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Vogt-Koyanagi-Harada disease diagnosed in members of the same family

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Abstract

Vogt-Koyanagi-Harada syndrome (VKH syndrome) is a rare granulomatous inflammatory disease that affects melanocyte pigment-producing melanocytes and primarily affects pigmented structures such as the eyes, inner ear, skin, meninges, and hair. VKT is an autoimmune disease, which is primarily a CD4 + Th1 T lymphocyte-mediated aggression to melanocytes. Melanin usually gives color to the skin, hair and eyes. Melanin is also found in the retina, where it plays a role in normal vision. The absence of ocular trauma or previous intraocular surgery differentiates VKHD from sympathetic ophthalmia, its main differential diagnosis. The disease has an acute onset of bilateral blurred vision with hyperemia preceded by flu-like symptoms. The acute uveitic stage is characterized by diffuse choroiditis with serous retinal detachment and optic disc hyperemia and edema. Fluorescein angiography at this stage demonstrates multiple initial hyperfluorescent dots. After the acute uveitic stage, pigmentary changes in the ocular and integumentary system may appear. Ocular findings may be accompanied by lymphocytic meningitis, hearing loss and/or tinnitus in a variable proportion of patients. Prompt diagnosis followed by early, aggressive, and long-term treatment with high-dose corticosteroids is most often followed by good visual results. However, some patients may have chronic uveal inflammation with functional deterioration of the eye.

Keywords: Uveitis; Vogt-Koyanagi-Harada Disease; Neurosensory Hypoacusis; Vertigo; Autoimmunity; Melanocytes

1. Introduction

Vogt-Koyanagi-Harada syndrome (VKHD) is a rare, multisystem, autoimmune, inflammatory disease that affects melanocytes and, consequently, pigmented structures, such as the retina, meninges, inner ear, skin and central nervous system. There is an immune cellular response mediated by TCD4+ lymphocytes against tyrosinase and derived peptides, which are found in the membrane of melanocytes and are responsible for the synthesis of melanin [1]. It is not known whether this process is idiopathic or triggered by some trigger, such as infections. There are indications that it is due to an infection, probably viral, as the Epstein-Barr virus was isolated in patients with the syndrome. However, this association needs to be better established [2-5].

It is predominant in individuals of Asian, Indian and Latin American origin, as well as in individuals with dark skin pigmentation such as mixed race and black people, with a higher proportion in females (2:1) [2,3,5,6]. The onset of the disease usually occurs between the second and fourth decade of life, and can occur at any age [4,5,6].

The incidence of VKHD varies. Among all uveitis cases, it is estimated to represent approximately 7% in Japan, 1–4% in the United States, and 3% in Brazil. Together with Behcet's disease, they represent the most prevalent causes of non-

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infectious uveitis in Brazil. In China, VKHD is one of the most common uveitis entities. In the United States, the incidence of VKHD is approximately 1.5 to 6 per 1 million patients [2-5.6].

VKH syndrome, also known as uveomeningitic syndrome, is an idiopathic inflammatory disease characterized by diffuse, chronic, bilateral granulomatous panuveitis often associated with neurological, auditory, and cutaneous findings. VKH disease has an acute onset involving multiple systems, primarily causing inflammation of melanocyte-containing tissues such as the uvea, ear, and meninges [2,3,6,7,8]. The disease may be associated with additional signs and symptoms, such as meningeal irritation and tegumentary signs of poliosis and vitiligo. Later stages of the disease lead to poliosis and vitiligo, making the diagnosis of VKH disease complete [3,5,8,9].

The disease has a predilection for affecting tissues containing melanocytes in the eye, central nervous system (CNS), inner ear and skin and appears in genetically susceptible individuals and is related to HLA-DRB1 * 0405. Patients usually have bilateral panuveitis preceded by a mild prodromal disease, associated with neurological and auditory features. [4,6,8,9,10]. However, it is common for patients to present isolated ocular involvement during the early stages of the disease, with the choroid being the main site of ocular inflammation, along with potential involvement of the iris and ciliary body [5,6,8,11].

