

# Role of Swept source optical coherence tomography in management of acute Vogt-Koyanagi-Harada's disease

Sudha K Ganesh, Saurabh Mistry, Nivedita Nair

**Purpose:** To evaluate the role of swept-source optical coherence tomography (SS-OCT) in the management of acute Vogt-Koyanagi-Harada's (VKH) disease. **Methods:** Retrospective analysis of SS-OCT images of acute VKH patients between January 2015 and February 2020 in a tertiary eye care hospital. **Results:** We studied 34 eyes of 17 patients with acute probable VKH disease. The mean age was  $31.6 \pm 10.4$  years. Twelve patients were women. The mean follow-up was  $17.1 \pm 9.3$  months. The mean visual acuity was 0.86 logMAR (Snellen equivalent: 6/45) at presentation and 0.18 logMAR (Snellen equivalent: 6/9) at the last follow-up. The mean subfoveal choroidal thickness (SFCT) was 784.97 microns at presentation, 431.40 microns at the first month of therapy, 453.94 microns at six months of therapy, and 405.83 microns at the last follow-up. Qualitative features noted on SS-OCT on presentation was subretinal fluid (SRF) in 29 (85%) eyes, subretinal hyperreflective dots in 34 (100%) eyes, subretinal septa in 33 (97%) eyes, RPE undulations in 21 (61.7%) eyes, posterior vitreous cells in 34 (100%) eyes, SRF around disc in 9 (26%) eyes, and disc swelling in 34 (100%) eyes. At the end of 1 year of follow-up, RPE undulations were absent in 30 eyes (88%) and disc swelling was notably absent in all 34 eyes (100%), though SRF around disc was noted in 4 eyes (11.7%) of 2 patients who had recurrences. **Conclusion:** SFCT, SRF around disc, RPE undulation, and disc swelling may be important indicators on SS-OCT to guide therapy and prognosticate recurrences in acute VKH.

**Key words:** Acute VKH, recurrence, RPE undulation, SFCT, Subfoveal choroidal thickness, SS-OCT, Swept-source optical coherence tomography, therapy

Vogt-Koyanagi-Harada's (VKH) disease is a bilateral chronic multisystem inflammatory autoimmune disorder directed against melanocytes in the eye, auditory system, meninges, and skin. The typical manifestation of acute VKH is bilateral panuveitis with multifocal serous retinal detachments, diffuse choroidal swelling, and optic disc edema or hyperemia. These patients require long-term systemic steroids and immunosuppressive therapy, though there is no consensus about the duration of therapy.<sup>[1]</sup> The currently available tools to diagnose, evaluate, and monitor disease progression in VKH disease include fundus fluorescein angiography (FFA), indocyanine green angiography (ICGA), optical coherence tomography (OCT), and fundus autofluorescence (FAF).

OCT is very helpful in the diagnosis of acute VKH disease. Besides the fine characterization of signs, it aids the diagnosis of initial onset disease by revealing SRF and choroidal thickening that may not be detected clinically. OCT offers the advantage of being a non-invasive and easy reproducible test and has now become an essential tool in the diagnosis and monitoring of therapy in VKH. Imaging of the choroid is possible with the enhanced depth imaging (EDI) technique in the spectral domain (SD) OCT and in the more recent swept-source (SS) OCT devices. The longer-wavelength SS-OCT technology improves the visualization of the choroid as swept laser light sources can rapidly sweep the required frequencies; the

acquisition of scans is much faster with better visualization of choroid-sclera interface in SS-OCT when compared with SD-OCT systems. Chee *et al.*<sup>[2]</sup> compared EDI-OCT and SS-OCT in the assessment of VKH disease and found that SS-OCT images are superior to EDI-OCT.

OCT features in VKH disease include findings such as retinal pigment epithelium (RPE) folds, subretinal (SR) membranous structures, SR hyperreflective dots and intraretinal edema, thickened choroid in the acute stage, and thinned choroid in the chronic stage.<sup>[3]</sup> Various other studies reports thickened choroid in VKH in the acute stage and at the time of recurrent inflammation.<sup>[4,5]</sup> Morphological signs on OCT have a high predictive value in the diagnosis of acute VKH.

