

CLINICAL PROFILE OF VOGT-KOYANAGI-HARADA SYNDROME IN A TERTIARY EYE CARE CENTRE

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ABSTRACT

BACKGROUND

Vogt-Koyanagi-Harada syndrome is a granulomatous panuveitis with multisystemic manifestations. It is characterised by exudative retinal detachments, cutaneous and neurological manifestations.

The main aim of this study is to document the epidemiological features, diverse clinical manifestations, angiographic and optical coherence tomography and characteristics of VKH disease.

MATERIALS AND METHODS

20 patients who were diagnosed as Vogt-Koyanagi-Harada syndrome were included in the study after applying appropriate inclusion and exclusion criteria were included in the study.

RESULTS

20 patients were included in the study, which included 18 females (90%) and 2 males (10%). The mean age of the study population was 39.21 years. All patients presented with complaints of defective vision, 17 patients (85%) had bilateral loss of vision and 3 patients (15%) had unilateral defective vision. One patient (5%) had poliosis and vitiligo and one patient (5%) had alopecia. The mean Best Corrected Visual Acuity (BCVA) at presentation was 1.33 LogMAR units. The mean post-treatment BCVA was 0.28 LogMAR units. The improvement in visual acuity following treatment was found to be statistically significant with a 'p' value <0.05. 17 patients (85%) presented with bilateral exudative retinal detachment. 26 eyes (70.27%) showed extensive exudative retinal detachment. 10 eyes (27.02%) showed multifocal exudative retinal detachment. All patients were treated with systemic corticosteroids resulting in decrease in inflammation and resolution of exudative retinal detachments. Patients whose inflammation was refractory to systemic corticosteroids were treated with immunosuppressants, namely azathioprine (1 patient, 5%).

CONCLUSION

In summary, Vogt-Koyanagi-Harada disease is a bilateral, diffuse, granulomatous uveitis associated with vitiligo, poliosis, alopecia, central nervous system and auditory signs, which responds to appropriate systemic steroid therapy.

KEYWORDS

Serous Detachment, Vogt-Koyanagi-Harada Syndrome, Panuveitis.

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BACKGROUND

Vogt-Koyanagi-Harada's disease (VKH disease) is an acute inflammatory immune-mediated noninfectious panuveitis, which typically affects both eyes of middle-aged adults. Poliosis with associated ocular inflammation was first described by Ali-ibn-Isa and Schenkl in 1873 by Hutchinson in 1892 and by Vogt in 1906. Harada reported cases of primary posterior uveitis with exudative retinal detachments

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in association with cerebrospinal fluid pleocytosis in 1926.¹ Koyanagi described patients with bilateral chronic iridocyclitis, patchy depigmentation of the skin, patchy hair loss and whitening of the hair and eyelashes in 1929. This constellation of findings was then combined by Babel in 1932 and by Bruno and McPherson in 1949 to represent a continuum of the same disease process, thereafter recognised as VKH syndrome. Melanocyte-containing organs such as the skin, ear, meninges and eye can be involved. Acute exudative panuveitis occurs in both eyes and causes visual loss.² Acute phase of the disease is characterised by neurosensory retinal detachments associated to multiple loci of aggressive choroidal exudation. Optic disc swelling may be associated in 70% of patients. A large dose of systemic steroids is a rewarding treatment for rapid resolution of exudative lesions.³ Immunosuppressants play a significant role in patients with suboptimal response to steroids and in those requiring long-term steroid therapy.

Aims and Objectives

The main aim of this study is to document the epidemiological features, diverse clinical manifestations, angiographic and optical coherence tomography characteristics of VKH disease.

MATERIALS AND METHODS

This was a retrospective study, which was conducted at Regional Institute of Ophthalmology and Government Ophthalmic Hospital from November 2015 to June 2017. A total of 20 patients who were labeled with the diagnosis of VKH disease according to the Revised Diagnostic Criteria for Vogt-Koyanagi-Harada Disease³ were included in the study. Patients with coexistent diabetes mellitus, recent history of ocular surgeries were excluded from the study. All the patients underwent detailed ophthalmic evaluation including recording Uncorrected Visual Acuity (UCVA), Best Spectacle Corrected Visual Acuity (BSCVA) using Snellen’s visual acuity chart (this was then converted to LogMAR for statistical purposes). Intraocular pressure measurement using Goldman’s applanation tonometer was done. A detailed slit-lamp examination and fundus assessment using slit-lamp biomicroscopy with a +90 D lens and indirect ophthalmoscopic examination was performed.

