MILITARY MEDICAL ACADEMY

Department „ Eye diseases, Ear, nose and throat diseases and oral surgery"

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AGE RELATED MACULAR DEGENERATION-

PROGNOSTIC RISK FACTORS, ULTRASTRUCTURAL CHANGES,

DIAGNOSTIC AND THERAPEUTICAL APPROACHES.

AUTOREFERAT

Of dissertation paper for acquiring the educational degree " DOCTOR OF SCIENCE"

Scientific speciality „ Opththalmology"

Sofia , 2021 г.

The dissertation work comprises of 288 pages and have 118 figures and 10 tables. The bibliography consists of 266 publications, 25 of which of Bulgarian authors and 241 in latin.
The scientific examinations have been carried out in the Department of " Eye diseases, Ear , nose and throat diseases and oral surgery", MMA. The experimental work has been carried out in the Department of anatomy histology and embrinology MU, Sofia.
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The dissertation work has been discussed , accepted and recommended for Public presentation infront of Scientific Jury by the department of Department of " Eye diseases, Ear , nose and throat diseases and oral surgery" on 15.07.2021 г.

The public presentation of the dissertation n will take place on 27. SEP 2021 г., in 13.0. at the Aula of MMA, Sofia, St. Georgi Sofiisky str. 3, at an open for everyone session of the scientific Jury. The materials for the public defence are published on the internet page of MMA.

Introduction:

Age related macular degeneration (AMD) is an illness with high social impact, leading to severe impairment of the visual acuity. It affects mainly people of 65 years of age and is one of the leading causes of blindness in economically developed countries. In USA and Great Britain age related macular degeneration is a cause of blindness in 50% of the cases and the numbers are rising as the life expectancy prolonges. It is a general belief that by 2025 the number of cases of AMD will double. Big epidemiological surveys show, that the disease is typical for approximately 2% of the population over 55-65 years and in 11% of the population over 65 years of age. People at the age of 80 and more are at 4 times higher risk of developing this patology .

Age related macular degeneration is a multifactorial disease, affecting central vision and leading to irreversible blindness. It is more common in white people and rearely can be found in black. It typically developes in both eyes, although it is assymetrical and tends to progress.

Social impact of AMD is due to the constantly increasing numbers of people affected (about 30% of people after 75 years of age). The disease requires regular monitoring, early diagnostics, prophylaxis and modern treatment of the diseased patients. Apart from the rutine ophthalmological examination, including anamnesis, visual acuity, biomicroscopy and ophthalmoscopy, of great importance for the proper diagnosis are some specialized methods such as : fluorescein angiography (FA), optical coherence tomography (OCT), autoflurescence, indocyanine geen angiography, OCT- A etc. Diagnostic abilities which these methods give us are of extreme importance in the diagnostics, prognosis and treatment of the disease.

Our aim is to show summerrised data of the literature on AMD and discuss the diagnostic and therapeutical abilities for the manegment of the disease and give answers to the topics in regard to the prognosis and treatment of AMD. Knowledge of the risk factors and possibilities of acurate prognosis will enable us to control the course of the disease.

AIM AND TASKS

2.1. AIM

The aim of the dissertation work is to investigate, summerise and analyse the risk factors for development and progression of AMD, and to evaluate the efficacy of different diagnostic methods. It is our goal to analyse the results of different therapeutic drugs in AMD.

2.2. Tasks:

1. To analyse and point out general and clinic-spesific risk factors, which determine the development and progression of AMD.
2. To analyse the efficacy of different diagnostic methods in AMD such as – FA, OCT, autofluorecence, angio OCT and to propose a diagnostic augorithm-work protocol comprising methods of higher efficacy in detecting different forms of the disease.
3. To investigate ultrastructurally the neovascular tissue and retinal drusen in wet AMD. To follow the ultrastructural changes in the CNV membranes under the influence of anti- VEGF drugs.
4. To compare the effectivity of different therapeutic drugs in AMD such as- Avastin (bevacizumab), Lucentis (ranibizumab), Eylea (aflibercept), and point out the possible complications after carrying out such therapy.
5. To examine and analyse the specific peculiarities in the diagnostics and treatment of atypical forms of AMD such as – retinal angiomatose proliferations and polypoidal chorioidal vasculopathy.

MATERIAL AND METHODS

3.1. Material

We included 274 patients, diagnosed and treated in Eye clinic " Zrenie" Sofia and Department of Ophhtalmology, Military medical academy Sofia fro the time period from 2008-2020 г. (11 years). From the group of patients 154 were men, and 130 women. All patients were in the age group 61 to 83 years of age, average age 69,6 years. They were dividied into 3 main groups:

1. *Patients with dry form of AMD – 134.*
2. *Patients with wet form of AMD – 126 .*
3. *Atypical forms of AMD – 14 patients- 9 of which with RAP and 5 with PCV.*

From the group of patients with wet form of AMD a specific sub group was developed, of AMD patients with haemophthalmus – 11 eyes, in which PPV has been done. In these group a subretinal tissue for electronmicroscopical and immunohystochemical investigation has been taken. All that was done in cooperation with the Department of Anatomy, histology and embryology MU, Sofia. A dondor material from corpse tissue – 2 eyes have been use dto analyze the ultrastructure of the retinal drusen in AMD.

Furthermore the AMD patients were divided into 3 groups in accordance to the treatment medications used. We had the following 3 sub groups of patients:

1. *Pateints with wet AMD, treated with МДСВ, лекувани с Avastin (bevacizumab) – 41 patients.*
2. *Patients with wet AMD, treated with Lucentis (ranibizumab) – 12 patients.*
3. *Patients with wet AMD, treated with Eylea (aflibercept) – 73 patients.*

All patients from the study groups were examined profoundly ophthalmoscopically, for VA, Amsler grid, as well as with OCT, FA, FAF, OCT-A. OCT examinations have been done on the Optovue (RTe Vue), Topcon 3 D OCT 2000 and Cirrius 500 Angiophlex (Zeiss). Colour pictures, FA pictures and FAF has been made on the Topcon 2000 Fa plus. We used the programmes for qualitative analysis of OCT apparatuses – EMM5, EMM5 progression and Macular cube 213. With the system for computer analysis we estimated the size of the lesion on the autofluorescent pictures.

3.2. Methods:

3.2.1. Diagnostic methods

In our study we used the following clinical-diagnostic methods we used in our patients such as: FA, FAF, optical coherence tomography.

3.2.2. Fluorescein angiography

One of the pioneers of the modern fluorescein angiography examination is Philip Gass (1967). In FA we use fluorescent abilities of the fluorescein natrium. In oder to initiate fluorescence it is important to enlighten the fluorescein with blue light with wave length of 465-490 nm, and the exicated light is in yellow or yellow- green light with wave length of – 520-530 nm.

In the methodology we use a fundus camera, with which we send the excitating blue light with blue filter and the photographs are made with the help of additional second filter, which is yellow. FA is the only examination method enabling us to follow the retinal circulation in dynamics. The single phases can be followed in sequence from the filling of the vessels of the retina to the emptiness of the vessels. There are specific FA phases, which gives us an information about the blood retinal flow.

3.3. Autofluorescence

Fundus autofluorescence is anew non invasive method of visualization of the eye fundus, in which the fluorescent abilities of lipofuscin at the level of the RPE . Autofluorescence is a spontaneous process, in which a light with a specific wavelength is emitted when specific fluorophors are emitted with light of a certain another wavelnght. This FAF is typically seen in the cells which are rich of the pigment of aging-lipofuscin, such as the cells of RPE.

3.4. Optical coherence tomography

OCT is one of the most modern technologies of diagnostics of retinal diseases and those of the optic nerve. It is a relatively new technology for noninvasive diagnostics. In which an optical sections of the investigated tissue are achieved with informativity similar to that of histological preparations . Namely that is the reason that methodology to be called an optical biopsy of the human eye . The main principle of the OCT technology is B-ultrasonography, but instead of ultrasound it uses light of a low coherent laser source with a wavelength of 840 nm. The defraction and absorbtion of the light from the tissues is based on the phenomenon of low frequent interferometry.

3.5. OCT-A – optical coherence tomography – angiography.

In historical view that is a relatively new technology which develops since 2014. OCT-A is a non-invasive method for diagnosing the retina, its circulation and that of the choroid. Images are obtained very quickly one after another and the technology detects the movement of the blood column - erythrocytes in the retinal vessels OCT-A segments the retina and provides information about vascular microcirculation in 3 zones - superficial retinal plexus, shows the vascular network between ILM and IPL, deep retinal plexus - shows the retinal vascular network between IPL and OPL. This plexus cannot be visualized with FA. The last area visible on OCT-A is avascular.

3.6 Electron microscopical and immuno chistochemical investigations.

Histochemically, the materials were processed according to the standard methodology of Nissl and Papanikolau. The electron microscope slides were prepared according to standard electron microscopy methods. More specific was the Safranin O technique for examining proteoglycan complexes in the intercellular matrix. The electron microscopy images were viewed on a Hitachi A 11 electron microscope. O.

3.7. Statistical methods

1. Descriptive statistics

Quantitative variables are presented by summarizing statistical characteristics - arithmetic mean (Mean), median (Median), standard deviation (SD);

The category variables are represented by absolute frequencies (n) and relative frequencies (%)

2. One-Sample Kolmogorov-Smirnov test to check the shape of the frequency distributions of the quantitative variables.

3. Chi-square test - when studying the relationships between descriptive (categorical) data with two or more categories.

RESULTS

Our study included 274 patients diagnosed and treated at the Medical Center "Zrenie" - Sofia, and Eye Clinic, Military Medical Academy - Sofia during the period 2008-2020 (11 years). Of these, 154 people were men and 130 women - fig. 7. Patients ranged in age from 61 to 83 years, mean age 69.6 years.

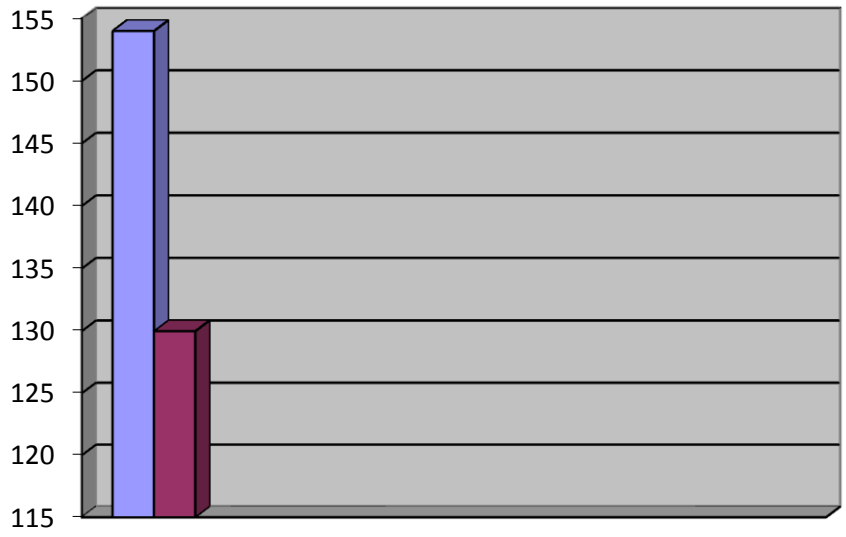

Fig.1. *Destribution of patients according to sex – 154 men and 130 women*

They were divided into three main groups:

1. Patients with dry form of AMD - 134 patients.

2. Patients with wet form of AMD - 126 patients.

3. Atypical forms of AMD - 14 patients, 9 of them with RAP and 5 with PVC.

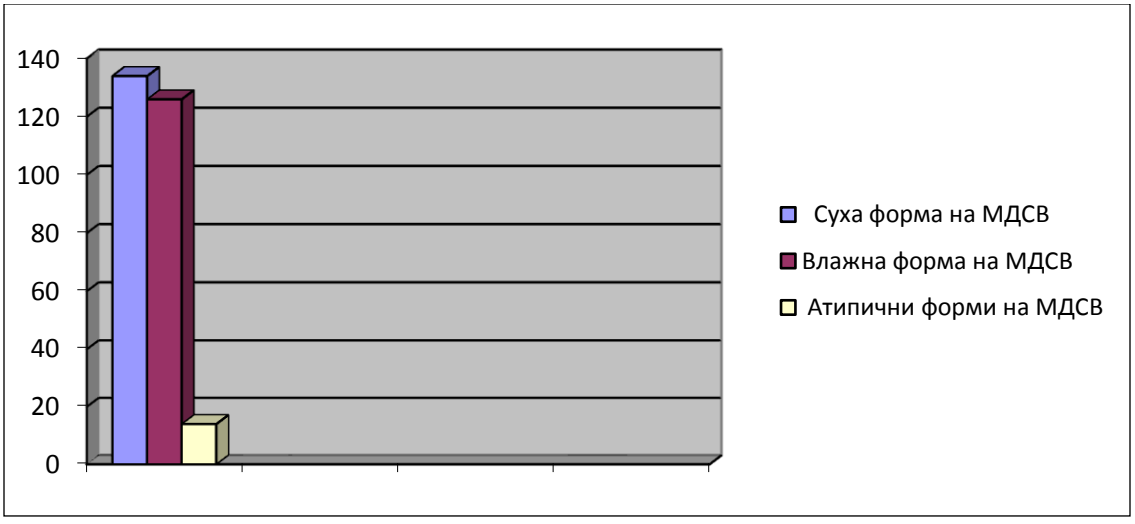

Fig. 2. *Destribution of the examined patients in groups according to the type of AMD- patients with dry form, wet and atypical AMD forms.*

The percentage distribution of the examined patients is as follows:

Patients with dry AMD are 50% of the total sample.

Patients with a wet form of AMD are 46% of the total sample.

Patients with atypical forms of AMD are 4% of the total sample.

From the group of patients with wet form of AMD was created a separate subgroup of patients with AMD and hemophthalmos - 11 eyes, which had PPV performed , in which material - subretinal tissue for electron microscopy and immunohistochemical examination was taken.

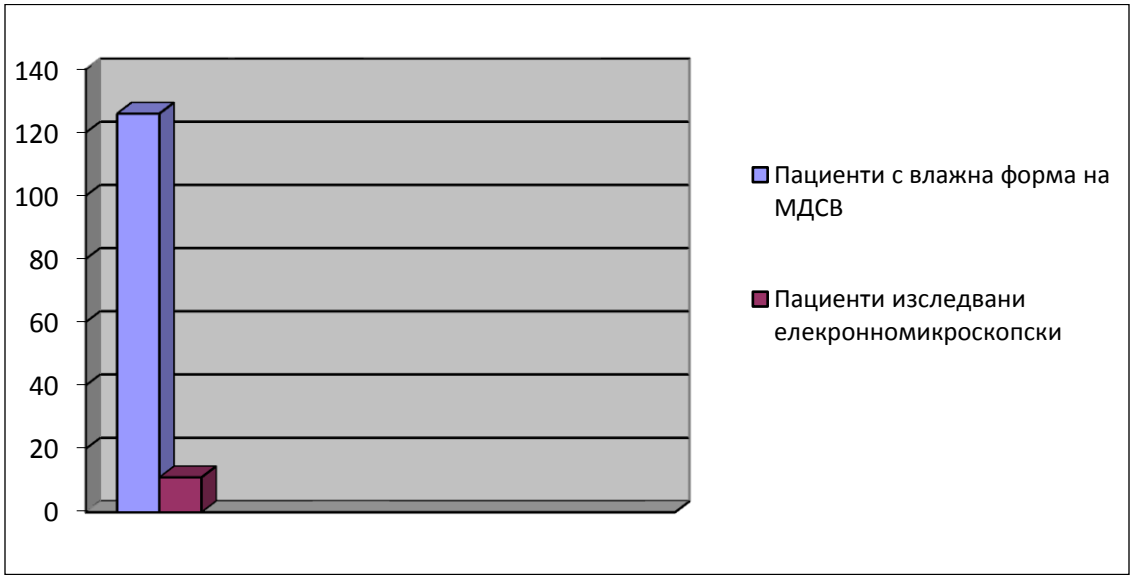

Fig. 3. *Distribution of the patients with wet form of AMD, used for electron microscopical investigation.*

Depending on the therapeutic agents used in the treatment of patients with the wet form of AMD, we had 3 subgroups:

1. Patients with wet form of AMD treated with Avastin (bevacizumab) - 41 patients.

2. Patients with wet form of AMD treated with Lucentis (ranibizumab) - 12 patients.

3. Patients with wet form of AMD treated with Eylea (aflibercept) - 73 patients.

The percentage distribution of the studied patients depending on the used anti-VEGF drugs is as follows:

30.4% of all with the wet form of AMD were treated with Avastin

17.4% of all with the wet form of AMD were treated with Lucentis

42.0% of all people with wet AMD were treated with Eylea.

