VOGT-KOYANAGI-HARADA SYNDROME

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Vogt-Koyanagi-Harada Syndrome

1. Discuss in detail about Vogt-Koyanagi Harada syndrome. (10) D2011
2. VKH Syndrome. (2005)(2001)

Introduction

- VKH syndrome is an uncommon multisystem disease of presumed autoimmune etiology that is characterized by
  - Chronic, bilateral, diffuse, granulomatous panuveitis
  - With accompanying integumentary, neurologic, and auditory involvement.

Epidemiology

- The disease most commonly affects certain ethnic groups (people with Asian, Asian Indian, Hispanic, Native American, and Middle Eastern ancestry).
- It is uncommon among whites; VKH syndrome is also rare among sub-Saharan Africans, suggesting that other factors, in addition to skin pigmentation, are important in its pathogenesis.
- The incidence of VKH syndrome varies geographically, accounting for up to 4% of all uveitis referrals in the United States and 8% in Japan. In Brazil and Saudi Arabia, it is the most commonly encountered cause of noninfectious uveitis.

Etiology and pathogenesis

- The precise etiology and pathogenesis of VKH syndrome are unknown,
- The current clinical and experimental evidence suggests a cell-mediated autoimmune process driven by T lymphocytes directed against self-antigens associated with melanocytes of all organ systems in genetically susceptible individuals.
- A genetic predisposition for the development of the disease & an immune dysregulatory pathogenesis are supported by strong association with HLA-DR4 among Japanese patients & HLA-DR1 or HLA-DR4 among Hispanic patients from southern California.
- The numerous clinical, pathologic, and genetic similarities between SO and VKH syndrome suggest that they share a similar immunopathogenesis, albeit with different triggering events and modes of sensitization.

Stages

- There are 4 stages of VKH syndrome: prodromal, acute uveitic, convalescent, and chronic recurrent.
- **Histologic findings** vary depending on the stage.

Acute uveitic stage
1. There is a diffuse, non-necrotizing, **granulomatous inflammation** virtually identical to that seen in SO, consisting of lymphocytes and macrophages admixed with **epithelioid and multinucleate giant cells**, with **preservation of the choriocapillaris**. 2. Proteinaceous fluid exudates are observed in the subretinal space between the detached neurosensory retina and the RPE. 3. Although the peripapillary choroid is the predominant site of the granulomatous inflammatory infiltration, the ciliary body and iris may also be affected.
Convalescent stage
1. It is characterized by **nongranulomatous inflammation**, with uveal infiltration of lymphocytes, few plasma cells, and the **absence of epithelioid histiocytes** 2. The number of choroidal melanocytes decreases with loss of melanin pigment, which corresponds with the characteristic clinical feature known as **sunset-glow fundus.** 3. The appearance of numerous nummular chorioretinal scars in the peripheral retina histologically corresponds to the focal loss of RPE cells with chorioretinal adhesions.
Chronic recurrent stage
1. It is characterized by **granulomatous choroiditis with damage to the choriocapillaris**

Clinical features

- The clinical features of VKH syndrome also vary depending on the stage of the disease.

I. Prodromal stage

1. The prodromal stage is marked by flulike symptoms.
2. Several days preceding the onset of ocular symptoms, patients may present with headache, nausea, meningismus, dysacusia, tinnitus, fever, orbital pain, photophobia, and hypersensitivity of the skin and hair to touch.
3. Focal neurologic signs, although rare, may develop and include cranial neuropathies, hemiparesis, aphasia, transverse myelitis, and ganglionitis.

4. Cerebrospinal fluid analysis reveals lymphocytic pleocytosis with normal levels of glucose in more than 80% of patients; this finding may persist for up to 8 weeks.
5. Auditory problems are observed in 75% of patients, frequently coincident with the onset of ocular disease.
6. Central dysacusia, usually involving higher frequencies or tinnitus, occurs in approximately 30% of patients early in the disease course, typically improving within 2–3 months; however, persistent deficits may remain.

II. Acute uveitic stage

1. The acute uveitic stage is heralded by the onset of sequential blurring of vision in both eyes, 1–2 days after the onset of CNS signs
2. It is marked by
   - bilateral granulomatous anterior uveitis,
   - a variable degree of vitritis,
   - thickening of the posterior choroid with elevation of the peripapillary retinal choroidal layer,
   - hyperemia and edema of the optic nerve,
   - Multiple serous retinal detachments.
3. The focal serous retinal detachments are often shallow, exhibiting a **cloverleaf pattern** around the posterior pole, but they may coalesce and evolve into large, bullous, exudative detachments.
4. Profound vision loss may occur during this phase.
5. Less commonly, mutton-fat KPs and iris nodules at the pupillary margin may be observed.
6. IOP may be elevated
7. The anterior chamber may be shallow because of forward displacement of the lens–iris diaphragm as the result of ciliary body edema or annular choroidal detachment, or it may be low, secondary to ciliary body shutdown.

