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Review

Vogt–Koyanagi–Harada syndrome: Perspectives for immunogenetics, multimodal imaging, and therapeutic options☆,☆☆

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ABSTRACT

Vogt–Koyanagi–Harada syndrome (VKH) is a bilateral, diffuse granulomatous uveitis associated with neurological, audiovestibular, and dermatological systems. The primary pathogenesis is T-cell-mediated autoimmune response directed towards melanocyte or melanocyte-associated antigens causing inflammation of the choroidal layer. This phenomenon usually leads to diffuse inflammatory conditions throughout most parts of eye before ocular complications ensue. The diagnosis is achieved mainly by clinical features according to the revised diagnostic criteria of VKH published in 2001, without confirmatory serologic tests as a requirement. However, ancillary tests, especially multimodal imaging, can reliably provide supportive evidence for the diagnosis of early cases, atypical presentations, and evaluation of management. Prompt treatment with systemic corticosteroids and early non-steroidal immunosuppressive drug therapy can lessen visually threatening ocular complications and bring about good visual recovery. Close monitoring warrants visual stabilization from disease recurrence and ocular complications. This article review aims not only to update comprehensive knowledge regarding VKH but also to emphasize three major perspectives of VKH: immunogenetics as the major pathogenesis of the disease, multimodal imaging, and therapeutic options. The role of anti-vascular endothelial growth factor therapy and drug-induced VKH is also provided.

Contents

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1. Introduction

The Vogt–Koyanagi-Harada (VKH) syndrome is a multisystem disorder characterized by ocular inflammation as well as neurological, audiovestibular, and dermatological symptoms. The disease was described at the beginning of the 20th century by Alfred Vogt followed by Yoshizo Koyanagi (1914) and Einosuke Harada (1926) [1]. Typical ocular features are chronic, bilateral, non-necrotizing, granulomatous panuveitis with exudative retinal detachment.

2. Epidemiology

VKH is prevalent in darkly pigmented races, mostly Asians, North Africans, Hispanics, and some natives of South America. A high prevalence of greater than or equal to 10% was reported from East Asia and Southeast Asia. In all the regions of Asia, VKH is in the top three most common identifiable noninfectious entities. The disease is uncommon in Caucasians [2]. Regarding gender predilection, females are classically involved in higher proportions than males in most studies, except for some studies from Japan and China, which showed no difference in prevalence by gender. The disease usually affects patients in the late third to early fifth decade of life [3]. Nevertheless, involvement in children was rarely reported in both genders [4–7].

3. Pathophysiology and mechanisms

Although the pathogenesis of VKH has been widely studied, the exact etiology of VKH remains unknown. The pathogenesis of VKH is thought to be multifactorial and primarily targets the choroidal layer. Many etiologies were previously reported, most of which were immunogenetic and environmental causes. Immunogenic factors can be categorized as human leukocyte antigen (HLA) related and non-HLA related.

3.1. Non-HLA-related immunogenetic factors

The immunologic process fundamentally driving the disease is a T-cell-mediated autoimmune response against one or more antigenic components of melanocytes [8–10]. Early studies implicated the T helper (Th) 1 subset of $CD4^+$ cells as the causal agents in the pathogenesis of autoimmunity. Th17 cells and Th17 cell-related genes were also implicated as the vital agents involved in the pathogenesis of uveitis in VKH [11,12]. In addition, Th17 effector cells are induced in parallel to Th1 with complexity and they counter-regulate each other [13]. A variety of non-HLA genes, including CTLA-4, MIF, MCP-1, IL23A, IL-23R, IL-17F, IL-27, and C4A, were found to be associated with VKH [14–20]. IL-23 stimulated the production of IL-17, which is a main cytokine of Th17 cells. This interaction was significantly increased in VKH patients with active uveitis [11]. IL-27, produced by activated dendritic cells and macrophages, has been shown to be an important immunoregulatory cytokine involved in the immune response and in the development of inflammation. The reduced IL-27 expression may result in higher Th17 in active VKH patients. Treatment with corticosteroids provides an upregulation of IL-27 and a downregulation of IL-17 contributing to the resolution of the intraocular inflammation [15]. Hou et al. recently reported a large cohort presenting associations of IL17F and IL23A with VKH. However, the study suggested that IL17F and IL23A, although important, are not specific enough to explain their genetic role in uveitis. This also indirectly indicated the existence of other environmental factors [16]. In addition, immunoregulatory mechanisms by $CD4^+CD25^{high}$ regulatory T cells and immunoregulatory cytokines (IL-10 and TGF-beta) were described in VKH [21,22].

3.2. HLA-related immunogenetic factors

The variation of HLA genes in VKH has been previously described [23,24]. The association of VKH with the HLA-DR4/DRw53 allele was found in Japanese, Chinese, North American, and Hispanic patients [23,25,26]. Also, HLA-DRB1 was reportedly associated with VKH in Japanese and Hispanic patients. Tiercy et al. studied genotyping analysis of a large cohort of VKH patients from southern India and found HLA-DRB1*0405 and HLA-DRB1*0410 alleles were significantly increased in VKH patients. However, the association of HLA-DRB1 with VKH seems weaker in Indian patients compared to Japanese or Hispanic patients, which may imply a different non-HLA immunogenetic background in Indian VKH patients [24]. Recently, a systematic review and meta-analysis by Shi et al. affirmed the association between VKH and HLA-DR4/DRB1*04, and identified HLA-DRB1*0404, 0405 and 0410 as risk sub-alleles, while 0401 was identified as protective sub-allele. The authors also found that strength of association is different in different ethnic groups [27].

Besides autoimmune responses to melanocytes, VKH appears to be caused by autoimmune responses to melanocyte-associated antigens. Tyrosinase and gp100, melanoma-associated antigen peptides, were reported to be recognized by T cells in HLA-DRB1*0405-positive VKH patients and could be associated with the cause and pathology of VKH [10,28,29]. KU-MEL-1 is another auto-antigen that is strongly expressed by most melanoma cell lines, melanoma tissue samples, and cultured melanocytes. Positive serum KU-MEL-1 antibody was significantly associated with HLA-DRB1*0405-positive VKH patients compared with other uveitis entities and healthy controls, which implies the possible involvement of KU-MEL-1-specific CD4+ T cells in the pathogenesis of VKH [30].