The purpose of the present study is to evaluate the role of SS-OCT as a non-invasive tool to aid in the diagnosis and management of acute probable VKH in Indian eyes.

## Methods

We retrospectively reviewed the records of consecutive bilateral acute probable VKH patients (treatment-naïve eyes) seen at a tertiary referral uveitis clinic in India between January 2015

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Medical Research Foundation, Sankara Nethralaya, Chennai, Tamil Nadu, India

**Correspondence to:** Dr. Sudha K Ganesh, Medical Research Foundation, Sankara Nethralaya 18, College Road, Chennai - 600 006, Tamil Nadu, India. E-mail: drskg@snmail.org

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and February 2020. The diagnosis was made based on the VKH international committee criteria published in 2001 as described by Read *et al.*<sup>[6]</sup> All acute probable VKH patients underwent a comprehensive ophthalmologic examination including measurements of the best-corrected visual acuity (BCVA), slit-lamp biomicroscopy, color fundus photography, FFA, and SS-OCT at every visit. We included only bilateral probable VKH (treatment-naïve eyes) in the acute uveitic phase. Serial SS-OCT at presentation (before treatment), at 1 month, 6 months, and last follow-up were obtained. We excluded VKH patients who had received treatment either with steroids or immunosuppressive prior to performing SS-OCT during acute stage of disease and patients with diabetic retinopathy, epiretinal membrane, and retinal vein occlusions that could cause SRF accumulation.

**SS-OCT Scanning:** All patients underwent examination with a prototype SS-OCT (swept-source imaging prototype; Topcon, Japan) system using 1050-nm wavelength for enhanced choroidal imaging. Twelve-millimeter radial scans were obtained, subfoveal choroidal thickness (SFCT) was measured, and choroidal and retinal details were studied. We evaluated choroidal thickness, RPE undulations, SRF, SR septa, posterior vitreous cells, SR hyperreflective dots, and disc swelling/SRF around disc. The measurements, grading and analysis of SS OCT images were performed by an independent reader to avoid bias.

#### Measurements and definitions

Choroidal thickness was defined as the vertical distance between the RPE line and the hyperreflective line behind the large choroidal vessel layers (i.e., subfoveal choroidoscleral interface). The SFCT measurements were taken from the outer margin of RPE to the sclerochoroidal interface by using the in built calipers available in the machine by an experienced technician. A thickness value of > 1000  $\mu\text{m}$  was assigned to those eyes where the choroid was so thick that the choroidal-scleral interface was not visible.<sup>[5,7]</sup>

The undulations of the RPE were defined as wavy protrusions of the RPE cell line toward the vitreous cavity. To semi-quantify them, we subjectively classified those into three grades based on the appearance of undulations: grade 1, slight undulations; grade 2, moderate undulations; and grade 3, severe undulations [Fig. 1a-f].

Subretinal fluid (SRF) was defined as a homogeneous hyporeflective space between the neurosensory retina and RPE. To semi-quantify them, we subjectively classified them into three grades: mild, moderate, and severe. Mild SRF was defined when minimal fluid was present, moderate was defined when pockets of SRF were present, and severe was defined when SRF with septae were present [Fig. 2a-f].

SRF around disc was defined as SRF present within one disc diameter area surrounding the optic nerve head [Fig. 3].

Subretinal septa was defined as a highly reflective line separated from the neurosensory retina and continuous with the junction of the photoreceptor inner and outer segments (IS/OS) in attached areas of the retina [Fig. 4a]. Posterior vitreous cells appeared as hyperreflective dots at the posterior vitreous face overlying the retina that were larger and of greater density than background speckle noise as previously described by Saito *et al.* [Fig. 4b].<sup>[8]</sup> SR hyper-reflective dots may represent clumps of inflammatory debris or macrophages engulfing shed

outer segments [Fig. 4a]. Special note was made in presence of disc swelling [Fig. 4c].

