Vogt-Koyanagi-Harada disease

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Vogt-Koyanagi-Harada (VKH) disease has been known, but not necessarily recognized in its complete form, for over a millennium. Despite this, information regarding the exact cause and best treatment regimen for this potentially blinding condition are not established. Manifesting ophthalmologically as a bilateral, granulomatous panuveitis, VKH disease seems to be a T-cell mediated systemic autoimmune process, which evidence increasingly suggests is directed at one or more antigens associated with melanocytes. As such, any organ system that contains melanocytes is a potential target of attack, including the eye, skin and hair, inner ear, and meninges. VKH disease occurs more frequently in certain ethnic groups. The disease has distinct phases, with acute disease involving primarily the ocular posterior segment, central nervous system, and inner ear. By contrast, chronic-recurrent disease involves the ocular anterior segment and integumentary system. Aggressive anti-inflammatory therapy is typically required, but no quality clinical trial data exist to guide the agent of choice, dosage, or duration of therapy. Complications are not uncommon and are typically the reason for decreased vision.

Many questions remain to be answered regarding VKH disease. Work toward these answers continues, as evidenced by the occurrence of an ongoing series of international workshops directed specifically at this disease. Out of the two workshops held to date, revised diagnostic criteria [1] have been issued and a disease severity grading scheme is in formation, both for use in planned prospective clinical trials.

Historical background

The association of poliosis with inflammatory eye disease was recognized as early as the 10th century AD, when Ali-ibn-Isa described what is now termed chronic VKH disease [2,3]. The current tripartite eponym stems from descriptions of the chronic disease phase by Vogt [4] in 1906 and Koyanagi [5] in 1929, and of the acute disease phase by Harada [6] in 1926. Babel [7] in 1932 and Bruno and McPherson [8] in 1949 realized that these descriptions were points on a disease spectrum and coalesced these entities under the rubric of VKH disease. Although the acute presentation is still occasionally referred to as Harada’s disease, recently published revised diagnostic criteria favor always using the full name, given the knowledge that this is one disease process [1].

Epidemiology

Vogt-Koyanagi-Harada disease occurs most commonly in certain ethnic groups. Although not established definitively, it is possible that the link between these groups arises from a common ancestry in the original peoples of Asia. Dispersion then occurred through migration across the Asian continent, over the Bering Strait land bridge, and into the Americas [9]. This susceptible group of individuals includes modern-day East and Southeast Asians, Asian Indians, Middle Easterners, Native Americans, and Hispanics. The disease occurs, but is uncommon, in whites and Africans [10]. An American Indian ancestry has been reported as important in patients from the United States [11,12]. Rarity in Africans suggests that amount of pigmentation alone is not the main factor in the etiology of VKH disease. Rather, something within...
the immune repertoire of susceptible individuals likely predisposes them to sensitization to antigens of melanocytic origin. Details of the relationship between genetics and VKH disease are discussed further in the next section.

Vogt-Koyanagi-Harada disease has been reported to be responsible for up to 9.2% of cases of uveitis clinics in Japan [2], is the main cause of autoimmune noninfectious uveitis in Brazilians [13], and is the second most common uveitic diagnosis made in Saudi Arabia [14]. In contrast, earlier publications from the United States reported a prevalence in uveitis clinics of 1% [15] to 4% [16]. Read et al [17] recently examined uveitic disease prevalence in a uveitis tertiary referral center in Southern California for the 3-year period 1996 to 1998. They found the frequency of VKH disease to be 7%. This more frequent occurrence compared with previous reports was believed to be secondary to the large Hispanic and Asian populations in Southern California and referral bias to this particular clinic. It is highly likely that as the demographics of the remainder of the United States continue to diversify, VKH disease will become a more frequently encountered entity in practices across the country.

Most series have reported an approximate female to male disease ratio of 2:1 [2,10,18]. Most patients have the onset of disease while in their third to fifth decade of life, but cases have been reported in children as young as 4 years of age [19,20]. It has been suggested that VKH disease in children may be more aggressive than in adults. In one series, Tabbara et al [21] found that 61% of children with VKH disease had final visual acuities of 20/200 or worse despite medical and surgical therapy. In a review of world literature on pediatric VKH disease, however, Rathinam et al [22] found that 85.7% of children had a final visual acuity of 20/30 or better in the best eye. The prognosis in this subpopulation seems to be quite variable, and final visual outcome may be related to as yet unknown differences between the various ethnic groups, time to treatment, type of treatment, and duration of treatment.