VKH disease is characterized by chronic onset and shows bilateral granulomatous uveitis with extraocular central nervous system manifestations such as cerebrospinal fluid (CSF) pleocytosis, dysacousia, tinnitus, vertigo, and in some cases, integumentary system vitiligo, poliosis, and alopecia. The ocular symptoms of the disease are characterized by multifocal serous retinal detachment, choroidal edema, and optic disc hyperemia in the acute phase [2,7,8,11-14].

1.1. Various stages of VKH disease include

- Prodromal Stage: Characterized by nonspecific symptoms such as malaise, fever, nausea, headache, dizziness and orbital pain and usually lasts 3 to 5 days. This stage can sometimes be associated with neurological manifestations such as meningismus and headache, cranial nerve palsy, hemiparesis, transverse myelitis, and optic neuritis. Eye symptoms such as photophobia and tearing may occur after systemic symptoms [3-8,14-17].
- Acute uveitic stage: This stage follows the prodromal phase and lasts for several weeks. At this stage, the patient mainly complains of visual impairment and most patients have bilateral posterior uveitis. But in some cases, there may not be simultaneous involvement of both eyes, which is followed by a short delay of 1 to 3 days. Thus, it is mandatory in suspected cases of unilateral manifestations and should be carefully evaluated for signs and symptoms in the adjacent eye. Uveitis commonly presents with multiple severe retinal detachments, optic nerve head hyperemia and swelling, and posterior choroidal thickening with elevation of the peripapillary retinochoroid layer [3-8,14-17].
- Chronic (Convalescent) Stage: This stage can last for months or even years, resulting in depigmentation that can be tegumentary and/or uveal. Vitiligo is usually symmetrical and mainly involves the face, eyelids, and trunk. The choroid undergoes depigmentation, giving the fundus a "sunset glow" appearance, where the choroid appears bright orange and the optic nerve appears pale. Sugiura's sign or perilimbal vitiligo is the earliest depigmentation to occur, usually 1 month after the onset of the disease [3-8,14-17].
- Chronic recurrent stage: manifests as recurrent anterior granulomatous uveitis, mainly. Posterior segment inflammation is rare during this phase. Complications such as glaucoma, cataracts and subretinal fibrosis and neovascular membrane formation usually develop at this stage. Factors associated with the development of complications are the duration of the disease and the number of recurrences [3-8,14-17].

Patients with the complete form of the syndrome must have all clinical criteria duly fulfilled. Patients with the incomplete form, on the other hand, present ocular involvement fulfilling the first three criteria associated with the presence of neurological and auditory alterations or cutaneous alterations. The syndrome is considered probable when it meets only the ophthalmologic criteria [13,15,18,19].

The goal of treatment is to suppress active eye inflammation, prevent disease recurrence, and prevent vision-threatening complications. Various therapeutic regimens are used combining both systemic immunosuppressive agents along with locally administered corticosteroids and anti-vascular endothelial growth factor (anti-VEGF) drugs. As VKHD can involve multiple organs, the mainstay of treatment is based on high doses of systemic corticosteroids given orally or intravenously. Oral prednisone at a dose of 1–2 mg/kg/day initiated at disease onset followed by tapering to prevent recurrences is the generally accepted regimen, while pulsed intravenous corticosteroid therapy of 1 g/day of methylprednisolone for 3 to 5 days, followed by oral prednisolone, is usually reserved for cases with severe inflammation [12,17,19,20,21].

Topical corticosteroids and cycloplegic agents are effective in controlling anterior segment inflammation. Addition of immunosuppressive agents such as mycophenolate mofetil, methotrexate, cyclosporine, or azathioprine are generally considered in patients who are not controlled with corticosteroids alone or cannot be tapered to a safe low dose for the long period of time they need to control their inflammation [13,17,20-24].

