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CASE REPORT

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Postinfectious complications in the posterior pole of the eye in children

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ABSTRACT

The diagnosis of visual disorders in children is often a challenge for ophthalmologists because of difficult cooperation with pediatric patients. That is why a thorough examination and an attempt to find the cause of pathologies in children are particularly important. The aim of this study is to describe rare complications in the posterior pole of the eye in children following upper respiratory tract infections. In a retrospective review, we describe bilateral maculopathy and optic nerve neuropathy in a 16-year-old boy and neovascular membrane formation in a 7-year-old boy based on our own experience. Both cases were preceded by an upper respiratory tract infection. These examples show that less common possible causes of visual disturbances in children should not be ignored and should be taken into account in the differential diagnosis.

KEY WORDS: postinfectious complications in children; retinitis; influenza virus; SARS-CoV-2 virus; choroidal neovascularization; anti-VEGF injection.

INTRODUCTION

Upper respiratory tract infections (URTI) are the most common reason for doctor's visits in developed countries. This is also true for children, and the frequency of URTI in this age group is estimated to be 3-8% per year [1]. The vast majority of URTI infections are of viral etiology and are mildly symptomatic and self-limiting [2]. However, some of these seemingly trivial infections may result in complications that can be significant in their consequences [3].

Among the many possible complications of viral URTI infections in children, we include inflammatory changes in the posterior pole of the eye in the form of retinitis, choroiditis, optic neuritis and those of mixed character [4].

Thanks to increasingly accurate and widespread studies of the genetic material of viruses and serological tests, it has been proven that many DNA and RNA viruses can cause pathological changes in the posterior pole. It is impossible to list all confirmed viral etiological agents. The most common include:

- DNA viruses: CMV [5], VZV and HSV [6], EBV [7],
- RNA viruses: Influenza A and B viruses [8], rubella virus [9], viruses of the arbovirus group, especially West Nile virus, Dengue virus, and Zika virus [10], Coxsackie viruses [11], and SARS-CoV-2 [12].

In the vast majority of cases, viruses cause mild changes in the form of conjunctivitis [13], but it is important not to forget about the possibility of pathologies that may lead to permanent loss of visual acuity, visual field loss, and even blindness. Such permanent changes in children may have an important impact on their further life not only in a direct, somatic manner but also through serious psycho-social consequences [14].

The RNA virus SARS-CoV-2, whose pandemic has so significantly affected our daily lives, deserves special attention in the differential diagnosis of posterior pole lesions of viral etiology. To date, it has been shown that, like most viruses, it causes conjunctivitis, but cases of posterior pole lesions in the form of optic neuritis, retinitis, and vasculitis have also been described [15, 16], both in adults and in children [17]. Although the impact of this RNA virus is still under investigation and the poor documentation of its potential to cause posterior pole complications necessitates more case reports and larger analyses of them, it is important to remember that this virus has the potential to cause such complications. Furthermore, studies on the potential of coronaviruses to cause such lesions in animal models have already been carried out several years ago [18, 19].

CASE REPORTS

Postinfectious damage to the retinal pigment epithelium

Among the most common causes of URTI infections in children worldwide are influenza viruses [20]. Influenza viruses belong to the group Orthomyxoviridae (ortho-

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myxoviruses), which includes 4 types of viruses: *Influenza A virus*, *Influenza B virus*, *Influenza C virus*, and *Influenza D virus*, usually called influenza virus types A, B, C, and D [21]. These viruses are transmitted through respiratory droplets and cause between 290,000 and 650,000 deaths worldwide each year [22]. In addition to fatal cases, they cause numerous negative sequelae in infected individuals. Complications after influenza virus infections among children affect as many as ¼ of those infected, with otolaryngological complications being the most frequent. Among these, otitis media is the most common [23]. However, one should not forget about rarer complications affecting other systems and organs, including the eye. Such complications are estimated at 0.45-0.70% among influenza patients [8]. In the eye, the sequelae after influenza virus infection range from mild conjunctivitis to vasculitis in the posterior pole resulting in atrophy of cells of the retinal pigment epithelium (RPE) [25]. The most common type of virus causing ocular symptoms is the *Influenza A virus* [8]. In a study conducted by Mansour *et al.* on a group of 89 patients with ocular manifestations in the course of confirmed *Influenza A virus* (H1N1 subtype) infection, the diagnoses were: 58 cases of acute conjunctivitis of varying severity, 7 cases of choroiditis, 4 cases of retinopathy, and 3 cases of optic neuropathy, of which 2 were bilateral [13]. Other cases of rare symptoms and complications associated with influenza virus infection have also been described in the literature: bilateral retinitis [25], bilateral vasculitis with subsequent bilateral maculopathy and optic neuropathy [26], and retinitis preceded by pneumonia and meningitis [27]. In 2009, Michaelis *et al.* investigated the affinity of the *Influenza A virus* for the RPE. They found that inflammation of the choriocapillaris can result in RPE cell atrophy, which, unlike most complications, is irreversible [24], resulting in permanent visual field loss. Fortunately, it has been shown that viral replication in the RPE cell, which not all types of influenza viruses are capable of, is necessary for apoptosis of the RPE cell [24].

