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Retinal pigment epithelium undulations in acute stage of Vogt-Koyanagi-Harada disease: Biomarker for functional outcomes after high-dose steroid therapy

Kouhei Hashizume MD[*]; Yutaka Imamura MD[†]; Takamitsu Fujiwara MD, PhD[*]; Shigeki Machida MD, PhD[*‡]; Masahiro Ishida MD[†]; Daijiro Kurosaka MD[*]

[*]Department of Ophthalmology, Iwate Medical University School of Medicine, Morioka, Iwate, JAPAN

[†]Department of Ophthalmology, Teikyo University School of Medicine, University Hospital Mizonokuchi, Kawasaki, Kanagawa, JAPAN

[‡]Department of Ophthalmology, Dokkyo Medical University Koshigaya Hospital, Koshigaya, Saitama, Japan

Correspondence: Yutaka Imamura MD, Department of Ophthalmology, Teikyo University School of Medicine, University Hospital Mizonokuchi, 3-8-3 Mizonokuchi, Takatsu-ku, Kawasaki, Kanagawa 213-8507, JAPAN

Tel: +81-44-844-3333, Fax: +81-44-844-3260

email:yimamura.ny@gmail.com

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Short title: RPE undulations in VKH

Summary: The retinal pigment epithelium undulations detected by enhanced depth imaging optical coherence tomography were found to be predictive of functional outcomes of Vogt-Koyanagi-Harada disease after high-dose steroid therapy.

Abstract

Purpose: To determine the clinical significance of retinal pigment epithelium (RPE) undulations in the acute stage of Vogt-Koyanagi-Harada (VKH) disease.

Methods: RPE undulations were detected and classified into 3 grades: grade 1, slight; grade 2, moderate; and grade 3, severe undulations, in the enhanced depth imaging optical coherence tomographic (EDI-OCT) images. The relationship between the clinical characteristics and the presence of RPE undulations was investigated.

Results: Among the 61 eyes of 31 VKH patients, 40 eyes had some degree of RPE undulations (grade 1=12, grade 2=15, and grade 3=13). The patients with RPE undulations in both eyes were significantly older at the onset (P=0.0002). The eyes with RPE undulations were more likely to develop posterior recurrences (P=0.032) and have worse vison at 12 months (P=0.043). Multiple regression analysis revealed that RPE undulations was an independent predictor of posterior recurrences (P=0.009) and poor visual outcomes (P=0.035).

Conclusion: RPE undulations detected by EDI-OCT are relatively frequent occurrences at the acute stage of VKH, and their presence is a predictor of posterior recurrences and poor visual outcomes after high-dose steroid therapy.

Introduction

Vogt-Koyanagi-Harada (VKH) disease is a granulomatous inflammatory disorder characterized by anterior chamber inflammation and serous retinal detachment in the acute phase.[1] VKH is caused by an autoimmune reaction to the melanocytes in the choroid.[1-4] Recent studies using optical coherence tomography (OCT) showed that the choroid is thickened in VKH eyes at the acute stage[5,6] and also at the time of recurrent inflammations.[7,8]

Choroidal folds are commonly observed in the acute stage of VKH, particularly in the fluorescein angiographic images with a frequency of 12% to 52%.[9,10] While fluorescein angiography is a convenient way to see choroidal folds, OCT is a better way to see the morphological changes of the choroid. Recent advances of OCT technology has allow clinicians to examine the structure of the choroid in greater detail. When examining the choroidal folds by OCT, undulations of the retinal pigment epithelium (RPE) is often observed.[11] Interestingly, OCT is able to show undulations of RPE even in eyes where choroidal folds are not visible in the fundus images or in the fluorescein angiographic images.

If the RPE undulations are a sign of choroidal inflammation, it may be related to the

severity of the inflammation. Thus, an OCT-based classification of the undulations would be a useful biomarker to predict functional outcomes.

Thus, the purpose of this study was to determine whether there is a significant correlation between the RPE undulations and the clinical characteristics of VKH patients after high-dose steroid therapy during the acute stage. We focused on the functional outcomes and the frequency of posterior recurrences which are known to affect the visual functions during the follow-up period.

