters. He has mentored 45 uveitis fellows. He has received 44 awards including Hari OM Ashram Alembic research award from ICMR given by the president of India.

He is a member of International Uveitis Study Group, American Uveitis society, International Ocular Inflammation Society

## Dr. Shwu-Jiuan Sheu



Dr Shwu-Jiuan Sheu graduated from Kaohsiung Medical University in 1984. She completed her residency and proceeded to attain fellowships in ophthalmology at the Taipei Veterans General Hospital, Taiwan, in 1989 and the Doheny Eye Institute, University of Southern California, USA, in 1992. She served as chairperson of Ophthalmology at the Kaohsiung Veterans Hospital (1995-2016) and president of Taiwan Retinal Society (2014-2015).

Professor Sheu is currently director and professor of ophthalmology at Kaohsiung Medical University in Taiwan. She is also serving as president of Taiwan Ocular Inflammation Society since 2021. Professor Sheu is a well-known retinal surgeon in Asia-Pacific and globally recognized for her research in clinical and bench to bed-site. She published extensively on vitreoretinal disease, diabetic retinopathy, age-related macular degeneration, retinal detachment, drug delivery in uveitis and basic and translational research.

## Dr. Annabelle A Okada



Dr Okada is a Professor of Ophthalmology in the Department of Ophthalmology at Kyorin University School of Medicine in Tokyo, Japan. She serves as Director of both the Ocular Inflammation Service and the Macular Disease Service at the Kyorin Eye Center of Kyorin University Hospital, the first truly comprehensive clinical and research eye center in Japan established in 1999.

Dr Okada is a longstanding member of numerous national and international societies including the American Academy of Ophthalmology, the Association for Vision and Research in Ophthalmology, the International Ocular Inflammation Society, the International Uveitis Study Group, the American Uveitis Society, the Retina Society, the Japanese Ophthalmological Society, the Japanese Ocular Inflammation Society, and the Japanese Vireoretina Society.

**1. How to differentiate between VKH in convalescent stage and other long standing chronic uveitic conditions like sarcoidosis or sympathetic ophthalmia?**

**Prof. Shwu-Jiuan Sheu**

The clinical manifestation of VKH and sympathetic ophthalmia (SO) is quite similar. Absence of ocular surgery or trauma history help rule out the diagnosis of SO. The choroid thickening is quite a characteristic sign of VKH in acute stage, but not in the convalescent stage. Ocular sarcoidosis should have more inflammatory sign in the vessels.

**Dr. Annabelle A Okada**

This can be difficult at times, and the best way would be to look at data during the early acute phase of disease where you should see choroidal thickening sometimes with RPE waving for VKH disease or sympathetic ophthalmia but not for sarcoidosis. Of course, if there is a history of penetrating trauma or intraocular surgery, sympathetic ophthalmia becomes more likely. Then, obviously, one could do systemic ancillary testing to rule-in or rule-out sarcoidosis. If HLA testing is available, both VKH disease and sympathetic ophthalmia have an association with DR4.

**Dr. Jyotirmay Biswas**

VKH in late stage will often show sunset glow fundus and Dalen Fuchs nodule. It is not seen in sarcoidosis but can be seen in sympathetic ophthalmia.

**2. Would you suspect VKH in a patient with history of headache, tinnitus and bilateral disc edema only without any other inflammatory signs?**

**Prof. Shwu-Jiuan Sheu**

Yes, some cases presented with headache, disc edema and choroid thickening. The inflammation responds well to steroid. Of course, infection should be fully surveyed before making this diagnosis and treatment.

**Dr. Annabelle A Okada**

I would suspect VKH disease in this patient if there was diffuse choroidal thickening bilaterally by EDI-OCT or SS-OCT. If ICG angiography is available, then the finding of multifocal “dark dots” in the choroid would also support the diagnosis of VKH disease. Cerebrospinal fluid analysis may reveal pleocytosis which would also be consistent with VKH disease, however viral meningitis may need to be ruled-out with PCR of cerebrospinal fluid. Finally, other neurological issues may need to be ruled-out by neuroimaging.

**Dr. Jyotirmay Biswas**

Yes.

### 3. Are there any clues to differentiate bilateral posterior scleritis and VKH?

#### Prof. Shwu-Jiuan Sheu

Although not pathognomonic, ocular pain is relatively more severe compared to blurred vision in cases of posterior scleritis. The pain is usually deep and dull. Ultrasonography helps to show the thickening of posterior sclera or even T sign, which is seldom noted in VKH.

#### Dr. Annabelle A Okada

Pain is a big clue and B-scan ultrasound showing a “T sign” would be helpful, both supportive of posterior scleritis. I rarely have VKH disease patients who complain of eye pain . . . it's always headache.

#### Dr. Jyotirmay Biswas

Granulomatous anterior uveitis, vitreous haze helps to differentiate. There is sometimes pain on movements of the globe. Ultrasound helps to show sclerochoroidal thickening and presence of T sign.

### 4. What is the role of investigations like B scan, FFA and ICG in diagnosis and management of VKH

#### Prof. Shwu-Jiuan Sheu

FFA and ICG is important in the initial diagnosis, although ICG is not available in every hospital. With the popularity of OCT, B scan is only considered in case of media opacity or try to differentiate with posterior scleritis.

#### Dr. Annabelle A Okada

All of these are important in the diagnosis of VKH disease, although B-scan ultrasonography is only necessary in select cases (see #3 above). For the management of VKH disease already on treatment, usually EDI-OCT is adequate for following treatment response and is an imaging modality that can be done easily at every patient visit.

#### Dr. Jyotirmay Biswas

All of them helps to diagnose VKH specially in atypical cases.

### 5. How often do you rely upon OCT and OCT angiography in your cases of VKH

#### Prof. Shwu-Jiuan Sheu

I use OCT EDI in nearly every visit to monitor the change of choroid thickness and vitreous haze. OCTA is done whenever I suspect something more than inflammation, such as choroidal neovascularization. Every now and then, I will repeat OCTA to check the vascular status.

#### Dr. Annabelle A Okada

As above, I perform OCT (EDI-OCT) at every patient visit. I would only obtain OCT angiography if I suspected choroidal neovascularization, a rare complication in chronic cases. However, future research in OCT angiography may show usefulness of this imaging modality for following treatment outcomes as well.

#### Dr. Jyotirmay Biswas

I depend on EDI OCT (Swept source) in the initial stage. It shows bacillary layer retinal detachment, subretinal septae and diffuse choroidal thickening.

## 6. How do you differentiate FFA in VKH and CSCR with multiple leaks

**Prof. Shwu-Jiuan Sheu**

CSCR seldom has sign of inflammation in the anterior or posterior segment. Smoke stack like leakage is seldom seen in VKH. The distribution of leaking points in CSCR is more irregular than VKH.

**Dr. Annabelle A Okada**

If one is considering fluorescein angiography in complete isolation, then the differentiating factors would be evidence of RPE atrophy (such as descending track) in longstanding central serous chorioretinopathy (CSC), and perhaps the absence of bilaterality. However, in reality, one makes a judgement based on other factors, such as presence of prodromal symptoms, OCT and EDI-OCT in particular. VKH disease would show diffuse and marked choroidal thickening as opposed to CSC which can have choroidal thickening in focal areas but not diffuse and not very marked.

**Dr. Jyotirmay Biswas**

Multiple point leaks in initial stage with late pooling of dye in multifocal CSCR

## 7. “Limited VKH” treated without immunomodulators (IMT) has been reported. Do you ever consider treating VKH without concurrent immunomodulatory therapy

**Prof. Shwu-Jiuan Sheu**

I usually start treatment with IVMP for acute phase or early recurrent cases followed by oral steroid unless steroid is contraindicated for the patients. I use the same protocol for limited VKH too. For chronic anterior uveitis without posterior segment involvement, topical or local treatment might help.

**Dr. Annabelle A Okada**

Yes, all the time, since the majority of my cases are referred in the acute early stage (still none to only mild anterior segment inflammation), at which time I admit them to the hospital and initiate pulse intravenous methylprednisolone (1-3 pulses) followed by an oral prednisolone taper over 12-18 months. In our hands, this results in a low recurrence rate and few complications (Nakayama et al. Clinical features and visual outcomes of 111 patients with new-onset acute Vogt-Koyanagi-Harada disease treated with pulse intravenous corticosteroids. Br J Ophthalmol 2019;103:274-278). Therefore, I only use immunomodulatory agents (usually cyclosporine) for patients that have recurrence of inflammation during the steroid taper, making it obvious that longer term immunosuppression is necessary, or in patients who are referred with more chronic disease (usually with more severe anterior segment inflammation). I also transition to cyclosporine (or adalimumab) early on as a steroid-sparing agent in patients who would be intolerant of corticosteroids, such as individuals with moderate-to-severe diabetes or history of psychiatric disease or osteoporosis/fractures, etc.

**Dr. Jyotirmay Biswas**

No.



## **8. Do you start IMT as soon as you have made the diagnosis of VKH**

**Prof. Shwu-Jiuan Sheu**

I usually start treatment with IVMP for acute phase or early recurrent cases followed by oral steroid unless steroid is contraindicated for the patients.

**Dr. Annabelle A Okada**

See #7 above.

**Dr. Jyotirmay Biswas**

Yes.

## **9. Is there any specific clinical presentation or any presenting signs at the presentation that prompts you to start IMT.**

**Prof. Shwu-Jiuan Sheu**

IMT only for early recurrence or refractory cases.

**Dr. Annabelle A Okada**

See #7 above. Evidence of chronicity at presentation, for example severe anterior segment inflammation, would prompt me to start IMT usually in conjunction with corticosteroids (or periocular corticosteroid injections in selected cases). One must keep in mind that IMT takes some time to kick in, while the effect of corticosteroids is rapid, so choice of treatment depends on the severity of active inflammation. Also, presence of sunset glow fundus but with active cells would be an indication for treatment as chronic VKH disease and IMT would be one option, again depending upon severity.

**Dr. Jyotirmay Biswas**

I do give IMT in every cases of VKH unless contraindicated.

## **10. Do you consider treating all cases of acute VKH with IVMP. If not then, when do you prefer IVMP over other routes of steroid administration in a case of VKH presenting with serous detachment?**

**Prof. Shwu-Jiuan Sheu**

I usually start treatment with IVMP for acute phase or early recurrent cases followed by oral steroid unless steroid is contraindicated for the patients.

**Dr. Annabelle A Okada**

See #7 above.

**Dr. Jyotirmay Biswas**

Yes in all cases whenever possible.

### 11. Which immunomodulatory agent do you prefer in VKH to start with?

**Prof. Shwu-Jiuan Sheu**

Cellcept.

**Dr. Annabelle A Okada**

Other than corticosteroids, the Japanese health insurance system only allows use of cyclosporine and adalimumab for the indication of non-infectious uveitis (and no systemic rheumatological disease indication which would allow use of many other IMT agents).

**Dr. Jyotirmay Biswas**

Mycophenolate or azathioprine. If nonresponsive switch to cyclophosphamide or cyclosporine. I also try triple immunosuppression like cyclosporine, azathioprine and prednisolone.

### 12. After how much duration do you consider discontinuation of IMT in a case of VKH and when and how would you stop IMT?

**Prof. Shwu-Jiuan Sheu**

I will keep IMT for 2 years before discontinuation. I taper the medication according to the clinical course.

**Dr. Annabelle A Okada**

As long as there are no major side effects, I generally wait 1-2 years for confirmation of no inflammatory recurrence on IMT alone (no concomitant corticosteroids) before starting to taper. In the case of cyclosporine, I usually reduce by 25 mg every 6 months while monitoring choroidal thickness by EDI-OCT and of course other inflammatory findings such as cells.

**Dr. Jyotirmay Biswas**

6 months minimum. Sometimes continue longer based on clinical and SSOCT findings.

### 13. What are the pre-op precautions you will take before cataract surgery in a case of VKH

**Prof. Shwu-Jiuan Sheu**

For non-emergent cataract surgery, I always wait for at least 3 months of silent period and keep or increase dose of the original medication a little bit before operation.

**Dr. Annabelle A Okada**

Once I have decided the patient should have cataract surgery, I usually will not taper further any systemic medications until after the surgery is over. I then will wait approximately 6 months post-surgery before taking the next step of tapering.

**Dr. Jyotirmay Biswas**

I will put the patient on tablet prednisolone 40 mg per day 3 days prior to surgery.

**14. Have you witnessed increased incidence of VKH-like disease during the pandemic? Would you start IMT in such cases?**

**Prof. Shwu-Jiuan Sheu**

Yes, I did see a slightly increased VKH-like disease. If infection can be ruled out, I treat as usual.

**Dr. Annabelle A Okada**

Yes, we have published this in relation to COVID-19 vaccination (Nakayama et al. COVID-19 vaccination-related intraocular inflammation in Japanese patients. Graefes Arch Clin Exp Ophthalmol 2022; online ahead of print). Of note, these cases are usually not very severe, and do well with corticosteroid monotherapy (IV pulse followed by oral taper).

**Dr. Jyotirmay Biswas**

No. I will avoid IMT in such cases.

**15. What is your experience on the use of newer biologicals in VKH. Which newer biological drug do you prefer.**

**Prof. Shwu-Jiuan Sheu**

Since only Humira was approved for uveitis and reimbursed in refractory pediatric cases, I have limited experience about it. It works in refractory case.

**Dr. Annabelle A Okada**

See #11 above. Adalimumab in our hands appears to work well in VKH disease just as in other forms of non-infectious uveitis.

**Dr. Jyotirmay Biswas**

I have used inj. Adalimumab in 2 cases resistant to IMT and steroid. They are on follow up.

**16. What is your line of management in pediatric VKH.**

**Prof. Shwu-Jiuan Sheu**

Steroid then MTX, Humira if still refractory.

**Dr. Annabelle A Okada**

The youngest patient I can recall was 19 years old, and this patient received the same treatment as an adult.

**Dr. Jyotirmay Biswas**

I will prefer not to put them on long term steroid to avoid growth retardation.

**17. How will you treat recalcitrant/recurrent VKH in pediatric VKH.**

**Prof. Shwu-Jiuan Sheu**

Intravitreal Ozurdex for refractor macular edema and try biologics.

**Dr. Annabelle A Okada**

Skip.

**Dr. Jyotirmay Biswas**

I use combination of mycophenolate and methotrexate.

**18. Will you start IMT immediately on diagnosing pediatric VKH. Which drug do you prefer in these cases.**

**Prof. Shwu-Jiuan Sheu**

I still use steroid first, but start MTX earlier to prevent long term steroid. For pediatric cases, I prefer to co-care with rheumatologists.

**Dr. Annabelle A Okada**

Skip.

**Dr. Jyotirmay Biswas**

Yes. Mycophenolate.

**19. What is your experience on iv cyclophosphamide in VKH. Which do you prefer- i.v or oral route. Is there any difference in response to treatment between these two routes of administration.**

**Prof. Shwu-Jiuan Sheu**

I usually ask the rheumatologist to combined care the patients. In severe or refractory cases, pulse iv works.

**Dr. Annabelle A Okada**

No experience with IV cyclophosphamide.

**Dr. Jyotirmay Biswas**

I give oral cyclophosphamide. There is not much difference between IV and oral cyclophosphamide.

**20. How will you manage inflammatory CNVM in VKH. What is your preferred anti- VEGF drug.**

**Prof. Shwu-Jiuan Sheu**

I treat CNVM in VKH with intravitreal injection of anti- VEGF and add or keep the current IMT/ steroid. Since our national insurance does not reimburse anti-VEGF for CNVM 2nd to uveitis, the choice of anti-VEGF depends on the patients' finance. Most patients respond well to various anti-VEGF.

**Dr. Annabelle A Okada**

Any anti-VEGF agent would work well, but I would choose ranibizumab since inflammatory CNVs are usually type 2 MNVs with adequate response to ranibizumab.

**Dr. Jyotirmay Biswas**

No preference . Either bvacizumab or ranibizumab.

# Crossword Puzzle



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# INVESTIGATIONS IN UVEITIS





## A. Ultrasound and fundus autofluorescence in Vogt-Koyanagi-Harada disease



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## 1. Introduction

Vogt-Koyanagi-Harada (VKH) disease is a severe bilateral granulomatous posterior or panuveitis associated with serous retinal detachments, disc oedema, and vitritis, with eventual development of a sunset glow fundus.

Imaging plays a major role in the diagnosis of VKH, monitoring of the intraocular inflammation and response to treatment, as well as the development of complications. In this chapter we highlight the role of ocular ultrasound and fundus autofluorescence in VKH.

