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УЛОГАТА НА ФУНДУС ФЛУРЕСЦЕНТНАТА АНГИОГРАФИЈА, АВТОФЛУРЕСЦЕНЦИЈАТА И ОПТИЧКАТА КОХЕРЕНТНА ТОМОГРАФИЈА

при дијагностицирање мултифокална pattern дистрофија

THE ROLE OF FUNDUS FLUORESCENCE ANGIOGRAPHY, AUTOFLUORESCENCE, AND OPTICAL COHERENCE TOMOGRAPHY

in the diagnosis of Multifocal pattern dystrophy

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Резиме

Цел: прикажување на клиничко сликовните процедури кои се неопходни за да се дијагностицира мултифокална pattern дистрофија на ретиналниот пигментен епител.

Приказ на случај и методи: жена на 57-годишна возраст со умерено намалување на видната острина беше евалуирана со фундус фотографија, автофлуресценција, оптичка кохерентна томографија на макулата и фундус флуресцинска ангиографија, при што се постави клиничка дијагноза за мултифокална pattern дистрофија.

Резултати: Сликовните техники прикажаа кремастожолтеникави дамки на места конфлуентни во парамакуларниот регион и по должината на крвните садови. На ОСТ промените беа во пределот на надворешните ретинални слоеви, со фокална деструкција на елипсоидната зона и надворешната лимитна мембрана. При FFA се добија хипофлуресцентни зони, обрабени со хиперфлу-

Abstract

Purpose: to present the clinical imaging procedures necessary to diagnose multifocal pattern dystrophy of the retinal pigment epithelium.

Case report and Methods: A 57-year-old woman, with moderate reduction of visual acuity, was evaluated with fundus photography, autofluorescence, optical coherence tomography and fundus fluorescence angiography, through which the clinical diagnosis of multifocal pattern dystrophy was made.

Results: Imaging techniques showed creamy-yellow spots in the paramacular region and along blood vessels. On OCT, the changes were in the area of the outer retinal layers, with focal destruction of the ellipsoid zone and the outer limiting membrane. FFA produced hypofluorescence zones, lined with hyperfluorescence in the macular region and along the vascular arcades.

Conclusion: The lesions described by the diagnostic modalities corresponded to the data and

ресценција во макуларната регија и по должината на васкуларните аркади.

Заклучок: лезиите што беа опишани со дијагностичките модалитети соодветствуваа со податоците и наодите што ги консултиравме од литературата, со што се постави дијагноза за мултифокална pattern дистрофија, исклучувајќи ги при тоа диференцијално-дијагностичките предизвици со кои се соочивме при евалуација на овој случај.

Клучни зборови: *мултифокална pattern дистрофија, макула, ретина, FFA, OCT*

findings we consulted from the literature and diagnosis of multifocal pattern dystrophy was made, excluding the differential-diagnostic challenges we faced in evaluating this case.

Keywords: *multifocal pattern dystrophy, macula, retina, FFA, OCT*

Introduction

Pattern dystrophies are disorders of the retinal pigment epithelium (RPE) that are inherited autosomal dominant. These diseases are characterized by the deposition of lipofuscin material in the macular and per macular regions of the retina. RPE is mainly involved due to its phagocytic and recycling role in retinal tissue [1].

Cases of pattern dystrophies were first described in the second half of the last century by Henrik Sjögren [2] (1950-reticular dystrophy), August Deutman [3] (1970- Butterfly-shaped pigment dystrophy), and Donald Gass [4] (1974- adult-onset Foveomacular Vitelliform dystrophy). According to the way the changes are distributed, today, these macular dystrophies are divided into five categories [5]:

a) Butterfly-shaped pigment dystrophy

b) Reticular dystrophy

c) Multifocal pattern dystrophy simulating Stargard's disease

d) Fundus pulverulentus

e) Adult-onset Foveomacular Vitelliform dystrophy

This classification of pattern dystrophies is more from a didactic point of view, because it is known that one form in the same patient can pass into another over time, and also one patient can have two different forms of these dystrophies in both eyes [6].

The changes seen on fundoscopic examination in patients with these diseases are not progressive, but there have been reported cases of slow progression [7,8]. Patients with these macular diseases are often diagnosed around the forties and fifties. It is not uncommon for these dystrophies to be misdiagnosed as age related macular degeneration (AMD) because of a similar aspect of the fundoscopic finding in both entities.

Most often these dystrophies are discovered accidentally during routine ophthalmological examinations. Symptoms in the patient may include a mild decrease in visual acuity as well as the appearance of metamorphoses.