Methods

We examined the medical records of consecutive patients with VKH in the Iwate Medical University, Morioka, Japan between February 2010 and December 2013. The diagnosis of VKH was made from the clinical characteristics, and the patients were classified into complete, incomplete, or probable VKH according to the Revised Diagnostic Criteria for VKH disease of the International Nomenclature Committee.[12] The procedures used to treat the patients and the examination of their medical records was approved by the Institutional Review Boards of Iwate Medical University. The diagnosis of VKH at the acute stage was made by the presence of iritis and exudative retinal detachment. None of the patients had a history of eye trauma,

intraocular surgery, or other types of uveitis. Patients presenting with exudative retinal detachment were treated with 1000 mg of intravenous methylprednisolone for 3 days and then with low-dose intravenous betamethasone and oral prednisolone.[6] Most of patients were maintained on oral prednisolone for at least for 3 months after the initial onset. A posterior recurrence was defined as posterior inflammations which were treated with increased dose of systemic steroid therapy.[7] These conditions included an increase of vitreous opacities, retinal edema, exudative retinal detachment, and/or choroidal folds, which appeared at least 3 months after the initial high-dose therapy.[7]

All patients underwent a comprehensive ophthalmologic examination including measurements of the best-corrected visual acuity (BCVA), slit-lamp biomicroscopy, color fundus photography, fluorescein angiography, and indocyanine green angiography at the acute stage. All of the eyes were examined with the Heidelberg Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany) with eye tracking, and the image averaging systems was used to obtain choroidal images before and after high-dose steroid therapy. The undulations of the RPE were defined as wavy protrusions of the RPE cell line toward the vitreous cavity seen in the EDI-OCT images. To semi-quantify them, we classified them into 3 grades based on the appearance of undulations (Figure 1): grade 1, slight undulations; grade 2, moderate

undulations; and grade 3, severe undulations. The grading of the undulations of the RPE was done by two authors independently who were masked to the other clinical findings (KH and YI). If there was a discrepancy between the grading of the two, then an open adjudication was performed by a third author (TF). To assess the degree of RPE undulations more quantitatively, we also measured the maximum peak-to-peak amplitude of the wavy RPE line seen in each OCT image and examined if the maximum peak-to-peak amplitude was significantly correlated with the grading of the undulations.

The choroidal thickness was measured with the EDI-OCT technique.[13] When the choroidal thickness was >1000 μm or the outer border of the choroid was not distinct, we designated a thickness of 1000 μm as was done in an earlier study on eyes with VKH disease.[6]

The data are presented as the means ± standard deviation (SD), and the Mann-Whitney *U* test or Kruskal-Wallis test was used to determine the significance of the differences in the choroidal thicknesses. Chi-squared tests were used to compare the male/female ratio and the history of recurrent inflammations. The best-corrected visual acuity was measured with a Landolt C chart, and the decimal values were

converted to the logarithm of the minimal angle of resolution (logMAR) units. Student *t* tests or one-way ANOVA was used to compare the visual acuity, age, time until pulse therapy, and time of follow-up. A *P* value less than 0.05 was considered statistically significant. Multiple linear regressions were used with stepwise selection of variables to evaluate the predictors of posterior recurrence and visual acuity. The statistical analysis was performed with SPSS software version 20 (SPSS Inc, Chicago, IL).

Results

We studied 31 patients who had exudative retinal detachment and iritis and were diagnosed with VKH at the Iwate Medical University Hospital. The mean age of the VKH patients was 50.0 ± 15.5 years, and 21 were women. Our patients consisted of 1 with complete VKH, 23 with incomplete VKH, and 7 with probable VKH. Thirty patients had bilateral VKH disease and 61 eyes of 31 patients had thickened choroids at the acute stage. The mean subfoveal choroidal thickness was 905 ± 150 μm. All were treated with high-dose intravenous methylprednisolone of 1000 mg for 3 days and then with low-dose intravenous betamethasone and oral prednisolone. Steroid pulse therapy was started 16.3 ± 11.5 days after the subjective notice of visual disturbances. The mean follow-up time was 17 ± 12 months, and 10 (16.4 %) eyes developed a posterior recurrence during the follow-up time.

