International Journal of Contemporary Dental and Medical Reviews (2020), Article ID 010321, 5 Pages

REVIEW ARTICLE

Vogt-koyanagi-harada disease: A potentially debilitating diagnosis of exclusion

Tungki Pratama Umar, Reynold Siburian

Department of Medical Profession, Faculty of Medicine, Sriwijaya University, Palembang, South Sumatera, Indonesia

Correspondence:
Tungki Pratama Umar, Faculty of Medicine, Sriwijaya University, Dr. Mohammad Ali Street, RSMH Complex, Km 3.5, Palembang 30126, Indonesia. Phone: +6285368708668.
E-mail: tungkipratama@gmail.com

Received 05 September 2020;
Accepted 22 November 2020

doi: 10.15713/ins.ijcdmr.156

How to cite this article:
Umar TP, Siburian R. Vogt-koyanagi-harada disease: A potentially debilitating diagnosis of exclusion. Int J Contemp Dent Med Rev vol.2020, Article ID: 010321, 2020.
doi: 10.15713/ins.ijcdmr.156

Abstract

Background: Vogt-Koyanagi-Harada (VKH) disease is a systemic autoimmune granulomatous disease that targets melanocyte-rich tissue with potentially visually-threatening outcome for patients. It is manifested in eyes, inner ears, skin, and hair. **Aim:** This review aims to give a brief information about VKH disease, especially regarding the diagnosis and treatment. **Conclusion:** VKH disease is a diagnosis of exclusion, a comprehensive history taking and physical examinations are required for prompt treatment using immunosuppressive agent to improve patient outcomes. **Clinical Significance:** It is possible to treat this condition by applying diagnostic criteria. This requires a very thorough review of possible differential diagnosis and should then be treated with high corticosteroid immunosuppressive drugs. This is solely responsible for stopping the visual impairment and recurrence of the disease.

Keywords: Corticosteroids, Human leukocyte antigen, Immunomodulator, Immunosuppressive agent, Vogt-Koyanagi-Harada disease

Introduction

Vogt-Koyanagi-Harada (VKH) disease, known also as uveomeningoencephalitis syndrome, is a systemic autoimmune granulomatous disease affecting melanocyte-rich tissue, including eyes, inner ears, skin, and hair.[1] It is mediated by autoimmune activity affecting the tyrosinase (TYR) family and gp100.[2] Ocular-related conditions related to this disease including choroidal thickening, multifocal serous retinal detachment, and optic disk hyperemia.[3] The term VKH disease was given by Bruno and McPherson to encompass the previous reported uveomeningeal syndromes as one broad-spectrum entity.[4] The name of the disease is eponymous for honoring the findings of Alfred Vogt (1906) in Switzerland as the first person to describe the disease, Einosuke Harada (1926) in Japan for reporting five case series of primary posterior uveitis correlated with exudative retinal detachment and cerebrospinal fluid pleocytosis, and Yoshizo Koyanagi (1929) in Japan for reporting six case series and reviewing the earlier findings of the disease.[5]

The prevalence of VKH disease varied across the world. Higher cases were described in Asian, Hispanic, Indian, Native American, and Mediterrania, accounted for 7–22.4% of cases of uveitis.[6,7] VKH disease is also common in Japan, with 6.8–9.2% of all cases of uveitis.[6,7] Epidemiological data showed that VKH disease is more commonly found in young women between the ages of 20 and 50 years with a ratio of 2:1 to male.[8] However, cases of VKH disease have also been identified in children, the elderly or even with an equivalent gender distribution.[2] This condition had unknown causes, but thought to be associated to the genetic susceptibility, mainly related to Human Leukocyte Antigen (HLA) DRB1×0405.[9] Genetic susceptibility is responsible for initiating auto-inflammatory stage after viral infection, mainly mediated by T lymphocyte which is targetting tyrosinase-related proteins (TRP).[3,10-12]

Diagnosis of VKH disease primarily focused on the exclusion of any other eye disease and sufficient history, including ocular penetrating injury or intraocular surgery, infection, and systemic rheumatic diseases.[13,14] Many treatment strategies have been developed to cure VKH disease, including systemic corticosteroid (regional, oral, or intravenous), anti-metabolic, and alkylating agent.[9] Inadequate immunosuppressive treatment could lead into the chronic condition, potentially disrupting the visual ability with its complication, such as cataract and secondary glaucoma.[15]