## 2. Ocular ultrasound

Ultrasound (US) is a diagnostic imaging technique that uses high-frequency sound waves to provide a dynamic view of ocular structures. The eye's fluid content and its superficial position make it ideally suited for examination with ultrasonography. It is one of the techniques of obtaining images of the posterior segment of the eye when the light-conducting media are opaque (1).

Although the vast majority of VKH is diagnosed by clinical examination, occasionally, the view to the posterior chamber is obscured because of dense vitritis, posterior synechiae, or the presence of a cataract. In such cases, ultrasonography can be used to make the diagnosis. The following features noted on ultrasound are consistent with the diagnosis of VKH(2,3):

- Diffuse, low to medium reflective thickening of the choroid posteriorly
- Serous retinal detachment(SRD) located inferiorly or at the posterior pole
- Mild vitreous opacities with no posterior vitreous detachment
- Thickening of the sclera and/or episclera posteriorly

Ultrasonography can also be used to follow response to treatment in the absence of a direct view, as, resolution of these findings occurs with appropriate steroid and immunomodulatory treatment. Ultrasonography, however, must be used carefully to distinguish between several different entities such as posterior scleritis, benign reactive lymphoid hyperplasia of the uvea, and diffuse melanoma of the choroid. Ultrasonographic features of VKH and sympathetic ophthalmia are the same with the distinguishing feature being the absence of prior intraocular surgery or ocular trauma in the former.

Diffuse low-to-medium reflective choroidal thickening and SRD are evident during acute VKH disease, especially when the SRD is too extensive. Swollen ciliary body with shallow anterior chamber, vitreous condensations, and scleral or episcleral thickening have also been seen on US in the acute stage. Subretinal fibrosis in chronic VKH disease was described on US in 64.8% of the eyes as a dome shaped, heterogeneous lesion; however, no other clinical signs of the chronic disease were detected on the US(4). Therefore, it is relatively unreliable in detecting subclinical recurrences and minor changes in choroidal thickness due to its limited resolution in comparison to OCT. Ultrasonography of the posterior pole also plays a useful role in the

diagnosis of atypical cases, eyes where the amount of subretinal fluid is too extensive to be imaged using an OCT, and where the fundal view is obscured by media opacity. Typically, the choroid thickening in VKH disease is diffuse, with low to medium reflectivity(3). This is in contrast to posterior scleritis, where the scleral thickening has high reflectivity and is frequently accompanied by retrobulbar oedema in the peripapillary region resulting in the “T” sign.

VKH can rarely present as acute angle closure. Yang P et al. have described that strikingly decreased visual acuity associated with mild to moderate increased IOP is a clue to the diagnosis. Diagnosis of VKH in such a scenario as the increased IOP responded well to corticosteroids but not to anti-glaucoma treatment. (4) Ultrabiomicroscopic (UBM) could be a valuable tool in arriving at a diagnosis in such cases. In acute cases ciliochoroidal detachment, unclear ciliary processes could be noted. In recurrent phase, pars plicata and pars plana thickening can be noted. (5)

To conclude, ocular imaging for diagnosis and repeat use of non-invasive modalities, such as B-scan ultrasonography to monitor disease activity, can promote early treatment and prevent the development of ocular complications.

### 3. Fundus Autofluorescence

Fundus autofluorescence (FAF) (short wave and near infrared(NIRAF) ) is a non-invasive, efficient imaging technique that provides valuable information on the retinal pigment epithelium(RPE) and outer retinal layers. Metabolic and functional activity of the RPE can be detected in different stages of VKH using short wavelength blue light FAF that has been used to detect lipofuscin abnormalities and near-infrared light FAF that has been used for melanin and melanin compound abnormalities. (4)

Autofluorescence signals correlate to the health of RPE and are useful in evaluating early damage to the RPE. Chorioretinal depigmented lesions or RPE clumping are seen as the late manifestations of VKH disease. (5) Different patterns of FAF have been demonstrated in different phases of VKH disease which supports the role of the RPE in the disease and allows repeated close monitoring of disease progression. In addition, wide-field scans are useful in documenting the extent of disease. (4)

The autofluorescent features can be described in various phases of VKH

#### 3 A. Acute phase:

In acute VKH (immediately after the onset of ocular symptoms), there will be areas of hypoautofluorescence surrounded by hyperautofluorescent halo (target lesion). Hypoautofluorescence is because of damaged or swollen RPE and is seen as window defect lesion in Fundus Fluorescein Angiography(FFA). The surrounding hyperautofluorescence corresponds to the area of sub retinal fluid(SRF) where there is accumulation of lipofuscin. Tian S et al. noted that hyperautofluorescent areas were consistent with that of fluorescein accumulation shown by FAF imaging and the fluorescence intensity showed a significant positive correlation with the volume of SRF detected by OCT. (6)

Resolution of the SRF after treatment is associated with the appearance of placoid areas of hyperautofluorescence in the macula and peripapillary regions. These FAF changes are more evident on the near-infrared FAF and typically resolve after 6 months of treatment. (4,5,7)

In patients of acute VKH, without treatment, for a period of 3-7 weeks, there is diffuse mottled hyperautofluorescence (clearer in NIRAF).

Zhu R et al. noted hyperautofluorescence around the macular edema in initial stages of VKH disease. In the convalescent stage, loss of photoreceptor and injury of RPE was detected on OCT at the same area, which was corresponded with the abnormalities in FAF.(8)

### 3B. Chronic phase

FAF shows hyperautofluorescence, hypo autofluorescence and lattice-like pattern in the peripheral fundus in chronic phase. Hypo autofluorescence pattern is due to the loss of RPE and involvement of the outer retina in the disease process. Peripapillary atrophy also manifests as hypoautofluorescence. Hyperautofluorescence could be due to the development of cystoid macular oedema, subretinal fibrosis or due to RPE proliferation. (2,4,9)

Because autofluorescence correlates to the health of the RPE, recurrent bouts of inflammation and subclinical inflammation can be evaluated well on FAF and wide-field imaging . (2)

Hence FAF could be a valuable non-invasive diagnostic tool in assessing the response to treatment and in prognostication of eyes with VKH. Table 1 summarises various FAF patterns described in different phases of VKH.(7-10, 12-14)

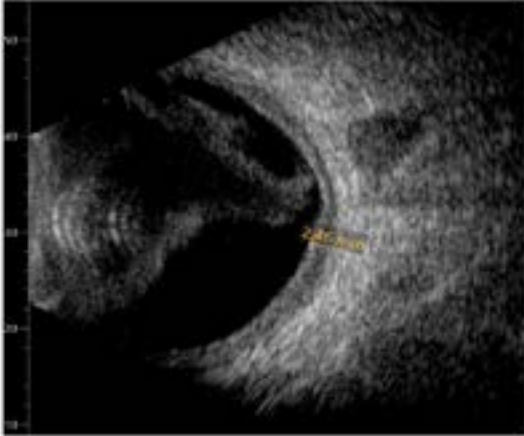
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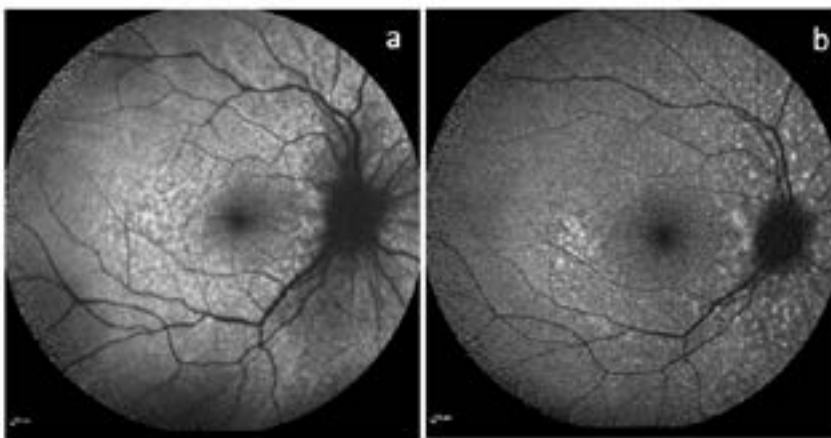
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## Figure Legends

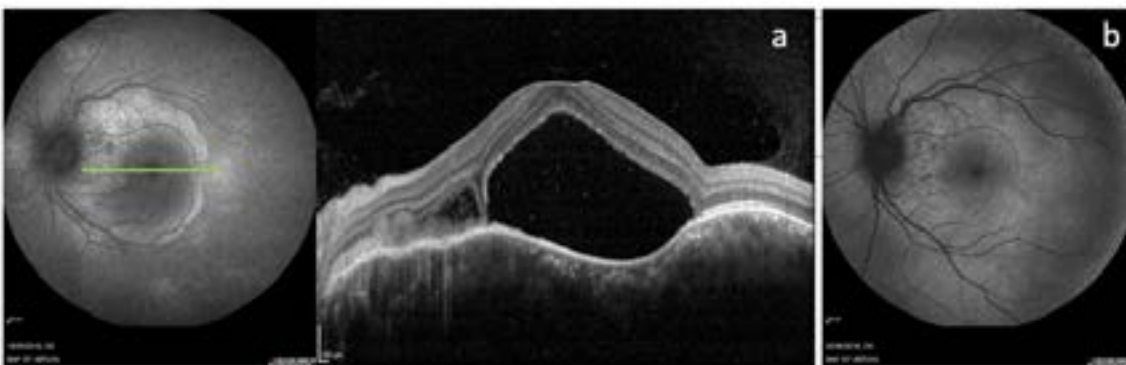
**Figure 1:** Ocular ultrasound showing retinal detachment with choroidal thickening



**Figure 2:** Blue-light autofluorescence of a patient with VKH (a) at presentation granular pattern with hypoautofluorescence granular dots surrounded with mild hyperautofluorescence halo (b) at 3 months follow up decrease in granularity noted with decrease in area of hyperautofluorescence



**Figure 3:** Blue-light autofluorescence of a patient with VKH (a) at presentation showing hypoautofluorescence at the area of subretinal fluid surrounded by hyperautofluorescence (b) at 1 month follow up FAF shows decrease in area of hyperautofluorescence





**Table1:**  
**Summary Of Recent Studies On Fundus Autofluorescence Patterns In Various Phases Of Vogt Koyanagi Harada Disease**

Author	Year	Title	FAF pattern described
Ayata et al <sup>9</sup>	2009	Autofluorescence findings in VKH disease	<p>Area of SRF appeared hypoAF (BL-AF and NIR-AF)</p> <p>4<sup>th</sup> day(after SRF resolution): Numerous hypoAF granular dots surrounded with mild hyperAF halo, scattered over the hyperAF background corresponding to the previous SRF areas in BL-AF and NIR-AF-more prominent in NIR-AF</p> <p>6 weeks: Decrease in granular dots &amp; hyperAF background</p> <p>These hypoAF dots were interpreted as damaged or swollen RPE</p>
Heussen et al <sup>12</sup>	2011	Ultra-Wide-Field Green-Light (532-nm) Autofluorescence Imaging in Chronic VKH Disease	<p>Studied 10 patients included 1 acute and 9 convalescent phase</p> <p>Predominantly peripheral multifocal hypoAF (corresponding to chorioretinal scars fundus photo) and very few hyperAF areas.</p> <p>One case with hyperAF lattice like pattern correlated with linear bands of hyperpigmentation in colour photo (these areas likely correspond to foci of RPE proliferation with a possibly spared outer retinal architecture)</p>
Tian et al <sup>8</sup>	2011	Autofluorescence combined with SDOCT for diagnosis & follow-up of acute VKH disease	<p>Noted 3 patterns in acute phase</p> <ul style="list-style-type: none"> <li>-HyperAF corresponding to SRF</li> <li>-Patches of relative hypoAF in the hyperAF areas</li> <li>-Granular hyperAF</li> </ul>
Soh-Eun Ahn et al <sup>13</sup>	2013	Ultra-wide-field green (532 nm) and red (633 nm) reflectance imaging of the "sunset glow" fundus in chronic VKH disease	<p>Studied cases with recurrent VKH:</p> <p>3 months after recurrence: normal background AF with multiple focal granular hyperAF. At macular area-numerous hypoAF dots surrounded by a relatively hyperAF halo (swollen RPE cells) resembling a target</p> <p>5 months after recurrence: disappearance of previous hyper AF</p>



Koizumi et al <sup>7</sup>	2015	Blue light and near-infrared fundus autofluorescence in acute VKH disease	<p>Studied FAF patterns in patients who were treated with early high-dose steroid :</p> <p>Acute phase: mild and uniform hyperAF in the macula mixed with hypoAF inside, but not in all areas of SRF</p> <p>After resolution of SRF: HyperAF remained for around 1 month (NIR-AF&gt; BL-AF).</p> <p>With time, hyperAF in the macula decreased in both size and intensity, and at 6 months FAF returned normal</p> <p>In patients who presented late (steroid pulse 3-7 weeks after the onset of symptoms):</p> <p>Initial presentation: Diffuse and mottled hyperAF clearer in NIR-AF.</p> <p>After SRF resolution: Placoid hyperAF in the macula, and surrounding scattered and radial patterns of hyperAF around the optic disc</p>
Morita et al <sup>14</sup>	2016	Fundus autofluorescence as a marker of disease severity in VKH disease	<p>In patients who were treated with early high-dose steroid:</p> <p>1 month: Granular/reticular pattern</p> <p>6 months: FAF returned to normal</p> <p>In patients who presented late:</p> <p>1 month: Diffuse or placoid pattern.</p> <p>6 months: persistence of same pattern</p>
Zhu et al <sup>10</sup>	2017	Photoreceptor Cell Injury Starts in the Initial Stage of VKH Disease	<p>Acute phase: hypoAF in SRF area with hyperAF around</p> <p>Chronic: perimacular hyperAF (interruption of ONL, myoid zone, and ellipsoid zone in SDOCT)</p>

## B. Optical coherence tomography in Vogt Koyanagi Harada disease(VKH)



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## **Optical coherence tomography in Vogt Koyanagi Harada disease(VKH)**

Optical coherence tomography (OCT) has revolutionized the world of uveitis , not only in disease diagnosis but also in establishing prognostic biomarkers. With the enhanced depth technology (EDI) in OCT, one almost gets cross-sectional, structural and quasi-histological information of retina and choroid in vivo. In the recent 2022 study , Herborg et al<sup>1</sup> proposed new diagnostic criteria for initial-onset VKH disease in which bilateral diffuse choroiditis remains a sine qua non criteria in the diagnosis of VKH and this must be verified with EDI-OCT .

Optical coherence tomography features in VKH disease have been extensively reported and include findings such as subretinal membranous structures, subretinal hyperreflective dots (which may represent clumps of inflammatory debris or macrophages engulfing shed outer segments), and intraretinal edema in the outer retinal layers, in addition to a thickened choroid in the acute stage, and potentially a thinned choroid in the chronic stage.