**Etiology and pathogenesis**

The exact cause of VKH disease is unknown. Most research on its pathophysiology has been directed at identifying the precise target of autoimmune attack and associations of the disease with specific immune profiles.

Ophthalmic histopathology has shown VKH disease to be a granulomatous panuveitis that has many similarities with sympathetic ophthalmia [23]. Immunohistochemical investigations have shown the predominant infiltrating cell in the choroid is the T lymphocyte, with a larger proportion of helper (CD4+) cells than cytotoxic (CD8+) cells [24]. Present also are epithelioid and multinucleated giant cells containing melanin [25]. Choroidal melanocytes have been shown to express major histocompatibility complex class II molecules on their surface in eyes from patients with VKH disease [24]. These molecules are required to participate in antigen presentation to CD4+ T cells. In the cerebrospinal fluid of VKH disease patients, activated CD4+ T cells predominate [26,27] and melanin-containing macrophages have been found [28,29]. Similar findings have been reported from studies of sites of vitiligo in VKH disease [30,31].

Animal studies have shown that a VKH-like disease is inducible in rats by immunization with peptides derived from proteins of the tyrosinase family, which are found in melanocytes [32]. In this disease, the rats develop uveitis 12 to 21 days after immunization, followed by fundus depigmentation at 2 to 3 months. Histopathologically, the disease revealed granulomatous inflammation in the choroid and iris, similar to that observed in patients with VKH disease [2].

With the exception of patient history, marked similarities exist between the clinical and pathologic manifestations of VKH disease and sympathetic ophthalmia. Because the latter condition is almost certainly caused by immune sensitization to uveal tissue following trauma, this provides further circumstantial evidence that VKH disease shares a similar immune pathophysiology, although dissimilar avenues of sensitization.

As in other autoimmune conditions, associations with certain HLA subtypes are not unexpected because these cell surface molecules are involved in antigen presentation and recognition. HLA typing and association studies have been performed in a number of different ethnic groups with high frequencies of VKH disease, including the Japanese [33], Koreans [34], Chinese [35], Vietnamese [36], Hispanics [37], Brazilians [13], Mexican Mestizos [38], and Italians [39]. In these studies, the strongest associations have been with the HLA-DR4 allele, and when further subtyping was performed, the greatest association has been found with HLA-DRB1*0405 or HLA-DRB1*0410. Analysis of the amino acid sequence of the HLA-DRB1*0405 allele indicates that a serine at position 57 or glutamine at position 70 may play a crucial role in determining disease susceptibility, because these locations are within the antigen-binding grove of the molecule [33,40]. Recent studies have shown that
lymphocytes from patients with VKH disease who possess the HLA-DRB1 * 0405 allele recognize peptides derived from melanocytes and melanoma proteins [41]. Among these peptides are those derived from tyrosinase [42] and other tyrosinase family proteins, such as tyrosinase-related proteins 1 and 2 [43]. Moreover, T-cell clones established from patients with VKH disease and stimulated with tyrosinase family peptides have demonstrated a predominately proinflammatory, Th1-type T-cell response [44].

Existing evidence points to a T-lymphocyte-mediated autoimmune process directed against a melanocyte-associated antigen or antigens, occurring in a permissive immune environment, more commonly found in certain groups. As in other autoimmune diseases, however, it seems likely that because there are a greater number of individuals with the susceptible genetic background than there are who actually develop the disease, some triggering event may be required. Multiple theories exist regarding a possible trigger. Epstein-Barr virus DNA has been isolated from the vitreous of patients with VKH disease [45] and the Epstein-Barr virus is able to activate B lymphocytes from patients with VKH disease more easily than B lymphocytes from patients with other uveitic entities [46]. VKH disease has also been reported to occur following cutaneous injury, presumably by direction of an autoimmune attack against cutaneous melanocytic antigens liberated at the site of injury [47].

