

Spectrum and visual outcomes of Vogt-Koyanagi-Harada disease in Argentina

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Abstract

• **AIM:** To review all cases of Vogt-Koyanagi-Harada (VKH) disease in an Inflammatory Eye Disease Service in Argentina and to describe the clinical profile and outcomes of treatment.

• **METHODS:** The records from patients with VKH disease between January 1980 and December 2008 were retrospectively analyzed for clinical profile, complications, and treatment. Patients were classified according to their initial treatment in group 1: high corticosteroid dose [≥ 1 mg/(kg·d)] within 2wk of illness onset; group 2: high corticosteroid dose, 2 to 4wk of onset and group 3: patients who received the high dose after 1mo of illness onset, patients who received lower oral doses than 1 mg/(kg·d) without regarding the time of beginning of the disease.

• **RESULTS:** A total of 210 eyes of 105 patients were included. The mean age at presentation was 32.6 ± 13 y (range: 10-74y), and 86.7% were female. The mean duration of follow up was 144 ± 96.6 mo. Patients in the group 1 had significantly higher visual acuity than the other groups ($P < 0.0001$), none had (loss of, or no) light perception at the end of follow up, whereas 24.7% patients in group 3 ended in light perception ($P < 0.004$).

• **CONCLUSION:** Patients with early high dose corticosteroid treatment have better visual acuity and fewer complications. Proper timing in referral and treatment is critical for better visual outcome in VKH disease.

• **KEYWORDS:** Vogt-Koyanagi-Harada disease; Argentine population; clinical spectrum; treatment

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INTRODUCTION

Vogt-Koyanagi-Harada (VKH) disease is a systemic illness of autoimmune etiology. Tissues containing pigmented cells (ear, integumentary and central nervous system) are involved. Therefore, clinical manifestations are seen at these locations. The role of Th1 and Th17 CD4+ lymphocytes which express IFN- γ and IL-17, respectively, has been suggested in the pathogenesis of VKH disease^[1]. The natural history of VKH disease can be divided into 4 stages: prodromal, acute-uveitic, chronic, and chronic recurrent^[2]. Clinical manifestations depend on the stage at which the patient is examined. Patients presenting soon after the onset of the disease may complain of auditory and neurologic manifestations followed by decreased vision due to exudative retinal detachments and optic disk hyperemia. Conversely, a patient presenting months to years after the initial episode will have the signs and symptoms of anterior uveitis, along with a diffuse choroidal depigmentation at fundus examination^[2]. According to the clinical criteria, the presence of bilateral ocular involvement is necessary for diagnosis. However, the uncommon possibility of unilateral manifestations is recognized^[3]. Ocular complications may include cataract, glaucoma, and subretinal neovascularization^[4]. The occurrence of these complications is associated with worse visual acuity outcomes^[4].

VKH disease affects the more pigmented ethnical groups, such as Hispanics (Mestizos), Asians, Native Americans, Middle Easterners, and Asian Indians, but not blacks of sub-Saharan African descent, and is relatively uncommon in whites^[2].

In a consecutive case series of 402 patients from our Uveitis Department at University of Buenos Aires, Argentina, VKH disease represented 34% of the noninfectious uveitis, and 22.9% of the etiologies of the adult population. Therefore, VKH disease was the most frequent noninfectious uveitic etiology of this series (presented at ARVO meeting May 4th 2014, ID number 685).

The present study aims to describe the clinical profile, visual outcomes and ocular complications of patients diagnosed with VKH disease in Argentine patients.

SUBJECTS AND METHODS

This is a retrospective case record review, approved by the Institution's Ethics Committee according to the principles of the Declaration of Helsinki. All VKH patients (diagnosed according to the criteria of the last International Committee