Case report

A 57-year-old woman came to the University Clinic for Eye Diseases in Skopje with a gradual decrease in vision that she has noticed in the past few months. We received anamnestic data from the patient about hypothyroidism and seropositive rheumatoid arthritis which are regularly monitored and controlled by an endocrinologist and rheumatologist, respectively. The best-corrected visual acuity (BCVA) at the time of examination was 0.5 in the right eye and 0.8 in the left eye, according to the Snellen optotype. The measured intraocular pressure in both eyes was within the normal range (Tou: 17.3mmHg). The mobility of the bulbomotors was normal in all directions, the convergence tests and the reaction of the pupils to light were also unchanged.

In order to perform a detailed clinical examination, mydriasis of the pupils was performed with Sol.Tropicamide 1%.

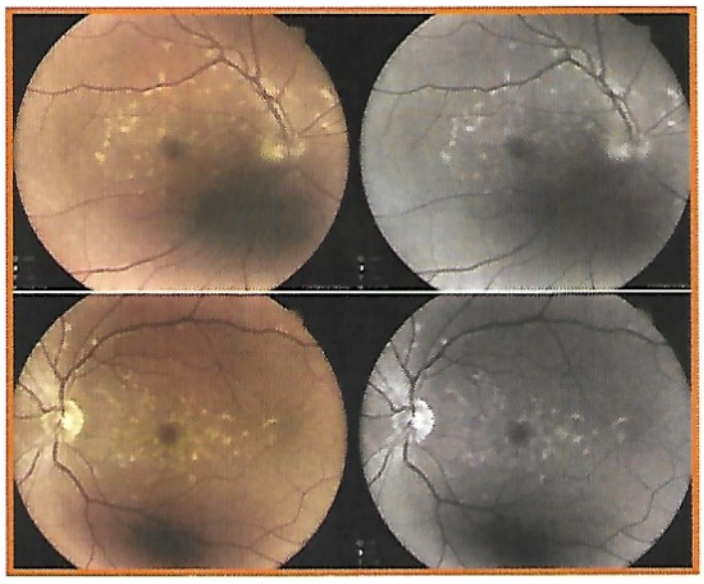

Figure 1: Native fundus photo and photo with red filter on right and left eye, respectively. The fundus photograph shows creamy-yellowish lesions in the macular region and around the vascular arcades, which are shown hyperdensely on the red filter photograph.

On biomicroscopic examination, subcapsular blurring of the lens cristalina was observed on both sides, which was more developed on the right eye. The remaining structures, from the anterior segment, were without clinically significant changes. Fundoscopically on both sides the optic disc was at the level of the retina, with C / D = 0.3, and blood vessels without obvious irregularities. However, perifoveal, paramacular, as well as next to the arcades, numerous creamy-yellow spots were noticed that conflued each other in some places (figure 1).

To document and better represent the changes, the patient underwent a native fundus photograph of both eyes, as well as optical coherence tomography of the macular region. The central macular thickness was 199μm on the right and 195μm on the left. The analysis showed involvement of the outer retinal layers, with discrete separation of the outer nuclear layer, more pronounced in the right eye. Hyper-reflective material was present on the apical side of the RPE, causing a focal disruption of the outer limiting membrane and ellipsoid zone in both eyes. The finding of OCT-A was normal, with the presence of artifacts at the level of choriocapillary, from shadows made by lesions above RPE (figure 2).

