Ocular Immunology & Inflammation
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713721577

Characteristics of Vogt-Koyanagi-Harada Disease in a French Cohort: Ethnicity, Systemic Manifestations, and HLA Genotype Data

S. Abad [a]; D. Monnet [b]; S. Caillat-Zucman [c]; S. Mrejen [b]; P. Blanche [d]; M. Chalumeau [e]; L. Mouthon [d]; R. Dhote [a]; A. P. Brézin [b]
[a] Service de Médecine Interne, Laboratoire de recherche clinique et thérapeutique UPRES EA3409, Université Paris XIII, Faculté Léonard de Vinci, Hôpital Avicenne, Assistance Publique-Hôpitaux de Paris, Paris, France
[b] Service d'Ophtalmologie, Université Paris Descartes, Faculté de Médecine, Hôpital Cochin, Paris, France
[c] Laboratoire d'Immunologie, Université Paris Descartes, Faculté de Médecine, Hôpital Necker, Paris, France
[d] Service de Médecine Interne, Université Paris Descartes, Faculté de Médecine, Hôpital Cochin, Paris, France
[e] Service de Pédiatrie, Université Paris Descartes, Faculté de Médecine, Hôpital St-Vincent de Paul, Paris, France

Online Publication Date: 01 January 2008
To cite this Article: Abad, S., Monnet, D., Caillat-Zucman, S., Mrejen, S., Blanche, P., Chalumeau, M., Mouthon, L., Dhote, R. and Brézin, A. P. (2008) 'Characteristics of Vogt-Koyanagi-Harada Disease in a French Cohort: Ethnicity, Systemic Manifestations, and HLA Genotype Data', Ocular Immunology & Inflammation, 16:1, 3 - 8
To link to this article: DOI: 10.1080/09273940801923895
URL: http://dx.doi.org/10.1080/09273940801923895

Ocular Immunology and Inflammation, 16:3–8, 2008

ISSN: 0927-3948 print; 1744-5078 online
DOI: 10.1080/09273940801923895

informa
healthcare

ORIGINAL REPORT

Characteristics of Vogt-Koyanagi-Harada Disease in a French Cohort: Ethnicity, Systemic Manifestations, and HLA Genotype Data

S. Abad
Service de Médecine Interne, Laboratoire de recherche clinique et thérapeutique UPRES EA3409, Université Paris XIII, Faculté Léonard de Vinci, Hôpital Avicenne, Assistance Publique-Hôpitaux de Paris, Paris, France

D. Monnet
Service d'Ophtalmologie, Université Paris Descartes, Faculté de Médecine, Hôpital Cochin, Paris, France

S. Caillat-Zucman
Laboratoire d'Immunologie, Université Paris Descartes, Faculté de Médecine, Hôpital Necker, Paris, France

S. Mrejen
Service d'Ophtalmologie, Université Paris Descartes, Faculté de Médecine, Hôpital Cochin, Paris, France

P. Blanche
Service de Médecine Interne, Université Paris Descartes, Faculté de Médecine, Hôpital Cochin, Paris, France

M. Chalumeau
Service de Pédiatrie, Université Paris Descartes, Faculté de Médecine, Hôpital St-Vincent de Paul, Paris, France

L. Mouthon
Service de Médecine Interne, Université Paris Descartes, Faculté de Médecine, Hôpital Cochin, Paris, France

R. Dhote
Service de Médecine Interne, Laboratoire de recherche clinique et thérapeutique UPRES EA3409, Université Paris XIII, Faculté Léonard de Vinci, Hôpital Avicenne, Assistance Publique-Hôpitaux de Paris, Paris, France

A. P. Brézin
Service d'Ophtalmologie, Université Paris Descartes, Faculté de Médecine, Hôpital Cochin, Paris, France

Received 16 May, 2007;
accepted January 15, 2008.

This study was financially supported by the Institut Servier, 164 avenue Achille Peretti, 92578 Neuilly sur Seine, Cedex, France.