The patients underwent fundus fluorescein angiography and optical coherence tomography was also performed when needed. Monitoring and follow up of patients was done by taking serial fundus photographs of patients using Kowa VX-10 along with routine fundus examinations.

Statistical Analysis- Statistical analysis was performed using SPSS 22.0.0.0. In order to summarise the data, descriptive statistics, namely mean and percentage were used.

Follow up- The patients were reviewed every week for assessment of visual acuity and for monitoring the resolution of uveitis and serous detachments. Serial fundus photographs were taken to document progression or regression of clinical condition. This was accompanied by optical coherence tomography when necessary.

RESULTS

20 patients were included in the study, which included 18 females (90%) and 2 males (10%). The mean age of the study population was 39.21 years (range 27-49, standard deviation 10.8, median 32) (Table 1).

| | |
|---------------------------|-------------|
| Number of Patients | 20 |
| No. of eyes | 37 eyes |
| No. of males | 2 |
| No. of females | 18 |
| Mean age | 39.21 years |
| Median age | 32 |
| Age range | 27-49 years |

Table 1. Demographic Features of Our Study Population

Prodromal symptoms included headache in 12 patients (60%), ocular pain in 6 patients (30%) and tinnitus and

hearing loss in 2 patients (10%). There was no evidence of fever or neck rigidity in any patient.

All patients presented with complaints of defective vision, 17 patients (85%) had bilateral loss of vision and 3 patients (15%) had unilateral defective vision. One patient (5%) had poliosis and vitiligo and one patient (5%) had alopecia.

The mean Best Corrected Visual Acuity (BCVA) at presentation was 1.33 LogMAR units. The mean post-treatment BCVA was 0.28 LogMAR units. The improvement in visual acuity following treatment was found to be statistically significant with a ‘p’ value <0.05. This indicates that the visual prognosis of patients with VKHS was fairly good following adequate treatment (Figure 1).

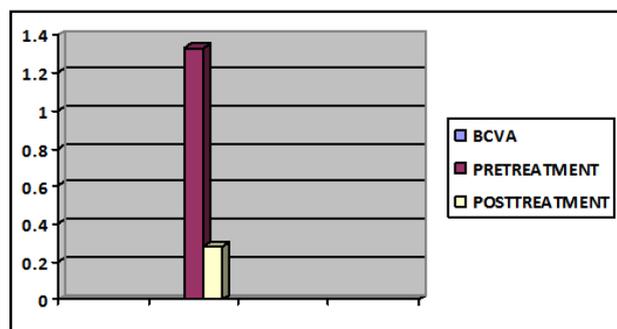


Figure 1. Visual Acuity of Patients before and after Steroid Therapy

All patients presented with exudative retinal detachment. 17 patients (85%) presented with bilateral exudative retinal detachment. 26 eyes (70.27%) showed extensive exudative retinal detachment. 10 eyes (27.02%) showed multifocal exudative retinal detachment. 3 patients (15%) presented with exudative retinal detachment in one eye. One patient (5%) presented with bilateral sunset glow fundus. 12 eyes (32.43%) had anterior uveitis. 11 eyes (29.72%) had cells in the vitreous. 7 eyes (18.9%) had optic disc oedema. The mean intraocular pressure was 12.68 mmHg (SD 3.58). None of the patients had Dalen-Fuchs nodules or Sugiura’s sign (Table 2). One patient had sunset glow fundus in both eyes.

| Clinical Features | Number of Eyes (%) |
|-------------------------|--------------------|
| Extensive exudative RD | 26 (70.27%) |
| Multifocal exudative RD | 10 (27.02%) |
| Anterior uveitis | 12 (32.43%) |
| Vitreous cells | 11 (29.72%) |
| Optic disc oedema | 7 (18.9%) |
| Sunset glow fundus | 2 (5.4%) |

Table 2. Clinical Features in Patients with VKHS Syndrome

Fundus Fluorescein Angiography (FFA) was performed in 18 patients (90%). 33 eyes (89.19%) showed multiple pinpoint hyperfluorescent leaks at the level of the retinal pigment epithelium. 9 eyes (24.32%) revealed staining of the optic disc. Optical coherence tomography was performed in nine patients, which showed multiple serous detachments.