**Management:** All patients diagnosed with acute VKH disease received treatment according to a standardized protocol: intravenous methylprednisolone (IVMP) 1 g daily for 3 days followed by 1 mg/kg bodyweight prednisolone daily tapered over a minimum of 6 months along with immunosuppressive therapy (IMT) with azathioprine or mycophenolate mofetil or methotrexate. Those patients who had refused immunosuppression were treated only with oral steroids. Subsequently, the medications were titrated based on response to therapy.

The study's primary outcome measure was the treatment outcome based on the improvement in visual acuity and resolution of inflammation noted clinically and structural changes on SS OCT at follow up visit at 1 month, 3 months, 6 months, and thereafter until the last follow up. The resolution of inflammation was defined according to standard nomenclature<sup>[9]</sup> as resolved, chronic/persistent, or recurrent disease. The study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional review board.

**Statistical analysis:** Descriptive statistics were computed for logMAR visual acuity values, and frequency distributions were calculated for demographic variables and clinical diagnosis variables. Individual parameters were expressed as quantitative or qualitative data. Quantitative data were presented as mean  $\pm$  SD. The statistical analysis was performed using a commercially available statistical software package SPSS Version 22.0 (SPSS Inc, Chicago, IL). Kaplan-Meier survival curve was constructed to determine the proportion of patients who had good visual outcomes.

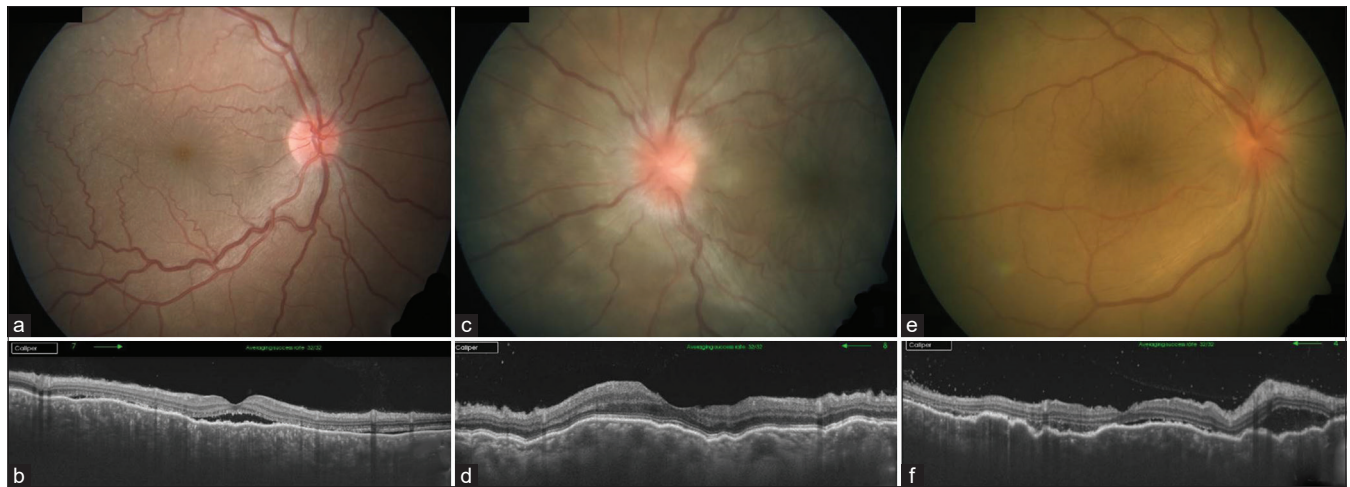
## Results

We studied 34 eyes of 17 patients diagnosed with acute probable VKH disease. The mean age was  $31.6 \pm 10.4$  years (range: 14–49 years), and 12 of them were women. All patients had bilateral disease at the time of presentation. The average duration of follow-up was  $17.1 \pm 9.3$  months (range: 6.1–32.6 months). The mean BCVA at baseline was  $0.86 \pm 1.03$  logMAR.