in 2001^[2]) were identified from the Inflammatory Eye Disease Service of the Jose de San Martin Clinics Hospital of the Buenos Aires University between January 1980 and December 2008. We selected the medical records of patients who had at least 12mo follow-up. Clinical information such as diagnostic categories for VKH disease (complete, incomplete and probable according International Committee in 2001^[2]), current medications, visual acuity, intraocular pressure, slit lamp examination, anterior chamber inflammation, vitreous examination, and the presence of complications were registered. The following variables were evaluated: sex, age of onset, clinical presentation (iritocyclitis, papillitis, exudative retinal detachment), and best-corrected visual acuity (logMAR) before and after treatment. For each patient, the average of the visual acuity of both eyes was used for statistical analysis. The typical treatment included high-dose corticosteroid therapy followed by a slow tapering of at least 6mo^[5]. Intolerant or non responsive patients were treated with other immunosuppressive drug therapy to minimize complications and to improve visual prognosis^[5]. We classified treatment regimens as follows: group 1 (G1): early administration of corticosteroid ≥ 1 mg/(kg·d) prednisone equivalent (orally or intravenously) within 2wk of symptom onset; group 2 (G2): late corticosteroid administration ≥ 1 mg/(kg·d) prednisone equivalent (orally or intravenously) 2 to 4wk after symptom onset; and group 3 (G3): low oral corticosteroid dose [less than 1 mg/(kg·d) prednisone equivalent] initiated at any time of the disease, or ≥ 1 mg/(kg·d) prednisone equivalent (orally or intravenously) after one month of symptoms onset^[6]. Patients were also treated with other immunosuppressive drugs along the course of the disease: antimetabolites (azathioprine and methotrexate), alkylating agents (chlorambucil), or biological agents (mainly adalimumab). They received one or more immunosuppressive drugs, frequently associated at the beginning of their administration with oral corticosteroids.

Signs of convalescence were classified as: 1) diffuse choroidal depigmentation (sunset glow fundus); 2) nummular depigmented scars; 3) retinal pigment epithelium clumping and/or migration. Presence of complications such as cataract (defined as the presence of 1+ nuclear sclerosis or 1+ cortical change, or trace posterior subcapsular changes in an eye in which no cataract was observed on previous visits), glaucoma (intraocular pressure of >21 mm Hg with pathologic cupping of the optic disk), choroidal neovascularization, subretinal fibrosis, and ocular hypotony (IOP equal to or less than 5 mm Hg on at least two examinations) were recorded^[2,7-8].

Statistical Analysis Data were entered on the standardized data entry form for statistical analysis. Categorical variables are presented as percentage, numeric variables are presented as mean \pm SD or mean (range), according to the distribution. To compare proportions we used the Chi-square test. To compare

Table 1 Clinical characteristics of patients with VKH disease

Characteristics	<i>n</i> (%)
No. of patients	105
Mean age (a)	32.6 \pm 13
Gender	
F	91 (86.7)
M	14 (13.3)
Bilateral disease	105 (100)
Initial clinical presentation	
Exudative retinal detachment	90 (46.2)
Iritocyclitis	88 (45.1)
Papillitis	17 (8.7)
Initial visual acuity (logMAR)	0.83 \pm 0.62
Final visual acuity (logMAR)	0.72 \pm 0.77
Signs of convalescence	
Diffuse fundus depigmentation	124 (59.0)
Nummular depigmented scars	70 (33.3)
Retinal pigment epithelium clumping and/or migration	58 (27.6)
Ocular complications	
Cataract	122 (58.1)
Glaucoma	91 (43.3)
Subretinal fibrosis	17 (8.1)
Choroidal neovascularization	6 (2.9)
Ocular hypotony	17 (8.1)

numerical variables between two groups, we used the Mann-Whitney test. To compare numerical variables between three groups, Kruskal-Wallis test was used as appropriate.

RESULTS

Study Population We studied 210 eyes of 105 patients, 86.7% of them were women ($n=91$). The mean age of the studied population was 43.8 \pm 14y, with a mean age at presentation of 32.6 \pm 13y (range: 10-74y). The mean time of VKH disease evolution in patients was 144 \pm 96.6mo. All patients had bilateral disease. The most common presentation of the disease was exudative retinal detachment (90 eyes, 46.2%), followed by iritocyclitis (88 eyes, 45.1%), and papillitis (17 eyes, 8.7%), presenting signs of the disease were unknown in 15 eyes. According to VKH diagnostic categories, we classified 27 patients as complete, 56 as incomplete and 22 as probable VKH disease. Visual acuity at the beginning of the follow up showed a mean of 0.83 \pm 0.62 (logMAR). Patients in G1 and G2 (58 cases) were diagnosed as acute stage, whereas patients in G3 (28 patients) were diagnosed as chronic recurrent disease. Nineteen patients were excluded from G1, G2, or G3, because they had not received systemic corticosteroid treatment previous to their admission to our service or during their follow up. All of them were diagnosed as chronic recurrent stage (Table 1).