Correspondence and reprint requests to: Dr. Sébastien Abad, Service de Médecine Interne, Hôpital Avicenne, 125 route de Stalingrad, 93009 Bobigny Cedex, France. E-mail: sebastien.abad@avc.ap-hop-paris.fr

ABSTRACT *Purpose*: To assess in patients followed in a French referral center the clinical spectrum of Vogt-Koyanagi-Harada (VKH) disease and the HLA-DRB1*04 genotype. *Methods*: Patients previously diagnosed as having VKH disease were re-evaluated in a cross-sectional study using the VKH Committee's revised criteria. High-resolution HLA-DRB1 genotyping was performed. *Results*: Eleven white patients satisfied ophthalmologic diagnostic criteria. All originated from Mediterranean countries. Nine and 3 patients had neurologic and/or cutaneous abnormalities, respectively. Among DRB1*04-positive patients, the HLA-DRB1*0405 subtype was 71%. *Conclusion*: These VKH patients predominantly had an incomplete form. The HLA-DRB1*0405 subtype allele was enriched in a group of Mediterranean stock.

KEYWORDS Ethnicity; HLA-DRB1*0405; uveomeningoencephalitides; vitiligo; Vogt-Koyanagi-Harada disease

Vogt-Koyanagi-Harada (VKH) disease is an inflammatory disorder affecting the eyes, the auditory system, the meninges, and the skin. Although its etiology remains unknown, immunologic studies suggest that VKH disease involves a T-lymphocyte-mediated autoimmune process directed against an antigen associated with melanocytes.[1–3]

VKH disease appears to primarily affect individuals whose ancestry is traceable to peoples from Asia, who migrated across the Bering strait to North America and further down to Central and South America.[4] This propensity, along with evidence of an increased frequency among individuals with particular HLA-DRB1 genotypes, points to a genetically determined pathophysiologic susceptibility to VKH disease.[5–7]

Because VKH disease is distinctly uncommon in Europeans, its clinical and demographic features and the presence of particular HLA-DRB1 genotypes have not been well characterized. In a retrospective study, we previously reported a series of patients diagnosed as having VKH disease, who were white Caucasians

or Africans, two unusual ethnic groups for VKH disease. As opposed to Japanese population, the cutaneous manifestations seemed to be significantly rarer.[8]

In a cross-sectional study, we assessed the clinical presentation and the HLA-DRB1*04 genotype in our patients diagnosed with VKH disease according to the VKH Committee's revised criteria.[9]

PATIENTS AND METHODS

The patients were recruited in a French academic referral center, where they were treated for uveitis. Consecutive patients previously diagnosed as having VKH disease between September 1996 and September 2005 were reevaluated for a routine cross-sectional standardized evaluation by two internists (AS, DR) and two ophthalmologists (MD, BAP). The study was approved by an academic medical research ethics committee and followed the tenets of the declaration of Helsinki.

All patients underwent a comprehensive examination. Gender, race, and age were recorded at the time of the study. Digital color fundus photography was systematically performed with a 60° Canon fundus camera. Based of the recent classification,[9] patients were cross-sectionally evaluated for early and late signs of VKH disease, corresponding with early ophthalmologic signs (section 3a), neurologic/auditory manifestations (section 4), and late ophthalmologic signs (section 3b), and intertegumentary findings (section 5). For the purpose of this cross-sectional study, we considered patients as being at the acute or /chronic stage of VKH disease according to the time of onset of the ocular disease, that is, less or more than 3 months.[10]

To complete these data, a history of initial trauma or surgery (section 1) and clinical or laboratory evidence suggestive of other ocular disease (section 2) were retrospectively sought. Patients with ophthalmic features compatible with sarcoidosis were excluded if they had noncaseating granulomas on bronchial or salivary gland biopsy, or relevant morphologic findings. All patients underwent initially a standard screening protocol including a medical history and laboratory tests for syphilis, *Borrelia burgdorferi* and HTLV-1 serology in patients with risk factors for the latter infection. Mean age at onset of VKH disease was recorded.

