Review Article

Vogt–Koyanagi–Harada (VKH) syndrome: A new perspective for healthcare professionals

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Abstract

Vogt–Koyanagi–Harada syndrome (VKH syndrome) is a rare granulomatous inflammatory disease that affects the melanin pigment producing melanocytes and mainly affects the pigmented structures such as eyes, ear, skin, meninges, and hair. VKT is an autoimmune disorder, which is mainly a T CD4+ Th1 lymphocyte–mediated aggression to melanocytes, in individuals with a genetic predisposition, in particular, the presence of HLA-DRB1 * 0405 allele. Melanin usually gives color to skin, hair, and eyes. Melanin is also found in the retina, where it plays a role in normal vision. This disease mainly leads to vision and hearing disturbances, followed by dermal problems. The most common symptoms include vitiligo, headaches, hair loss (alopecia), and hearing loss. This article describes the various signs and symptoms of VKH disease and its pathogenesis.

Keywords: Melanin, syndrome, VKH

Introduction

VKH syndrome, also known as the uveomeningitic syndrome, is an idiopathic inflammatory disease characterized by bilateral, chronic, and diffuse granulomatous panuveitis frequently associated[1] with neurological, auditory, and integumentary findings.[1] VKH disease has an acute onset that involves multiple systems mainly causing inflammation of melanocyte-containing tissues such as the uvea, ear, and meninges. The disease may be associated with additional signs and symptoms like meningeal irritation and integumentary signs of poliosis and vitiligo. Later stages of the disease lead to poliosis and vitiligo, thus making the diagnosis of complete VKH disease.

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VKH syndrome involves T-cell-mediated autoimmune deregulation, targeting melanocytic self-antigens. The tyrosinase family proteins and gp100 are common antigenic targets for VKHD. The disease has a predilection for affecting melanocyte-containing tissues in the eye, the central nervous system (CNS), the inner ear, and the skin and appears in genetically susceptible individuals and is related to HLA-DRB1*0405. Patients usually present with bilateral panuveitis preceded by a mild prodromal illness, associated with neurological and auditory features. However, it is common for patients to present with isolated ocular involvement during the early phases of the disease, with the choroid being the main site of ocular inflammation together with the potential involvement of the iris and ciliary body.[2]

Although VKH sydrome rarely affects the pediatric population, Katsuyama A *et al*. reported a case of a similar syndrome in a

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3-year-old girl having severe bilateral panuveitis with posterior synechiae of the iris, marked optic disk swelling, and serous retinal detachment in both eyes. The clinical course tends to be aggressive, and the visual prognosis was worse than that in adult patients due to severe ocular complications secondary to recurrent inflammation.[3]

VKH disease is characterized by chronic onset and shows bilateral, granulomatous uveitis with extraocular manifestations in the central nervous system such as cerebrospinal fluid pleocytosis (CSF), dysacousia, tinnitus, vertigo and, in some cases, integumentary system vitiligo, poliosis, and alopecia.[4] The ocular symptoms of the disease are characterized by multifocal serous retinal detachment, choroidal swelling, and optic disk hyperemia in the acute stage.[5]

Various stages of VKH disease include:-

1. Prodromal Stage: This stage is characterized by nonspecific symptoms like malaise, fever, nausea, headache, dizziness, and orbital pain and this usually lasts for 3–5 days. This stage may sometimes be associated with neurologic manifestations like meningismus and headache, cranial nerve palsies, hemiparesis, transverse myelitis, and optic neuritis. Eighty percent of the patients will show lympocytic pleocytosis in cerebrospinal fluid for 8 weeks. Moreover, ocular symptoms such as photophobia and tearing may occur after the systemic symptoms.[4]
2. Acute Uveitic Stage: This stage follows the prodromal phase and lasts for several weeks. In this stage, the patient mainly complains of visual impairment and most of the patients present with bilateral posterior uveitis. But, in few cases, there may not be simultaneous involvement of both the eyes which is further followed by a short delay of 1 to 3 days. Thus, it is mandatory in cases suspected with unilateral manifestations and must be evaluated carefully for the signs and symptoms in the adjacent eye. The uveitis commonly presents with multiple serious retinal detachments, hyperemia, and edema of the optic nerve head, and the thickening of the posterior choroid with elevation of the peripapillary retinochoroidal layer.[6]
3. Chronic (Convalescent) Stage: This stage can lasting for months or even years results in depigmentation that may be integumentary and/or uveal. Usually, vitiligo is symmetrical and involves mainly the face, eyelids, and trunk.[4] The choroid undergoes depigmentation giving the ocular fundus a "sunset-glow" appearance where the choroid appears bright-orange in color and the optic nerve appears pale. Sugiura's sign or perilimbal vitiligo is the earliest depigmentation to occur, often within 1 month after disease onset.[7]
4. Chronic Recurrent Stage: Manifests as a recurrent, mainly anterior granulomatous uveitis. Posterior segment inflammation is rare during this phase. Complications such as glaucoma, cataract, and subretinal fibrosis, and neovascular membrane formation usually develop at this stage. Factors that are associated with the development of complications are duration of the disease and the number of recurrences.[4]

Vitligo forms an important clinical sign in the diagnosis of complete VKH syndrome. Vitiligo reversal has been mentioned in only one previous study. Reduction of vitiligo marks the reversal of the autoimmune destruction of melanocytes following corticosteroid or any other immunosuppressive therapy. Reversal of vitiligo can be considered as one of the prognostic indicators for the resolution of VKH syndrome.