Of the 61 eyes, 40 (65.6 %) eyes had undulations of the RPE in the OCT images. Fluorescein angiography showed choroidal folds in 19 of these eyes (31.1 %), and all 19 had RPE undulations in the OCT images. However, the other 21 with undulations in the EDI-OCT images (10 with Grade 1, 5 with Grade 2, and 6 with Grade 3) did not show choroidal folds in the fluorescein angiograms.

When we graded the RPE undulations (Figure 1), there were 12 (19.7 %) eyes with grade 1, 15 (24.6 %) eyes with grade 2, and 13 (21.3 %) eyes with grade 3. The grades was highly correlated with the maximum peak-to-peak amplitudes (rs = 0.6908, *P* = 0.00007, N = 47 eyes; Spearman's rank correlation coefficient). There was significant correlation between the grade of the undulations in both eyes (rs = 0.9091, *P* = 0.00002, N = 30; Spearman's rank correlation coefficient).

Patients with any grade of RPE undulations were significantly older at the onset (56.4 ± 11.7 years) than those without RPE undulations (36.4 ± 13.8 years, *P* = 0.0002, Student *t* test). In addition, eyes with any grade RPE undulations were more likely to develop posterior recurrences (*P* = 0.032, chi-squared test) and have worse vison at 12 months (*P* = 0.043, Student *t* test) than those without RPE undulations (Table 1).

The clinical characteristics of the groups classified according to the grade of RPE undulations are summarized in Table 2, and representative VKH cases with severe RPE undulations (Grade 3) and without RPE undulations are shown in Figure 2 and Figure 3, respectively. Eyes with more severe RPE undulations had significantly worse vison at 6 months and at 12 months ($P = 0.032$, $P = 0.004$, one-way ANOVA), had thicker initial choroidal thickness ($P = 0.048$, Kruskal-Wallis test), and were more likely to develop posterior recurrences ($P = 0.008$, chi-squared test; Table 2).

Of the 28 eyes with Grade 2 or 3 RPE undulations at the acute phase, the BCVA of five eyes was less than 20/40 at 12 months of follow-up. The decrease of their visual acuity was due to cataract in four eyes, macular atrophy in two eyes, and anterior ischemic optic neuropathy (AION) in one eye. On the other hand, of the 33 eyes without or with grade 1 RPE undulations at the acute phase, none had a BCVA less than 20/25.

Multiple regression analysis showed that the grade of the RPE undulations was an independent predictor of posterior recurrences ($P = 0.009$, Table 3) and poor BCVA at 12 months ($P = 0.035$, Table 4).

Discussion

Our results showed that eyes with more severe RPE undulations had thicker choroids before high-dose steroid therapy. In addition, the presence of RPE undulations before the high-dose steroids was an independent predictor of posterior recurrences and poorer vision. These findings indicated that the degree of RPE undulations represented the severity of the inflammation and can be used to predict the development of posterior recurrences and poorer visual outcomes after high-dose steroid therapy.

In our cases of VKH, significant visual disturbances were seen only in eyes with RPE undulations, and the decrease in vision was caused by cataracts, macular atrophy, or AION. Cataracts and macular atrophy can be caused by prolonged or persistent ocular inflammations in patients with VKH.[14] AION is reported to be associated with VKH[15] and probably a consequence of the severe posterior inflammation affecting the optic nerve.

The EDI-OCT images showed that the choroid at the acute stage of VKH is thicker than that of normal eyes, and steroid therapy led to a decrease in the thickness. The

choroid was also thickened at the time of posterior recurrences[7] and became thin in the convalescent stage.[16]

VKH is caused by autoimmune reactions to melanocytes, and the results of the studies with EDI-OCT demonstrated that the choroid is the major site of the immune reactions in VKH disease.[1-4] The choroidal thickness changes dynamically reflecting the severity of inflammation.[5-8] Because the choroid is thicker in eyes with more severe RPE undulations, we suggest that the RPE undulations is caused by severe infiltrations of lymphocytes into the choroid which then pushes the RPE layer toward the vitreous cavity. Choroidal folds are also seen in eyes with central serous chorioretinopathy,[17] and the choroid of these eyes is also thickened.[18] This provides additional evidence that the choroidal folds and RPE undulations are the results of a thickening of the choroid.