In our center, we experienced the negative consequences of influenza type A virus infection in the form of bilateral maculopathy and optic neuropathy.

Patient 1

A patient (age 16) presented to the ophthalmologic emergency department due to deterioration of both eyes' (OU) visual acuity over the week preceding the visit. The boy mainly reported central vision disturbance in the form of a fixed black spot in the center of the OU visual field. He had a visual defect corrected by prescription glasses since the age of 6. History: the described symptoms were preceded by a fever up to 39°C, runny nose, cough, abdominal pain, and diarrhea. Three cousins the patient had been in close contact with presented similar symptoms of infection but without visual disturbances. Influenza A viral infection was confirmed in one of the cousins.

Ophthalmological examination revealed

BCVA (best corrected visual acuity) tested on Snellen charts in OD was 0.9 and in OS 1.0; intraocular pressure (IOP) in OD was 18 mmHg, IOP in OS was 17 mmHg. Slit-lamp examination of both eyes: anterior segment without abnormalities, fundus of OU: optic nerve heads with slightly blurred borders from the nose, irregularly shaped yellow focus in the macula (Figure 1 – top row [arrows indicate artefacts]).

Laboratory tests:

- Complete blood count performed 2 times – normal, electrolytes – normal, ASO – normal, CRP – 13.2 mg/l (norm up to 5.0 mg/l);
- *Toxoplasma gondii* IgG and IgM antibodies – non-reactive;
- *Cytomegalovirus* (CMV) IgG and IgM antibodies – non-reactive;
- *Borrelia burgdorferi* IgG and IgM antibodies – non-reactive;
- *Toxocara canis* IgG antibodies – non-reactive;
- Influenza type A IgG antibodies – positive.

Additional tests:

OCT (optical coherence tomography) examination of the OU maculae showed a disruption of the RPE with an associated hyperreflective focus in the outer layers of the retina in the foveal projection (Figure 2 – top row middle and right side).

OCT examination of the optic nerve heads showed increased retinal nerve fiber layer thickness nasally in the OD and nasally in the OS (Figure 2 – top row left).

Static visual field examination showed focal temporal visual field loss, but in the OD a high percentage of false positives undermines the reliability of the examination (Figure 3).

Fluorescein angiography (FA) showed no abnormalities.

The following treatments were administered: topically to the OU: dexamethasone, bromfenac; systemically: prednisone, vitamin supplementation.

Follow-up visits took place regularly every 4-5 weeks. During the visits, slit-lamp ophthalmoscopy with anterior

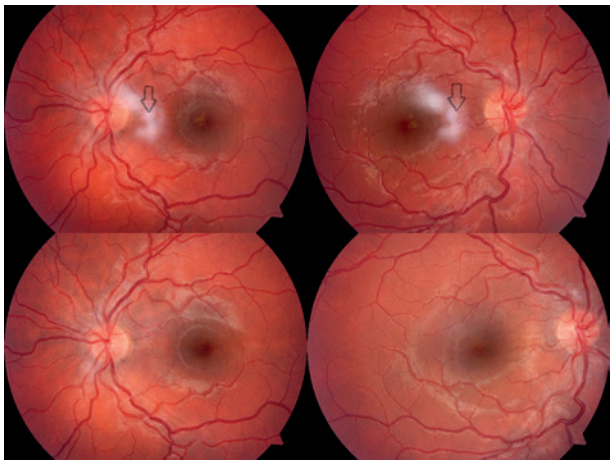

Figure 1. OU fundus images on admission (top row) and at follow-up after 5 months (bottom row). [Artefacts are indicated by arrows]