The International Committee on Nomenclature established revised criteria for the diagnosis of VKH disease. The revised criteria defined the following 3 categories of disease.[8]

1. Complete VKH disease
2. Incomplete VKH disease
3. Probable VKH disease.

Complete VKH disease

Early manifestations of complete VKH disease include diffuse choroiditis, which may include serous retinal detachment or focal areas of subretinal fluid. Patients without these findings must have diffused choroidal thickening as seen using ultrasonography with fluorescein angiographic abnormalities, including focal areas of delayed choroidal perfusion, multifocal pinpoint leakage, areas of placoid hyperfluorescence, pooling of subretinal fluid, and optic nerve staining.[9,10]

Late manifestations of complete VKH disease include evidence of previous early manifestations of the disease along with ocular depigmentation and nummular chorioretinal scars, retinal pigment epithelium (RPE) clumping and migration, or anterior uveitis.[8,11]

The neurologic and auditory signs include the following:

1. Meningismus - Malaise, fever, headache, nausea, abdominal pain, stiffness of the neck and back, or a combination of these factors[8]; headache alone is not sufficient to meet the definition of meningismus.
2. Tinnitus
3. Cerebrospinal fluid pleocytosis

Integumentary signs include the following:

1. Alopecia
2. Poliosis
3. Vitiligo

However, the integumentary signs should not occur prior to the onset of ocular signs and central nervous system signs.

Incomplete VKH disease

Patients with incomplete VKH disease have either

Probable VKH disease neurologic and auditory manifestations or integumentary signs, but not both.[9]

Patients with probable VKH disease include those with isolated ocular disease.VKH syndrome is still an enigmatic condition to most ophthalmologists. It affects all age groups from 5 years to 80 years. The prevalence of disease in uveitis cohorts is 1.4%-3.5% in India. Etiology of the disease being mostly genetic but the actual mode of inheritance is not yet revealed completely. Integumentary findings such as vitiligo occurs as late clinical manifestations of VKH syndrome; however, recurrence of the intraocular inflammation marks simultaneous presence of acute uveitic state and late integumentary findings.

Histopathological Features

Histopathological features of VKHD vary according to the stage of disease. The primary pathological feature of VKHD is, however, diffuse thickening of the uveal tract (more prominent in the juxtapapillary choroid). In the acute stage there is a granulomatous process. In the acute uveitic stage, it is of note a diffuse lymphocytic infiltration with focal aggregates of epithelioid cells and multinucleated giant cells containing pigment devoid apparent choroidal necrosis. Choroidal infiltrate consists of T lymphocytes, which exhibit the markers of helper (CD4+) and suppressor/cytotoxic cells, along with melanocytes expressing class II major histocompatibility complex molecules. In the acute uveitic phase, the subretinal fluid of the serous retinal detachment contains an eosinophilic proteinaceous material. Basically, being a stromal choroidoidopathy, there is diffuse infiltration of lymphocytes, epithelioid histiocytes, and multinucleated giant cells. But the RPE and choriocapillaries are spared in this stage due to a special protein called RPE protein.[12]

Focal collections of hyperplastic/modified RPE, macrophages, epithelioid cells and lymphocytes located between RPE and Bruch's membrane may form the Dalen-Fuchs nodules.[13,14]

During the convalescent stage, there is a nongranulomatous inflammation, the hispathology of which shows mild to moderate nongranulomatous inflammatory cell infiltrate with focal aggregates of lymphocytes and occasional macrophages. The loss of melanin granules of choroidal melanocytes renders a pale, depigmented aspect to the choroid. Thus, the "sunset glow fundus" appearance in the convalescent stage results from the immune-mediated insult to choroidal melanocytes.

During the chronic recurrent stage, granulomatous choroiditis with damage of choriocapillaris is observed. Furthermore, one may observe a granulomatous infiltrate with less-prominent diffused uveal thickening than that observed in the acute stage. Chorioretinal adhesions with atrophy and/or proliferation of RPE are frequent. Focal areas of hyperpigmentation in depigmented fundi are the consequence of RPE proliferation. This may be accompanied by subretinal neovascularization and elevated pigmented lesions.[14] Immunohistochemical markers CD3 and CD 20 are found to be positive for the cases of VKH syndrome. Significance of CD3 positivity indicates T-cells involvement.[15]

Pathogenesis

The exact molecular mechanism of VKH disease is not known, but it has been suggested that VKH disease is associated with autoimmune or infectious process. Recent concept involves the destruction of melanocyte-related antigen (member of the tyrosinase family of proteins) mediated by autoimmune T-cell reaction.