These markers are usually bilateral and they help in not only establishing the diagnosis but also in titrating the dose of corticosteroids based on the improvement in the OCT markers and predicting future recurrences . The only limiting factor is that the OCT may not always detect disease reactivation since choroidal thickness is globally reduced in chronic VKH

## Acute VKH

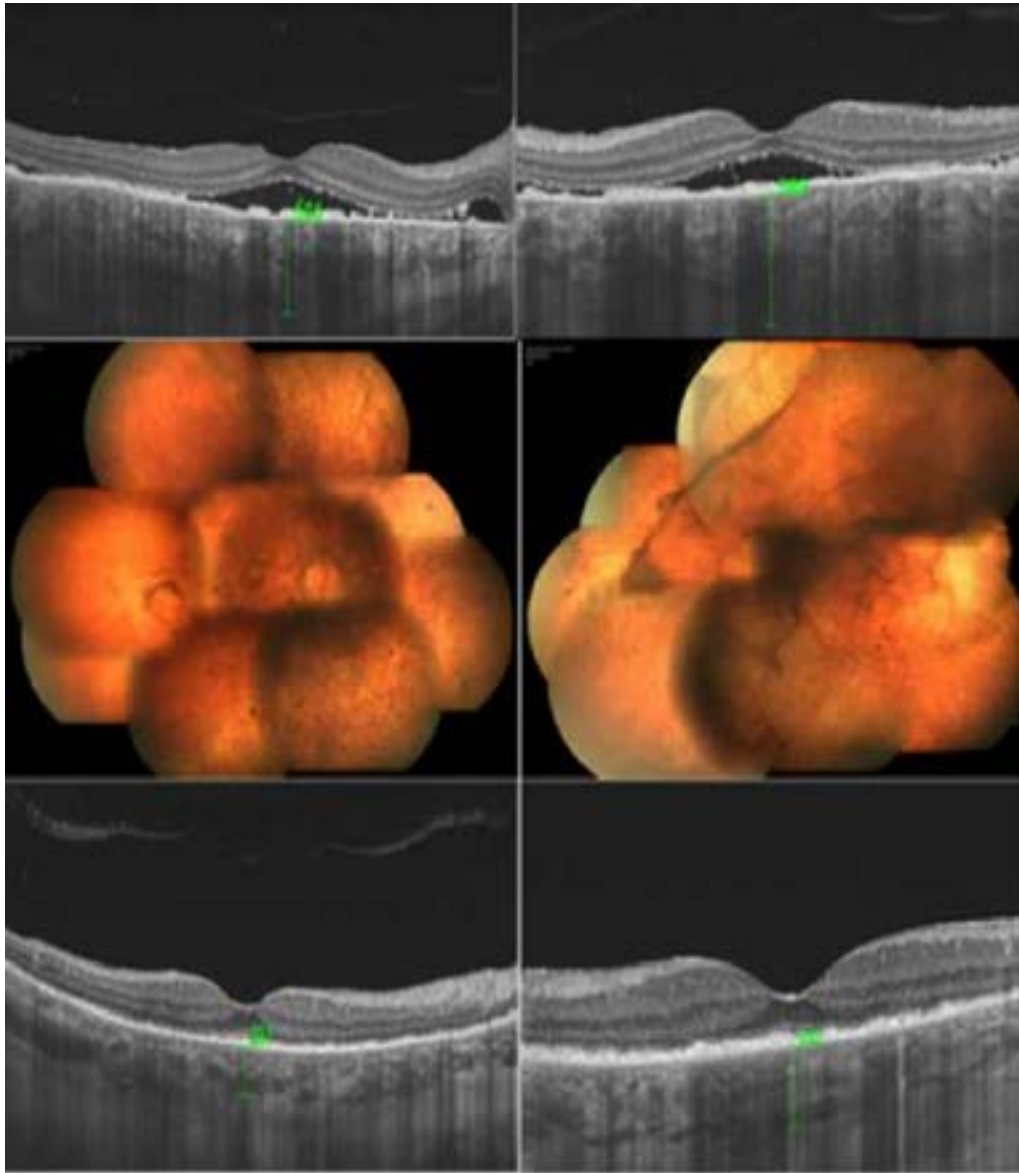
Following are the OCT findings in acute VKH

### 1. Diffuse choroidal thickening :

The importance of OCT in acute VKH is the ability to detect increase in choroidal thickness even before signs like serous retinal detachment appear clinically.

Whether its spectral domain OCT (SD-OCT) or swept source-OCT ; the choroidal thickness is measured from the outer border of the RPE to the inner border of the sclera using enhanced depth technology (EDI) and it is usually determined manually by the observer. Digital calipers are placed at the outer edge of the hyperreflective RPE line and the inner border of the hyperreflective surface located behind the large choroidal vessels, which is the scleral/choroidal interface. These two points are chosen so that the line traced between them is perpendicular to the RPE line. The measurements commonly are performed under the geometric center of the fovea and can be repeated at regular intervals from the center of the fovea of varying sizes and locations. The subfoveal choroidal thickness (CT) is defined as the distance between these two points (figure 1). Various studies have evaluated the reproducibility of subfoveal CT measurements and there is a very good intersystem, interobserver, and intervisit reproducibility of CT measurements despite the lack of automated software<sup>2</sup>

In a study by Maruko et al<sup>3</sup> , the choroid was markedly thickened by EDI-OCT, with a mean subfoveal CT of 805  $\mu\text{m}$  at presentation. After 3 days of intravenous corticosteroids the mean subfoveal CT decreased to 524  $\mu\text{m}$ . The patients continued treatment using oral corticosteroids, and the mean subfoveal CT was 341  $\mu\text{m}$  at 2 weeks. Hence , subfoveal CT can be used a OCT biomarker in assessing the response to steroid/ immunosuppressives treatment. However, if the thickening of the choroid is 1000  $\mu\text{m}$  or above , visualization of the boundary between the choroid and the inner sclera may be difficult but measuring the thickness still has diagnostic utility at this point because a choroidal thickness of 1,000 mm is much greater than normal<sup>3</sup>

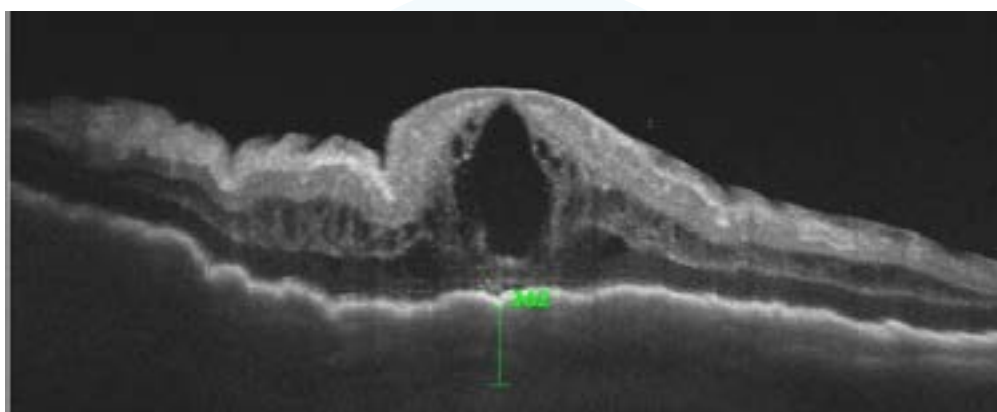


**Figure 1 :** SS-OCT of an acute VKH patient showing SFCT of 526μ and 589μ with subretinal fluid and RPE irregularity in right and left eye respectively. Patient was treated with intravenous methylprednisolone followed by oral steroids. At 4 months, colour fundus photo showing depigmented fundus with a decrease in SFCT to 231μ and 243μ in the respective eyes along with complete resolution of inflammation.

## 2. Choroidal folds (CFs)/ RPE undulations :

Choroidal folds (CFs) are undulations or wrinkles in the retinal pigment epithelium (RPE), Bruch's membrane, and inner choroid. They are usually found more often in older patients and in eyes associated with disc swelling. CFs (Figure 2) indicate a thickened choroid and VKH with CFs have a longer disease duration and more likely to have recurrences and sunset-glow fundus, which indicate they are important prognostic marker<sup>4</sup>

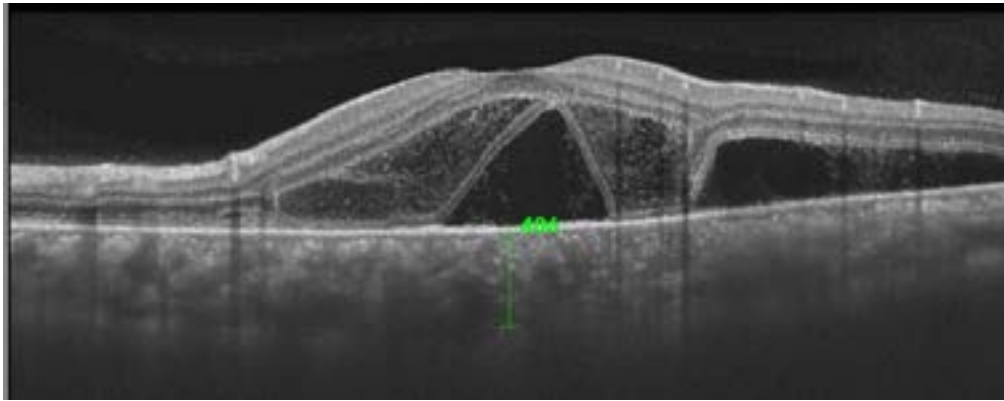
The undulations correspond to choroidal striations seen as hypofluorescent lines in the early phase on fluorescence angiograms, whereas the bumps over the undulations correspond to the pinpoint hyperfluorescent dots on the angiograms



**Figure 2:** Choroidal folds with RPE undulation (yellow arrow) seen in acute VKH

## 3. Subretinal membranous structures :

The most valuable feature of all the OCT features was the presence of subretinal membranes (figure 3). The positive predictive value and negative predictive value of this OCT sign is 97.0 and 73.3%, respectively. The presence of subretinal membranous structures, a high retinal detachment, subretinal hyperreflective dots, and RPE folds had a rather high diagnostic value with respect to their sensitivity and specificity for the diagnosis of acute VKH disease<sup>5</sup>



**Figure 3 :** Subretinal septae with subretinal membranous structures (yellow arrow) presenting as multilobular serous detachments with subretinal hyperreflective dots (yellow star)

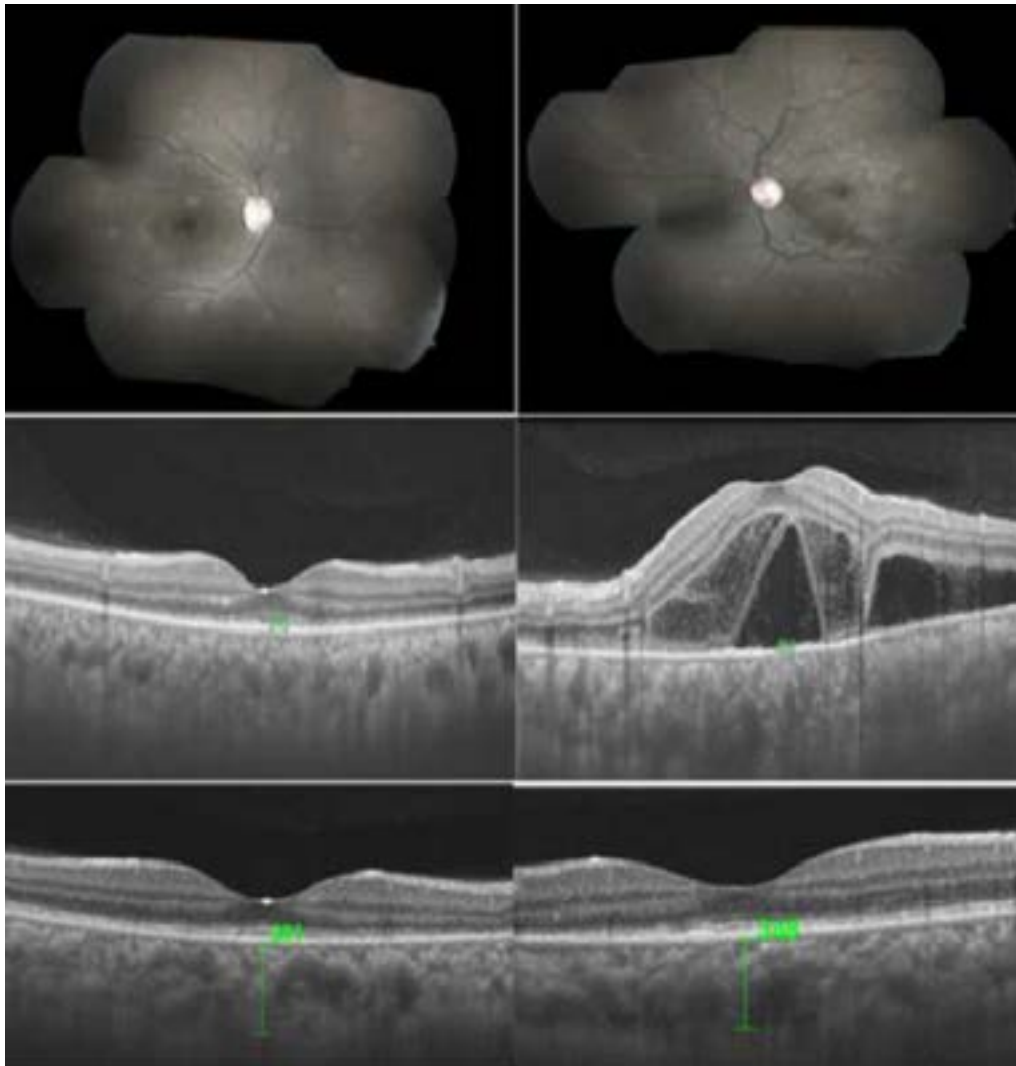
#### 4. Subretinal septa

The subretinal septa (figure 4 yellow arrow) are composed of inflammatory products like fibrin and they promptly resolve post steroid therapy. These septae are seen as vertical hyperreflective lines on OCT and they divide the fluid into subretinal and outer retinal compartments forming multi-lobular cystoid spaces (figure 4)

They seem to act as a barrier to the spread of the fluorescein dye and are responsible for multilobular dye pooling in serous retinal detachment in VKH disease. In the subretinal space, a membranous structure was situated on the RPE serving as the outer wall of the subfoveal compartment, or sometimes it is detached from the RPE in the perifoveal area. The detached membrane extends toward the posterior border of the detached retina, forming a septum between the subfoveal and perifoveal compartments.. After steroid pulse therapy, the subretinal septa promptly resolve along with absorption of the subretinal fluid (figure 4 & 5).

VKH disease is characterized by diffuse granulomatous uveal inflammation. Inflammatory cells infiltrate not only the choroid but also the choriocapillaris. The inflammatory cells even penetrate the RPE and infiltrate into the subretinal space. Break down of the barrier function of the RPE allows influx of exudative fluid into the subretinal space. A fibrin membrane develops on the RPE, which forms a posterior wall of the subretinal space and also forms a blunt angle at the outer margin of the retinal detachment. The fibrin membrane overlying the RPE (figure 3 yellow arrow) and the blunt-angled margin of the subretinal space looks like fluid accumulation

in the outer retina on OCT. Further leakage from the RPE pushes the fibrin membrane upward and partly detaches it from the RPE. This detached fibrin membrane forms septa, which divide the subretinal space into a few compartments. If the fibrin membrane is widely detached from the RPE, a pseudo-cystoid space is formed by the detached retina and the subretinal fibrin membrane. The dark rim of the multilobular dye pooling on FA corresponded to the subretinal septa on OCT. The membranous or dot reflex in the subretinal space ( figure 3 star) suggests the presence of protein rich subretinal fluid.<sup>6</sup>



**Figure 4 :** Acute VKH showing sub-retinal septae along with sub-retinal fluid and SFCT of around 395 $\mu$  and 486 $\mu$  in right and left eyes respectively.

At 1 month following treatment, SS-OCT showing complete resolution of sub-retinal septae and fluid and also decrease in SFCT to 391  $\mu$  and 348 $\mu$  in the respective eyes.



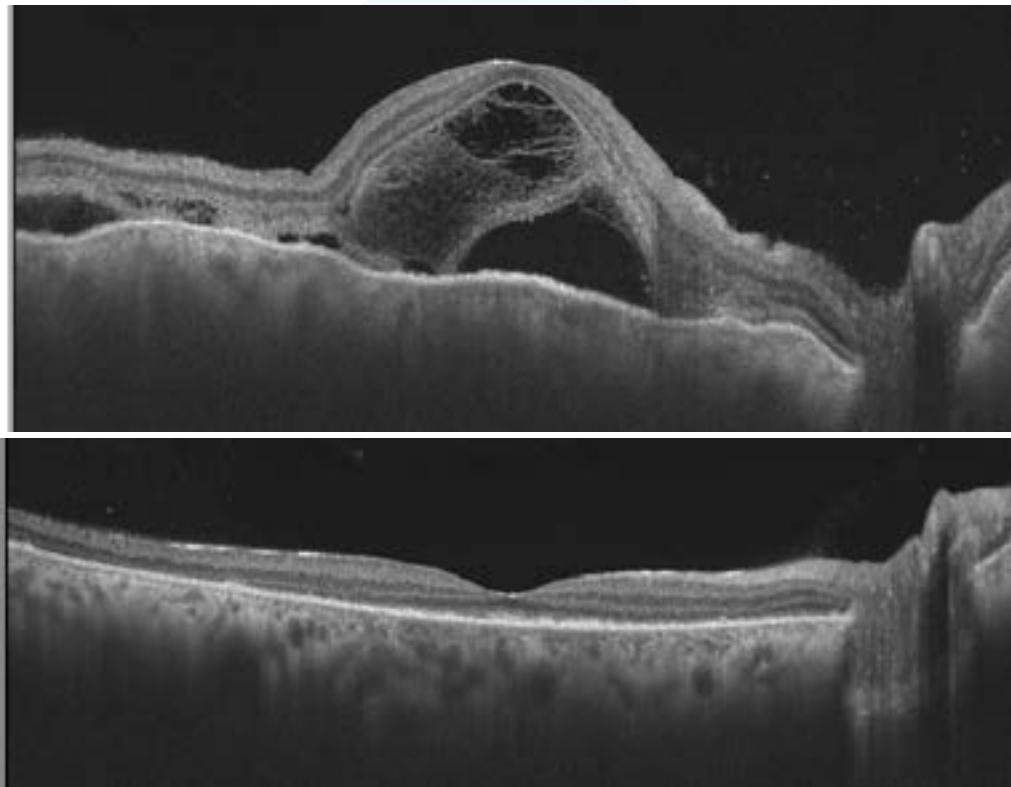
**Figure 5 :** Structural improvement in OCT post treatment with steroids

### 5. Bacillary layer detachment(BLD)

BLD (figure 6 ) is a split in the photoreceptor layer at the level of inner segment myoid. This separation leaves the “bacillary layer” (remaining myoids, ellipsoids, and outer segments) attached to the RPE, whereas the external limiting membrane (ELM) and remaining anterior retinal structures detach and move anteriorly<sup>7</sup>

Agarwal et al<sup>7</sup> observed that the BLD resolved within a mean of 3.4 days after the initiation of corticosteroid therapy even before the resolution of subretinal detachment and was accompanied by significant visual improvement.

