Vogt-Koyanagi-Harada syndrome: Experience in a Belgian university hospital and review of the literature

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ABSTRACT

Introduction: The Vogt-Koyanagi-Harada syndrome (VKHS) is rare in Europe. Bilateral panuveitis is the defining characteristic, but the disease can affect other tissues containing melanin, such as the inner ear, the meninges, and the skin. Therefore, patients may present not only to ophthalmologists, but also to internists, dermatologists, ENT-physicians and neurologists. Early and aggressive immunosuppressive treatment is necessary in order to prevent permanent visual loss or systemic complications.

Objective: We retrospectively studied 12 patients diagnosed and treated in a specialized uveitis clinic in Leuven (Belgium) between 2005 and 2013, and we compared our data with literature.

Results: The most common extra-ocular manifestations were neurological, with headache (100%) and lymphocytic meningitis (75%) as main findings. Tinnitus was present in 50%, and vertigo in 42%. Vitiligo was the most frequent dermatological manifestation and present in 42%. Uveitis recurred in 67% of patients with 1 to 4 relapses per patient and a median time to recurrence of 6 months (range 1-11). Normal visual acuity was seen in 75% of patients at the end of follow-up (5 to 60 months), but 3 patients had at least some degree of permanent visual impairment in at least one eye.

Conclusion: VKHS is a rare, multisystem disorder, characterized by bilateral uveitis and variable neurologic, auditory and skin symptoms. A lumbar puncture increases the diagnostic yield. A fast diagnosis allows timely initiation of adequate therapy, and if treated correctly, VKHS has a favorable prognosis. It is unclear if initial intravenous therapy improves frequency and time to remission.

Key Words: Vogt-Koyanagi-Harada syndrome, Lymphocytic meningitis, Uveitis

1. INTRODUCTION

Vogt-Koyanagi-Harada syndrome (VKHS) is a rare and potentially severe multisystem autoimmune disease that affects tissues containing melanin, such as the eye, the inner ear, the meninges, and the skin. The autoimmune destruction of melanocytes leads to a bilateral panuveitis, with a variable involvement of ears (tinnitus, hearing loss or vertigo in 50%-75% of patients), central nervous system (meningitis in 80%) and skin (vitiligo, alopecia or poliosis [decrease or loss of pigmentation in the scalp hair or any hairy area] in 25%-60%). The most consistent and distinctive feature is the ocular involvement with a symmetric, bilateral, diffuse panuveitis in all patients.

The exact etiology remains unknown, but most likely an infectious trigger (e.g. Epstein Barr virus infection) leads...
to an immune mediated destruction of melanocytes, in a genetically susceptible host (e.g. HLA-DRB1*0405).\[^{1,2}\]

VKHS is responsible for only a small percentage of uveitis (1%–8% depending on the series\[^{3}\]). It is more common in women, with a female/male ratio of 2 to 1, and usually occurs between the age of 20 and 50 years, with a peak in the third decade. The syndrome is more frequent in people with darker skin pigmentation (e.g. in Asia, the Middle East and South America), but it is rare in the African population. The presence of extra-ocular symptoms varies in different ethnic groups.\[^{2–4}\]

The classic clinical course of VKHS can be divided into 4 clinical stages.\[^{3}\] The prodromal phase is short (days) and resembles a viral infection, with non-specific symptoms as fever, nausea, headache and photophobia, and is associated with a lymphocytic pleocytosis of the cerebrospinal fluid (CSF). This pleocytosis persists for weeks,\[^{5}\] and after 3 to 5 days the majority of the patients will progress to the acute uveitic phase, consisting of an acute bilateral panuveitis presenting with blurred vision, photophobia, conjunctival injection, and possible visual loss; auditory manifestations usually occur in this phase. The convalescent phase is characterized by depigmentation of the skin and the choroid membrane. About 2 in 3 patients evolve into a chronic recurrent phase, characterized by recurrent episodes of uveitis.

### Table 1. Vogt-Koyanagi-Harada revised diagnostic criteria (2001)^7^

| Complete disease (criteria 1 to 5 must be present) |
|--------------------------------------------------|
| 1)  No history of penetrating ocular trauma or surgery |
| 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 |
| - diffuse choroiditis (focal areas of subretinal fluid, bullous serous retinal detachments) |
| OR |
| - characteristics fluorescein angiography findings AND echographic evidence of diffuse choroidal thickening |
| b)  Late manifestations |
| - history suggestive of prior uveitis with the above described characteristics AND, ocular depigmentation (sunset glow fundus, Sugiura sign\[^{#}\]) |
| - AND other ocular signs (nummular chorioretinal depigmented scars, retinal pigment epithelium clumping and/or migration, or recurrent or chronic anterior uveitis) |

| 4)  Neurological/auditory findings. |
| - Meningismus OR tinnitus, OR cerebrospinal fluid pleocytosis |

| 5)  Dermatological manifestations |
| - alopecia, OR vitiligo, OR poliosis\[^{†}\] |

Incomplete disease (criteria 1 to 3 and either 4 or 5 must be present)

Probable disease (isolated ocular disease; criteria 1 to 3 must be present)

\(^{#}\) Sugiura sign is when perilimbal vitiligo is present at ophthalmological examination.

