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DIAGNOSTIC CHALLENGE OF ADULT-ONSET VITELLIFORM MACULAR DYSTROPHY

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Abstract

The aim of this study is to present the structural and functional changes in patients with adult-onset vitelliform retinal dystrophy (AOVMD) initially misdiagnosed as age-related macular degeneration or central chorioretinitis.

Twelve eyes of six patients with AOVMD underwent a complete clinical examination, fundus autofluorescence (FAF), fluorescein angiography (FA), optical coherence tomography (OCT), electrophysiological studies – full-field and multifocal electroretinography (ffERG and mfERG), thanks to which the diagnosis was established, and confirmed genetically.

A classic phenotype of AOVMD was found in twelve eyes of six women in adulthood (from 41 to 69 years old) with slightly reduced visual acuity, and altered colour vision in two patients. On FAF, hyperautofluorescence was found in the macular area in each eye. On OCT, bilateral yellowish rounded subfoveal deposits in the retinal pigment epithelium (RPE) were visualized, on FA – hypo- and hyperfluorescent zones in the foveal area were found in all eyes with partial resorption and atrophic areas in the RPE in two eyes. The electrophysiological studies found absence of diffuse photoreceptor involvement. The local mfERG photopic response was mildly decreased, to a greater extent in the oldest female. The relatively good functional results in contrast to the pronounced structural changes support the diagnosis, confirmed also genetically.

Adult-onset hereditary retinal dystrophy is a diagnostic challenge that requires thorough clinical, electrophysiological, and genetic testing to distinguish it from some acquired retinal diseases.

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Key words: hereditary retinal dystrophies, electrophysiology, rare eye diseases, Best disease, adult-onset vitelliform retinal dystrophy, age-related macular degeneration, central chorioretinitis

Introduction. The hereditary macular dystrophies belong to the group of hereditary retinal dystrophies, which constitute a large proportion of "the rare eye diseases" [1].

They are genetic diseases characterized by an irreversible gradual central vision impairment with a significant decrease of the visual acuity at a relatively young age [2].

Best vitelliform dystrophy is the second most common hereditary maculopathy after Stargardt disease. The prevalence of Best disease is 1 in 16 500 to 1 in 21 000. It includes several congenital diseases with different mechanisms of transmission. It usually appears in the first decade of life, affects both eyes, but asymmetrically and progresses very slowly. It is due to a defect in the genes responsible for the synthesis of protein bestrophin, which regulates the transport of fluids and ions in the cell membranes of retinal pigment epithelium (RPE) and thereby changes the connection between the RPE and the photoreceptors, which causes an accumulation of lipofuscin-like material in the macular area. This leads to the appearance of the characteristic yellowish colour of the macula with sharp borders – appearance of egg yolk. Gradually, it leads to thinning and atrophy of RPE. Fundus autofluorescence (FAF) reveals hyperautofluorescence from the deposited lipofuscin-like material. On optical coherence tomography (OCT), the accumulated material in RPE is visible as a hyperreflective area. This disease is characterized by a large dissociation between the severely altered fundus structure and the relatively preserved visual function. The electroretinography (ERG) is slightly affected [2–6].

The adult-onset vitelliform macular dystrophy (AOVMD) was first reported by Gass in 1974 [7]. It was found in 1 in 7400 to 1 in 8200 people [2]. AOVMD is presented with a fundus picture, similar to that in Best disease, but occurs in older patients with onset around the fourth to sixth decade, and may be misdiagnosed as early-onset age-related macular degeneration (AMD) or central chorioretinitis. In contrast to Best disease, in AOVMD the visual acuity is mildly affected. In the fundus, a typical picture is observed in the macula – bilateral, smaller, yellow, round, subfoveal deposits in the RPE. Atrophic areas in the RPE can be also observed. Sometimes the disease can be asymptomatic and is discovered incidentally during ophthalmoscopy [7, 8].