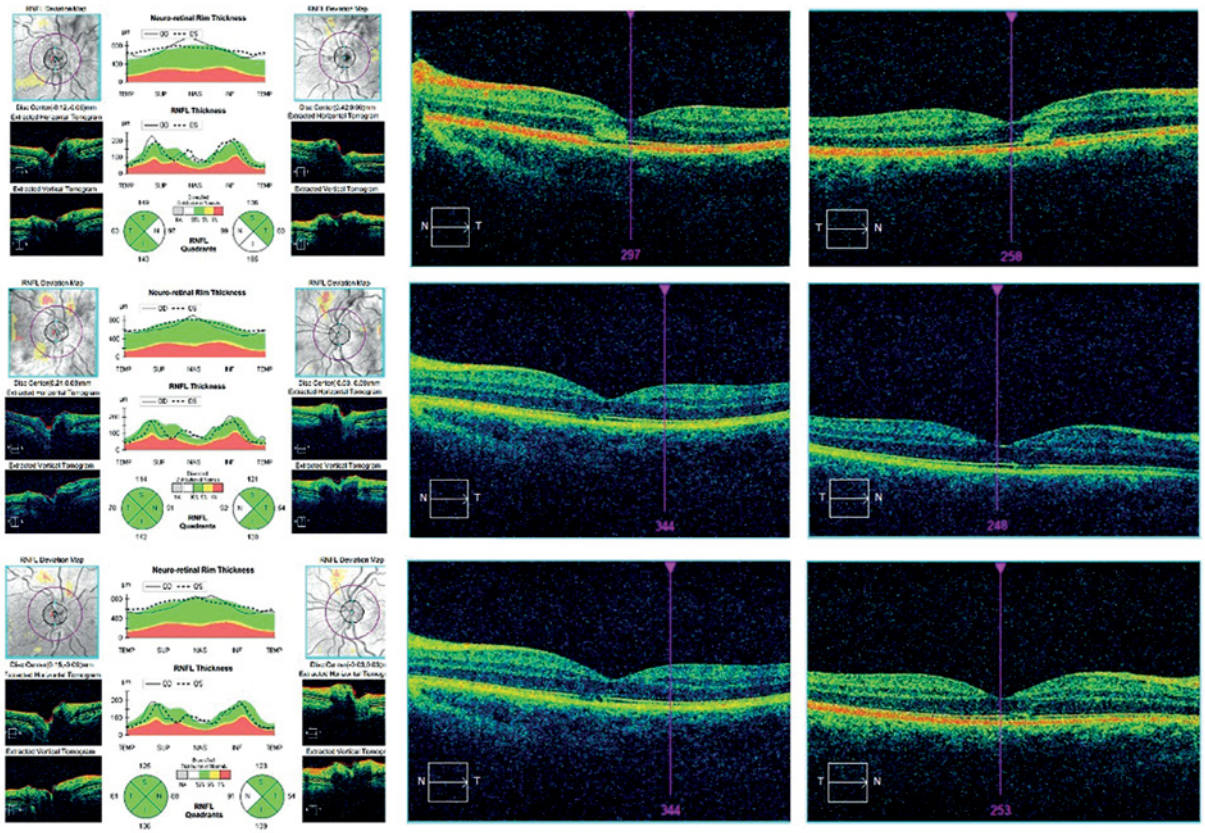

Figure 2. OCT of optic nerve heads and maculae on admission (top row), follow-up after one month (middle row), and after 6 months (bottom row). Changes regress over time – description in text