Prior early manifestations, which might have resolved by the time of examination, were reevaluated, including analysis of fluorescein angiography and/or ultrasonography (section 3a). Regarding more recent patients, optical coherence tomography (Zeiss Humphrey OCT-3, San Leandro, California, USA) was used to confirm presence of subretinal fluid or bullous serous retinal detachment. Presence of cerebrospinal fluid pleiocytosis was recorded when cerebro-spinal fluid (CSF) analysis was performed (section 4). Hearing loss was assessed by audiogram examination. According to the revised diagnostic criteria for VKH disease, patients could finally be classified as having a complete or an incomplete VKH disease or an isolated ocular disease.[9]

DNA was extracted from the peripheral blood using a classic salting-out procedure. HLA class II DNA typing was performed by means of hybridization with sequence-specific oligonucleotide probes following amplification of the second exon of the DRB1 gene by the polymerase chain reaction (PCR), using the InnoLipa HLA typing kit (Abbott, France), which provides a low-resolution genotyping for the major HLA-DRB1 alleles. In HLA-DRB1*04-positive samples, high-resolution DRB1*04 subtyping was performed using sequence-specific primer amplification (Dynal, France).

Patients who did not fulfill the diagnostic revised criteria for VKH disease were excluded from the analysis. All quantitative data were expressed as means ± SD. HLA-DRB1 allele frequencies were determined by counting in the different groups.

RESULTS

Twenty-three patients were contacted. All were living in a large Paris suburban geographic area. Five patients defaulted and 3 others refused to participate. Finally, 15 patients were evaluated for the revised diagnostic criteria for VKH disease (Figure 1). All 3 patients seen at the acute stage fulfilled diagnostic criteria, while among patients seen at the chronic stage, 4 patients were excluded on the basis of section 3 of the VKH Committee's criteria. Reasons for exclusions included absence of relevant retrospective data at the acute phase in 1 patient and no evidence of ocular depigmentation or chronic uveitis in 3 patients considered as being at the chronic phase.

The characteristics of the 11 patients classified as having VKH disease are listed in Table 1, according to the VKH disease diagnostic category (complete, incomplete, or probable). All 11 VKH patients originated from Mediterranean regions, predominantly North Africa (8/11). These latter were therefore white as well as 3 European Hispanic patients. Among the 4 patients who did not fulfill the VKH Committee's criteria, only

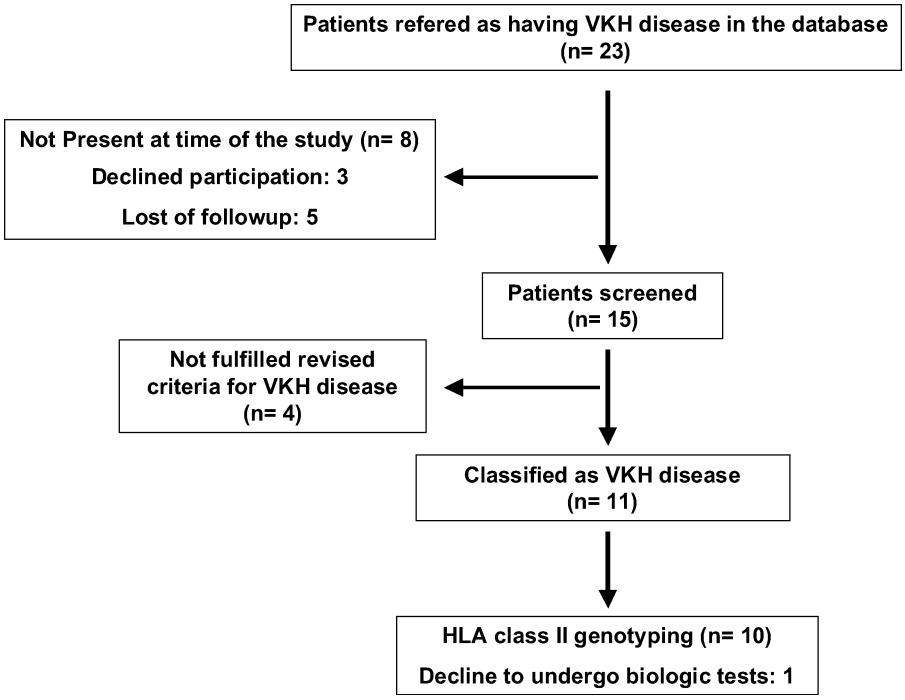

FIGURE 1 Flow diagram of the study cohort

1 originated from North Africa. Six of the 11 VKH patients were males. Mean age (years ± SD) at current evaluation was 41.7 ± 15.4 years while age at the onset of VKH disease was 33.5 ± 14.2 years.