III. Convalescent stage

1. The convalescent stage occurs several weeks later and is marked by resolution of the exudative retinal detachments and gradual depigmentation of the choroid, resulting in the classic orange-red discoloration, or sunset-glow fundus.
2. Small, round, discrete depigmented lesions develop in the inferior peripheral fundus.
3. Juxtapapillary depigmentation may also be seen.
4. In Hispanic patients, the sunset-glow fundus may show focal areas of retinal hyperpigmentation or hypopigmentation.
5. Perilimbal vitiligo (Sugiura sign) may be present in up to 85% of Japanese patients but is rarely observed among white patients
6. Integumentary changes, including vitiligo, alopecia, and poliosis, typically appear during the convalescent stage in about 30% of patients and correspond with the development of fundus depigmentation.
7. In general, skin and hair changes occur weeks to months after the onset of ocular inflammation, but in some cases they may appear simultaneously.
8. Between 10% and 63% of patients develop vitiligo, depending on ethnic background; among Hispanic patients, the incidence of cutaneous and other extraocular manifestations is relatively low.

IV. Chronic recurrent stage

1. The chronic recurrent stage is marked by
   - repeated bouts of granulomatous anterior uveitis,
   - with the development of KPs,
   - posterior synechiae,
   - iris nodules,
   - iris depigmentation,
   - And stromal atrophy.
2. Posterior segment recurrences (vitritis, papillitis, multifocal choroiditis, and exudative retinal detachment) have been reported but are uncommon during this stage.
3. Anterior segment recurrence, however, may occur concomitantly with subclinical choroidal inflammation, requiring systemic therapy.
4. Visually debilitating sequelae of chronic inflammation develop during this stage and include posterior subcapsular cataract, glaucoma, CNV, and subretinal fibrosis.

- Based on these clinical features and their distinctive appearance within the overall disease course, comprehensive diagnostic criteria for the complete, incomplete, and probable forms of VKH syndrome were revised in 2001.

- Regardless of the form of the disease, essential features for the diagnosis of VKH syndrome include bilateral involvement, no history of penetrating ocular trauma, and no evidence of other ocular or systemic disease.

Table 6-3 Revised Diagnostic Criteria for Vogt-Koyanagi-Harada Syndrome

Complete Vogt-Koyanagi-Harada syndrome

I. No history of penetrating ocular trauma or surgery
II. No clinical or laboratory evidence of other ocular or systemic disease
III. Bilateral ocular disease (either A or B below must be met):
  A. Early manifestations
    1. Diffuse choroiditis as manifested by either:
      a. Focal areas of subretinal fluid, or
      b. Bullous serous subretinal detachments
    2. With equivocal fundus findings, then both:
      a. Fluorescein angiography showing focal delayed choroidal perfusion, pinpoint leakage, large placoid areas of hyperfluorescence, pooling of dye within subretinal fluid, and optic nerve staining
      b. Ultrasonography showing diffuse choroidal thickening without evidence of posterior scleritis
  B. Late manifestations
    1. History suggestive of findings from IIIA, and either both 2 and 3 below, or multiple signs from 3
    2. Ocular depigmentation
      a. Sunset-glow fundus, or
      b. Sugiura sign
    3. Other ocular signs
      a. Nummular chorioretinal depigmentation scars, or
      b. RPE clumping and/or migration, or
      c. Recurrent or chronic anterior uveitis
IV. Neurologic/auditory findings (may have resolved by time of examination):
  A. Meningismus
  B. Tinnitus
  C. Cerebrospinal fluid pleocytosis
V. Integumentary findings (not preceding central nervous system or ocular disease)
  A. Alopecia
  B. Poliosis
  C. Vitiligo

Incomplete Vogt-Koyanagi-Harada syndrome

Criteria I to III and either IV or V from above

Probable Vogt-Koyanagi-Harada syndrome

Criteria I to III from above must be present
Isolated ocular disease

Diagnosis and investigation

- The diagnosis of VKH syndrome is essentially clinical.
- Exudative retinal detachment during the acute disease and sunset-glow fundus during the chronic phase are highly specific to this entity.

- In patients presenting without extraocular changes, FA, ICG angiography, OCT, FAF imaging, lumbar puncture, and ultrasonography may be useful confirmatory tests.