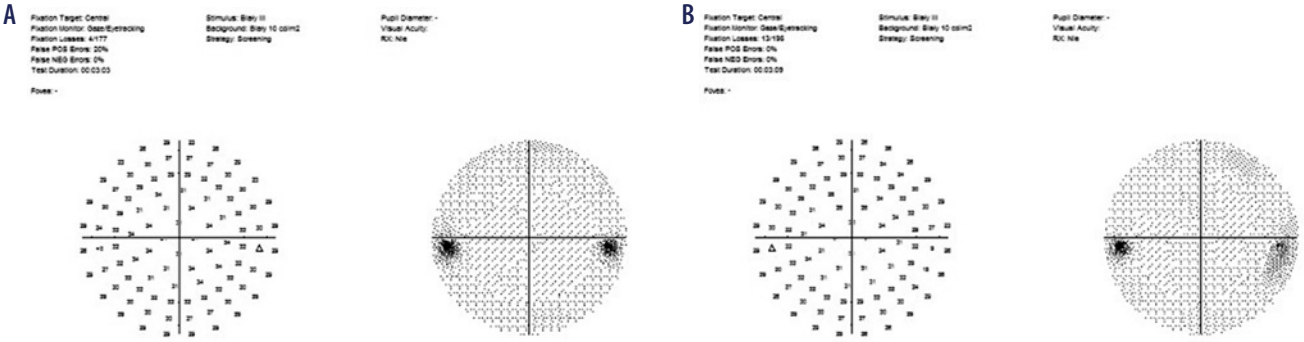

Figure 3. Visual field examination

and posterior segment evaluation was performed, as well as additional examinations, including OCT of the maculae and optic nerve heads (Figure 2 – middle and bottom rows) and documentation of fundus OU (Figure 1 – bottom row). Reduction and regression of the anatomical imaging changes and improvement in clinical status were observed.

The patient has learned to ignore the punctate visual field loss and notices it with significant fatigue. He remains under ophthalmological control.

Postinfectious choroidal neovascularization

Another rare postinfectious ocular complication is choroidal neovascularization (CNV). CNV is the pathologic growth of vessels from the choroid to the subretinal space with the disruption of Bruch's membrane. The most common cause of this pathology in adults is age-related macular degeneration (AMD), followed by CNV in the course of high myopia [28]. In children, the most common etiology of CNV is CNV in the course of inflammatory processes [29, 30]. The cause of this is still unclear. However, it has been postulated that a generalized inflammatory process coexists with a local inflammatory process in the choroid and adjacent Bruch's membrane, which, when combined with an autoimmune response, results in the production of growth factors including vascular endothelial growth factor (VEGF), leading to the formation of pathological vessels [31]. CNV is a possible

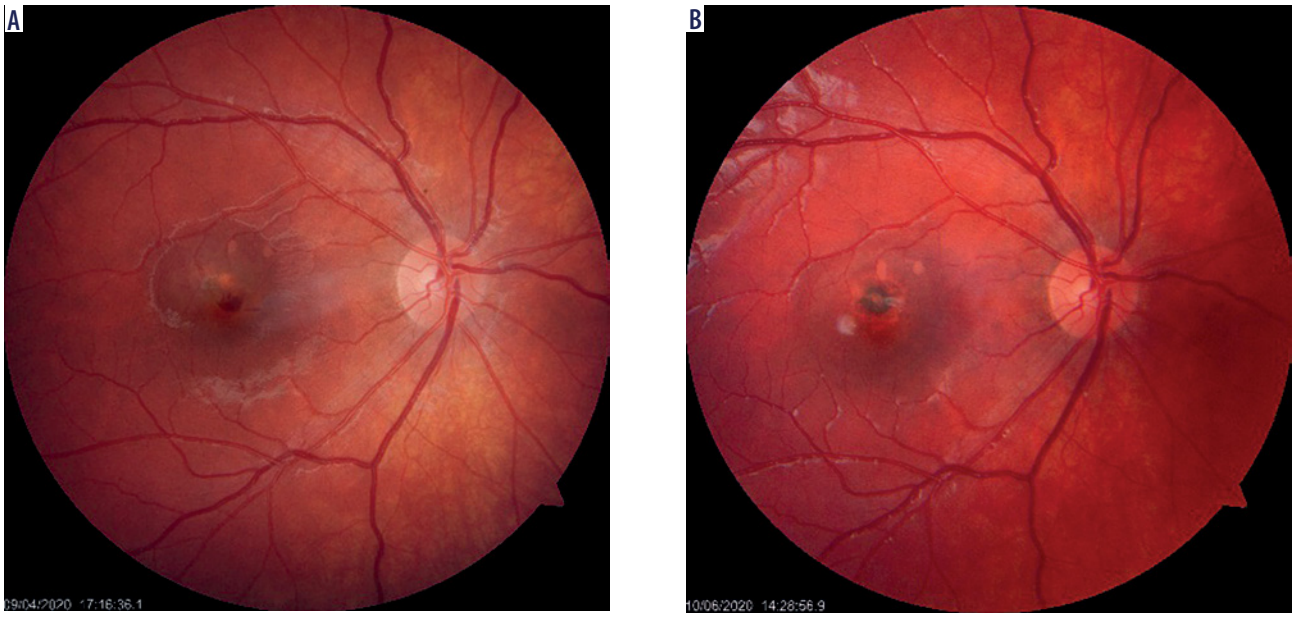

Figure 4. Color photo of the fundus of the eye on admission (image on the left) and a month after anti-VEGF injection (image on the right)