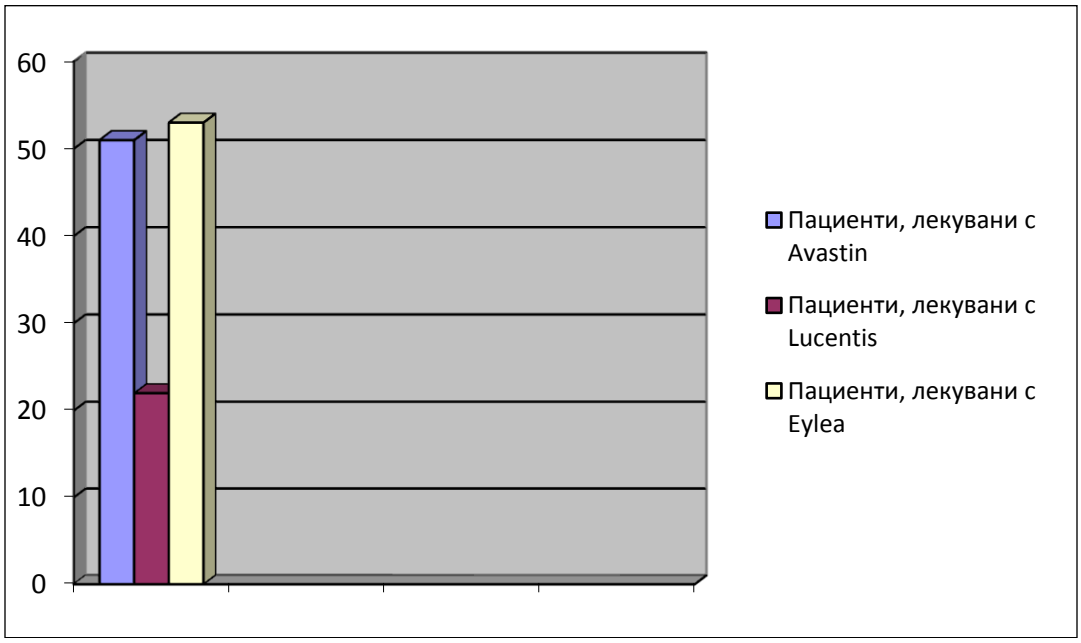

Fig. 4. *Distribution of patients with wet form of AMD depending on the terapeutical agents, used in their treatment.*

It is clear that the proportion of patients treated with Eylea and Avastin is relatively higher than those treated with Lucentis. The reason for this is the lack of accessibility of our patients to this preparation.

The main risk factors for the development of AMD and its progression were taken into account. These were:

Age of patients

Presence of concomitant diseases - arterial hypertension, high cholesterol, obesity

Clinical characteristics of lesions leading to increased risk.

In general, the risk factors for the development of AMD can be divided into two major groups:

Risk factors of a general nature

Clinical risk factors

Of particular risk factors are the age of the patient and concomitant comorbidities.

The main risk factor for the development of the disease remains age.

Age remains a major risk factor, and in our sample it turned out that the highest percentage of progression of the condition is in patients over 65 years of age. As patients age, the risk of developing AMD and its progression doubles every 10 years. Of interest is the fact that gender is also important risk factor for the development and progression of AMD. It turns out that statistically in our sample the disease develops more often in women than in men (2: 1), and in the presence of the disease already in one eye the tendency to progression is greater (p = 0.004).

Table 1. Correlation between sex and frequemcy of AMD

Chi-Square Tests

Пол		**МДСВ в едното око**		**Общо**	**X^2**	**df**	**p**
		Не	**Да**				
Мъже	N	86	45	131	8,11	1	0,004
	%	55,1%	37,8%	47,6%			
Жени	N	70	74	144			
	%	44,9%	62,2%	52,4%			
Общо	N	156	119	275			
	%	100,0%	100,0%	100,0%			

Elevated blood pressure is often associated with risk factors for the progression of AMD, as in these patients the blood flow through the choroid is reduced, which is a

prerequisite for degenerative changes in this area and the occurrence of degeneration. As early as 1977, Kahn et al. in their studies, reported a link between AMD and hypertension (Framingham Eye Study). Our studies show an increased incidence of AMD in patients with hypertension.

Table 2. 9 times higher risk of AMD development have patients with increased blood pressure.

Chi-Square Tests

Хипертония		**МДСВ в едното око**		**Общо**	**X^2**	**df**	**p**
		Не	**Да**				
Не	N	62	26	88	9,93	1	0,002
	%	39,7%	21,8%	32,0%			
Да	N	94	93	187			
	%	60,3%	78,2%	68,0%			
Общо	N	156	119	275			
	%	100,0%	100,0%	100,0%			

Our results also show a relationship between the development of AMD and the duration of hypertension. For example, if the hypertension is more than 10 years old, there is a twice as high risk of developing AMD. In over 60% of patients with 10 and more years of hypertension, we observed progression of AMD. Of the hypertensive patients we observed, 32% had elevated diastolic blood pressure, and these were patients who progressed to the wet form of AMD. Elevations in serum cholesterol and abnormal lipid status are also important risk factors for the progression of AMD.

An important risk factor for the progression of AMD is the increase of serum cholesterol and pathological lipid status. As early as 1992, The Eye Disease Case-Control Study Group consortium published results showing an increased risk of progression of AMD to neovascular form in patients with elevated serum cholesterol. In our study, we observed an association between elevated blood cholesterol and triglyceride levels and the progression of geographic atrophy in patients with dry AMD. In 30% of cases of elevated serum cholesterol, we observed progression of geographical atrophy.

People without these diseases are 2 times more protected from developing AMD. In addition to elevated cholesterol levels, weight gain is a serious risk factor of

developing and progressing of AMD. Being overweight is a known risk factor for the development of AMD. Seddon et al. (2003) found that patients with a BMI ≥ 30 had a 2.35-fold higher risk of developing a wet form of AMD than those of normal weight.

Comparative analysis between patients with and without disease

Table 3. Higher risk of AMD developmeny in patients with different comorbidities- hypertension, bad lipid status, obesitas.

Mann-Whitney Test

Показател	МДСВ в едното око	N	Mean	Median	SD	Min	Max	p
Systolic Blood pressure	Не	156	134,28	134,00	14,34	110,00	180,00	0,004
	Да	119	139,24	142,00	15,06	100,00	200,00	
Diastolic blood pressure	Не	156	88,22	90,00	10,63	60,00	110,00	0,002
	Да	119	91,67	95,00	13,83	10,00	110,00	
Cholesterol	Не	156	5,61	5,35	1,27	3,00	8,10	< 0,001
	Да	119	6,25	6,00	1,30	2,00	8,50	
BMI	Не	156	29,76	29,00	6,69	20,00	60,00	< 0,001
	Да	119	33,18	33,00	7,33	20,00	58,00	

There is a proportional relationship between elevated BMI and the development of AMD. The higher the BMI, the higher the risk of developing the condition.
We can summarize that the highest risk for the development and progression of AMD has a person over 70 years of age, female, with hypertension for more than 10 years, with elevated diastolic pressure and overweight. Prevention of these common risk factors reduces the risk of AMD progression.
In addition to the general risk factors, the clinical risk factors, which are strictly individual in each patient, are also of particular importance.

RESULTS OF THE STUDY OF PATIENTS WITH DRY FORM OF AMD - RISK FACTORS.

Among the specific risk factors for the dry form of AMD, the size of the druses was of particular importance.

With the help of a computer system it was possible to measure the dimensions of the soft druses.

Depending on their size, we divided them into several subgroups:

- Soft druses with small sizes up to 150-200μ.

- Soft druses with medium sizes - 250-300μ.

-Soft druses with large dimensions over 350 μ.

Follow-up of patients with multiple druses from these groups over a period of 2 years showed progression of the condition, especially in patients with soft druses with *large sizes of 350μ.* and more, in whom there is an active leakage of fluorescein from the lesions in the late stages of angiography. In 65% of the studied cases, progression to a wet form of the disease was observed when such druses were combined with druse-like detachment of RPE (Fig.5).

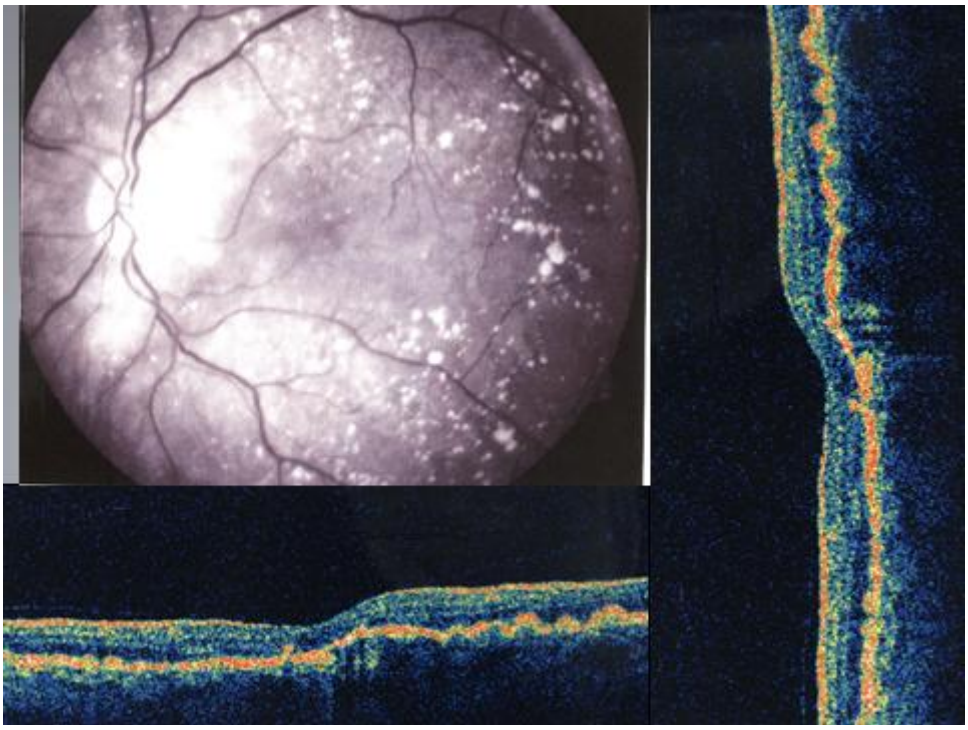

Fig. 5. *Patient with AMD and confluating soft druses in combination of RPE detachment in wet form of AMD.*

In the patients we observed with a mean size of 250-350μ druses, an atrophic lesion often developed at the site of the confluent druses over a 2-year period. The incidence of atrophy increased by 25% in cases of added druse detachment of RPE, simultaneously with the presence of such druses.

Statistical data processing and the analysis of variance used allowed us to determine the probability factor of disease progression in the presence of RPE detachment. It turns out that the presence of such increases 4 times the possibility of progression to either wet or atrophic form of AMD, in contrast to the cases when it is absent.

The results of our studies showed that the greatest risk of progression in over 65% of cases is the presence of nodular druses. In essence, they are soft druses with larger sizes than usual - over 350 μ, which are characterized by increased hyperreflextivity than usual. This is most likely due to the deposition of hyaline or calcium salts in these structures. In all nodular druses, there is damage to the integrity of the Bruch membrane and rupture of the RPE line, which is the reason for the high risk of development of a

neovascular membrane in these patients. By the second year of follow-up, a neovascular membrane developed in 65% of the patients we observed.

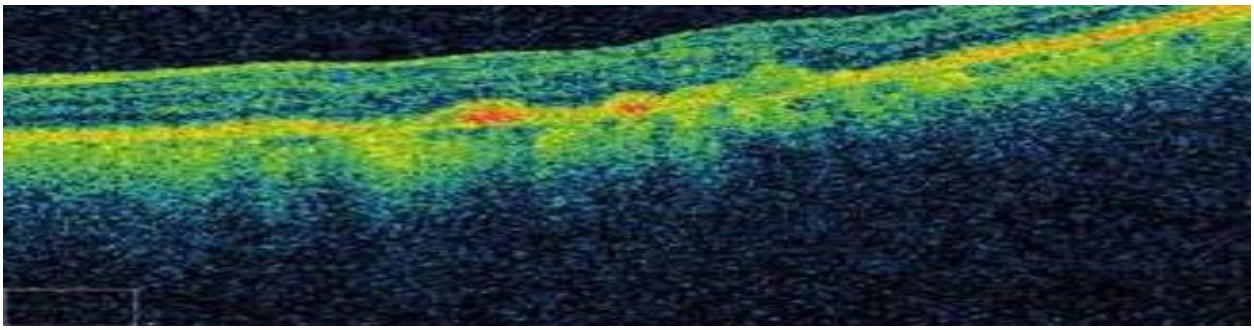

Fig.6 Nodular druses - disrupting the structure of the layer RPE , choroid , Bruch membrane, high risk clinical sign for AMD progression.

Histological preparations of cadaveric material taken from the Department of Anatomy, Histology and Embryology, MU - Sofia, in patients with dry form of AMD - 2 eyes, showed the following results:

The structures of the studied druses were clearly visible on the Nilson preparations. In general, they consisted of a central core up to 20 mk in size and a peripheral part of the druse. Typically, the nucleus of the hard druses or those of the peripheral part of the retina was composed mainly of cholesterol and lipids, with no disturbances in the roof of the hard druse. The whole structure seemed homogeneous on the histochemical preparations. Unlike hard druses, soft ones located in the central areas of the macula had a different and heterogeneous structure. The nucleus was more hypodense and, in addition to the lipid component, contained a large amount of proteins that are responsible for the immunogenic effect of these druses. The peripheral membrane is thinner, often composed of amyloid substances, but sometimes comprised of elements of the intercellular matrix or small surface cell proteins.

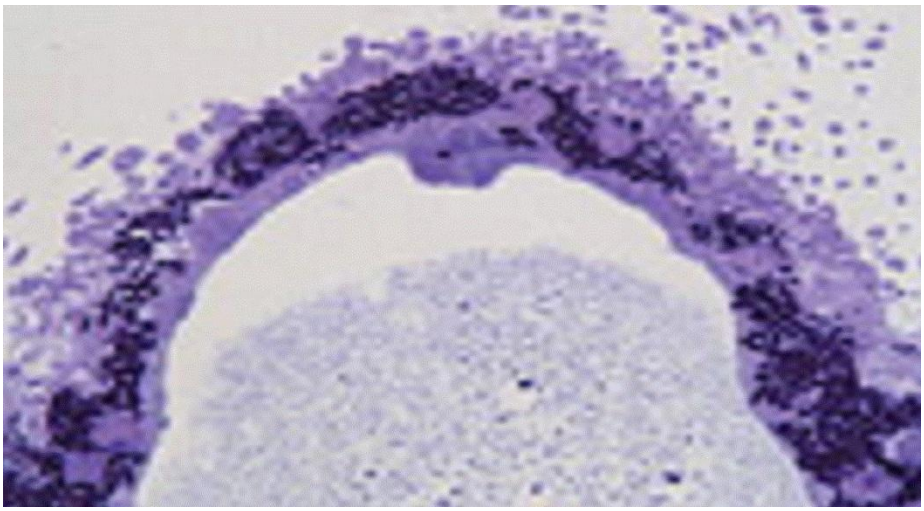

Fig.7 Histochemical preparation of a soft druse made with Alcian blue

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Another significant difference we observed in soft druses is the presence of membranous bodies and teardrop-like hyaline deposits in the inner collagen layer of the Bruch's membrane. The presence of hyalinized droplets in the Bruh membrane at the base of the druses is a sign that indicates progression.

It is believed that hyaline droplets stimulate the deposition of new hyaline in the structure of the membrane, leading to its destruction with a subsequent increase in the size of the druses and subsequent atrophy. In none of the hard druses such depositions were not observed. These particular findings were mainly visible at the electron-microscopical pictures.

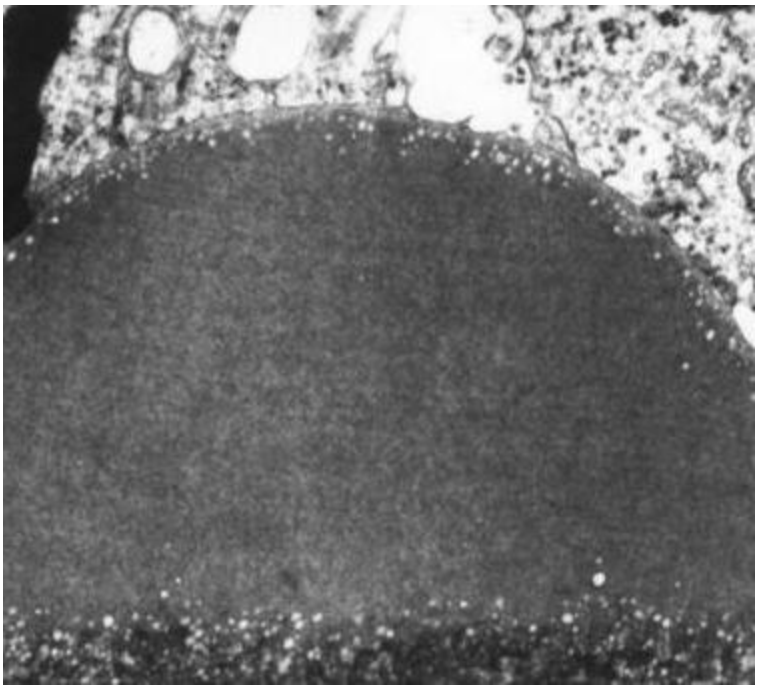

Fig8. *Electronogramme of the structure of a soft druse- hyaline depositions on its surface and at the inner collagen layer of the Bruch membrane are found which are considered to be a sign of progression.*

Results in dry form of AMD - risk factors in dry form of AMD and geographical atrophy

In patients with advanced dry form of AMD, we most often observed an area of geographical atrophy resulting from atrophy of the RPE, photoreceptor cells, and the Bruh membrane in the affected area.

On fluorescein-angiographic plaques, these areas were depicted as lesions with clear outlines and pronounced hyperfluorescence due to the loss of the shielding effect of RPE (Fig. 9).

