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Running title: Recurrent VKH with hearing loss

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Abstract

Purpose We report a case of Vogt-Koyanagi-Harada (VKH) disease that recurred with sensorineural hearing loss and choroidal thickening.

Methods We measured the choroidal thickness using enhanced-depth imaging optical coherence tomography (EDI-OCT) in a patient with VKH during corticosteroid-tapering therapy.

Results A 71-year-old man presented with fever, headache, and anorthopia associated with wavy choroidal folds and a serous retinal detachment (SRD). The EDI-OCT images showed choroidal thickening (> 600 μm at the subfovea), and he was diagnosed with VKH disease. After treatment with pulsed intravenous methylprednisolone, the choroidal folds and SRD resolved and the choroidal thickness decreased. About 6 months after subsequent treatment with an oral corticosteroid started, headache, tinnitus, and sensorineural hearing loss developed, and increased choroidal thickness was observed without other evidence of increased ocular inflammation. A high-dose corticosteroid was injected and tapered, and the sensorineural hearing loss improved immediately and the choroidal thickness decreased.

Conclusions In the current case, sensorineural hearing loss occurred with recurrent VKH disease; however, there were no ocular inflammatory signs except for rebound choroidal thickening. Measuring the choroidal thickness using EDI-OCT can sensitively identify recurrent VKH disease.

Keywords Vogt-Koyanagi-Harada disease, Choroidal thickness, Enhanced-depth imaging optical coherence tomography, Sensorineural hearing loss

Introduction

Vogt-Koyanagi-Harada (VKH) disease is a granulomatous inflammatory disorder affecting pigmented structures, i.e., eye, inner ear, meninges, and skin [1]. The choroid is the main site of autoimmune inflammation in ocular tissue [2]. Enhanced-depth imaging optical coherence tomography (EDI-OCT) has provided new information about the overall choroidal thickness [3]. Increasing evidence shows that patients with acute VKH disease have marked choroidal thickening, possibly related to inflammatory infiltration and increased choroidal exudation [4-6]. In addition, the choroidal thickness decreases after high-dose corticosteroid treatment but increases again in recurrent VKH disease [5, 6].

We present a patient with VKH disease and sudden hearing loss without ocular symptoms except increased choroidal thickness during oral corticosteroid tapering.

Case report

A 71-year-old man reported bilateral anorthopia a few days after a mild fever and headache. His best-corrected visual acuity (BCVA) levels were 0.9 in the right eye and 0.8 in the left eye. The intraocular pressure was normal. A few cells but no flare were present in the anterior chamber, and no cells were present in the vitreous. Ophthalmoscopy

showed choroidal folds radiating from the hyperemic optic discs bilaterally (Fig. 1a). Fluorescein angiography showed weak hyperfluorescent pooling corresponding to a serous retinal detachment (SRD) near the disc, multiple hyperfluorescent spots within the area, and a hyperfluorescent disc in the late phase (at about 15 minutes) (Fig. 1b). Indocyanine green angiography showed hypofluorescent dark spots in the intermediate phase (Fig. 1c) and in the late phase (at 20 minutes). Spectral-domain OCT (SD-OCT, Heidelberg Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany) confirmed the choroidal folds and SRD near the optic disc (Fig. 1d, e). These images also showed choroidal thickening across the macular area (>600 μm at the subfovea), but it was difficult to precisely measure the choroidal thickness because the boundary between the choroid and sclera was unclear (Fig. 1d, e) [6]. The test for the human leukocyte antigen-DRB1*0405 haplotype was positive.

According to the revised diagnostic criteria proposed by the International Nomenclature Committee [7], the patient was diagnosed with incomplete VKH disease because of the absence of integumentary findings. Intravenous methylprednisolone pulse therapy (1 g/day) for 3 days was prescribed followed by oral prednisolone (60 mg/day)

based on body weight (1 mg/kg/day) tapered over time. After pulse therapy, the choroidal folds and SRD resolved immediately and the choroidal thickness at the fovea decreased (Fig. 2a). Four months later (during oral prednisolone 10 mg/day therapy), the BCVA was 1.5 bilaterally, and the choroidal thickness decreased further (Fig. 2b).

About 6 months after the initial therapy (5 mg oral prednisolone on alternate days), headache, tinnitus, and hearing loss developed suddenly and the choroidal thickness increased (Fig. 2c, d). Moreover, there was a slight reduction in hyperreflective dots in the inner choroid (Fig. 2c) compared to the images obtained during the convalescent phase (Fig. 2b). At that time, his BCVA was 1.5 bilaterally, and there were no cells and flare in the anterior chamber and no cells in vitreous. Audiogram showed bilateral sensorineural hearing loss (Fig. 2e). Corticosteroid therapy (100 mg/day) was started for the recurrent VKH disease with sensorineural hearing loss and tapered. One week later, the hearing loss improved immediately (Fig. 2f), and the choroidal thickness decreased.

