CASE REPORT

Vogt-Koyanagi-Harada Syndrome in Children

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SUMMARY

Vogt-Koyanagi-Harada (VKH) syndrome is a multisystemic disease characterized by granulomatous panuveitis with exsudative retinal detachment and often associated with neurological and skin symptomatology.
In the paper is presented a rare case of probably VHK syndrome in 11-year old caucasian race boy in which was found the bilateral granulomatous panuveitis with exsudative retinal detachment without other systemic symptomatology with typical clinical characteristics and course. Systemic corticosteroid therapy in a patient gradually improved the state, which was then complicated by the occurrence of juxtapapillary subretinal neovascular membrane on both eyes. The following administration of intravitreal injection anti-VEGF (bevacizumab) was modified visual acuity and reduced neovascular membrane.

Key words: Vogt-Koyanagi-Harada syndrome, children, juxtapapillary choroidal neovascular membrane, anti-VEGF, bevacizumab.

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INTRODUCTION

Vogt-Koyanagi-Harada (VKH) syndrome is an idiopathic multisystem T-lymphocyte mediated autoimmune disease attacking antigenic components of melanocytes, causing inflammation of the tissues containing melanocytes such as the uvea, ears, skin and meninges (14). It is characterised by granulomatous panuveitis with exudative retinal detachment and is frequently associated with neurological and skin manifestation (4). The syndrome occurs most frequently in darkly pigmented races, in Asians, American Indians, Hispanics and black people. The age of manifestation is most frequently between 20 and 50 years. From the quantity of published works, the occurrence in children aged under 16 has been less than 5%. In the literature there are only a few documented cases of VKH syndrome in children; in our work we present a case of an 11-year-old patient with VKH syndrome, which was complicated by the formation of a juxtapapillary choroidal neovascular membrane.

CASE STUDY

An 11-year-old boy of Caucasian race was sent to our workplace with a 2 week anamnesis of sudden deterioration of vision in both eyes. In the past he had not been treated for any eye disorders, had not suffered an eye injury or undergone an operation. Two weeks before the beginning of the problems he was vaccinated with the PRIORIX vaccine. The only symptom was a visual disorder, he had no other general complaints. At the first examination with his ophthalmologist his central visual acuity (CVA) was 5/30 bilaterally and upon examination of the fundus hyperaemia of the disc of the optic nerve (DON) was diagnosed. He was subsequently admitted at the district eye clinic and sent for a brain scan by nuclear magnetic resonance (NMR), where a finding of an extra axial cystic lesion in the pineal area was determined. Due to the MRI finding the patient was transferred to the Paediatric Neurology Clinic at the Paediatric University Hospital and Clinic in Bratislava. No neurological, skin or hearing manifestations were found, and a cerebrospinal fluid scan (CFS) did not find any abnormalities.
The first eye examination at the Paediatric Ophthalmology Clinic at the Paediatric University Hospital and Clinic determined a persisting disorder of CVA 5/30 bilaterally and bilateral panuveitis with multifocal serous retinal detachment (fig. 1) and with impairment of the visual field (fig. 2). At the same time a suspicion of probable VKH syndrome was expressed. Other causal linkage with another inflammatory or infectious disease was diagnostically excluded. HLA typification determined HLA class I: HLA A2, A11, B51, B7 and HLA class II: DR01 and DR11. For the patient the ultrasonographic (USG) image (fig. 3), the finding on optical coherence tomography (OCT) (fig. 4) and fluorescence angiography (FAG) corresponded to the uveitic stage of VKH syndrome. Initiated was the pulse corticoid therapy with methylprednisolone 500 mg intravenously for 3 days with subsequent oral administration of prednisone in a dose of 1 mg/kg/day.
After 1 month a control MRI scan determined a finding of cisterna magna permagna and a cyst of the epiphysis. The neurosurgeon stated that this concerned a possible ordinary finding without a clinical correlation to visual disorder. During general corticosteroid treatment the patient recorded a progressive improvement of CVA in a period of 1.5 months to 5/7.5 in the right eye and 5/10 in the left eye, as well as an improvement in the visual field, subsidence of retinal detachment and attenuation of anterior uveitis. Oedema of the DON persisted in the ophthamoscopic image, as well as disorders of the pigment retinal epithelium (PRE), which was destroyed in the macula. Depigmentations occurred in the periphery and central periphery (fig. 5), to which the FAG image also corresponded (fig. 6), and on