Etiology

The exact cause of VKH disease is still unknown, mostly related to the genetic factor, but the actual inheritance pattern is still under investigation.[3] Some genes expression thought to be

associated with this condition, include HLA DRB1×0405 gene expression.[9] Evidence of HLA involvement as the key risk factor for this disease has been found in Brazil, Korea, Vietnam, Saudi Arabia, Japan, and Europe (especially Italy).[9,16] The gene expression causes autoimmune activation against melanocyte-associated antigens after viral infection, such as Epstein-Barr virus and cytomegalovirus.[17,18]

Hypothetical evidence has shown that this disorder is linked to autoimmune reactions mediated by T-Helper 2 cells against TYR-like proteins in melanocyte, melanin, or retinal epithelial pigment, triggering inflammatory cascades involving cytokine, interleukin (IL)-17, IL-23, and IL-35.[10,11] The manifestation of VKH disease is related to the target tissue (melanocyte-rich), causing ocular (uveitis), neurological (meningitis), (auditory) dysacousia, or even dermatological manifestation (vitiligo).[19,20]

Pathogenesis

The exact molecular mechanism of VKH disease is unknown, but the condition is believed to be associated with autoimmune mechanisms or infections. Recent concepts include the destruction of melanocyte-related antigens mediated by autoimmune T cell reactions.[3] These include TRP1 and 2 (TRP2) TYR, Pmel17/gp100, and MART-1/Melan A.[3] Stimulated T lymphocytes are responsible to express the transmembrane protein CD 25, which is the alpha chain of the IL-2 receptor. Meanwhile, other cells express CD26 related to the deployment of the next T cell function.[21,22] This disease process is closely linked to several HLAs such as HLA-DR4, DR1, DRB1×0405, and DRB1×0410.[22]

Diffuse, non-necrotic granulomatous inflammation of the uvea is typical of VKH disease. Histopathological changes vary depending on the stage of the disease, ranging from granulomatous inflammation throughout the uvea, diffuse infiltration of lymphocytes and macrophages, the presence of epitheloid cells and giant cells showing ingested pigment granules, and serous retinal detachment.[22] When the process is chronic, there is a decrease in choroid melanocytes (sunset glow fundus), loss of epithelial retinal pigment cells, and development of chorioretinal adhesions. The mechanism leading to chronic recurrence will cause hyperplasia and metaplasia of the retinal pigment epithelium.[22]

Diagnosis

Diagnosis criteria for VKH were first published by the American Uveitis Society in 1978. This has two main components:[23]

1. No history of ocular trauma or surgery, and
2. Three of four potential findings of diagnosis (chronic bilateral iridocyclitis, posterior uveitis, neurological symptoms, and skin manifestations).[23]

The parameters were then amended by the International Nomenclature Committee in 2001. Its criteria include five components:

1. No history of penetrating injuries or eye surgery
2. No evidence of any other eye condition
3. Bilateral eye involvement
4. Neurological dysfunction, and
5. Skin disorder.

After applying these criteria, the patient is then graded as taking complete disease (fulfilling all criteria), incomplete disease (following 1–3 results but only one out of 4 or 5), and probable disease (only meeting criteria 1–3).[1]

For a physician, while there are specific guidelines for the diagnosis of VKH disease, there are still drawbacks to be found, such as potentially temporary signs and symptoms, minimal or undetectable ocular and skin manifestations, as well as a variety of ocular manifestations of the disease by racial, geographical, and ethnic differences.[24]

After VKH disease was diagnosed, physician needs to classify it according to the disease stages which will shows very broad disease manifestations. It includes the prodromal phase (viral-like symptoms, neurological [meningitis, cranial nerve paralysis, and focal lesion], auditory manifestation), acute uveitis phase (blurred vision, vitritis, papillitis, hyperemia, disc edema, and exudative retinal detachment), convalescent phase (alopecia, vitiligo, poliosis, and depigmented fundus sunset glow), and perilimbal vitiligo (Sugiura sign), as well as chronic recurrent phase (accompanied with complication including glaucoma, cataract, choroidal neovascularization, and fibrosis of the retina or choroid).[1,25]

