Original Article

Initial misdiagnosis of Vogt-Koyanagi-Harada disease

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Abstract

Purpose: To report the initial misdiagnosis of patients with Vogt–Koyanagi–Harada (VKH) disease.

Methods: The medical records of 76 consecutive patients diagnosed with VKH disease were reviewed retrospectively at The Eye Center, Riyadh, Saudi Arabia. Patients were referred to The Eye Center from Saudi Arabia and other Middle Eastern countries. The initial diagnosis was made by an ophthalmologist or neurologist. The main outcome measure was to evaluate cases with VKH disease who were initially misdiagnosed.

Results: In 7 (9.2%) out of the 76 patients the initial diagnosis was incorrect. Patients were initially misdiagnosed as optic neuritis (1.3%), intracranial hypertension (1.3%), brain tumor (1.3%), Susac disease (1.3%), migraine (1.3%), rhegmatogenous retinal detachment (1.3%) or anterior granulomatous uveitis of unknown etiology (1.3%). Patients underwent unnecessary tests including MRI and invasive procedures including CSF analysis and anterior chamber paracentesis.

Conclusion: The initial diagnosis of patients with VKH disease was incorrect in 9 % of the cases. Delay in the diagnosis of VKH disease may lead to delay in management and may cause irreversible damage to the photoreceptors with poor visual outcome.

Keywords: VKH, uveitis, optic nerve, misdiagnosis

Introduction

Vogt–Koyanagi–Harada (VKH) disease is a multisystem granulomatous inflammatory disease affecting the eyes, auditory system, meninges, and integuments.1 Patients usually present with bilateral panuveitis preceded by a prodromal phase, which may be associated with neurological and/or auditory involvement.2 Meningeal involvement in patients with VKH disease may cause severe headache simulating other types of headaches.3 In VKH disease, optic nerve involvement is common and is one of the important clinical signs.2 Swollen and hyperemic optic discs may be the only presenting signs and may lead to a misdiagnosis of papillitis or papilledema.2 Skin changes such as alopecia, poliosis and vitiligo appear late in the course of the disease.3 Cases presenting with headache and bilateral optic disc swelling without any other ocular or systemic features may be easily mistaken for intracranial hypertension. In some patients massive exudative retinal detachment may be misdiagnosed as rhegmatogenous retinal detachment. In this study we retrospectively reviewed the medical records of 76 patients with definite VKH disease. In 7 patients the initial diagnosis was incorrect and subsequent management was inappropriate. Six out of the seven patients were initially diagnosed elsewhere and presented to our center at later stages of the disease and the seventh patient presented initially to our center. The characteristic ophthalmologic and systemic findings of VKH disease developed late in the course of the disease.

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leading to correction of the initial diagnosis and initiation of appropriate therapy.

Methods

The medical records of 76 consecutive patients diagnosed with VKH disease were reviewed retrospectively at The Eye Center, Riyadh, Saudi Arabia. Patients were referred to The Eye Center from Saudi Arabia and other Middle Eastern countries between from September 1996 to July 2017. The clinical diagnosis of VKH disease was established based on the revised criteria of the International Committee on VKH disease.1 We analyzed seven cases that were initially misdiagnosed, six were initially diagnosed elsewhere and presented to our center at later stages of the disease and one patient presented to our center initially. Five patients presented initially with headache, blurring of vision and or optic disc swelling without exudative retinal detachment or systemic manifestations. One patient presented with massive bilateral retinal detachment that was erroneously misdiagnosed as rhegmatogenous retinal detachment and was subjected to sclera buckling at another institute. Another patient presented with anterior granulomatous uveitis of unknown etiology. Each patient completed a uveitis questionnaire. Patient clinical history and demographic data were recorded. Each patient underwent a complete ophthalmic examination, medical evaluation for systemic illness, and laboratory investigations where indicated. Fundus fluorescein angiography (FFA) and optical coherence tomography (OCT) were performed. The protocol was approved by the Institution Review Board of The Eye Center, Riyadh, Saudi Arabia. The study design was retrospective and complied with the standards set forth by the Declaration of Helsinki.