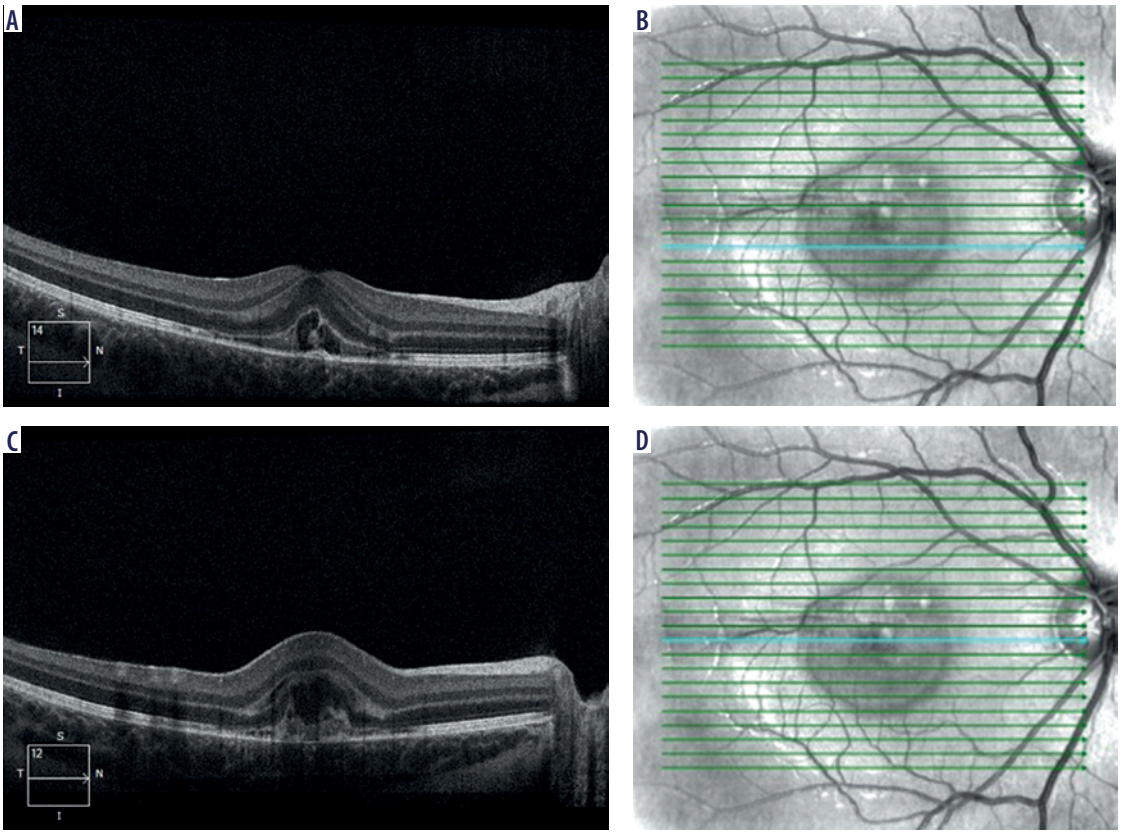

Figure 5. OCT imaging on admission

cause of severe loss of visual acuity, which in children may be associated with serious psycho-social consequences, due to a longer relative life expectancy than in adult patients [14]. Most commonly, however, CNV in children differs from CNV in adults, including through the absence of calcification and thinning of Bruch's membrane [32], resulting in a better prognosis in both the natural course of the disease process and in response to treatment [33]. The post-inflammatory etiology of choroiditis with coexisting CNV in children still usually remains unknown [29]. Despite the lack of clear guidelines for the treatment of CNV in children, the currently accepted treatment for children with post-inflammatory CNV is