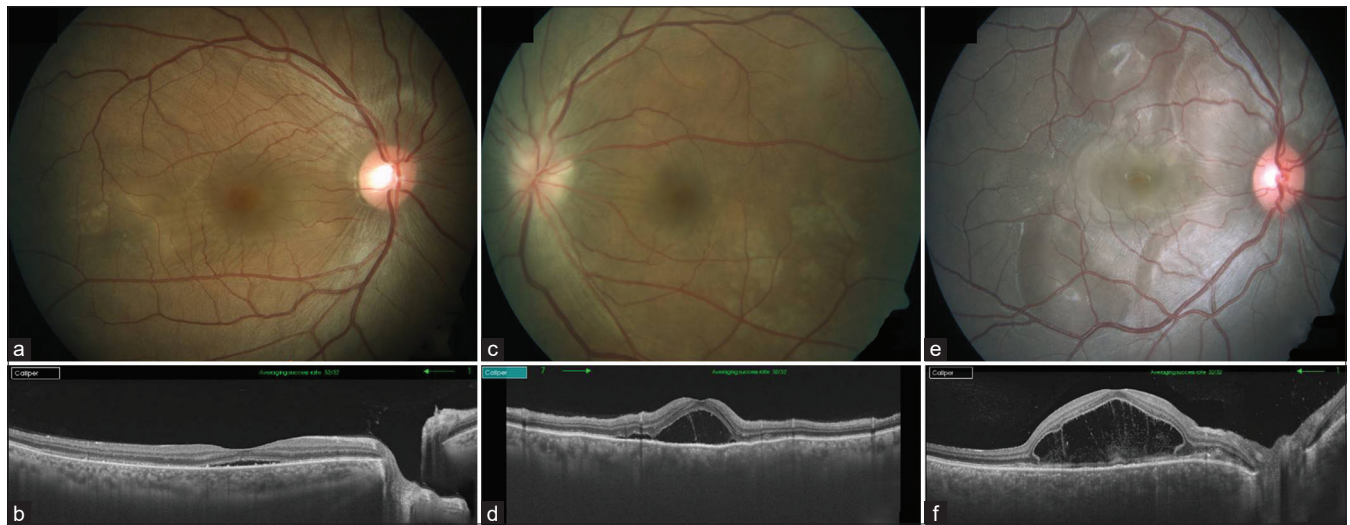
**Treatment Profile:** Initial treatment of acute VKH disease consisted of IVMP 1 g for 3 days in 14 patients (28 eyes), whereas three patients (six eyes) received only high-dose oral steroids for management of acute attack. Following initial steroid therapy, 12 patients received IMT along with oral steroids. The remaining patients were continued with oral steroids alone in titrated doses.

**SS-OCT at presentation:** Quantitative findings of SS-OCT: The mean SFCT at presentation was  $784.97 \pm 426.98$  microns. In 15 eyes, the SFCT was not measurable and an arbitrary value of >1000 microns was assigned to these eyes. Qualitative features noted on SS-OCT were presence of SRF (29 eyes, 85%), SR hyperreflective dots (34 eyes, 100%), SR septa (33 eyes, 97%), RPE undulations (21 eyes, 61.7%), posterior vitreous cells (34 eyes, 100%), and SRF around disc (9 eyes, 26%). Disc swelling was noted in 34 eyes (100%) [Table 1].

We graded SRF into minimal, moderate, and severe. Based on this, there were six eyes with minimal SRF, five eyes with moderate SRF, and 18 eyes with severe SRF. When we graded



**Figure 1:** Color fundus photographs and corresponding SS-OCT images showing retinal pigment epithelium (RPE) undulations and grading in the acute stage of VKH disease. (a and b) Grade 1- slight undulations; (c and d) Grade 2- moderate undulations; (e and f) Grade 3- severe undulations



**Figure 2:** Color fundus photographs and corresponding SS-OCT images showing subretinal fluid (SRF) grading during the acute stage of VKH disease. (a and b) Mild SRF: Minimal fluid present, (c and d) Moderate SRF when pockets of SRF are present, (e and f) Severe SRF when SRF with septa present

