VOGT-KOYANAGI-HARADA SYNDROME

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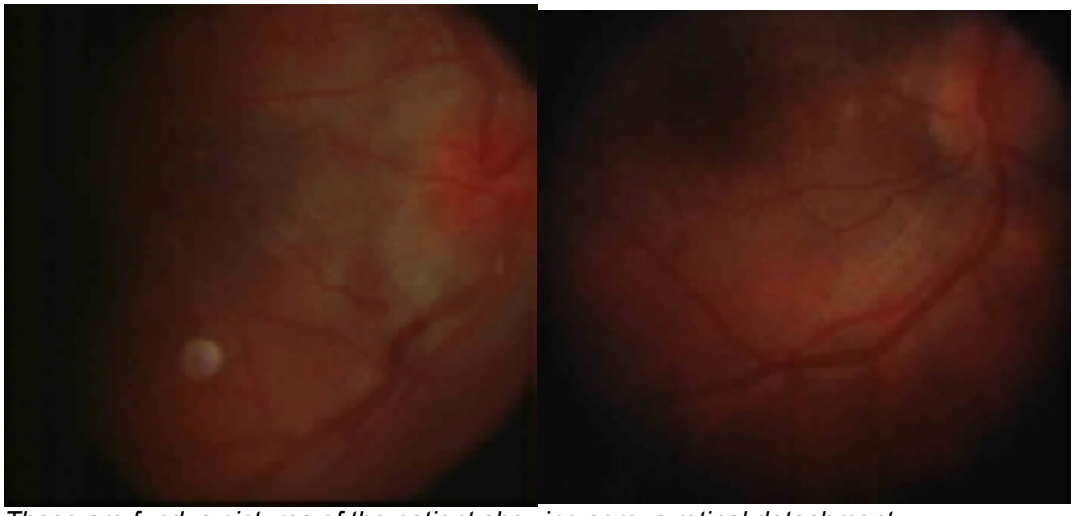
CASE PRESENTATION

A 20 year old Asian male was referred with the complaint of decreased vision in both eyes for a year. His past medical and surgical histories were unremarkable. His family history revealed thyroid disease in his mother. Review of systems were remarkable for alopecia and headache at the time when his eye problems began.

The first eye exam from his referring ophthalmologist revealed a visual acuity of 20/60 in both eyes with normal intraocular pressure (IOP). Slit lamps exam showed mutton fat keratic precipitates (KP) and 2+ anterior chamber cells and flare in both eyes. Dilated fundus examination disclosed serous detachment of the retina in each eye.



These are fundus pictures of the patient showing serous retinal detachment and disc hyperemia, OU.

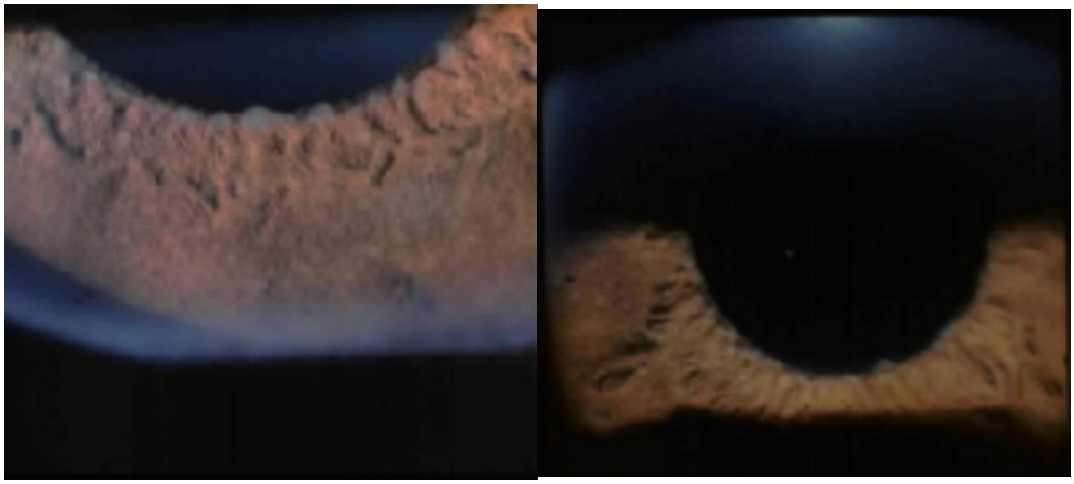
In this case, according to the history and eye examinations, the diagnostic entity considered most likely was Vogt-Koyanagi-Harada syndrome (VKH). The patient was started on oral and topical steroids. Despite the initial treatment, the patient progressed to total retinal detachments, and he was hospitalized for intravenous steroid treatment, which improved the condition dramatically. The patient was maintained on oral steroids, with vision improved to 20/20 OU.