\(^{†}\) Poliosis is the decrease or absence of melanin (or color) in head hair, eyebrows, eyelashes or any other hairy area.

The diagnosis of VKHS is based on clinical diagnostic criteria (see Table 1). The most frequently used criteria are the 2001 Revised Diagnostic Criteria established by the International Nomenclature Committee.\[^{6–8}\] These criteria divide patients in three groups according to the diagnostic certainty (complete, incomplete and probable VKHS), and thus allow diagnosis both in the acute and in the chronic phase, and even in the absence of neurological or dermatological manifestations.\[^{3,6}\] In the differential diagnosis, it is important to exclude other inflammatory causes of an uveo-meningeal syndrome (e.g. Behçet’s disease or sarcoidosis), as well as infections or malignancy.\[^{9}\]

Early (< 15 days) and aggressive treatment with high dose corticosteroids (1-2 mg oral prednisolone per kg per day +/- intravenous pulses of 1 g methylprednisolone during the first 3 days) is the first-line treatment in the acute uveitic phase, in order to prevent recurrent uveitis and to avoid evolution to a chronic phase. Intravitreal injections can be applied to treat intra- or subretinal fluid.\[^{10,11}\] Second or third line immunomodulating therapy (e.g. methotrexate, azathioprine, cyclosporine, rituximab, adalimumab) is given in case of corticosteroid resistance or side effects.\[^{1–4,10–15}\] Ocular complications linked to both disease activity and treatment may lead to permanent visual loss after extinction of the uveitic phase.\[^{3,10}\]

The visual prognosis of VKHS varies and depends mainly on early diagnosis and rapid appropriate treatment.\[^{10}\] The most important factor associated with poor prognosis is inadequate
treatment: start of corticosteroids more than 15 days after onset, at a suboptimal dose or for less than six months.\textsuperscript{16}

We performed a retrospective case series review from an internist’s viewpoint, focusing on the extra-ocular manifestations in patients presenting with VKHS in a Belgian referral hospital. Our aim was to describe patient characteristics in our population, and to compare them with literature data.