Signs of Convalescence and Complications All eyes examined ($n=210$) presented with one or more signs of convalescence, the most frequent finding was diffuse fundus depigmentation in 59.0% ($n=124$), followed by nummular depigmented scars in 33.3% ($n=70$) and retinal pigment epithelium clumping and/or migration in 27.6% ($n=58$). The presence of one or more complication was commonly observed, found in 67.1% ($n=141$) of the cases. The most frequent complications were cataract in 58.1% of the eyes ($n=122$) and glaucoma in 43.3% of cases ($n=91$). Among the patients with glaucoma as complication, 7 patients needed antimetabolite trabeculectomy surgery (7.7%), and 2 patients received valve implant (2.2%); the remaining glaucoma patients were controlled with topical treatment. Subretinal fibrosis was found in 8.1% of the eyes ($n=17$), ocular hypotony in 8.1% ($n=17$) and choroidal neovascularization in 2.9% ($n=6$). There was no statistically significant correlation between the age of illness onset and the number of complications ($P=0.07$), but complications were statistically significant more prevalent in the late treatment groups: 56.1% vs 78.7% in G1 and G3, respectively ($P=0.001$), and in G2 vs G3: 58.6% vs 77.86% ($P=0.001$) (Table 1).

Treatment and Final Visual Outcome One hundred and one patients had available initial treatment information, while these data were incomplete for the other 4 patients. Twenty-nine patients (28.7%) received G1 scheme, 29 patients (28.7%) were treated with G2 regimen, and 28 patients (27.7%) were received G3 regimen. The remaining patients received other form of treatment such as topical administration of steroids.

Data about immunosuppressive treatment administration was available in 103 patients. Fifty-seven out of 103 patients (55.3%) were treated with one or more immunosuppressive drugs over the course of their disease, being 23.3% of the cases ($n=24$) with antimetabolites drugs, 35.9% ($n=37$) with alkylating agents, and 3.9% ($n=4$) received biological agents. Forty-three patients (41.7%) received a single immunosuppressive agent and 13.6% ($n=14$) received two or more.

During the course of their disease, 13 patients (44.8%) who underwent G1 regimen, 18 patients (62.1%) who underwent G2 regimen, and 16 patients (57.1%) who underwent G3 regimen received immunosuppressive treatment.

Statistically significant improvement of the visual acuity was achieved only by G1 ($P=0.002$). Mean initial visual acuity was 0.53 ± 0.62 logMAR units (20/67) in G1, 0.62 ± 0.52 logMAR units (20/83) in G2, and 1.15 ± 0.46 logMAR units (20/283) in G3. Mean final visual acuity was 0.09 ± 0.17 logMAR units (20/25) in G1, 0.48 ± 0.57 logMAR units (20/60) in G2, and 1.29 ± 0.76 logMAR units (20/390) in G3. G1 had better vision at the end of follow up than the other groups ($P<0.0001$), while G2 had better vision at the end of follow up than G3 ($P<0.0001$). A final visual acuity of 20/40 or better was observed in 101 out of 172 eyes (58.7%) in all the 3 studied

Table 2 Comparison of initial and final mean visual acuity of all the patients between different therapeutic schemes groups

VA (logMAR)	G1 ($n=29$)	G2 ($n=29$)	G3 ($n=28$)	<i>P</i>
Initial VA	0.53 ± 0.62	0.62 ± 0.52	1.15 ± 0.46	0.0001 ^a
Final VA	0.09 ± 0.17	0.48 ± 0.57	1.29 ± 0.76	<0.0001 ^a

^aKruskal-Wallis test.

groups. Only 4 out of 58 eyes (6.9%) had a final visual acuity less than 20/40 in G1. In G2, 36 out of 58 eyes (62.1%) had a final visual acuity of 20/40 or better. In G3, 11 out of 56 eyes (19.6%) had a final visual acuity of 20/40 or better.

DISCUSSION

This case series describes the clinical features of 105 patients with diagnosis of VKH syndrome. This ailment, as it is shown above, is a substantial fraction of our patient population (ARVO meeting 2014, ID number 685), likely due to the fact that our service is a tertiary center.

It is well known, as described by other authors, that the mean age of the disease onset is between 31-37y, although it has also been described to appear in children^[6-7,9-10], being the youngest recorded patient a 3 years old girl^[11]. In the present study, most patients debuted at 32 years of age, while the youngest patient was diagnosed at 10 years of age.

Our series also shows that VKH disease is more common in women, as was noted in other studies in Turkey, North Africa, and South India^[9,12-13]. However, equal sex distribution was observed in a reported study from Singapore^[6].

We found that the most common presentation of the disease was exudative retinal detachment in 45.7% of the cases, similar to the cases in South India (60%), but lower than those observed in other group of hispanic patients (91%)^[14]. In North Africa, Khairallah *et al*^[13] reported equal distribution of the presentation of VKH disease as panuveitis and posterior uveitis in 51% and 49% of the cases, respectively. In South India, Murthy *et al*^[9] described disc edema in 68% of the cases, in contrast with the 8.6% found in our series, similar to that reported by Sukavatcharin *et al*^[14]. The final visual acuity is variable and many authors agree that best visual acuity outcome rests upon promptly initiation of corticosteroids (>1 mg/kg), use of immunomodulatory treatment and the influence of prognostic factors such as initial visual acuity of >20/200^[15]. Murthy *et al*^[9] reported that 60% of patients retained vision of 20/30 or better in a case series of 45 patients in South India. Our series showed similar visual outcomes, with 58.7% of 172 eyes with a final visual acuity of 20/40 or better.

