Review Article

VOGT-KOYANAGI-HARADA SYNDROME AND ITS MULTISYSTEMIC EFFECTS

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ABSTRACT
Vogt-Koyanagi-Harada's syndrome is a rare disease that affects tissues containing melanocytes, such as the eyes, central nervous system, inner ear and skin. Some ethnic groups have a higher probability of developing the disease, including Asians, Indians and Latin Americans and females are affected more often. Methods: Literature was reviewed in books, articles published on the internet and papers available in the online databases MEDLINE, LILACS and SciELO. Texts were selected that focused on otorhinolaryngological symptoms. Literature review: The disease probably has autoimmune etiology, with aggression occurring on the surface of melanocytes by promoting inflammatory reaction in which T lymphocytes predominate. The allele most often found in association with this disease is HLA DRB1*0405. Clinical manifestations are divided into four stages: prodromal, uveitic, chronic and recurrent. Otorhinolaryngological symptoms occur during the uveitic stage and are characterized by bilateral sensorineural hearing loss, tinnitus and vestibular symptoms. Diagnosis is made according to the diagnostic criteria for the disease. Treatment is primarily with corticosteroids. Conclusions: It is important that professionals in other specialties are able to recognize Vogt-Koyanagi-Harada's syndrome, because late diagnosis can lead to ocular and cutaneous sequelae.

Key words: Uveomeningoencephalitic syndrome. Uveitis. Vertigo. Tinnitus.

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Introduction

Vogt-Koyanagi-Harada syndrome (VKHS) is a rare multisystemic disease which probably has autoimmune etiology and which affects tissues that contain melanin. Also known as uveomeningoencephalitic syndrome, the disease is characterized by chronic bilateral panuveitis associated with a varying constellation of neurological, auditory and cutaneous manifestations[1]. The first descriptions of this disease were written in the 12th century by an Arab physician, Ali IBN ISA, and in the 19th century Jacobi, Nettelship and Tay also described it. Many of these cases were actually different diseases, but many of them were clearly VKHS cases. The syndrome continued to be described at the beginning of the 20th century by the Swiss physician Alfred Vogt and by Japanese researchers. Yoshizo Koyanagi published his first report in 1914 and in 1926 Einosuke Harada published an article based on a series of cases of patients who exhibited signs and symptoms that are characteristic of the disease. It is now accepted that the cases described by Vogt, Koyanagi and Harada represented a single entity with the wide spectrum of clinical variation of a syndrome which now has the names of all three authors[2]. The disease is more common among certain ethnic groups. Susceptible groups include the Asian populations in the east and southeast of the continent, Middle Eastern and Indian populations, Native Americans and Hispanics. Although uncommon, the syndrome also affects Caucasians and Africans. The disease's rarity among Africans suggests that the quantity of pigmentation in isolation is not the principal factor in its etiology[3]. In Japan, 8% of all cases of uveitis are caused by VKHS, whereas in the United States and Brazil it accounts for 0.9% and 2.5% of cases, respectively[4]. One study conducted at the uveitis clinic of a tertiary healthcare center found that 13% of their patients were diagnosed with VKHS, making it the institution's second most common cause of uveitis and their most common endogenous cause[5]. Females are generally affected more, at a proportion of 2:1 with relation to males, although this is not the case in the Japanese population. The age group most affected compromises people in their second to fifth decades of life and prevalence is even greater in the third decade. Children are rarely affected, but when they are the clinical course is more aggressive that in adult cases[6]. The youngest VKHS patient described was a 4-year-old child[1]. The objective of this article is to emphasize the importance of recognizing this syndrome in general clinical practice and

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in the specialties, with a focus on its etiology and pathogenesis, clinical manifestations and the many different forms of treatment that are currently proposed.