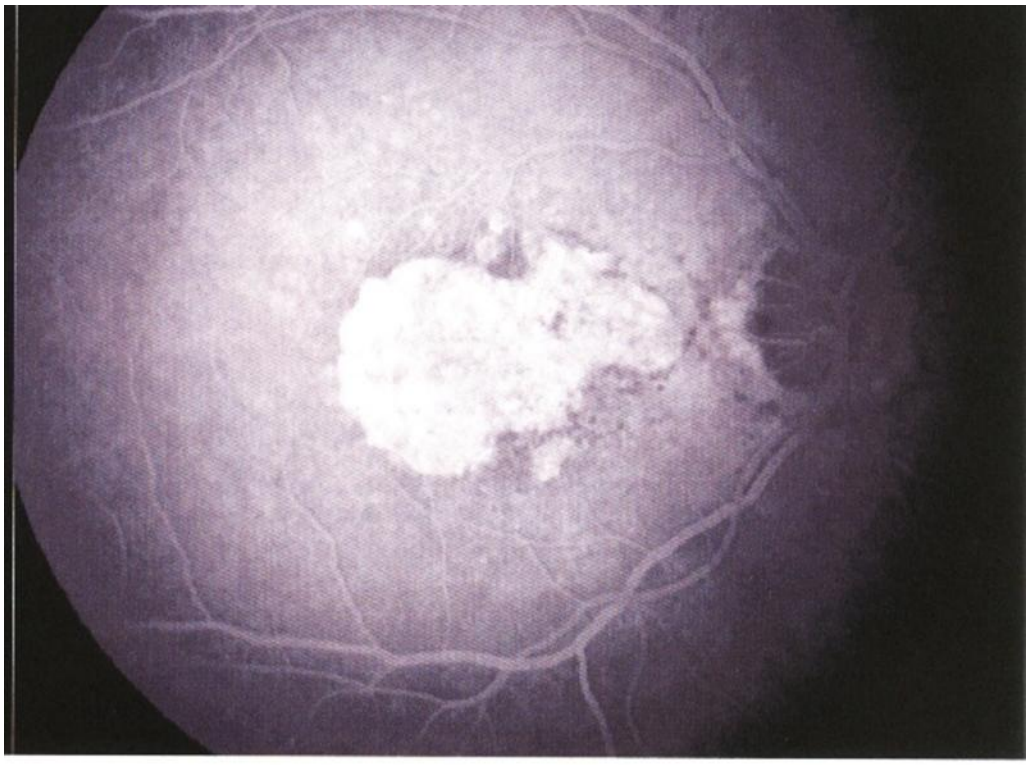

Fig. 9. *Fluorescein- angiographic picture of geographic atrophy of the macula in advanced dry AMD.*

The OCT examination was able to assess the main characteristics of the lesion, size, depth, destruction of photoreceptor cells and the Bruch's membrane. Depending on the depth of the atrophic changes, the lesions we observed were distinguished:

-initial atrophy- the integrity of the photoreceptor cells is still preserved

-advanced atrophy in which all layers in the affected area are completely destroyed.

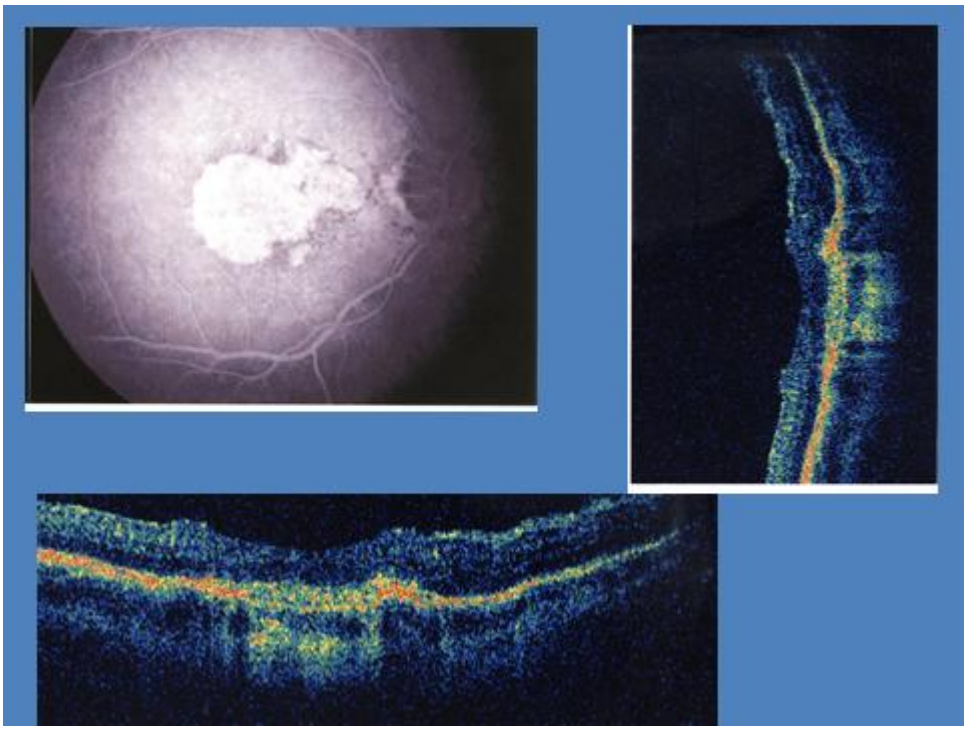

Fig. *10 OCT picture of geographic atrophy- complete destruction of the RPE is present as well as of photoreceptor cells and Bruch's membrane.*

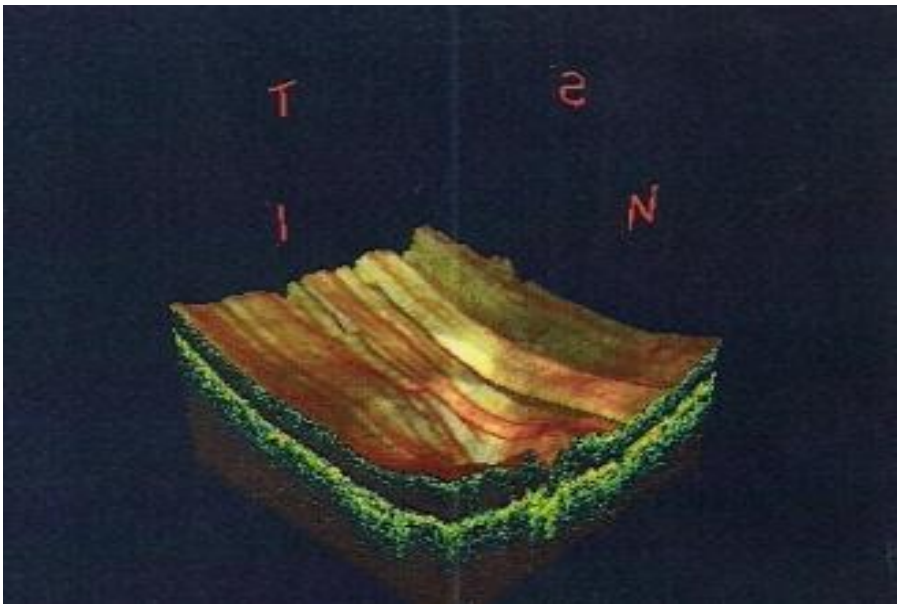

Fig. 11 Three dimentional picture of the atrophic zone- the surface looks like a deepening, resulting of the distruction of the RPE and thining of the retina.

All 134 of our patients with dry AMD were obligatorily examined with fluorescein autofluorescence (FAF). Depending on the autofluorescence in the border zone atrophy-normal retina in the 134 patients studied, we observed the following groups:

- There were 52 without pathological autofluorescence in the border zone.

- With focal autofluorescence were – 24 patients

- With line-shaped (spotted) type AF – 14 patients

- With diffuse AF in the border area and around it – 44 patients.

It is extremely important to monitor the size of the lesion over time in patients with different types of AF in the border area. In the patients we followed without pathological AF in the border zone - 52 people (39%), in 48 there was no change in the size of the lesion for the follow-up time of 2 years.

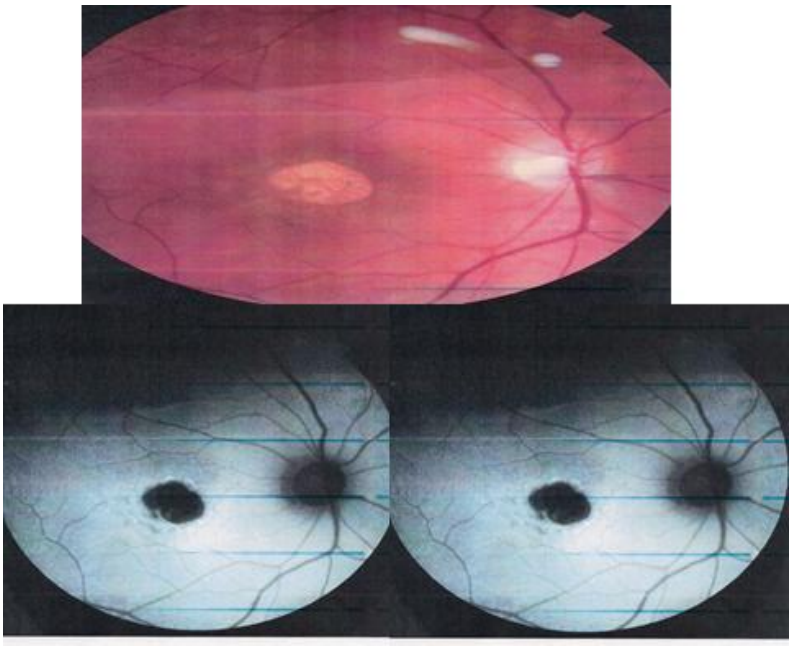

Fig.12. Patient with dry form of AMD and geographic atrophy. On the FAF examination no AF in the border zone is seen. The lesion preserves its size the same in a 2 years follow up time.

The most interesting of all the monitored groups was the one with diffuse type AF. Increased AF was observed not only in the border area, but also in the surrounding tissue - diffuse glow. We observed this in 44 of the studied patients - 33% of the entire sample, which is a fairly common case. This type of AF is shown in fig. 8. The increase in the size of the atrophic zone is diagnosed and measured with the program for quantitative analysis of the OCT program - EMM6. It can be seen that the increase in this case is almost double from 2.53 mm2 to 4.09 mm2.

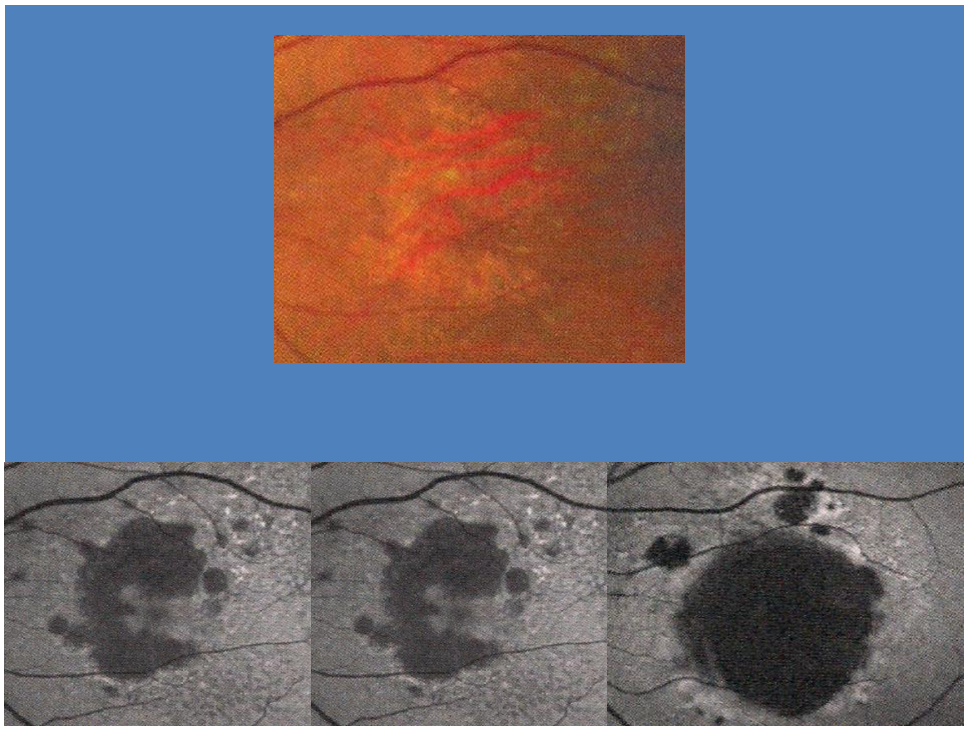

Fig. 13. *Patient with diffuse type of AF at the border zone in the beginning of the disease and on the second year of follow up. We see that the lesion has doubled its size.*

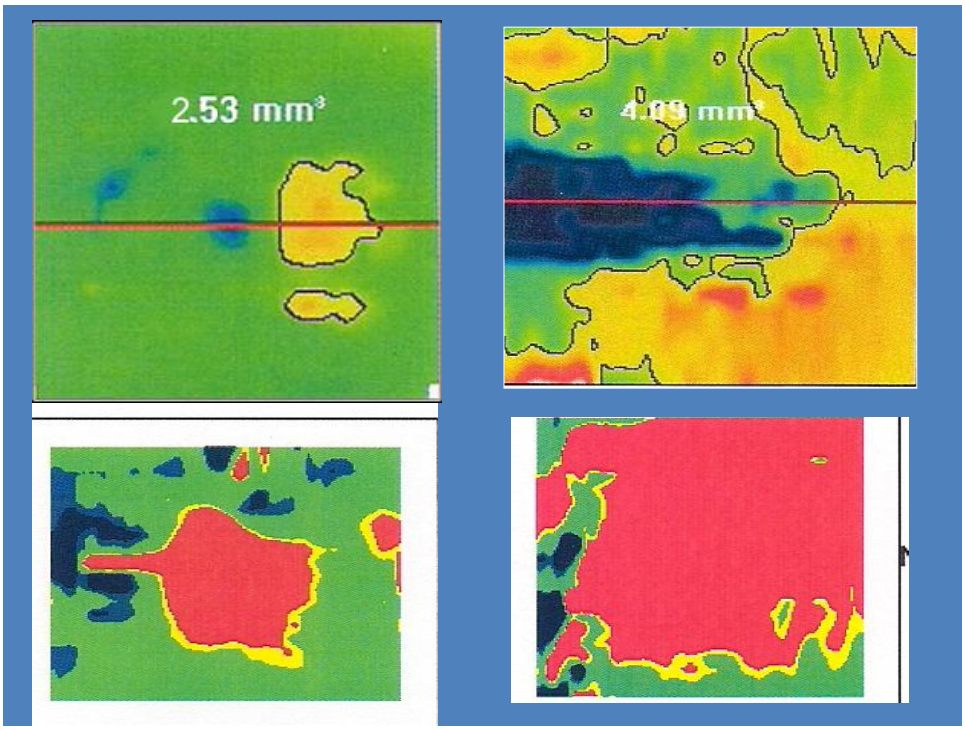

Fig.14. *OCT map of quantitative analysis- the size of the lesion is enlarged almost twice during the follow up period.*

This progression leads to a deterioration in the visual acuity of the observed patients, which decreases by almost 2 rows. In a large number of cases, visual acuity decreases from an average of 0.3-0.4 to 0.1. This was not observed in the other cases of dry form of AMD, where AF was not of diffuse type.

Statistical data processing shows that in:

- geographical atrophy without AF in the border zone the change in the size of the lesion is by 1 mm2 for 2 years.

- geographical atrophy with focal AF in the border zone, the change in the size of the lesion is 2-3 mm2 for 2 years.

- geographical atrophy with band-like type AF in the border zone, the change in the size of the lesion is 2-5 mm2 for 2 years.

- geographical atrophy with diffuse type AF in the border zone, the change in the size of the lesion is 10 mm2 for 2 years.

From the statistical analysis of the data it is clear that the patients with diffuse type AF in the border zone have the highest percentage of probability of progression, while the patients with the lowest risk of developing the disease are the patients without AF in the border zone. Patients with linear AF showed a moderate course of progression.

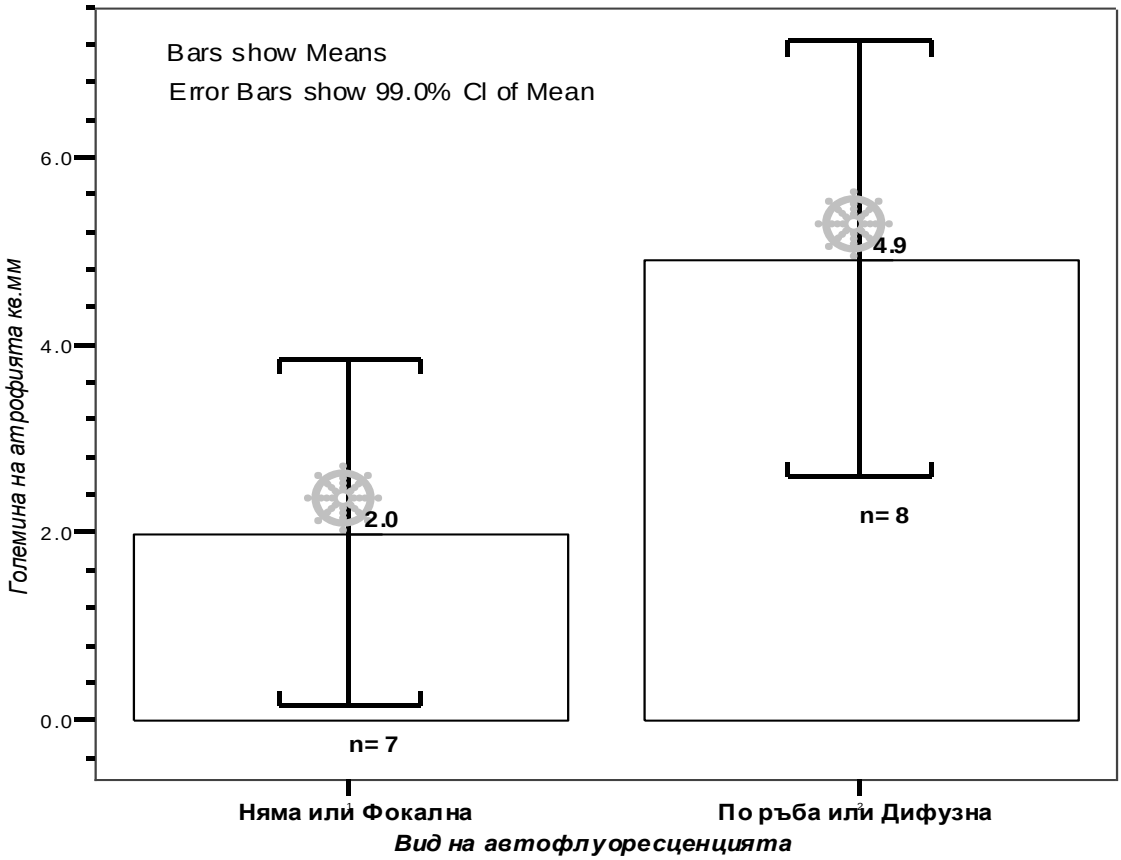

Fig. 15 *Progression of different types of geographic atrophy in patients with AMD. The biggest rate of progression of atrophic type of AMD have the patients with diffuse type of AF.*

Depending on the course of the disease, and especially the progression or not of the atrophic zone, it was found that patients with dry form of AMD and geographical atrophy can be divided into following groups according to the rate of progression:

- Patients with a slow rate of progression are those in whom the atrophic lesion hardly increases in size in two years. These are patients without AF in the border area and

those with focal AF. In them the change in the size of the lesion is not more than 2 mm3 and most likely the disease is stationary.