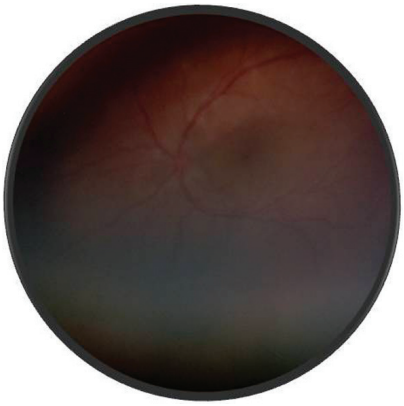

Fig. 1. Photograph of fundus o. sin – multifocal serous retinal detachment – the uveitic stage of VKH syndrome

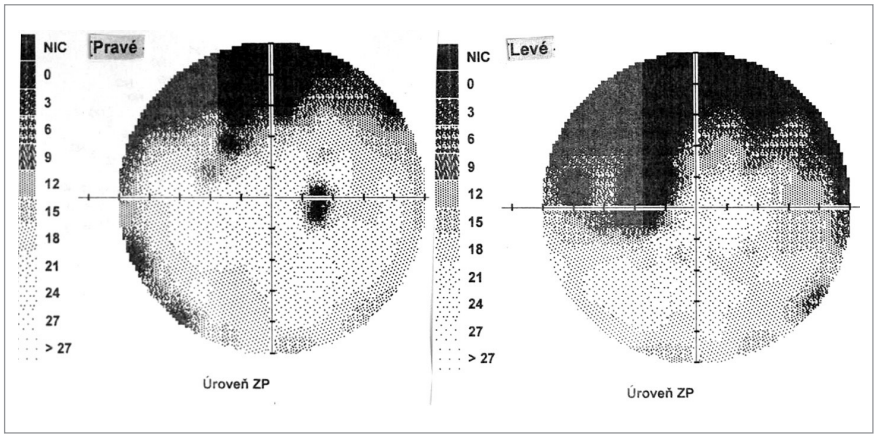

Fig. 2. Perimetric finding – the uveitic stage of VKH syndrome

OCT retinal detachment had attenuated (fig. 7 a, b). The values of intraocular pressure were within the norm. We evaluated the state as a chronic stage of VKH syndrome.

After 3 months from the prodromes of the illness, CVA is 5/5 bilaterally, in the clinical picture there is recurrence of anterior uveitis, without manifestations of posterior uveisits, oedema of the DON persists; the patient has been left on general corticoid therapy in a dose of 10 mg/day.

After 6 months from the beginning of the disease, the patient in the clinical picture has no manifestations of anterior uveitis, a fundoscopic examination revealed formation of a juxtapapillary choroidal neovascular membrane (CNVM) at the temporal edge of the DON bilaterally. Its presence was confirmed by a FAG and an OCT examinations. CVA was 5/5 bilaterally, on the perimeter an extended blind spot (fig. 8).

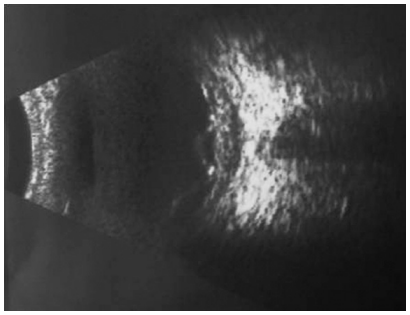

Fig. 3 USG finding in o. sin – the uveitic stage of VKH syndrome

10 months after the beginning of the disease the patient had no manifestations of anterior uveitis. Fundoscopic examination revealed progression of the juxtapapillary CNVM at the temporal edge of the DON bilaterally, which extended into the macula (fig. 9 a, b). Peripapillary, hyperfluorescence spreading temporally from the disc was seen on the FAG image, extending into the area of the macula with delayed infiltration (fig. 10). The OCT image determined a juxtapapillary CNVM with submacular fluid, with a central macular thickness (CMT) of 381 μm in the right eye and 364 μm in the left eye (fig. 11a, b). CVA was 5/10 bilaterally, the perimetric finding showed paracentral scotoma with an extended blind spot. For this reason, after obtaining informed consent from the legal representative of the patient, we applied 1 injection of anti-VEGF bevacizumab intravitreally in a dose of 0.75 mg/0.1 ml into the right eye and 1.25 mg/0.1 ml into the left eye.