Discussion

The choroid is a vascular layer that plays a vital role in VKH disease. Histopathologic study has shown that the choroid thickens with lymphocytic infiltration during

inflammation [8]. In patients with acute VKH disease, EDI-OCT images clearly showed bilateral diffusely thickened choroids that decreased over time with corticosteroid treatment [4-6]. In the current case, we clearly visualized the full-thickness choroid except in the untreated phase and the decreasing choroidal thickness during tapering of oral prednisolone.

However, the choroidal thickness increased with the onset of hearing loss (Fig. 2c, d). Nakayama *et al* [5] defined rebound choroidal thickening as an increase exceeding 100 μm over the previous lowest measurement obtained during corticosteroid tapering; they reported that five eyes with rebound choroidal thickening had no recurrent inflammation by slit-lamp biomicroscopy or funduscopy during follow-up. However, Nakai *et al* [6] reported that a SRD developed again in four eyes with anterior inflammation and the choroidal thickness again increased markedly. The choroid appears to be primarily affected in VKH disease initially; therefore, rebound choroidal thickening seen on EDI-OCT images could be regarded as recurrent VKH disease, as in the current case, despite no clinical evidence of recurrent ocular inflammation. Furthermore, Fong *et al* [9] reported that EDI-OCT highlighted a loss of focal hyperreflectivity in the inner choroid of

eyes with VKH and proposed that it might be due to inflammatory infiltration causing the choroidal thickening and compression and nonperfusion of small choroidal vessels in the inner choroid. The observation of the reduction in hyperreflective dots in the inner choroid (Fig. 2c) may support the evidence of the recurrent VKH disease in the current case.

VKH disease is a systemic autoimmune disorder against antigens associated with melanocytes in the choroid, the meninges, and inner ear. The extraocular symptoms are predominantly neurologic/auditory manifestations: meningismus, tinnitus, and sensorineural hearing loss [10]. Ondrey *et al* [11] reported that 33.3% of patients with VKH disease had sensorineural hearing loss in the acute phase despite the small sample size and that patients with untreated VKH disease might have more severe hearing abnormalities than that observed in their study, because all had already been treated for severe ocular inflammation. Although sensorineural hearing loss in VKH disease has been reported to have characteristic features such as bilaterality, association with tinnitus, sloping sensorineural hearing loss at 4 kHz and above, or mild-to-moderate low-frequency sensorineural hearing loss [11], the hearing loss is generally nonspecific. It is less helpful in the differential diagnosis of VKH disease from other forms of hearing loss such as

autoimmune sensorineural hearing loss and sudden hearing loss. In the current case, sensorineural hearing loss occurred suddenly during tapering of oral prednisolone for VKH disease and was accompanied by rebound choroidal thickening exceeding 100 μm. Therefore, we diagnosed the current case as recurrent VKH disease with the primary symptom of hearing loss and administered relatively high-dose corticosteroid injections. Choroidal observation using EDI-OCT might have been useful in the differential diagnosis of sensorineural hearing loss in this case. However, this case report documented one episode in one patient; further studies are needed to investigate the relationship between recurrent VKH disease and rebound choroidal thickening.

In summary, observing the choroidal thickness using EDI-OCT may be useful not only for diagnosing and following ocular inflammation in VKH disease but also for monitoring extraocular symptoms in VKH disease such as sensorineural hearing loss.