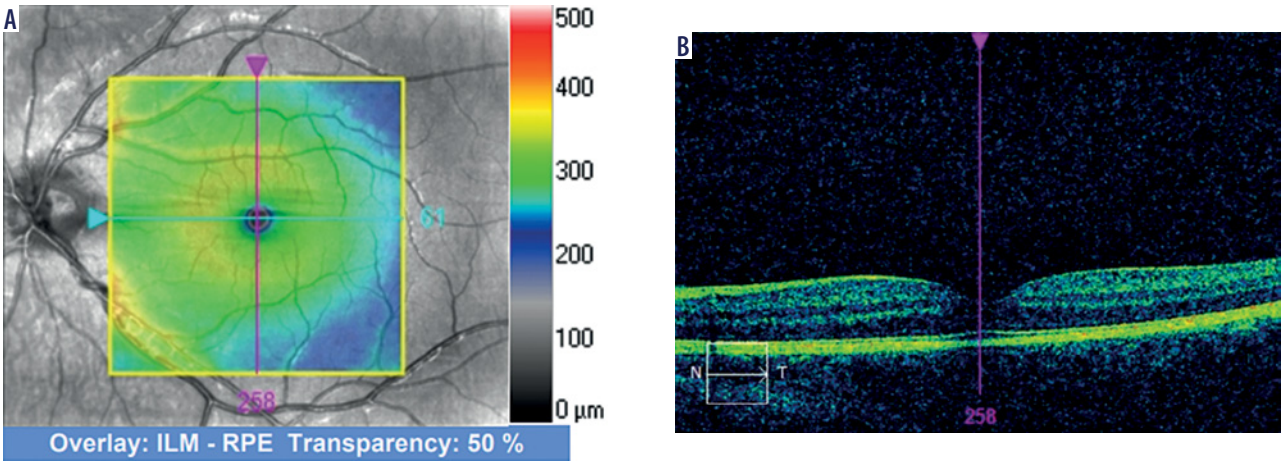

Figure 6. OCT of the macula of the OS (healthy)

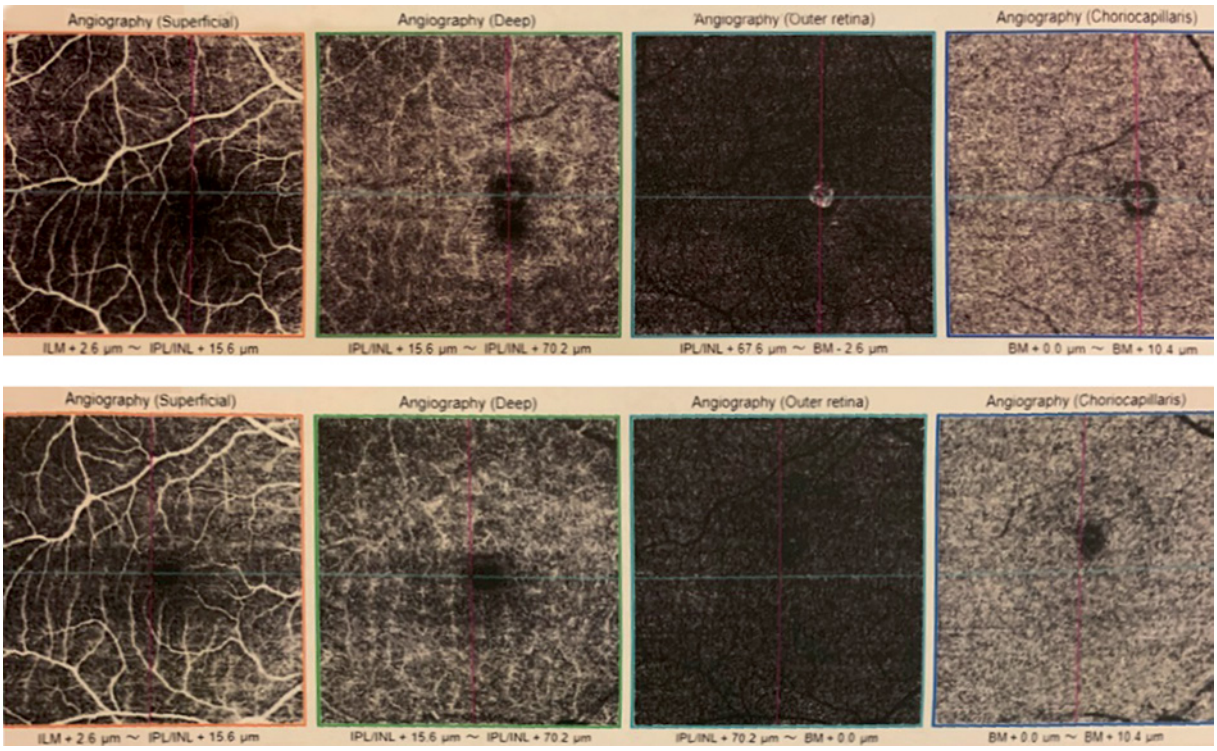

Figure 7. Angio-OCT before anti-VEGF injection (upper row) and a month after injection (lower row)