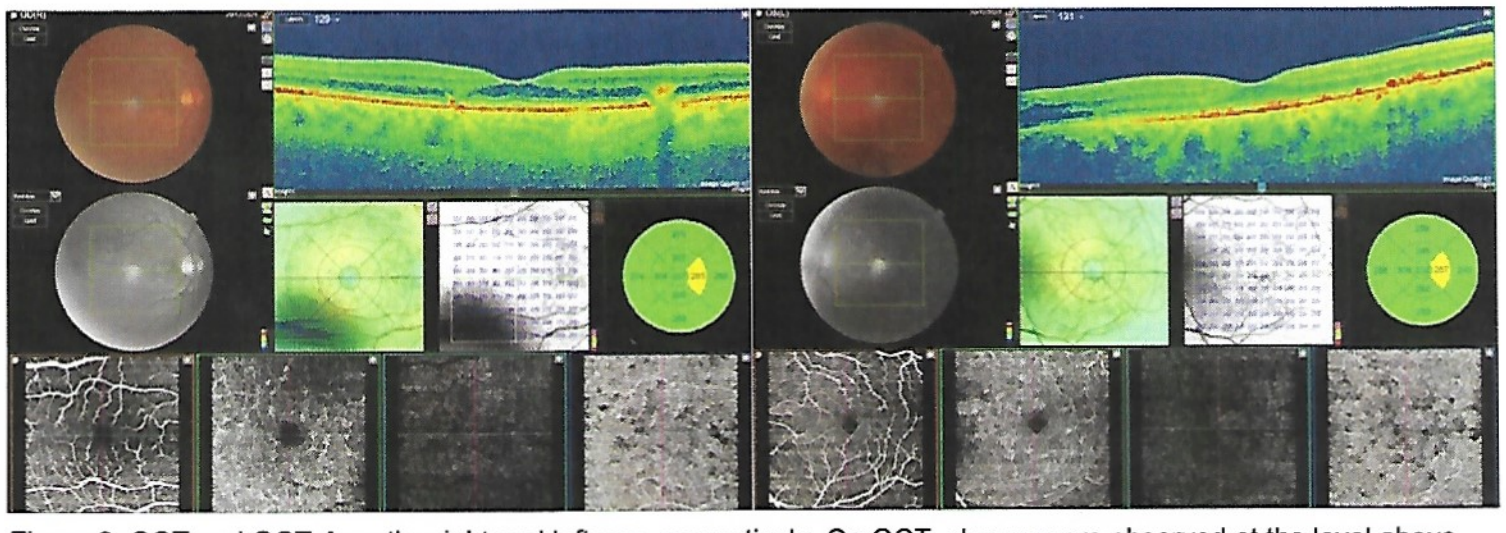

Figure 2: OCT and OCT-A on the right and left eye, respectively. On OCT, changes are observed at the level above the RPE, causing a focal disruption of the outer limiting membrane and ellipsoid zone in both eyes. The OCT-A has a superficial and deep plexus with a normal vascular network. At the level of choriocapillary, small dark zones are noted, artifacts of creamy-yellowish changes previously described above RPE.

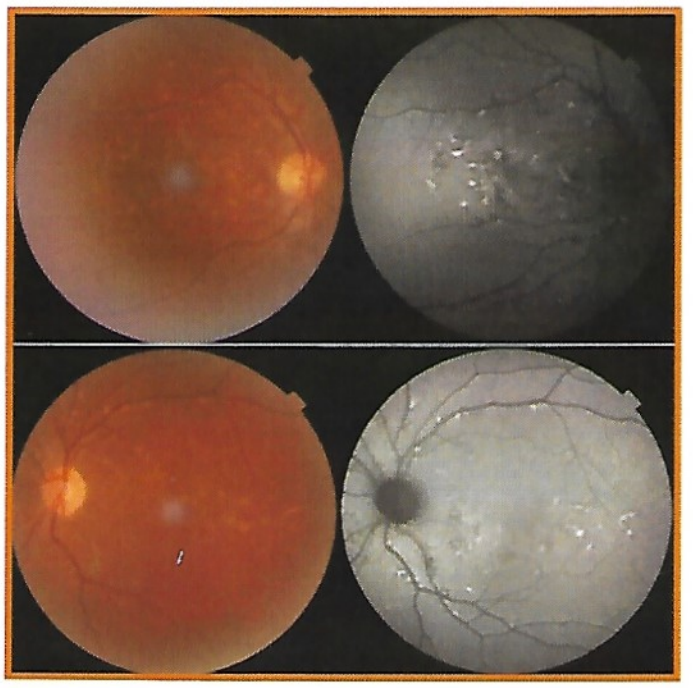

Figure 3: Fundus photography (left) and autofluorescence (right) of the right and left eye, respectively. The fundus photograph shows creamy-yellowish changes in the macular region and around the vascular arcades. These changes on autofluorescence photography are presented as hyperautofluorescent lesions lined with a hypoautofluorescent rings.

Both, Autofluorescence and FFA were also made on this patient. On autofluorescent photographs, the changes were shown as hyperautofluorescent lesions, lined with hypoautofluorescent halos (figure 3). When performing FFAs, paramacularly in the early stages of the recording, clearly limited hyperfluorescence zones (window defect) corresponding to the area of RPE loss were obtained, with accompanying central hypodense change (locations of preserved RPE). The yellow spots that appeared on the fundus photograph blocked the fluorescence and were more numerous than they were visible on the fundoscopic examination. The presence of the same hyper-hypodense changes is noted along the upper and lower temporal vessels. In the macular region on both sides the fluorescence intensity gradually decreased in the late stages of recording (figure 4).

Based on the findings of the examination and the data obtained from the literature, the diagnosis of multifocal Pattern dystrophy of RPE was made.