The initial visual acuity has been found to correlate well with the final outcome in previous studies^[15]. However, Chee *et al*^[16] found that the visual acuity at one month after starting treatment was a more important prognostic factor than initial visual acuity.

In our experience, final visual acuity was better in those cases who were treated early (*e.g.* within 2wk from the beginning

of symptoms of the disease). Those patients achieved a statistically significant improvement of their vision in the long term, from an average of 0.53 logMAR units (20/67) to an average of 0.09 logMAR units (20/25). Chee *et al*^[16] showed that treatment regime was not such a good prognostic factor as it was visual acuity at 1mo, probably due to a variable response of each individual to an early high dose of corticosteroids. In our study, we did not assess visual acuity at 1mo as a predictor of visual outcome, but we observed that treatment regime had influence in final visual acuity in the long term in our patients. A better final visual acuity was shown in those patients who received early high dose of corticosteroids (G1) in a long term follow up. More than 85% of our patients received oral corticosteroids, but more than half of them received it in a late manner (G2 and G3). This fact could explain the poor final visual acuity in those latter groups.

In many other studies, almost all of the patients were treated from the beginning with high dose oral corticosteroids^[9,12-15]. In our case series it was not possible to do so, due to fact that a significant proportion of our patients were referred late in the course of their disease.

The average time of follow up of the patients of our series is far larger (about 12y) than other case series previously reported^[9,12-16]. Therefore, the final visual outcomes of our patients may be more representative of what actually happens in the long term management of patients with VKH syndrome.

Though high-dose systemic corticosteroids remain the gold-standard therapy in the acute stage of the disease, cases who are refractory or intolerant to corticosteroids and patients in the chronic-recurrent stage may need other agents (cyclosporine A, antimetabolites, alkylating agents and biologics)^[17-19]. In spite of a proper early treatment, evolution to the chronic-recurrent stage occurs very frequently, as it was shown by Sakata *et al*^[17] (79%), Chee *et al*^[6] (66%), and Tugal-Tutkun *et al*^[12] (95%). Immunosuppressive treatment was administered to more than 60% of the patients who evolved to the chronic recurrent stage in the latter mentioned studies. In our study, 55% of the patients received at least one immunosuppressive agent. In other retrospective cohort study of 152 patients there were no differences in outcomes between first-line immunomodulatory treatment and prednisone alone/late immunomodulatory treatment in the entire VKH group. However, in a subset of patients, there was a significant better functional outcome with earlier immunomodulatory treatment initiation^[20]. Most of the patients in our series received immunosuppressive agents when chronic recurrent stage developed. Therefore, we cannot assess the impact in visual outcome of the early administration of these drugs.

Convalescence signs consistently have a high prevalence as late manifestations in the present and other studies, likely as a consequence of chronic subclinical inflammatory activity^[12,21].

Moreover, Keino *et al*^[22] have shown in their study that sunset glow fundus was more common in patients with chronic inflammation.

In our series, a large number of cases presented with disease complications which were more frequently observed in G3, followed by G2 and finally G1, suggesting the pivotal relevance of early treatment in final outcome. Nevertheless, the most common complication, as seen in other studies, was cataract, followed by glaucoma, both mostly attributed to corticosteroid treatment. Although, more than half of our patients received immunosuppressive agents, as we have shown, complications were frequent in the long term. Therefore, the best treatment with the least long-term risk of complications is still unknown^[6,9,13]. It has been suggested that long duration of the ailment and chronic intraocular inflammation are risk factors for the development of subretinal fibrosis and choroidal neovascularization^[12]. Choroidal neovascularization, a complication of high visual morbidity, occurs in 1%-10% according to various publications of cases, being comparable to that of our series (3%)^[6,9,13]. Abu El-Asrar *et al*^[15] states that patients older than 16 years age significantly developed more complications and worst visual prognosis. In our study no relationship was found between the incidence of complications and older age of onset.

In summary, we presented a case series of patients with VKH disease with the longest time of follow up reported so far. Patients receiving timely treatment at the proper dose (G1) showed a better final visual acuity and fewer complications than late treatment groups in the long term^[6,9-10]. As a conclusion, suitable timing in referral and treatment is critical in the evolution of VKH disease.

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