Methods

This review covers books and articles indexed on MEDLINE, LILACS and SciELO and published from 1978 to 2009. The keywords used were Vogt-Koyanagi-Harada syndrome, uveomeningoencephalitic syndrome and dizziness. The search returned 90 references, 62 of which were selected on the basis that they dealt with the disease in a more all-encompassing manner and focused on its otorhinolaryngological manifestations, which often go unrecognized and can be a significant cause of deterioration of patients' quality of life.

Etiology and pathogenesis

The pathogenesis of VKHS has not yet been fully elucidated. However, the wide spectrum of the disease's manifestations suggests a central mechanism that results in systemic involvement. Inflammatory processes and destruction of melanocytes have been described in many tissue types, including skin, the inner ear, meninges and uvea. These histopathological findings suggest that that the disease has an infectious or autoimmune origin[7,8]. Studies conducted within otorhinolaryngology have concluded that the immune system can damage the inner ear and the cochlear and vestibular nerves. It is known that the disease's effects on in this system are provoked by destruction of the melanocytes found inside the inner ear, causing hearing and balance disorders[9]. It is currently believed that VKHS is a cell-mediated autoimmune disease which affects melanocytes. Immunohistochemical studies have demonstrated the presence of cellular infiltrate primarily composed of helper T lymphocytes (CD4), in addition to multi-nuclear giant cells containing melanin[10]. Studies with animals have demonstrated that proteins from the tyrosinase family, TRP1 and TRP2, which are found in melanocytes have great importance for the pathogenesis of VKHS, because they encourage recognition of these cells by T lymphocytes[10]. There are other proteins found in melanocytes that may also function as autoantigens in VKHS, including MART 1, PMel-17/gp100, KU-MEL-1, PAX3 and uveal autoantigen (UACA)[11]. However, it is not only cellular immunity that appears to be important in development of this syndrome, but humoral immunity also plays a part, since analysis of an eyeball enucleated from a patient with the disease also detected B lymphocytes in affected tissues[12]. A recent study of VKHS patients also detected a significant reduction in the number and activity of regulatory T cells (CD4 and CD25), which are responsible for negative regulation of the autoimmune response[13,14]. It was found that VKHS patients had lymphocytes that were relatively resistant to the apoptosis process mediated by the anti-Faz antibody[15]. Recently, interleukins (IL) IL-23 and IL -17 have been shown to play a relevant role in development and maintenance of autoimmune diseases. It was found that patients with VKHS had heightened expression of the gene that codes for production of IL-23, which is jointly responsible for perpetuating inflammatory activity[16]. Melanocytes located in the choroid of patients with VKHS exhibit major histocompatibility complex type II (MHC II). These molecules are necessary for expression of antigens to CD4 T cells[17]. The immunogenetic predisposition in patients who have the syndrome appears to be related to the HLA haplotypes. The same HLA-DR4 allele was identified in monozygotic twins from Vietnam who had the syndrome[18]. The disease has the strongest association with the HLA-DR4 allele in different groups of patients, but other alleles have also shown themselves to be determinants of the syndrome's emergence, including HLA-DR53, DQ54, DQ7 and DR1[7,19]. The allele subtypes that have the most significant associations with the disease are HLA-DRB1*0410 and HLA-DRB1*0405, with the second of these being most common in different populations, including the Brazilian population[20]. Many authors have been attempting to elucidate the cause or "trigger" that results in the immune system disorder and emergence of the syndrome. Some studies have suggested the possibility that the Epstein-Barr virus is responsible for the process of disease reactivation, since particles of this virus' DNA have been isolated from the vitreous humor of patients with the syndrome[21]. One publication described six cases of patients who had had contact with each other and who presented with the initial stages of VKHS almost simultaneously. That report supports the hypothesis that an external factor, such as a viral infection, may be involved in development of the disease[22]. Several isolated reports have attempted to make a contribution towards elucidation of the pathogenesis of the disease. There are cases in which the syndrome emerged after skin injuries, two cases after treatment with BCG for melanoma and another in which onset was after surgery for malignant metastatic melanoma[23]. There is also a case report that suggests that even a closed head trauma, which results in direct trauma to tissues containing melanocytes, such as the eyes, can lead to VKHS[24]. Cases of the syndrome have also been reported in patients with malignant lymphoma[25] and patients with chronic hepatitis C who were taking interferon-alpha and ribavirin[26]. Several other autoimmune diseases may be associated with VKHS, such as Graves' disease[27], IgA nephropathy[28], polyglandular autoimmune syndrome type I[29], recurrent polychondritis[30], aortitis[31], Guillain-Barré syndrome[32], *Diabetes mellitus*[33] and scleroderma[34].

