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Case Report

Best's Disease: Diagnostic Criteria and Antiangiogenic Therapy Efficacy - A Case Report

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Abstract

Purpose: To present a case report of diagnosis and management of a child's macular neovascularization (MNV) associated with Best's vitelliform macular dystrophy.

Material and Methods: A 15-year-old patient with decreased vision in both eyes (more left than right). The vision decrease was first detected during an examination, including the determination of the best corrected visual acuity (BCVA), the vision field, and the collection of a genealogical history; OCT and OCTA revealed macular degeneration and active MNV.

Results and Discussion: Stabilization of the pathological process in the form of adhering of the neuroepithelium detachment over the MNV was achieved only in the right eye after the 1st ranibizumab injection. Relapses and continued activity of newly formed vessels were noted in the left eye.

The lack of sufficient suppression of de novo vessels can be explained by 1 MNV type, deposition of lipofuscin-like material and presence of a large adductor vessel - a branch of the posterior short ciliary artery, which in general are prognostically unfavorable factors determining possible relapses and progression of pathological retinal changes. At the same time, during the natural disease course, the vitelliform material was displaced by gravity into the lower segments of the macular region and its further resorption, while the active adductor vessel was preserved.

Conclusion: Kids' diagnosis of Best's vitelliform macular dystrophy is based on a complex of studies, including the collection of genealogical history, OCT, OCTA, autofluorescence. It is possible to verify the disease at early stages of the pathological process, to conduct timely therapy and adequate monitoring with an assessment of the activity degree of newly formed vessels and structural retinal changes. The key factors determining the need for antiangiogenic therapy in children with Best's disease are not only the active form of MNV, but also structural retinal changes and the state of visual functions.

Keywords: Best's Disease; Macular Neovascularization (MNV); Vitelliform Macular Dystrophy; Bestrophin; Antiangiogenic Therapy

Abbreviations

MNV: Macular Neovascularization; BCVA: Best Corrected Visual Acuity; OCT: Optical Coherent Tomography; OCTA: Optical Coherent Tomography Angiography; BD: Best's Disease; PDT: Photodynamic Therapy

Introduction

Best's disease (BD) or vitelliform macular dystrophy is one of the most common hereditary macular dystrophy in children. The exact prevalence of the disease is unknown. According to the literature review, its frequency varies from 1 to 9 cases per 100 thousand people.

The disease is inherited by an autosomal dominant type and is caused by a mutation in the BEST1 gene located on chromosome 11q13 in the interval between the marker genes D11S986 and D11S4801 and encoding the protein bestrophin. Bestrophin is localized on the membrane of retinal pigment epithelium cells and is necessary for their normal functioning. It should be noted that a number of other hereditary eye diseases are also associated with mutations in the BEST1 gene [1-3].

Bestrophin 1 (Best1), a protein encoded by the BEST1 gene, has been the subject of a large amount of researches since it was first identified.

Today we know that Best1 functions as a pentameric anion channel and a regulator of intracellular Ca^{2+} signaling. Best1 is an integral membrane protein that is uniquely expressed in the retinal pigment epithelium in the eye, where it is predominantly localized in the basolateral plasma membrane.

Mutations in the BEST1 gene are causally associated with five clinically different degenerative diseases of the retina, which are collectively called "bestrophinopathies". These five diseases are: vitelliform Best's macular degeneration, autosomal recessive bestrophinopathy, vitelliform macular dystrophy in adults, autosomal dominant vitreoretinochorioidopathy and retinitis pigmentosa. The most common of these is Best's vitelliform macular dystrophy [4].

In adults, it is necessary to differentiate Best's disease with adult fovea macular vitelliform dystrophy (from among pattern dystrophies), age-related macular degeneration, dominant druses, central serous chorioretinopathy, North Carolina macular dystrophy, toxoplasmous chorioretinitis, retinochorioiditis, solar retinopathy, macular hole or other causes of central atrophy, such as myopic degeneration [5,6].

Abnormal electrooculography is characteristic of BD: a low constant potential and a decrease in the Arden coefficient - the ratio of the light peak to the dark decline, which confirms the generalized lesion of the retinal pigment epithelium. At the same time, the total electroretinogram remains normal [3].