Results

Seven (9.2%) out of the 76 patients were incorrectly misdiagnosed at initial presentation. The 7 patients presented initially with various clinical findings including symptoms of headache, numbness, blurring of vision, ocular pain and signs of optic disc swelling without exudative retinal detachment or systemic manifestations, retinal detachment in absence of systemic features, and anterior granulomatous inflammation with no other systemic involvement. Patients were initially misdiagnosed with optic neuritis (1.3%), intracranial hypertension (1.3%), brain tumor (1.3%), Susac disease (1.3%), migraine (1.3%), rhegmatogenous retinal detachment (1.3%) and anterior granulomatous uveitis of unknown etiology (1.3%) as shown in Table 1. The characteristic ophthalmologic and systemic findings of VKH disease developed late in the course of the disease. Proper diagnosis and treatment led to improved visual acuities compared to the initial visual acuity at presentation particularly in cases without ocular structural damage (Table 2).

Case 1. A 33-year-old female patient gave history of headache, ocular pain and blurring of vision in both eyes of three months duration. Fundus examination revealed swollen optic nerve heads. She was suspected of having intracranial hypertension. MRI was ordered and revealed no mass lesions or focal abnormal signal intensity. Based on the clinical and MRI findings, she was presumed to have optic neuritis and the diagnosis of multiple sclerosis was made elsewhere. She was started on treatment with Interferon beta-1a. Three months later, she developed panuveitis, dizziness, tinnitus, decreased hearing and hair loss. Optical coherence tomography revealed exudative retinal detachment. Later she developed poliosis of scalp hair and vitiligo. A diagnosis of complete VKH disease was established. She was admitted to hospital and was given intravenous methylprednisolone. She was later placed on oral steroids and mycophenolate mofetil.

Table 1. Initial misdiagnosis of patients with Vogt-Koyanagi-Harada Disease.

| No | Age | Gender | Symptoms                        | Signs                          | Initial Diagnosis         | Subsequent findings                        |
|----|-----|--------|---------------------------------|--------------------------------|---------------------------|------------------------------------------|
| 1  | 33  | F      | Headache, ocular pain, blurring of vision | Disc swelling                  | Optic neuritis             | Panuveitis, tinnitus, alopecia, dizziness |
| 2  | 24  | F      | Severe headache blurring of vision | Disc swelling                  | Intracranial hypertension  | Multifocal choroiditis, tinnitus, alopecia |
| 3  | 21  | M      | Headache blurring of vision       | Disc swelling                  | Brain tumor                | Exudative retinal detachment, tinnitus    |
| 4  | 44  | F      | Headache blurring of vision       | Normal discs                   | Susac disease              | Posterior uveitis, dysacusis, poliosis     |
| 5  | 19  | F      | Headache blurring of vision       | Disc hyperemia                 | Migraine                   | Panuveitis, alopecia, poliosis            |
| 6  | 40  | F      | Blurring of vision                | Retinal detachment             | Rhegmatogenous retinal detachment | Dysacusis, poliosis, alopecia, vitiligo |
| 7  | 7   | F      | Blurring of vision                | Anterior uveitis               | Anterior granulomatous uveitis | Poliosis, vitiligo choroiditis           |

Table 2. Pre and posttreatment visual acuities in the initial misdiagnosed patients.

| No | Age | Gender | Pretreatment visual acuity | Posttreatment visual acuity |
|----|-----|--------|---------------------------|----------------------------|
|    |     |        | OD | OS | OD | OS |
| 1  | 33  | F      | 20/200 | 20/120 | 20/20 | 20/20 |
| 2  | 24  | F      | 20/35 | 20/20 | 20/35 | 20/20 |
| 3  | 21  | M      | 20/20 | 20/20 | 20/20 | 20/20 |
| 4  | 44  | F      | 20/40 | 20/200 | 20/120 | 20/200 |
| 5  | 19  | F      | 20/25 | 20/20 | 20/20 | 20/16 |
| 6  | 40  | F      | 20/30 | 20/400 | 20/35 | 20/400 |
| 7  | 7   | F      | 20/100 | 20/100 | 20/30 | 20/30 |
Case 2. A 24-year-old female patient gave history of severe headache and blurring of vision in both eyes of 1 month duration. Slit lamp biomicroscopy revealed quiet anterior chamber and vitreous. Fundus examination revealed normal maculae and swollen optic discs. Based on the clinical findings, she was suspected of having intracranial hypertension. MRI of the brain and orbits were ordered and revealed no abnormalities. She was diagnosed with bilateral neuroretinitis and was treated with systemic steroids and azithromycin. One month later, she developed multifocal choroiditis, tinnitus, alopecia, and neck rigidity. Fundus fluorescein angiography revealed juxtapapillary leakage. Optical coherence tomography revealed exudative retinal detachment. A diagnosis of complete VKH disease was established. She was admitted to hospital and was given intravenous methylprednisolone. She was then put on oral steroids and mycophenolate moefetil.