Mehta et al<sup>8</sup> proposed that the rapid exudation of fluid may preferentially split the inner segment myoid , which is inherently weaker than the attachment of photoreceptor outer segments to the RPE with which they inter-digitate.



**Figure 6:** OCT image of a patient showing bacillary layer detachment and complete resolution post treatment with azathioprine

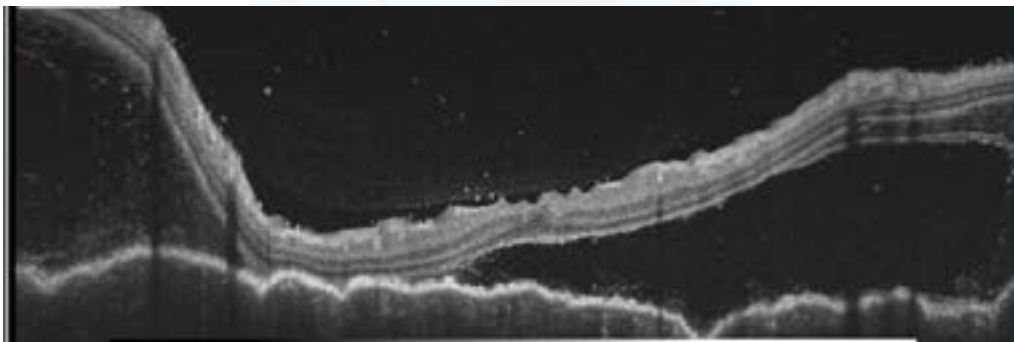
## 6. Reduction in the number of hyper-reflective dots in the inner layer of choroid

Numerous hyperreflective dots were observed in the inner layer of the choroid in all eyes, more in abundance toward the Bruchs membrane . Their reflective intensity was the same as retinal vessels and may represent cross-sectional views of pericapillary arterioles and venules. Each dot averaged around 50 mm in diameter (measured using digital calipers provided on the OCT ). There was a significant reduction in the number of these hyperreflective foci in the choroid of VKH patients

In the acute stage, compression and nonperfusion of small choroidal vessels from massive infiltration of inflammatory cells and granulomas may account for the observed reduction in hyperreflective foci<sup>8</sup>.

## 7. Internal limiting membrane fluctuations :

First, the inflammatory cells infiltrated in vitreous may cause local constriction of ILM (Figure 7). Second, the inflammation may cause diffuse but uneven edema of retina and choroid. The retina may bulge inside in some location and lead to folding of ILM.



**Figure 7:** Acute phase of VKH showing ILM fluctuations along with neurosensory detachment and sub-retinal and intra-retinal fluid accumulation with vitreous inflammation

## 8. Inner retinal thickness:

The inner retinal thickness as measured from the inner limiting membrane to the inner plexiform layer was significantly greater in the acute phase than in the convalescent phase

## Chronic VKH

Following are the OCT findings in chronic VKH

1. Choroidal atrophy as evidenced by choroidal thinning and global reduction in choroidal thickness and/or distortion of vascular structure on EDI- OCT
2. In the convalescent stage, reduction of hyperreflective foci may represent shrinkage and dropout of small choroidal vessels caused by stromal scarring<sup>9</sup>

### VKH -OCT findings- structure wise

Peripapillary	Swollen
Inner retina	RNFL and perivascular thickening
Retina	<ul style="list-style-type: none"><li>-ILM fluctuations</li><li>-Subretinal septa</li><li>-Subretinal membranous structures</li><li>-Subretinal fluid compartments with hyperreflective material</li><li>-Supra-membranous fluid with increased reflectivity</li></ul>
RPE	RPE folds/undulations
Choriocapillaris	Decreased reflectivity with thickening and loss of the physiological hyperreflective dotted pattern
Choroid	<ul style="list-style-type: none"><li>Diffuse thickening</li><li>Loss of choroidal architecture</li></ul>

## Differentiating features of VKH vs CSCR on OCT VKH

VKH	Central serous chorioretinopathy
Fluctuations of the inner limiting membrane	No ILM fluctuations
Subretinal septa	No subretinal septa
Subretinal fluid has hyperreflective material and fluid is exudation	Subretinal fluid is transudation from hyperpermeable choroidal vessels through the RPE with pinpoint breakdown. There is no inflammation in the choroid per se.
RPE folds / undulations	RPE bulge probably due to RPE hyperplasia , RPE detachment
Distortion of RPE layer in acute VKH was significantly severe than acute CSCR .  This may be due to choroidal congestion caused by the infiltration of inflammatory cells	
The inner retinal thickness as measured from the inner limiting membrane to the inner plexiform layer was significantly greater in the acute phase than in the chronic phase	The inner retinal thickness did not differ between the acute and chronic phases

**Conclusion:** OCT is a reliable diagnostic marker of VKH. EDI-OCT can be used for monitoring the disease activity in VKH. OCT can also detect various complications of VKH like choroidal neovascular membrane and cystoid macular edema.

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## C. Optical Coherence Tomography Angiography in Vogt-Koyanagi-Harada disease



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**Keywords:** OCTA; VKH disease; choroidal granuloma; choriocapillaris flow deficit

## **Abstract**

Optical coherence tomography angiography (OCTA) is a recently introduced non-invasive imaging modality that has a plethora of applications in inflammatory eye conditions including Vogt-Koyanagi-Harada's (VKH) disease. OCTA imaging reveals abnormalities in the choriocapillaris and the deeper choroid in eyes with VKH, which agree well with traditional invasive dye-based angiographies such as indocyanine green angiography and fluorescein angiography. It is relevant to interpret and analyze OCTA images properly and correlating the changes with other imaging tools such as optical coherence tomography (OCT), and dye-based angiographies. In this review article, various applications of the use of OCTA in eyes with VKH disease has been illustrated.

## **1. Introduction**

Vogt-Koyanagi-Harada's (VKH) disease is a multi-systemic condition characterized by multifocal serous retinal detachment, multiple choroidal granulomas, and other associated neurological and integumentary features.<sup>1-5</sup> The hallmark of VKH disease is the presence of diffuse choroidal thickening and infiltration due to presence of round-to-oval choroidal granulomas.<sup>1,3-5</sup> Due to the presence of intense inflammatory reaction, involvement of the retinal pigment epithelium (RPE) and the photoreceptors in the outer retina can occur, leading to permanent visual loss. Clinically, this appears as a depigmented choroid termed as "sunset glow fundus".<sup>3,6,7</sup> Therapeutic intervention is aimed at preventing such a profound photoreceptor and RPE loss in patients with VKH.

Indocyanine green angiography (ICGA) and fluorescein angiography (FA) are important in the diagnostic armamentarium of VKH disease, and to distinguish it from other causes of multifocal exudative retinal detachments such as central serous chorioretinopathy (CSC), metastasis, and other inflammatory disorders.<sup>3,8-11</sup> In the recent times, there is a shift towards use of less invasive imaging modalities such as optical coherence tomography (OCT) and OCT angiography (OCTA) in the diagnosis and follow-up of patients with several uveitic diseases, including VKH. Although there are limited studies in the literature that have evaluated the role of OCTA in the management of VKH disease, there is strong evidence to suggest that OCTA provides valuable information that can help in treatment decision-making and follow-up of these patients.<sup>12-14</sup>

In this manuscript, we have comprehensively reviewed the role of OCTA in the diagnosis and management of VKH disease. We have also compared the findings of VKH disease on OCTA with other imaging modalities such as ICGA, FA and OCT.

## **2. Imaging Characteristics**

ICGA and FA have been extensively evaluated in the analysis of eyes with VKH disease. In the acute stage of VKH disease, FA shows typical pinpoint hypofluorescent lesions in the fundus during the early phase of dye injection, which become hyperfluorescent in the late phase with pooling of dye in the areas of exudative retinal detachment. The pinpoint areas of leakage result in the formation of a "starry-sky" appearance and occurs due to the focal RPE damage.<sup>15-17</sup>

ICGA is a very sensitive tool in detecting choroidal abnormalities in VKH diseases. Therefore, ICGA is useful not only in the acute phase of VKH, but also in detecting subclinical recurrences. In the acute phase, ICGA shows hypofluorescent dark dots in the fundus, which remain either hypofluorescent or become isofluorescent in late phase depending on the size of the inflammatory foci/granulomas. Full-thickness choroidal granulomas tend to remain hypofluorescent even in the late phase, whereas partial thickness choroidal granulomas become isofluorescent in the late phase.<sup>3,6,15-17</sup>

## 2.1. OCTA Features of VKH

OCTA provides detailed information on the choriocapillaris and possibly deep choroidal involvement in VKH disease. Typically, there are no retinal microvascular abnormalities noted on OCTA in VKH disease since it does not involve the retinal circulation. However, in a recent study in 50 eyes of acute and convalescent VKH by Ye et al done using 15 × 9 mm<sup>2</sup> wide field, macular, peripapillary OCTA, the authors observed reduction in retinal vascular parameters in the retinal plexuses compared to healthy control subjects. The authors observed reduced vessel perfusion density and vessel length density (apart from choriocapillaris flow deficit areas) in the retinal plexuses compared to control subjects.<sup>18</sup> The changes in the choriocapillaris are much more prominent on OCTA in VKH disease. In the acute stage of the disease, OCTA reveals multiple areas of flow deficit in the choriocapillaris layer appearing as dark dots on en face imaging. The shape and size of these dark dots can be variable, but usually they co-localize well with ICGA imaging. In addition, comparison of the structural en face image with the OCTA does not reveal signal loss, thereby indicating that the hypo-reflective areas are indeed representative of true flow loss.<sup>14</sup>

The introduction of wide-field and ultra-wide field imaging (including OCTA) has allowed detection of choroidal granulomas much beyond the macular center. Recently, it has been shown that OCTA can detect greater number of choroidal granulomas compared to ICGA imaging, making it more sensitive tool to detect the pathology, at least in the initial stages.<sup>19-21</sup>

When the patients are treated with corticosteroids/immunosuppressive agents, serial follow-up on OCTA reveals reduction in the flow deficit areas on en face imaging, suggestive of resolution of the choroidal granulomas. Thus, OCTA can be used to judge the response to treatment in these patients. If the disease is sub-optimally treated, or if there is a recurrence, OCTA can reveal increase in the areas of flow deficit that correlates with OCT signs such as reappearance of subretinal fluid or increase in choroidal thickness.<sup>14</sup> In a case report, Interlandi et al observed a 37-year-old lady with VKH disease undergoing routine clinical examination during remission of the disease. The authors observed increase in the choroidal thickness on OCT and increase in the choriocapillaris flow deficit areas on OCTA. The patient demonstrated clinically evident reactivation of VKH disease one week later.<sup>22</sup>

## 2.2. Correlation of OCTA features with OCT

OCT imaging, especially enhanced-depth imaging (EDI) and swept-source (SS)-OCT, can provide a highly detailed anatomical structural analysis of the choroid.<sup>4,23,24</sup> EDI-OCT and SS-OCT can detect hypo-reflective areas in the deep choroid with back-shadowing, suggestive of choroidal granulomas. Such choroidal granulomas are differentiated from large choroidal vessels which also have hypo-reflective round-to-oval appearance because blood vessels do



not have back-shadowing. The choriocapillaris directly overlying the granuloma are ischemic, and this appears as hypo-reflective dark areas on OCTA imaging as well as hypofluorescent patches on ICGA. Thus, OCT shows a very good spatial correlation with the OCTA imaging.<sup>19,23,24</sup>

In the acute stage of the disease, presence of subretinal fluid may not always lead to reduction in signal; therefore, we may be able to obtain adequate quality OCTA imaging unless there is a massive exudative retinal detachment in the central macula. Similarly, if the disease is recurrent and there is a thin layer of subretinal fluid, good quality OCTA imaging is still possible. However, patients with fibrinous exudation can have a reduction in flow signal and poor-quality OCTA scans.<sup>4,14</sup>

OCT imaging has several other features that can be identified in eyes affected by VKH disease. These include compartmentalization of fluid into intraretinal and subretinal spaces (which has been recently termed as bacillary layer detachment).<sup>25</sup> However, such OCT features cannot be identified on OCTA imaging. Choroidal neovascularization that occurs in some cases with chronic VKH disease can, however, be identified very easily on en face OCTA imaging especially if it is aided with proper segmentation and analysis of the flow signal in the affected area.<sup>26,27</sup>

Recently, Fayed et al compared the choroidal thickness on OCT with the blood flow in the choroid (measured as adjusted flow index: AFI) on OCTA in 23 eyes of VKH. The authors measured the choroidal thickness and AFI at baseline and after remission, and observed that as the choroidal thickness decreased at remission, the AFI increased, suggestive of improved blood flow with the resolution of the choroidal granulomas.<sup>28</sup>

### 2.3. FA and ICGA Correlation with OCTA

As mentioned in the preceding sections, FA and ICGA provide a host of information about the pathological involvement in VKH disease. Both FA and ICGA have the disadvantages of being an invasive procedure requiring dye injection, and rare but possible chances of allergic reactions. Obtaining FA and ICGA become more challenging in the presence of other systemic comorbidities such as renal or hepatic compromise. Repeating FA and ICGA at every visit is impractical and cumbersome, and the patients may not agree for an invasive procedure each time. Therefore, OCTA has distinct advantages of providing high quality imaging without the need for an intravenous dye injection.<sup>12,13,15,17,20</sup>

Since there are no retinal microvascular abnormalities in typical VKH patients, correlation between FA and OCTA is not very relevant. However, detection of inflammatory choroidal neovascularization requires good quality FA, but despite which, the clinician may not be sure if there is really an underlying choroidal neovascularization, or the leak is due to an inflammatory focus.<sup>26,27,29</sup> In such instances, OCTA is very helpful as it can identify the neovascular network and detect choroidal neovascularization almost 100% of the times.<sup>27</sup>

ICGA studies play an important role in disease detection in VKH. OCTA shows an excellent agreement with ICGA imaging, with exact co-localization of hypo-reflective areas on OCTA with the hypofluorescent areas on ICGA. These indicate the presence of choroidal flow abnormalities and the granuloma of VKH disease. Follow-up imaging on ICGA shows resolution of the granuloma if the patient has received adequate treatment with simultaneous reduction in

the flow deficit areas on OCTA.<sup>14</sup> Due to its high sensitivity, OCTA is very useful in determining subclinical recurrence without the need for dye injection as it can detect very small areas of flow deficit. However, one must remember that the choriocapillaris diameter in the macular area is 16-20 microns. Therefore, in general, hypo-reflective areas less than 24 microns are considered to be physiological.<sup>30</sup>

### **3. Differentiating VKH from other conditions based on OCTA**

OCTA can not only be useful in diagnosing and monitoring VKH disease, but it can also help differentiate VKH from other close mimickers non-invasively, such as CSC.<sup>31</sup> Usually, CSC presents as an acute disease with subretinal fluid accumulation and few areas of either inkblot or smoke-stack pattern of leakage. In rare cases, CSC may present with large exudative retinal detachments, sometimes bullous in nature, confusing the disease with VKH and other inflammatory conditions.<sup>32,33</sup> In such instances, ICGA imaging is very helpful as it demonstrates choroidal vascular hyperpermeability and possible vortex vein engorgement in eyes with CSC. In VKH disease, ICGA shows the distinct presence of hypofluorescent choroidal granulomas scattered throughout the fundus, which are conspicuously absent in eyes with CSC. On OCTA imaging, eyes with CSC do not show the hypo-reflective dark dots or flow deficit areas that have been explained to occur in VKH disease. On the other hand, OCTA shows near normal choriocapillaris morphology in CSC. Occasionally, there may be well-defined hypo-reflective areas in acute CSC on OCTA that are false areas of flow deficit due to the incorrect segmentation because of pigment epithelial detachments, commonly seen in CSC eyes.<sup>14,31</sup>

In chronic CSC, there may be geographic areas of choriocapillaris loss on OCTA and other modalities of imaging such as fundus autofluorescence and ICGA. The appearance of these lesions is very different from hypo-reflective dark dots due to VKH disease.<sup>34,35</sup>

### **4. Summary and Conclusions**

OCTA has a significant role in the diagnosis and management of VKH disease, and it augments the knowledge obtained using other imaging tools such as FA, ICGA and OCT. OCTA has very rare false positive or false negative findings, making it a reliable and precise imaging modality. OCTA can help in detecting choroidal granuloma, choriocapillaris ischemia, choroidal neovascularization, besides distinguishing VKH from other conditions such as CSC which have a diametrically opposite treatment. OCTA can also serve to detect subclinical recurrence of VKH, helping the clinician in taking therapeutic decisions before the development of blinding visual complications.