Best's disease can be complicated by the development of macular neovascularization (MNV) (5-91%), in rare cases, the formation of a macular hole is observed [5,7]. Macular neovascularization occurs in about 20 % of patients. Best's vitelliform macular dystrophy is characterized by two subforms of MNV. Exudative MNV is rare and can develop in the early stages of the disease in combination with bleeding and the formation of subretinal fluid. Nonexudative MNV very often develops in the late stages of Best's vitelliform macular dystrophy without any exudative manifestations [8].

Currently, intravitreal administration of anti-VEGF agents is used to treat complications associated with Best's dystrophy, in particular MNV. Intravitreal administration of anti-VEGF agents may be effective for the treatment of exudative macular neovascularization at the vitelliform stage of Best's vitelliform macular dystrophy; however, in the late stages of the pathological process, there is no information on the efficacy of anti-VEGF agents. Thus, it is necessary to examine all family members with abnormal electrooculogram and confirmed mutation for the detection of vitelliform changes and macular neovascularization. The decision on treatment with intravitreal administration of anti-VEGF agents should be made individually, since the only indication for intravitreal administration to children in the Russian Federation is retinopathy of prematurity [9-16].

Another method of MNV treatment in Best's disease is photodynamic therapy (PDT) with verteporfin. According to Ozdek S. and co-author (2012), even one PDT session lead to a significant increase in visual acuity [17]. PDT can be an effective method of treating MNV associated with Best's vitelliform macular dystrophy in children [18].

Due to the fact that the vast majority of publications devoted to Best's disease are descriptions of isolated clinical cases without systematization of available data, the assessment of the clinical efficacy of anti-VEGF therapy in a child with Best's vitelliform macular dystrophy is quite relevant [19-22].

The purpose of this study was to present a clinical case of diagnosis and management of a child with MNV associated with Best's vitelliform macular dystrophy.

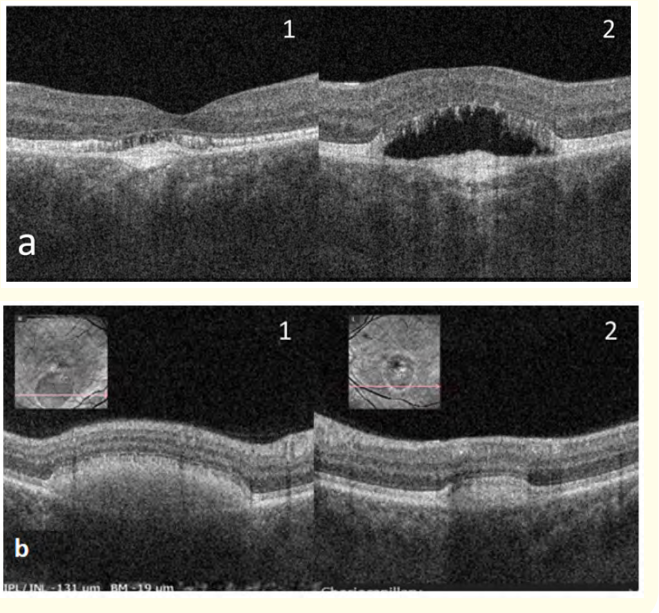
Materials and Methods

A 15-year-old patient was examined and treated with complaints of decreased vision in both eyes (the left is more). The vision decrease was first detected during a medical examination, in the

process of further diagnostic search according to structural OCT and OCT in the angiography mode, macular degeneration and the active form of MNV were diagnosed. A comprehensive examination, including the determination of best corrected visual acuity (BCVA), the field of vision, and the collection of a genealogical history was performed. The study was approved be the Local Ethics Committee of Irkutsk Branch of S. Fyodorov "Eye Microsurgery" Federal State Institution (Protocol №3-1, 12.02.2021). The study was conducted in accordance with the Declaration of Helsinki Ethical Principles. The informed consent was obtained from the parents of the patient.