Clinical features

Vogt-Koyanagi-Harada disease typically consists of four phases: (1) prodromal, characterized by neurologic and auditory manifestations; (2) acute uveitic, characterized by a diffuse choroiditis, which may result in exudative retinal detachments and papillitis, and possibly an intraocular cellular reaction; (3) chronic, characterized by depigmentation of various structures, including ocular (fundus and limbus) and integumentary (poliosis and vitiligo, also possibly with alopecia); and (4) chronic-recurrent, with an iridocyclitis that may be recurrent, chronic, or both [2]. Based on these features and their distinctive timing within the overall disease course, diagnostic criteria were recently revised and published (Table 1) [1].

Prodromal phase

Vogt-Koyanagi-Harada disease has been termed a uveomeningitis, which although accurate and useful in directing the clinician’s differential diagnosis, is not inclusive of the entire potential disease process. Nevertheless, this term does emphasize two of the most prominent areas of acute disease involvement, although not in chronologic order. Melanocytes contained within the meninges [48] are apparently the first site of autoimmune attack, along with the inner ear, although lack of knowledge of the initiating events in this disease prohibits definitive conclusions about the initial site of involvement. As mentioned previously, the occurrence of VKH disease following cutaneous trauma [47] raises the possibility that perhaps similar subclinical sensitizing events are present in all VKH disease patients. Regardless, patients typically report severe headaches, nuchal rigidity, possibly fever and nausea, and auditory symptoms (mainly tinnitus and dysacusia) as initial disease manifestations. Occasionally, cutaneous symptoms, such as skin erythema [49] and scalp tenderness [50], may occur early in the disease course, presumably as a consequence of inflammatory cell infiltration into the skin. The prodromal stage of VKH disease may last from only a few days to several weeks [51]. Patients have been admitted to the hospital with a diagnosis of aseptic meningitis before the onset of ocular disease led to the full diagnosis [52]. Cerebrospinal fluid analysis at this point usually reveals a pleocytosis, possibly with melanin-laden macrophages, suggesting VKH disease [52]. The pleocytosis resolves despite persistence of disease manifestations elsewhere, so if performed, lumbar puncture must be carried out early in the disease course. If sufficient neurologic symptoms exist followed by the expected ocular signs, then lumbar puncture is not required for diagnosis by the VKH Workshop Revised Criteria [1].

Hearing loss, if present, usually involves the higher frequencies and may persist for years. Audiometric abnormalities, as measured by pure tone stimuli, middle ear analysis, and auditory brainstem responses, were shown in 20 of 26 patients from the National Eye Institute [51].

Acute uveitic phase

The ocular hallmark of acute VKH disease is a diffuse inflammatory cell infiltrate into the choroid, producing thickening detectable on ultrasonography [53]. This is commonly accompanied by hyperemia of the optic nerve head. Leakage of fluid from the choroid through the retinal pigment epithelium occurs, with the resultant formation of focal areas of subretinal fluid accumulation, development of larger bullous detachments, or both. Fluorescein angiography performed at this stage typically reveals focal areas of delay in choroidal perfusion, multifocal areas of pinpoint leak-
Table 1
Vogt-Koyanagi-Harada disease workshop revised diagnostic criteria

