

Vogt-Koyanagi-Harada Syndrome - A Neurologist's Perspective

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Abstract

Vogt-Koyanagi-Harada (VKH) syndrome is an immune-mediated granulomatous disease which affects melanin-rich organs like eyes, skin, nervous system, and ears. Neurological and auditory manifestations usually precede the involvement of other sites. Patients may manifest with “complete” or “incomplete” syndrome. We report two patients who presented with acute headache and impaired vision. Fundus examination revealed optic disc hyperemia and exudative retinal detachment which provided a clue for the diagnosis at the bedside. Fundus fluorescein angiogram (FFA) revealed abnormal dye leakage, whereas B scan showed choroid thickening. Cerebrospinal fluid (CSF) pleocytosis contrasted with unremarkable brain magnetic resonance imaging and lack of meningeal signs. Melanophagocytosis was evidenced by melanin-laden macrophages in CSF and skin biopsy. This finding is specific for VKH syndrome and helps to clinch the diagnosis even when the complete syndrome is not present cross-sectionally. VKH syndrome should be suspected in patients with aseptic meningitis if tests for common infectious and immune-mediated diseases are negative.

Keywords: Aseptic meningitis, brain-eye-ear (BEE) syndromes, exudative retinal detachment, melanin-laden macrophages, poliosis, Vogt-Koyanagi-Harada syndrome

What is known?

- Vogt-Koyanagi-Harada syndrome is a granulomatous disorder affecting melanocyte-rich tissues (eye, ear, meninges, skin).
- It is a rare but treatable cause of vision loss.
- Aseptic meningitis is the most common neurological manifestation, whereas cranial neuropathies, encephalopathy, and myelitis are rare.
- Current diagnostic criteria stress on ocular findings and classify the disease as complete, incomplete, and probable based on non-ocular features.
- Early recognition and treatment are crucial for improving outcome.

What is new?

- Neurological manifestations precede characteristic ocular and skin involvement and may pose a diagnostic challenge.
- Diligent examination for fundus abnormalities and subtle skin findings like poliosis may help in recognizing this disease at the bedside.
- Cerebrospinal fluid examination for melanin-laden macrophages can confirm the diagnosis even in the absence of other features, especially during the prodromal stage when ocular and skin findings are absent.
- Skin biopsy, even from clinically unaffected regions may also help in early diagnosis.

INTRODUCTION

Vogt-Koyanagi-Harada (VKH) syndrome is a granulomatous disorder which affects melanocyte-rich tissues like eye, inner

ear, skin, and the meninges.^[1,2] This syndrome has been recognized for more than a hundred years but continues to pose a diagnostic challenge because of its rarity and fragmentary manifestations. The nervous system is commonly involved early in the disease course, mainly in the form of aseptic meningitis although other neurological manifestations, like cranial neuropathies,^[3] encephalopathy,^[4] and myelitis^[5] can also occur. Neurologists should consider VKH in the differential diagnosis of aseptic meningitis, particularly if additional ocular and cutaneous involvement are present. We describe two patients with VKH syndrome and emphasize the clinical phenotype and utility of cerebrospinal fluid (CSF) analysis and skin biopsy in establishing the diagnosis.

CASE REPORTS

Patient 1 was a 35-year-old lady who presented with acute redness, pain, and epiphora affecting both eyes, followed

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by diminished vision. This was associated with intermittent fever, holocranial headache, photophobia, vomiting, tinnitus, and vertigo. Patient 2 was a 60-year-old man who presented with acute, continuous, bi-frontal headache followed by binocular horizontal diplopia and impaired vision and hearing. There was no associated redness or discharge from the eyes, floaters, ear pain, ear discharge, or tinnitus. Table 1 and Figures 1 and 2 summarize the clinical findings, investigations, and treatment details of these patients.