6 months from the first eye symptoms, the patient has been noted to have neovascularization of the disc (NVD), and his intraocular pressure became markedly elevated and difficult to control. Beside his physical problems, the patient developed significant emotional problems while being on steroids and he attempted suicide. His ophthalmologist attempted to taper his topical and oral steroids without success in lowering the pressure while still maintaining control of the inflammation. Cyclosporine A (CsA) was added to his therapy but the patient's inflammation increased as his steroid was tapered and the pressure remained high.

At the time the patient was referred to us (10/21/93), his VA was 20/30 OU. Intraocular pressures were 21 OD, 18 OS. The patient was on 300 mg a day of CsA, 20 mg every other day of Prednisone and 500 mg of Diamox twice daily. Topical medications included Timoptic 0.5% bid OU, Pred forte OU bid which was stopped 2 weeks prior to his visit with us, and cyclogyl once a day. Anterior segment exam showed 1+cells and moderate posterior subcapsular cataracts (PSC) bilaterally. 1+ cells were also present in the vitreous. Posterior segment exam showed chorioretinal scarring, choroidal nodules, neovascularization of the disc and inferior vitreous hemorrhage OU. For treatment, CsA was increased to 400 mg a day, steroids were tapered and

PRP was suggested.

3 month later (1/25/94), the patient returned to the clinic with the complaints of pain and decreased vision in both eyes. His VA dropped to 20/60 OD and counting finger at 5 feet OS. He was currently on CsA 550 mg a day, Timoptic bid OU and Cyclogyl qd OU. SLE revealed mutton fat KP, 3+ A/C cells, multiple iris nodules, PSC and 3+ vitreous cells in both eyes. Fundus exam showed RPE clumping, NVD and vitreous hemorrhage. The patient absolutely refused oral Prednisone and so was treated with transeptal steroid injection bilaterally (Kenalog 40 mg). Imuran was started at the dosage of 150 mg a day.



These pictures illustrate the iris nodules in this patient.

10 days later (2/4/94), the patient's VA improved to 20/40 OD and 20/30 OS with 1+ A/C cells and 2+ vitreous cells. The intraocular pressure was 17 and 21, right and left eye respectively. Fundus fluorescein angiography revealed multiple diffuse pigment hyperplasia foci, chorioretinal atrophy, NVD in both eyes. SRNVM was noted in the right eye.
His medications were maintained and laser treatment was suggested.

Pan retinal photocoagulation was performed in both eyes 1 month later (3/9/94). His VA was 20/60 and 20/50 in the right and left eye respectively and the eyes were quiet. CsA and Imuran were continued at the same dosages.

2 months later (5/13/94), the patient had mild iritis OU that responded to topical steroid treatment. The inflammation was well controlled for another 3 months with topical steroids twice daily, CsA 550 mg a day and Imuran 150 mg a day. However, his PSC became more troublesome and required surgical intervention. Phacoemulsification with IOL implantation was performed (8/22/94) unevenfully in the left eye.

A month after his cataract surgery (9/23/94), the patient had a flare up in both eyes which responded to CsA 550 mg, Imuran 200 mg daily and Inflamase hourly. His best corrected visual acuities 2 months after the operation (10/14/94) were 20/80 and 20/32 in the right and left eye respectively. His IOP was normal and the inflammation was inactive. Topical steroids were tapered and systemic immunosuppressive medications were maintained.
Significant after cataract developed in the left eye 1 month after the surgery, for which YAG capsulotomy was performed 2 months later (11/18/94). The inflammation was well controlled for the next 2 months and Imuran was discontinued (12/23/94).

Phacoemulsification and IOL implantation was performed in the right eye a month later (1/23/95) with a satisfactory result. The inflammation was well controlled during the following 2 months with VA of 20/40 and 20/20 in the right and left eye respectively. CsA dosage was decreased to 500

mg daily due to a rising creatinine level.

A month later (4/28/95), the intraocular pressures were 30 in the right eye and 19 in the left despite being on Timoptic 0.5% twice daily. There was no sign of active inflammation; topical steroids were tapered.