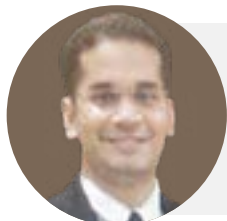
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# D. Fundus Fluorescein Angiography and Indocyanine Green Angiography in Vogt-Koyanagi-Harada Disease



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## Abstract

Vogt-Koyanagi-Harada (VKH) disease is a multisystem, chronic, autoimmune disease of unknown etiology. It presents in the eyes as a bilateral chronic granulomatous panuveitis, with propensity for recurrences and risk of loss of vision. Untreated or inadequately treated VKH disease can progress to a sunset-glow fundus. Angiographic imaging modalities like fundus fluorescein angiography (FFA) and indocyanine green angiography (ICGA) are useful not only for diagnosis of VKH disease, but also for monitoring the therapy. In acute VKH disease, FFA may show “starry sky appearance” with multiple pinpoint leaks at the level of the retinal pigment epithelium, along with subretinal pooling of dye suggestive of exudative detachments, as well as disc leak, in addition to other signs like choroidal folds, choroidal hypofluorescence. In acute stages, ICGA may show early choroidal hypo- and hyperfluorescent patches, hypofluorescent dark dots suggestive of choroidal granulomas, fuzzy leakage from stromal choroidal vessels. In clinically inactive disease, ICGA may show subclinical foci of choroidal stromal inflammation in the form of hypofluorescent dark dots. In acute VKH disease, FFA appearance is characteristic and may help in diagnosis. Monitoring of therapy with periodic ICGA may help to titrate the treatment. Despite the utility of angiographic modalities, they are limited by the fact that they are invasive, costly and time-consuming. They carry the risk of anaphylaxis to the dye and have to be avoided in pregnant patients or patients with severe renal disease.

### (1) **Introduction**

Vogt-Koyanagi-Harada (VKH) disease is an immune-mediated systemic disease affecting melanocyte-rich tissues in the skin, eyes, inner ear and meninges. It is characterized by a bilateral granulomatous panuveitis, along with systemic manifestations such as aseptic meningitis, headache, poliosis, alopecia, vitiligo, and dysacusis.<sup>1</sup>

The initial site of ocular inflammation in VKH disease is within the stromal choroidal melanocytes, with retinal pigment epithelium and the retina involved secondarily.<sup>2</sup> Hence, imaging modalities that allow visualization of the choroidal layers i.e., B scan ultrasonography, fundus fluorescein angiography (FFA) and indocyanine green angiography (ICGA) are useful in the evaluation, diagnosis and follow-up of patients with VKH disease.

In VKH disease, there are distinct angiographic findings on FFA and ICGA, and they change as the disease progresses through various stages from acute to chronic recurrent. Recognizing the findings helps in diagnosing and staging the disease as well as in understanding the extent of severity of inflammation. This article aims to provide a review of the various angiographic patterns observed in different stages of VKH on FFA and ICGA.

## (2) Fundus Fluorescein Angiography in VKH disease

In early phases, FFA may show focal areas of deep choroidal hypofluorescence leading to an irregular and mosaic pattern of choroidal fluorescence, while the retinal arteries fill normally.<sup>3</sup> This is followed by the appearance of several hyperfluorescent pinpoint at the level of retinal pigment epithelium (RPE) suggestive of RPE damage. These RPE alterations have been proposed to occur secondary to choroidal hypoperfusion and has been demonstrated in humans by angiography<sup>4,5</sup> and experimentally in animals.<sup>6</sup> The hyperfluorescent pinpoint give rise to the classical “starry sky” appearance on FFA. The pinpoint leakage of dye may fill up any overlying exudative retinal detachment in subsequent frames. Choroidal folds are visualized as hypofluorescent lines radiating from the optic disc. Pooling of dye in late phase is suggestive of subretinal fluid and serous retinal detachment. (Figures 1c & 1f)

The most commonly seen features on FFA include early pinpoint hyperfluorescence in the posterior pole and optic disc hyperfluorescence.<sup>7</sup> Arellanes-Garcia L et al.<sup>8</sup> have observed optic disc hyperfluorescence to be the most frequent (76.6%) fluorescein angiographic finding, followed by spotted hyper- and hypofluorescence (58.3%), described as “salt and pepper” pattern.

In acute VKH, the most common finding was disseminated spotted choroidal hyperfluorescence, suggestive of choroiditis,

( Figures 1 and 2) whereas in chronic VKH the most common findings were optic disc hyperfluorescence and spotted hyper- and hypofluorescence. Retinal pigment epithelium (RPE) migration is seen as blocked choroidal fluorescence on FFA. In convalescent stage as well, the most common FFA finding was spotted hyper- and hypofluorescence<sup>8</sup>. Subretinal pooling of dye has not been found in convalescent stage of VKH.<sup>8</sup> Retinal vascular wall hyperfluorescence, suggestive of retinal vasculitis, may be seen in acute as well as chronic stage of VKH. Depigmented RPE lesions seen in chronic VKH demonstrate staining on FFA. It has been suggested that retinal vasculitis may occur secondary to inflammation of the uveal tissue in VKH, and may be an epiphenomenon.<sup>8,9</sup>

FFA also helps to diagnose the complications of VKH such as optic disc neovascularization, choroidal neovascularization, arteriovenous and retino-choroidal anastomosis.<sup>1,10</sup> On FFA, neovascularization is observed as filling of abnormal new hyperfluorescent vessels having leakage with fuzzy borders with increase in the intensity of fluorescence in late phase. FFA helps to differentiate between VKH disease and multifocal central serous chorioretinopathy (CSCR). Presence of hypofluorescent spots on FFA and disc leakage favors the diagnosis of VKH as opposed to CSCR which lacks disc leakage and may have focal leaks and pigment epithelial detachments with pooling of dye.



### (3) **Indocyanine Green Angiography in VKH disease**

Indocyanine green angiography is very sensitive in detecting choroidal inflammation. In addition to delineating the structural changes, ICGA helps to evaluate the functional status of choroidal vasculature. It provides information on choriocapillaris circulation and helps to reveal small choroidal inflammatory foci.( Figure 3).<sup>11</sup>

The characteristic ICGA features that are consistently seen with VKH disease include: choroidal stromal hyperfluorescence in early phase, hypofluorescent dark dots (HDDs) in intermediate and late phases, fuzzy hyperfluorescence of large choroidal stromal vessels in the intermediate phase, and optic disc hyperfluorescence in the late phase.<sup>2</sup> There may be delayed choroidal perfusion resulting in hypofluorescence in the early phase. This is due to impaired physiological impregnation of the choroidal vessels by ICG molecules secondary to choroidal inflammation.<sup>12</sup>

Hypofluorescent dark dots (HDDs) are the most constant sign on ICGA in VKH disease. They indicate choroidal space-occupying lesions in the form of granulomas or scarred areas of choroid.<sup>2,13</sup> If the HDDs persist from intermediate phase (8-12 min) through the late phase (20 min onwards), it indicates that they are full-thickness choroidal granulomas or scars. They also cause additional choriocapillaris non-perfusion, another cause for their hypofluorescence.<sup>2,14,15</sup> If the HDDs become isofluorescent in late phases, it indicates that they are small, partial-thickness choroidal inflammatory foci or granulomas. It is important to emphasize that dark dots do not always mean active granulomas, they may also represent stromal scarring. Scarred choroidal stroma appears shrunken in size and shows dyspigmentation on fundus photography. To differentiate between HDDs secondary to stromal inflammatory foci or stromal scarring<sup>13</sup>, it is recommended to repeat ICGA after anti-inflammatory treatment and observe for any decrease in size. HDDs show resolution following treatment. Reappearance of HDDs may occur in the absence of any significant clinical or fluorescein angiographic signs, despite the continuation of systemic steroid and systemic immunosuppressive therapy. This indicates subclinical recurrence of inflammation and a possible need to step-up the therapy.<sup>2</sup> ICGA also helps to determine the presence of choroidal neovascular membranes (CNVMs) in areas of vascularized pigment epithelial detachments. On ICGA, three morphologic types of CNVM have been described: hot spot or focal spot, plaque (poorly defined or well defined), and mixed or combined (both hot spot and plaque are present).<sup>16</sup> ICGA also helps to differentiate between active and inactive CNVM.

Histopathologic studies<sup>17</sup> have found the juxtapapillary choroid to be one of the sites of the most severe inflammation in VKH. The optic disc on a normal ICGA appears dark and non-fluorescent. Optic disc hyperfluorescence suggestive of papillitis indicates a very severe form of disease.<sup>2</sup> It usually resolves following initial high-dose anti-inflammatory treatment, and acts as a good indicator for evaluating the response to therapy. In very severe and acute disease, there is presence of hyperfluorescent pinpoint leakage at the level of RPE seen on FFA as well as ICGA. In some cases, subretinal fluid may also be visualized on ICGA. Choroidal folds appear hypofluorescent on ICGA.

When considered in isolation, most of the ICGA signs in VKH are not pathognomonic of the disease. Similar ICGA signs may be found in other granulomatous choroidal inflammatory diseases such as tuberculosis<sup>18</sup>, sarcoidosis<sup>19</sup>, sympathetic ophthalmia<sup>20</sup>, and bird-shot chorioretinopathy<sup>21</sup>. However, when all the ICGA signs are considered along with the FFA findings and fundus appearance, they reach a pathognomonic significance.<sup>14</sup>

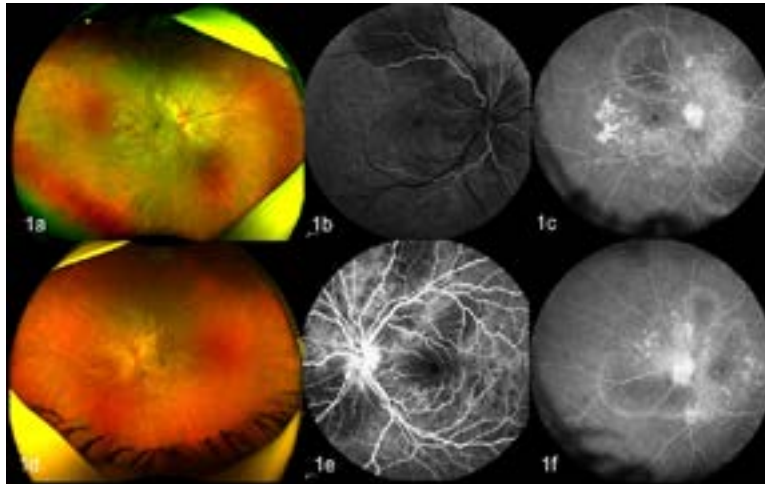
#### (4) **Discussion**

Both imaging modalities provide valuable information about the disease. Table 1 summarizes the various findings observed in acute and chronic active stage of VKH disease on FFA and ICGA. Since the primary pathology in VKH disease is that of a diffuse stromal choroiditis, ICGA helps to monitor residual or recurrent inflammation following treatment. FFA performs better to identify serous retinal detachments (Figure 1), retinal vasculitis and neovascularization of the disc, among other complications. Often, the fundus may appear normal clinically and the FFA may reveal a normal angiogram whereas ICGA unmasks the true status of choroidal vasculature (Figure 2).

Imaging modality	Findings in acute VKH disease	Findings in chronic active VKH disease
<b>Fundus fluorescein angiography</b>	Focal areas of choroidal hypofluorescence due to delay in choroidal filling	Patchy choroidal filling in early phase due to choroidal scars and areas of stromal choroiditis
	Pin-point hyperfluorescence at level of RPE suggestive of RPE damage	Choroidal hypofluorescence due to delay in choroidal perfusion
	Localized choroidal hyperfluorescence secondary to leakage from inflamed vessels or choroidal neovascularization	Disseminated spotted choroidal hyperfluorescence
	Alternating bands of hyper- and hypofluorescence suggestive of choroidal folds	Optic disc hyperfluorescence and leakage

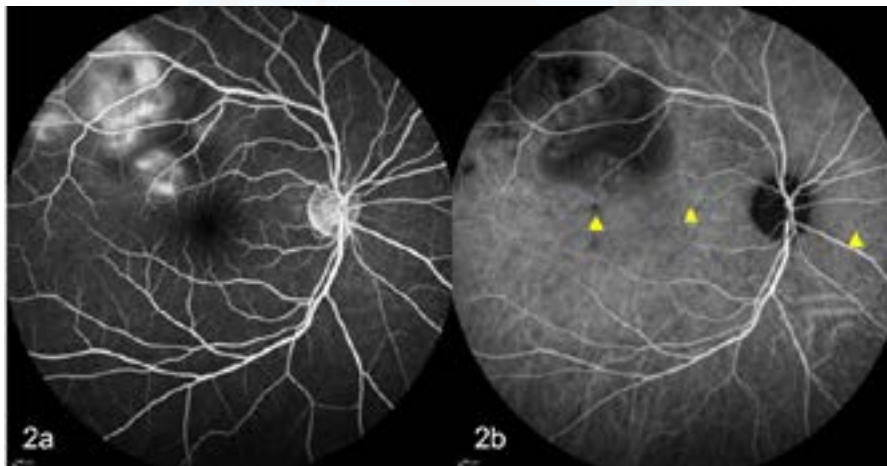
	Pooling of dye suggestive of subretinal fluid accumulation	Late pooling of dye suggestive of subretinal fluid
	Optic disc hyperfluorescence and leakage	
	Retinal vascular wall hyperfluorescence suggestive of retinal vasculitis	Retinal vascular wall hyperfluorescence suggestive of retinal vasculitis
<b>Indocyanine green angiography</b>	Choroidal hypofluorescence due to delay in choroidal perfusion	Similar to acute VKH findings
	Early choroidal stromal vessel hyperfluorescence and leakage due to inflammation and dilation of choroidal vessels	
	HDDs which may or may not persist into late phase suggestive of choroidal granulomas which may be partial-thickness or full-thickness	
	Fuzzy hyperfluorescence of large choroidal stromal vessels suggestive of stromal choroiditis	
	Optic disc hyperfluorescence	

**Table 1:** Findings in acute and chronic active stage of VKH disease on FFA and ICGA.



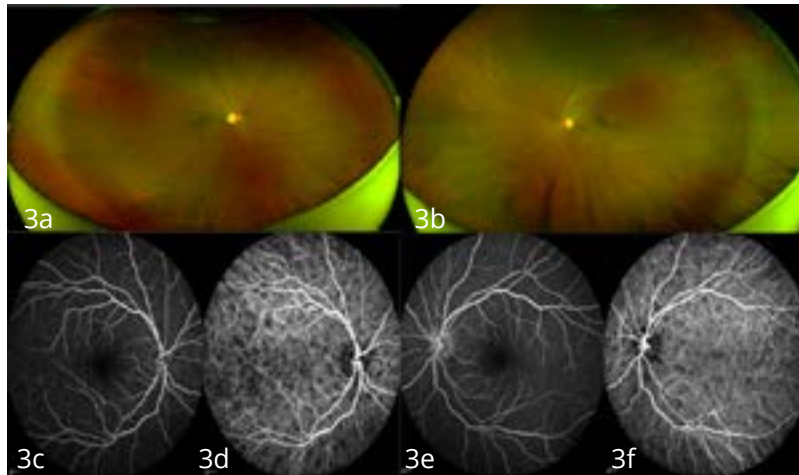
**Figure 1:**

A 41-year-old male presented with blurring of vision in both the eyes. Fundus examination revealed hyperemia of the disc with multiple serous elevations in the retina in both the eyes suggestive of VKH disease (figure 1a and 1d). Early phase of FFA revealed areas of hypofluorescence in the right eye (figure 1b), disc hyperfluorescence (figure 1e) with late disc hyperfluorescence and multiple points of hyperfluorescence with late pooling of the dye (figure 1c and 1f).