2. Case reports

2.1. Case 1

S.F.M, female, white, 32 years old, had a history of headache and low visual acuity in both eyes for 1 year due to exudative retinal detachment, and treatment with systemic corticosteroids 1mg/kg/day was initiated. It evolved after a few weeks with vertigo and tinnitus. At follow-up, after the end of the systemic corticoid, the patient showed improvement in ophthalmological and otorhinolaryngological symptoms. After this initial episode, the patient noticed the appearance of madarosis and alopecia.

Two months after the initial episode, she presented a new condition of low visual acuity after an attempt to slowly wean the systemic steroid, but this time associated with conjunctival hyperemia, anterior chamber reaction, keratic precipitates and posterior synechiae. In view of this, it was decided to start a systemic immunomodulator.

Past pathological history did not present systemic comorbidities, surgeries or ocular trauma. He denied daily use of eye drops and family members with known eye pathologies. On dermatological examination, discrete areas of vitiligo in the lumbar region.

On examination, the best corrected visual acuity (VA) was 20/25 in both eyes (BE). Biomicroscopy showed pigmented keratic precipitates and posterior synechiae. (Figures 1 and 2)

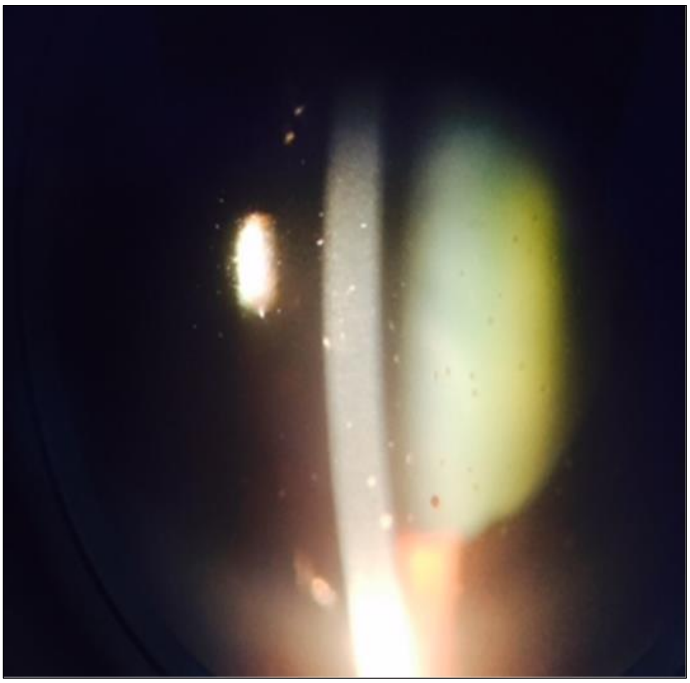

Figure 1 Biomicroscopy showed pigmented keratic precipitates and posterior synechiae

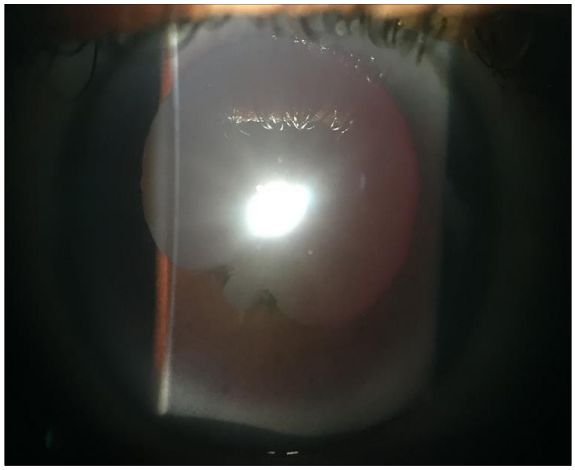

Figure 2 Biomicroscopy showed pigmented keratic precipitates and posterior synechiae