Results

In the family history, there was a significant decrease in visual acuity in the patient's father and her brother. Active diagnostic tactics, examination of the child's parents allowed the girl's father to reveal a decrease in the BCVA of both eyes to 0.6 and to establish pathological changes in the fundus corresponding to the pseudohypopion stage in the right eye, the vitelleruptive stage of Best's disease in the left eye. According to OCT data, a subfoveolar fibrovascular scar was detected in both eyes, neuroepithelium detachment from the slit in the right eye to the average height in the left eye, elongation and destruction of the outer segments of photoreceptors, the pigment epithelium was preserved (Figure 1a). Perifoveolar accumulation of vitelliform material under a layer of photoreceptors in the lower quadrant (Figure 1b), a large main vessel with single loops and anastomoses (Figure 1c).



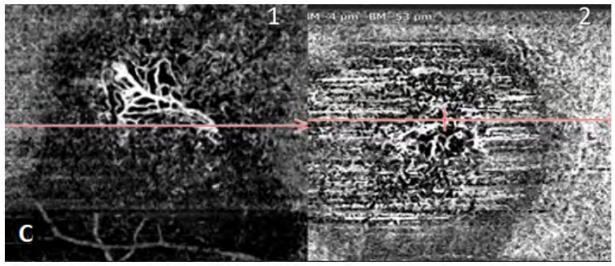


Figure 1: a) OCT protocol of retina of the patient's father: 1 - right eye - slit-like neuroepithelium detachment; 2 - left eye - widespread detachment of the neuroepithelium; in both eyes, a subfoveolar fibrovascular scar, elongation and destruction of the outer segments of photoreceptors, pigmented epithelium preserved. b) Perifoveolar accumulation of vitelliform material under a layer of photoreceptors in the lower quadrant 1 - right eye; 2 - left eye. c) Large trunk vessel with single loops and anastomoses 1 - right eye; 2 - left eye.

In a child, the BCVA of the right eye is reduced to 0.85, the left eye - to 0.5. On the fundus of both eyes in the macular region, a yellow-shaped projecting focus was visualized in the right eye with a diameter of 1 DD, with perifocal retinal edema (Figure 2a), in the left eye with a diameter of up to 0.5 DD, also with perifocal retinal edema and microhemorrhagias (Figure 2b).

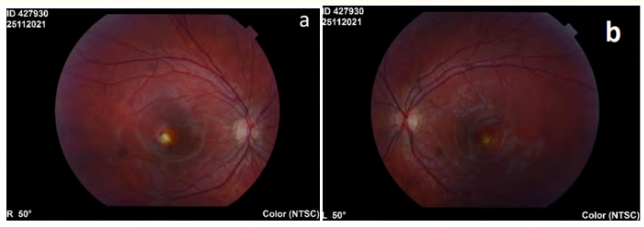


Figure 2: Fundus image. a) Right eye - a prominating lesion of a rounded yellow shape with a diameter of 1 DD, with perifocal retinal edema. b) Left eye - a prominating lesion of a rounded yellow shape with a diameter up to 0.5 DD with perifocal retinal edema and microhemorrhagia.

According to OCT, in the macular area of the right eye, a dome-shaped deformation of the foveolar profile, a subfoveolar subretinal hyperreflective focus between the pigment epithelium and the Bruch membrane, with clear boundaries, tooth-shaped,

neuroepithelium detachment with areflective contents, elongation of the outer segments of photoreceptors was revealed. Changes in the structure of the choroid were characterized as pachychoroid. In addition, increased transmission of the pigment epithelium, excavation of the choroid subfoveolar in the projection of the focus was found (Figure 3a).

In the left eye, a similar deformation of the foveolar profile was revealed, a subfoveolar subretinal hyperreflective focus of spherical shape between the pigment epithelium and the Bruch membrane, the boundaries of the focus are mostly blurred. Neuroepithelial detachment, hyperreflective foci, sensorineural retinal edema and fine suspension in the projection and around the focus, Bruch membrane defects were determined. Changes in the structure of the choroid are similar to the right eye (Figure 3b).

