A comparison of contrast sensitivity in early mild and early intermediate age-related macular degeneration after adjusting for age and visual acuity

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Background. It has been suggested that contrast sensitivity can provide valuable information about visual function in addition to visual acuity assessment. Some patients retain relatively good visual acuity, yet complain of poor vision. In these patients, other tests of visual function such as contrast sensitivity should be evaluated.

Methods. We examined patients with early mild stage age-related macular degeneration (group 1), and early intermediate stage age-related macular degeneration (group 2). Digital analysis methodology was used for retina drusen localisation and its diameter measurement. Functional acuity contrast sensitivity tests (FACT) were performed using a Ginsburg Box, VSCR-CST-6500.

Results. The nighttime results without glare in group 2 were worse at 1.5, 3, 6 and 18 cycles per degree of the visual angle, the daytime results without glare were worse at 3 and 6 cycles per degree. The nighttime results with glare were worse at 1.5, 3, 6 and 18 cycles per degree, and the daytime results with glare were worse at 1.5 and 3 cycles per degree. Results after adjusting for age and visual acuity to 1.0 in the group 1 patients were better compared to the group 2 patients and the p value was 0.0005.

Conclusions. The test results in patients with early intermediate age-related macular degeneration, in comparison to early mild age-related macular degeneration, showed a significant decrease mostly in the nighttime either with or without glare in high and medium spatial frequencies (cycles/degree). After adjusting for age and visual acuity the FACT results were even worse in early intermediate AMD patients.

Key words: functional acuity contrast sensitivity test, age-related macular degeneration, drusens

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BACKGROUND

Age-related macular degeneration (AMD) affects the macula and is a leading cause of significant and irreversible loss of central visual acuity. AMD is the most common cause of visual loss in persons aged over 60 in developed countries (1). Population estimates have placed the prevalence of AMD approximately from 7 to 10% in adults aged between 40 and 90 years (2–6). More than 30% of adults ≥75 years of age have AMD; in ~6–8% of these individuals, the disease progresses, causing the most severe degree of visual loss (3). The numbers of persons with AMD are expected to double between 2000 and 2030 (4). However, the aetiology of this condition remains unclear and treatment options are limited. AMD is a multifactorial etiology disease, the development of which is determined by environmental risk and genetic factors (7). Risk factors such as age, gender, cigarette smoking, colour of the iris, nutrition, body mass index, oxidative stress, inflammatory process, and genetic factors and their interrelationship may influence the development of age-related macular degeneration. For a detailed visual examination, various functions are tested, such as cognitive perception and the central processing function. Studies have shown that the assessment of visual acuity tested by the typical Snellen chart using the Landolt rings (C optotypes) alone is insufficient for visual function testing, because it provides limited information about the central vision, and it is necessary to determine not only the visual acuity but also the contrast sensitivity (8). Contrast sensitivity is an important measurement of visual function in patients with AMD, and visual acuity together with contrast sensitivity might provide complementary (9) and valuable information about visual function (10–12).

AMD includes early and advanced stages. Early AMD consists of a combination of multiple small drusen and several intermediate (63–124 μm diameter) drusen, or retinal pigment epithelial abnormalities; intermediate AMD is characterized by the presence of extensive intermediate drusen and at least one large giant druse (≥125 μm diameter), or geographic atrophy (GA) not involving the centre of the fovea (13).

So, the aim of this research is to assess the scores of contrast sensitivity in patients with early mild and early intermediate age-related macular degeneration, and also to compare results after adjusting for age and visual acuity to 1.0 in patients with early mild and early intermediate AMD.

MATERIALS AND METHODS

Of the 410 AMD patients who had visited the Department of Ophthalmology at the Lithuanian University of Health Sciences during the period of 2nd January 2009 to 20th December 2012, and agreed to participate in this ophthalmologic study, 109 (217 eyes) patients were enrolled in further analysis according to the subject inclusion and exclusion criteria. Patients were divided into two groups acording to the *Age-Related Eye Disease Study* classification: early mild AMD (group 1), and early intermediate AMD (group 2).

Having obtained Permission No. BE-2-14 from the Kaunas Regional Biomedical Research Ethics Committee, the study was conducted in the Department of Ophthalmology, Lithuanian University of Health Sciences.