– Patients with moderately progressive geographical atrophy are those in whom the lesion increases in size but slowly and never exceeds more than 5 mm2. This was observed in the case of band-type AF.

- Patients with rapidly progressive geographical atrophy are those who show diffuse AF on autofluorescent images. In them, the lesion rapidly increases in size - almost doubling at the end of the 2nd year. The rate of progression is on average 10 mm2 for 2 years. The progression of the different types of AF is best represented in FIG. 10.

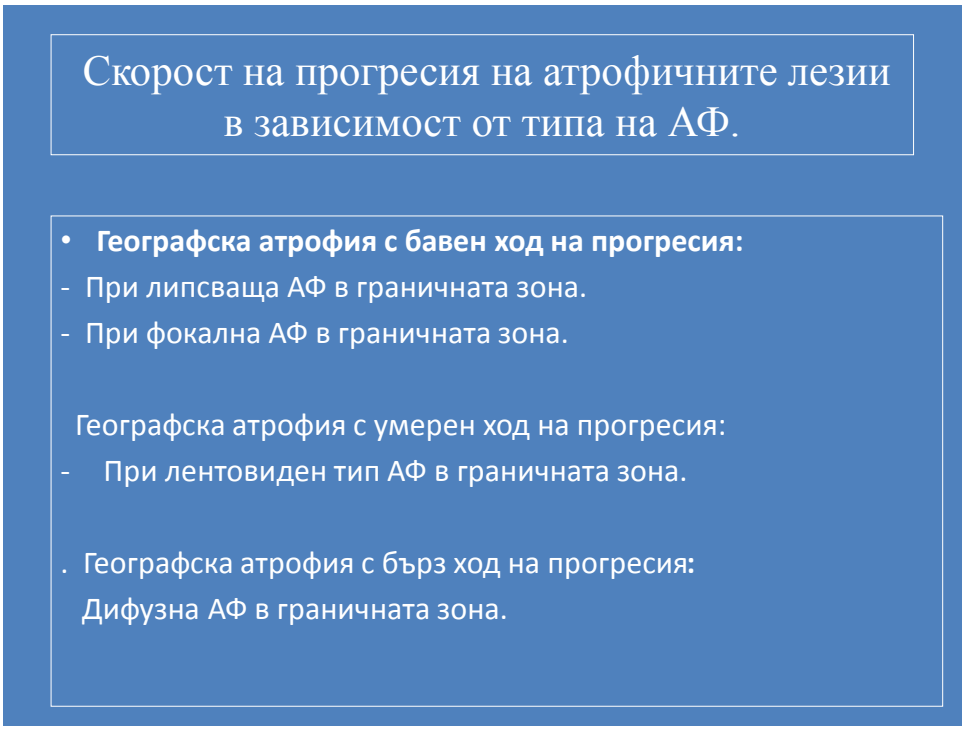

Fig.16. Distribution of patients with dry form of AMD according to the type of AF and the rate of progression.

The work protocol we developed for the diagnosis of patients with dry AMD is as follows:

WORKING PROTOCOL

In patients with dry AMD

---

1. Visual acuity:

VOD-

VOS-

2. Color photo of the fundus of both eyes - features:

3. Autofluorescence of both eyes

- No AF in the border area.
- With focal AF in the border area.
- With band-type AF in the border area.
- With diffuse type AF in the boundary zone.

4. OCT examination of both eyes.

Rtvue (Optovue)

Hd line, Cross line, EMM5.

3D OCT 2000 Topcon

H D line, 5 Cross line, 3 D Macula.

5. High-risk characteristics - a sign of progression:

- soft druses over 350 mk or nodular druses
- druse-like detachment of RPE
- band or diffuse type AF in the area of the atrophy border.

Size of the atrophic lesion in mm

Progression of the atrophic zone: Yes / No

Size of atrophic zone progression in mm

The use of this work protocol in daily ophthalmological practice would support the accurate and precise diagnosis of the condition.

RESULTS OF THE STUDY OF PATIENTS WITH WET FORM OF AMD-RISK FACTORS FOR PROGRESSION IN WET FORM OF THE DISEASE.

126 patients with the wet form of AMD were included in the present study.

Separately, 14 patients with atypical forms of - retinal angomatous proliferation (RAP) and polypoid choroidal vasculopathy (PCV) were included. There were 9 patients with RAP and 5 patients with PVC. Another group of AMD patients with heamophthalm- 11 patients was created and they were operated with PPV and subretinal tissue was taken for electron microscopy and immunochistochemical investigation. The main diagnostic methods we used in patients with the wet form of AMD were FA, OCT, and less commonly autofluorescence.

4.2.1. Fluorescein angiography. FA risk factors

Fluorescein angiography is still considered the gold standard for diagnosing a wet form of AMD, and in some European countries such as Germany it is a mandatory requirement for this diagnosis.

In the patients we examined, FA allowed us to find the exact location and determine the presence or absence of a neovascular membrane (CNV).

FA makes it possible to divide by type, location and prognosis neovascular membranes into those of classical and occult type. This separation is purely fluorescein-angiographic and uses only the signs of FA.

According to this classification and FA characteristics, the wet form of AMD can be divided into:

1Wet form with a classic type of neovascular membrane.

2. Wet form with occult type neovascular membrane:

- Type 1 - occult membrane / fibrous detachment of RPE.

- Type 2 - occult membrane with diffuse exudation.

3. Wet form with detachment of RPE:

- serous detachment

- serohemorrhagic

– *hemorrhagic*

4. Fibrous / scarring stage of AMD.
5. Retinal angiomatous proliferations.

In the patients we examined, FA allowed us to find the exact location and determine the presence or absence of a neovascular membrane (CNV). In most cases, the membranes were characterized by early hyperfluorescence in initial FA phases, which intensified in later times. Dye diffusion during the late phases of angiography was very typical due to the increased permeability of the vessel walls of the new vessels. FA makes it possible to divide by type, location and prognosis the neovascular membranes into those of classical and occult type.

In the group of patients we observed, the classic type of CNV was 28% (36 patients) of the entire sample.

It is believed that the classic type of neovascular membrane has a better prognosis and is generally a more favorable option for therapy with anti-VEGF drugs. This is confirmed by our research.

In 52 of the patients we observed another type of FA picture - occult type of neovascularization.

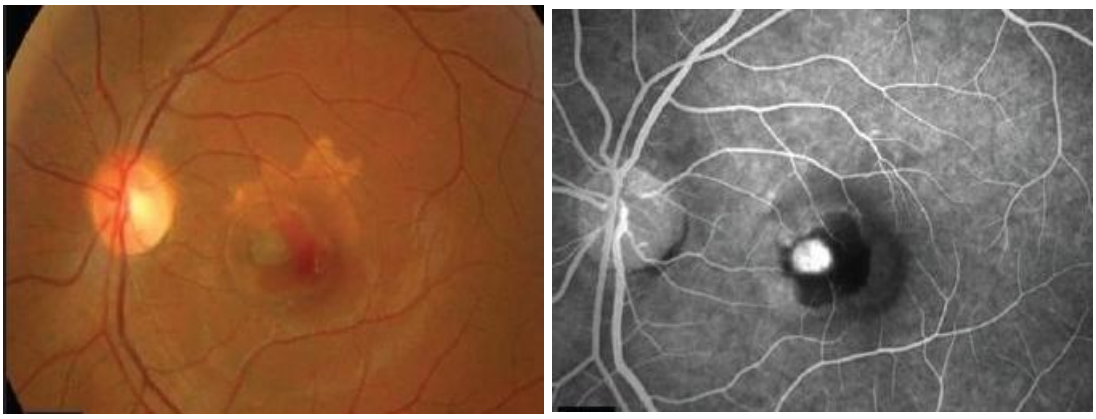

Fig. 17 *Colour photo and fluorescein angiography of pateient with wet form of AMD. The hyperfluorescence of developing neovascular membrane are clearly seen.*

We observed two angiographic types of occult neovascular membrane: type 1 - occult CNV / fibrovascular detachment of RPE and type 2 - occult CNV / with diffuse exudation.

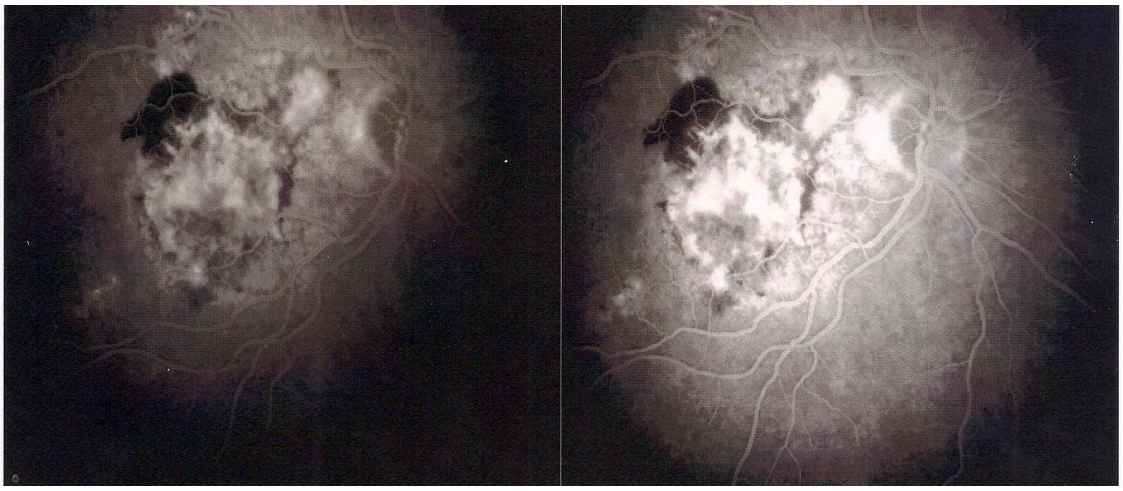

Fig. 18. *Wet form of AMD – occult type 1 neovascular membrane*

Statistical processing of the results showed a proportional relationship between the type of neovascular membrane and disease progression. It turns out that patients with occult type of neovascular membrane are at higher risk of progression - 1.4% higher risk than in the classical type of CNV (p = 0.0003, Table 5).

Table 4. Correlation between AMD progression and type of neovascular membrane. Occult type of CNV has a higher rate of progression and is with higher risk.

Chi-Square Tests

Окултен тип НВМ		**МДСВ в едното око**		**Общо**	**X^2**	**df**	**p**
		Не	**Да**				
Няма окултен тип мембрана	N	70	55	125	3,24	3	0,0003
	%	44,9%	46,2%	45,5%			
Има окултен тип мембрана	N	79	57	136			
	%	50,6%	47,9%	49,5%			
Общо	N	156	119	275			
	%	100,0%	100,0%	100,0%			

Fluorescein angiography is especially important in the diagnosis of the atypical form of AMD - retinal angiomatous proliferations. RAP was first mentioned by Harnett et al. in 1992, who described it as a condition associated with neovascular proliferation originating from the retinal arteries.

Much later Yannuzzi et al. (2001) demonstrate that proliferations originate from the deep retinal layers, which grow and form retino-choroidal anastomoses. They also describe the 3 main stages of the disease, namely:

Stage I - RAP I: Intraretinal neovascularizations

At this stage, vascular proliferations are located in the retina and originate from the deep capillary plexus, retino-retinal anastomoses are present. There are many scattered hemorrhages and edema, there are retino-retinal anastomoses.

Stage II - RAP II: Subretinal neovascularization

Neo-vessels enter the subretinal space - above the retinal pigment epithelium. Intra- and preretinal haemorrhages, often neurosensory retinal detachment or serous RPE detachment, have been reported.

Stage III - RAP III: Choroidal neovascularization (CNV)

At this stage, retino-choroidal anastomoses are observed, often combined with RPE detachment and severe retinal edema syndrome.

FA is especially useful in the diagnosis of the condition, and especially in the initial forms. In the patients we observed - 9, 4 of which with initial forms of disease, on FA plaques we observed increased hyperfluorescence from developing macular edema. The caliber of the vessels was changed and they did not narrow distally like normal retinal vessels, on the contrary, they expanded their lumen towards the end of the vessel (Fig. 13).

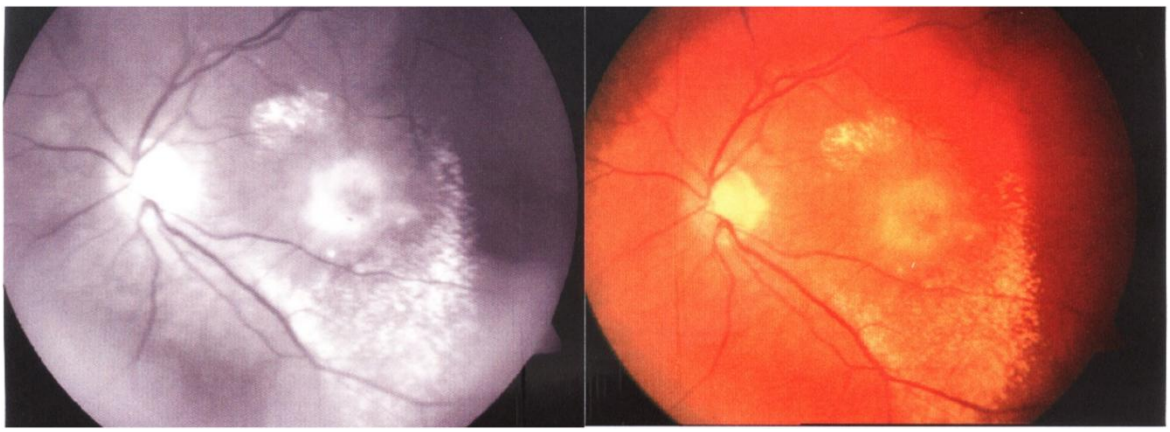

***Fig. 19**. PAII I – we see intraretinal proliferations and significant macular edema in the retina.*

In RAP III the sites of retino-choroidal anastomoses can be seen on FA where the vessel is telangiectatically dilated and appears to sink into the layers of the retina to the choroid. Sometimes this picture is blurred by the developing diffuse retinal edema. We can conclude that FA is particularly appropriate and important in early forms of RAP, where changes in vascular caliber, the presence of edema, and retinal hemorrhage lead us to the correct diagnosis. The most accurate diagnostic method for proving RAP remains indocyanine green angiography, which allows to objectify the vessels of the choroid. This method shows more accurately the leakage of the dye in the late stages due to intraretinal edema and can clearly distinguish retinal-choroidal anastomoses.

The diagnostic value of OCT-A in these cases of RAP can also be very accurate, as it allows to diagnose the changes in the deep vascular plexus of the retina and to prove the retino-choroidal anastomoses.

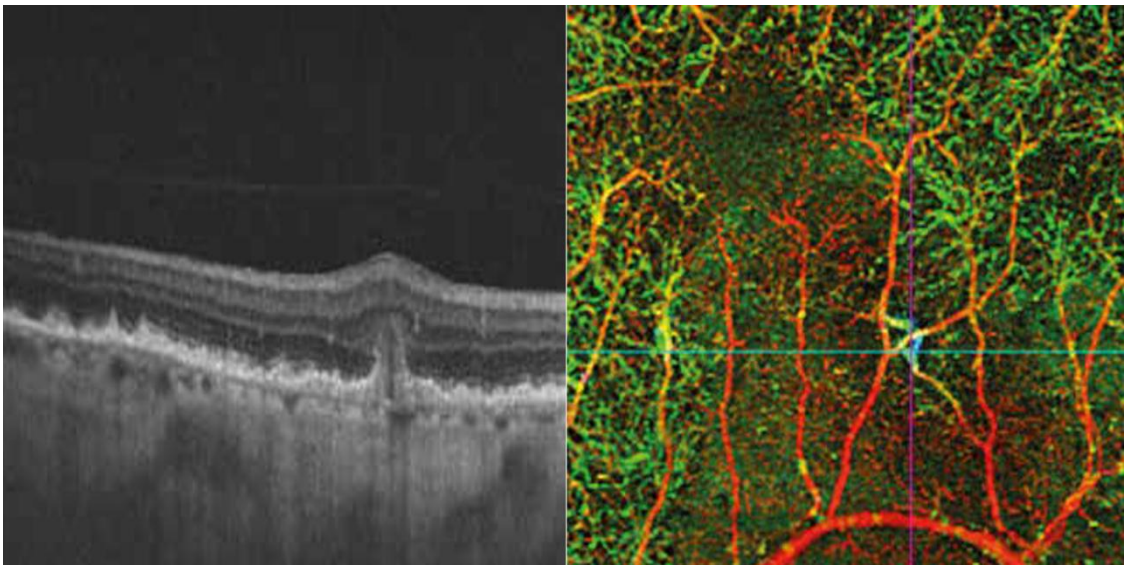

Fig. 20. *OCT and OCT-A in RAP lesion. The place of retinal- choroidal anastomoses are clearly seen.*

In 5 of the examined patients we observed polypoid choroidal vasculopathy - PCV. It is a relatively rare disease, more typical for patients over 70 or even 80 years of age. It is more common in Asians and Africans.