**Table 1: Qualitative features noted on SS-OCT**

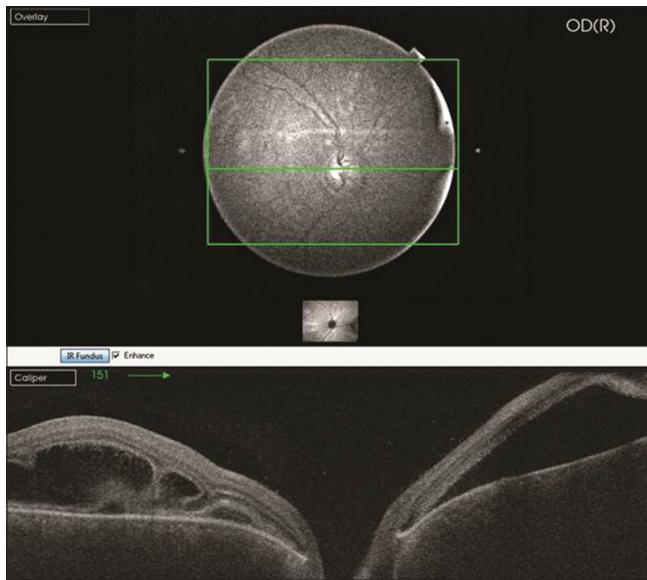
SS-OCT parameters (n=34 eyes)	On presentation	One month follow-up	Six months follow-up	One Year follow-up
SRF	29	8	7	5
SRF around disc	9	0	5	4
Subretinal hyperreflective dots	34	18	13	8
Subretinal septa	33	0	2	8
RPE undulation	21	2	6	4
Posterior vitreous cells	34	32	34	8
Disc swelling	34	8	4	0

SS-OCT- Swept-source optical coherence tomography, SRF: Subretinal fluid, RPE: Retinal pigment epithelium

the RPE undulations, there were 16 eyes with grade 1, four eyes with grade 2, and one eye with grade 3.

**SS-OCT at 1 month** Quantitative findings: The mean SFCT was  $431.40 \pm 183.95$  microns Qualitative features: Presence of SRF (8 eyes, 23.5%), SR hyperreflective dots (18 eyes, 52.9%), SR

septa (0 eyes, 0%), posterior vitreous cells (32 eyes, 94%), SRF around disc (0 eyes, 0%), disc swelling (8 eyes, 23.5%). There were seven eyes with minimal SRF, and one eye with a moderate amount of SRF. RPE undulations were characteristically absent in 32 eyes. The remaining two eyes (5.8%) had grade 1 RPE undulations [Table 1].



**Figure 3:** SS-OCT image of acute VKH shows SRF around disc in the absence of disc swelling

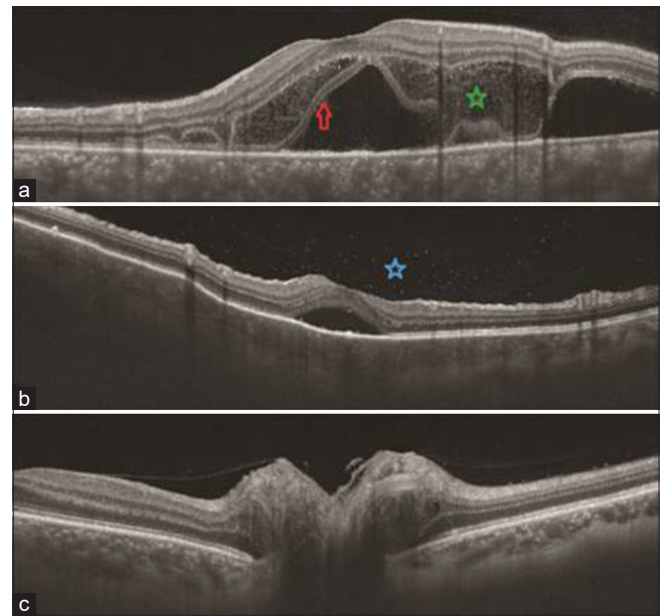
**SS-OCT at 6 months** Quantitative findings: The mean SFCT was  $453 \pm 257.5$  microns. Qualitative features: Presence of SRF (7 eyes, 20.5%), SR septa (2 eyes, 5.8%), posterior vitreous cells (34 eyes, 100%), SR hyperreflective dots (13 eyes, 38.2%), SRF around disc (5 eyes, 14.7%), and disc swelling (4 eyes, 11.7%) [Table 1]. There were two eyes with a severe amount of SRF, two eyes with a moderate amount of SRF, and three eyes with minimal SRF. There was one eye with grade 1, three eyes with grade 2, and two eyes with grade 3. RPE undulations were notably absent in 28 eyes. Subfoveal scar was noted in two eyes.