Six weeks later (6/9/95), the patient had recurrence of panuveitis with pressures of 18 mm bilaterally. Because of a rising creatinine and blood pressure, CsA dosage was reduced to 400 mg daily. Transeptal steroid injections were performed in both eyes. The inflammation responded well to the treatment.

Six weeks later (7/21/95), the patient complained of headache and stated that he could not tolerate CsA anymore. His best-corrected visual acuities were 20/30 OD and 20/25 OS. IOP were 13 bilaterally. Anterior chamber showed 1-2 cells and flare. The patient refused dilation. His blood pressure and serum creatinine was within normal range and his uveitis was under control. CsA was decreased to 350 mg daily.

5 months later (12/5/95), the patient came back to the clinic for a second opinion about glaucoma surgery, which had been recommended by his primary care ophthalmologist. He was taking CsA 300-mg daily, PF qd OU, Trusopt tid OU, Timoptic bid OU and Iopidine tid OD. His visual acuity was 20/100 in the right eye and 20/30 in the left. Despite his maximal glaucoma medications, his pressures were 46 and 18 mm in the right and left eye respectively. His primary ophthalmologist suggested surgical intervention; the patient was reluctant. He had no active anterior chamber inflammation and once again, refused dilation.
Because the patient's pathology had been posterior which required frequent and thorough fundus examination, which he refused, and because he could not keep up with his appointment schedule, it seemed to us unsafe to keep the patient on immunosuppressive therapy. We discontinued CsA and Imuran and sent the patient back to his primary ophthalmologist.

VKH

Background

VKH syndrome or uveomeningitic syndrome is a systemic disorder involving many organ systems, including the eye, ear, integumentary and nervous system. It was first described by an Persian physician (Ali-ibn-Isa 940-1010A.D.) who reported poliosis associated with inflammation of the eyes (Pattison EM. Arch Neurol 1965;12:197-205). Schenkl reported this association again in 1873, in 1892 by Hutchinson and in 1906 by Vogt. Babel in 1932 combined the disorders described by Vogt, Koyanagi and Harada and suggested that these symptoms were manifestations of the same disease process. Since then, the uveomeningo-encephalitic syndrome has been known as Vogt-Koyanagi-Harada syndrome.

Epidemiology

The disease has been reported throughout the world but has a predilection for more darkly pigmented races such as Asians, Hispanic, and American Indians. It is uncommon in Caucasians. It is a common type of endogenous uveitis in Japan, making up at least 8% of these cases (Sugiura S. Jpn J Ophthalmol 1978;22:9-35). In the United States, it accounts for 1-4% of all uveitis referrals with a predilection for more darkly pigmented races and American Indian ancestry.(Ohno S. et al Am J Ophthalmol 1977; 83: 735-40)(Snyder DA. et al Am J Ophthalmol 1980; 90:69-75)
There appears to be some global variation in sexual predilection for VKH; most studies suggest that women are affected more frequently than men. (55-78% women in North America) However, in the Japanese there is no such preponderance. (In Sasamoto's study 38% of the patients are female.)
Most patients are in the second to fifth decade of life at the onset of the disease. However, the youngest patient was a 4-year-old boy reported by Cunningham et al.

Etiology and Pathogenesis

The exact etiology of VKH is still unknown. An autoimmune process in a genetically susceptible individual who contacts a viral infection is the most likely mechanism.
The autoimmune aspect in VKH includes a cellular immune response against melanocytes. Matsuda and Sugiura demonstrated close contact between lymphocytes and melanocytes in their patient's eye. (Jpn J Ophthalmol 1971). Lymphocytes from peripheral blood and CSF of patients with VKH exhibit cytotoxic activity against the B-36 melanoma cell line in the studies of Agira (Nippon Ganka Ogakkai Zasshi 92; 1988) and Norose (IOVS 31;1990). McClellan et al also found IL-2 dependent T cells that reacted specifically toward normal melanocytes as well as melanoma cells. In vitro lymphocytic proliferation in the presence of retinal antigens have shown contradictory results: DeSmet et al (AJO 110;1990) indicated no response in chronic VKH patients while Naidu's study (IOVS suppl 32; 1991) showed a positive response to retinal S antigen and interphotoreceptor retinoid binding protein (IRBP) in active untreated patients. Autoantibodies against photoreceptor outer segments and Muller cells in the sera of VKH patients have been detected (Chan et al. Ophthalmology 92; 1985). However, these antibodies could be a secondary response which follows the retinal damage in VKH patients.