The condition is characterized as neovascularization associated with changes in the choroidal vessels. Degenerative changes affect both the arterioles and the capillaries and venules of the choroid. Aneurysmal dilatations and the formation of polypoid formations are observed. In addition, there is a pronounced exudation of fibrin and plasma around the lesion.

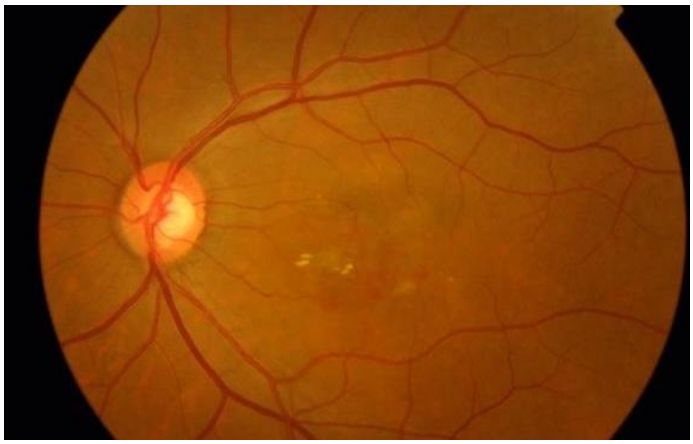

Fig. 21. Colour photo of a female patient with PCV. Alterations of the vessels are typical with teleangictatic dilatations and hard exudates in the posterior pole.

F. A may in some cases provide important information about the disease. What we observed most often in the patients we examined was branching and telangiectatic dilation of the choroidal vessels.

4.2.2. Optical coherence tomography in patients with wet form of AMD. OCT risk factors in wet AMD

As it became clear from the literature review, there are many classifications of AMD, relying on different criteria. Depending on the stage of development of the disease we have the following classification.

- Early form of AMD, which is defined as the presence of druses with an average size of 63-125 μm and no pigment abnormalities.

- Intermediate form, with large, often confluent druses larger than 125 μm and the presence of pigment anomalies.

Advanced AMD - characterized by neovascular membrane or geographical atrophy.

Our studies of patients with an intermediate form of AMD show that of particular importance for disease progression are:

-Druze area

- Their size

- The presence of hyporeflective zones

- The regression of the Druze

Of all the listed criteria, the size of the druses is of the greatest importance. Following 32 patients with an intermediate form of the disease, in about 80% of the cases of drusen with a size of 71 μm and less, no development to the advanced form was observed.

In patients with a druse size of 100-122 μm in more than 60% progression to a developed form of AMD is observed. In all 126 patients with wet form of AMD, in

addition to FA, we applied OCT examination, with the programs HD line, Cross line and those for qualitative analysis of the lesions - EMM5, EMM5 progression and Macular test 523x125.

The OCT criteria we were interested in to determine the prognosis of the disease were:

- *Size of neovascularization*
- *Type - classical or occult*
- *Violations of the integrity of the RPE layer / RPE detachment*
- *Hyperreflectiveness of the lesion*
- *Presence and degree of retinal edema.*

For the first time through OCT diagnostics it became possible to have information about the preservation or not of the integrity of RPE. When it has preserved or only locally damaged integrity, as in fig. 18, patients have a good prognosis and these are the most favorable cases for anti-VEGF therapy. Diffuse disruption of RPE integrity in combination with serous detachment of the neurosensory retina is a poor prognostic factor and reduces by up to 30% the chances of a favorable response to anti-VEGF therapy.

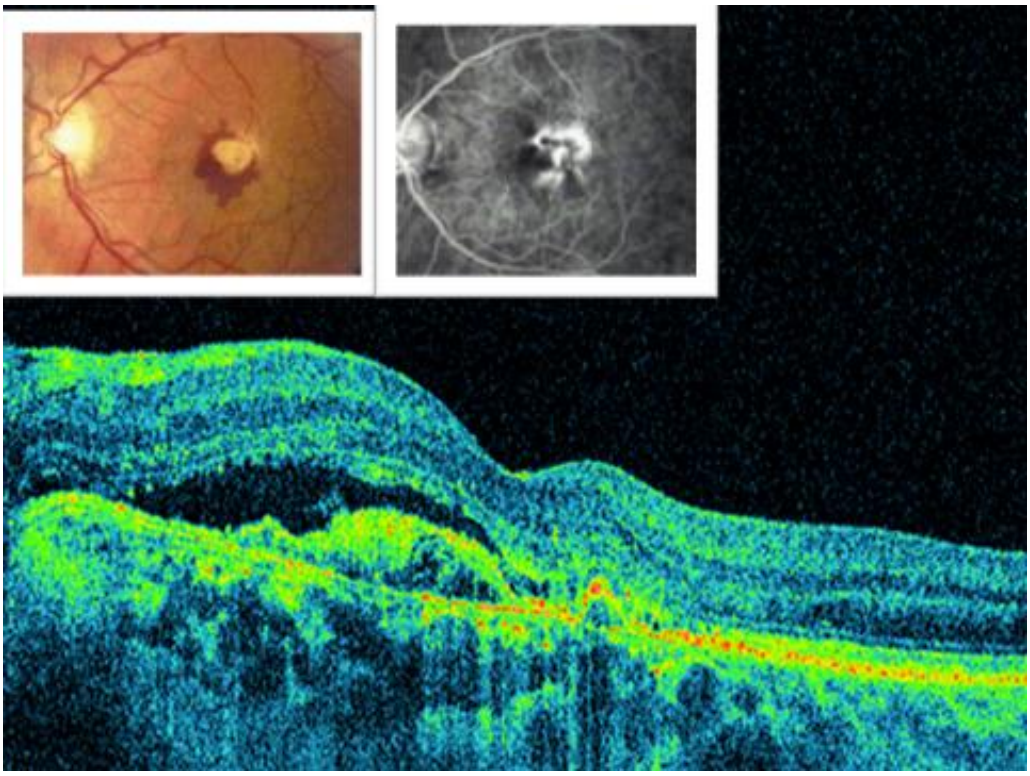

FIG. 22. Patient with wet form of AMD and neovascular membrane of classic type, but with diffuse disruption of the RPE integrity and serous retinal detachment , has a poor prognosis

OCT-A in patients with a wet form of MDSV.

OCT-A risk factors

Optical coherence tomography-angiography - OCT-A, is a relatively new, non-invasive method for assessing changes in the structure of the retina and its blood circulation. OCT-A is a faster and easier to perform method, allowing to obtain cross-sectional and en face images of the retina and choroid, with three-dimensional visualization of choroidal lesions.

With the help of the methodology we can see the structure of the neovascular membrane, even in cases when it is subclinical - ie. there are no accumulations of fluid in the retina.

Our studies of 126 patients with the wet form of AMD showed that patients with an existing subclinical neovascular membrane detected by OCT-A were 15 times more likely to progress to the condition than those without such a lesion.

Through OCT-A we had the opportunity to study the structure of neovascular membranes.

According to our studies, there were 3 subtypes of neovascular membranes according to their characteristics of OCT-A. Type 1 neovascular membranes originating from the choroid, penetrating the Bruch's membrane and located below the RPE.

In more than 55% of cases, the neovascular membrane in these patients was in the shape of a "medusa" - a number of radially protruding and branching vessels originating from one main feeding vessel.

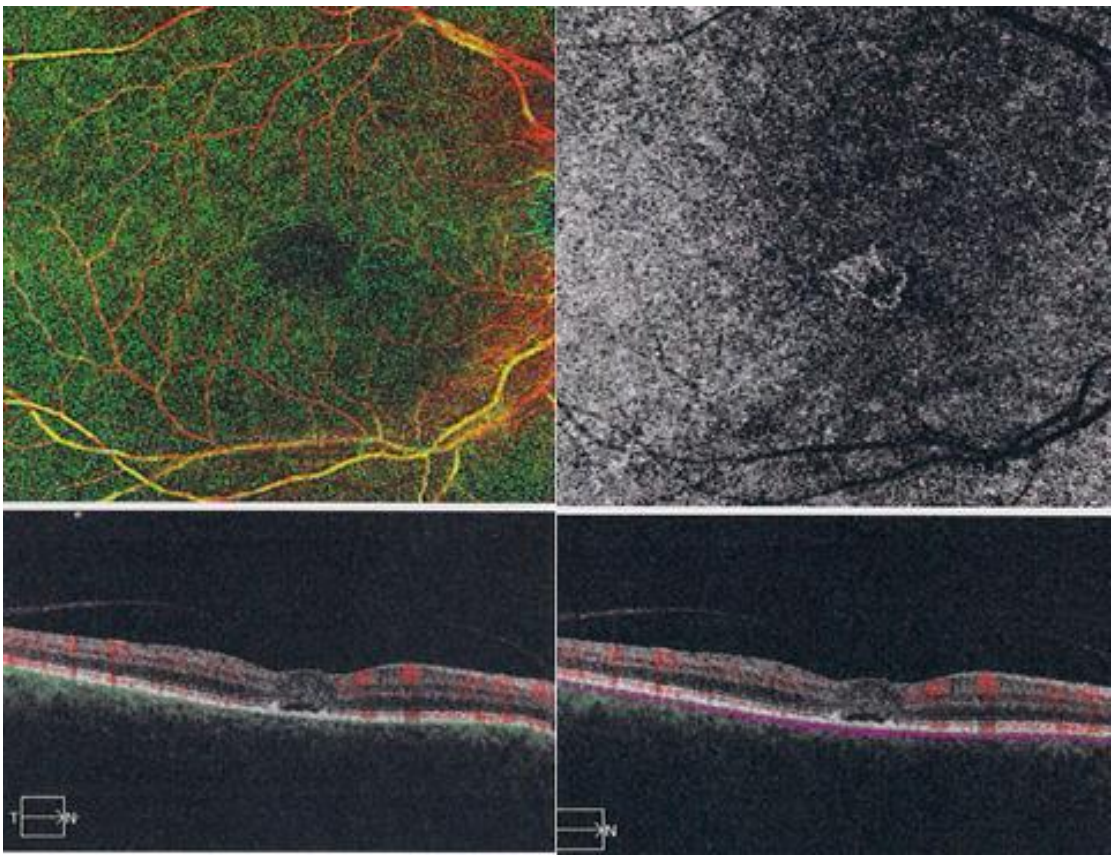

Fig.23. On OCT-A a subbclinical CNV is found in the deep retinal plexus, which can not be found in normal OCT

Of particular importance were 5 patients with multiple rough large vessels of large caliber, with multiple peripheral branches, which were high risk and progressed to a developed form of AMD.

In Type 2 neovascular membranes (CNV), which we observed in 54 patients, the lesion originated again from the choroid, but was located between the RPE and the neurosensory retina. These are the lesions that give a classic type of CNV on angiofluorographic plaques.

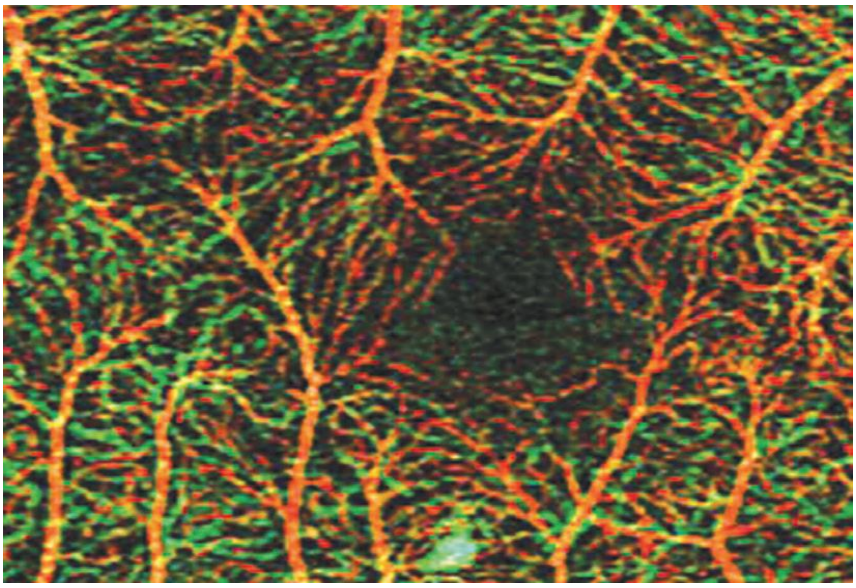

Fig.24. Patient with neovascular membrane – „Medusa“ type on OCT- A pictures.

The OCT-A structural features of CNV in these patients is of "glomerulus" type, a plurality of branching, small vessels with varying degrees of hyporeflexivity.

Statistical processing of the data showed that we had a significant difference in the degree of progression of AMD in patients with existing rough neu-vessels on OCT-A and those without. Patients with this high-risk characteristic are about 2 times more likely to progress. Another risk factor of therapeutic importance is the presence of anastomoses between the vessels. The presence of a network of many young capillaries, twisting and anastomosing with each other, is a sign of an active membrane. Those with smaller, non-

anastomotic vessels - such as a "dead tree", in the patients we studied showed a low degree of activity and progression.

Table 5. Correlation between the progression of the disease and the presence of rough large in calliber neu vessels.

Chi-Square Tests

Груби неосъдове на ОСТА		**МДСВ в едното око**		**Общо**	**X^2**	**df**	**p**
		Не	**Да**				
Не	N	127	70	197	16,95	1	< 0,001
	%	81,4%	58,8%	71,6%			
Да	N	29	49	78			
	%	18,6%	41,2%	28,4%			
Общо	N	156	119	275			
	%	100,0%	100,0%	100,0%			

Based on diagnostic tests in patients with the wet form of AMD, we propose the following work protocol to assist in the accurate diagnosis of the disease and to assess the presence of risk factors for the progression of the condition.

WORKING PROTOCOL

In patients with a wet form of AMD.

---

1. Visual acuity:

- VOD-

- VOS-

2. Color photo of the fundus of both eyes - features:

3. FA in both eyes:

- - Presence of dye leakage - presence of active neovascularization.
- - Type of neovascular membrane - classical, occult, mixed.

4. OCT examination of both eyes.

- Rtvue (Optovue)
- Hd line, Cross line, EMM5.
- 3D OCT 2000 Topcon
- H D line, 5 Cross line, 3 D Macula.
- - Presence and size of novascularization.
- - Presence of any of the signs of progression:
- - Violations of the integrity of the RPE layer
- - Detachment of RPE.

- Hyperreflectiveness of the lesion.
- Presence and degree of retinal edema.

5. OCT- A.

- Presence of neovascular membrane (Subclinical)
- Location of the neovascular membrane
- Membrane structure.
- Density of the vascular network of the neovascular membrane.

6. Auto fluorescence.

- only in case of doubt about the condition and integrity of the RPE in the lesion.

The work protocol allowed us to diagnose very accurately patients with a wet form of macular degeneration and to determine the main risk factors for the progression of the condition.

The main risk factors for progression in patients with dry AMD according to our studies are the following:

1. The area of the druses is over 100 microns
2. Size of druses over 300-350 microns
3. Presence of hyporeflective zones
4. Tearing of the integrity of the RPE line
5. Geographical atrophy with a ribbon-like type of auto fluorescence in the border zone.
6. Geographical atrophy with diffuse type of autofluorescence in the boundary zone.
7. Presence of subclinical neovascularization, visible only on OCT-A.

Of the criteria listed above, the most important are 6 and 7 as they carry 8 times and 15 times higher risk of progression, respectively, in patients who have them. We calculated the risk index of the patients we examined and for each indicator without 6,7 we gave 1 point when it was available.
The presence of 6 or 7 criteria brought 2 points to the risk index
Taking into account the risk index in the 134 patients we studied with dry form of AMD, we found that:
-76 patients had a progression risk index of 4 or less.
14 patients were at risk 5.
44 patients had an index of 6-9.
Following the patients for a period of 2 years, we found that patients with a risk index of 4 or less did not show progression of the disease for two years. Most often, their condition is stationary and does not progress.
The main risk factors in patients with the wet form of AMD are the following:

1. Occult type neovascular membrane (type 1 or 2).
2. Neovascular membrane size greater than 3 mm.
3. RPE detachment - serous, serohemorrhagic, hemorrhagic.
4. Presence of diffuse edema up to 350 microns.
5. Presence of cystic edema over 350 microns.
6. Structure of the medusa-type membrane of OCT A
6. Structure on the OCT A glomerular type.

Calculating the risk index in the patients we monitored with exudative form of AMD, it turned out that: Of the 126 patients with wet form of AMD, in 36 patients we had a risk index of 3 or lower, and in none of them was observed progression of the condition over a period of 2 years.In 24 people the risk index was between 4-5 and only in 30% there was a progression of the condition, which manifested itself by the end of the first year. In 52 patients with high-risk 6 and above, up to 9 , a rapid progression to fibrotic stage was observed in the first year. And in this group, a higher risk index means a greater chance of progression.