Table 2. Summary of the main characteristics of the 12 VKH-patients

| Gender, age, origin | Symptoms (a) and clinical phase (b) | Lumbar puncture (1) | Treatment (2): delay (a) and first-line (b) | Relapse: frequency and average time (months) | Complications outcome (b) | Follow-up (months) |
|---------------------|------------------------------------|---------------------|--------------------------------------------|------------------------------------------|--------------------------|-----------------|
| Pt 1: F, 39, Morocco | Loss of vision, conjunctival injection, headache, vertigo | -                   | 408 WBC, 95%, lymphocytes protein 153 glycemia 50 | (a) 7 days CS 32 mg tapering for 12 m | (a) Complete remission after 42m, normal vision | 60 m |
| Pt 2: F, 24, Belgium | Loss of vision, headache, tinnitus | -                   | 288 WBC, 95%, lymphocytes protein 653 glycemia 40 | (a) 28 days CS IV, CS 64 mg tapering for 6 m | (a) Bilateral cataract, subretinal fibrosis Complete remission after 13m, normal vision | 45 m |
| Pt 3: F, 37, Belgium | Loss of vision, headache, nausea, tinnitus, vitiligo, alopecia | -                   | 0.4 WBC protein 538 glycemia 51 | (a) CS 32 mg tapering for 6 w | (a) OD: Cataract en glaucoma OD: persistent retinal edema without inflammation | 40 m |
| Pt 4: M, 51, Bangladesh | Loss of vision, conjunctival injection, headache, photophobia | -                   | 323 WBC, 98%, lymphocytes protein 643 glycemia 65 | (a) 10 days CS IV, CS 64 mg tapering for 6 m | (a) Complete remission after 21m, normal vision | 40 m |
| Pt 5: F, 44, Belgium | Loss of vision, conjunctival injection, headache, photophobia, vertigo, vitiligo | Convalescent phase | 88 WBC, 96%, lymphocytes protein 460 glycemia 56 | (a) 3 days CS IV, CS 64 mg tapering for 6 m | (a) Complete remission after 3 m, normal vision | 19 m |
| Pt 6: M, 51, Morocco | Loss of vision, headache | -                   | 78 WBC, 94%, lymphocytes Protein 542 glycemia 68 | (a) 5 days CS IV, CS 64 mg tapering for 12 m | (a) Complete remission after 11 m, normal vision | 11 m |
| Pt 7: M, 42, Ethiopia | Loss of vision, headache, photophobia, tinnitus, vitiligo | Convalescent phase | 2 WBC protein 742 glycemia 58 | (a) 7 days CS 64 mg tapering for 6 m | (a) No remission, recurrent uveitis with impaired vision | 33 m |
| Pt 8: F, 32, Morocco | Loss of vision, conjunctival injection, headache, photophobia, vertigo, tinnitus, vitiligo, polyopia | Convalescent phase | 2.2 WBC protein 529 glycemia 74 | (a) 105 days CS 64 mg tapering for 3 m | (a) OD: Persistent inflammation and impaired vision | 34 m |
| Pt 9: F, 30, Armenia | Loss of vision, headache | Uveitic phase | 78 WBC, 98%, lymphocytes protein 591 glycemia 58 | (a) 17 days CS 64 mg tapering for 3 m | (a) Complete remission after 6m, normal vision | 14 m |
| Pt 10: F, 27, Morocco | Loss of vision, conjunctival injection, headache, nausea, vertigo, tinnitus, hearing loss | Uveitic phase | 139 WBC, 100%, lymphocytes protein 637 glycemia 47 | (a) 21 days CS IV, CS 64 mg tapering for 6 m | (a) OS: Cataract Recurrent uveitis, stable inflammation and normal vision at end of follow-up | 17 m |
| Pt 11: M, 29, Spain | Loss of vision, conjunctival injection, headache, photophobia, nausea, vertigo, tinnitus | Uveitic phase | 104 WBC, 97%, lymphocytes protein 421 glycemia 50 | (a) 120 days CS 64 mg tapering for 3 m | (a) Complete remission after 2 m, normal vision | 7 m |
| Pt 12: F, 48, Belgium | Loss of vision, headache, vitiligo | Uveitic phase | 21 WBC, 98%, lymphocytes protein 489 glycemia 56 | (a) CS 16 mg tapering for 3 m | (a) OS: Cataract, atrophy iris and ciliary body Normal vision | 35 m |

2. METHODS

A database with all patient records from the specialized uveitis clinic from 2005 to 2013 was questioned through the electronic patient file system for the terms “VKH” or “Harada” in the “Conclusion/Decision” field of the medical reports. The selected patient files were then manually reviewed. Based on the revised diagnostic criteria of 2001 (see Table 1), 13 patients were included in the study. Patient files were reviewed for demographic data (gender, age, and ethnicity), duration of follow-up, stage of disease, ocular and extra-ocular manifestations, presence of symptomatic lymphocytic meningitis, differential diagnosis, treatment and
side effects, number of recurrences, complications and time to complete remission. One patient was excluded from further study because of insufficient information about diagnosis and treatment duration.

Ophthalmologic evaluation consisted of slit lamp biomicroscopy, ocular tonometry, funduscopic examination, optical coherence tomography (OCT) and a fluorescein angiogram. Visual acuity was tested with the Snellen chart, and reported as a decimal scale. Normal vision was defined as 0.8 or more on the decimal visual acuity scale. Complete ophthalmological remission was defined as the absence of signs of active disease during ophthalmologic evaluation at the end of follow-up.

The study was approved by the Ethics Board of Leuven University Hospitals.

3. RESULTS

Patient characteristics at diagnosis of the 12 patients included in the study are listed in Table 2. Follow-up time ranged from 7 to 60 months (median 33 months). Median age at diagnosis was 34 years (range 24 to 51 years). Eight (67%) patients were female.

At presentation, four (33%) patients were initially classified as complete VKHS, the remaining 8 (67%) patients as incomplete VKHS. During follow-up 2 patients (patients 4 and 9) developed alopecia and evolved from incomplete VKHS to complete VKHS. None of the patients presented in the prodromal phase, 8 (67%) patients presented in the acute uveitic phase, 3 (25%) in the convalescent phase, and 1 (8%) in the chronic recurrent phase.

The majority of patients (n = 10; 83%) presented initially via the ophthalmology department, and two patients (17%) via the internal medicine department. Half of the patients self-referred at our hospital, the remainder was referred by an external specialist. Time between first symptoms and the first presentation at our hospital was recorded for 10 patients, and ranged from 3 to 64 days (median 10 days).