Immunohistology
Immunohistochemical study of eyes affected by VKH by Sakamoto et al revealed an increased ratio of T helper to T suppressor cells and activated T lymphocytes with CD 25 and 26 marker within choroidal inflammatory foci. Class II MHC has been found on choroidal melanocytes and endothelium of choriocapillaris (Arch Ophthalmol 109:1270-4: 1991). Inomata and Sakamoto demonstrated a disappearance of choroidal melanocytes in VKH eyes (Curr Eye Res9(suppl):35-40:1990). These findings suggested that delayed type hypersensitivity against melanocytes that express class II MHC might be responsible for the inflammatory process in VKH.

Genetic factors
Among Chinese and Japanese, there is a strong association between HLA-DR4 and Dw53 with VKH with a relative risk of 16 for HLA-DR4 and 34.2 for HLA-Dw53 in Chinese. In a study of Zhang et al (AJO 113: 567-72; May 1992) HLA-DR4 was identified in 75% of VKH patients but only 23.1% in normal controls. Martinez et al reported HLA-DRw 52 in VKH patients of Cherokee Indian ancestry (AJO 114: 615-20; 1992). A genetic role in VKH is strengthened by the reports of familial cases.

Clinical manifestations
Typical clinical manifestations of VKH syndrome (Moorthy RS et al. Survey of Ophthalmology 1995; 39(4): 265-92)

1. Bilateral panuveitis in association with multifocal serous retinal detachment.
2. Central nervous system manifestations
    - Meningismus
    - Headache
    - CSF pleocytosis
3. Auditory manifestations
    - Hearing loss
    - Tinnitus
4. Cutaneous manifestations
    - Vitiligo
    - Alopecia
    - Poliosis

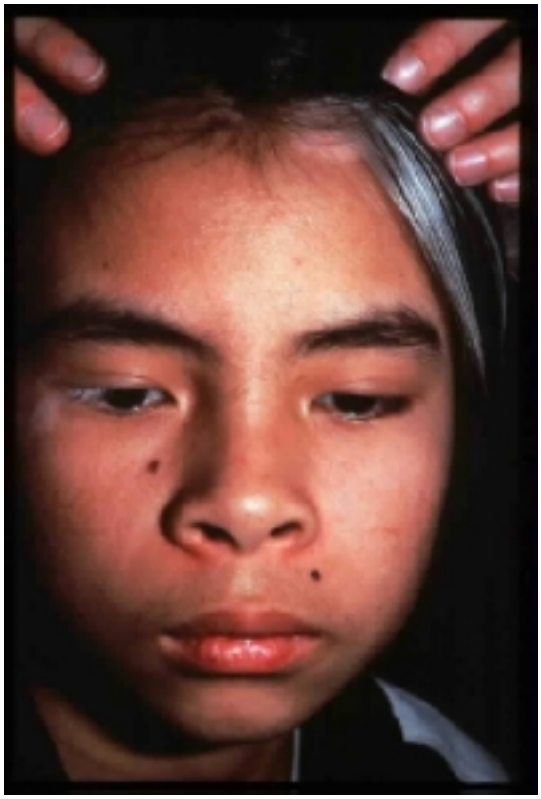
Most patients, present with severe bilateral uveitis associated with exudative retinal detachment and signs of meningismus just like our patient. Because of the variations in clinical presentation, the American Uveitis Society adopted the criteria for the diagnosis of VKH syndrome in 1978 as follows:

1. No history of ocular trauma or surgery.
2. At least three of four of the following signs:
    1. Bilateral chronic iridocyclitis.
    2. Posterior uveitis, including exudative retinal detachment, disk hyperemia or edema, and sunset glow fundus.
    3. Neurologic signs of tinnitus, neck stiffness, cranial nerve or CNS problems or CSF pleocytosis.
    4. Cutaneous findings of alopecia, poliosis or vitiligo.