Ophthalmologic Features

Among the late manifestations of VKH disease (section 3b), pigmented scars and chronic anterior uveitis, were predominantly present by the time of the study in the 8 patients seen at the chronic stage. Retrospectively, all 11 patients had evidence of early ophthalmic manifestations of VKH disease (section 3a). Nine of them underwent a fluorescein angiography (7/11) or an ultrasonography (2/11), showing in all patients typical choroidal changes or evidence of a choroidal thickening, respectively. OCT disclosed bullous serous retinal detachment in the other 2 cases.

General Features

At the time of study, 3 of the 8 VKH disease patients seen at the chronic phase had some intertegumentary findings, including alopecia (1/8), poliosis (1/8), and vitiligo (2/8), which exclusively affected the eyelids or the sacral area in 2 patients. Retrospectively, presence of meningismus, tinnitus, or hearing loss were recorded in 8, 2, and 3 patients, respectively. In case of hearing loss, the audiogram found bilateral cochlear deafness. CSF analysis was carried out in 8 of the 11 VKH patients, Three patients were excluded from statistical analysis because of concomitant corticosteroid treatment (1/11) or unavailable data (2/11). Six of these 8 patients had pleocytosis in CSF ranging from 20 to 500 cells/mm^3 with increased numbers of lymphocytes (>80%), and protein levels ranging from 0.4 to 1.5 g (normal value < 0.4 g) per liter (data not shown in Table 2). Overall, 8 of the 11 VKH patients were considered to have some type of neurologic/auditory abnormality. According to these findings, 1 patient was diagnosed as suffering from a complete form of VKH disease, and 9 patients as having an incomplete VKH disease, while 1 patient had a probable disease, that is, isolated ocular involvement.

HLA Class II Distribution

HLA class II genotyping was performed in 10 out of the 11 VKH patients. The distribution of HLA-DRB1 allele frequencies and HLA-DRB1*04 subtype frequency in the VKH different patients subgroups is shown in Table 2. As compared with all the HLA DRB1 alleles, the HLA-DRB1*04 allele frequency was highest in VKH patients (35%). Six patients with complete or incomplete VKH disease carried the DRB1*04 allele, while the only 1 with isolated ocular disease did not. Moreover, the HLA-DRB1*0405 subtype was mostly present in DRB1*04-positive patients (71%). Of the 6

TABLE 1 **Screening of patients for signs of VKH disease**

	VKH disease			Total patients
	Complete $n = 1$	Incomplete $n = 9$	Probable[§] $n = 1$	$n = 11$
Epidemiologic characteristics				
Age at the time of the study (years ± SD)	59	42.3 ± 13.4	15	41.7 ± 15.4
Age at the onset (years ± SD)	52	32.7 ± 12	15	33.5 ± 14.2
Male – n°/n	1	5/9	0	6/11
Origin – n°/n				
North African	1/1	6/9	1/1	8/11
European Hispanic	0/1	3/9	0/1	3/11
Ocular characteristics				
Early manifestations – n°/n	1/1	9/9	1/1	11/11
Choroiditis (SRF/BSRD) – n°/n	1/1	9/9	1/1	11/11
Angiography (FA/MA/LPA/ONS) – n°/n	ND	6/6	1/1	7/7*
Choroidal thickening – n°/n	1/1	1/1	ND	2/2**
Late manifestations – n°/n	1/1	7/7	—	8/8[&]
Ocular depigmentation (SGF/SS) – n°/n	1/1	3/7	—	4/8[&]
Other signs (NCDS/RPEC/CAV) – n°/n	1/1	6/7	—	7/8[&]
Extraocular characteristics				
Early manifestations – n°/n	1/1	7/9	0/1	8/11
Cerebrospinal fluid pleocytosis > 5 cell/mm^3 – n°/n	1/1	5/7[$]	[§]	6/8[$§]
Cerebrospinal fluid lymphocytosis $> 80\%$ – n°/n	1/1	5/7[$]	[§]	6/8[$§]
Hearing loss – n°/n	0/1	3/9	0/1	3/11
Tinnitus – n°/n	1/1	1/9	0/1	2/11
Meningismus – n°/n	1/1	7/9	0/1	8/11
Late manifestations – n°/n	1/1	2/7	—	3/8[&]
Alopecia – n°/n	0/1	1/7	—	1/8[&]
Poliosis – n°/n	0/1	1/7	—	1/8[&]
Vitiligo – n°/n	1/1	1/7	—	2/8[&]