<table>
<thead>
<tr>
<th>Complete Vogt-Koyanagi-Harada disease (1–5 must be present)</th>
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<tbody>
<tr>
<td>1. No history of penetrating ocular trauma or surgery preceding the initial onset of uveitis</td>
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<tr>
<td>2. No clinical or laboratory evidence suggestive of other entities</td>
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<tr>
<td>3. Bilateral ocular involvement</td>
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<tr>
<td>A. Early manifestations of disease</td>
</tr>
<tr>
<td>There must be evidence of a diffuse choroiditis (with or without anterior uveitis, vitritis, or optic nerve hyperemia) which may manifest as:</td>
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<tr>
<td>1. Focal areas of subretinal fluid</td>
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<td>2. Bullous serous retinal detachments</td>
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<td>or both of the following in the face of equivocal fundus findings:</td>
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<td>3. Ultrasonography: diffuse choroidal thickening, without evidence of posterior scleritis</td>
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<tr>
<td>4. Fluorescein angiography: focal areas of delay in choroidal perfusion, multifocal areas of pinpoint leakage, large placoid areas of hyperfluorescence, pooling within subretinal fluid, optic nerve staining (listed in chronologic order of occurrence)</td>
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<tr>
<td>B. Late manifestations of disease (with history suggestive of prior presence of findings from 3A) and</td>
</tr>
<tr>
<td>1. Ocular depigmentation</td>
</tr>
<tr>
<td>a. Sunset glow fundus</td>
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<tr>
<td>or</td>
</tr>
<tr>
<td>b. Sugiura sign</td>
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<tr>
<td>AND</td>
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<tr>
<td>2. One of the following other signs (or 2 of the following in the absence of above depigmentation findings)</td>
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<tr>
<td>A. Chorioretinal nummular scars (previously referred to as Dalen-Fuchs nodules)</td>
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<td>B. RPE clumping or migration</td>
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<tr>
<td>C. Recurrent or chronic anterior uveitis</td>
</tr>
<tr>
<td>4. Neurologic-auditory findings (manifesting in initial stage of disease or reliable documentation of such)</td>
</tr>
<tr>
<td>A. Meningismus (headache alone is not sufficient to meet definition of meningismus)</td>
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<tr>
<td>or</td>
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<tr>
<td>B. Tinnitus</td>
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<td>or</td>
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<tr>
<td>C. Cerebrospinal fluid pleocytosis</td>
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<tr>
<td>5. Integumentary (not preceding onset of central nervous system or ocular disease)</td>
</tr>
<tr>
<td>A. Alopecia</td>
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<td>or</td>
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<tr>
<td>B. Poliosis</td>
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<tr>
<td>or</td>
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<td>C. Vitiligo</td>
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Incomplete Vogt-Koyanagi-Harada disease (1–3 must be present and either 4 or 5)

1. No history of penetrating ocular trauma or surgery preceding the initial onset of uveitis
2. No clinical or laboratory evidence suggestive of other entities
3. Bilateral ocular involvement and either
4. Neurologic-auditory findings or
5. Integumentary findings

Probable Vogt-Koyanagi-Harada disease (isolated ocular disease) (1–3 must be present)

1. No history of penetrating ocular trauma or surgery preceding the initial onset of uveitis
2. No clinical or laboratory evidence suggestive of other entities
3. Bilateral ocular involvement

Table 1 (continued)

Chronic

The chronic phase of VKH disease is characterized by depigmentation of various structures. On the external ocular surface, pigmentation seen at the limbus in more heavily pigmented races may disappear, termed Sugiura’s sign [58]. Within the eye, loss of choroidal melanocytes results in an orange coloration to the fundus, termed the sunset-glow fundus, more commonly seen in Asians and Hispanics than whites [59]. Migration of retinal pigment epithelial cells may result in pigment clumping in
various areas of the fundus. Rounded hypopigmented lesions appear, primarily inferiorly. These lesions have most commonly been referred to as resolved Dalen-Fuchs nodules [2], but a recent report shows that although these areas represent a loss of retinal pigment epithelial cells, there is no direct evidence that they are or were Dalen-Fuchs nodules [60]. Why these lesions appear primarily inferiorly is unknown.

Chronic-recurrent

The chronic-recurrent phase does not affect all patients, but by definition only those in whom recurrent bouts of intraocular inflammation occur. When recurrent inflammation does occur, it is usually an anterior uveitis, in stark contrast to the primarily posterior involvement in acute disease. When recurrent posterior segment disease occurs, it is usually within 6 months of the initial onset, and is a consequence of a too rapid taper of medication [61]. Multiple recurrences of exudative retinal detachments have been reported, occurring as long as 35 months after disease onset [62], although this is considered an uncommon disease course.

It is during the chronic-recurrent phase of the disease that many of the vision-reducing complications associated with VKH disease are most likely to occur, including cataract, glaucoma, choroidal neovascular membrane development, and subretinal fibrosis. Read et al [10] recently reviewed the records of 101 patients with VKH disease, reporting on the frequencies of complications and predictive factors for final visual acuity. Out of the 202 eyes included, 103 eyes (51%) developed at least one complication, including cataract in 84 eyes (42%), glaucoma in 54 eyes (27%), choroidal neovascular membranes in 22 eyes (11%), and subretinal fibrosis in 13 eyes (6%).