The incidence of the ocular and extra-ocular symptoms and signs is shown in Table 3. Most frequent symptoms were headache and decrease of vision, in all patients (100%). Only 5 patients (42%) mentioned meningeal signs, but lumbar puncture was performed in all patients, revealing a sterile lymphocytic meningitis in 9 (75%) of them. Of the 3 patients without confirmed lymphocytic meningitis, 2 also complained of photophobia, probably due to the uveitis. The most frequent auditory and cutaneous manifestations were tinnitus (n = 6; 50%) and vitiligo (n = 5; 42%) respectively.

3.1 Diagnostic tests performed

The choice of technical investigations was made by the attending ophthalmologist in consultation with an internist and/or a neurologist. To exclude infectious or other inflammatory causes, extensive serology (at least syphilis, Lyme disease, sarcoidosis) and a basic immunology screen (antinuclear antibodies) were done in all patients, and also testing for tuberculosis was performed (QuantiFERON or tuberculin skin test). Additionally, a chest X-ray was performed in search for clues suggestive for sarcoidosis or active tuberculosis. In the majority of cases (n = 10; 83%), also a brain MRI was performed, to exclude an underlying lymphoma or retroocular tumor. A mild increase of inflammatory parameters (C-reactive protein, CRP, and erythrocyte sedimentation rate, ESR) was only seen in 4 patients (CRP range 7-20 mg/L, ESR 13-27 mm/h). Three (25%) patients had mild liver test abnormalities (less than 2 times the upper limit of normal).

3.2 Therapy

Corticosteroids were used as first-line therapy in all patients. The time between first symptoms and start of corticos-
steroids ranged from 3 to 120 days with a median of 13 days. Seven patients were started on high-dose oral prednisone, the other 5 patients received pulse doses of methylprednisolone 1 g intravenously daily for 3 days. The dose of corticosteroids was gradually tapered over a long period of time. In case of relapse, several immunomodulating drugs were used: methotrexate (n = 8; 67%), adalimumab (n = 3; 25%), azathioprine (n = 2; 17%) or cyclosporin (n = 2; 17%). Immunomodulating therapy was prescribed in 10 (83%) patients and never as a first-line treatment. Topical steroids were used in all patients, either as an addition to the initial treatment or in case of recurrent uveitis.

Of the 5 patients receiving intravenous steroids first, 4 (80%) reached complete remission, after a median of 12 months (range 3-21). Of the 7 patients receiving oral steroids first, 3 (43%) reached complete remission, after a median of 6 months (range 2-42).

### 3.3 Long term follow-up
After treatment with corticosteroids, the vision of all patients improved when compared to baseline.

Three patients (25%) had severe visual loss in at least one eye at the end of follow up, ranging from 0.125 to 0.5 on the decimal visual acuity scale. Complete ophthalmological remission with visual acuity of ≥ 0.8 was achieved in 7 (58%) patients after a median period of 11 months (range 2-42); two additional patients had normal vision at the end of follow-up without achieving complete ophthalmological remission. Therefore 9 of the 12 patients (75%) patients had a normal vision at the end of follow-up.

Nineteen episodes of recurrent uveitis were documented in 8 patients, mainly after reduction or withdrawal of the corticosteroids. Patients suffered 1 to 4 relapses. Median time to relapse was 6 months (range 1-11 months). Of the 5 patients treated initially with intravenous steroids, 3 patients had a total of 6 relapses (range 1 to 3). Of the 7 patients treated initially with oral steroids, 5 patients had a total of 13 relapses (range 1 to 4).

Ocular complications linked to the underlying disease or treatment occurred in 5 (42%) patients, and consisted of cataract (n = 5; 42%), glaucoma (n = 1; 8%), ciliary body atrophy (n = 1; 8%), and subretinal fibrosis (n = 1; 8%). Cataract was treated with phaco-emulsification in all cases.

### 4. DISCUSSION
Our aim was to describe a series of VKHS patients from an internist’s viewpoint. As VKHS is a diverse syndrome, with symptoms that are often volatile, variable in time and affected by treatment, a good history and a full clinical examination are crucial. Therefore, a general physician can certainly play an important role in the diagnostic process. The age and gender distribution of our patients, with twice as many women as men and a median age of 34 years at diagnosis, is consistent with literature.17,18

A comparison of extra-ocular symptoms between previous and the present case series is presented in Table 4, showing a higher frequency of extra-ocular manifestations reported in our population. Especially headache seems to be more frequently in our patients (100% vs. 49%-67% in older case series). A possible explanation could be that a neurologist was involved in every diagnostic procedure, performing a lumbar punctures and taking a thorough history from the patient focusing on neurological symptoms. Also auditory symptoms were more frequently reported (tinnitus in 50% vs. 16%-36% in previous series) and vertigo in 42% vs. 2%-8% in previous series. Vitiligo as a dermatological manifestation seemed to be more frequent (33% vs. 5%-15%), affecting 3 out of 5 of the Caucasian patients.