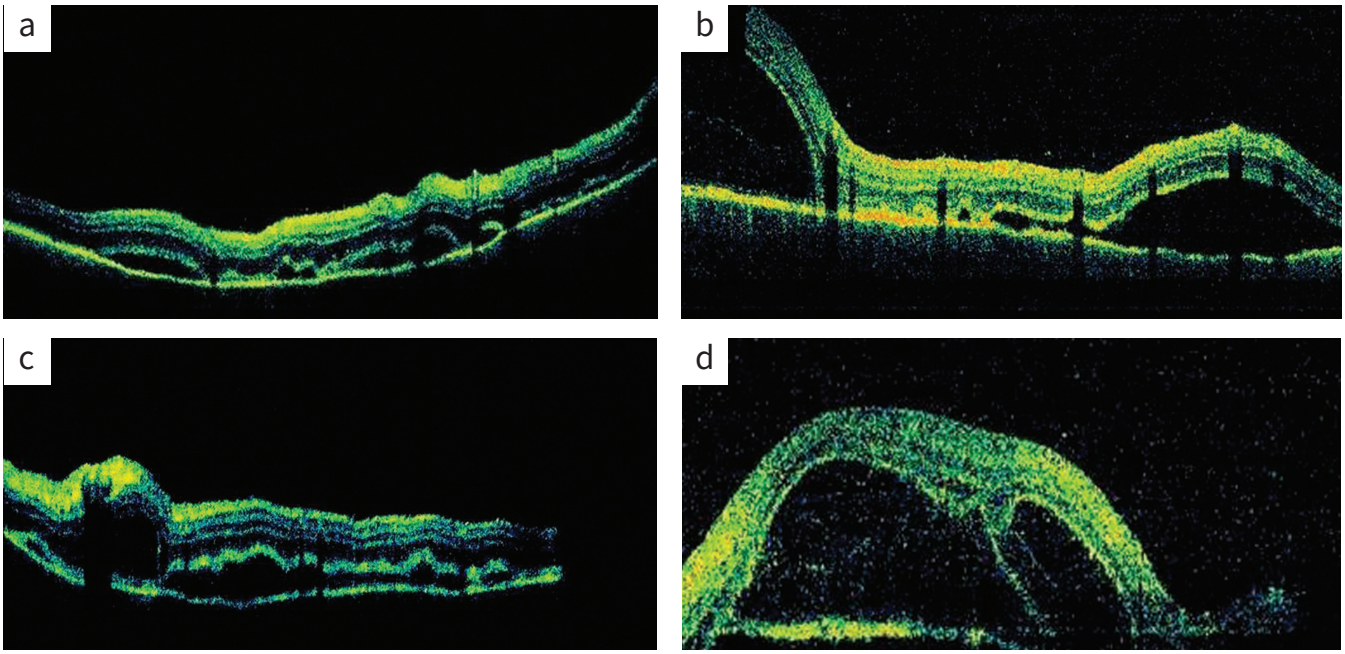

Fig. 4. OCT retinal finding – the uveitic stage of VKH syndrome a) o. dx horizontal scan, b) o. dx vertical scan, c) o. sin horizontal scan, d) o. sin vertical scan

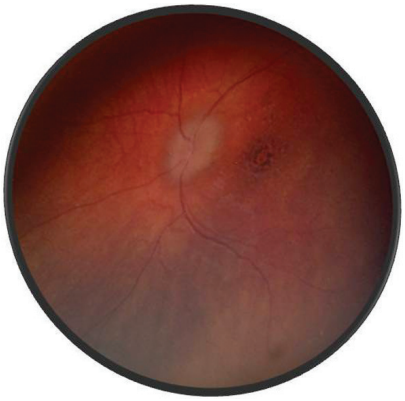

Fig. 5. Photograph of o. sin fundus – the chronic stage of VKH syndrome

Fig. 6. FAG of o. sin – the chronic stage of VKH syndrome

Subsequently within 1 month there was a correction of CVA to 5/5 in the right eye and 5/7.5 in the left eye with regression of the juxtapapillary CNVM visibly on the FAG and OCT examinations (CMT 247/264 μm), though juxtapapillary subretinal fibrosis persists. 11 months after the beginning of the disease, general treatment with prednisone was terminated.