All patients were treated with systemic corticosteroids resulting in decrease in inflammation and resolution of

exudative retinal detachments. Among them, three patients were put on intravenous methyl prednisolone 500 mg twice daily for 3 days followed by tapering dose of oral prednisolone for 3 months. The initial IV loading dose was decided because of the extensive bilateral serous detachments for rapid restoration of vision and resolution of serous detachments. The average initial dose of corticosteroids was 71.42 mg (SD 27.57, range 40 mg to 100 mg). The mean duration of systemic corticosteroid therapy was 4 months (SD 3.2, range 3 months to 14 months). Patients with anterior uveitis were treated with topical steroids and cycloplegic agents. Patients whose inflammation was refractory to systemic corticosteroids were treated with immunosuppressants, namely azathioprine (1 patient, 5%). Two patients (with bilateral involvement) had a recurrence within one month of stopping corticosteroids.

As ocular inflammation and retinal detachments resolve in VKH disease, the fundus undergoes depigmentation. 11 eyes (29.72%) showed fundus pigmentary atrophy. Chronic anterior uveitis was seen in 4 eyes (10.81%). One patient (5%) developed secondary glaucoma, 4 eyes (10.81%) developed cataract and 2 eyes (5.40%) developed subretinal fibrosis. None of the patients developed choroidal neovascular membrane or optic neuropathy (Table 3).



Figure 2. Multiple Serous Detachment in the Posterior Pole in Both Eyes

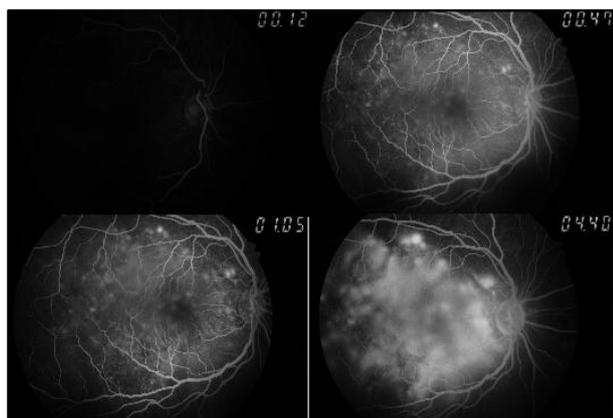


Figure 3. FFA of the Right Eye Showing Hyperfluorescent Pinpoint Leaks Increasing in Intensity in the Late Phase

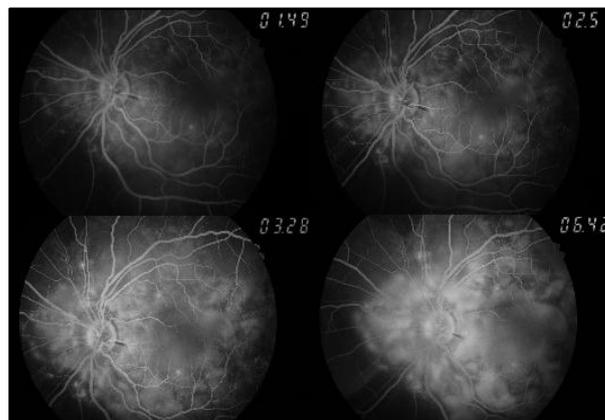


Figure 4. FFA of the Left Eye Showing Hyperfluorescent Pinpoint Leaks Increasing in Intensity in the Late Phase