**Figure 2:**

A 38-year-old lady presented with complaint of decreased vision in the right eye for one day, diagnosed to have acute VKH disease. FFA shows early hypo- with late hyperfluorescence with subretinal pooling of dye suggestive of serous retinal detachment (figure 2a). ICGA shows hypofluorescence in areas of serous retinal detachment, along with hypofluorescent dark dots (figure 2b, yellow arrowheads).



**Figure 3:**

A 54-year-old lady, known case of chronic VKH disease, underwent simultaneous FFA and ICGA. The fundus appearance (figure 3a, 3b) and FFA (figure 3c, 3e) were normal, whereas ICGA (figure 3d, 3f) demonstrated hypofluorescent dark dots suggestive of subclinical foci of choroidal inflammation in both eyes.

Early phase peripapillary pinpoint hyperfluorescence has been found to occur in patients that present early in the course of the disease as compared to late presentation. Chee et al.<sup>7</sup> have found this to be a good prognostic indicator as it suggests that the disease is in the hyperacute stage and early treatment with high dose anti-inflammatory therapy is associated with a better prognosis. Thus, FFA is not only useful as a diagnostic tool, but also for prognosticating the treatment outcome. Another study by Chee and Jap<sup>21</sup> found that using ICGA to monitor the efficacy of immunomodulatory treatment in patients with VKH resulted in a significantly longer duration of treatment and a need for more immunosuppressants compared with monitoring of treatment efficacy using clinical features alone. Patients monitored on ICGA as well as those patients monitored with clinical features, both achieved equally good visual outcomes in their study. Pretreatment FFA has a greater prognostic value than a pretreatment ICGA. However, ICGA is valuable in guiding the duration and dose of therapy.<sup>2,14,23</sup>

Despite the enormous clinical utility of FFA and ICGA, they are limited by the fact that they are invasive, costly, time-consuming, carry the risk of anaphylaxis, and require trained personnel and adequate support staff with arrangements to address possible adverse events. They cannot be repeated at frequent intervals, and are relatively contraindicated in pregnancy. FFA is contraindicated in patients with severe asthma and significant renal or cardiac disease. FFA carries the invariable side effect of nausea immediately following the fluorescein injection, and staining of skin and urine following the procedure. ICGA is contraindicated in patients who are allergic to iodine and seafood, and patients who have significant hepatic or cardiac disease.

## Conclusion

In patients presenting with exudative retinal detachments, FFA helps to demonstrate optic disc leakage, pinpoint hyperfluorescence, subretinal pooling of dye and any associated complications like choroidal neovascularization and retinal vasculitis. Thus, FFA helps not only to diagnose VKH disease in its acute or chronic stage but also to determine the extent of inflammation and structural changes and prognosticate the disease. ICGA is an excellent tool to diagnose and delineate the extent of choroidal inflammation in patients of VKH disease. ICGA signs of choroidal inflammation can be suppressed completely with initial high-dose anti-inflammatory therapy. ICGA also helps to diagnose subclinical choroidal inflammation, and helps to identify subclinical recurrences of inflammation. Periodic follow-up on ICGA helps to detect smoldering subclinical inflammation and monitor therapy appropriately in a bid to prevent the eventual evolution of a sunset glow fundus despite apparently adequate treatment. 2

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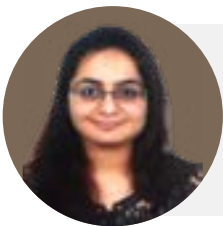
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# Treatment in VKH



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## TREATMENT OF VKH

VKH is a systemic autoimmune disorder in which there is autoimmunity against the melanocytes in the uveal tissue, meninges, skin and inner ear. The two phases of VKH that have been recognized are- initial onset VKH and chronic VKH.<sup>1,2</sup> With the understanding of immunopathogenesis of VKH, there has been a paradigm evolution in the treatment of VKH.

The principle of treatment in acute VKH is to suppress the inflammation aggressively with corticosteroids and to start immunosuppression as steroid sparing agents, whilst the corticosteroids are being tapered. This early treatment has been shown to shorten the duration of acute phase, prevent the progression to chronic phase and reduce the incidence of systemic manifestations.<sup>3,4,5</sup>

## SYSTEMIC TREATMENT

Corticosteroids were introduced as the mainstay of treatment of VKH since 1950s.<sup>6</sup> The preferred regimen in acute phase of VKH is treatment with high dose intravenous corticosteroids (intravenous methylprednisolone 500-1000 mg/day for 3-5 days) followed by high dose oral corticosteroids (1mg/kg/day) for 4-6 weeks. Though no additional advantage of initial intravenous corticosteroid administration has been reported,<sup>7</sup> initial intravenous steroids are a preferred mode of treatment for rapid resolution of inflammation. Starting aggressive treatment within the “window of therapeutic opportunity” drastically improves the disease outcome. This window lies between 2 to 4 weeks from the onset of disease activity.<sup>8</sup>

Immunomodulatory therapy (IMT) has been used widely as an adjunct to steroids in the treatment of VKH.<sup>3,4,5</sup> Immunosuppressive agents that have shown to be effective are: anti- metabolites, alkylating agents, tumor necrosis factor- alpha (TNF-alpha) inhibitors and monoclonal antibodies.<sup>3,4,5,11,12,13</sup>

Immunosuppressive agents include- cyclosporine (3-5 mg/kg/day), azathioprine (2-3 mg/kg/day), methotrexate (7.5 mg-20 mg/week) and mycophenolate mofetil (1.5-2g/day). No specific immunosuppressive agent has shown superiority over others. Azathioprine and methotrexate have shown to be as effective as cyclosporine in these patients.<sup>14,15,16,17,18</sup> Paredes and colleagues have shown superior visual outcomes of prompt IMT when compared with steroid monotherapy or delayed addition of IMT.<sup>4</sup> Papasavvas et al reported that chronic evolution and sunset glow fundus respectively occurred in 44% and 59% of the patients who received corticosteroids alone, as compared to 2.3% and 17.5% of the patients who received dual therapy i.e steroids and non-steroidal immunosuppression.<sup>19</sup> This highlights the role of immunosuppression as an adjunct to steroids in decreasing the chronicity as well reducing recurrences in VKH.

Recently, biological response modifiers (BRM) have been shown to be efficacious in treating uveitis refractory to conventional immunosuppressive agents.<sup>20</sup>

Adalimumab inhibits the TNF- alpha which is produced by Th1 cells in VKH.<sup>20</sup> Its role has recently been studied in treating recalcitrant cases, patients who developed steroid related complications and in challenging pediatric cases. Su et al described a case of 12 years Chinese American female who was successfully treated with adalimumab when she failed to respond to high dose corticosteroids and mycophenolate mofetil.<sup>21</sup> Cuoto et al showed

complete resolution of inflammation in 28 eyes with recalcitrant disease who were treated with adalimumab. The median dose of corticosteroid could be reduced from 20 mg at baseline to 4mg at 6 months with initiation of adalimumab. Also, adalimumab was found to be a safe and effective option reducing the need of corticosteroids and conventional IMT.<sup>22</sup>

Infliximab is a chimeric immunoglobulin monoclonal antibody against TNF- alpha. It is delivered as an intravenous infusion, usually at a dose of 3–10 mg/kg, although doses of 10–20 mg/kg have been used with few side-effects.<sup>20</sup> Infliximab has shown efficacy in recalcitrant as well challenging pediatric cases of VKH.<sup>23,24</sup> However, there are certain safety concerns with use of TNF-alpha inhibitors. These include – reactivation of infections especially tuberculosis, demyelinating diseases and malignancies.<sup>25</sup>

Rituximab, a chimeric monoclonal antibody against CD20 has also demonstrated efficacy in the treatment of recalcitrant cases of VKH in a few case reports. Abu El- Asrar presented long term follow up of 9 cases of refractory uveitis secondary to VKH treated with rituximab. All nine patients were resistant to conventional IMT and TNF- alpha blockers.<sup>26</sup> Adjuvant rituximab led to control of inflammation and also reduced the dose of daily immunosuppression. Bolletta et al in their study demonstrated the efficacy of rituximab in 5 patients with refractory VKH.<sup>27</sup> Excellent response to rituximab therapy highlighted the role of B cell mediated inflammation in recalcitrant cases of VKH.

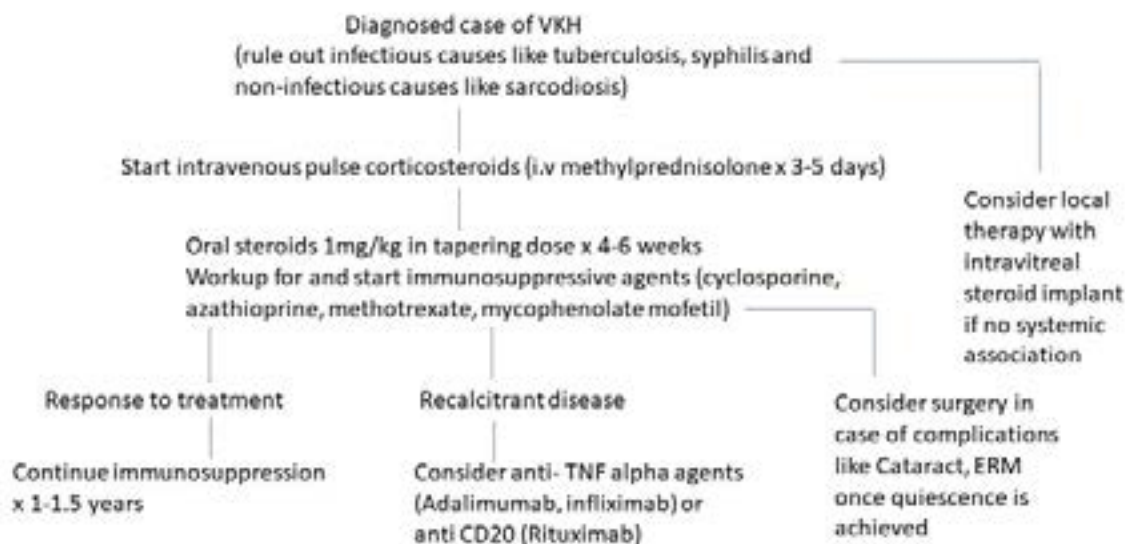
## LOCAL THERAPY

Local injection of corticosteroids has also been used as a treatment modality in the acute VKH. Sub-tenon triamcinolone acetonide injection was investigated as a primary treatment in acute VKH disease by Hosoda et al. In their study, 77.8% eyes achieved complete resolution of inflammation, but ocular inflammation remained refractory in 22.2% eyes. Most of the patients who remained refractory to treatment also had headache as one of the presenting complaints.<sup>9</sup> This study highlighted that isolated sub- tenon triamcinolone could be a useful treatment option for patients who did not have associated systemic disease. The role of intravitreal dexamethasone implant as an adjunct to systemic steroid treatment in acute VKH was reported by Chen et al.<sup>10</sup> Since VKH is a systemic disease, providing local treatment does not treat the auditory, central nervous system and the integumentary symptoms. Thus, treatment with sub-tenon triamcinolone or intravitreal dexamethasone implant could be considered as an option for patients who are already on immunosuppression or those who have no systemic involvement.

Topical steroids (prednisolone acetate 1% or betamethasone 0.1%) are used in cases of VKH with associated anterior uveitis. The frequency of instillation depends on the severity of inflammation. In addition to topical steroids, topical cycloplegic agents (homatropine 2% and atropine 1%) are used in cases with associated anterior uveitis to treat ciliary spasm as well to prevent the formation of posterior synechiae.

## SURGICAL MANAGEMENT

The role of surgery in VKH is limited to treating the complications of the disease like cataract, glaucoma, epiretinal membrane and subsequent macular hole.



VKH disease treatment flowchart for initiation and maintenance therapy and recalcitrant cases.

	SYSTEMIC THERAPY	LOCAL THERAPY
Indication	VKH with systemic manifestations	Can be considered in VKH without systemic symptoms or in cases with unilateral recurrence
Treatment options	-Intravenous and oral steroids -Immunosuppressive agents	-Sub tenon triamcinolone -Intravitreal dexamethasone implant
Advantages	-Will treat integumentary, auditory and CNS symptoms in addition to ocular findings - can be withdrawn/ replaced with another agent in case of any complication	No systemic side effects
Disadvantages	Systemic side -effects of respective agent	Can result in recurrences

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# Vogt Koyanagi Harada disease in a pregnant woman – Challenges in treatment



Uveitis Society (India)

## Dr. Jyotirmay Biswas

Director of uveitis and ophthalmic pathology

Sankara Nethralaya, Chennai

He has published 508 articles in pubmed indexed journals, 62 chapters. He has mentored 45 uveitis fellows. He has received 44 awards including Hari OM Ashram Alembic research award from ICMR given by the president of India.

He is a member of International Uveitis Study Group, American Uveitis society, International Ocular Inflammation Society





## Introduction:

Vogt Koyanagi Harada disease is a chronic bilateral diffuse granulomatous panuveitis characterized by anterior uveitis, serous retinal detachment, diffuse choroidal thickening with or without auditory symptoms and integumentary changes. The systemic steroid is mainstay of the treatment however in pregnant patient systemic steroid treatment in the early stage can precipitate spontaneous abortion and fetal abnormality. We report a case of Vogt Koyanagi Harada disease developed during pregnancy and was treated with intravenous methyl prednisolone ,intravitreal steroid (Triamcinolone acetonide) injection and oral steroids.. Patient delivered a healthy baby, had complete resolution of the disease. However vision did not improve to full extent.

## Case report

A 22 year old female who was 12 week pregnant, presented for the first time in 2019 with both eyes diminished vision which had been preceded by headache. .Her BCVA in right eye was 3/60 and in left eye was 2/60.On ocular examination intraocular pressure was normal in both eyes ,anterior chamber had 1+ cells, exudative retinal detachment with disc edema in both eyes.Neurologist,gynaecologist opinion were consulted and they ruled out toxemia of pregnancy and any other systemic abnormalities. Thus a diagnosis of VKH was made. During the pregnancy the patient was treated with, intravenous methyl prednisolone ,intravitreal steroid (Triamcinolone acetonide) injection and oral steroids and the inflammation was controlled. A healthy baby was delivered .After delivery the BCVA in right eye was 6/24,left eye was 2/60,both eyes were quiet and fundus examination revealed sunset glow with subretinal fibrosis. During the following four year course of the disease the patient had waxing and waning of the inflammation .The right eye was eventually treated for uveitic glaucoma, cystoid macular edema, peripapillary choroidal neovascular membrane and underwent cataract surgery. The left eye developed hypotony and she underwent lensectomy and vitrectomy for the same. At present the BCVA in both eyes is 6/60,intraocular pressure in right eye was 4 and left eye 2 respectively ,quiet eyes, sunset glow fundus in both the eyes and is currently on immunosuppressives

## Discussion

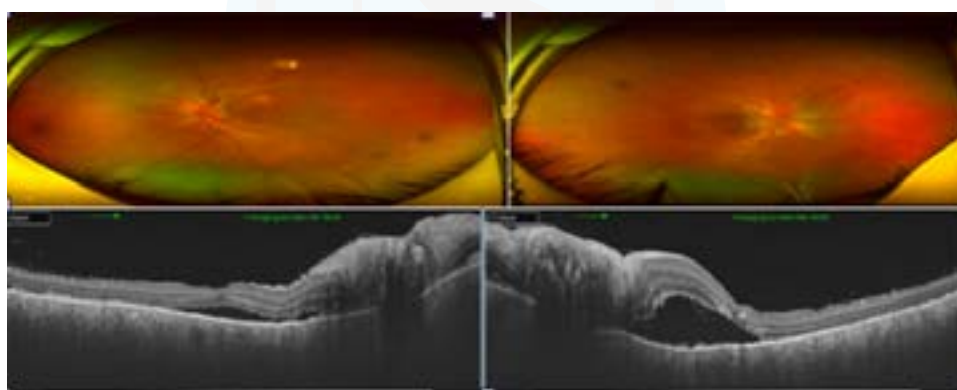
In pregnant patient with VKH syndrome high dose of corticosteroid administration effect on the fetus is controversial. Sugita et al reported ac a case report of treating a pregnant lady with VKH with low dose (5 mg )of oral steroids resulting in complete resolution of the acute phase with no fetal complications [1]. A pregnant VKH patient treated with a high-dose systemic corticosteroid delivered a low-birth-weight infant with an epibulbar dermoid, lipodermoids, and preauricular appendages,noted that the causative relationship between VKH disease, systemic corticosteroids, and congenital malformation was not clear [2].Other documented side effects of steroids in pregnancy in VKH cases include spontaneous abortion,preterm delivery,meningoencephalitis,cleft palate and also fetal death [3,4,5].

high dose corticosteroid administration to pregnant women may induce adrenal dysfunction in the delivered babies and intrauterine growth restriction. In the gestational mother steroids causes complications like gestational diabetes, hypertension, osteoporosis. Because of minimal foetal uptake prednisolone and methylprednisolone are the drugs of choice during pregnancy. Ingolotti et al had treated a pregnant VKH women with oral azathioprine, resulting in control of inflammation and the baby had no complications.[7] Certolizumab pegol - a PEGylated Fc-free anti-TNF therapy differs from others anti-TNF because it does not bind the neonatal Fc receptor (FcRn), no neonatal complications were noted when used to treat pregnant VKH patients[8].