The imaging modality is also essential for VKH disease identification. Some types include fundus fluorescein angiography, which is critical not only for the diagnosis but also for the follow-up and prognosis assessment,[2] indocyanine green angiography (ICG),[2,26] an invasive procedure responsive to the visualization of choroidal circulation,[2,24] B-scan ultrasonography, fundus autofluorescence for illustrating retinal epithelial pigment and outer layer of retina,[2] as well as optical coherence tomography (OCT) for determining choroidal thickness, measuring disease activity, and therapeutic response.[2] Full-field electroretinography (ERG) or multifocal ERG for the assessment of the electrophysiological function of the retina and microperimetry for the determination of light intensity in various parts of the retina (in conjunction with OCT) are other diagnostic modalities.[2] Specific causes of eye inflammation, such as erythrocyte sedimentation rate, C-reactive protein, antinuclear antibody, p-/c-antineutrophil cytoplasmic antibodies, and lumbar puncture for undetermined VKH disease (pleocytosis), may be established.[27]

Differential Diagnosis

Whenever a patient has neurological, ocular, otorhinolaryngological, and cutaneous manifestation, VKH

disease should always be considered. The differential diagnosis of sympathetic ophthalmia, central serous chorioretinopathy, epitheliopathy, and any retinal detachment that is secondary to systemic hypertension should be excluded from the investigation. Systemic lupus erythematosus, Wegener granulomatosis, amyloidosis, or sarcoidosis can be associated with the observations of immune-mediated sensorineural hearing loss.[24] In addition, malignancy (intraocular lymphoma, diffuse bilateral melanocytic uveal hyperplasia, and systemic lymphoma/leukemia), inflammation (bilateral posterior scleritis, Multiple evanescent white dot syndrome) or infection (bacteria, fungus, tuberculosis, and syphilis) may also be identified as a differential diagnosis.[4,9]

Management

Two main processes of VKH disease therapy should include the treatment of the early uveitic/exudative acute stage and the maintenance of adequate therapy, including first-line non-steroidal immunosuppressive medications, long enough to contribute to choroidal inflammation resolution, in addition to ICGA-assisted therapy tapering wherever possible.[28] Several treatment strategies have been implemented for the patient with VKH disease, including intravenous (methylprednisolone), oral (prednisone, methylprednisolone), or regional corticosteroid, antimetabolites, azathioprine, cyclosporine, as well as alkylating agents.[9,12]

VKH disease treatment primarily linked to systemic corticosteroid therapy. There are some principles for the implementation of this procedure: Early initial treatment in accordance with intense treatment (high dose of prednisolone/prednisone, 1 mg/kgBW daily, with a maximum dose of 80 mg/day) and long-term therapy (at least 6 months).[16] While aggressive therapy with systemic corticosteroids is underway, refractory cases are very high, as seen with active inflammation. This is the site of immunomodulatory therapy (IMT).[29]

Acute phase of VKH disease needs high-dose corticosteroids given as early as possible.[30] Administration of intravenous methyl-prednisolone (500–1000 mg/day) for 3 days is recommended, which is followed by high-dose oral prednisone (1.0–1.2 mg/kg) for 4–6 weeks. Intravenous corticosteroid use has not really been proven, but it can help to achieve rapid resolution of the inflammation.[31]

Cases of subacute phase VKH disease may benefit from the early introduction of non-steroidal immunosuppressive agents. To achieve choroiditis-free disease resolution, early application of non-steroidal immunosuppressive therapies (e.g., mycophenolate mofetil, 1000 mg twice daily, or mycophenolic acid, and 720 mg twice daily) was very successful and generally well tolerated.[32] The use of these agents is responsible for generating pronounced corticosteroid-sparing effects, dramatically improve visual outcomes, rather significantly reduced the development of chronic persistent inflammation and late complications.[33,34]

As mentioned above, refractory patient groups had a better functional outcome with early IMT therapy.[29] In the early stages of the disease, corticosteroid therapeutic responses should be evaluated for the possible value of IMT. Such an indicator, including baseline visual acuity <20/200, fundus depigmentation, and chronic disease stages.[29] Current evidence indicates the benefits of IMT use as a first-line treatment.[16] IMT treatment used included many classes of antimetabolic agents (methotrexate, azathioprine, and mofetil mycophenolate), alkylating agents (cyclophosphamide), biological agents (adalimumab and infliximab), and calcineurin inhibitors (cyclosporin A).[1]