Retinography showed diffuse atrophy of retinal pigment epithelium and peripheral Dalen-Fuchs nodules in BE. (Figures 3 and 4)

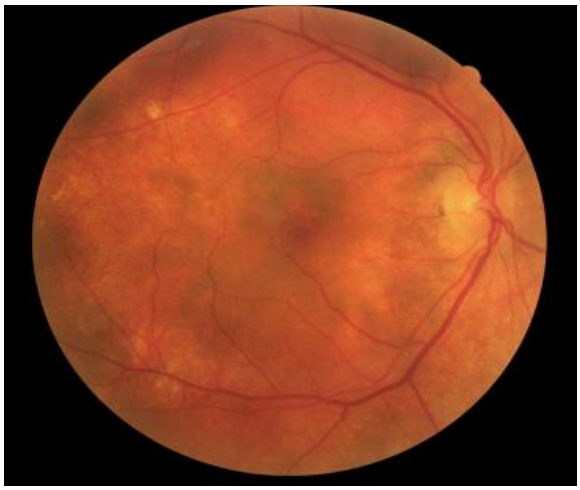

Figure 3 Retinography showed diffuse atrophy of retinal pigment epithelium and peripheral Dalen-Fuchs nodules in BE

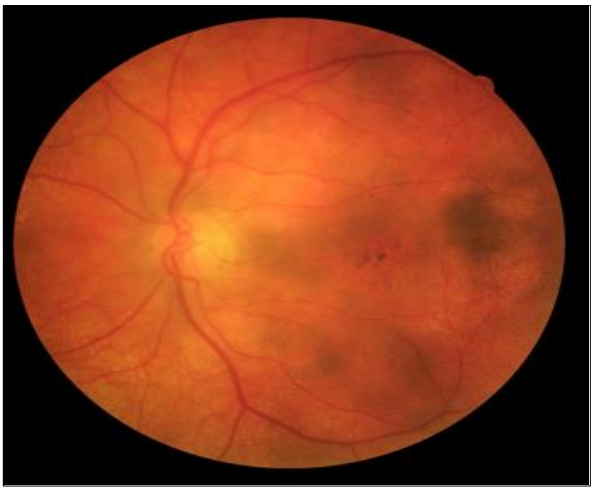

Figure 4 Retinography showed diffuse atrophy of retinal pigment epithelium and peripheral Dalen-Fuchs nodules in BE

Currently, using Prednisone 20mg/day and Azathioprine 60mg/day, no complaints. It maintains regular follow-up in the retina sector in prednisone weaning and surveillance of otoneurological and dermatological symptoms with the respective specialties.

2.2. Case 2

Patient T.L.M., female, 42 years old, presented visual clouding, tinnitus, headache and vertigo 14 days before the initial medical care. He denied previous systemic comorbidities, allergies and similar conditions, but stated that a cousin had presented symptoms similar to those presented by her. No systemic manifestations so far.

AV was 20/50 in the right eye and 20/60 in the left eye.

Biomicroscopy showed only 2+/4+ conjunctival hyperemia. Pio was 12/12 mmHg. (2:30 pm)

Retinography showed swollen optic discs, cup/disc ratio difficult to assess, tortuous vessels, free macules and retinal exudative detachment below the macula. (Figures 5 and 6)

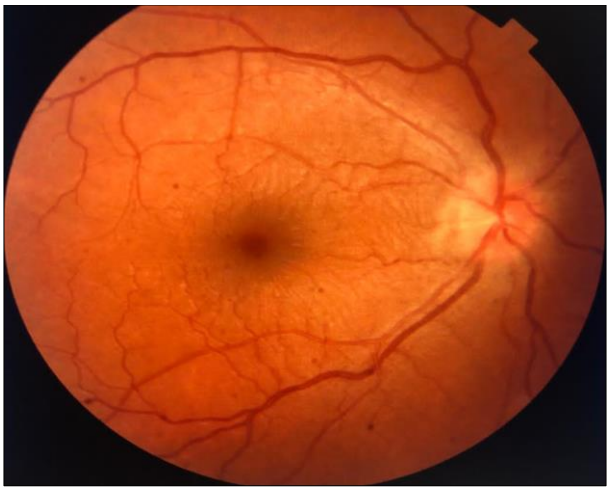

Figure 5 Retinography showed swollen optic discs, cup/disc ratio difficult to assess, tortuous vessels, free macules and retinal exudative detachment below the macula