The clinical course follows four stages. Initially there is a **prodromal stage** that mimics a viral infection and characterized by fever, headache, nausea, vertigo, orbital pain and neurological symptoms. This stage is followed within 3 to 5 days by an **acute uveitic phase**. 70% of the patients present with bilateral posterior uveitis (Sugiura S. Jpn J Ophthalmol 22:9-35;1978). In 30%, there may be a short delay of one to three days before the second eye became involved. The first sign is a thickening of the posterior choroid, which manifests as an elevation of the peripapillary retinochoroidal layer, disk hyperemia or edema. The RPE barrier breaks down causing subretinal fluid accumulation and multiple serous RD. Eventually, the inflammation extends to the anterior segment. Mutton fat KP, iris nodules can be found. (Moorthy RS et al. Survey of Ophthalmology 1995; 39(4): 265-92) Anterior chamber may be shallow due to ciliary edema and suprachoroidal fluid collection, which will resolve after inflammation subsides. The chronic **convalescent phase** follows gradually with skin and uveal depigmentation. Sugiura's sign or perilimbal vitiligo is the earliest depigmentation to occur, often within one month after the onset (Friedman AH et al Ophthalmology 88:1159-65; 1981). Depigmentation of the choroid causing sunset-glow fundus occurs two or three months after the uveitic phase. Foci of hyperpigmentation from RPE alterations can be found. Dalen Fuchs' nodules appear in the mid-periphery. This stage may be interrupted by the **chronic recurrent stage**, which manifests as a recurrent, mainly anterior uveitis. Recurrent posterior uveitis is uncommon. Another characteristic finding in this stage is the iris nodule. Complications such as glaucoma, cataract and SRNVM usually develop at this stage.
VKH syndrome-Clinical course (modified from Moorthy RS et al. Survey of Ophthalmology 1995; 39(4): 265-92)

1. Prodromal stage
    - fever, headache, nausea, vertigo, orbital pain
    - neurologic signs and symptoms: meningismus, cranial nerve palsies, optic neuritis, CSF pleocytosis.
2. Acute uveitis stage
    - serous retinal detachment
    - disk hyperemia and edema
    - anterior uveitis
    - shallow A/C
3. Convalescent or Chronic stage
    - Sugiura's sign
    - uveal depigmentation: Sunset-glow fundus
    - integumentary depigmentation: vitiligo, poliosis
4. Recurrent stage
    - recurrent, mainly anterior uveitis, iris nodules
    - complications: glaucoma, cataract, SRNVM

Extraocular manifestations
Integumentary
The integumentary system involvement is seen at various stages of the disease.
Sensitivity of hair and skin to touch prodromal
Poliosis of the eyebrows, eyelashes, hair convalescent
Vitiligo (10-63% depending on race) convalescent



This picture illustrates poliosis, vitiligo and whitening of hair in VKH patient.

Neurologic
Stiff neck, headache, confusion, CSF lymphocytic pleocytosis, and focal neurologic signs: cranial neuropathies, hemiparesis, aphasia, transverse myelitis and ganglionitis.
Auditory
Inner ear problem (75%): dysacusis, vertigo, hearing loss (high frequency) which usually improves in two to three months.
Vestibular dysfunction is uncommon.

Investigations
Fluorescein angiography
Characteristic FA in acute stage of VKH demonstrates multiple punctate hyperfluorescent dots at the level of RPE. These hyperfluorescent dots gradually enlarge and stain the subretinal fluid. 70% of the patients have disc leakage. In chronic stage, the angiogram shows multiple hyperfluorescent RPE window defects without progressive staining. Alternating hyper and hypofluorescence from RPE alteration causing "moth eaten" appearance can be found. SRNVM, retinochoroidal anastomoses, and NVD were also documented. (Brinkley et al Ophthalmology suppl 99: 151; 1992)
Ultrasonography
Ultrasonography is often helpful in making a diagnosis when fundus viewing is obscure, when presentation is atypical and extraocular signs are absent. It is a sensitive test which can demonstrate choroidal thickening in subclinical VKH when VA and fluorescein angiography is still normal. (Foster DJ. AJO March 1991; 111(3): 380-2) Echographic manifestations of VKH were described by Foster et al as follow:

1. Diffuse thickening of the posterior choroid with low to medium reflectivity.
2. Serous RD around posterior pole or inferiorly.
3. Vitreous opacities without PVD.