DISCUSSION

VKH syndrome is bilateral granulomatous pan-uveitis with skin, eye, and auditory-vestibular involvement. It is named after three ophthalmologists, Alfred Vogt of Switzerland and Yoshizo Koyanagi and Einosuke Harada of Japan who independently described the syndrome in patients with uveitis and exudative retinal detachment and extraocular manifestations including CSF pleocytosis, dermatological, and auditory signs.^[6] It is an immune-mediated disorder, the putative

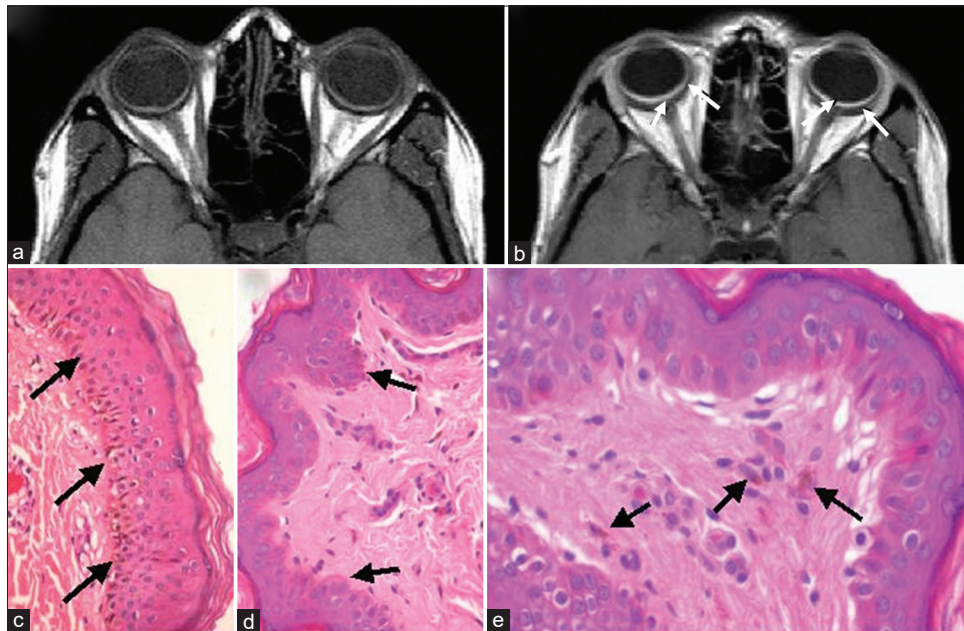


Figure 1: Axial T1-weighted and post-contrast T1-weighted sections of the orbit in patient 1 show choroid enhancement (a and b, white arrows). Histopathology of skin in VKH: Normal skin (c); axillary skin biopsy in patient 1 showing melanin depletion (d, black arrows); melanophagocytosis in dermal macrophages (e, black arrows)