Clinical manifestations

Four clinical stages of VKHS have been described; the prodromal, uveitic, chronic and recurrence phases[3]. The prodromal or meningoencephalitic phase is seen in approximately 50% of cases and has a duration of a few days to a few weeks and frequently mimics a viral infection[35]. The severity and range of symptoms can vary and they are very often attributed to inflammatory arachnoiditis or to subarachnoid adhesions[36]. Patients may present with headache, mild fever, photophobia, generalized muscle weakness, hemiparesis, cerebellar ataxia, transverse myelitis, dysarthria, aphasia, mental confusion, psychosis and meningism[37], which is one of the most common manifestations during this phase of the disease[38]. Photophobia and lacrimation may develop,

and also feelings of hypersensitivity in the skin and hair. An analysis of the cerebrospinal fluid during this phase finds lymphocytic pleocytosis in more than 80% of cases, increased cerebrospinal pressure and elevated protein[6]. In the majority of patients, the disease will progress to the uveitic phase 3 to 5 days after the prodromal phase. This phase lasts a number of weeks and is the main culprit for patients seeking medical attention. The most common symptom is bilateral blurred vision, which is present in 70% of cases. Other symptoms include ocular pain, photophobia, conjunctival hyperemia, photophobia, loss of visual acuity and even total loss of vision[6,37]. ocular findings are characterized by bilateral posterior uveitis with retinal edema, hyperemia or edema of the optic disc, serous retinal detachments, iridocyclitis and increased intraocular pressure. The anterior ocular chamber may also be involved with formation of mutton-fat keratic precipitate and iris nodules[39,40]. CIt is generally in this phase that the otorhinolaryngological manifestations of VKHS appear[37]. The chronic phase of the disease lasts from months to years and is characterized by the process of depigmentation of several tissues containing melanocytes, primarily the eyes and skin[41]. typical ocular findings are sunset glow fundus, Dalen-Fuchs nodules, and migration or accumulation of the pigmented epithelium of the retina[39]. Around two to three months after the onset of syndrome symptoms, it becomes possible to detect cutaneous findings such as vitiligo, alopecia and poliosis, which last is present in 80 to 90% of patients[10,42]. The recurrent phase does not affect all patients, but by definition just those who suffer with repeated outbreaks of ocular inflammation. Multiple ophthalmological complications occur during this phase of the disease, such as repeated retinal detachment, glaucoma, the formation of subretinal neovascular membranes, subretinal fibrosis and cataracts, which are the most common complication[37,43]. While VKHS is primarily identified on the basis of ocular and cutaneous symptoms, from the point of view of the otorhinolaryngologist, the auditory symptoms must also be identified, since they are present in around 50 to 75% of cases, impacting on patients' quality of life[7,35]. The inner ear had traditionally been considered to be protected from autoimmune aggression. However, that point of view fell into discredit in 1979 when McCabe described 18 cases of patients with sensorineural hearing loss who responded to treatment with corticosteroids and cyclophosphamide. That was when the clinical entity "immunomediated sensorineural hearing loss" was introduced[44]. The otorhinolaryngological manifestations of VKHS are the results of an autoimmune aggression suffered by structures of the inner ear and the cochlear and vestibular nerves. They include: hearing loss, tinnitus, dizziness and vertigo[35,45]. The form of hearing loss observed in the syndrome is sensorineural, rapidly progressive and bilateral[45]. Nevertheless, sometimes hearing loss may also present unilaterally at the start of the case, be asymmetrical and fluctuate, coinciding with inflammatory relapses. Habitually, the syndrome affects the capacity to understand spoken words, raises the threshold for pure high-frequency sounds or for all sounds and causes auditory recruitment in some cases. Tinnitus is present in 50% of cases[35,46]. The dizziness and vertigo are caused by inflammation compromising the vestibular system. Dysfunctions in this system, although less common among carriers of this syndrome, can cause abnormalities in ocular motricity leading to spontaneous horizontal nystagmus, abnormalities in slow eye movements and abnormalities in the oculovestibular reflex[47]. It is possible that patient with the syndrome may suffer more severe auditory dysfunctions if not treated correctly[44].