4.3. Results of the pathomorphological studies of subretinal membranes of patients with wet form of AMD

From the group of patients with wet form of AMD - 126 in number, a separate subgroup of patients with AMD and hemophthalmos - 11 eyes, in which PPV was performed. During the procedure a material was taken - subretinal tissue for electron microscopic and immunohistochemical examination. Electron microscopic images were taken according to a standard protocol for transmission and scanning electron microscopy. The histochemical study with Safranin O was first proposed by Shepard and Mitchel, with the aim of proving the proteoglycan complexes in the extracellular matrix.

In all patients observed by us - 11 in number, a wet form of AMD was diagnosed with a pronounced degree of neovascular membrane (CNV).

Subretinal membranes were composed mainly of fibroblasts of varying degrees of maturity, single or grouped RPE cells, and multiple blood elements, most commonly macrophages, erythrocytes, and leukocytes. This can be clearly seen in fig. 19. It is clear that mainly mature fibroblasts are seen in the membranes. They are characterised with spindle like form and average nuclear cytoplasmic index.

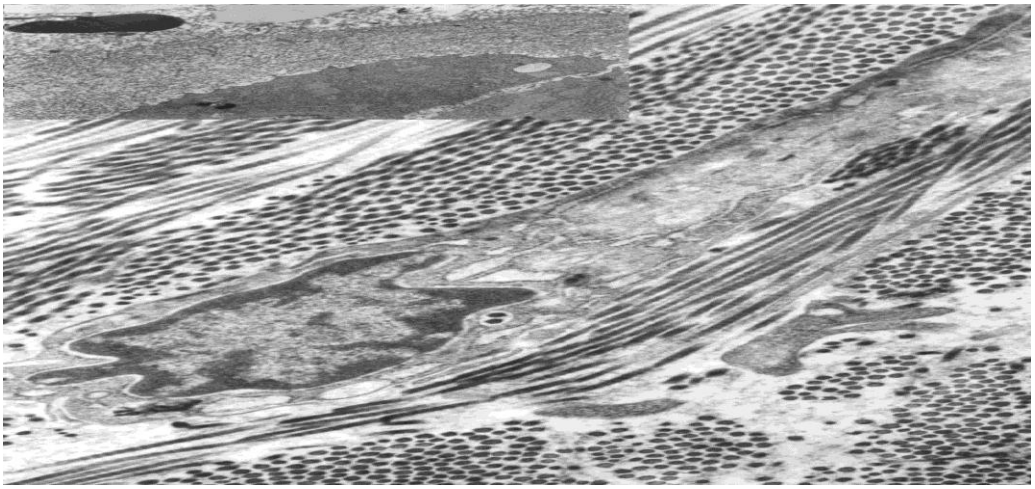

Fig.25 Electron – microscopical image of the subretinal membranes in patients with AMD. Mature fibroblasts and multiple collagen bandles and extracellular elements are clearly seen.

Subretinal membranes in AMD are primarily fibrovascular membranes that abound in vessels of varying degrees of maturity. Although more difficult due to the scarce amount of material we received, we were able to study the structure of these non-vessels. It was characteristic that we observed both capillaries of young (early) non-vessels and of "mature" (developed) non-vessels. The capillaries of the young nue-vessels have a wider lumen. Their wall is composed of a thin layer of fenestrated endothelial cells, with a flattened shape and eccentrically located nuclei (Fig. 20). The cells do not form contacts with each other. Due to the fenestrated type of endothelial cells, the lack of a basement membrane and lack of intercellular contacts young nuevessels are extremely permeable to plasma and shaped elements of the blood that pass freely through the vessel wall.

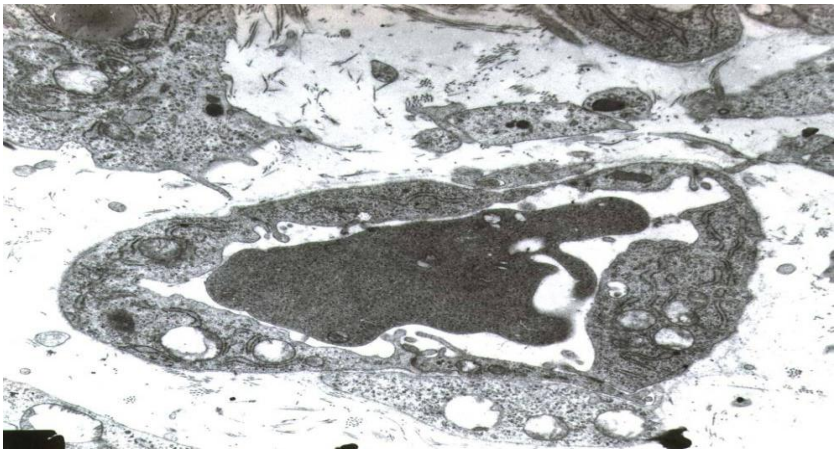

Fig.26 Capillaries of a young neu vessel from subretinal membrane of wet form of AMD. The fenestrated endothelial cells are clearly seen as well as the lack of basal membrane.

"Mature" nue vessels were less common. They were characterized by a narrower lumen and a well-formed basement membrane. A layer of fenestrated endothelial cells with an elongated shape with intercellular connections between endothelial cells was present. The specialized intercellular contacts of the zonulae occludens type, characteristic of normal vessels, are completely absent here. (Фиг.21). The cytoplasm of the cells contains a certain amount of pinocyte vesicles, both from the lumenal surface and in the peripheral part. They are a sign of immaturity and damage to endothelial cells. There are no pericytes in the capillaries of the "mature" vessels, which makes them unstable, brittle and easily susceptible to external factors.

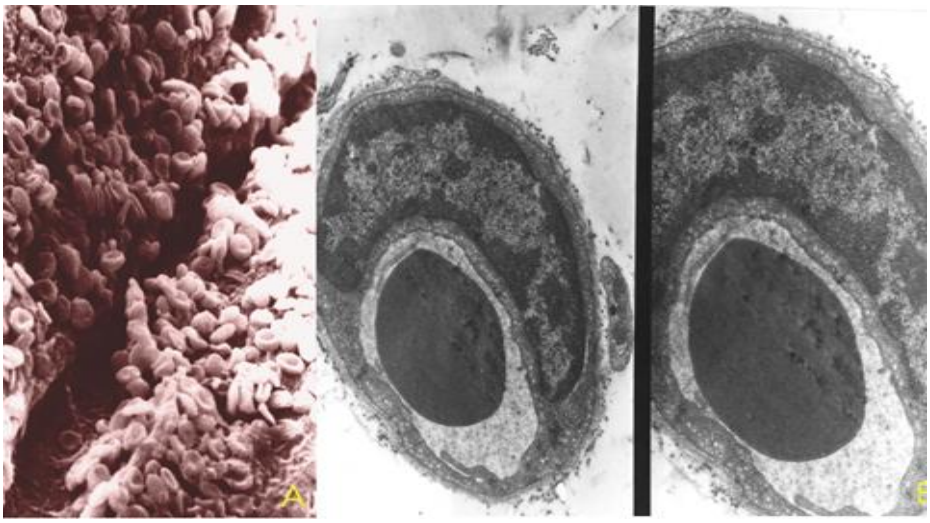

Fig.*27. Capillaries of „ mature“ neuvessels, which are found in the fibrovascular tissue of the subretinal membranes in wet form of AMD.*

In the patients with anti-VEGF treatment, we observed platelet and erythrocyte accumulations in the capillary lumen, which most often led to the development of thrombotic microangiopathy, with subsequent occlusion of the respective neu-vessels. All this leads to a decrease in vascular permeability, cessation of proliferative processes and occlusion of existing nue-vessels. In patients treated with Aflibercept, the process of thrombotic microangiopathy is much more pronounced than in patients treated with other anti- VEGF drugs. In this case, we observe the involvement of many macrophages and leukocytes, which together with platelets and erythrocytes fill and occlude the capillary lumen. These cells were significantly larger in number in older patients. They are irregular in shape and have long cytoplasmic processi, with which they participate in phagocytic processes (Fig. 28).

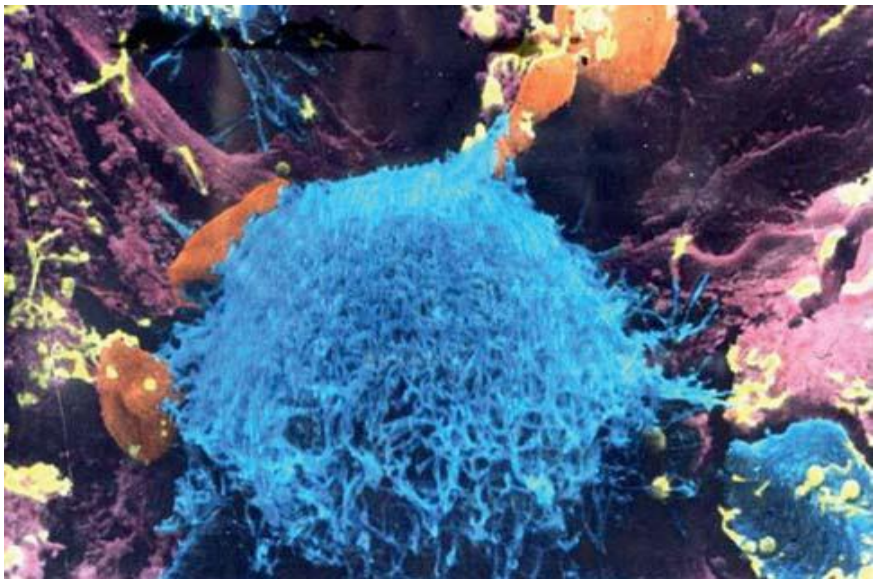

Fig.28. Scanning electron microscopy of a macrophage with multiple pseudopodia.

The macrophages we observe in neovascular membranes have been shown to have pro- and antiangiogenic effects, which are subject to complex regulation, mostly by cytokines. These cells are thought to have dualistic characteristics and influence neoangiogenesis. It turns out that degenerative changes in the cell affect its ability to participate in neoangiogenesis. Most probably the cells lose their ability to inhibit and regulate the processes of angiogenesis. That is why we accept that the cells of inflammation play a key role in the pathogenesis of AMD.

Results from the application of anti-VEGF preparations in patients with a wet form of AMD.

Our study included 274 patients divided into three main groups:

1. Patients with dry form of AMD - 134 patients.
2. Patients with wet form of AMD - 126 patients.
3. Atypical forms of AMD - 14 patients, 9 of them with RAP and 5 with PVC

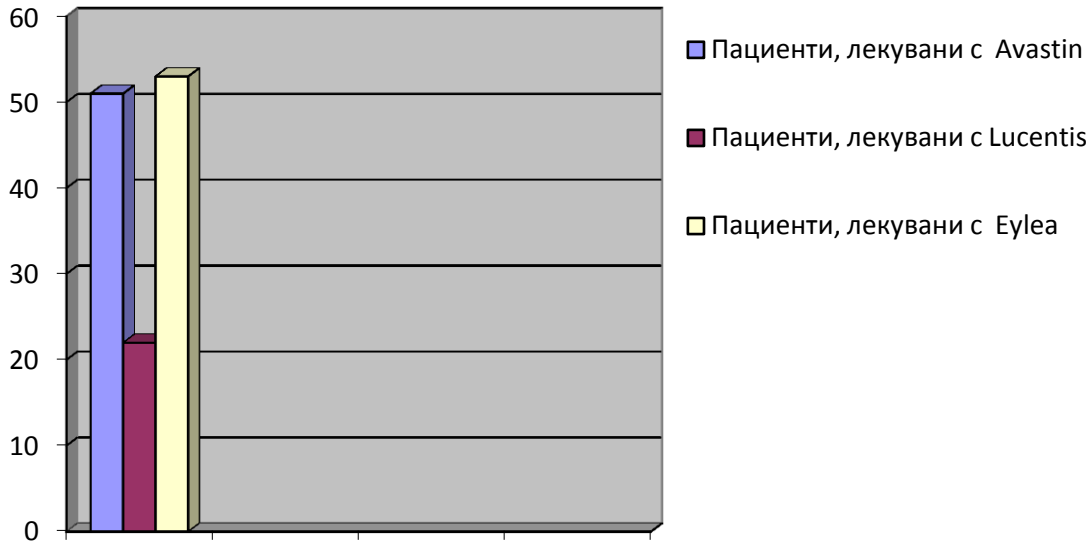

Fig. 29. *Distribution of patients with wet form of AMD according to the treatment drug*

The percentage distribution of the studied patients depending on the used anti-VEGF drugs is as follows:

40.4% of all with the wet form of AMD were treated with Avastin

17.4% of all with the wet form of AMD were treated with Lucentis

42.0% of all people with wet AMD were treated with Eylea.

It is clear that the proportion of patients treated with Eylea and Avastin is relatively large and almost equal, and the number of patients treated with Lucentis is significantly smaller.

All patients in the sample were examined in detail ophthalmologically, for visual acuity, Amsler's grid, as well as with OCT, OCT-A, fluorescein angiography and autofluorescence.

The OCT study was performed on Optovue (RTeVue), Topcon 3D OCT 2000, and Angiophlex Zeiss OCT-A. Color photos, FA photos, FAF were performed on Topcon 2000 Fa Plus. The size of the lesions in autofluorescent images was measured and evaluated using a computer analysis system.

Intravitreal injections are one of the most common manipulations in ophthalmology. It is associated with the placement of a drug in the vitreous. It is believed that the

intravitreal administration of drugs was first proposed by Ohm, 1911, when during retinal surgery used air for air tamponade of the retina.

Intravitreal injections have been shown to be a very effective selective therapy. It achieves the maximum therapeutic effect, at the exact desired place with minimal systemic complications. In general, the characteristics of intravitreal injections can be summarized as follows:

- Very effective selective therapy.
  - Injection of drugs through the pars plana into the vitreous.
  - Maximum therapeutic effect and minimal systemic complications.
  - The most common ophthalmic manipulation worldwide.

The main characteristics of Anti VEGF preparations, which are used in AMD and DR are:

- Reduce vascular permeability and tissue edema.
- Reduce the progression of neu vessels.
- Reduce the risk of vitreal hemorrhage.
- Have a rapid effect up to 24 hours after application.
- Lead to improved visual acuity.

The main mechanisms by which these drugs act in AMD are related to the blocking of VEGF molecules, which reduces the formation of nue-vessels, reduces the permeability of vascular walls, reduce the tissue edema and lead to stabilization of the vision. The most commonly used treatment anti-VEGF drugs in wet AMD are the following:

-Pegaptanib (Macugen),
-Bevacizumab
-Ranibizumab
-Aflibercept

Patients with wet form of AMD treated with Avastin (Bevacizumab) - 41 patients.

Patients were treated with intravitreal injections of Bevacizumab (Avastin) at a dose of 0.05ml (25 mg / ml).

Follow-up was performed according to the TAE protocol, initially administered 3 applications every 4 weeks as an initial saturating dose. In patients without evidence of no fluid activity on the OCT charts, subsequent injections were given after a 2-week prolongation of the interval. The shortest administration interval was 4 weeks. If we observed a recurrence of the disease, an increase in the amount of fluid in the macula, this led to a reduction in the injection interval by two weeks. Usually the individual interval of therapy is the time interval at which relapse occurs minus 2 weeks. In cases of lack of effect of the therapy, proven by OCT and VA, they switched to an alternative drug or other type of therapy - photodynamic therapy and others.

Our studies have shown good results with Avastin (bevacizumab). In most cases, there was a rapid improvement in visual acuity and OCT picture even after the initial saturating 3 doses. In some cases, a very fast result was observed - up to one week after application of the preparation (Fig. 24). Typically, patients with such a rapid response to therapy were younger between the ages of 60 and 65, with a relatively healthy retina and very little retinal edema.

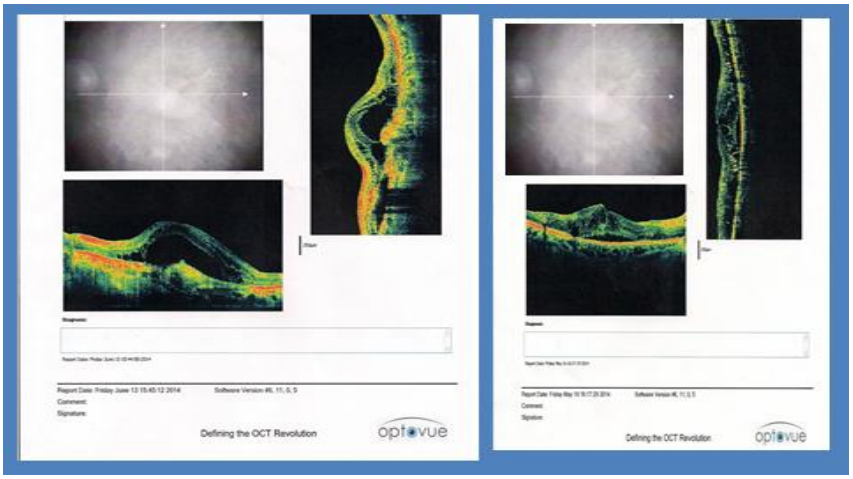

Fig.30 *Patient with wet form of AMD before and after the treatment with Avastin. A reduction of the intraretinal edema is seen.*

Less frequently, a delayed to absent effect of Avastin therapy was observed. Patients with lack of response were older than -70-80 years, with more advanced retinal changes and a significantly larger edema area. In the majority of patients, 60% had an improvement in their condition, which was reported with an increase in visual acuity and a decrease in retinal thickness. The mean macular thickness-CMT was 356 microns. The reduction in retinal thickness averaged up to 253 microns. The mean reduction in retinal thickness was 100 microns. We observed that in 84% of the cases the change appeared within the first month after the first 3 injections. The mean initial visual acuity of the observed patients was 0.1 (SD 0.35). The increase in mean visual acuity was to 0.2-0.3 (SD 0.3: P <0.001). We can say that we observed an increase in visual acuity by an average of 1-1.5 lines (SD 1.2). In 40% of the treated patients VA remained the same as the initial one in the course of the therapy. Only in (2%) we observed a decrease in visual acuity to 1 row from the original.