Same gene mutations have been found in patients diagnosed with AOVMD or Best disease, suggesting a considerable overlap in the aetiology of AOVMD and Best disease. The majority of cases are caused by mutation in the PRPH2 (RDS) or BEST1 gene [9–11].

The aim of this study is to present the structural and functional changes in

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Clinical characteristics of patients

Patients *N*	Age	Age of onset	Sex	VA		Colour vision	Macular appearance		Initial diagnosis	Gene mutation
				RE	LE		RE	LE		
1	56	55	F	20/32	20/32	not affected	vitelliform	vitelliform, partial RPE atrophy	AMD	BEST 1
2	69	68	F	20/32	20/32	affected	vitelliform	vitelliform	AMD	PRPH2
3	41	39	F	20/32	20/25	not affected	vitelliform, partial RPE atrophy	vitelliform	CHR	BEST 1
4	54	53	F	20/25	20/25	not affected	vitelliform	vitelliform	MD	BEST 1
5	48	46	F	20/32	20/25	not affected	vitelliform	vitelliform	AMD	BEST 1
6	62	61	F	20/32	20/32	affected	vitelliform	vitelliform	AMD	PRPH2

VA – visual acuity; RE – right eye; LE – left eye, AMD – age-related macular degeneration, CHR – central chorioretinitis

patients with AOVMD, initially misdiagnosed as age-related macular degeneration or central chorioretinitis.

Materials and methods. We present six patients (12 eyes) which have been referred to us for a second opinion. They have been examined in a specialized ambulatory practice for a period of 3 years. The patients underwent a complete clinical examination, fundus-autofluorescence (FAF), fluorescein angiography (FA), optical coherence tomography (OCT) (Zeiss Cirrus Photo), electrophysiological studies – full-field and multifocal electroretinography (ffERG and mfERG) (Neuro-MEP 4, Neurosoft Company), thanks to which the diagnosis was established and confirmed genetically. The patients' clinical characteristics are presented in Table 1.

The study followed the tenets of the Declaration of Helsinki. Informed consent was obtained from all subjects after the nature and possible consequences of the study had been explained.

Results. A classic phenotype of AOVMD was found in twelve eyes of six women in adulthood (from 41 to 69 years old) with slightly reduced visual acuity (Best-corrected visual acuity (BCVA) from 20/25 to 20/32 (Snellen charts) in the different patients) and altered colour vision in two patients (confusing the blue and green colours). The patients' complaints started about a year or two ago. None of the patients had a family history of macular dystrophy.

On fundoscopy bilateral, yellowish, rounded, subfoveal deposits in the RPE were found in all patients. On FAF, hyperautofluorescence of the macular area corresponding to the deposited material was observed in both eyes in each patient. On FA hypo- and hyperfluorescent zones in the foveal area with partial deposit's resorption and atrophic areas in the RPE in two eyes were found (Fig. 1).

On OCT, hyper-reflective material associated with RPE, similar to Best disease, was visualized. Well circumscribed elevation of RPE above a moderately reflective region in all eyes was observed. The retinal layers above the lesion appeared compressed. The macular lesions associated with partially faded vitelliform changes (one eye) appeared as a low reflecting, well circumscribed space beneath the retinal layer, detachment of the photoreceptors layer, resembling an accumulation of subretinal fluid. The layer beneath the optical clear space was less reflective than the normal RPE and choriocapillaris (Fig. 2).

The electrophysiological studies demonstrated absence of diffuse scotopic and photopic photoreceptor involvement in all patients. The local mfERG photopic response was slightly decreased, to a greater extent in the oldest female, compared with those in normal controls (Fig. 3).

The relatively good functional results in contrast to the pronounced structural changes support the diagnosis, confirmed also genetically.

All patients except the third one were initially misdiagnosed as AMD. The youngest patient's initial diagnosis was central chorioretinitis, possibly due to her younger age.