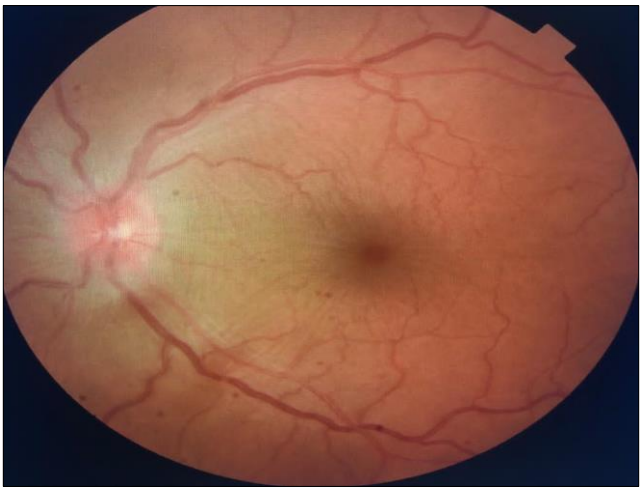

Figure 6 Retinography showed swollen optic discs, cup/disc ratio difficult to assess, tortuous vessels, free macules and retinal exudative detachment below the macula

Fluorescein angiography of the LE revealed hyperfluorescence and blurring of the optic disc. (Figure 7) and optical coherence tomography showed serous macular detachment of the LE. (Figure 8)

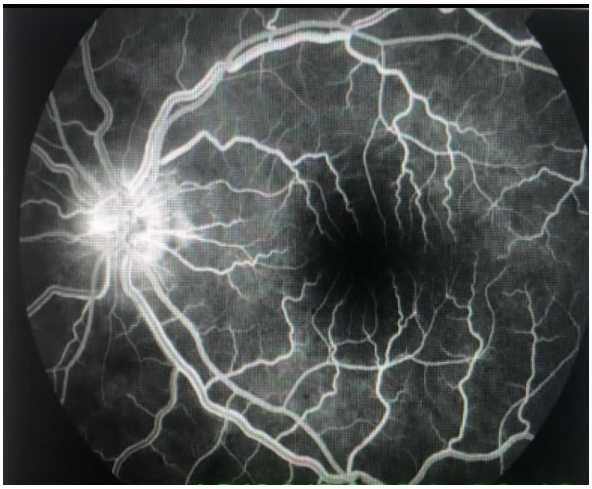

Figure 7 Fluorescein angiography of the LE revealed hyperfluorescence and blurring of the optic disc

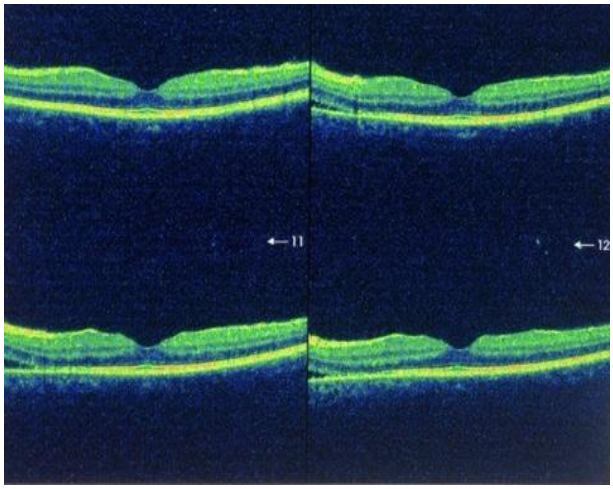

Figure 8 Optical coherence tomography showed serous macular detachment of the LE

Oral corticosteroid therapy (2mg/kg/day prednisone) was performed, with symptom improvement after 3 weeks. The uveitic episode went into remission and the patient is under regular follow-up by the retinal sector and uveitis without recent uveitic episodes.