**Disease Recurrence:** Four patients (8 eyes, 20.5%) developed disease recurrence during the 6-month follow-up period. On recurrence, quantitative findings of SS-OCT were as follows: The mean SFCT was  $763 \pm 222$  microns. On recurrence, qualitative features noted were presence of pockets of SRF (6 eyes, 85.7%), SR septa (2 eyes, 28.5%), posterior vitreous cells (8 eyes, 100%), and SRF around disc (5 eyes, 71.4%). There was one eye (14.2%) with grade 1, four eyes (57.1%) with grade 2, and one eye (14.2%) with grade 3.

**Treatment profile on recurrence:** Three patients were on a maintenance dose of azathioprine and oral steroids, whereas one patient had stopped the treatment a week prior to the visit. Once recurrence was confirmed, three patients who were already on a maintenance dose of IMT; the dosage of azathioprine and oral steroids were hiked. One patient who had stopped all medications was given a course of IVMP and restarted on azathioprine 1–1.5 mg/kg body weight and oral steroids at 1 mg/kg body weight.

**Disease Recurrence beyond 6 months:** In total, three patients had recurrence of inflammation beyond 6 months till the last follow-up visit. The mean duration of follow-up of these three patients was 22.06 months (range: 14.7–32.6 months). The duration of onset of recurrence ranged from 1.2 to 9.9 months.

One patient had only anterior segment recurrence, which was treated with topical steroids alone. The remaining two patients had posterior segment recurrence. In both patients, the dosage of azathioprine and oral steroids was hiked. However, one of



**Figure 4:** (a) SS-OCT image of acute VKH subretinal septa (red arrow) and subretinal hyperreflective dots (green star); (b) SS-OCT image of acute VKH showing posterior vitreous cells (blue star); (c) SS-OCT image of acute VKH with disc swelling on presentation

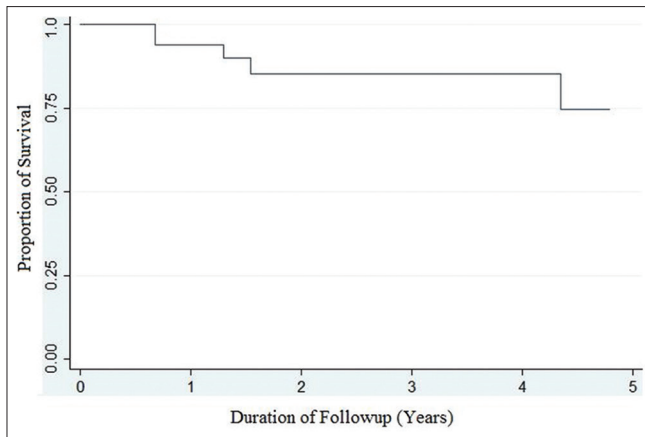
the patients continued to have repeated recurrences despite IMT and oral steroids and hence was started additionally on cyclosporine. Triple immunosuppression ensured remission. Importantly, in this patient, SS-OCT scans during an episode of recurrences showed the presence of SRF around disc.

**Treatment Outcomes:** The mean SFCT was 784.97 microns at presentation, 431.40 microns at the first month of therapy, 453.94 microns at 6 months of therapy, and 405.83 at the last follow-up at 1 year.

At the end of 6 months, RPE undulations were notably absent in 28 out of 34 eyes. Disc swelling had completely resolved in 30 eyes, SRF around disc was noted in five eyes, and subfoveal scar was noted in two eyes. At the end of 1 year of follow-up, RPE undulations were absent in 30 eyes (88%) and disc swelling was notably absent in all 34 eyes, although SRF around disc was noted in four eyes (11.7%) of two patients who had recurrences [Table 1]. The mean visual acuity was 0.86 logMAR (Snellen equivalent: 6/45) at presentation, 0.36 logMAR (Snellen equivalent: 6/15) at 1 month follow-up, and 0.18 logMAR (Snellen equivalent: 6/9) at 6 month follow-up. None of the cases in this series developed sunset glow fundus or pigmentary changes at the macula during the follow-up period. A Kaplan–Meier survival curve [Fig. 5] was constructed to determine the proportion of patients who survived with a good visual outcome of better than 6/9. It shows that the proportion of survival at year 1 is 90%, at year 2 is 82%, at year 3 is 82%, at year 4 is 75%, and it remains stable after year 4.