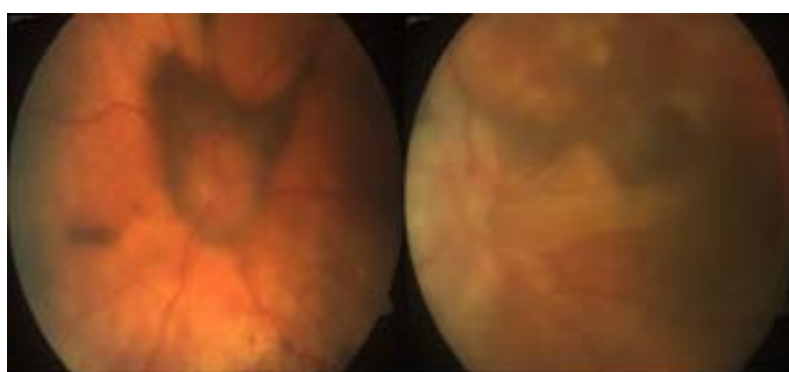
Usually in pregnancy state is favourable as there is high levels of corticosteroid production, suppressed cellular immunity, reduced cytokine production there is high levels of corticosteroid production is high. Because of these immunological conditions, the inflammation caused by VKH disease during the first and second trimesters of pregnancy may be mild. The challenge lies in the diagnostic and the treatment of uveitis in pregnant ladies as dye based ancillary tests are contraindicated and the pregnant mothers are not in favour of systemic medication.

This leads to inadequate control of underlying inflammation in the initial period of presentation, resulting in the vision worsening complications.

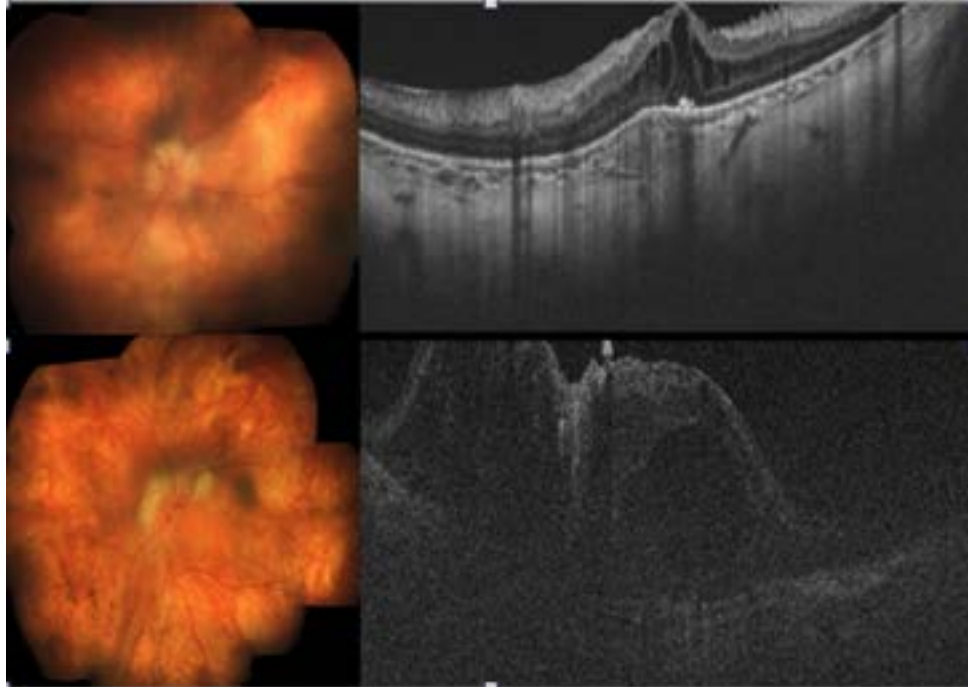
**FIG 1** At first visit above fundus photo of both eyes showing acute VKH, below OCT showing subretinal fluid



**FIG 2-** After delivery fundus photo of both eyes showing sunset glow fundus with subretinal fibrosis.



**FIG-3** After delivery



Above picture of right eye ,fundus photo shows disc edema and sunsetglow fundus,OCT of right eye shows cystoid macular edema.

Below picture of left eye ,fundus photo shows disc edemawith sunset glow fundus.OCT of left eye shows media haze ,dragged fovea.

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# Literature Review



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Am J Ophthalmol. 2021  
Aug;228:205-211. doi:  
10.1016/j.ajo.2021.03.036

## Classification Criteria for Vogt-Koyanagi-Harada Disease. Standardization of Uveitis Nomenclature (SUN) Working Group.

Jabs et al.

To determine the  
classification criteria

Purpose

Study  
Participants

- VKH
- 5 other panuveitides
- Early-stage VKH
  - exudative retinal detachment with characteristic fluorescein angiogram or optical coherence tomography or
  - panuveitis with  $\geq 2$  of 5 neurologic symptoms/signs.
- Late-stage VKH
  - history of early-stage VKH
  - and either (1) sunset glow fundus or (2) uveitis
  - and  $\geq 1$  of 3 cutaneous signs

- 1022 cases - panuveitides,
- 156 cases - early-stage VKH
- 103 cases - late-stage VKH
- Overall accuracy for panuveitides was 96.3% in the training set and 94.0% in the validation set (95% confidence interval 89.0, 96.8).
- The misclassification rates in the learning and validation sets for early-stage VKH were 8.0% and 7.7%, respectively, and for late-stage VKH 1.0% and 12%, respectively.

Result

Methodology

- Informatics-designed preliminary database for case collection
- Agreement on the diagnosis, using formal consensus techniques
- Split into a training set and a validation set
- Multinomial logistic regression used on the training set to minimize the misclassification
- Resulting criteria were evaluated on the validation set.

Conclusio

- The criteria had a low misclassification rate
- Perform well for use in clinical and translational research.

Ocul Immunol Inflamm. 2022  
Aug;30(6):1303-1308. doi:  
10.1080/09273948.2021.18806

## Efficacy of Rituximab Treatment in Vogt-Koyanagi-Harada Disease Poorly Controlled by Traditional Immunosuppressive Treatment

Bolletta E et al.

To evaluate the efficacy of Rituximab (RTX) therapy in patients affected by Vogt-Koyanagi-Harada (VKH) disease poorly controlled by traditional immunosuppressive treatment

### Purpose

### Study Participants

Recurrent VKH uveitis treated with intravenous RTX between January 2019 and November 2020.

- Five patients were included.
- All patients received at least 3 RTX infusions.
- Mean BCVA improved from 20/32 Snellen equivalent at baseline to 20/28 Snellen equivalent ( $p = .008$ ).
- Mean SFCT on EDI-OCT showed a reduction from 564.4  $\mu\text{m}$  (SD = 176.2) to 280.0  $\mu\text{m}$  (SD = 140.4) ( $p = .015$ ).
- Follow-up –
  - range - 12 to 21 months
  - mean -  $18.2 \pm 3.7$  months

### Result

### Methodology

- Complete ophthalmic examination,
- Best-corrected visual acuity (BCVA),
- Fundus photography,
- Subfoveal choroidal thickness (SFCT) measurement on enhanced depth imaging optical-coherence tomography (EDI-OCT),
- Fluorescein, and indocyanine green angiography

### Conclusion

- RTX was effective in VKH disease poorly controlled by traditional immunosuppressive treatment.



Int Ophthalmol. 2022 Aug  
9. doi: 10.1007/s10792-  
022-02415-1

Outcomes of initial-onset acute uveitis  
associated with Vogt-Koyanagi-Harada disease  
occurred during pregnancy

Alromaih AZ et al.

To investigate the outcomes of  
initial-onset acute uveitis  
associated with Vogt-Koyanagi-  
Harada (VKH) disease that  
occurred during pregnancy.

#### Purpose

Study  
Participants

Initial-onset acute uveitis  
associated with VKH disease

#### Result

- 112 patients evaluated
- 67 (59.8%) were females.
- Among the female patients, 10 (14.9%) were pregnant.
- 5 patients - the first trimester,
- 3 patients - second trimester
- 2 patients -the third trimester.
- Mean follow-up period -  $35.2 \pm 28.3$  months.
- At presentation, 80% patients had anterior segment (AS) inflammation
- Complications - "sunset glow fundus", cataract and subretinal fibrosis noted in patients with initial-onset acute VKH disease with AS inflammation.
- 40% patients developed pregnancy-related complications - abortion, systemic hypertension and premature rupture of membrane.
- No congenital anomalies in all born babies.
- Best-corrected visual acuity of  $\geq 20/20$  was achieved in 80% eyes at the final follow-up.

Methodology

- Retrospective case series.
- January 2001 and December 2021

#### Conclusion

- Primary treatment with combined systemic corticosteroids and cyclosporine in initial-onset acute uveitis associated with VKH disease was safe and effective

J Ophthalmol. 2019  
Oct 3;2019:3853794.  
doi:

## Identification of Underlying Inflammation in Vogt-Koyanagi-Harada Disease with Sunset Glow Fundus by Multiple Analyses

Murata T et al.

To evaluate underlying  
subclinical ocular inflammation  
in Vogt-Koyanagi-Harada (VKH)  
disease with sunset glow fundus  
(SGF) by multiple analyses.

### Purpose

Study  
Participants

VKH patients with SGF

- The mean age of presentation -  $57.3 \pm 16.3$  years
- Mean duration from the initial onset of uveitis -  $47.1 \pm 22.1$  months.
- Although clinical ocular inflammation was observed only in 4 eyes (11.8%), inflammatory signs were observed in 23 out of 34 eyes by LFP (67.6%), in 27 eyes by ICGA (79.4%), and in 10 eyes by SFCT (29.4%).
- Active inflammatory signs detected by ICGA were observed in 77.8% by LFP and in 25.9% by SFCT.
- The strength of agreement (Cohen's kappa coefficient) between positive ICGA score and positive flare score was 0.406 (95% CI: 0.076-0.7359,  $P < 0.01$ ), but there was no association between positive ICGA score and increased SFCT.
- In addition, positive flare count was the significant prognostic factor of positive ICGA score with odds ratio 11.7.

### Result

Methodology

Retrospective observational study. Laser flare photometry (LFP), enhanced depth imaging optical coherence tomography (EDI-OCT), and indocyanine green angiography (ICGA) performed on the same day were reviewed

### Conclusion

- Subclinical ocular inflammation signs were detected in most VKH patients with SGF by ICGA
- A substantial proportion of which were also detected by LFP,
- SFCT was less sensitive to detect subclinical inflammation

Retina. 2022 Sep  
1;42(9):1788-1795. doi:  
10.1097/IAE.0000000000  
0003525.

# OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY REVEALS PARADOXICALLY DECREASING CHOROIDAL THICKNESS AND INCREASING BLOOD FLOW IN REMITTING VOGT-KOYANAGI- HARADA SYNDROME

Fayed AE et al.

To assess changes in choroidal thickness and blood flow in active Vogt-Koyanagi-Harada syndrome and after remission using optical coherence tomography angiography.

## Purpose

## Study Participants

Active early uveitis secondary to Vogt-Koyanagi-Harada syndrome.

- Thirty-nine eyes of 25 patients were initially recruited.
- After excluding eyes with media opacity, submacular fibrosis, and choroidal neovascularization, 23 eyes of 14 patients were included.
- The mean follow-up period was  $8.7 \pm 2.5$  months.
- Mean choroidal thickness in activity and remission was  $581.65 \pm 108.29 \mu\text{m}$  and  $318.34 \pm 72.85 \mu\text{m}$  respectively ( $P < 0.01$ ).
- Mean adjusted flow index in the  $3 \times 3\text{-mm}$  slabs activity and remission were  $0.495 \pm 0.027$  and  $0.519 \pm 0.0336$  ( $P = 0.011$ ), and the  $6 \times 6\text{-mm}$  slabs were  $0.487 \pm 0.037$  and  $0.517 \pm 0.052$  respectively ( $P = 0.025$ ).

## Result

## Methodology

- Prospective study of patients with
- Optical coherence tomography angiography imaging twice: at baseline and after remission on treatment.
- $3 \times 3\text{-mm}$  and  $6 \times 6\text{-mm}$  choriocapillaris slabs
- Mean choroidal thickness of 3 points subfoveally and 2 points  $300 \mu\text{m}$  parafoveally.

## Conclusion

- Decreasing choroidal thickness with paradoxically increasing choroidal flow on optical coherence tomography angiography in remitting Vogt-Koyanagi-Harada syndrome.
- Might reflect inflammatory infiltrations or granulomas increasing choroidal thickness during activity and causing sluggish circulation of the choriocapillaris, and a reversal of this process with remission.

Ocul Immunol  
Inflamm. 2022 Jun  
24:1-9. doi:

## Efficacy and Safety of Adalimumab for Exacerbation or Relapse of Ocular Inflammation in Patients with Vogt-Koyanagi-Harada Disease: A Multicenter Study

Nakai S et al.

To evaluate the efficacy and  
safety of adalimumab (ADA)  
treatment for exacerbation or  
recurrence of Vogt-Koyanagi-  
Harada (VKH) patients.

### Purpose

### Study Participants

VKH patients who received ADA  
treatment for more than  
6 months

- The mean age -  $54.8 \pm 15.1$  years,
- Male/female ratio - 34/36,
- Sunset glow fundus - 71.4%.
- Subfoveal choroidal thickness, indocyanine green angiography scores, and corticosteroid and cyclosporine doses were significantly reduced by ADA
- LogMAR and flare counts were also improved (though statistically insignificant.)
- Adverse events were observed in 17.1%, in which tuberculosis was at 7.14% and psoriasis was at 2.86%; however, ADA treatment was continued in 91.4%.

### Result

### Methodology

Retrospective analysis of the  
medical records

### Conclusion

- ADA was shown to be effective to achieve remission of VKH disease refractory to conventional treatments
- Well tolerated with few serious adverse events.

Ophthalmol Retina.  
2019 Feb;3(2):161-169.  
doi:

## Choroidal Vasculature from Ultra-Widefield Images without Contrast Dye and Its Application to Vogt-Koyanagi-Harada Disease.

Kakiuchi N et al.

To develop a method to obtain ultra-widefield choroidal vessel images with a fundus camera without using dye, and its application in Vogt-Koyanagi-Harada (VKH) disease.

### Purpose

### Study Participants

Patients with unilateral retinal disorders and those with VKH disease who had undergone ultra-widefield imaging.

- The matching ratios for the overall area, the peripheral area, and the posterior pole area of the ICGA image and the Optos635-nm image were 64.09%, 74%, and 63.10%, respectively.
- The correlations between the choroidal blood vessel matching ratio and the ocular axial length and refractive error were not significant, but the matching ratio was correlated significantly with the age.
- The average clarity score in 12 VKH disease patients was  $1.6 \pm 0.85$  before treatment, which was significantly improved to  $4.2 \pm 0.75$  after 1 month ( $P < 0.05$ ).
- Many hyporeflective spotty lesions were observed on the Optos635-nm images, which coincided with hyperfluorescent dots on the ICGA images.
- The lesions gradually disappeared and the vortex vein became visible after treatment.

### Result

### Methodology

- Experimental study and case series.
- Indocyanine green angiography (ICGA) and the 635-nm wavelength Optos ultra-widefield fundus photography (Optos, United Kingdom) images (Optos635-nm) were processed by KagoEye 3 software.
- The 2 types of images were overlapped.
- The degree of overlapped blood vessel areas of the ICGA image was taken as the matching ratio.
- The matching ratio was obtained for the peripheral, posterior pole, and overall areas.
- Changes in the fundus findings were followed up with Optos635-nm image analysis.
- The degree of visibility of the choroidal vessels was evaluated for 5 stages.
- The matching ratios between the ICGA images and the Optos635-nm images processed by KagoEye3 software were determined.