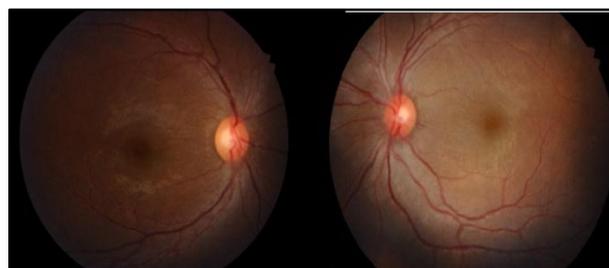


Figure 5. Complete Resolution of the Serous Detachment in Both Eyes After Systemic Steroid therapy

| Complications | No. of Eyes Percentage |
|---------------------------|------------------------|
| Fundus pigmentary atrophy | 11 (29.72%) |
| Chronic anterior uveitis | 4 (10.81%) |
| Secondary glaucoma | 2 (5.40%) |
| Cataract | 4 (10.81%) |
| Subretinal fibrosis | 2 (5.40%) |

Table 3. Complications in Patients with Vogt-Koyanagi-Harada Syndrome

DISCUSSION

VKH syndrome also known as uveomeningitic syndrome is a systemic disorder involving many organ systems including eye, ear, integumentary and nervous system. The disease has been reported throughout the world, but has a predilection for darkly pigmented races. There appears to be some global variation in sexual predilection for VKH. Most studies suggest that women are affected more frequently than men. Most patients are in second to fifth decade of life at the onset of the disease. The exact aetiology is still unknown.⁴ The autoimmune aspect in VKH includes cellular immune response against melanocytes. Matsuda and Sugiura demonstrated close contact between lymphocytes and melanocytes in their patient’s eye. In the study conducted by Agira and Noose, the lymphocytes in the peripheral blood were demonstrated to have activity against B36 melanoma cells. This was also confirmed by studies by McClellane et al, who demonstrated IL2 dependant T cells in patients with VKHS reacted against both normal melanocytes as well as melanoma cells. However, some studies have also demonstrated autoantibodies against photoreceptor outer segments and Muller’s cells in serum of

patients with VKHS. However, these antibodies could be a secondary response, which follows the retinal damage in VKHS patients.⁵

In a study conducted by Zhang et al, HLA-DR4 was identified in 75% of VKHS patients, but only 23.1% in normal controls. A genetic role in VKHS is strengthened by the reports of familial cases.

Clinical manifestations of VKH syndrome depends on the stage of the disease. The four stages are prodromal stage, acute uveitic stage, chronic or convalescent stage and recurrent stage. The prodromal stage will resemble a viral illness characterised by headache, fever, orbital pain, nausea and dizziness, which lasts for 3-5 days. Patients usually complain of blurred vision, photophobia, hyperaemia of the conjunctiva and ocular pain. Uveitic stage presents with blurred visual acuity in both eyes, one eye will be affected first. In 94%, second eye will be affected within 2 weeks. This condition is characterised by thickening of the posterior choroid. This manifests clinically as hyperaemic oedematous optic disc, multiple serous detachments in the posterior pole, which can be extensive retinal oedema with elevation of peripapillary region. When the inflammation increases, it involves the anterior chamber presenting as a granulomatous panuveitis.

Chronic stage also known as the convalescent stage develops weeks after the uveitis has subsided. This characterised by depigmentation of the fundus and development of cutaneous features like poliosis and vitiligo. Perilimbal vitiligo (Sugiura's sign) is also seen in this stage. The sunset glow fundus is due to the depigmentation of the peripheral fundus, which leads to a pale disc and reddish orange choroid.

Recurrent stage consists of panuveitis with acute exacerbation of anterior uveitis. Iris nodules may appear in this stage. During this phase, most of vision-threatening complications like cataract, glaucoma and subretinal neovascularisation will develop.

FFA during acute stage of the disease shows various pinpoint areas of leakage at the level of RPE in early phase. In later phase, the localised hyperfluorescent spots increase in size coalesce and expand into the subretinal space in areas of serous detachment leading to large area of leakage. In chronic stage, the presence of diffuse scattered pigmentary changes with markedly pigmented areas adjoining hypopigmented areas (moth-eaten appearance) are the hallmark.