Topical corticosteroids (dexamethasone eye drops 0.1% or prednisolone acetate 1%) can be used in patients with iridocyclitis (anterior uveitis). It is combined with cycloplegic (example: Tropicamide eye drops 1%) to avoid post-synechiae and minimize ciliary spasm.[1]

Immunosuppressive therapy is responsible for downregulating several pro-inflammatory cytokines, including IL2, IL3, IL4, IL5, IFN-γ, TNF-α, and granulocyte necrosis factor, while upregulating the IL-10. It can be used to inhibit the destruction of melanocyte mediated by the T1 helper cell.[3]

Complications

Chronic recurrent inflammation is linked to ocular disorders, including cataract, glaucoma, and choroid neovascularization. Other more uncommon conditions, including cystoid macular edema, bulbar phthisis, and optic disk atrophy. It is closely linked to the time of referral and onset of illness. Patients who arrive faster than 4 weeks of onset (early stage of illness) tend to be less likely to develop a complication and recurrence than those who arrive later than that.[1]

Prognosis

With rapid and accurate diagnosis, prompt high-dose steroid use and immunomodulator at early onset of disease, the prognosis of VKH disease is good, although irreversible conditions with undesired visual outcome are likely to develop.[11,35,36] Good prognosis of visual function is not always accompanied favorable outcome of retinal epithelial pigment, which is unpredictable.[35] Complications, including glaucoma, cataract, and choroidal neovascularization, found to be associated with the potentially visual-threatening progression of VKH disease, especially in chronic disease phases.

Recent Reports on the Manifestation of VKH Disease

VKH disease did not always come with typical signs and symptoms. Unilateral eye involvement is not commonly reported, but it can be presented to the hospital, showing specific signs on imaging modality.[37] As mentioned above, there are some complications of VKH disease, but it is not always come in the

later stage of the disease, a report stated the presence of bilateral acute angle closure glaucoma as the initial presentation,[38] meanwhile, retinal hemorrhage on funduscopy can also be seen in the acute stage of the disease,[39] in addition to bilateral disc edema.[40] VKH disease also reported to happen simultaneously with treatment procedure, including chemoimmunotherapy or biologic agent (nivolumab) administration.[41,42]

Conclusion

VKH disease is a diagnosis of exclusion, a comprehensive history taking and physical examinations are required for prompt treatment of the disease due to its potentially disabling adverse effects on the visual function. Early administration of corticosteroids is typically used as an agent to improve patient outcomes. Further research on this subject is required to organize the most effective treatment modality in a widely agreed algorithm.