The exclusion criteria for subjects were the following: (i) unrelated eye disorders, e. g. high refractive error, cloudy cornea, lens opacity except minor opacities (nuclear, cortical, or posterior subcapsular cataract), keratitis, acute or chronic uveitis, glaucoma, or diseases of the optic nerve; (ii) systemic illnesses, e. g. diabetes mellitus, malignant tumors, systemic connective tissue disorders, chronic infectious diseases, or conditions following organ or tissue transplantation; (iii) ungraded colour fundus photographs resulting from obscuration of the ocular optic system or because of fundus photograph quality; (iv) patients whose functional acuity contrast sensitivity test values were 0.

The inclusion criteria for subjects were as follows: (i) patients aged ≥50 of both genders, diagnosed with early mild or early intermediate AMD in whom no other eye disorders were found on detailed ophthalmologic examination; (ii) the diagnosis confirmed by colour fundus photography; (iii) participation consent.

At each examination intraocular pressure was measured. Pupils were dilated with tropicamide 1%, after which fundoscopy, using a direct monocular ophthalmoscope, and slit-lamp biomicroscopy, using a double aspheric lens of +78 diopters, were performed. Results of eye examinations were recorded on specially standardized forms. The study

subjects were evaluated by slit-lamp biomicroscopy to assess corneal and lenticular transparency. For a detailed evaluation of the macula, stereoscopic colour fundus photographs of the macula, centered at 45° and 30° to the fovea, were obtained.

The classification system of AMD formulated by the *Age-Related Eye Disease Study* (13) was used: *early mild AMD* consisting of a combination of multiple small drusen and several intermediate drusen (63–124 μm diameter), or retinal pigment epithelial abnormalities; *early intermediate AMD* characterized by the presence of extensive intermediate drusen and at least one large giant druse (≥125 μm diameter), or geographic atrophy (GA) not involving the centre of the fovea; and *advanced stage AMD* was characterized by GA involving the fovea and/or any of the features of neovascular AMD (13). Diagnosis of early mild stage AMD was made if confirmed by two ophthalmologists and by one ophthalmological technician, and if no other eye disorders were found during a detailed ophthalmological examination. All patients' fundus photography was also analysed by a genetic opthalmologist, and in some cases genetic research was done to avoid inherited macular dystrophies. Optical coherence tomography(OCT) was performed on all AMD patients, and fluorescence angiography was performed on patients where there was a suspicion of advanced AMD after the OCT examination. Advanced AMD was diagnosed in two patients and these patients were excluded from further study. Five patients were excluded from this study because inherited macular dystrophies were suspected.

DIGITAL ANALYSIS OF RETINAL IMAGES WAS EMPLOYED TO LOCATE DRUSEN IN THE RETINA AND TO MEASURE THEIR DIAMETERS

For retina drusen localization and drusen diameter measurement a digital analysis was used (14). A standard mobile grating comprised of three concentric circles with diameters of 1 000, 3 000 and 6 000 μm was used for measurements. A real drusen diameter was estimated according to the average diameter of the optic nerve disc, and having calculated a coefficient which allowed computing the distances in digital pictures of the ocular fundus in microns (14).

The estimations of the real calculated diameter of the drusen in the digital picture:

– according to the diameter average of the optic nerve disc (1 500 μm), a coefficient k was defined which allowed computing the distances in a digital picture of the ocular fundus in microns:

$k = \phi_\circ / l_\circ$, where $\phi_\circ$ is the known diameter of the optic nerve disc (μm), $l_\circ$ is the diameter of the optic nerve disc computed in the digital photograph and expressed in points;

– the estimated diameter of the drusen in the digital photograph ld, expressed in points;

– the real calculated diameter of the drusen ϕd, (μm):

$\phi d = ld\ k$ (14).

Contrast sensitivity was measured employing a Ginsburg Box, VSCR- CST-6500 with a Functional Acuity Contrast Test chart at photopic (85 cd/m) and mesopic (3 cd/m) luminance with and without glare at five standard spatial frequencies: 1.5; 3; 6; 12; 18 cycles per degree of the visual angle (15). The log of the obtained values was taken to obtain the contrast sensitivity values. A difference level of 0.15 log unit between the test at given spatial frequency was selected to determine clinical significance. Functional acuity contrast sensitivity was performed in the case of the best-corrected visual acuity.