Note. *Angiography and **echography provided evidence of VKH disease in all patients who underwent such explorations.
[§]Patients receiving systemic corticosteroids, and [$]those for whom result of lumbar puncture was not available were excluded from statistical analysis. [&]Patients seen at the chronic phase. SRF, serous retinal fluid; BSRD, bullous serous retinal detachments; FA, focal areas of delay in choroidal perfusion; MA, multifocal areas of pinpoint leakage; LPA, large place areas of hyperfluorescence; ONS, optic nerve staining; SGF, sunset glow fundus; SS, sugiura sign; NCDS, nummular choriretinal depigmented scars; RPEC, retinal pigment epithelium clumping; CAV, chronic anterior uveitis; ND, not done.

HLA-DRB1*04-positive patients, 4 expressed the HLA-DRB1*0405 subtype and 1 of them was homozygous for this allele.

DISCUSSION

Vogt-Koyanagi-Harada disease is frequently found among Japanese, Spanish-Americans, American-Indians, or Brazilians, primarily in their third to fifth decades, with a feminine predominance.[11–15] Our study originally described 11 white VKH patients, predominantly of North African origin (8/11) or European Hispanics (3/11), who are known to share a common ancestry. Indeed, during the first millennium, Arab invasions via the Gibraltar strait led to a mix-up with the populations from South Europa. VKH disease has been recently reported among the most common causes of uveitis in a referral center in Tunisia, a North African country.[16] In our patients, mean age at onset (33 years) was comparable to that reported in the largest series of VKH patients but the majority of our patients were males.

Systemic manifestations are diverse and race dependent. Previous studies found that, when compared with Japanese patients, Hispanics from California tended to have a lower incidence of hearing impairment (11 vs. 80%), vitiligo (8 vs. 25%), alopecia (17 vs. 60%), and poliosis (6 vs. 60%) despite the fact that they had typical ocular and neurologic manifestations.[12,17]

Until recently the diagnostic criteria for VKH disease took into account the cutaneous involvement as the major criterion, and this led to underdiagnosing VKH disease in patients at the early phase.[18] Actually, cutaneous findings are not typically present at the initial

TABLE 2 HLA DRB1 allele frequency and HLA DRB1*04 subtype frequency of vogt-koyanagi-harada disease

HLA-DRB1 alleles	VKH disease			Total VKH patients $n = 20$
	Complete $n = 2$	Incomplete $n = 16$	Probable $n = 2$	
	DRB1- n°./n (%)*			
01	0	0	0	0 (0%)
03	0	2	0	2 (10%)
04	1	6	0	7 (35%)
0401	0	1	0	1 (14%)
0402	0	0	0	0 (0%)
0403	0	0	0	0 (0%)
0404	0	1	0	1 (13%)
0405	1	4	0	5 (71%)
0406	0	0	0	0 (0%)
0407	0	0	0	0 (0%)
0408	0	0	0	0 (0%)
07	0	2	0	2 (10%)
08	0	0	0	0 (0%)
09	0	0	0	0 (0%)
10	0	1	0	1 (5%)
11	1	1	1	3 (15%)
12	0	0	0	0 (0%)
13	0	2	1	3 (15%)
14	0	2	0	2 (10%
15	0	0	0	0 (0%)
16	0	0	0	0 (0%)

Note. HLA-DRB1allele genotyping and HLA-DRB1*04 allele subtyping were performed in 10 and 6 patients, respectively.

phase of the disease. The revised criteria rightly take into account different periods in the progression of the disease. With the new criteria, VKH disease can be sorted into three distinct forms: complete, incomplete, or probable.

This diagnostic system is a more reliable way to classify VKH patients. Kitamura et al. have recently confirmed that these revised criteria were highly specific (100%) of VKH disease.[19] From this standpoint, our study appears to be based on homogenous groups of patients. Based on ophthalmologic criteria, we excluded one-third of patients previously diagnosed as having VKH disease on the grounds of incomplete data or wrong criteria.