References

1. Lavezzo MM, Sakata VM, Morita C, Rodriguez EE, Abdallah SF, da Silva FT, *et al*. Vogt-Koyanagi-Harada disease: Review of a rare autoimmune disease targeting antigens of melanocytes. Orphanet J Rare Dis 2016;11:29.
2. Baltmr A, Lightman S, Tomkins-Netzer O. Vogt-Koyanagi-Harada syndrome - current perspectives. Clin Ophthalmol 2016;10:2345-61.
3. Patil YB, Garg R, Rajguru JP, Sirsalmath M, Bevinakatti VA, Kumar M, *et al*. Vogt-Koyanagi-Harada (VKH) syndrome: A new perspective for healthcare professionals. J Fam Med Prim Care 2020;9:31-5.
4. Hernandez-Camarena J, Gonzalez-Gonzalez LA, Shaikh M, Rodríguez-García A, Foster CS. Vogt-Koyanagi-Harada syndrome. Contemp Ophthalmol 2010;9:1-7.
5. Herbort CP, Mochizuki M. Vogt-Koyanagi-Harada disease: Inquiry into the genesis of a disease name in the historical context of Switzerland and Japan. Int Ophthalmol 2007;27:67-79.
6. Silpa-Archa S, Noonpradej S, Amphornphruet A. Pattern of uveitis in a referral ophthalmology center in the central district of Thailand. Ocul Immunol Inflamm 2015;23:320-8.
7. Al Dhahri H, Al Rubaie K, Hemachandran S, Mousa A, Gikandi P, Al-Mezaine H, *et al*. Patterns of uveitis in a university-based tertiary referral center in Riyadh, Saudi Arabia. Ocul Immunol Inflamm 2015;23:311-9.
8. Wang Y, Chan C. Gender differences in Vogt-Koyanagi-Harada disease and sympathetic ophthalmia. J Ophtalmol 2014;2014:157803.
9. O'Keefe GA, Rao NA. Vogt-Koyanagi-Harada disease. Surv Ophthalmol 2017;62:1-25.
10. Elahi S, Herbort CP Jr. Vogt-Koyanagi-Harada disease and birdshot retinochoroidopathy, similarities and differences: A glimpse into the clinicopathology of stromal choroiditis, a perspective and a review. Klin Monatsbl Augenheilkd 2019;236:492-510.
11. Marcelo TT, Iguban EB. A case report on Vogt-Koyanagi-Harada disease seen at a tertiary hospital in the Philippines. Ophthalmol Open J 2018;3:1-4.
12. Johal B, Johal H, Lukaris A. The clinical presentation and diagnosis of Vogt-Koyanagi-Harada syndrome. Univ Br Columbia Med J 2015;6:20-2.
13. Yang P, Zhong Y, Du L, Chi W, Chen L, Zhang R, *et al*. Development and evaluation of diagnostic criteria for Vogt-Koyanagi-Harada disease. JAMA Ophthalmol 2018;136:1025-31.
14. Crosson JN, Laird PW, Debiec M, Bergstrom CS, Lawson DH, Yeh S. Vogt-Koyanagi-Harada-like syndrome after CTLA-4 inhibition with ipilimumab for metastatic melanoma. J Immunother 2015;38:80-4.
15. Lodhi S, Reddy J, Peram V. Clinical spectrum and management options in Vogt-Koyanagi-Harada disease. Clin Ophthalmol 2017;11:1399-406.
16. Urzua CA. Vogt-Koyanagi-Harada disease. In: Rodriguez-Garcia A, Foster CS, editors. Advances in the Diagnosis and Management of Uveitis. 1st ed. London: Intech Open; 2019. p. 9-18.
17. Bassili S, Peyman G, Gebhardt B, Daun M, Ganiban G, Rifai A. Detection of Epstein-Barr virus DNA by polymerase chain reaction in the vitreous from a patient with Vogt-Koyanagi-Harada syndrome. Retina 1996;16:160-1.
18. Sugita S, Takase H, Kawaguchi T, Taguchi C, Mochizuki M. Cross-reaction between tyrosinase peptides and cytomegalovirus antigen by T cells from patients with Vogt-Koyanagi-Harada disease. Int Ophthalmol 2007;27:87-95.
19. Damico FM, Bezerra FT, da Silva GC, Gasparin F, Yamamoto JH. New insights into Vogt-Koyanagi-Harada disease. Arq Bras Oftalmol 2009;72(3):413-20.
20. Adam M, Rahimy E, Dunn J. Tattoo-associated uveitis. JAMA Ophthalmol 2015;133:e144543.
21. Concha del Río L, Arellanes-García L. Vogt-Koyanagi-Harada disease in the developing world. Int Ophthalmol Clin 2010;50:189-99.
22. Rao PK, Rao NA. Vogt-Koyanagi-Harada disease and sympathetic ophthalmia. In: Pleyer U, Foster CS, editors. Uveitis and Immunological Disorders. 1st ed. Berlin: Springer; 2007. p. 145-55.
23. Salcedo HR, Palestine A, Feldman BH, Fingerhut D, O'Keefe GD, Salcedo HR, *et al*. Vogt-Koyanagi-Harada Disease. EyeWiki; 2019 Available from: https://www.eyewiki.aao.org/Vogt-Koyanagi-Harada_disease. [Last accessed on 2020 Apr 18].
24. Mota LA, dos Santos AB. Vogt-Koyanagi-Harada syndrome and its multisystem involvement. Rev Assoc Med Bras (1992) 2010;56:590-5.
25. Salmon JF. Kanski's Clinical Ophthalmology. 9th ed. New York: Elsevier; 2019. p. 445-7.
26. Knecht P, Mantovani A, Herbort C. Indocyanine green angiography-guided management of Vogt-Koyanagi-Harada disease: Differentiation between choroidal scars and active lesions. Int Ophthalmol 2013;33:571-7.
27. Mai AP, Tran C, Wilson CW, Fox AR, Boldt HC. Vogt-Koyanagi-Harada (VKH) Disease. EyeRounds; 2019. Available from: http://www.eyerounds.org/cases/284-vogt-koyanagi-harada.htm. [Last accessed on 2020 Apr 18].
28. Herbort CP, Abu El Asrar AM, Yamamoto JH, Pavésio CE, Gupta V, Khairallah M, *et al*. Reappraisal of the management of Vogt-Koyanagi-Harada disease: Sunset glow fundus is no more a fatality. Int Ophthalmol 2017;37:1383-95.
29. Urzua C, Velasquez V, Sabat P, Berger O, Ramirez S, Goecke A, *et al*. Earlier immunomodulatory treatment is associated with better visual outcomes in a subset of patients with Vogt-Koyanagi-Harada disease. Acta Ophthalmol 2015;93:475-80.