## Discussion

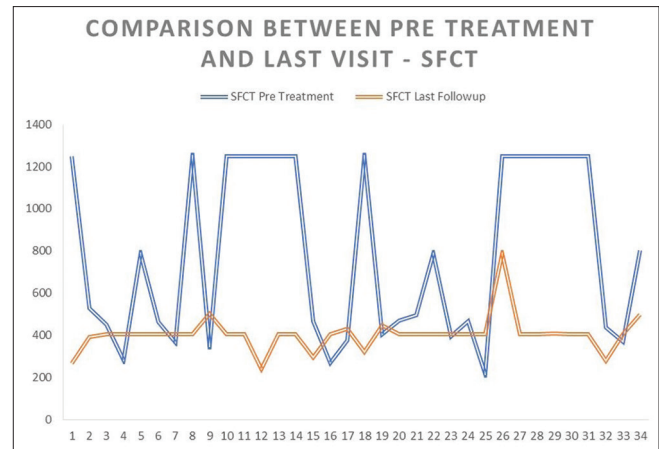
In the present study, we analyzed the SS-OCT parameters in patients presenting with acute probable VKH disease at presentation and after treatment at 1 month, 6 months, and at last follow-up. Our study is an attempt to evaluate the role of SS-OCT as a tool not only to diagnose but also to monitor and aid in the therapy of acute probable VKH in Indian eyes.



**Figure 5:** Kaplan Meier survival curve was constructed to determine the proportion of patients who survived with good visual outcome better than 6/9. From the above survival graph, it is seen that the proportion of survival at year 1 is 90%, the proportion of survival at year 2 is 82%, the proportion of survival at year 3 is 82%, the proportion of survival at year 4 is 75% and it remains stable after year 4

Choroidal inflammation is thought to be the main pathophysiologic mechanism by which choroidal thickening occurs in VKH. The thickening is related to both inflammatory infiltration and increased exudation. A study done by Maruko *et al.*<sup>[7]</sup> found that the choroidal thickness with active VKH disease was much greater than that of normal eyes and the thickness dramatically decreased following corticosteroid therapy. The mean choroidal thickness reduction percentage from baseline was 35% at day 3, 58% at day 14, and by the end of 1 month of corticosteroid therapy, the choroidal thickness was normal. A study done by Akhtar *et al.*<sup>[10]</sup> in normal Indian subjects by using SS-OCT found that the mean SFCT and macular choroidal thickness (MCT) were  $307 \pm 79 \mu\text{m}$  and  $285 \pm 75 \mu\text{m}$ , respectively. In our study, the mean SFCT was  $784.97 \pm 426.98$  microns at presentation,  $431.40 \pm 183.95$  microns at 1 month,  $453.94 \pm 257.5$  microns at 6 months, and  $405.83 \pm 149.71$  microns at last follow-up. This reveals that in Indian eyes, even after 6 months of therapy, the mean SFCT may not reach that of normal Indian subjects, as reported by Maruko *et al.*<sup>[7]</sup> Thus, we may infer that many patients in our study may not have achieved complete remission by the end of 6 months of aggressive therapy and required additional immunosuppression for several months. However, our study did reveal that there is a positive correlation between SFCT and disease resolution [Fig. 6]. This indicates that the mean SFCT reduction from baseline is an important parameter and can be considered as a positive marker for potential treatment success, and one may consider tapering the corticosteroids and immunosuppressive medications. However, if SFCT remains elevated, it is important to continue the treatment or increase the dosage of immunosuppressant/steroids, especially in Indian eyes. Premature cessation of therapy may increase the chance of recurrence.