3. Discussion

The VKH Syndrome presents clinically in four stages: prodromal, uveitic, chronic and recurrent. The prodromal one usually lasts from three to five days and is characterized by generalized constitutional symptoms, in addition to headache, meningismus, and orbital pain and tearing, manifestations present in both patients in the case [1,4,7,9,12,18].

The uveitic or acute state can last weeks to months and is characterized by bilateral ophthalmopathy, which is marked by transient conjunctival hyperemia, ocular pain, and bilateral posterior uveitis. At this stage, otorhinolaryngological symptoms also appear, such as bilateral sensorineural hearing loss, associated with tinnitus in 50% of cases, dizziness and a feeling of discomfort, symptoms also present in patients [14,17,19-21].

The chronic form lasts for months to years, being marked by pigmentary changes, such as eyelash, eyebrow and hair poliosis, and symmetrical vitiligo of the face, trunk, sacral region and gluteal region. In the uvea, these changes appear approximately three months after the onset of symptoms and appear mainly as choroidal depigmentation, known as sunset glow image, and Dalen-Fuchs nodules, findings present only in the first patient [8,14,15,18,19].

Finally, the recurrent phase, marked by panuveitis associated with recurrent episodes of anterior uveitis and the development of ocular complications such as cataract, glaucoma, subretinal neovascular membrane, and subretinal

fibrosis were not present. The patient in the first case showed this phase with anterior uveitis, with keratic precipitates and with posterior synechiae. [7,8,9,13,17] In addition, probable recurrent cases of serous retinal detachment were evidenced through the appearance of diffuse atrophy of the pigmented epithelium.

In addition to identifying diagnostic criteria throughout the phases, our patients epidemiologically fit into the most prevalent group, which is composed of female patients in the third and fourth decades of life [1,3,5,6,15].

Therefore, to avoid delay in treatment and the development of vision-threatening complications, which tend to occur primarily in patients with long-standing ocular inflammation, it is important to recognize the variable clinical presentations of the disease. The use of diagnostic imaging methods, such as optical coherence tomography, is essential to monitor disease activity, in order to promote early treatment and prevent the development of ocular complications [2,9,17,20-22].

Early aggressive treatment with systemic corticosteroids during the acute phase is recommended. The use of immunomodulatory agents such as Azathioprine, Mycophenolate Mofetil and Cyclosporine reduced the risk of developing eye complications. However, a considerable number of patients still progress to chronic stages, suffer relapses and progress to visual loss, probably due to undetectable and undertreated subclinical inflammation [8,11,18,21-24].

4. Conclusion

The rarity of VKH Syndrome makes its diagnosis a challenge, but speed in diagnosis and treatment are essential. Although the clinical criteria for the syndrome are well established, there is often great difficulty in diagnosing it due to the fact that patients present at different stages of development of the disease at the time of their consultation and its manifestations are often not perceived in their proper chronological order of appearance.

To avoid underdiagnosis and increase therapeutic precocity, it is worth mentioning that patients with deafness, tinnitus and dizziness should always be considered as having VKH. In addition, multidisciplinary assessment optimizes adequate systemic assessment and follow-up, since early diagnosis and a multidisciplinary approach are key components of the management of this complex syndrome.

Compliance with ethical standards

Acknowledgement

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Disclosure of conflict of interest

The author, the co-authors, the guiding professor and the reviewer suggested for evaluation of the work entitled Vogt-Koyanagi-Harada Disease Diagnosed in Members of the Same Family do not present any form of conflict of interest regarding the above

Statement of informed consent

Informed consent was obtained from all individual participants included in the study."

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