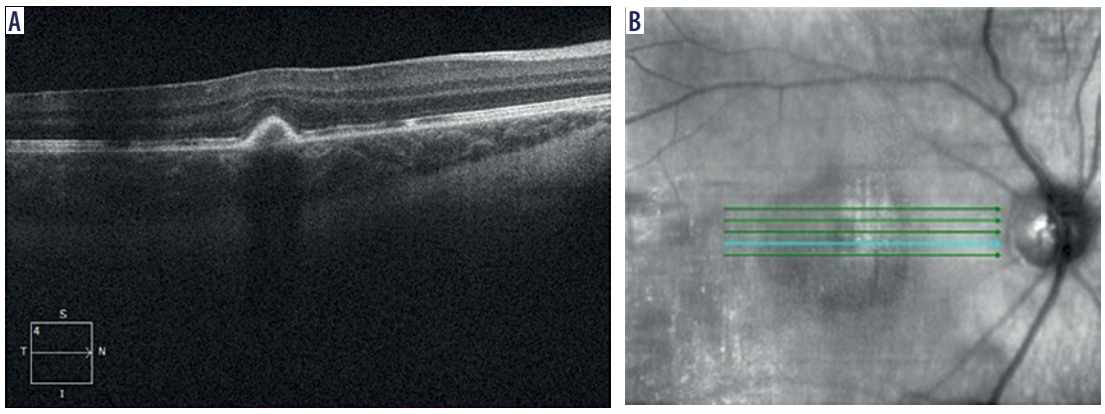

Figure 8. OCT of the macula a month after anti-VEGF injection

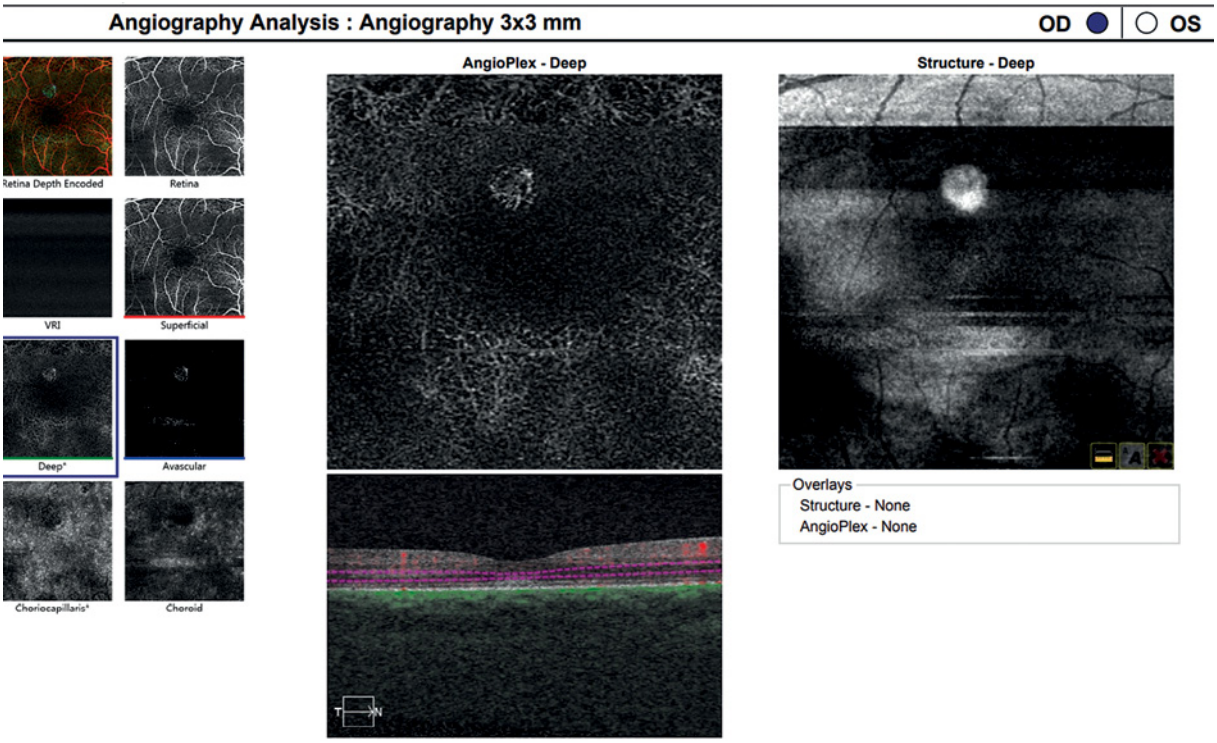

Figure 9. Angio-OCT 4 months after anti-VEGF injection

the administration of anti-vascular endothelial growth factor (anti-VEGF) into the vitreous chamber. At this time, no adverse effects have been documented following the procedure of intravitreal administration of anti-VEGF in children [34-36]. Furthermore, fewer injections are sufficient to stabilize the CNV membrane in children than in adults [35], reducing the risk of potential complications. Despite the favorable prognosis of both untreated and treated cases of post-inflammatory CNV in the youngest patients, it is important to keep patients under ophthalmological control because of the possible reactivation of the CNV membrane and the associated consequences, including scar formation and permanent, significant visual impairment.

In our center, we had to deal with a complication of active CNV of the OD after an infectious disease with influenza-like symptoms.

Patient 2

A patient (age 7) presented to the ophthalmologic emergency room due to deterioration of OD visual acuity since 2 days prior to this visit. He had not received ophthalmologic treatment to date. History: URTI 3 weeks before onset of visual disturbances.

Ophthalmologic examination revealed

BCVA tested on Snellen charts in OD was 0.2 and in OS was 1.0; IOP in OD was 16 mmHg, IOP in OS was 15 mmHg. Slit lamp examination of both eyes: anterior segment without abnormalities, fundus of OD: optic nerve head normal, in posterior pole 3 small, oval, cream-colored foci with edema and parafoveal petechiae, the posterior pole of OS without changes (Figure 4 – left photo).

Laboratory tests:

- Complete blood count performed twice – normal, electrolytes – normal, ASO – normal, CRP – normal;
- *Toxoplasma gondii* IgG and IgM antibodies – non-reactive;
- *Cytomegalovirus* (CMV) IgG and IgM antibodies – non-reactive;
- *Borrelia burgdorferi* IgG and IgM antibodies – non-reactive;