In a study by Liu *et al.*<sup>[3]</sup> the authors noted SD-OCT features with the highest sensitivity and specificity for diagnosis of VKH as SR membranous structures, high retinal detachment, SR hyper-reflective dots, and RPE folds. They reported that the most common OCT features were hyperreflective SR dots (88%), SR membranous structures (80%), retinal detachment higher than  $450 \mu\text{m}$  (79%), and retinal pigment epithelium (RPE) folds (55%). We found similar results in our study of SS-OCT of



**Figure 6:** Comparison of SFCT at presentation and final follow-up. The graph compares the SFCT at presentation and final follow-up. The SFCT at final follow-up is less compared to the SFCT at presentation

34 eyes with acute VKH. We noted SR hyper-reflective dots (34 eyes, 100%), SR membranous structures/septae (33 eyes, 97%), SRF (29 eyes, 85%) and RPE undulations (21 eyes, 62%) as most likely OCT features. In the eyes with SRF, retinal detachment higher than  $450 \mu\text{m}$  was noted in 21 eyes (72%) in our study. We also evaluated the presence of SRF around optic disc (9 eyes, 26%) and disc swelling (34 eyes, 100%) [Table 1].

In the present study, at 6-month follow-up, eight eyes developed disease recurrence. We tried to look at SS-OCT features that may help to predict disease recurrence. Interestingly, six out of eight eyes with recurrence had a high SFCT of more than 1000 microns at baseline. We also found that among eight eyes of four patients with disease recurrence, RPE undulation was present in six eyes at presentation. During disease recurrence at 6 months, six eyes had a more severe grade of RPE undulation than at presentation (one eye with grade 1, four eyes with Grade 2, and one eye with Grade 3 RPE undulation). This was in consensus with a study by Hashizume *et al.*,<sup>[5]</sup> which concluded that eyes with more severe RPE undulations had significantly worse vision at 6 and 12 months, had greater initial choroidal thickness, and were more likely to develop posterior recurrences. Hosoda *et al.*<sup>[11]</sup> also reported that eyes with acute VKH disease show an increased RPE undulation index in addition to an increased choroidal thickness.

Additionally, we found that among eight eyes with disease recurrence, five eyes of three patients with recurrence had SRF around disc at presentation, which resolved at 1 month of therapy and reappeared during recurrence. One patient did not show SRF around disc at presentation and at 6 months follow-up but subsequently developed SRF around disc during recurrences beyond the 6-month period. This patient required triple immunosuppression (oral steroids, oral azathioprine, and oral cyclosporine) to control the inflammation and induce remission. In our series, none of the cases had developed the typical sunset glow or pigment deposition in the macula. Early and prompt treatment may prevent progression to advanced disease and its sequela. Herbolt *et al.*<sup>[12]</sup> in a recent review stated that timely and adequate treatment led to substantial improvement of disease outcome and prevented chronic evolution and "sunset glow fundus," and very early treatment led to the cure after discontinuation of therapy in acute VKH.

## Conclusion

In summary, our study of SS-OCT features in acute VKH disease in Indian eyes found raised SFCT, RPE undulations, SR hyperreflective dots, SR membranous structures/septae, SRF, disc swelling, and the presence of SRF around optic disc.

SS-OCT can be used not only to diagnose acute VKH but also to guide therapy and to predict recurrences. SS-OCT can be used as a tool to monitor choroidal inflammation and plan the titration of therapy. SS-OCT features such as thicker choroid at baseline, RPE undulations, and SRF around disc may indicate severe disease that may require aggressive therapy for a longer duration. The mean SFCT reduction from baseline is an important parameter. When SFCT remains elevated on follow-up visits, premature cessation of therapy may increase the risk of recurrence, especially in Indian eyes. To the best of our knowledge, this is probably the first study evaluating SS-OCT changes in acute VKH in Indian eyes over a period of time and correlating the findings with disease recurrences.

However, our study was retrospective with a small sample size; thus, future prospective studies on SS-OCT may be required in a larger number of patients to explore correlations between choroidal/retinal/optic nerve head lesions in eyes with acute VKH and recurrent VKH syndrome.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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