In the 17th and 23rd months from the beginning of the disease two recurrences of anterior uveitis appeared bilaterally, with occurrence of posterior synechieae (fig. 12), which corresponds to a recurring stage of the disease. No manifestations of regression of posterior uveitis were determined. Upon the

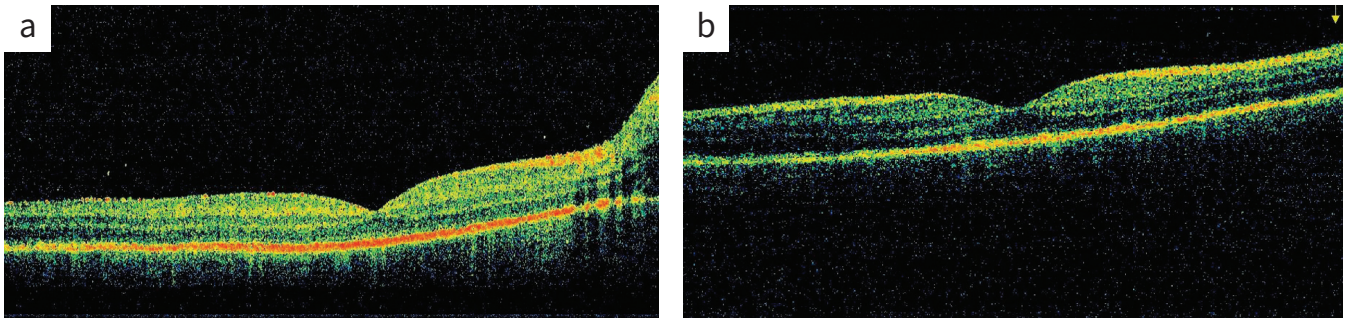

Fig. 7. OCT finding – the chronic stage of VKH syndrome a) o. dx, b) o. sin

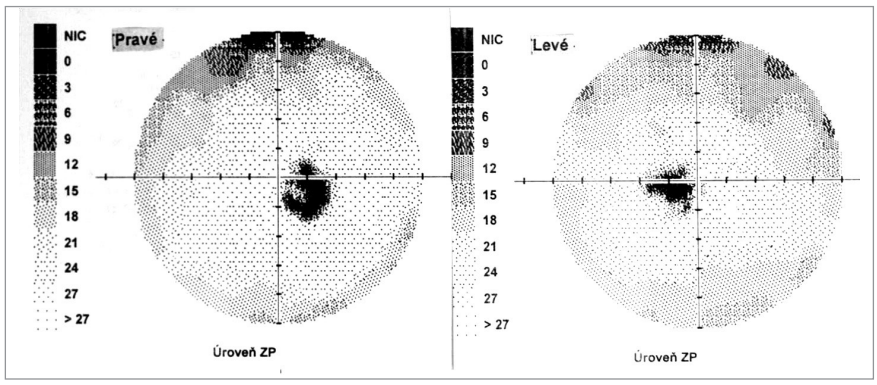

Fig. 8. Perimetric finding – the chronic stage of VKH syndrome

first recurrence the inflammation was managed by a local corticoid therapy, and upon the second recurrence by an oral corticoid therapy with prednisone in a dose of 1 mg/kg with gradual reduction over the course of 2 months. At present, 32 months after the onset of the disease, CVA is 5/5 in the right eye and 5/7.5 in the left eye. The patient has no signs of anterior or posterior uveitis bilaterally. No glaucoma or cataract was found in the patient. However, the patient manifests chronic changes in the anterior and posterior segments, and defocusing of the