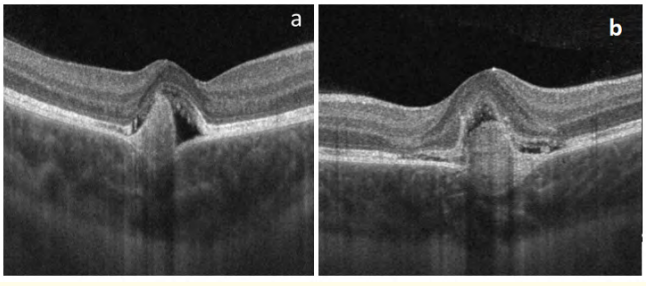


Figure 3: OCT macular protocol. a) Right eye - dome-shaped deformation of the foveolar profile, subfoveolar subretinal hyperreflective focus with clear boundaries, tooth-shaped, between the pigment epithelium and the Bruch membrane, detachment of the neuroepithelium with a reflective contents, elongation of the outer segments of photoreceptors. Changes in the choroid structure - pachychoroid. In addition, increased transmission of the pigment epithelium, excavation of the choroid subfoveolar in the projection of the focus. b) Left eye - dome-shaped deformation of the foveolar profile, subfoveolar subretinal hyperreflective focus of spherical shape between the pigment epithelium and Bruch's membrane, the boundaries of the focus are mostly blurred. The detachment of the neuroepithelium, hyperreflective foci, edema of the sensorineural retina and fine suspension in the projection and around the focus, defects of the Bruch membrane are determined. Structure choroid changes are similar to the right eye.

OCT angio determined the presence of newly formed vessels in both eyes. The MNV in the right eye had an indistinct vascular profile, a rare vascular network, and a weakening of the pattern of choriocapillaries around the focus. On the left eye, the MNV had a well-defined vascular profile, a dense vascular network with a large number of anastomoses and loops, and a hyporeflective areole (Figure 4 a, b).

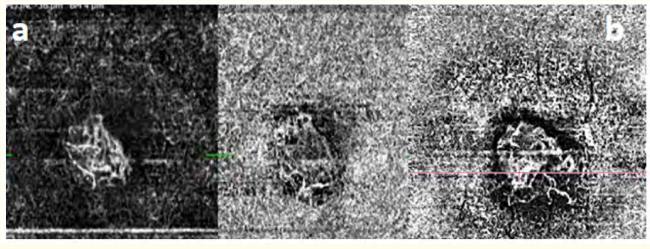


Figure 4: OCTA protocol. a) Right eye - MNV has an indistinct vascular profile, a rare vascular network, a weakening of the pattern of choriocapillaries around the focus. b) Left eye - MNV has a well-defined vascular profile, a dense vascular network with a large number of anastomoses and loops, a hyporeflective areole.

With autofluorescence of the fundus in the macular zone, a focus of heterogeneous hyperautofluorescence was determined, corresponding to the accumulation of vitelliform material with its partial resorption, surrounded by a zone of hypoautofluorescence. Autofluorescence is blocked in the hemorrhagic projection on the left. Beyond the pathological changes, the fluorescence of lipofuscin of the pigment epithelium did not differ from normal (Figure 5 a, b).

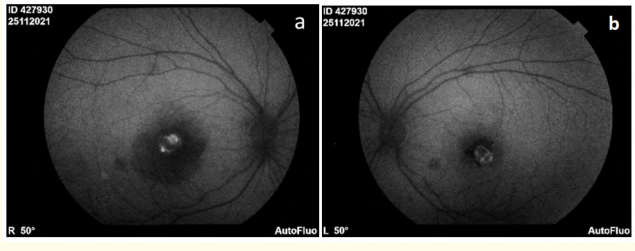


Figure 5: Fundus autofluorescence. a) Right eye - in the macular zone, a focus of inhomogeneous hyperautofluorescence is determined, corresponding to the accumulation of vitelliform material with its partial resorption, surrounded by a zone of hypoautofluorescence. b) Left eye - autofluorescence is blocked in the projection of hemorrhage. Beyond pathological changes, the fluorescence of pigment epithelium lipofuscin does not differ from normal.

Based on the data obtained, the diagnosis of Best's Vitelliform macular dystrophy, vitelliform stage; Active type 1 MNV; Mild OU hypermetropia was established. Taking into account the anamnesis data, the dominant type of inheritance of this disease was confirmed.