Our main criteria for switching therapy to another drug were:

1. Decrease in visual acuity (5 letters)

2. Increase of the central retinal thickness by 100 microns. / keeping the same retinal thickness /

3. New hemorrhage in the macula.

4. Classic type new CNV.- FA

5. Persistent retinal fluid more than 1 month after the last injection.

In cases where at least two of the above criteria were met, we assumed that these were drug-resistant cases and switched to therapy with another drug.

Patients with the wet form of AMD treated with Lucentis (Ranibizumab) -12 patients.

Patients treated with intravitreal injections of Lucentis (Ranibizumab) at a dose of 0.5 mg / ml were 12. The mean age was 67 years (+/- 4). The mean number of intravitreal injections was 11 (SD 2.4 from 3 to 12). Patients were followed for 2 years. As in the previous group, the best results were observed in younger patients, those with initial retinal changes and smaller lesions. The mean initial visual acuity of the observed patients was 0.1 (SD 0.45) The increase in mean visual acuity was to 0.2-0.3 (SD 0.3: P <0.001). We can say that we observed an increase in visual acuity by an average of 2 lines (SD 2.3).

In 9 of the patients (40%) an improvement in visual acuity by 15 or more signs was seen. In 11 (50%) of the treated patients VA remained the same as the initial one in the course of the therapy. Only in 2 patients (1%) we observed a decrease in visual acuity with 1 row from the original.

The mean macular thickness-CMT was 370 microns. The reduction in retinal thickness averaged to 244 microns. The mean reduction in retinal thickness was 156 microns. We observed that in 81% of the cases for VA and in 85% for the retinal thickness the change was observed within the first month after the first 3 injections.

The patients in whom no improvement in VA was observed were mostly patients with advanced forms of AMD, patients with RPE detachment or with severe bleeding.

Comparing the two groups of patients treated with Lucentis and Avastin, we can say that almost the same results are observed in terms of changes in visual acuity and central retinal thickness, respectively: average improvement in visual acuity in Avastin - 0.1-0.2 (SD 0.3: P <0.001) mean improvement in visual acuity in Lucentis-0.2-0.3 (SD 0.3: P <0.001). For central retinal thickness measured with OCT, things were similar - the mean change in Avastin-treated patients was 100 mk, while the mean change in retinal thickness in Lucentis-treated patients was 150 mk. We can logically conclude that the two preparations have equal effectiveness in terms of influencing VA. and central retinal thickness. At the same time, there is a general tendency for both to have a better effect in patients at a younger age and with smaller lesions. We can also note that Avastin is significantly more effective in cases of hemorrhagic activity, as it directly promotes the disintegration of erythrocytes in the retina and vitreous. On the other hand, although on a small number and without statistical significance, we observed a better therapeutic effect with Lucentis in patients with RAP than with Avastin. The TAE regimen was extremely effective in both groups, but the individual interval for injections was different for both preparations. Using Avastin we were able to prolonge the applications to those every 10 weeks, while Lucentis required more frequent injections. The longest interval during which no recurrence was observed was 8 weeks. Patients with RAP required significantly more frequent injections every 4 to 6 weeks to maintain a stable condition.

Patients with wet form of AMD treated with Eylea (aflibercept) -73 patients

Patients treated with intravitreal injections of Eylea (aflibercept) at a dose of 2 mg (0.05 ml) were 73. The mean age was 63 years (+/- 4). The mean number of intravitreal injections was 7 (SD 3.4 from 3 to 16). Patients were followed for 2 years.

The main properties of Aflibercept can be summarized as follows:

A protein designed to block endothelial growth factor VEGF as well as placental growth factor PIGF. Fully human protein with higher affinity for growth factors much more than the native receptor - VEGF trap.

- Longer acting and higher affinity for binding to VEGF than other drugs.
- The majority of cases responded well, as in the following exemplary clinical case to:
  -61 years old female- A.P.
  -wet form of AMD in both eyes.
  -VOD-0.1, VOS-0.01.
  - OCT pronounced edema, active CNV.
  -therapy with Eylea according to the T&E scheme.
  Even after the first 3 injections of aflibercept, there was an improvement in VA- which reached 0.3 and there was almost complete subsidence of RPE detachment and reduction of retinal thickness to 250 microns. All this is clearly visible in Fig. 31.

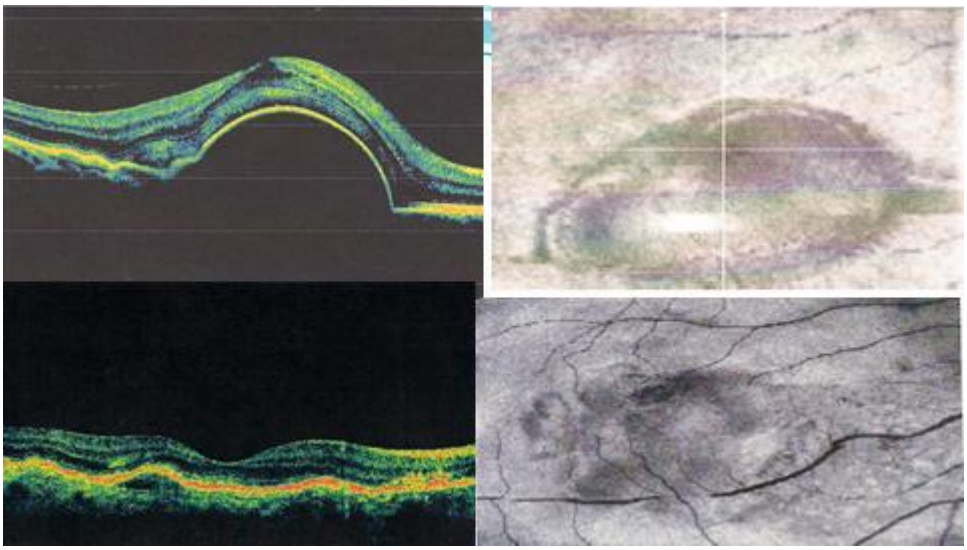

Fig.31 The patient before and after the therapy with Eylea. Initially there was a detachment of RPE and active CNV.

At the end of the second year of treatment according to this scheme, 94% of patients showed preservation or improvement of visual acuity, and 71% showed an increase in vision by more than 6 letters.

Statistics show that the increase in VA is almost the same in patients treated with Avastin and Lucentis and much better in patients treated with Eylea. The mean improvement in visual acuity in this observed group was up to 0.4 (SD 0.4: P <0.001). At the same time, there was a reduction in retinal thickness as reported in OCT measurements. Such a decrease was reported after the initial saturating dose, after 1 year and at the end of the second year.

There was also a strong reduction in central retinal thickness (CRT) from baseline. From the initial mean retinal thickness (400 ± 130 μm), at 6 months of therapy it was (288 ± 74 μm). The mean retinal thickness in the first year was reduced to (294 ± 75 μm) and at the end of the second year was (288 ± 70 μm,).

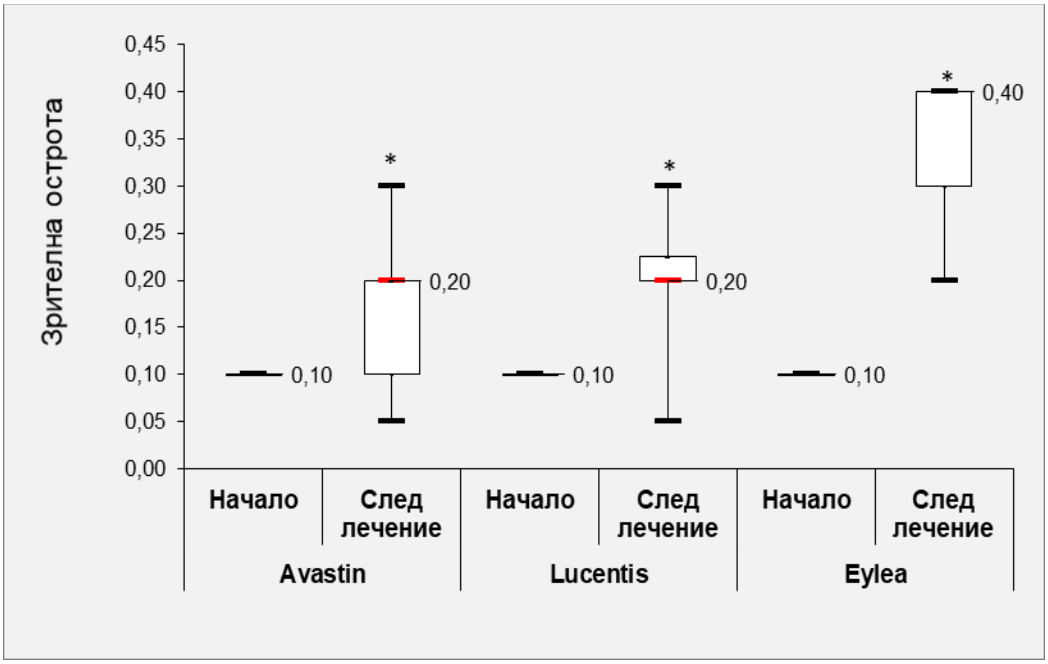

Table 6. The change in the VA is shown on the table, as a number of letters gained in the period of 2 years. It is evident that the increase of the VA is almost the same for Avastin and Lucentis and bigger for the Eylea group.

In our study, especially in patients treated with aflibercept (Eylea), we observed a gradual decline in RPE detachment, which was most pronounced after the first 3 loading doses of intravitreal injections (Fig. 32).

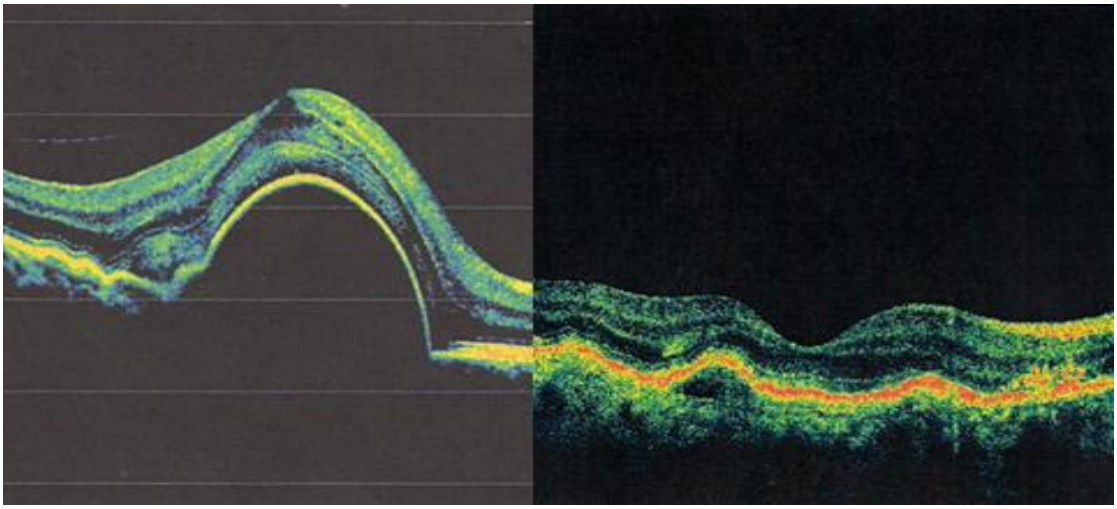

Fig.32 Patient with RPE detachment before and after the application of Eylea.

Comparative analysis between the different treatment drugs.

Kruskal Wallis Test

Показател	Препарат за лечение на МДСВ	N	Mean	Median	SD	Min	Max	p
Начална зрителна острота	Avastin	20	0,10	0,10	0,00	0,10	0,10	n/a
	Lucentis	22	0,10	0,10	0,00	0,10	0,10	
	Eylea	84	0,10	0,10	0,00	0,10	0,10	
Крайна зрителна острота на 2 година	Avastin	20	0,18	0,20	0,07	0,05	0,30	<0,001
	Lucentis	22	0,20	0,20	0,07	0,05	0,30	
	Eylea	84	0,36	0,40	0,06	0,20	0,40	
Брой букви повече	Avastin	20	4,15	5,00	2,62	0,00	7,00	<0,001
	Lucentis	22	4,86	5,50	2,38	0,00	8,00	
	Eylea	84	7,55	8,00	0,68	5,00	8,00	
ретинна дебелина начало	Avastin	20	350,75	345,00	51,11	230,00	450,00	0,003
	Lucentis	22	371,86	363,50	42,90	250,00	450,00	
	Eylea	84	391,70	400,00	43,94	310,00	460,00	
ретинна дебелина след лечение	Avastin	20	248,75	230,00	55,31	200,00	400,00	0,695
	Lucentis	22	242,82	220,00	74,25	120,00	400,00	
	Eylea	84	241,32	230,00	48,04	160,00	350,00	

Table *7. On the table the results for the retinal thickness and VA for the 3 treatment drugs for the period of 2 years. The results are almost the same for the drugs as only for Eylea we have relatively better result s from the other two.*

Statistics show that all three drugs have a statistically significant effect - ie they are effective in the treatment of patients with AMD. It can be seen that for all three preparations $p < 0.001$, ie for all three we have statistical reliability.

The data from the comparative analysis show that the preparations Avastin and Lucentis have almost the same effect in terms of VA and retinal thickness. Both preparations lead to an improvement of VA in the second year to 0.2 or an average of 5 letters.
In the same way, the two preparations lead to an almost identical reduction of the retinal thickness to 230 μm.

Complications of treatment with anti-VEGF drugs.

Complications after anti-VEGF therapy can be divided into two major groups:

- Complications due to the injection itself

- Complications due to the development of AMD.

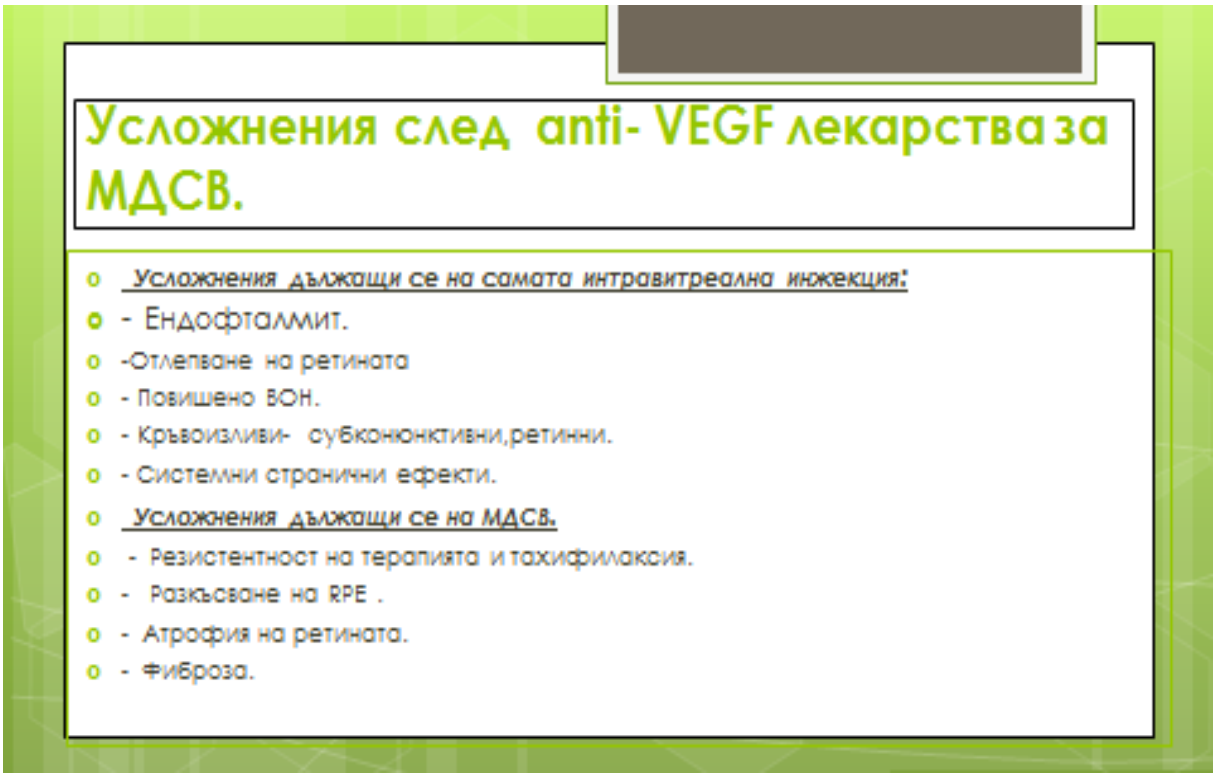

Fig. 33. Types of complications after anti- VEGF therapy.

From the sample we considered, the complications due to the injection of intravitreal drugs – IVM itself was quite low below 7%. Of these, we mainly observed the presence of subconjunctival hemorrhages and elevated IOP. Endophthalmitis occurred in 1 of the patients studied. We did not observe patients with retinal detachment or retinal hemorrhages. Subconjunctival hemorrhages were quite common - in about 10% of all patients treated with intravitreal drugs, and were more common in those who were on anticoagulant therapy. These hemorrhages are usually benign and go away on their own after about 7 days. Very rarely, more severe bleeding is seen caused by some of the larger vessels.

Elevated IOP after intravitreal injection was a common complication that was observed in 30% of injected patients.

The most common increase in pressure was observed in patients suspected of glaucoma or with proven glaucoma and occurred about 30 minutes after injection to the first hour. IOP variations were in the range of 23-26 mm Hg and none of our patients had a pressure above 30 . That is why no therapeutic paracentesis was required. A persistent increase in IOP and the need for anti-glaucoma therapy was observed in 25 of the observed patients.