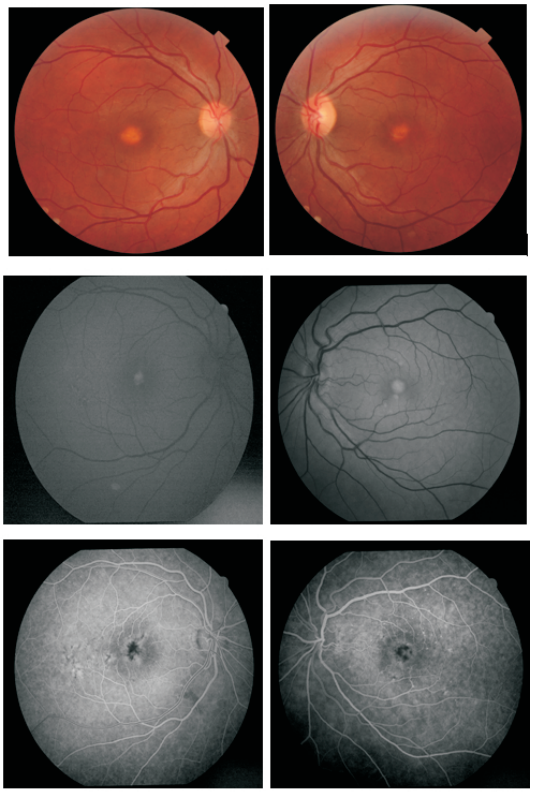

Fig. 1. Fundus-photography, FAF and FA of the right eye and left eye of the first patient (explanations are in the text)

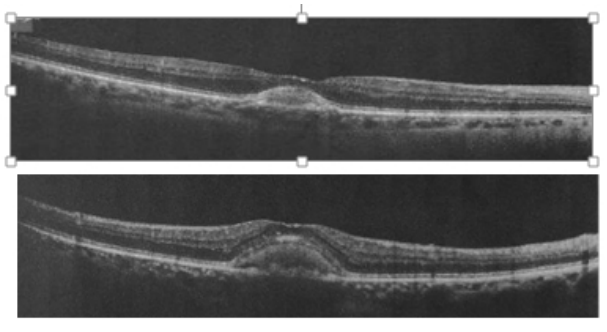

Fig. 2. OCT of the right eye and left eye of the first patient (the explanations are in the text)

Discussion. The adult-onset vitelliform retinal lesions are similar to Best disease but occur in older patients. The first symptoms appear in adulthood, therefore, in a standard full ophthalmological examination without additional spe-

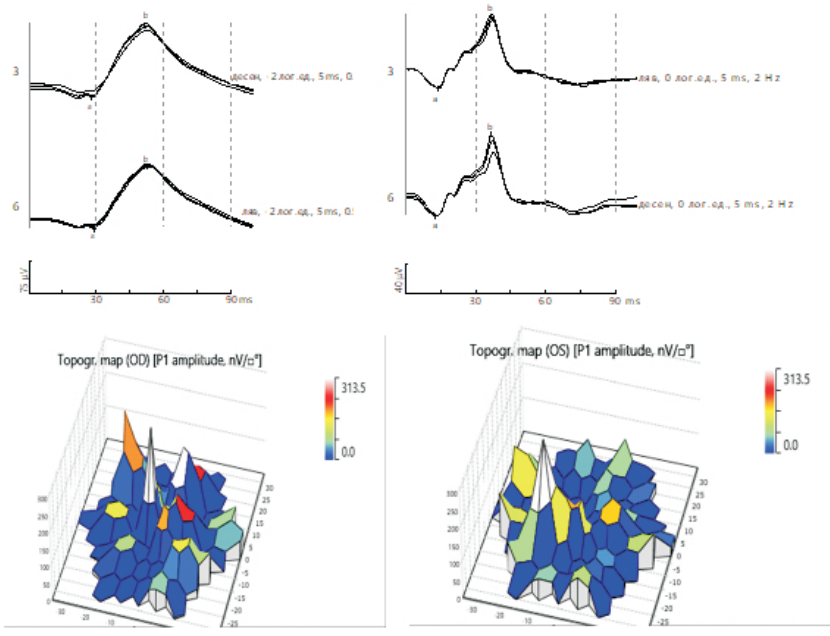

Fig. 3. Electrophysiological studies – ffERG and mfERG of the right eye and left eye of the first patient (the explanations are in the text)

cialized tests, they could easily be misdiagnosed as AMD and less often as central chorioretinitis [10].