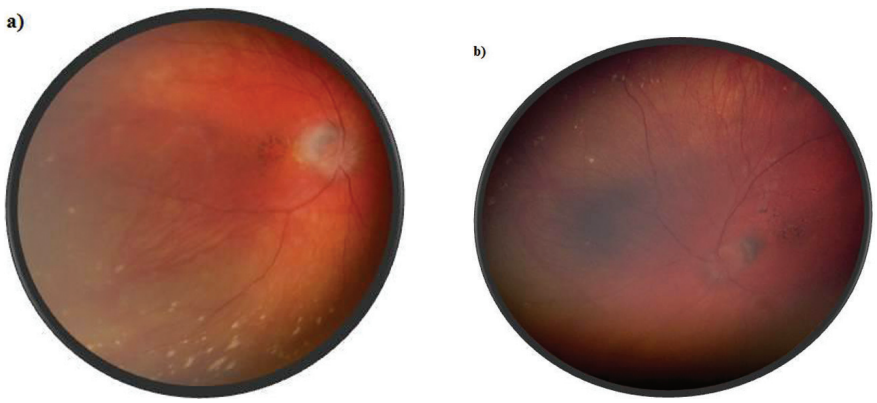

Fig. 9. Photograph of fundus – juxtapapillary CNVM a) o. dx, b) o. sin

Fig. 10. FAG finding of o. sin – classic juxtapapillary CNVM

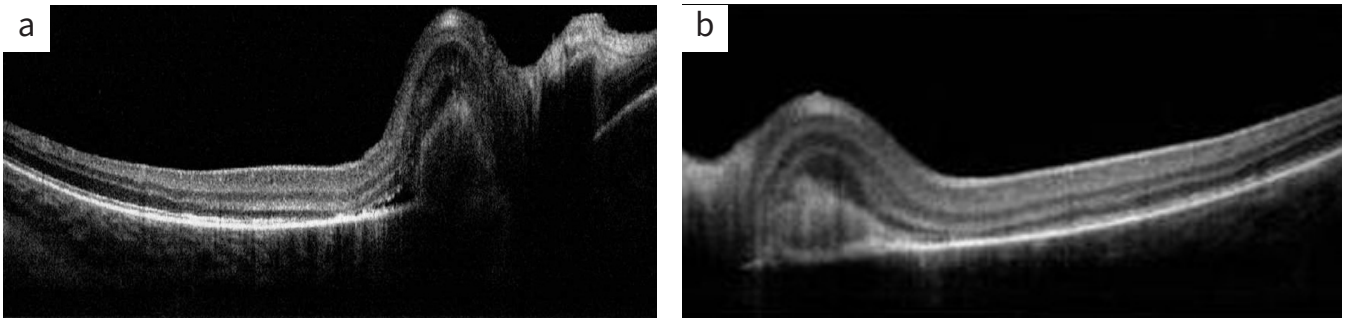

Fig. 11. OCT finding – juxtapapillary CNVM a) o. dx, b) o. sin

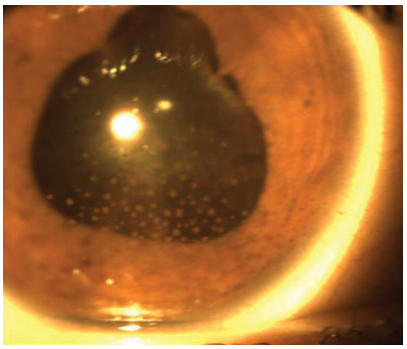

Fig. 12. Photograph of the anterior segment of o. sin – recurring stage

DON is persisting due to the finding of juxtapapillary subretinal fibrosis, paracentral scotoma is persisting in the visual field in the place of the blind spot. Central macular thickness is 249 µm in the right eye and 255 µm in the left eye. The patient remains under our observation.

DISCUSSION

Vogt (1906), Koyanagi (1929), Harada (1926) – independently described a number of patients with bilateral uveitis, exudative retinal detachment, with neurological abnormalities and skin problems. Despite the differences in the individual cases and the assumption that this concerned various different diseases, other authors subsequently came to the conclusion that the disorder could be named Vogt-Koyanagi-Harada syndrome. The international commission for nomenclature set the criteria for diagnosis of VKH syndrome. The revised criteria define 3 categories of the disorder: complete VKH, incomplete VKH and probable VKH disease (4, 20) (table 1). Our patient met the criteria for the probable VKH disease.

The pathogenesis of the disorder is unknown, inflammation and loss of melanocytes was determined in a number of organs – in the skin, the inner ear, meninges and uvea. On the basis of the histopathological findings, the disorder is assumed to have an infectious or autoimmune base. VKH disease most frequently occurs in patients with a genetic predisposition to the disorder. An association was determined with HLA-DRB1, HLA-DR4, HLA-DR5 and HLA-DQ4 (13).