We did not observe a complication of retinal tearing and detachment in our patients. Such complications are very rare and are due to improper intravitreal injection technique, especially the wrong place of placement and different from the required distance from the limbus. Of greater importance were the complications due to the development of AMD.

The most severe and unpleasant of these was the development of subretinal fibrosis associated with irreversible visual acuity impairment. Unfortunately, this complication was not uncommon and in most cases was associated with the use of stronger anti-VEGF drugs.

DISCUSSION

The dissertation deals with a disease with high social impact - AMD, which is inherently one of the leading causes of blindness worldwide along with glaucoma. Its prevalence is widespread and it is estimated that by 2026 there will be more than 210 million people with AMD. Although widely studied in recent years, this disease still represents unprecedented scientific interest and raises a number of questions, some of which we have tried to give a clear answer. Our research shows that in general the risk factors for AMD can be divided into two major groups - general risk factors and clinically specific ones.

Among the common risk factors, in our opinion, the most important for the appearance and progression of the condition are age, hypertension, poor lipid status and obesity. One thing we can be said, given the epidemiological factors, the patient with the highest risk profile of AMD progression is a patient over 70 years, female, with prolonged

hypertension over 10 years, elevated diastolic pressure and elevated cholesterol and blood lipids .

The presence of the disease in one eye also turns out to be a risk factor for the development of AMD.

Among the risk factors for disease progression are clinical risk factors: the type of degeneration, its stage, and some specific diagnostic signs.

The current understanding of AMD indicates that it is a neurodegenerative disease that selectively affects the macula. The disease is classified as an early form, moderate and advanced form, depending on the severity of symptoms and the size of the drusen, as well as the presence of hyper and hypo pigmentation, the presence or absence of a neovascular membrane. This classification is best described by the Age-Related Eye Disease Study (AREDS) where a 4-point scale is used. Eyes without the presence of AMD are placed in category 1- (AREDS1). Group 2 (AREDS2) included patients with initial changes in AMD with small druses <63 μm (also called 'hard' druses), a single medium-sized druse 63–124 μm, and or retinal pigment changes. Category 3 (AREDS3) includes eyes with a developed form of AMD, with more druses, with at least one larger druse> 124 μm ("soft" druse), multiple medium-sized druses with geographical atrophy, which still does not affect the central macula. Category 4 (AREDS4) are eyes with geographical atrophy of the central macula and or neovascular membrane. Of the clinical risk factors - the most important according to the present paper are the size of the druses and their location.

As in the results of other authors, in our study the combination of large druses over 350 mk and detachment of RPE in 65% of cases was the reason for the development of neovascular membrane and progression to a wet form of the disease.

Our research shows that in the initial forms of AMD, the following are important as high-risk for progression:

- soft druses, with dimensions over 350 mk

- the presence of druse-like detachment of RPE and / or hyperpigmentation.

In summary, we can conclude that from the clinical signs of early AMD soft confluent druses with blurred borders, nodular druses, pigment abnormalities are the main risk factors for the progression of the condition.

In our study, we paid special attention to the study of autofluorescence in the border zone around geographical atrophy, as we believe that this autofluorescence predetermines the progression of the disease. All 134 patients with dry AMD were tested with FAF. Depending on the autofluorescence in the border zone and according to the classification of the FAM study group, we divided them into the following 4 main groups: patients without pathological autofluorescence in the border zone, those with hyper- autofluorescence but only in the border zone (focal, banded, spotted), patients with hyper- autofluorescence in the border area and around it - diffuse type. In our classification, we used the FAM study group classification, but we combined the band and spotted types into one category and added the group of patients without hyperautofluorescence.

Of the 134 patients studied:

- There were 52 without pathological autofluorescence in the border zone.
- With focal autofluorescence - 24
- With linear type AF - 14
- With diffuse AF - 44.

Statistically, this shows that the most common cases are those in which there is no AF or it is of diffuse type. There is much debate as to why hyper-autofluorescence is observed in the boundary zone around geographical atrophy. Some authors believe that this is related to RPE cells, which undergo hyperplasia in this area, that often phagocytose melanin and photoreceptor cell debris and cause increased glow. In our opinion, hyperautofluorescence in the surrounding tissue is associated with the accumulation of lipofuscin in RPE cells around atrophy and is a sign of ongoing dysfunction and damage to these cells. The probable area of future atrophy of RPE cells is shown. Statistical data processing shows that in:

- geographical atrophy without the presence of AF in the border zone - the change in the size of the lesion is 1-2 mm2 for 2 years.

- geographical atrophy with focal AF in the border area - the change in the size of the lesion is -2-3 mm2 for 2 years.

- geographical atrophy with band-type AF in the border area - the change in the size of the lesion is 5 mm2 for 2 years.

- geographical atrophy with diffuse type AF in the border zone - the change in the size of the lesion is 10 mm2 for 2 years.

Depending on the course of the disease and especially the progression or not of the atrophic zone, patients with dry form of AMD and geographical atrophy can be divided into the following groups according to the rate of progression:

- Geographic atrophy with slow rate of progression: In the absence or focal AF in the border zone

- Geographical atrophy with moderate rate of progression: In banded, spotted, linear AF in the border area.

From our studies and the conducted statistical analysis of the data it is clear that the patients with diffuse type AF in the border zone have the highest probability of progression, while the patients with the lowest risk of developing the disease are the patients without AF in the border zone.

In the wet form of AMD FA signs were indicative of progression. We can say that the type of neovascular membrane is a risk factor for progression. Patients with an occult type of neovascular membrane showed a more pronounced progression. Most often the CNV was located under RPE or masked by detached RPE or hemorrhage.

We observed two angiographic types - occult neovascular membrane:

- Type 1 - occult CNV / fibrovascular detachment of RPE.

- Type 2 - occult CNV / with diffuse exudation.

In the second type of occult form, the neovascular membrane is not delineated, rather diffuse leakage of dye and edema is observed , the source of which cannot be well differentiated.

It was in these cases of occult type 2 CNV membrane that we observed an increased progression of the disease. Our studies, as well as those of other authors, show that patients with occult-type neovascular membranes have a 2-fold higher risk of progression than those with classical-type neovascular membranes.

Histopathological examinations of subretinal membranes in patients with occult CNV showed morphological differences between the two types. It turns out that the vessels at 2 CNV are significantly larger in caliber and hence the greater leakage of dye on the FA plates Histopathological examinations of subretinal membranes in patients with occult CNV showed morphological differences between the two types. It turns out that the vessels at 2 CNV are significantly larger in caliber and hence the greater leakage of dye on the FA plates.

In contrast, CNV1 has smaller nue vessels and a highly developed fibrous component, which is the reason why the lesion is not well visible in the photographs, as well as a lower tendency to progression.

The OCT signs of activity and risk of progression in the wet form of AMD are:

- Size of neovascularization
- Type - classical or occult
- Hyperreflectiveness of the lesion.
- Violations of the integrity of the RPE layer / RPE detachment.
– -Presence and degree of retinal edema.

The following are considered as OCT-A biomarkers for lesion activity and marked as risk factors of progression:

- *subclinical neovascular membrane.*
- *a neovascular membrane of the fan or lace type with a plurality of branching capillaries.*
- *presence of large, coarse nue-vessels in the neovascular membrane.*
- *presence of anastomoses between vessels.*
- presence of anastomoses between vessels.
- peripheral arcades and branches at the end of the neovascular membrane.

The presence of a network of many young capillaries, twisting and anastomosing with each other, is a sign of an active membrane.

Discussion of the results of the use of anti-VEGF drugs in patients with wet form of AMD

Of the many drugs on the market, three have been developed solely for use in AMD, namely ranibizumab (Lucentis), aflibercept (Eylea) and brolucizumab (Beovu)

Only bevacizumab (Avastin) was originally intended for the treatment of various cancers, mostly colorectal cancer, but is used in many countries as an off-label preparation for the treatment of AMD. Comparing the patients treated with Lucentis and Avastin, we can say that almost the same results are observed in terms of changes in visual acuity and central retinal thickness, respectively: average improvement in visual acuity in Avastin - 0.2-0.3 (SD 0.3: P <0.001) mean improvement in visual acuity in Lucentis - 0.3-0.4 (SD 0.3: P <0.001). The average improvement of VA is about 4-5 signs. For central retinal thickness measured with OCT, things are similar - the mean change in Avastin-treated patients is 100 mk, while the average change in retinal thickness in Lucentis-treated patients is 150 mk. We can logically conclude that both preparations are equally effective in terms of affecting the VA and central retinal thickness. At the same time, there is a general tendency for both drugs to have a better effect in younger patients and with smaller lesions. We can also note that Avastin is significantly more effective in cases of hemorrhagic activity, as it directly promotes the disintegration of erythrocytes in the retina and vitreous. Our studies fully correlate with the data from the View 1-2 study that Eylea gives comparable, even in some initial forms, slightly better results than other anti-VEGF drugs, and the effect of the drug in RPE detachments is undoubtedly better. This is probably due to its direct protective effect on RPE cells. Therefore, Eylea is the drug of choice in patients with RPE detachment

Discussion of the complications of anti-VEGF therapy

In general, complications after anti-VEGF therapy can be divided into two major groups - complications associated with the administration of intravitreal injection, and complications due to the main retinal disease - AMD.

Complications associated with the manipulation - intravitreal injection, which do not depend so much on the disease and the agent used are:

Complications associated with the manipulation - intravitreal injection, which do not depend so much on the disease and the agent used are:

- Endophthalmitis, iridocyclitis
- Retinal detachment
- Increase of IOP
- Hemorrhages - subconjunctival, retinal
- Systemic side effects of medications.

Complications associated with the main retinal disease - AMD are:

- No response to therapy or lack of effect of a drug.
- Rupture of RPE
- Retinal atrophy
- Fibrosis.

Subretinal fibrosis is a serious complication of intravitreal therapy in AMD, leading to a significant reduction in visual acuity. The main risk factors for the occurrence of this complication are: *low visual acuity, age over 50 years; increased retinal thickness MI> 20; large area of neovascularization and significant leakage of fluorescein from the lesion. The development of subretinal fibrosis is also much more common in patients with myopia, in whom relapses are much more common. Preventing the development of fibrosis is quite difficult to achieve.*

The main thing that should guide us in the treatment with anti-VEGF is the understanding that the duration of VEGF suppression is not a constant value, but depends on the chosen preparation and the individual characteristics of the particular patient.

Longer-acting preparations allow us to administrate at longer intervals, significantly reducing the number of applications in the eye. In most cases, these drugs lead to a longer remission - 3-4 years.

The individualized approach to treatment eliminates the need for follow-up visits, prevents restart of the disease and maintains the achieved good results for a longer time. It is clear that the therapy with anti-VEGF substances is not perfect. It is necessary to improve this therapy, which is related to two main areas:

- complex therapy with blocking of more and different growth factors and proteins besides anti-VEGF.

- prolonging the effect of drugs and reducing the frequency of injections by using new systems for the introduction of drugs into the eye such as long lasting delivery systems, port delivering systems, refilling systems.

At the same time, it is necessary to timely identify the risk factors for complications in order to prevent them.

CONCLUSION

AMD is a complex disease with many factors that determine its development and progression. New and new pathogenetic mechanisms for the development of this condition are still being discovered, new "hidden players" are emerging, supporting the mechanisms of neoangiogenesis. In the treatment of patients with AMD, it is very important to consider the risk factors, both environmental and demographic, as well as to recognize the typical clinical biomarkers that contribute to the progression or stationing of the condition. Knowing the risk factors, some of which are prognostic for the course of the disease, helps us to successfully treat these patients and to include at certain times one or another drug. It is the risk factors - environmental or genetic, that cause the development of inflammation, anatomical changes and dysfunction of photoreceptor cells, with subsequent loss of visual acuity.

Last but not least, working with patients and informing them about the various risk factors and their possible prevention is the strongest mechanism for the prevention of retinal diseases and AMD.

CONCLUSIONS

1. Risk factors for the development and progression of AMD can be divided into general and clinically specific. The most common risk factors are age, the presence of hypertension more than 10 years old, higher diastolic pressure, poor lipid status and obesity (BMI> 20), the presence of the disease in one eye.

2. The clinically specific risk factors responsible for the progression of AMD are

- Size of druses (over 350 mk)
- Presence of hyperpigmented foci at the RPE level
- Diffuse type of hyperautofluorescence around atrophic lesions
- The type and size of the neovascular membrane (membrane - occult type CNV 2 with a size over 3 mm).
- Detachment of RPE (druse-like, serous)
- OCT-A biomarkers (subclinical neovascular membrane, coarse-caliber fan-type non-vessels, vascular anastomoses).

3. Morphological studies have shown that there is a morphological difference between hard and soft druses. It is the different morphological structure that determines the higher reactivity and immunogenicity of the soft druses, which determines the progression of AMD and the activation of immune reactions in the body. Morphological studies show the similarities of the processes in the wet form of AMD and the reparative processes in healing wounds and prove the importance of both the elements of fibrosis and inflammatory cells.

4. The risk factors associated with the progression of atypical forms of AMD-RAP and PCV are different from those of standard forms. They include:

- Presence of a main feeding vessel
- Presence of retino-choroidal anastomoses
- Detachment of RPE
- Reduced thickness of the choroid - thinning of the choroid.

- In PCV, central serous chorioretinitis and elevated levels of C-reactive protein in the blood are of particular importance.

5. The results of the therapy in patients with AMD show that Avastin and Lucentis have a similar effect in terms of VA and retinal thickness. Avastin is more effective in patients with severe haemorrhagic activity.

Eylea, on the other hand, gives better results in terms of VA and is the drug of choice for RPE detachments. The use of the TAE scheme gives a good result, the number of applications is reduced without allowing a restart of the disease.

6. The main thing that should guide us in the treatment of AMD is the understanding that the duration of VEGF suppression is not a constant value, but depends on the chosen drug and the individual characteristics of the particular patient. The individualized approach to treatment of AMD eliminates the need for follow-up visits, prevents restart of the disease and maintains the achieved good results for a longer time
7. Atypical forms of AMD pose a serious therapeutic challenge. Treatment of RAP is difficult and requires a choice of specific drugs (ranibizumab, aflibercept), and more frequent injections . RAP is always associated with an increased risk of serious complications such as rupture of RPE. In the case of PCV, the current combination of PDT and anti-VEGF treatment is positive.

CONTRIBUTIONS OF THE DISSERTATION

1. For the first time in Bulgaria a study of the general and clinical risk and prognostic factors for the development of AMD is performed.The clinical risk factors and their significance for the progression of AMD as the size of the druses (over 350 mk), Diffuse hyperautofluorescence around the atrophic lesions, the type and size of the neovascular membrane, detachment of RPE are presented in detail.

2. For the first time in Bulgaria, the importance of autofluorescence in assessing the condition and likelihood of progression of the dry form of AMD has been shown. A system for assessing the risk of progression depending on the type of autofluorescence in the boundary zone is proposed.

3. The importance of different diagnostic methods in the diagnosis of patients with dry and wet forms of AMD has been thoroughly studied and work protocols have been proposed to facilitate the examination and assessment of the risk of progression in these patients.

4. A detailed ultrastructural and morphological study of the druses and subretinal neovascular membranes was performed, describing in detail the features of these structures and the changes in them under the influence of anti-VEGF drugs, which is of a contributing nature to clarify the pathogenesis of the disease.

5. For the first time in Bulgaria the effect of various anti-VEGF drugs on patients with AMD is studied in detail. A summary of the effectiveness of each of them is made, as well as a comparative analysis of the results.

6. For the first time, the atypical clinical forms of AMD are studied and the clinical features are discussed and combined regimens for the treatment of these conditions are proposed.

7. The possible complications of anti-VEGF therapy and the methods for their prevention are widely discussed.

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AGE RELATED MACULAR DEGENERATION- PROGNOSTIC RISK FACTORS, ULTRASTRUCTURAL CHANGES, DIAGNOSTIC AND TERAPEUTICAL MODALITIES.

Aim:

The aim of the dissertation work is to analyze and evaluate the prognostic risk factors for progression of AMD. To estimate the efficacy of different diagnostic methods and to analyze the results from the treatment of different anti- VEGF drugs.

Material and methods:

We enrolled 274 patients, diagnosed and treated for AMD in MMA for the period from 2008 to 2020 (11 years). From them 154 were men and 130 women. The age range was from 61 to 83, mean age 69, 6 years. The patients were divided as follows:

1. Patients with dry AMD-134.
2. Patients with wet AMD-126.
3. Atypical forms of AMD- 14 patients- 9 with RAP and 5 with PHV.

Results :

Risk factors for AMD progression can be divided into general and clinical specific. From the general risk factors of greater importance are age, hypertension lasting more than 10 years, high level of lipids in the blood, BMI > 20, AMD in the other eye.

The clinical risk factors comprise:

-The size of the drusen

-Hyperautoflurescence in the border zone in the atrophic lesions.

- type and size of neovascular membranes – occult type CNV, size over 3 mm.

- OCT –A biomarkers- subclinical neovascular membranes, rough new vessels.

The results from the anti-VEGF therapy show that Avastin and Lucentis have a similar effect on the VA and CRT. Avastin is more effective in patients with haemorrhagic

activity. Eylea on the other hand showed better results in terms of VA and is a drug of treatment in PDR detachment.

The T&E regiment is the perfect treatment regimen giving the opportunity for individualized treatment.

Knowing the risk factors and prognostic factors is of great importance for better treatment and achievement of good results.

Conclusion:

Knowledge of prognostic risk factors is important in predicting the course of the disease and thus enables us to better treat and prevent AMD.

KEY WORDS: AMD, Prognostic risk factors, anti-VEGF treatment.