Various investigations suggested that the tyrosinase family proteins are reactive against the lymphocytes of VKH patients that further implicates that these proteins are the target antigens of immune reactions in VKH disease.

The immune response is aimed at proteins associated with melanocytes. Melanocyte-specific proteins, are known to have a major role in differentiation, such as tyrosinase (TYR), tyrosinase related protein 1 (TRP1) and 2 (TRP2), MART-1/Melan A and Pmel17/gp100, expressed in human melanoma cell lines and are recognized by T lymphocytes of patients with melanoma and are involved in tumor regression.[16]

It has been reported that vitiligo lesions of patients with VKH disease showed helper/inducer CD4+ lymphocytes and an altered ratio of CD4+/CD8+ (3:1) cells. Other investigations related to dermal lesions in which the melanin-laden cells of the epidermis were shed off and the connective tissue consisted of infiltrates with T-cells suggested cell-mediated immune response as the mainstay in the pathogenesis.[17]

Stimulated T lymphocytes express a transmembrane protein CD 25 which is an alpha chain of the receptor for the interleukin-2 (IL-2).While other cells express CD26 that is a T cell activation antigen and cause cell activation leading to subsequent exertion of T cell effector function.[18] Histopathology demonstrates diffuse infiltration of activated T cells in the uvea sparing the choriocapillaris. Infiltrate predominantly shows the presence of lymphocytes along with other cellular components like epithelioid cells, plasma cells, and multinucleated giant cells.

Vitligo is characterized by autoimmune destruction of melanocytes resulting in the absence of melanin from epidermis. Immunohistochemical analysis has shown marked infiltration of helper T1 cells in epidermis along with increased CD4/CD8 and IL2 expression that correlate positively with degree of amelanosis. Immunosupressive therapy with steroids and various other immunomudulators have found to downregulate various proinflammatory cytokines such as IL2, IL3, IL4, IL5, IFN gamma, TNF alpha, and granulocyte necrosis factors; on the other hand, it leads to upregulation of IL-10 and thus inhibits unchecked destruction of melanocytes by helper T1 cells.[19]

Diagnostic criteria

The diagnosis of VKHD is primarily based on clinical features. Several criteria have been proposed to clarify the diagnostic

approach, including the American Uveitis Society (AUS) in 1978 and the Sugiura's Criteria in 1976. The AUS adopted the following diagnostic criteria:

- No history of ocular trauma and/or surgery;
- At least three of the following four signs:

A. Bilateral chronic iridocyclitis
B. Posterior uveitis (multifocal exudative retinal or RPE detachments
C. Disc hyperemia or edema; or "sunset glow fundus", which is an yellow-orange appearance of the fundus due to the depigmentation of the RPE and choroid

The limitations of AUS criteria includes differentiation of acute and chronic cases but an inadequate consideration of acute cases as two of the four cardinal signs characteristically occur in the convalescent/chronic stages of disease. Moreover, fluorescein (FA) and indocyanine angiography (ICGA), as well ultrasonographic findings were not taken into account by AUS criteria. Later on, another criteria was put forward in 2001 by the International Nomenclature Committee, namely the Revised Diagnostic Criteria (RDC). The RDC classifies the disease into three categories: complete, incomplete, and probable VKH based on the presence of extraocular findings.[20-22]

Implications for clinical practice

The primary care physician is the first contact of a patient for the consultation of illness. Early diagnosis and a multidisciplinary approach are the key components of managing this complex syndrome. Increased awareness and research in this field have facilitated the identification of risk factors and causation pathways. Certain therapies have shown promise that need evaluation in prospective clinical trials. The goal of treatment in VKHD is to suppress active ocular inflammation, prevent disease relapse, and avoid sight-threatening complications. As such, early diagnosis and rapid commencement of treatment are important in preserving the visions of young patients.[23] Multiple therapeutic regimens are used combining both systemic immunosuppression agents together with locally administered corticosteroids and antivascular endothelial growth factor drugs (anti-VEGF). Because VKHD can involve multiple organs, the mainstay of the treatment is based on high-dose systemic corticosteroids, administered either orally or intravenously.[24] Early administration of oral prednisone at a dose of 1–2 mg/kg/day followed by slow tapering to avoid recurrences is the generally accepted regimen, while pulse intravenous corticosteroid therapy of 1 g/day of methylprednisolone for 3–5 days followed by oral prednisolone is usually reserved for cases with severe inflammation. Slow tapering of the corticosteroid dose, with frequent follow-up examinations, is warranted to avoid the recurrence of posterior segment inflammation.[25,26] An aggressive corticosteroid treatment strategy in patients with new-onset acute VKH disease, followed by cyclosporine, resulted in excellent visual outcomes and low rates of recurrence.[27]

Conclusion

Vitiligo reversal may be considered as a favorable prognostic indicator to corticosteroid therapy in VKH syndrome. Moreover, repigmentation of vitiligo correlates well with the remission of disease process.

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Conflicts of interest

There are no conflicts of interest.

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