The frequency of incidence of VKH disease is low, most frequently it afflicts people of darkly pigmented races. Pigmentation of the skin alone is not a predisposing factor in the pathogenesis of the disease. Women are afflicted more often than men. The disorder afflicts people between 20 and 50 years of age, most often in the third decade, occurrence in children is rare. In the literature there are only a few recorded cases of occurrence in children (1, 3, 7, 10, 15, 18, 21, 23).

Neurological symptoms may persist for weeks, usually subsiding after corticoids, whilst skin manifestations persist despite the treatment, hearing complaints subside after a corticoid therapy after weeks to months.

Clinical manifestation – we distinguish 4 stages of the disorder (table 2).

Diagnosis of the disease is based on the clinical picture and the symptoms, there are no laboratory tests specific for this disease. FAG, ICG, OCT, USG, MRI, examination of liquor (CSF), eletrophysiological tests and audiometry are useful in diagnosis. HLA typification is not significant for diagnosis and as a result it is not routinely recommended.

The purpose of treatment is to manage uveitis and prevent complications. Treatment of VKH syndrome with systemic corticoids should be started sufficiently in time and aggressively – methylprednisolone up to 1 g/d intravenously for several days, in children 10 mg/kg/d, subsequently predisone 1 mg/kg/d orally, length and reduction of dose individually, sometimes 6-12 months but no less than 3 months due to the risk of recurrence (2, 12, 19). We too respected this recommendation. In patients not responding to corticoids or in whom the treatment produced adverse reactions, an immunomodulation therapy is recommended – methotrexate, cyclosporine, infliximab, tacrolimus, azathioprine, cyclophosphamide (10, 24).

Treatment in children with VKH syndrome is challenging. Various models of treatment have been described in the literature, with varying effects; no definitive treatment module has yet been determined and treatment is usually individual in cases of VKH in children (3). In previous publications, the most useful substances in the treatment of VKH syndrome in children were corticosteroids, whereas combinations of therapy with cyclosporine, methotrexate or azathioprine were used with favourable results in refractory cases (7). In our case the disorder was managed with systemic corticoid therapy, on which the patient was left for 11 months.

In the treatment of complications, it is most often necessary to resolve secondary glaucoma or cataract, which did not occur in our patient, and choroidal neovascular membrane (CNVM). Choroidal neovascularisations occur in 15% of patients with VKH and are associated with an unfavourable prognosis for sight (25). Bevacizumab is a human monoclonal antibody, which binds to all subtypes of vascular endothelial growth factor (VEGF). It has been successfully used in the treatment of secondary CNVM in the case of various disorders. Intravitreally administered bevacizumab is an effective medication in the treatment of CNVM in eyes with VKH syndrome (8, 17, 18, 22). A similar effect in the treatment of CNVM in eyes with VKH syndrome was achieved also upon intravitreal administration of ranibizumab (11). In our case the patient was treated for complicated juxtapapillary CNVM in both eyes with bevacizumab. One intravitreal administration of bevacizumab was sufficient and stabilised CVA. However, persistent subretinal fibrosis

Table 1 Revised criteria for the Vogt-Koyanagi-Harada disease (4, 20)

Complete VKH disease (Criteria 1-5 must be met)
1. absence of penetrative eye trauma and surgery before manifestations of uveitis
2. absence of clinical and laboratory connection with any other eye disorder
3. bilateral affliction of eyes (a. or b. must be met depending on the stage in which we examine the patient)

a. early manifestation of disease
- 1. diffuse choroiditis (without or with anterior uveitis, reaction in vitreous body, hyperaemia of the optic nerve), which may be manifested as
  - a) focal areas of subretinal fluid
  - b) bullous serous retinal detachment
- 2. with subsequent symptoms on fundus (both symptoms must exist)
  - a) focal areas with delayed choroidal perfusion, multifocal areas with point infiltration, large placoid surfaces of hyperfluorescence, with accumulated subretinal fluid, enhancement of optic nerve on FAG
  - b) diffuse choroidal coarsening, without presence of scleritis on USG

b. late manifestation of disease
- 1. anamnestic presumption of presence of symptoms from 3.a, and either (2) or (3) below, or multiple symptoms from (3)
- 2. ocular depigmentation (one of the following is sufficient)
  - a) "sunset glow" fundus
  - b) Sugiura's symptom – perilimbal vitiligo
- 3. other ocular symptoms
  - a) nummular chorioretinal depigmented scars
  - b) RPE clusters or shifts
  - c) recurrent or chronic anterior uveitis