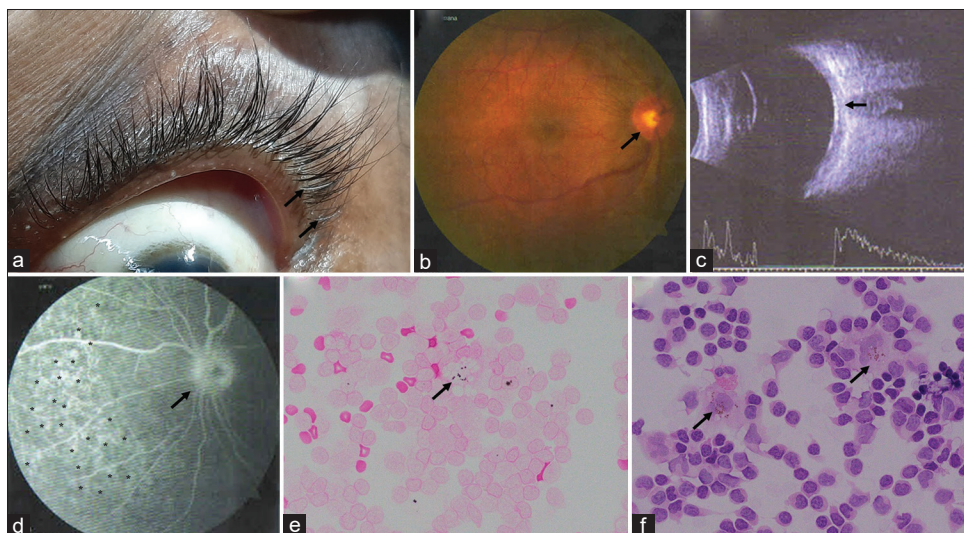


Figure 2: Shows loss of melanin pigment in a few eyelashes suggesting poliosis (a, arrows), optic disc hyperemia in fundus photograph (b, arrow), choroid thickening on B-scan of the orbit (c, arrow), abnormal optic disc staining (d, arrow), and leakage of dye in fundus fluorescein angiogram (d, asterisks) and melanin laden macrophages in cerebrospinal fluid (e and f, arrows) in patient 2

Table 1: Clinical findings and laboratory investigations of the patients reported in the present study

	Patient 1 (35 years/female)	Patient 2 (60 years/male)
Clinical examination		
Duration	Four days	Seven days
Other medical illnesses	Nil	Diabetes mellitus
Ocular	Fundus-exudative retinal detachment Visual acuity - Perception of light bilaterally	Fundus-optic disc edema and exudative retinal detachment, visual acuity- 6/24 RE & 6/36 LE
Ear	Normal	Bilateral SNHL
Skin	Normal	Poliosis (left upper eyelashes)
Neurological	No deficits or meningeal signs	Diplopia on looking to left, no meningeal signs
Investigations		
Complete blood count; Peripheral smear; ESR	Complete blood count - normal ESR- 40 mm/1st hour	Hemoglobin- 18.4 gm%, Leucocyte count: total- 10,400/mm ³ , differential- neutrophils 57.1%, lymphocytes 29.7%, monocytes 7.2%, eosinophils 5.7%, basophils 0.3%; Peripheral smear- normocytic normochromic, no malignant cells; ESR- 4 mm /1 st hour
Renal and liver function tests	Normal	Normal
Serum VDRL	Non-reactive	Non-reactive
Serum ACE	ND	25 U/L (normal)
Vasculitis work up (ANA, Rheumatoid factor, ANA profile and/or ANCA)	Negative	Negative
Mantoux test	Negative	Negative
Chest imaging (X-ray/CT)	Normal	Normal
Brain imaging (CT/MRI)	Normal	Normal
MRI of orbit	Choroid enhancement and retinal detachment	ND
B scan of orbit	Mild to moderate choroid thickening	Choroid thickening
OCT	ND	Retinal detachment and RPE undulation
Fundus fluorescein angiogram	Leakage of dye at disc and multiple pinpoint leakage from the choroid	Dye leakage at disc and multiple points from the choroid
Pure tone audiometry	ND	Bilateral SNHL
CSF analysis	Clear, Cells- 450/mm ³ (all lymphocytes), Protein- 78 mg%, Glucose- 52 mg%, Gram stain, VDRL, India ink, Anti-mycobacterial* and cysticercal antibody (ELISA)- negative Cytospin- admixture of reactive lymphocytes, monocytes and foamy histiocytes and no atypical cells	Clear, Cells- 320/mm ³ (all lymphocytes), Protein- 136.1 mg%, Glucose- 96 mg% Gram stain, AFB stain, TB-PCR, India ink and cryptococcal antigen, bacterial culture, Brucella antibody, Weil-Felix test- negative Cytospin- mature, reactive lymphocytes with melanin-laden macrophages and no atypical cells
Skin biopsy	Melanin depletion in basal cell layers and melanophagocytosis	No diagnostic pathology
Treatment given	Steroids	Steroids and azathioprine
Condition at discharge	Improved	Improved