Case 3. A 21-year-old male gave history of headache, blurring of vision and optic nerve head swelling in both eyes of one year duration. He was suspected of having brain tumor. CT scan of the head was done and revealed normal findings. The headache increased in severity and was accompanied by severe visual loss. CSF analysis revealed increased white blood cells. At that stage, he was diagnosed with meningitis elsewhere and was given intravenous antibiotics. Two months later, he developed tinnitus, panuveitis and exudative retinal detachment. Diagnosis of incomplete VKH disease was established (there were no intemetary findings). He was admitted to hospital and was given intravenous methylprednisolone and then put on oral steroids and mycophenolate moefetil.

Case 4. A 44-year-old female gave history of severe headache, blurring of vision in both eyes of one year duration, decreased hearing and numbness of hands. The patient was initially suspected of having Susac disease. MRI of the head was done and revealed insignificant findings. CSF examination was normal with negative oligoclonal bands, normal cell count, normal protein and glucose with negative culture and gram stain. Her laboratory work up was extensive and essentially negative. Few months later, she developed dysacusis and poliosis. Ocular findings included posterior uveitis. B scan ultrasonography showed diffuse choroidal thickening, fluorescein angiography showed large pooling of the sub RPE space and OCT revealed serous subretinal fluid in both eyes. Diagnosis of complete VKH disease was established and she was treated with high dose oral steroid and mycophenolate moefetil.

Case 5. A 19-year-old female gave history of headache and blurring of vision in both eyes. CT scan of the head was done and revealed normal findings. Based on the clinical findings and normal CT scans, she was erroneously diagnosed with migraine. One year later, she developed panuveitis with multifocal neurosensory retinal detachments. Systemically, she developed alopecia and poliosis of the scalp hair. She was diagnosed with complete VKH disease. She was given intravenous pulse injections of methylprednisolone and later on was maintained on oral steroids.

Case 6. A 40-year-old female gave history of severe loss of vision in the left eye. The patient was initially diagnosed with bilateral rhegmatogenous retinal detachment. She underwent bilateral pars plana vitrectomy and drainage of subretinal fluid, and sclera buckle in the left eye elsewhere. Three years later, she presented with sunset glow fundus, dysacusis, alopecia, vitiligo and poliosis. Diagnosis of complete VKH disease was established and she was treated with high dose oral steroids.

Case 7. A 7-year-old female gave history of loss of vision in both eyes. Ocular examination revealed anterior uveitis. Our initial diagnosis was anterior granulomatous uveitis of unknown etiology. There was poor visualization of the posterior segment and ultrasonography showed no retinal detachment. Work up included MRI of the brain, PPD test, FTA-ABS test, ACE, lysozyme, CT of chest and anterior chamber paracentesis. All tests were unremarkable. Later, the patient developed multifocal choroiditis, one white eyelash and vitiligo. She was diagnosed as having incomplete VKH disease 3 months following presentation and later received the appropriate therapy.

Discussion

Delay in the diagnosis of VKH disease may lead to irreversible damage to the photoreceptors and if therapy is delayed, patients may have poor visual outcome. In our study, 7(9%) out of 76 patients with VKH disease presented with initial features suggestive of other systemic or ocular conditions. The confusing symptoms included headache, numbness, hearing loss, blurring of vision in addition of the signs of bilateral optic disc swelling. In 6 patients, uveitis and systemic manifestations were absent making the diagnosis of VKH disease extremely unlikely. In case 7, the uveitis was localized only anteriorly. In our patients, brain imaging was ordered to rule out space occupying lesions, intracranial hypertension, cerebral vasculitis or multiple sclerosis. Furthermore, two patients were subjected to the more invasive procedure of CSF aspiration and analysis. In case 7, unnecessary anterior chamber samples were obtained through paracentesis. The most dramatic sequel was noted in case 6 where inappropriate initial diagnosis with rhegmatogenous retinal detachment led to the unnecessary surgical intervention and the patient ended up with very poor visual acuity in her left eye.