30. Bouchenaki N, Morisod L, Herbort CP. Vogt-Koyanagi-Harada syndrome: Importance of rapid diagnosis and therapeutic intervention. Klin Monbl Augenheilkd 2000;216:290-4.
31. Read RW, Yu F, Accorinti M, Bodaghi B, Chee SP, Fardeau C, *et al*. Evaluation of the effect on outcomes of the route of administration of corticosteroids in acute Vogt-Koyanagi-Harada disease. Am J Ophthalmol 2006;142:119-24.
32. Bouchenaki N, Herbort CP. Indocyanine green angiography guided management of vogt-koyanagi-harada disease. J Ophthalmic Vis Res 2011;6:241-8.
33. Abu El-Asrar AM, Hemachandran S, Al-Mezaine HS, Kangave D, Al-Muammar AM. The outcomes of mycophenolate mofetil therapy combined with systemic corticosteroids in acute uveitis associated with Vogt-Koyanagi-Harada disease. Acta Ophthalmol 2012;90:e603-8.
34. El-Asrar AMA, Dosari M, Hemachandran S, Gikandi PW, Al-Muammar A. Mycophenolate mofetil combined with systemic corticosteroids prevents progression to chronic recurrent inflammation and development of 'sunset glow fundus' in initial-onset acute uveitis associated with Vogt-Koyanagi-Harada disease. Acta Ophthalmol 2017;95:85-90.
35. Manethova K, Ernest J, Hrevus M. Vogt-Koyanagi-Harada syndrome (uveomeningoencephalitic syndrome). Eur J Ophthalmol 2017;27:e5-8.
36. Akram S, Ahmad K. Vogt-Koyanagi-Harada syndrome. J Coll Physicians Surg Pak 2014;24(9):692-4.
37. Hosseini SM, Dourandish M, Mazouchi M. Unilateral presentation of Vogt-Koyanagi-Harada syndrome. J Ophthalmic Vis Res 2020;15:99-103.
38. Yuan F, Zhang Y, Yan X. Bilateral acute angle closure glaucoma as an initial presentation of Vogt-Koyanagi-Harada syndrome: A clinical case report. Eur J Ophthalmol 2020:1120672120951442. Doi: 10.1177/1120672120951442.
39. Ali S, Oo HH, Agarwal R, Khee PK. Concurrent presence of retinal hemorrhages in the setting of acute Vogt-Koyanagi-Harada syndrome - an unusual presentation. J Ophthalmic Inflamm Infect 2020;10:1-4.
40. Nichani P, Christakis PG, Micieli J. Headache and bilateral optic disc edema as the initial manifestation of Vogt-Koyanagi-Harada disease. J Neuroophthalmol 2020;41:e128-30.
41. Kurono Y, Takeda T, Kunimatsu Y, Tani N, Hashimoto I, Hirose K. Vogt-Koyanagi-Harada disease during chemoimmunotherapy for non-small cell lung cancer. Respirol Case Rep 2020;8:e00545.
42. Kikuchi R, Kawagoe T, Hotta K. Vogt-Koyanagi-Harada disease-like uveitis following nivolumab administration treated with steroid pulse therapy: A case report. BMC Ophthalmol 2020;20:1-6.