Gass originally described the AOVMD lesions as bilateral, smaller, yellowish, rounded, slightly elevated subfoveal deposits in the RPE [7]. With the cases reported since then, the ophthalmoscopic criteria have been expanded and the presence of atrophic changes of the RPE, have become optional diagnostic criteria [12–15]. In our AOVMD patients, all patients demonstrated the characteristic fundus appearance with two eyes of different patients, which showed the typical macular lesions and partial RPE atrophy, described by Saito at al. [12].

In the fundus, the bilateral, yellowish rounded, subfoveal deposits in the RPE look like the drusen, typical for AMD. The distinction between them is made by performing and evaluating the results of FAF, FA, OCT and ERG, in which significant changes in the structure characteristic of Best disease are established with slight functional changes in the macula [10].

The OCT images of the macular lesions of AOVMD patients were first demonstrated by Puliafito et al. [16]. The OCT images in our patients had similar macular appearances corresponding to their ophthalmoscopic appearance with a large clump of extracellular pigment in the foveal area corresponding to the central pigment spot ophthalmoscopically. Patrinely et al. [13] presented a patient with partial RPE atrophy similar to the two eyes of our two different patients.

Jaffe and Schatz [14] studied a case of AOVMD with detached sensory retina by pale eosinophilic fluid, as we found in one eye of our patients [14]. Dubovy et al. [15] reported similar fundus changes in three patients with AOVMD.

In contrast, in the wet form of AMD, the presence of a neovascular membrane with exudation is found on OCT, and in the dry form, the presence of atrophic changes with absence of the characteristic lipofuscin-like deposits of the macula [17–19].

The electrophysiological studies demonstrated absence of diffuse scotopic and photopic photoreceptor involvement in all patients. This is typical for the maculopathies in which diffuse alteration of photoreceptors is absent [6, 20]. In our patients the local mfERG photopic response was slightly decreased, to a greater extent in the oldest female, compared with those in normal controls. These findings correspond to the slightly reduced visual acuity of our patients. Similar electrophysiological changes were reported by Saito et al. [12]. In contrast, in AMD the central focal responses in mfERG are substantially reduced.

In AMD, the visual acuity is much more reduced, as well as in central chorioretinitis, in which exudation in the macula is also observed, as well as the presence of an inflammatory component, which was absent in our patients [17–19].

The late onset, the relatively preserved function in contrast to the pronounced structural changes in the retina gave us the reason to make the diagnosis of late-onset vitelliform retinal lesions, which was also confirmed genetically. The differentiation from the other two diseases is extremely important because of the differences in the therapeutic approach and prognosis.

In our country we did not find any presented cases of this disease. Thanks to the advances in medicine and the development of modern diagnostic techniques and the achievements of genetics, it has become possible to diagnose this disease.

Conclusion. The adult-onset hereditary retinal dystrophy is a diagnostic challenge that requires thorough clinical, electrophysiological, and genetic testing to distinguish it from some acquired retinal diseases. Although the AOVMD is a rare genetic eye disease, we should think about it in the presence of macular changes even in older patients, in which the appearance of vitelliform lesions is not characteristic.

Further studies of the morphology and visual functions combined with genetic analyses will be necessary to clarify the pathogenesis of AOVMD, and reconcile the relation between AOVMD, Best disease, and age related macular degeneration.

It is imperative to create a registry of "rare eye diseases" in our country, in order to determine their frequency, as well as the presence of carriers.

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