In agreement with the Japanese study cited above, a similar proportion of our patients could be identified as having a complete, incomplete, or probable VKH disease (1/11, 9/11, 1/11, respectively). However, in a recent series of Chinese patients, a large proportion of patients (67%) were diagnosed as having a complete VKH.[20] In agreement with the Kitamura et al. findings, a number of them (8/11) had neurologic/auditory disorders and to a lesser extent some type of intergumentary lesions (3/8). Interestingly, in this cross-sectional study conducted 8 years after disease onset, systematic examination disclosed vitiligo in 2 of the 8 VKH patients seen at the chronic phase and poliosis or alopecia in another patient. This indicates that cutaneous lesions are not as rare as previously reported in our VKH patients with lower levels of skin pigmentation when sought.[8] Of note, in our patients, vitiligo had a particular topography with a symmetric distribution on the eyelids or the trunk, especially the sacrum. However, the majority of our patients originating from Mediterranean regions did not have the complete form of the VKH disease as recently observed in Tunisian patients.[21]

Our study showed a high percentage of HLA-DRB1*04-positive patients fulfilling the new revised criteria of VKH disease. An increased frequency of DRB1*04 has previously been observed in Hispanic,[6] Japanese,[7] Chinese,[22] Korean,[23] Brazilian,[24] and Italian patients.[25]

Among HLA-DRB1*04 subtypes, a high frequency of the HLA-DRB1*0405 allele was observed, suggesting a significant association with VKH disease as described in Asian or Brazilian populations.[23,24,26] Two-thirds of our HLA-DRB1*04-positive, not selected, patients carried the HLA-DRB1*0405 allele. To the best of our knowledge, it is the first time that this has been observed in patients originating from Mediterranean countries. As opposed to the Brazilian patients, none of our patients was of Japanese or Asian descent. Studies using controls matched for their ethnic group are required to confirm whether the HLA-DRB1*0405 allele is strongly associated with the VKH disease in these patients.

According to a recent study,[27] VKH patients carrying the HLA-DRB1*0405 allele recognize a more diverse array of peptides derived from melanocyte differentiation proteins TYR, TRP1, TRP2, and Pmel17, which supports a major role of HLA-DRB1*0405 in the presentation of melanocyte epitopes. Along with previous reports in different populations of various ethnic and geographic origins, our results reinforce the notion that VKH disease may occur worldwide in HLA-DRB1*0405 positive patients, and strengthen the hypothesis that the pathogenesis of VKH disease might be related to an abnormal immune response against melanocyte-derived peptides in HLA susceptible individuals.

In summary, our VKH patients originating from Mediterranean regions appeared to have a presentation similar to that of Japanese or Tunisian patients according to the new revised criteria for VKH disease.

REFERENCES

[1] Kondo I, Yamagata K, Yamaki K, et al. Analysis of the candidate antigen for Harada's disease. *Nippon Ganka Gakkai Zasshi—Acta Societatis Ophtalmologicae Japonicae.* 1994;98:596–603.

[2] Sugita S, Sagawa K, Mochizuki M, et al. Melanocyte lysis by cytotoxic T lymphocytes recognizing the MART-1 melanoma antigen in HLA-A2 patients with Vogt-Koyanagi-Harada disease. *Int Immunol*. 1996;8:799–803.

[3] Norose K, Yano A. Melanoma specific Th1 cytotoxic T lymphocyte lines in Vogt-Koyanaghi-Harada disease. *Br J Ophthalmol*. 1996;80:1002–1008.

[4] Moorthy RS, Inomata H, Rao NA. Vogt-Koyanagi-Harada Syndrome. *Surv Ophthalmol*. 1995;39:265–292.

[5] Numaga J, Matsuki K, Tokunaga K, et al. Analysis of human leukocyte antigen HLA-DR beta amino acid sequence in Vogt-Koyanagi-Harada syndrome. *Invest Ophthalmol Vis Sci*. 1991;32:1958–1961.

[6] Weisz JM, Holland GN, Roer LN, et al. Association between Vogt-Koyanagi-Harada sydrome and HLA-DR1 and HLA-DR4 in hispanic patients living in southern California. *Ophthalmology* 1995;102:1012–1015.

[7] Shindo Y, Ohno S, Yamamoto T, et al. Complete association of HLA-DRB1*04 and DQB1*04 alleles with Vogt-Koyanagi-Harada's disease. *Human Immunol.* 1994;39:169–176.