4. Neurological/hearing disorders (may have subsided at time of examination)
a. meningism
b. tinnitus
c. pleocytosis in CSF

5. Skin symptoms (follow after manifestation of CNS or eye affliction)
a. alopecia or
b. poliosis or
c. vitiligo

Incomplete VKH disease (criteria 1-3 and 4 or 5 must be met)
1. absence of penetrative eye trauma and surgery before manifestations of uveitis
2. absence of clinical and laboratory connection with any other eye disorder
3.bilateral affliction of eyes (as defined for the complete VKH disease)
4. neurological/hearing disorders (as defined for complete VKH disease)
5. skin symptoms (as defined for complete VKH syndrome)

Probable VKH syndrome
1. absence of penetrative eye trauma and operation before manifestations of uveitis
2. absence of clinical and laboratory connection with any other eye disorder
3. bilateral affliction of eyes (as defined for complete VKH syndrome)

Table 2 Clinical stages of disorder

1. Prodromal stage	Persists for several days, fever, headache, meningism, nausea, vertigo, tinnitus, dysacusis, CFS pleocytosis, photophobia, epiphora, hypersensitivity of skin and hair. Less frequent paralysis of nerves, neuritis n.II, some patients do not have prodromal symptoms
2. Uveitic stage	Follows prodromal stage after a number of days, frequent deteriorated vision, in 70% bilaterally, if unilaterally the second eye is afflicted a few days later. Bilateral uveitis with retinal oedema, cells in anterior vitreous body, hyperaemia of papilla of the optic nerve or oedema, multifocal serous retinal detachment, granulomatous anterior uveitis with streaked precipitates, Busacca and Koeppe nodules, increase of IOP, the stage persists for several weeks
3. Chronic stage	Typical eye and skin manifestation. Dallen-Fuchs nodules, posterior synechia, pupillary membrane. Subsidence of detachment. Depigmentation of choroidea begins first 3 months from beginning of disease, RPE alteration – depigmentation, hyperpigmentation of fundus, demarcation lines in periphery and central periphery of retina, lesions fade and atrophy. Skin symptoms – vitiligo, poliosis of eyelashes, eyebrows, hair. Dysfunction of inner ear is corrected after several months. Stage persists for several months.
4. Recurring stage	Recurring or chronic anterior uveitis, weaker choroidal inflammation accompanying anterior uveitis diagnosed by ICG angiography (11). Recurrence of posterior uveitis is rare. Ocular complications are frequent – cataract, glaucoma – pupillary block or with closed angle, atrophy of disc of optic nerve, choroidal neovascularisation, neovascularisation of disc of optic nerve and retina, vitreous haemorrhage, subretinal fibrosis.

is a cause of paracentral scotoma in the visual field in both eyes.

Corticosteroids are used due to their angiostatic and antipermeable properties. It is necessary to suppress the inflammation process by immunosuppression. A combination of an intravitreally applied anti-VEGF and a corticosteroid together with a systemic immunosuppressive therapy was effective in the treatment of inflammatory CNVM without serious systemic or ocular side effects (22).

Laser photocoagulation, photodynamic therapy, surgical excision and corticosteroid therapy have been used in the treatment of secondarily occurring CNVM in VKH with varying degrees of success (5, 6, 9, 16).

The visual prognosis of VKH in adults as well as in children is generally favourable. The clinical finding upon manifestation of the disease, the interval between occurrence of the first symptoms and the initiation of treatment, repeated inflammations, development of complications, use of intravenous corticosteroids and the method of reducing of systemic corticosteroids are significant prognostic factors.

CONCLUSION

VKH syndrome is a serious disease which in rare cases also afflicts children. If extraocular symptoms are not present, the diagnosis may be complicated and treatment of the acute phase requires immediate bolus corticoid therapy. VKH syndrome requires monitoring for several years due to its chronic character. Prognosis quo ad visum is favourable in child patients. The deterioration of visual acuity in patients with VKH syndrome is frequently caused by complications such as cataract, glaucoma and choroidal neovascularisation. Choroidal neovascularisation is the main cause of later loss of sight.

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