### Conclusion

- The ultra-widefield Optos635-nm images processed by KagoEye3 software can exaggerate images of the choroidal vessels in widefield fundus images without using dye.

Eur J Ophthalmol. 2022  
Nov;32(6):3482-3488. doi:  
10.1177/112067212210854  
20.

## Suprachoroidal triamcinolone acetate injection: a novel therapy for serous retinal detachment due to Vogt-Koyanagi Harada disease

Tabl AA et al.

To assess the efficacy and safety of Suprachoroidal triamcinolone acetate injection [SCTA] as an adjunctive therapy in management of Vogt-Koyanagi Harada [VKH] serous retinal detachment.

### Purpose

### Study Participants

VKH patients having bilateral multiple serous retinal detachment in acute phase on systemic steroids.

- BCVA at one and three months was significantly better in eyes received SCTA than in non-injected eyes (p-value = 0.026 for each).
- CFT at one and three months was significantly higher in non-injected eyes than in eyes received SCTA (p-value = 0.028 for each).
- IOP showed no significant differences between both groups

### Result

### Methodology

- Prospective parallel group study.
- Each patient received single SCTA injection (SCTA group, n = 6 eyes) and the other non-injected eye (Standard treatment group, n = 6 eyes),
- Followed for 1, 3, and 6 months
- Changes in best corrected visual acuity [BCVA], central foveal thickness [CFT] and intraocular pressure [IOP] between both groups assessed.
- MAIN OUTCOME MEASURES: The primary end point was changes in BCVA from baseline till 6th months follow-up.
- Secondary end points were changes in CFT and IOP from baseline to 6 months of follow-up.

### Conclusion

- SCTA is an effective adjuvant treatment for VKH serous retinal detachment
- Without any serious ocular adverse effects or increase in IOP
- Causing significant reduction in CFT
- Rapid improvement in BCVA

Ocul Immunol  
Inflamm. 2020 May  
18;28(4):626-631.

10.1080/09273948.201  
9.1609527

## Ultrabiomicroscopic Findings in Acute Uveitic, Convalescent and Chronic Recurrent Stage of Vogt-Koyanagi-Harada Syndrome

Pachón-Suárez DI et al.

To describe the  
ultrabiomicroscopy (UBM)  
characteristics

### Purpose

Study  
Participants

Acute uveitic, convalescent, and  
chronic-recurrent phases.

- Ninety-one eyes analyzed.
- The most characteristic findings of the uveitic phase - Ciliochoroidal detachment (20%) and unclear ciliary processes (15%)
- At 1 and 3 months - ciliochoroidal detachment no longer observed.
- In recurrent phase - pars plicata and pars plana thickness increases again and then decreases after the first month of treatment.
- Convalescent phase - no significant differences in UBM variables

### Result

### Methodology

- Prospective, non-interventional, and observational study,
- UBM variables measured pars plicata and pars plana thickness, ciliochoroidal detachment, angle chamber, anterior chamber depth, and ciliary processes

### Conclusion

- A role in evaluating response to treatment
- In the early detection of recurrences



Semin Ophthalmol. 2022  
Feb 17;37(2):187-192.  
doi:10.1080/08820538.202  
1.1948067.

## Vogt Koyanagi Harada Disease In Paediatric Age Group: Clinical Characteristics, Remission, Recurrences and Complications in Asian Indian Population.

Kaza H et al.

To describe disease  
characteristics and outcomes

### Purpose

Study  
Participants

≤16 years of age

- 72 eyes of 36 patients
- Mean age at presentation of  $13.7 \pm 2.34$  years
- Mean duration of symptoms -  $9.88 \pm 17.3$  weeks
- Mean follow up duration - 55 months.
- Clinical signs at presentation - anterior uveitis, granulomatous keratic precipitates, posterior synechiae, disc edema, neurosensory retinal detachments and sunset-glow fundus
- Best corrected visual acuity (BCVA) at the time of presentation - 1.3logMAR or a Snellens equivalent of 20/400
- BCVA at final follow up - 0.51logMAR or a Snellens equivalent of 20/63
- Remission achieved in 61.1% cases.
- More than half of patients developed one or more complications.

### Result

Methodology

- Retrospective chart analysis.
- Clinical presentations, complications, recurrences and outcomes were reviewed

### Conclusion

- Have a worse visual acuity at the time of presentation as compared to adult
- Rates of remission low
- high risk of complications
- A need for prolonged immunosuppression.

# Awards and Recognitions



## *Dr. Jyothirmay Biswas*

*was invited to deliver the oration dedicated to*

***Dr. K S Ratnakara***

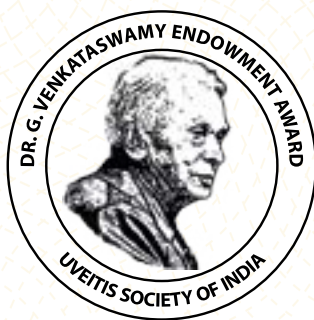
*at the Meeting of the Indian College of Pathologist*

*on 3<sup>rd</sup> December 2022*

*The (ICP) oration was a part of the APCON 2022 conference*

*held at Ramaiah Medical College , Bengaluru*

**Title: Ophthalmic Pathology- My Journey of 33 years**



*The Uveitis Society (India) is privileged and honored to confer the  
Dr. G. Venkataswamy Endowment Award on*



*Prof. Dr. Vishali Gupta*

*in appreciation of her outstanding  
contributions in the field of Ophthalmology.*

**15<sup>th</sup> October, 2022, Hyderabad**

## AWARD WINNERS 2022

### Free Paper Presentation Winners

#### Prof . Narsing A Rao Award

**Dr. Manisha Agarwal**

**Topic:** Adjunctive Intravitreal Anti-vascular Endothelial Growth Factor and Moxifloxacin Therapy in Management of Intraocular Tubercular Granulomas

**Institute:** Dr Shroff's Charity Eye Hospital, Delhi

#### Dr. Carl Herbort Travel Grant

**Dr. Cherukuri Navya**

Vogt Koyanagi Harada syndrome(VKH) masquerading as angle closure

**Institute:** LV Prasad Eye Institute, Hyderabad

#### Appreciation Award-1

**Dr. Anup Kelgaonkar**

**Topic:** Line probe assay as a diagnostic modality in cases of 'severe', 'non-responsive' and/or 'atypical' cases of posterior tubercular uveitis

**Institute:** LV Prasad Eye Institute, Bhubaneswar

#### Appreciation Award- 2

**Dr. Ajay Aurora**

**Topic:** Evaluate Efficacy & Safety of centrifuged Triamcinolone (cTA) in Suprachoroidal Space (SCS) in Non Infectious Uveitis with Macular Edema

**Institute:** Vision Plus Eye Centre & MMR Eye Institute, Delhi

#### Appreciation Award-3

**Dr. Nikitha Ayyadurai**

**Topic:** Double Trouble: When Scleritis Complicates Tubercular Serpiginous-like Choroiditis Or Vasculitis!

**Institute:** PIGMER, Chandigarh

# AWARD WINNERS 2022

## Dr. Amod Gupta Young Researchers Award Winners

### Dr. Atul Arora

**Topic:** Imaging characteristics of Subretinal Hyperreflective Material (SHRM) in patients with healed posterior uveitis.

**Institute:** Advanced Eye Center, P.G.I.M.E.R, Chandigarh

### Dr. Hrishikesh Kaza

**Topic:** CLINICAL PREDICTORS OF TUBERCULAR RETINAL VASCULITIS IN A HIGH ENDEMIC COUNTRY

**Institute:** Addenbrookes Hospital, Cambridge University Hospitals

## E Poster Prizes Winners

### First Prize

#### Dr. Sanjay S

**Topic:** Correlation of Choroidal and Central Macular Thickness with Treatment in Post Fever retinitis

**Institute:** Narayana Nethralaya , Bengaluru

### First Prize

#### Dr. Samendra Karkhur

**Topic:** Case of chronic ocular hypotony following Endogenous endophthalmitis: a management challenge!

**Institute:** AIIMS Bhopal

## Appreciation Award-1

#### Dr. Vipin Rana

**Topic:** Fern-like leak of capillary leakage on Ultrawide Field Fundus Fluorescein Angiography: A Comparative Study between Behcet's and Non-Bechet's etiology.

**Institute:** PGIMER, Chandigarh

## Appreciation Award-2

#### Dr. Gazal Patnaik

**Topic:** Histopathologic and immunohistochemical study of an enucleated specimen of a case of end stage pars planitis

**Institute:** Sankara Nethralaya, Kolkata



# AWARD WINNERS 2022

## Photo Contest Winners

### First Prize

**Dr. Radhika T**

**Topic:** Scleral nodule as tip of the iceberg.

**Institute:** Aravind Eye Hospital and Post Graduate Institute Of Ophthalmology, Madurai

### First Prize

**Dr. Ashish Khalsa**

**Topic:** Let not the whitish fibrin sway the attention away from pockets of subretinal fluids: a case of VKH

**Institute:** CL Gupta Eye Institute, Muradabad

### Appreciation Award-1

**Dr. Anjana Somanath**

**Topic:** Vitreous infiltrates in Chronic Myeloid Leukemia

**Institute:** Aravind eye hospital and post graduate institute of ophthalmology, Madurai



# AWARD WINNERS 2022

## Challenging Case Presentation Winners

### First Prize

**Dr. Manisha Agarwal**

**Topic:** What are we dealing with ?

**Institute:** DR SHROFF'S CHARITY EYE HOSPITAL, Delhi

### Second Prize

**Dr. Vipin Rana**

**Topic:** Bilateral Rapidly progressive Macular Necrotizing Retinitis  
in an unvaccinated Child

**Institute:** PGIMER, Chandigarh

### Appreciation Award-1

**Dr. Sanjay S**

**Topic:** Unilateral recalcitrant uveal effusion

**Institute:** Narayana Nethralaya , Bengaluru

### Appreciation Award-2

**Dr. Gazal Patnaik**

**Topic:** Uveal effusion syndrome as a manifestation of  
WNT10A mutation – First case report

**Institute:** Sankara Nethralaya, Kolkata

### Appreciation Award-3

**Dr. P Priyadharshini**

**Topic:** Double Trouble-Juvenile idiopathic arthritis with inflammatory  
choroidal neovascular membrane.

**Institute:** Sankara Nethralaya, Chennai



# **CME Conducted Under the Aegis of Uveitis Society (India)**

# Bengal Uveitis Summit 2022

11<sup>th</sup> December 2022

at Sushruta Auditorium in Eastern Command Hospital in Kolkata



# IGNITE 2023

## 15<sup>th</sup> January 2023

### at hotel Radisson Blu, Kochi

Amrita Institute Of Medical Sciences conducted IGNITE 2023 , our Annual CME on Uveitis and Ocular inflammation, under the aegis of Uveitis Society of India, Kerala Society of Ophthalmic Surgeons and Cochin Ophthalmic Club on January 15<sup>th</sup> at hotel Radisson Blu, Kochi. The CME was conducted from 9am to 5pm and had 6 sessions in all, including a virtual session by Dr. Vishali Gupta, from PGIMER Chandigarh. We started with basic sessions and had case presentations followed by a very stimulating discussion. Ask the Rheumatologist session was done by Dr. Suma Balan, Dr. Joe Thomas and Dr. Mithun C.B from Kochi and it was a very illuminating session for all the attendees. The National faculty who attended were Dr. Kalpana Babu Dr. Soumyava Basu, Dr. Mudit Tyagi, Dr. Sharanya Abraham and Dr.Vedhanayaki Rajesh and the state faculty who attended were Dr. Divya M Nair, Dr.Dahlia Krishnan , Dr. Reesha K R, Dr. Kiran K R, Dr. Amita Nair and Dr. Divya Balakrishnan. It was attended by 130 delegates across the state and was well appreciated by all. For the first time, we also had the competitive PG case presentation session, in which Dr. Binuja from Kottayam medical college was declared the winner





## CROSSWORD ANSWERS

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With due perseverance and hard work of the editorial and scientific committee members, we have been able to publish this edition of the USI Newsletter for the readers. I sincerely wish to convey my heartfelt special thanks to Dr. Vishali Gupta Dr. Kalpana Babu, Dr. Manisha Agarwal Dr. Sudharshan S, Dr. Jyothimay Biswas, Dr. S R Rathinam, Dr. Padmamalini Mahendradas Dr. Reema Bansal, Dr. Parthoprathim Dutta Majumder, Dr. Soumyava Basu, Dr. Dipankar Das Dr. Ankush Kawali, Dr. Aniruddha Agarwal, Dr. Mudit Tyagi, Mrs. Veidhehi J and Design Team of Hallmark Events for sparing their precious time to co-edit the contents of this issue. Thanks to all the fraternity members who have contributed their manuscript.

The encouragement from all my friends and seniors is highly appreciated.

With high regards,  
Dr. S Bala Murugan

**Editor-in-chief**

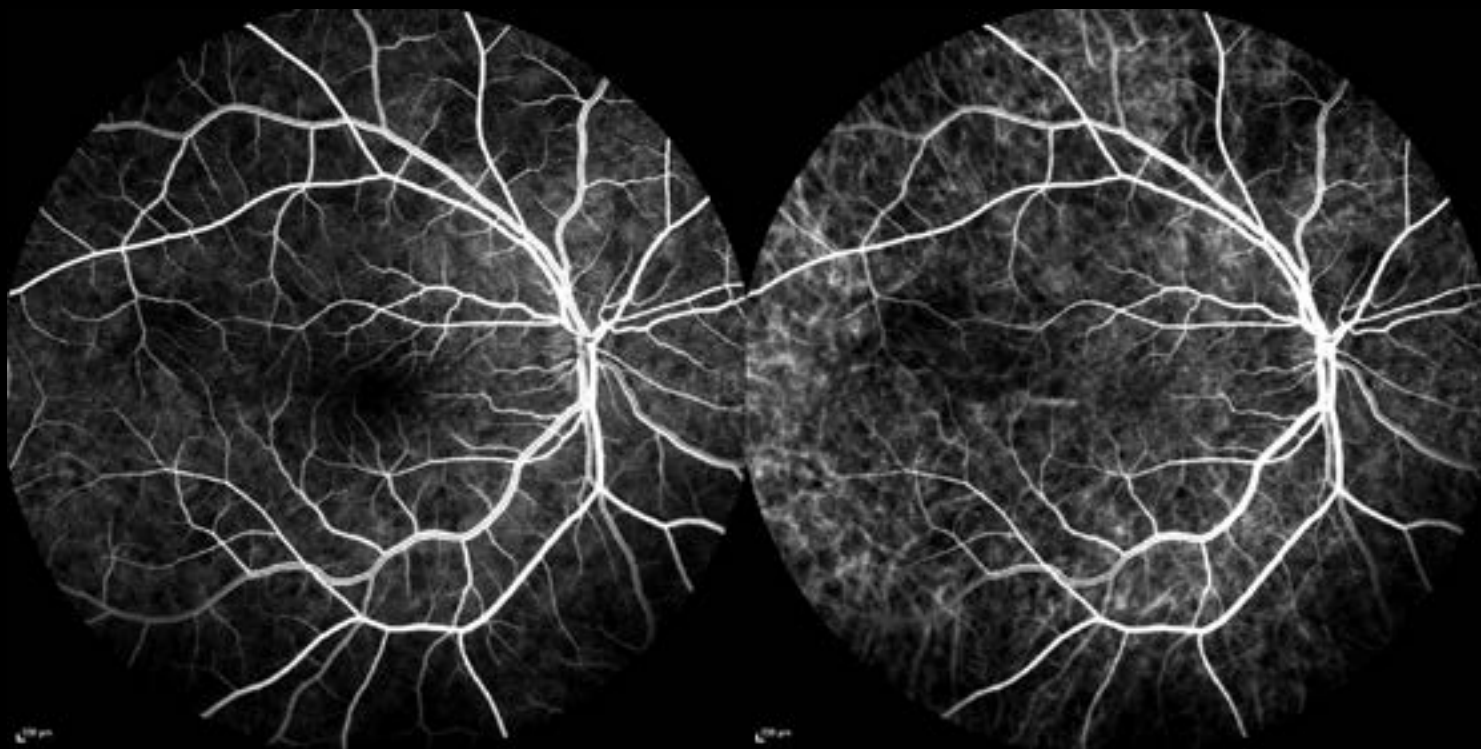
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***The scientific committee wishes to thank Dr. Lita Pragnaya and Dr. S Bala Murugan for the cover page images of a FFA findings of VKH in early and late phases respectively.***



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*Designed by*



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