[8] Guenoun JM, Parc C, Dhote R, et al. Vogt-Koyanagi-Harada Disease: clinical features, therapy and long-term visual outcome in a Caucasian and African population. *J Fr Ophtalmol*. 2004;27:1013–1016.

[9] Read RW, Holland GN, Rao NA, et al. Revised diagnostic criteria for Vogt-Koyanagi-Harada disease: report of an international committee on nomenclature. *Am J Ophthalmol.* 2001;131:647–652.

[10] Jabs DA, Nussenblatt RB, Rosembaum JT. Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data: results of the First International Workshop. *Am J Ophthalmol.* 2005;140:509–516.

[11] Ohno S, Char DH, Kimura SJ, et al. Vogt-Koyanagi-Harada's syndrome. *Am J Ophthalmol*. 1977;83:735–740.

[12] Beniz J, Forster DJ, Lean JS, et al. Variations in clinical features of the Vogt-Koyanagi-Harada Syndrome. *Retina.* 1991;11:275–280.

[13] Nussenblatt RB. Clinical studies of Vogt-kayanagi-Harada's disease at the National Eye Institute, NIH, USA. *Jpn J Ophthalmol.* 1988;32:330–333.

[14] Belfort Junior R, Nishi M, Hayashi S, et al. Vogt-Koyanagi-Harada's disease in Brazil. *Jpn J Ophthalmol.* 1988;32:344–347.

[15] Sheu SJ. Update on uveomeningoencephalitides. *Curr Opin Neurol*. 2005;18:323–329.

[16] Khairallah M, Yahia SB, Ladjimi A, et al. Pattern of uveitis in a referral centre in Tunisia, North Africa. *Eye.* 2007:21:33–39.

[17] Sugiura S. Vogt-Koyanagi-Harada disease. *Jpn. J Ophthalmol.* 1978;22:9–35.

[18] Read RW, Rao NA. Utility of existing Vogt-Koyanagi-Harada syndrome criteria at initial evaluation of individual patient: a retrospective analysis. *Ocular Immunol Inflamm*. 2000;8:227–234.

[19] Kitamura M, Takami K, Kitachi N, et al. Comparative study of two sets of criteria for the diagnosis of Vogt-Koyanagi-Harada's disease. *Am J Ophthalmol*. 2005;139:1080–1085.

[20] Yang P, Ren Y, Li B, et al. Clinical characteristics of Vogt-Koyanagi-Harada syndrome in Chinese patients. *Ophthalmology.* 2007;114:606–614.

[21] Khairallah M, Zaouali S, Messaoud R, et al. The spectrum of Vogt-Koyanagi-Harada disease in Tunisia, North Africa. *Int Ophthalmol.* 2007;27:125–130.

[22] Zhao M, Jiang Y, Abrahams IW. The association of HLA antigens with VKH syndrome in a Han Chinese population. *Arch Ophthalmol.* 1991;109:368–370.

[23] Kim MH, Seong MC, Kwak NH, et al. Association of HLA with Vogt-Koyanagi-Harada Syndrome in Koreans. *Am J Ophthalmol.* 2000;129:173–177.

[24] Goldberg AC, Yamamoto JH, Chiarella JM, et al. HLA-DRB1*0405 is the predominant allele in Brazilian patients with Vogt-Koyanagi-Harada disease. *Hum Immunol*. 1998;59:183–188.

[25] Pivetti-Pezzi P, Accorinti M, Colabelli-Gisoldi RA, et al. Vogt-koyanagi-Harada disease and HLA type in Italian patients. *Am J Ophthalmol*. 1996;122:889–891.

[26] Shindo Y, Inoko H, Yamamoto T, et al. HLA-DRB1 typing of Vogt-Koyanagi-Harada's disease by PCR-RFLP and the strong association with DRB1*0405 and DRB1*0410. *Br J Ophthalmol*. 1994;78:223–226.

[27] Damico FM, Cunha-Neto E, Goldberg AC, et al. T-Cell recognition and cytokine profile induced by melanocyte epitopes in patients with HLA-DRB1*0405-positive and negative Vogt-Koyanagi-Harada Uveitis. *Invest Ophthalmol Vis Sci.* 2005;46:2465–2471.