Diagnosis

In 1999, diagnostic criteria were the subject of discussion at the first international workshop on the disease. In 2001, the results of this meeting were published by the international committee on nomenclature in the form of revised diagnostic criteria that included: 1- absence of previous history of ocular trauma or surgery; 2- no evidence of other ocular diseases; 3- early bilateral ocular involvement (with focal areas of subretinal fluid or serous retinal detachment) or late bilateral ocular involvement (depigmentation, sunset glow fundus, Dalen-Fuchs nodules and migration or accumulation of the pigmented epithelium of the retina); 4- history or presentation of auditory and/or neurological symptoms; 5- cutaneous symptoms that appear during or after the neurological and ocular manifestations. On the basis of these criteria, VKHS may be classified as complete, when all criteria are met; as incomplete, when criteria 1, 2 and 3 plus 4 or 5 are met, or probable, when only criteria 1, 2 and 3 are met[1,38,40]. Although the criteria for VKHS are well-established, care should be taken when patients are classified, because several factors can affect this classification. First, the signs and symptoms of the disease are very often transitory, take place at different times, often exhibiting an atypical progression over time, and can be affected by treatment. Later ocular complications and dermatological abnormalities, for example, may be minimal or even absent if the patient has received early treatment, and at this point they may be classified as a probable or incomplete VKHS case. Furthermore, the prevalence of extraocular manifestations may differ between populations and, although rare, unilateral ocular involvement can be observed in VKHS[48,49]. Diagnosis of VKHS is essentially clinical, but certain supplementary tests can help to exclude other diseases and even contribute to early diagnosis[7]. There is no specific laboratory test for this disease, but some tests such as complete blood count, white blood cell count, erythrocyte sedimentation rate, rheumatoid factor, antiDNA antibodies, antiphospholipid antibodies, C3 and C4 and an antinuclear antibody test can indicate the presence of the syndrome's inflammatory activity and help with investigations for differential diagnosis and identifying concurrent diseases[37]. Although there are a considerable number of cases of VKHS with certain forms of HLA, a study of patients with uveitis and syndrome found that HLA typing had a positive predictive value that was too low to be used as a diagnostic method (>0.5)[50]. The most common imaging exams are angiography with fluorescein or with indocyanine green[7], the second of which is very sensitive for detecting subclinical injuries to the choroid[11,51]. Patients who exhibit symptoms caused by involvement of the auditory system should be tested for vestibular audiologic function and

undergo tonal, vocal and brainstem audiometry and tests for abnormal vestibular reflexes[48].

Differential diagnosis

Vogt-Koyanagi-Harada syndrome should always be considered whenever a patient has symptoms involving neurological, ocular, otorhinolaryngological and cutaneous manifestations[52]. DInfectious diseases such as syphilis, tuberculosis, toxoplasmosis, fungal infections and AIDS should be ruled out during the early phases of the disease. With regard to ocular manifestations, differential diagnosis should aim to exclude sympathetic ophthalmia, intraocular lymphoma, central serous chorioretinopathy, scleritis, epitheliopathy and multiple retina detachments secondary to systemic arterial hypertension[7,52]. The cutaneous symptoms may lead us to consider diagnostic possibilities such as Alezzandrini's syndrome, alopecia areata, vitiligo and piebaldism[10]. Other than VKHS, immunomediated sensorineural hearing loss could be related to systemic lupus erythematosus, rheumatoid arthritis, Wegener's granulomatosis, ulcerative colitis, Sjögren's syndrome, amyloidosis, sarcoidosis or Cogan syndrome. However, the incidence of inner ear involvement in autoimmune diseases varies greatly[45,53].