A statistical analysis was performed using the computer program SPSS/W 13.0 (Social Sciences Statistical Package Program for Windows, Inc., Chicago, Illinois, USA). The data are presented as real numbers (per cent), the average values and standard deviations. In order to determine the difference between two independent groups, the Mann–Whitney U criterion was used. The c^2 test was used for comparing frequencies of qualitative variables. A statistically significant difference was considered if $p < 0.05$.

RESULTS

109 (217 eyes) patients were enrolled in further analysis according to the subject inclusion and exclusion criteria. Group 1 consisted of 79 persons, group 2 consisted of 30 persons. 73 females and 36 males were investigated. Group 1 consisted of 30.2% men and 69.8% women. Group 2 consisted of 29.1% men and 70.9% women. The group 1 patients' ages ranged from 35 to 88 years. The group 2 patients' ages ranged from

50 to 93 years. The group 2 patients were statistically significantly older. The results of the study show that the visual acuity in group 1 was significantly higher than that in group 2 (Table 1).

Our results revealed that in patients with early intermediate age-related macular degeneration, in comparison to early mild age-related macular degeneration, the subjects showed a significant decrease in all spatial frequencies, except in 12 cycles per degree of the visual angle, and it decreased from 5.58 to 29.24%. It is very interesting that the nighttime results without glare and with glare in 12 cycles per degree decreased by 23.42 and 29.24%, respectively. The daytime results without glare decreased only in medium spatial frequencies (3 and 6 cycles per degree), and the daytime results with glare decreased at low (1.5 cycles per degree) and at medium (3 cycles per degree) frequencies. The daytime results with and without glare were worse from 2.08 to 9.81% (Table 2).

Table 1. The contingent/factor of the groups 1 and 2 patients

Contingent/factor	Group 1 patients, n = 79 (158 eyes) (early AMD)	Group 2 patients, n = 30 (59 eyes) (intermediate AMD)	p value
Males, n (%)	24 (30.2)	9 (29.1)	DSI
Females, n (%)	55 (69.8)	21 (70.9)	DSI
Age ± SD	62.85 ± 11.88	72.15 ± 9.93	0.047
Non-corrected visual acuity ± SD	0.53 ± 0.35	0.39 ± 0.32	0.014
Best-corrected visual acuity ± SD	0.82 ± 0.26	0.64 ± 0.31	0.0005

SD is standard deviation; DSI is difference statistically insignificant; p value is significance level.

Table 2. The results of functional acuity contrast sensitivity test (FACT) in groups 1 and 2 and the comparison of the results between groups 1 and 2 in time/per cent

Spatial frequencies	AMD form	FACT results mean ± SD (minimum/maximum)	Decrease between groups in per cent	P value
		Functional acuity contrast sensitivity at mesopic luminance without glare		
A (1.5)	Group 1	3.61 ± 0.65 (1.10–4.61) *3.71 ± 0.92 (0.76–5.52)	11.92 *19.41	0.005 *0.005
	Group 2	3.18 ± 0.48 (2.12–4.26) *2.99 ± 1.22 (0.95–5.88)		
B (3)	Group 1	3.78 ± 0.69 (1.90–5.08) *4.62 ± 1.23 (1.58–5.41)	10.85 *25.11	0.005 *0.005
	Group 2	3.37 ± 0.56 (2.30–4.74) *3.46 ± 0.59 (1.21–4.94)		
C (6)	Group 1	3.41 ± 0.78 (1.39–4.86) *3.45 ± 1.38 (1.22–4.58)	11.74 *27.83	0.015 *0.005
	Group 2	3.01 ± 0.84 (1.39–4.23) *2.49 ± 1.77 (0.89–3.85)		
D (12)	Group 1	2.69 ± 2.69 (0.99–3.76) *1.91 ± 0.65 (0.52–2.75)	5.58 *20.95	0.849 *0.004
	Group 2	2.54 ± 0.63 (2.08–3.76) *1.51 ± 0.62 (0.34–1.56)		
D (18)	Group 1	1.58 ± 0.53 (0.26–2.08) *1.24 ± 0.29 (0.19–1.49)	23.42 *23.39	0.010 *0.005
	Group 2	1.21 ± 0.73 (0.26–2.06) *0.95 ± 0.17 (0.12–1.13)		