Our data show that, even in the absence of signs of meningeal irritation, a lymphocytic meningitis was found in the acute uveitic phase of VKHS (8/8 patients vs. 80% of patients in

| UZ Leuven (present study) | USA Rao et al. [18] | USA Beniz et al. [17] | Canada Ehmann et al. [20] | Turkey Tutkun et al. [21] |
|--------------------------|--------------------|-----------------------|---------------------------|--------------------------|
| n = 12                   | n = 180            | n = 48                | n = 19                     | n = 45                   |
| Headache 100             | 49                 | 67                    | 53                        | 59                       |
| Menigism 42              | 33                 | 69                    | 16                        | 73                       |
| Tinnitus 50              | 36                 | 17                    | 16                        | 31                       |
| Vertigo 42               | -                  | 8                     | -                         | 2                        |
| Vitiligo 33              | 5                  | 10                    | 0                         | 16                       |
| Alopecia 8               | 10                 | 13                    | 26                        | 11                       |
| Poliosis 8               | 5                  | 6                     | 16                        | 13                       |

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previous series). A lumbar puncture therefore seems mandatory, not only to exclude other causes of headache (such as infectious meningitis), but also to accelerate diagnosis of VKHS and to determine those patients with acute uveitis that will benefit from rapid administration of high dose intravenous steroids. The data thus emphasize that headache and general symptoms may be more frequent signs of underlying meningitis than objective signs (e.g. nuchal rigidity), and that the absence of the latter should not be an argument to refrain from performing a lumbar puncture in all patients with a suspicion of VKHS, not only those with clear signs of meningitis.

Brain MRI was done in 10 (83%) patients, primarily to exclude underlying malignancy or demyelinating disease. Meningeal enhancement was seen in none of our patients, so this sign does not appear to contribute to the detection of the diagnosis in an early stage, in contrast to what was previously suggested by Lohman et al. [19]

According to therapeutic guidelines, initial treatment in all our patients consisted of high dose corticosteroids, either by mouth or intravenously. The use of intravenous pulse therapy as an initial treatment is still controversial, and has not yet proven to result in better visual acuity afterwards [3, 10, 11, 13]. In our case series patients seemed to reach complete remission more often (80% vs. 42%) when treated with iv steroids initially.

Treatment of less than 6 months or started after 15 days is known to be associated with more relapses and worse visual outcome [10, 11, 13]. Because a delay of referral after the onset of symptoms (median of 10 days, range 3-64 days) and diagnosis, 5 patients in our study were started late (after > 15 days) on therapy, with complete remission in 3 patients. Four of the five patients who were started on corticosteroids within the advised 15 days had a complete remission.

Although ocular complications occurred in 5 patients, nine (75%) patients had a normal vision at the end of the follow-up, which confirms previous data that VKHS generally had a favorable outcome if treated correctly. Recurrent uveitis occurred in 8 out of 12 patients during follow-up, with a total of 19 relapses. This reflects the chronic nature of the disease, necessitating a long-term treatment, preferably with a corticosteroid-sparing regimen. [16]

Our study has several limitations. It is a retrospective study of a series of patients, selected by their referral to a university hospital, probably because of more severe disease: comparison with the general Belgian population is therefore not possible. This is similar, however, to literature data, also mainly originating from referral centers. As our series is small, our aim was not to obtain statistically significant associations, but rather to describe symptoms, signs and outcome of VKHS patients referred to a university hospital.

5. CONCLUSION

VKHS is a rare, multisystem disorder, and patients may therefore present not only to ophthalmologist (to whom the syndrome is probably better known), but also to internists, dermatologists, ear-nose-throat-physicians and neurologists. A delay in diagnosis may lead to a delay in adequate therapy and to a prolonged disease course with important morbidity through diminished visual acuity in one or both eyes. We therefore hope that this overview contributes to increasing awareness of this rare syndrome and to a faster diagnostic and therapeutic process for the patients with VKHS.

CONFLICTS OF INTEREST DISCLOSURE

The authors declare that there is no conflict of interest regarding the publication of this paper.

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