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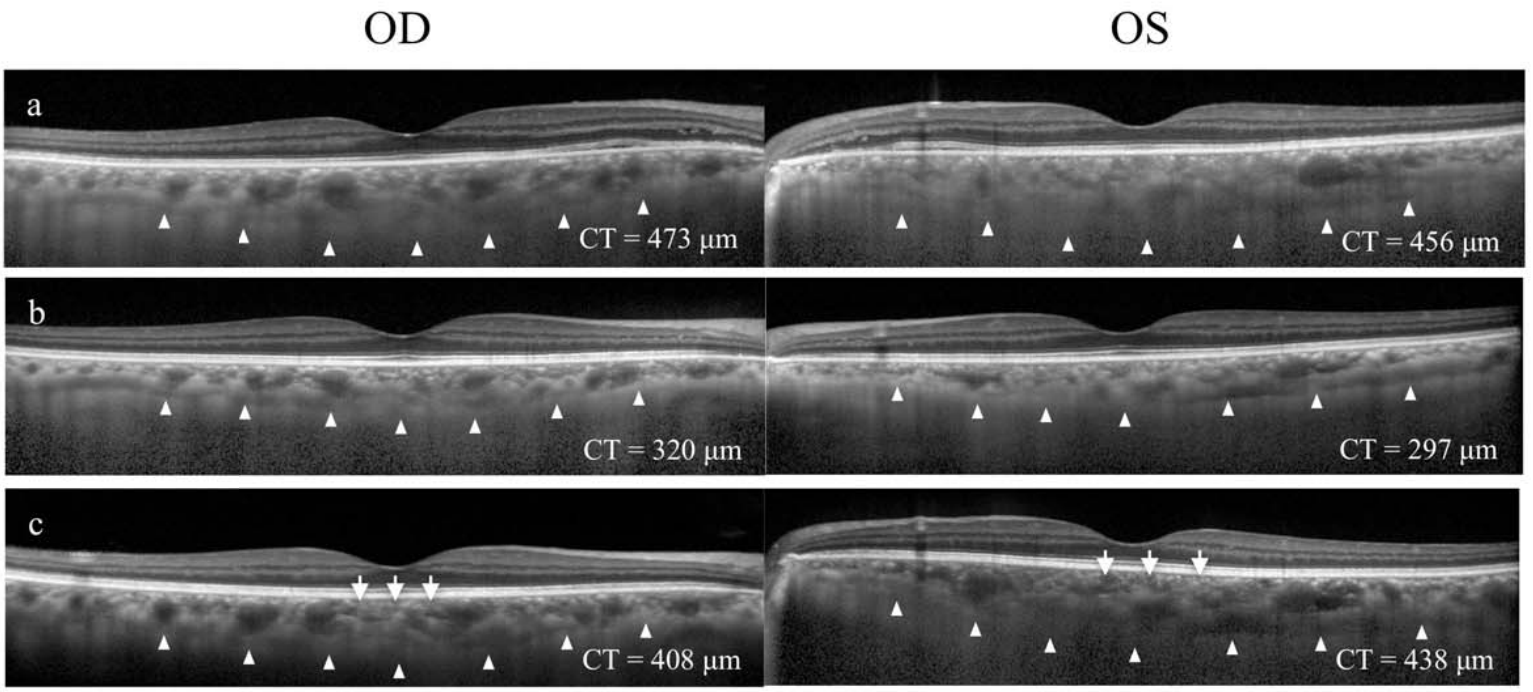
Legends

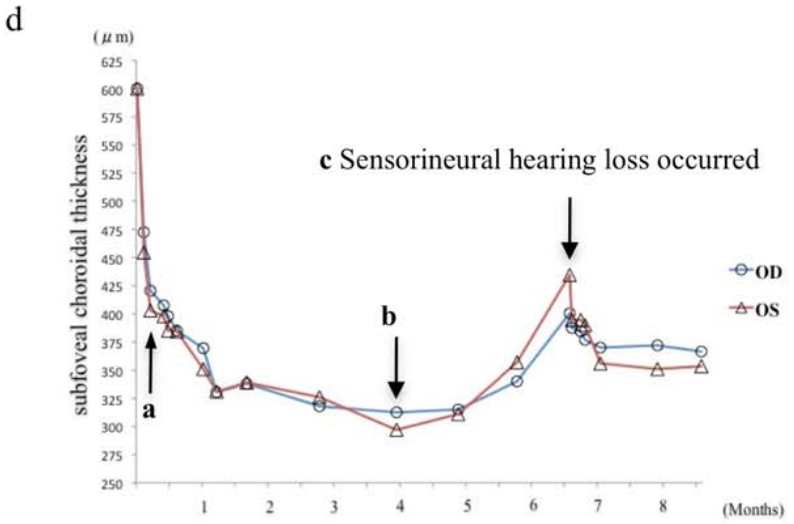
Fig. 1 a Choroidal folds radiating from the hyperemic optic discs are seen bilaterally. **b** Fluorescein angiography shows weak hyperfluorescent pooling (*arrows*) corresponding to a SRD near the disc, multiple hyperfluorescent spots within the area, and a hyperfluorescent disc in the late phase (at about 15 minutes). **c** Indocyanine green angiography shows hypofluorescent dark spots (at about 7 minutes). **d** SD-OCT in a horizontal line at the fovea shows retinal pigment epithelium (RPE) irregularity, a SRD near the optic disc (*arrows*), and choroidal thickening across the macular area (>600 μm at the subfovea); however, it is difficult to measure the choroidal thickness precisely because the boundary between the choroid and sclera is unclear. **e** SD-OCT in a vertical line clearly shows a wavy RPE and choroidal folds bilaterally.