Table 2 (continued)

		Functional acuity contrast sensitivity at photopic luminance without glare		
A (1.5)	Group 1	3.61 ± 0.54 (1.95–4.61) *3.69 ± 0.84 (2.19–4.85)	9.7 *22.49	0.95 *0.005
	Group 2	3.26 ± 0.45 (2.20–3.91) *2.86 ± 0.26 (2.08–2.6)		
B (3)	Group 1	3.83 ± 0.68 (1.90–5.08) *4.14 ± 0.28 (2.58–5.49)	7.83 *9.96	0.002 *0.005
	Group 2	3.53 ± 0.58 (1.90–4.38) *3.73 ± 0.71 (2.39–4.49)		
C (6)	Group 1	3.82 ± 0.71 (1.39–5.19) *4.39 ± 0.44 (1.32–4.94)	6.28 *20.05	0.003 *0.005
	Group 2	3.58 ± 0.57 (2.08–4.50) *3.51 ± 0.89 (1.79–4.41)		
D (12)	Group 1	2.91 ± 0.55 (0.99–3.88) *1.96 ± 0.79 (0.59–2.75)	6.87 *28.78	0.49 *0.005
	Group 2	2.71 ± 0.55 (1.61–3.76) *1.41 ± 0.89 (0.39–1.85)		
D (18)	Group 1	1.99 ± 0.67 (0.26–3.04) *1.72 ± 0.39 (0.21–2.82)	5.03 *16.86	0.61 *0.005
	Group 2	1.89 ± 0.79 (0.26–2.83) *1.43 ± 0.46 (0.19–2.41)		
		Functional acuity contrast sensitivity at mesopic luminance with glare		
A (1.5)	Group 1	3.61 ± 0.64 (0.93–4.61) *3.51 ± 0.81 (0.85–4.38)	12.75 *12.25	0.0005 *0.005
	Group 2	3.15 ± 0.57 (1.95–4.61) *3.08 ± 0.42 (1.78–4.39)		
B (3)	Group 1	3.68 ± 0.66 (1.61–5.08) *3.71 ± 0.73 (1.76–5.14)	7.07 *8.09	0.002 *0.005
	Group 2	3.42 ± 0.51 (2.30–4.38) *3,41 ± 0.65 (2.27–4.36)		
C (6)	Group 1	3.44 ± 0.74 (1.39–5.09) *3.04 ± 0.92 (1.19–4.59)	9.04 *28.62	0.007 *0.005
	Group 2	3.12 ± 0.53 (2.30–4.16) *2.17 ± 0.51 (2.49–4.18)		
D (12)	Group 1	2.64 ± 0.45 (2.08–3.66) *1.76 ± 0.7 (0.68–2.86)	9.09 *21.59	0.66 *0.003
	Group 2	2.40 ± 0.38 (1.67–2.71) *1.38 ± 0.45 (0.43–2.38)		
D (18)	Group 1	1.95 ± 0.60 (0.69–2.62) *1.20 ± 0.89 (0.34–2.21)	29.24 *15	0.034 *0.002
	Group 2	1.38 ± 0 (1.39–1.39) *1.12 ± 0.4 (0.21–1.91)		
		Functional acuity contrast sensitivity at photopic luminance with glare		
A (1.5)	Group 1	3.67 ± 0.51 (1.95–4.69) *3.92 ± 0.81 (2.19–4.85)	9.81 *15.05	0.005 *0.003
	Group 2	3.31 ± 0.46 (1.95–4.26) *3.33 ± 0.52 (1.98–4.32)		

Table 2 (continued)