Management

Medical

The mainstay of management of VKH disease remains corticosteroids, and because of the potential for visual morbidity, treatment should be both prompt and
aggressive [63]. In the United States, most clinicians begin with high-dose oral corticosteroids, typically in the range of 1 to 2 mg/kg/day of oral prednisone [2]. Supplemental regional corticosteroid injections may be used. If the retinal detachments fail to resolve, intravenous therapy may be tried, usually with methylprednisolone, 1 g/day over 3 consecutive days. If corticosteroid therapy is effective, retrospective data suggest that tapering the therapy over a minimum of 6 months is required to minimize complications and recurrences [2,61]. Outside the United States, clinicians may frequently admit patients to the hospital for intravenous therapy as a first-line treatment, based on anecdotal evidence that this early, aggressive treatment reduces recurrences and the development of complications. Whether this is in fact the case remains to be proved in a prospective clinical trial.

Patients with resistant or recurrent disease may require noncorticosteroid immunosuppressive therapy [2]. Multiple therapeutic classes and agents have been used, including the antimetabolite azathioprine, and the alkylating agents cyclophosphamide and chlorambucil [64]. Based on the etiologic discussion presented previously, such agents as cyclosporine and tacrolimus, which target T-lymphocyte function, seem ideal. In fact, these agents have been used with success in cases of corticosteroid intolerance or resistance [65–68]. All of these agents have significant potential side effects, and their use should be under the direction of an experienced clinician.

Topical corticosteroids are mainly an adjunctive therapy in VKH disease. In acute disease, they are wholly inadequate in treating the posterior segment manifestations. In chronic disease, where the inflammation is primarily anterior, topical therapy is still frequently insufficient, because recurrent disease is notoriously resistant to treatment. Cycloplegics should be used to prevent posterior synechiae and improve comfort. Nonsteroidal anti-inflammatory drugs have essentially no role.

Surgical

Surgical therapy in VKH disease is limited primarily to addressing the complications induced by the disease. Rarely, surgical drainage of subretinal fluid that was resistant to medical therapy may be indicated.

Cataracts, which may develop in up to 42% of eyes [10], seem to be safe to remove if the disease has been controlled for at least 3 months [69]. The decision of whether or not to implant a lens should be based on the patient’s past disease course, including whether there is a demonstrated tendency to develop posterior synechiae [2]. Moorthy et al [69] reported a significant improvement in visual acuity following cataract extraction with lens implantation.

Glaucoma may occur in up to 45% of patients with VKH disease [61]. Forster et al [70] reported that in 31% of patients with VKH disease and glaucoma, medical therapy alone was sufficient, whereas 69% required surgical therapy. This study was published in 1993, when many of the currently available medications for intraocular pressure control were not yet approved in the United States.

Choroidal neovascular membranes may occur in up to 11% of eyes [10]. Typically ill-defined in nature, these neovascular membranes may be treated inadequately with photocoagulation therapy [71]. Increased anti-inflammatory therapy may result in resolution, as reported for other posterior and panuveitis entities [72–74]. One small series showed an improvement of vision in two of three eyes following surgical removal of subretinal neovascularization [75].

Prognosis

In their review of complications and visual outcomes in VKH disease, Read et al [10] found that a longer median duration of disease and a greater number of recurrent episodes of inflammation were significantly associated with the development of complications. A poor final visual acuity was predicted by greater numbers of complications developing, older age at disease onset, a longer median duration of disease, and greater number of recurrent episodes of inflammation. The better the visual acuity at presentation, the more likely that eye was to have a better visual acuity at final follow-up. In their study, 49% of eyes obtained a final visual acuity of 20/40 or better, 22% of eyes obtained 20/50 to 20/100, and 29% of eyes obtained a final visual acuity of 20/200 or worse [10]. African-Americans did worse overall, with 70% of eyes having final visual acuities of 20/200 or worse.

Many questions remain to be answered regarding VKH disease. Identification of the exact target antigen may allow development of more specific therapies. Until that point, prospective clinical trials are needed to identify the most efficacious therapeutic protocols to control acute disease and prevent future vision-limiting complications.

References