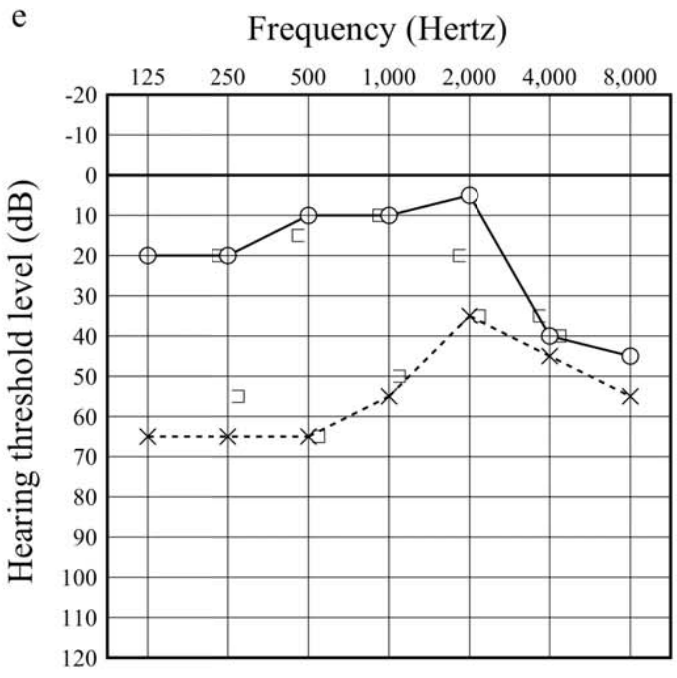
Fig. 2 EDI-OCT horizontal images of the right eye (OD) (left column) and the left eye (OS) (right column). The outer border of the choroid could be delineated (*arrowheads*). **a** The choroidal thickness at the subfovea is 473 μm OD and 456 μm OS just after methylprednisolone pulse therapy. **b** The choroidal thickness decreases to 320 μm OD and

297 μm OS 4 months after the initial therapy (during administration of 10 mg/day oral prednisolone). **c** The choroidal thickness increases to 408 μm OD and 438 μm OS when sensorineural hearing loss occurred about 6 months after the initial therapy (during administration of 5 mg oral prednisolone on alternate days). There is a slight reduction in the focal hyperreflectivity in the inner choroid (*arrows*) compared to the images obtained during the convalescent phase (b). **d** The course of the choroidal thickness changes in both eyes during corticosteroid therapy. **e** An audiogram from a patient with VKH disease. About 6 months after the initial therapy (during administration of oral prednisolone 5 mg on alternate days, Fig. 2c), the patient presents with sudden hearing loss in the left ear. The hearing thresholds are elevated especially in the left eye but also bilaterally. **f** A week after corticosteroid-tapering therapy from 100 mg/day was started, an audiogram shows improved hearing thresholds bilaterally. dB = decibels; CT = choroidal thickness at the subfovea, ○ = right ear air conduction, ⊏ = right ear bone conduction, × = left ear air conduction, and ⊐ = left ear bone conduction.

Figure 2


OD
OS
a
CT = 473 μm
CT = 456 μm
b
CT = 320 μm
CT = 297 μm
c
CT = 408 μm
CT = 438 μm


d
(μm)
subfoveal choroidal thickness
c Sensorineural hearing loss occurred
a
b
OD
OS
(Months)


e
Frequency (Hertz)
125
250
500
1,000
2,000
4,000
8,000
Hearing threshold level (dB)

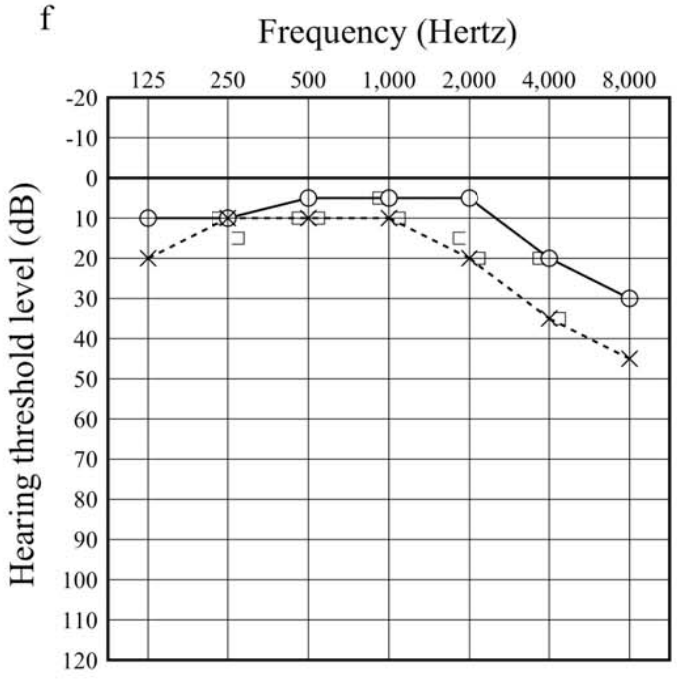

f
Frequency (Hertz)
125
250
500
1,000
2,000
4,000
8,000
Hearing threshold level (dB)

Figure 1