B (3)	Group 1	3.97 ± 0.53 (2.30–5.08) *4.48 ± 0.52 (3.12–5.41)	7.56 *10.05	0.0014 *0.005
	Group 2	3.67 ± 0.71 (1.19–4.43) *4.36 ± 0.81 (1.94–4.7)		
C (6)	Group 1	3.84 ± 0.70 (1.39–5.19) *4.11 ± 0.54 (1.79–5.32)	2.08 *25.55	0.119 *0.005
	Group 2	3.76 ± 0.45 (2.71–4.50) *3.96 ± 0.21 (1.41–5.2)		
D (12)	Group 1	3.13 ± 0.54 (1.61–4.09) *2.88 ± 0.57 (1.53–3.93)	4.79 *25.69	0.112 *0.005
	Group 2	2.98 ± 0.50 (2.08–4.09) *2.14 ± 0.67 (1.48–3.56)		
D (18)	Group 1	2.17 ± 0.53 (0.99–3.50) *1.79 ± 0.47 (0.69–2.48)	6.45 *14.44	0.192 *0.001
	Group 2	2.03 ± 0.60 (0.99–2.83) *1.51 ± 0.54 (0.45–2.31)		

* Age and visual acuity adjusted.

The results after adjusting for age and visual acuity to 1.0 in the group 1 patients were better compared to those of the results of group 2 and the *p* value was 0.0005 as shown in Table 2. The nighttime results without and with glare were worse in all spatial frequencies, and decreased from 8.09 to 28.62%, and the daytime results without glare and with glare were worse from 9.96 to 28.78%.

DISCUSSION

There are no studies comparing functional acuity contrast sensitivity changes in these two early AMD forms. Our results revealed that in patients with early intermediate age-related macular degeneration, in comparison to early mild age-related macular degeneration, subjects' nighttime results without and with glare showed a significant decrease in all spatial frequencies, except in 12 cycles per degree of the visual angle, and it decreased from 5.58 to 29.24%, respectively. The daytime results with and without glare were worse from 2.08 to 9.81%. It appears that contrast sensitivity is the best test for quantifying early changes in the visual function, because our results show that this test can detect even slight changes of visual system performance, and visual functions are mostly impaired at nighttime with and without glare. The results after adjusting for age and visual acuity to 1.0 in the group 1 patients were better compared to those of the group 2

patients and the *p* value was 0.0005 as shown in Table 2. The nighttime results without and with glare were worse in all spatial frequencies, which means when we are trying to avoid the visual acuity role in FACT decreasing, it can be seen that the results are worse because of early intermediate AMD compared to early mild AMD.

There are not many studies analyzing FACT results, changes in age-related macular degeneration especially in its early stages separately, and results analyzing contrast sensitivity in AMD patients are inconsistent. Some authors have suggested that functional acuity contrast sensitivity is diminished (lower) in high spatial frequencies in AMD patients (16, 17), while the others having detected such changes in both medium and high spatial frequencies (18, 19), as we found in our study of patients with early intermediate AMD. Segato et al. reported that functional contrast sensitivity is lower in all spatial frequencies in patients with early age-related macular degeneration (20). In a study by Žaliūnienė et al. it was assessed that contrast sensitivity at mesopic luminance or at photopic luminance in patients aged 60 years and older with an early mild and early intermediate AMD with or without glare was found to be more dependent on cataracts as opposed to AMD. As Žaliūnienė reported, the results of functional acuity contrast sensitivity testing were found to be better in AMD patients compared to those who were diagnosed with

cataracts or with both cataracts and AMD (21, 22). Žaliūnienė et al. results showed that following surgical treatment contrast sensitivity at photopic and mesopic luminance with or without glare improved in cataract patients and in patients with both cataracts and AMD (21). However, contrast sensitivity remained minimal in patients diagnosed with both illnesses. This could be explained by the higher influence of cataracts on the decrease in contrast sensitivity in comparison to the decrease in the visual acuity (21). To check this hypothesis it was decided to compare these two groups with early mild AMD patients with normal visual acuity, but the results were even worse in patients with early intermediate AMD.