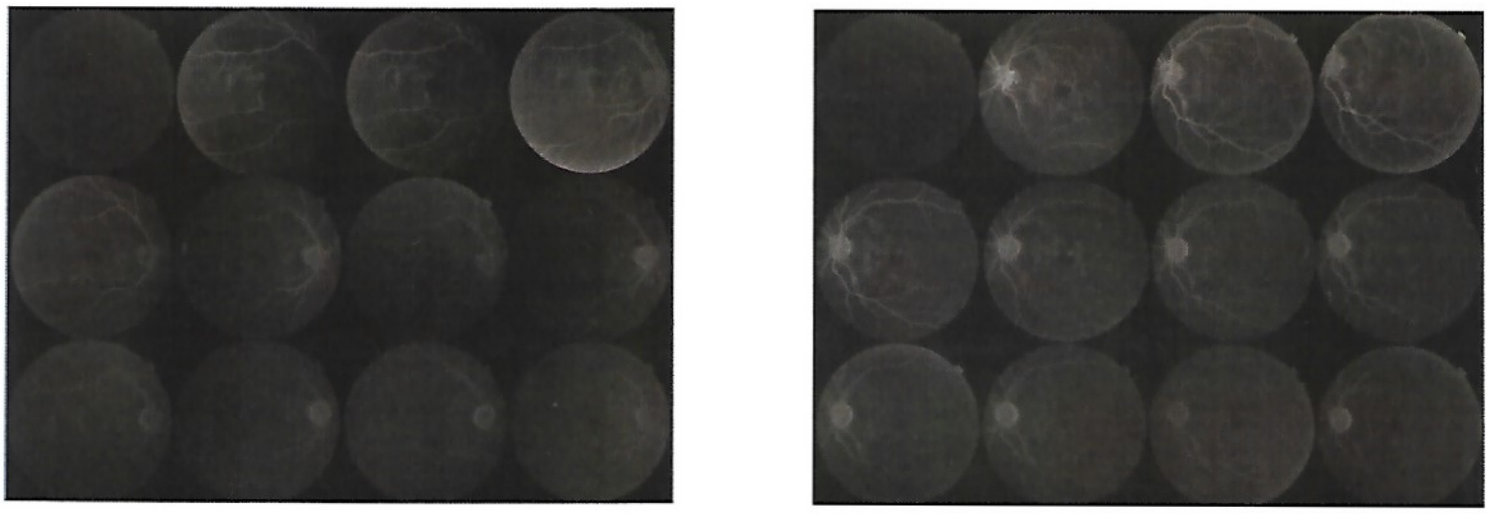

Figure 3: Fundus photography (left) and autofluorescence (right) of the right and left eye, respectively. The fundus photograph shows creamy-yellowish changes in the macular region and around the vascular arcades. These changes on autofluorescence photography are presented as hyperautofluorescent lesions lined with a hypoautofluorescent rings.

We explained to the patient the need for regular ophthalmological examinations to monitor the condition, as well as the manner of autosomal dominant inheritance. The patient's parents have already died, to see if they also have some kind of pattern dystrophy, while her son, who is 28 years old, has not had any changes on the fundoscopic examination so far. The patient was also advised to use the Amsler grid for possible early detection of choroidal neovascularization.

Discussion

Multifocal pattern dystrophy (MPD) is one of five types of autosomal dominant inherited pattern dystrophies [5]. The disease is due to an inherited mutation in the PRPH-2 gene, also known as the RDS gene (retinal degeneration slow gene), which is responsible for the synthesis of the peripherin-2 protein [9]. Although genotypically quite similar to the others, phenotypic MPD is characterized by its own specific manifestation. It is identified by its demarcated, irregular creamy-

yellow spots that have a triangular configuration and are distributed throughout the posterior pole of the eye, including the area around the vascular arcades.

The etiologic factor for pattern dystrophies are mutations in the PRPH2 gene, located on the short arm of chromosome 6 (6p21.1), which is responsible for producing the protein peripherin-2 [1,10]. This peptide is a glycoprotein located on the surface of the outer segment of photoreceptor cells. It has the role of an adhesive molecule, a stabilizer of rods and cons discs. Different types of missense and nonsense mutations are responsible for different types of pattern dystrophies as well as other types of macular diseases [1,11,12].

The mechanism of occurrence is not fully understood, but it is believed that a genetic mutation leads to the omission of important amino acids in the peripherin-2 peptide chain. Thus, due to the omission of the amino acid cysteine, disulfide bonds cannot be formed in the peptide itself, which disrupts the stability of the protein and the membrane integrity of the photoreceptor cells disks. All of this leads to trophic changes in photoreceptor cells, an increased degradation of photoreceptor cells discs whose material accumulates in RPE in the form of lipofuscin. Over time, RPE decompensates and begins to atrophy. In a small number of cases the process progresses to complete atrophic lesions of the RPE or to the growth of a neovascular network from the underlying choroid [1,8,10,13].