The most confusing features were the symptom of headache and the sign of swelling of optic nerve head. Headache is a common symptom in patients with VKH disease; however, it is not usually the only presenting symptom and is most commonly accompanied by symptoms of visual impairment. Tugal-Tutkun et al found that headache was the most frequent symptom in their series which occurred in 69% patients. However, headache alone does not fulfill the diagnostic criteria and is insufficient for the diagnosis of VKH disease. On the other hand, optic disc hyperemia or swelling is a common finding in patients with VKH disease. Ohno et al found that optic disc swelling was found in 87% of their patients at presentation. VKH disease classically has four clinical phases including prodromal; acute uveitic; chronic convalescent; and chronic recurrent stage. The prodromal phase usually lasts few days and patients typically complain of neurological and auditory symptoms. Optic disc swelling is rare in this early prodromal phase. However, during the acute uveitic phase, optic disc hyperemia is a frequent finding. In this stage impairment of vision occurs due to diffuse choroiditis and multiple serous retinal detachments. Several weeks later, the disease progresses to the convalescent phase, which is characterized by depigmentation of the choroid "sunset glow fundus". In this phase, the optic disc may appear pale.

Our patients developed uveitis and variable extraocular manifestations later in the course of the disease. In some
patients with subtle posterior segment involvement, FFA and OCT may play an important role in establishing the diagnosis of VKH disease. Swelling of the optic nerve head in the absence of other clinical signs is one of the major misleading signs leading to delay in the diagnosis of VKH disease. VKH disease is an immune mediated insult against melanin bearing cells found in the eyes, optic nerve, auditory nerve, meninges and skin leading to symptoms related to variable inflammatory reactions. Mechanical compression of the optic disc by inflammation of the juxtapapillary choroid and inflammatory infiltration may play a major role in the optic disc changes. In VKH patients with crowded discs, impairment of the arterial supply to the optic disc (the optic branches of the short posterior ciliary artery and/or centripetal branches from the peripapillary choroid) secondary to severe choroidal inflammation may induce axonal flow stasis and secondary axonal swelling of the optic nerve head.\(^6\)

Meningeal involvement in patients with VKH disease may cause severe headache simulating other types of acute onset headaches. Symptoms might be interpreted as optic neuritis, pituitary apoplexy or intracranial hypertension if headache is associated with ocular findings.\(^7\) Furthermore, dermatological manifestations such as alopecia, poliosis, vitiligo appear only late at the convalescent stage of the disease.\(^8\)

It is not unusual event that the affected VKH patients without exudative retinal detachment had been referred with an erroneous diagnosis of other diseases including primary optic nerve disease, mostly papilledema. Previous reports have also shown that VKH associated optic disc swelling may be misdiagnosed as optic neuritis, anterior ischemic optic neuropathy, or diabetic papillopathy.\(^3,6,9,10\) Recently, several studies reported that OCT revealed RPE folds/undulations in VKH affected eyes without exudative retinal detachment and this finding has shown a high sensitivity to diagnose acute VKH disease.\(^11–15\) Accordingly, employing these new OCT findings in the work up of suspected cases of VKH may enhance the diagnostic accuracy and help in avoiding unnecessary invasive investigations.

Diagnostic ambiguity is often encountered in any medical practice. A recent study was conducted to compare referral diagnoses to final diagnoses found that in 21% of cases (62/286), final diagnoses were distinctly different than referral diagnoses.\(^15\) In our study, 9% rate of misdiagnosis was noted. Our study, however, suffers from certain limitations. This is a retrospective study with self-evident drawbacks. Further studies are needed to compare the rates between VKH and other uveitis diseases.

In conclusion, VKH disease should be considered in the differential diagnosis of patients presenting with headache, blurring of vision and optic nerve head swelling. Careful eye examination and funduscopy may help in arriving at a correct diagnosis of VKH disease and in avoiding unnecessary tests, imaging and wrong management. Neurologists should be aware of this condition and to consider it in the differential diagnosis of multiple sclerosis and causes of papilledema.

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