ACE=angiotensin converting enzyme, AFB=acid fast bacillus, ANA=anti-nuclear antibody, ANCA=anti-neutrophil cytoplasmic antibody, CSF=cerebrospinal fluid, CT=computed tomogram, ESR=erythrocyte sedimentation rate, LE=left eye, MRI=magnetic resonance imaging, ND=not done, OCT=optical coherence tomography, PAS=periodic acid Schiff, PCR=polymerase chain reaction, RE=right eye, RPE=retinal pigment epithelium, SNHL=sensorineural hearing loss, TB=tuberculosis, VDRL=Venereal Diseases Research Laboratory. * Antimycobacterial antibody by ELISA is a sensitive immunodiagnostic method to detect tubercular meningitis

autoantigens being melanocyte-specific proteins like tyrosinase and tyrosine-related proteins 1 and 2. It is postulated that a viral infection in a genetically susceptible individual triggers autoimmunity and causes the disease. The genetic influence is supported by observations that there is increased prevalence in people of certain ethnicities viz Asian, Hispanics, and Native Americans as well as with specific Human Leucocyte Antigen (HLA) haplotypes (HLA DRB1*0405 and HLA DQ4).^[2] The clinical manifestations, stages, and diagnostic criteria are summarized in Table 2. The clinical course of VKH syndrome can be divided into prodromal, acute uveitic, convalescent,

and chronic recurrent stages. Neurological and auditory involvement occur in the prodromal stage. Ocular involvement occurs in acute uveitic, convalescent, or chronic recurrent stage, whereas skin involvement occurs in the convalescent stage.^[7] History of ocular trauma or surgery must be absent. Based on the diagnostic criteria, a patient can be classified as having complete, incomplete, or probable VKH.^[8] Patient 1 in the present report had incomplete VKH syndrome, whereas patient 2 had complete VKH syndrome.

The key features in our patients were acute headache, visual, and auditory symptoms with CSF pleocytosis. In both patients, brain

Table 2: Clinical manifestations, staging, and diagnostic criteria of Vogt-Koyanagi-Harada (VKH) syndrome (adapted from Refs.⁷ and⁸)

Ocular	Early- (i) Diffuse choroiditis with subretinal fluid and bullous serous retinal detachment, anterior uveitis, vitritis, optic disc hyperemia. (ii) On fundus fluorescein angiography- 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. (iii) On ultrasonography- diffuse choroidal thickening Late- (i) Sunset glow fundus ^a , (ii) Sigiura sign ^b , (iii) nummular chorioretinal depigmented scars, (iv) RPE clumping/migration, (v) recurrent/chronic anterior uveitis
Neurologic/auditory	(i) Meningismus - fever, headache, nausea, vomiting, malaise, neck and back stiffness (ii) CSF pleocytosis (iii) Deafness, tinnitus, vertigo (iv) Rarely encephalopathy, myelitis, cranial neuropathies
Skin	(i) Alopecia (ii) Poliosis (iii) Vitiligo
Stages	(i) Prodromal- predominantly neurologic/auditory involvement (ii) Acute uveitic- predominantly ocular involvement (iii) Convalescent- predominantly ocular and skin involvement (with evidence of depigmentation) (iv) Chronic recurrent- predominantly ocular involvement
Diagnostic criteria (as proposed by the First International Workshop on VKH syndrome)	Mandatory (i) Absence of preceding ocular trauma/surgery (ii) No clinical or laboratory evidence of other ocular disease Complete VKH syndrome- Bilateral ocular involvement with Neurologic/Auditory AND skin findings Incomplete VKH syndrome- Bilateral ocular involvement with Neurologic/Auditory OR skin findings Possible VKH syndrome- Bilateral ocular involvement only

CSF=cerebrospinal fluid, RPE=retinal pigment epithelium. ^aSunset glow fundus: Choroidal depigmentation resulting in bright-orange appearance of fundus, ^bSigiura sign: Perilimbal depigmentation