Treatment

Early and aggressive treatment with corticosteroids and/or immunosuppressive drugs is essential to avoid the morbidity that this disease has the potential to cause and which is primarily related to its ophthalmological complications[3,54]. Administering these drugs systemically is the principle means of treatment and oral corticosteroids should be given in high doses, generally prescribing 1-2 mg/kg/day of oral prednisone. For more severe cases, pulse therapy is given with 1g/day methylprednisolone for 3 to 5 days. The duration of treatment and the subsequent rest periods should be personalized for each patient. Treatment should be continued for a minimum of 6 months to 1 year before starting the process of withdrawing corticosteroid treatment. Stopping systemic treatment during the first 3 months is not recommended because of the risk of the disease recurring[54,55]. Patients may exhibit resistance to corticosteroid therapy with prednisone and/or prednisolone and may suffer liver dysfunction induced by the corticosteroids. In these cases there is the option of using 20mg/day of betamethasone or 30mg/day of dexamethasone[56]. The efficacy of different routes of corticosteroid administration has been studied, but there was no evidence in the prognostic results comparing oral and intravenous routes[54]. For patients who do not respond well to corticosteroids or who develop side effects because of them, such as Cushing's syndrome, systemic arterial hypertension or diabetes, immunomodulators are recommended[57]. Options are methotrexate, etarnecept, tacrolimus, cyclosporine, mycophenolate mofetil, azathioprine, cyclophosphamide, chlorambucil and adalimumab[58]. Patients who present with aggressive forms of the disease may benefit from triple immunosuppressive therapy, which consists of prednisolone, azathioprine and cyclosporine used in conjunction[59]. In cases where patients are resistant to corticosteroids and also fail to respond to be immunomodulatory therapy, intravenous immunoglobulin may be a viable treatment option[60]. An intravitreous injection of triamcinolone can clear up the inflammatory process and the intraretinal and subretinal exsudate leading to significant improvements to visual acuity[61].

Prognosis

With this disease, prognosis depends greatly on how early it is diagnosed and correctly treated. Disorders of the auditory system respond well to treatment and are generally completely reversed in 2 to 3 months, whereas the cutaneous lesions are permanent[35]. Prognosis for the vision is extremely variable, although generally favorable. It has been found that the three most important prognostic factors are: good visual acuity 1 month after starting treatment, early high-dose corticosteroids and age at disease onset, with evidence that younger patients suffered a lower rate of ocular complications[54, 62].

Final comments

The difficulties with diagnosing this disease are the result of its rareness and the fact that it is relatively unknown among the medical classes. More often than not the syndrome is only recognized by the specialists who treat the systems affected by the disease. This fact has contributed to data on the incidence of the disease being scarce, particularly in Brazil.

The fact that the disease is unknown is the result of a lack of coverage of VKHS in the medical literature. There is, however, a great deal written on the subject in the literature of the specialties, primarily ophthalmology, in the form of textbooks and scientific articles. Although the clinical criteria for the syndrome are well-established, there is very often great difficulty in diagnosing it because patients present at clinical consultations in different stages of disease development and its manifestations are not seen in their correct chronological order of appearance. The auditory symptoms, which are present in the majority of cases of this disease, should direct differential diagnosis towards diseases that involve other systems, such as the ophthalmological, as is the case of Cogan syndrome. It is recommended that initial treatment for VKHS is with intravenous corticosteroids. The patient's sensitivity to corticosteroids should be taken into account and also the risks of using these drugs and, if necessary, intravenous immunoglobulin or immunomodulators should be used instead.

Conflicts of interest: none

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