OCT will demonstrate the presence of subretinal fluid with choroidal thickening. B-scan ultrasonography during acute stage shows diffuse choroidal thickening with low-to-medium reflectivity, serous retinal detachments, vitreous opacities without posterior vitreous detachments and scleral or episcleral thickening. CSF analysis during acute phase will reveal pleocytosis and elevation of protein levels in early stage.

The diagnosis of VKHS is based on the revised diagnostic criteria devised by Read RW et al,³ which classifies VKHS in to complete, incomplete and probable VKHS. The criteria is as follows-

1. No history of penetrating ocular trauma or surgery preceding the initial onset of uveitis.
2. No clinical or laboratory evidence suggestive of other ocular disease entities.
3. Bilateral ocular involvement (a or b must be met depending on the stage of disease when the patient is examined).
 - a. Early manifestations of disease.

Evidence of diffuse choroiditis (with or without anterior uveitis, vitreous inflammatory reaction or optic disk hyperaemia), which may manifest as (a) Focal areas of subretinal fluid or (b) Bullous serous retinal detachments.
 - b. Late manifestations of disease.
 - (i) History suggestive of prior presence of early findings noted in 3a and either (i) or (iii) below or multiple signs from 3.
 - (ii) Ocular depigmentation- either (a) Sunset glow fundus or (b) Sugiura's sign.
 - (iii) Other ocular signs including (a) Nummular chorioretinal depigmented scars, (b) Retinal pigment epithelium clumping and/or migration or (c) Recurrent or chronic anterior uveitis.
4. Neurological/auditory findings (may resolve by time of evaluation).
 - a. Meningismus (malaise, fever, headache, nausea, abdominal pain, stiffness of the neck and back or a combination of these factors); note that headache alone is not sufficient to meet the definition of meningismus.
 - b. Tinnitus.
 - c. Cerebrospinal fluid pleocytosis.
5. Integumentary finding (not preceding onset of central nervous system or ocular disease).
 - a. Alopecia.
 - b. Poliosis.
 - c. Vitiligo.

To diagnose a complete VKHS, all criteria from 1-5 should be present. In an incomplete VKHS, 1-3 with either 4 or 5 should be present. Probable VKHS is an isolated ocular disease in which criteria 1-3 should be present.

Differential diagnosis of VKHS includes other causes of multiple posterior pole serous detachments like multifocal CSCR, posterior scleritis and sympathetic ophthalmia. Multifocal CSCR is usually unilateral occurring in middle-aged men and can be triggered by steroid exposure. Fluorescein angiography in acute CSR shows leaks at the levels of retinal pigment epithelium in two main patterns- smoke stack or inkblot pattern.⁶

Posterior scleritis is usually an unilateral inflammatory condition. The clinical form depends on the location and severity of inflammation. It is common in women presenting in the second decade of life. Most common symptoms are decreased visual acuity due to macular exudation and retro-orbital pain increases with extraocular movements. Ocular ultrasonography shows marked thickening of the sclera.

Retrobulbar oedema surrounding the optic nerve called T sign is seen in B scan ultrasonography.

Sympathetic ophthalmia is differentiated by the history of a previous ocular trauma or rarely intraocular surgeries. Other rare differential diagnosis includes primary B cell lymphoma, ocular Lyme disease, sarcoidosis, acute multifocal posterior pigment epitheliopathy and uveal effusion syndromes.

Treatment of VKHS involves high-dose steroids of 1-1.5 mg/kg, which is tapered slowly over a period of 3-6 months. Rapid tapering of steroids causes recurrence in first 3-6 months in 43%-52% of patients.⁷ Some authors also advocate a pulse steroid intravenous therapy before oral steroids. Cytotoxics and immunosuppressive agents are reserved for the cases, which are refractory to steroids and intolerant to steroids.

Three major complications in VKHS are cataract, glaucoma and subretinal neovascularisation.

CONCLUSION

In summary, Vogt-Koyanagi-Harada disease is a bilateral, diffuse, granulomatous panuveitis, which occurs more in females of the middle age. Presence of bilateral extensive serous detachments with intraocular inflammation and prodromal symptoms should raise the suspicion of Vogt-Koyanagi-Harada syndrome. Institution of prompt systemic steroid therapy or immunosuppressive therapy helps in the control of inflammation and prevention of complications.

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