FA
1. During the acute uveitic stage, FA typically reveals numerous punctate hyperfluorescent foci at the level of the RPE in the early stage of the study, followed by pooling of dye in the subretinal space in areas of neurosensory detachment. 2. The vast majority of patients show disc leakage, but CME and retinal vascular leakage are uncommon. 3. In the convalescent and chronic recurrent stages, focal RPE loss and atrophy produce multiple hyperfluorescent window defects without progressive staining.
ICG angiography
1. ICG angiography highlights the choroidal pathology, disclosing a delay in choriocapillaris and choroidal vessel perfusion, early choroidal stromal vessel hyperfluorescence and leakage, disc hyperfluorescence, multiple hypofluorescent spots throughout the fundus thought to correspond to foci of lymphocytic infiltration, and hyperfluorescent pinpoint changes within areas of exudative retinal detachment. 2. The hypofluorescent spots may be present even when the funduscopic and FA findings are unremarkable; thus, they serve as sensitive markers for the detection and monitoring of subclinical choroidal inflammation.
USG
1. Ultrasonography may be helpful in establishing the diagnosis, especially in the presence of media opacity. 2. Findings include diffuse, low to medium reflective thickening of the posterior choroid that is most prominent in the peripapillary area, with extension to the equatorial region; exudative retinal detachment; vitreous opacification; and posterior thickening of the sclera.
OCT
1. OCT may be useful in the diagnosis and monitoring of serous macular detachments, CME, and choroidal neovascular membranes. 2. Patients may have characteristic fibrin bands extending from the retina to the RPE in the acute phase, and choroidal thickening is commonly seen. 3. SD-OCT using enhanced depth imaging demonstrates choroidal thickening in the acute phase that decreases with treatment.
FAF
1. The combined use of SD-OCT and FAF imaging, which shows granular hyperautofluorescence in areas of inflammation, offers a noninvasive assessment of RPE and outer retinal inflammation that may not be apparent on clinical examination in patients with chronic VKH syndrome.

- In highly atypical cases—particularly patients presenting early in the course of the disease with prominent neurologic signs and a paucity of ocular findings—a lumbar puncture, revealing lymphocytic pleocytosis, may be useful diagnostically.
- However, in the vast majority of cases, the history and clinical examination, together with results of FA and/or ultrasonography, are sufficient to establish the diagnosis.

Differential diagnosis

uveal effusion syndrome primary intraocular lymphoma	posterior scleritis sarcoidosis	uveal lymphoid infiltration	SO APMPPE

- These entities may be differentiated from VKH syndrome by a thorough history, review of systems, and physical examination, together with a directed laboratory evaluation.

Treatment

- The acute stage of VKH syndrome is responsive to early and aggressive treatment with corticosteroids.
- Initial dosages typically are 1–1.5 mg/kg/day of oral prednisone or up to 1 g of intravenous methylprednisolone daily for 3 days followed by high dose oral corticosteroids.
- Oral versus intravenous routes of administration show no demonstrable differences in visual acuity outcome or the development of visually significant complications.
- For patients intolerant of systemic therapy, use of intravitreal corticosteroids, including the intravitreal fluocinolone acetonide implant, is an option.
- Systemic corticosteroids are tapered slowly according to the clinical response, on average over a 6–12 month period, in an effort to prevent progression of the disease to the chronic recurrent stage and to minimize the incidence and severity of extraocular manifestations.
- Tapering corticosteroids too soon can result in early recurrence.
- Despite adequate initial treatment with systemic corticosteroids, many patients experience recurrent episodes of inflammation.

- This risk has led many experts to initiate IMT (including cyclosporine, azathioprine, mycophenolate mofetil, chlorambucil, cyclophosphamide, and infliximab) earlier to achieve more prompt inflammatory control and to facilitate more rapid tapering of corticosteroids.

Prognosis

- The overall visual prognosis for patients treated in this fashion is fair, with up to 70% of patients retaining visual acuity of 20/40 or better.
- Recently, the use of either oral corticosteroids or IMT with extended follow-up was shown to reduce the risk of vision loss and the development of some structural complications.
- Specifically, oral corticosteroids reduced the risk of CNV and subretinal fibrosis by 82% and the risk of visual acuity decline to 20/200 or worse in better-seeing eyes by 67%. IMT was associated with risk reductions of 67% for vision loss to 20/50 or worse and 92% for vision loss to 20/200 or worse in better-seeing eyes.

Complications

- Structural complications associated with ocular morbidity include cataract formation (50%); glaucoma (33%); CNV (up to 15%); and subretinal fibrosis, the development of which is associated with increased disease duration, more frequent recurrences, and an older age at disease onset.