In standard cases, the active form of MNV is an indication for the anti-VEGF therapy. However, the appointment of this therapy to the child became possible after a consultation and receiving a positive decision of the Local Ethics Committee. The lack of systematic data on the effects of anti-VEGF therapy and possible complications of this type of treatment of Best's disease in children justified the sequential injections of the anti-VEGF agent into the right and left eyes under general anesthesia [23,24]. After the first injection, there was a fit of the neuroepithelium detachment and an increase in visual acuity to 0.9/0.9 in both eyes. This condition persisted in the right eye for the entire follow-up period (8 months). It was not possible to achieve a persistent effect in the left eye, despite 4 monthly injections, 1 every 1-2 months. Resorption of the subretinal fluid was replaced by an edema increase and neuroepithelium detachment.

Discussion

To date, it is known that patients with Best's vitelliform macular dystrophy primarily complain of blurred vision, difficulty reading text with small print, metamorphopsies. The most typical age of complaints is from preschool to youth. Visual acuity can vary depending on the stage of the disease from 0.02 to 1.0. In most cases, the changes are bilateral, often asymmetric. Depending on the changes in the macular area determined ophthalmoscopically, there are 5 stages of the disease: 1st (previtelliform) - there are no visible changes in the macula or minimal pigmentation disorders in the form of small yellow foci in the macula; 2nd (vitelliform) - subretinal deposition of a yellowish lipofuscin-like substance, resembling an egg yolk during ophthalmoscopy; 3rd (pseudohypopion) - lipofuscin-like material is liquefied and shifted downward under the action of gravitational forces, and also breaks through the retinal pigment epithelium, which more often occurs at puberty; 4th ("scrambled eggs", vitelleruptive) - resorption of cyst contents; 5th (atrophic) - formation of fibroglial scar. Histologically, the accumulation of lipofuscin granules in the pigment epithelium of the macula and other parts of the retina is determined, the result of which is the degeneration of the outer segments of photoreceptors. Thus, in Best's disease, the mechanism of vision itself suffers when the visual pigment molecule does not perform one of the two main physiological functions: against the background of a decrease in the spectral range of the photoreceptor cell, the photoreceptor process suffers. With a decrease in the thickness of the retina in the central parts with Best's dystrophy, the number of rods and cones decreases, more in the central zone [2].

Thus, based on the presented pathogenesis and classification of the disease, therapeutic measures can be effective in the initial stages of Best's disease, before the formation of a fibroglial scar, in the case when the function of photoreceptors and retinal ganglion cells is preserved.

Based on the presented clinical case, the patient applied to the clinic in the vitelliform stage of the pathological process and the presence of active type 1 MNV, which allowed predicting the clinical effect of antiangiogenic therapy. Stabilization of the pathological process in the form of attachment of the detachment of the neuroepithelium over the MNV was achieved only in the right eye after the 1st injection. Relapses and continued activity of newly formed vessels were noted in the left eye.

The lack of sufficient suppression of de novo vessels can be explained by type 1 of MNV, deposition of lipofuscin-like material and the presence of a large adductor vessel, which is a branch of the posterior short ciliary artery, which in general are prognostically unfavorable factors determining possible relapses and progression of pathological changes in the retina [25].

At the same time, during the natural course of the disease, the vitelliform material was displaced by gravity into the lower segments of the macular region and its further resorption, while the active adductor vessel was preserved. According to Parodi M.B., *et al*. (2020), the accumulation of subretinal fluid occurs along with the deposition of vitelliform material [26].

Conclusion

Diagnosis of Best's vitelliform macular dystrophy in children is based on a complex of studies, including the collection of genealogical anamnesis, OCT, OCTA, autofluorescence, which makes it possible to verify this disease at the early stages of the pathological process, to conduct timely therapy and adequate monitoring with an assessment of the degree of activity of newly formed vessels and structural changes in the retina.

The key factors determining the need for antiangiogenic therapy in children with Best's disease are not only the activity of MNV, but also structural changes in the retina and the state of visual functions.

Conflict of Interest

The Authors declare that there is no conflict of interest

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