imaging was unremarkable and meningeal signs were absent despite significant CSF pleocytosis. The differential diagnosis of a patient with brain, eye, and ear (BEE) involvement and CSF pleocytosis is broad and includes (i) infections: syphilis, tuberculosis, human immunodeficiency virus (HIV), herpes virus, Lyme disease etc., (ii) immune-mediated disorders: multiple sclerosis, sarcoidosis, Behcet disease, systemic lupus erythematosus, VKH syndrome, and (iii) neoplastic diseases: lymphomatous and carcinomatous meningitis and skull base neoplasms.^[9] Bedside fundus examination may provide clues to the underlying diagnosis. Specific findings include choroid tubercles in disseminated tuberculosis, retinal microangiopathy in HIV, progressive retinal necrosis in herpes virus infection, perivenous exudates, or “candle wax drippings” in sarcoidosis and combined arteritis and phlebitis in Behcet disease. In VKH syndrome, early fundus changes include optic disc hyperemia and exudative retinal detachment.^[10] In our patients, the specific ocular findings suggested a diagnosis of VKH syndrome. Further, FFA shows characteristic leakage of dye at the optic disc and from the choroid, whereas B scan shows choroid thickening as was noted in both our patients.^[8] Thus, any new-onset headache or a different type of headache in a patient with pre-existing headaches associated with blurred vision is a red flag; VKH syndrome has to be considered in the list of differential diagnosis, despite the fact that this entity has not been emphasised in the 3rd edition of International Classification of Headache Disorders (ICHD-3), and a meticulous ophthalmological assessment is recommended to clinch the diagnosis at an early stage.

CSF examination is non-specific and usually reveals varying degrees of lymphocytic pleocytosis in BEE syndromes. In VKH, the CSF may show evidence of melano-phagocytosis in the form of melanin-laden macrophages, which occurs as a result of cell-mediated immunity against melanocytes in the leptomeninges.^[2,11] However, their demonstration requires special techniques, such as silver impregnation, periodic acid Schiff staining or immunocytochemical studies. Hence, a neurologist must recognize the clinical findings in order to suspect VKH at the bedside and guide the pathologist to perform the specific stains. The finding of melanin-laden macrophages is specific for VKH, but the sensitivity is not known since data from large studies are lacking.

In the skin absence of melanin granules in the basal layer and mononuclear infiltrates has been described in biopsy of affected regions.^[12] Patient 1 in the present study did not have skin lesions, nevertheless, skin biopsy from an apparently unaffected site revealed melanin depletion with melano-phagocytosis. The role of skin biopsy before the development of skin lesions in the diagnosis of VKH syndrome needs to be explored further since this is a relatively non-invasive test.

There is no consensus on treatment of VKH syndrome. Although systemic steroids are the mainstay of treatment, use of other immunosuppressants i.e., cyclosporine, methotrexate, azathioprine, mycophenolate, and biologicals have recently been recommended as first-line therapy. Early recognition and institution of treatment is an important prognostic factor for visual recovery. Aggressive systemic treatment is very effective

in preventing visual loss. As patients may have persisting inflammation for several months to years and given the risks of long-term steroid use, early use of immunomodulatory therapy should be strongly considered in these patients.^[1,2]

VKH syndrome commonly presents to ophthalmologists,^[13,14] but neurologists may occasionally encounter this disease. Diagnostic difficulty occurs as neurological features often precede ocular involvement and many patients have an incomplete syndrome. It is important to consider VKH syndrome in any patient with aseptic meningitis if tests for common infectious and inflammatory diseases are negative. It is common practice in India to treat patients with meningitis of undetermined etiology with antiviral or antitubercular agents empirically based on the local epidemiological patterns. Bedside examination of the fundus and a diligent search for subtle skin findings like poliosis is pivotal in narrowing the differential diagnosis. CSF analysis and skin biopsy with appropriate stains plays a vital role in establishing the etiology even when the complete syndrome is not present cross-sectionally. Follow-up of patients with careful observation for development of other features is essential. Accurate diagnosis is important since it has therapeutic implications.

CLINICAL PEARLS

VKH syndrome is a rare but treatable condition which can involve the brain, eye, and ear (“BEE syndrome”).

Meticulous ophthalmologic examination for specific findings can help in diagnosing this disease at the bedside.

CSF analysis and skin biopsy to look for evidence of melano-phagocytosis can establish the diagnosis in the prodromal stage when ocular involvement may or may not be present.

Early diagnosis and treatment with immunomodulators (including early use of steroid sparing agents) can improve visual prognosis of patients with VKH syndrome.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published

and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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