- *Toxocara canis* IgG antibodies – non-reactive;
- Coxsackie B2, B3, B4, titer <1:16 (negative);
- Coxsackie type A and B IgG using IIF: Coxsackie virus type A7 positive, Coxsackie type B1 positive;
- Influenza A and B viruses – negative.

Additional tests:

OCT examination of the OD macula showed a disruption of the RPE, a marked increase in retinal thickness in the center of the macula with a prominent hyperreflective focus in the choroidal neovascularization (CNV) projection, and a large hyporeflective zone over the line of the pigment epithelium (Figure 5).

OCT examination of the OS macula was unchanged (Figure 6).

OCTA (optical coherence tomography angiography, angio-OCT) of the OD on admission showed a prominent CNV membrane (Figure 7 – top row).

Topical treatment was administered to the OD: dexamethasone, bromfenac + ranibizumab injection into the vitreous chamber of the OD.

Systemically: prednisone, vitamin supplementation.

At the follow-up visit one month after anti-VEGF injection BCVA OU was 1.0, no CNV membrane was visualized on OCTA (Figure 7 – bottom row).

OCT showed elevation but no signs of CNV activity (Figure 8).

Color images of the OD fundus one month after anti-VEGF injection (Figure 4 – right photo).

At the follow-up visit 4 months after anti-VEGF injection BCVA OU was 1.0, higher resolution OCTA showed a CNV membrane without features of activity (Figure 9).

The patient remains under constant ophthalmological follow-up.

SUMMARY

The diagnosis of visual disturbances in children is a complex problem and requires an in-depth analysis, in which the medical history and physical examination often play a key role. The discussed cases demonstrate that common viral infections of the upper respiratory tract may cause complications in the form of pathologies in the posterior pole of the eye and should not be forgotten in the differential diagnosis of visual disturbances in children.

DISCLOSURE

The authors declare no conflict of interest.

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