It is interesting that multiple regression analysis showed a significant correlation with RPE undulations rather than choroidal thickness. We assume that as the choroidal infiltration becomes more severe, the choroid will push the RPE toward the vitreous cavity because choroidal expansion is limited in the scleral direction due to the presence of a rigid sclera. Therefore, RPE undulations may represent severe

choroidal inflitrations more accurately than the choroidal thickness.

We also showed that the presence of RPE undulations before high-dose steroids was an independent predictor of posterior recurrences and poor vision at 12 months of follow-up. Because there is no definite regimen for tapering the dose of steroids after the initial steroid pulse therapy, we suggest that the degree of tapering can be monitored by examining the grade of RPE undulations. This should reduce or eliminate posterior recurrences and decreased vision during the follow-up period. An earlier study reported the possibility that the eyes with choroidal folds can have poorer final vision than those without.[10] However, that study evaluated the choroidal folds by fluorescein angiography which is less likely to detect RPE undulations than OCT as demonstrated in our study.

Thus, we recommend that EDI-OCT be used to detect and grade the RPE undulations, and then these findings can be used as biomarkers of functional outcomes after high-dose steroid therapy for VKH. It should be noted that these undulations may not always be detectable by fluorescein angiography.

There are several limitations in this study. The number of cases was relatively small,

and no control group was studied. The length of follow-up might not have been long enough to evaluate the rate of recurrences of VKH. The grading of the RPE undulations was done subjectively and not quantitatively, however this classification was highly correlated with maximum peak-to-peak amplitudes calculated from the RPE undulations. We are aware that there was an earlier report which analyzed the choroidal folds in VKH more quantitatively,[19] however the authors did not show any significant correlations between the choroidal fold and functional outcomes.

In conclusion, we have demonstrated that RPE undulations are seen relatively frequently in the EDI-OCT images at the acute stage of VKH. The RPE undulations are more detectable by OCT than fluorescein angiography, and appear to be a biomarker for posterior recurrences and poor visual outocomes after high-dose steroid therapy. More cases with longer follow-up periods are needed to confirm the biological significance of RPE undulations in VKH disease.

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Figure Legends

Figure 1: Retinal pigment epithelium (RPE) undulations in the acute stage of Vogt-Koyanagi-Harada disease (arrows). Representative cases showing grade 1, slight undulations (A: left and right); grade 2, moderate undulations (B: left and right); and grade 3, severe undulations (C: left and right).

Figure 2: Findings in a 71-year-old woman with Vogt-Koyanagi-Harada (VKH) disease. Color fundus photographs showing serous retinal detachment at the acute stage of both eyes (A, B). Her visual acuity was 20/63 in both eyes. EDI-OCT images showed a retinal detachment, grade 3 RPE undulations(arrows), and very thick choroid at the acute stage (C, D). The serous retinal detachment and RPE undulations are not detected one month after high-dose steroid treatment and visual acuity recovered to 20/20 in both eyes. Increased inflammations with serous retinal detachment and choroidal folds appeared 4 months, 11 months, and 18 months after the first high-dose steroid therapy. At the time of the third recurrence, serous retinal detachment appeared in both eyes and anterior ischemic optic neuropathy developed in the left eye (E, F). Sunset glow fundus present in both eyes and the optic disc of the left eye is pale 2 months after the third recurrence (G, H). Her final visual acuity

decreased to 20/40(right eye) and 20/80 (left eye) due to cataracts in both eyes and visual field defects in the left eye.

Figure 3: A 39-year-old man with Vogt-Koyanagi-Harada disease. Color fundus photographs showing bilateral serous retinal detachments at the acute stage (A, B). His visual acuity was 20/32 in both eyes. EDI-OCT images show a retinal detachment and thickened choroid, but no RPE undulations at the acute stage (C, D). Serous retinal detachment not present 3 weeks after treatment (E, F), and his visual acuity recovered to 20/20 in both eyes. He had no posterior recurrences during the follow-up period, and his final visual acuity kept 20/20 in both eyes.