Patients with MPD generally have small changes in visual acuity and rarely metamorphoses. Like other pattern dystrophies, this is often detected accidentally during routine ophthalmologic examinations. Its progression is quite slow, but cases with large atrophic macular changes or with developing of neovascular network from underlaing choroid have been reported. In most patients, MPD is presented bilaterally, symmetrically, between the fourth and sixth decades of life [5,9].

To date, pattern dystrophies have been associated with several systemic diseases such as: myotonic dystrophy, pseudoxanthoma elasticum and maternally inherited diabetes and deafness [5,14,15].

The differential diagnostic disorders of MPD include fundus flavimaculatus, Stargard's disease, and basal laminar drusen. Multifocal pattern dystrophy is also known as Multifocal pattern dystrophy simulating Stargard's disease due to its similarity in fundus presentation [9,16,17].

Stargard's disease and fundus flavimaculatus are two variants of the same pathological mechanism. They are inherited autosomally recessively, due to a mutation in the ABCA4 gene on chromosome 1. In both, creamy-yellowish retinal spots are found on the macular region and around the vascular arcades. Typically, Stargard's disease occurs in childhood with a progressive decline in visual function in the first two decades of life. Specific for this disease is the appearance of "betten bronze" change in the central macular region. In contrast, fundus flavimaculatus presents in young adulthood, with a similar retinal presentation as Stargard disease. According to the progression of reduced visual function, some studies have shown a more benign course compared to Stargard, while others have shown opposite results. [16,18,19].

Because of these features, fundus flavimaculatus is a differential diagnosis challenge to MPD because the age of onset of the two pathologies is similar. The main points of distinction between MPD and these two pathologies are: age of onset, visual function, which remains far better in MPD compared to the other two, and of course the "beaten bronze" changes in Stargard and fundus flavimaculatus, not found in MPD. These changes in the central macular region are shown as dark choroid in FFA and are not present in MPD.

Another clinical entity that may present a differential diagnostic problem in the diagnosis of MPD is the basal laminar drusen. They are presented as yellowish irregular shapes distributed focally or diffusely across the retina and give a similar aspect to the creamy-yellowish changes in MPD [17]. Today these two pathologies can be differentiated with the help of OCT. In the first, the changes are drusen located between the RPE and the Bruch membrane. On the other hand, in MPD, lipofuscin is deposited in RPE and above, which leads to focal disruption of the outer layers of the

neurosensory retina. According to the clinical manifestation, the two conditions are quite similar, with a mild decrease in visual acuity and the possibility of metamorphosis. Other potentially differential diagnostic difficulties may be: AMD and other forms of macular dystrophies [20].

These days, differential diagnostic distinction is possible with a number of imaging and functional techniques. With the help of fundus photography and autofluorescence, the characteristic lesions present in MPD can be seen. The location of the changes in the retinal layers can be defined using the OCT of the macular region. With OCT, focal hyper-reflective changes are observed over RPE, which perform a discontinuity of the ellipsoid zone of the retinal tissue, and in some cases, like ours, on the outer limiting membrane and gently stratify the outer nuclear layer. The final clinical diagnosis is made by FFA, which shows areas of hypofluorescence lesions surrounded by hyperfluorescence rings, suggesting discontinuity of RPE. Such changes are visible in the early stages and gradually diminish in the late shots of the recording. Electrophysiological tests can also help evaluate the condition. The results of the electroretinogram (ERG) can be from normal to undetectable, and those from the electrooculogram (EOG) are in the range from normal to subnormal, similar to other pattern dystrophies [5,10,21,22].

Treatment for this condition is usually not needed due to the good prognosis of visual acuity. Most patients with MPD have visual acuity ranging from 0.5 to 1.0 according to the Snellen optotype. Very few cases to date have been described in the literature in which choroidal neovascularization has developed. Such cases should be carefully evaluated for possible treatment with anti-VEGF [23]. A key point in MPD patients is monitoring the condition, training in the use of the Amsler grid for early detection of possible neovascularization, and explaining how the disease is inherited across generations.

Conclusion

Through this paper we have tried to present a case of multifocal pattern dystrophy, as a rare entity in ophthalmic practice. It is usually diagnosed accidentally during routine ophthalmological examinations. Knowledge of pattern dystrophies is important for differential diagnostic distinction from AMD, common ophthalmic pathology, and Stargard's disease and fundus flavimaculatus as entities with poor visual acuity. Today, OCT, autofluorescence, and especially FFA can help diagnose this not so common disease.

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