It should be noted that the prognostic value of visual acuity is better in AMD patients whose contrast sensitivity is less affected or intact in comparison to other patients whose contrast sensitivity is worse (23). Moreover, for AMD patients treatments with vascular endothelial growth factor inhibitors, as well as both photodynamic therapy and laser photocoagulation were found to be more effective only if contrast sensitivity is less affected (24). It should also be noted that early diagnosis of AMD can help prevent blindness in the future and functional acuity contrast sensitivity might be useful for early detection of the age-related macular progress in the absence of clinical changes in fundus when compared to previous fundus photography. Haegerstrom-Portnoy's results demonstrate that low contrast vision functions can successfully predict subsequent loss of high contrast visual acuity (25).

The facts are that contrast sensitivity is affected more in patients with early intermediate age-related macular degeneration, especially at mesopic luminance with and without glare, but the main limitation of this study was a relatively small sample size. In group 2, especially when adjusted for age and visual acuity, it was very difficult to find persons with early intermediate AMD and visual acuity 100%. These results need to be confirmed in a large-scale cohort study involving patients with early mild and early intermediate AMD.

CONCLUSIONS

The test results in patients with early intermediate age-related macular degeneration, in comparison to early mild age-related macular degeneration,

showed a significant decrease mostly in the night-time results either with or without glare in high and medium spatial frequencies (cycles per degree), after adjusting age and visual acuity. The FACT results were even worse in early intermediate AMD patients.

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**FUNKCINIO KONTRASTINIO JAUTRUMO
PALYGINIMAS TARP PACIENTŲ, SERGANČIŲ
PRADINE LENGVA IR PRADINE VIDUTINE
AMŽINE GELTONOSIOS DĖMĖS
DEGENERACIJA, SUVIENODINUS GRUPES
PAGAL AMŽIŲ IR REGĖJIMO AŠTRUMĄ**

Santrauka

Įvadas. Kontrastinis jautrumas gali suteikti vertingos informacijos apie regėjimo funkciją kaip papildomas tyrimas po regos aštrumo įvertinimo. Kai kurie pacientai, pasižymintys geru regėjimo aštrumu, skundžiasi prastu regėjimu. Tokiems pacientams turėtų būti tiriamos ir kitos regėjimo funkcijos, pavyzdžiui, funkcinis kontrastinis jautrumas.

Metodika. Ištyrėme pacientus, sergančius pradine lengva amžine geltonosios dėmės degeneracija (I grupė), ir pacientus, sergančius pradine vidutine amžine geltonosios dėmės degeneracija (II grupė).

Drūzų lokalizacija ir drūzų skersmuo buvo nustatyti taikant tinklainės drūzų lokalizacijos, jų skersmens matavimo bei šių vaizdų skaitmeninės analizės metodiką. Funkcinis kontrastinis jautrumas tirtas pagal Arthuro P. Ginsburgo metodiką OPTEC 65VSCR-CST-6500 aparatu.

Rezultatai. II grupės pacientų rezultatai buvo blogesni nakties metu be akinančios šviesos esant 1,5; 3; 6; 18 erdviniams dažniams ir dienos metu be akinančios šviesos esant 3 ir 6 erdviniams dažniams. Nakties sąlygomis rezultatai buvo blogesni su akinančia šviesa esant 1,5; 3; 6 ir 18 erdviniams dažniams ir dienos sąlygomis su akinančia šviesa esant 1,5 ir 3 erdviniams dažniams. Atrinkus pacientus pagal amžių ir regos aštrumą – $p = 1,0$; I grupės rezultatai buvo geresni už II grupės rezultatus ($p = 0,0005$).

Išvada. Rezultatai rodo, kad pacientų, sergančių pradine lengva amžine geltonosios dėmės degeneracija, palyginti su pacientais, sergančiais pradine vidutine amžine geltonosios dėmės degeneracija, funkcinio kontrastinio jautrumo rezultatai statistiškai reikšmingai sumažėjo labiausiai nakties metu su akinančia šviesa ir be akinančios šviesos esant aukštiems ir vidutiniams erdviniams dažniams (ciklai / laipsnis). Suvienodinus grupes pagal amžių ir regėjimo aštrumą, funkcinio kontrastinio jautrumo rezultatai vis tiek buvo blogesni sergant pradine vidutine amžine geltonosios dėmės degeneracija.

Raktažodžiai: funkcinio kontrastinio jautrumo tyrimas, amžinė geltonosios dėmės degeneracija, drūzos