4. Posterior thickening of the sclera or episclera.

Lumbar puncture
LP has not been used routinely in most recent studies. In a study by Ohno et al, more than 80% of the patients had CSF pleocytosis consist mostly of lymphocytes. CSF pleocytosis occurs in 80% of the case within one week and resolves within eight weeks.
EEG, ERG and EOG
Electrophysiologic tests are nondiagnostic and cannot be relied upon in making the diagnosis.
MRI
MRI discriminates the sclera from the choroid, which is not possible with computerized tomography and allows the detection of subclinical ocular and CNS disease. Choroidal thickening can be demonstrated even when the fundus and fluorescein angiogram appear normal. (Ibanez et al Retina 14; 164-8: 1994)
Serologic tests
There are no specific serologic tests that help to establish the diagnosis of VKH syndrome.

Differential Diagnosis
(Moorthy RS et al. Survey of Ophthalmology 1995; 39(4): 265-92)

- sympathetic ophthalmia
- primary intraocular B cell lymphoma
- ocular lyme disease
- sarcoidosis
- APMPPE
- MEWDS
- bilateral diffuse melanocytic hyperplasia
- lupus choroidopathy
- uveal effusion syndrome
- posterior scleritis
- other systemic disorders causing exudative retinal detachment such as toxemia of pregnancy, renal disease.

Treatment
Corticosteroids
The treatment of VKH usually begins with early and aggressive use of systemic steroids followed by slow tapering over three months. Rubsamen and Gass found that recurrences occur in 43 and 52% of their patients in the first three to six months respectively and these were associated with rapid tapering of the steroids. In the same study, 66% of their patients had VA of 20/30 or better on last examination.
Hayasaka et al suggested that less steroid might be needed for the Harada's form of the disease as compared with the Vogt Koyanagi form of the disorder. (Grafes Arch Clin Esp Ophthalmol 218:1982)
Cytotoxic and immunosuppressive agents
Cytotoxic and immunosuppressive agents are reserved for the cases which are refractory to steroids. They also offer an alternative for patients intolerant of corticosteroid side effects. Various immunosuppressive or cytotoxic agents used in the management of VKH are listed;
(Moorthy RS et al. Survey of Ophthalmology 1995; 39(4): 265-92)
1.Corticosteroids

- 2 mg/kg/day of prednisone
- pulse therapy of 1 g/day methylprednisolone x 3days , 1 mg/kg/day of prednisone

2.Cytotoxic agents

1. Cyclophosphamide
    - 1-2 mg/kg/day
2. Chlorambucil
    - /day adjust every 3 weeks to maximum of 18 mg/day
3. Azathioprine
    - 1-2.5 mg/kg/day

3. Immunosuppressives

1. Cyclosporine
    - 5 mg/kg/day, trough 0.1-0.4 mcg/ml
2. FK 506
    - 0.1-0.15 mg/kg/day, trough < 20 ng/ml

Helveston et al (Neurology, Feb 1996, 46(2);584-5) described a patient with steroid intractable VKH who responded to a combination of azathioprine and intravenous immunoglobulin (IVIg) therapy. Treatment with IVIg was associated with rapid improvement. The improvement was not permanent and recurrences required repeated treatment. The mechanisms of the treatment are unknown.

Prognosis

The use of corticosteroids and immunosuppressive agents has greatly improved the visual outcome in VKH patients. Visual Prognosis are as shown: (Moorthy RS et al. Survey of Ophthalmology 1995; 39(4): 265-92)

AUTHOR	NUMBER OF EYES	% OF EYES WITH VA>=20/40	MEAN FOLLOW-UP (MONTHS)
Ohno	102	50%	NA
Synder	40	48%	>12
Sasamoto	94	93%	14.5
Minnakawa	372	85%	NA
Rubsamen	52	>66%	53
Moorthy	130	66%	28

Recently, Rubsamen and Gass reported that 66% of the patients had final visual acuity of 20/30 or better with corticosteroids and/or immunosuppressive treatment. 7% of the eyes had VA of less than 20/400. Moorthy et al showed that 53% of their patients had final VA of 20/30 or better after treatment for a mean period of 5.6 months.

Complications

Three major complications in VKH patients are cataracts, glaucoma and SRNVM. Optic atrophy and pigmentary changes are also common. The prevalence of the three common ocular complications in VKH syndrome are as listed here in the slide: (Moorthy RS et al. Survey of Ophthalmology 1995; 39(4): 265-92)

AUTHOR	NUMBER OF EYES	% CATARACTS	% GLAUCOMA	% SRNVM
Ohno	102	30	20	NA
Synder	40	16	NA	2.5
Minnakawa	372	10.5	6	NA
Rubsamen	52	36	45	9

Forster	84	NA	38	NA
Moorthy	130	38	NA	12

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