• Clinical Research •

The vitreomacular interface in different types of age-related macular degeneration

Mohamed Abd ElMonaem El-Hifnawy, Hisham Ali Ibrahim, Amir Ramadan Gomaa, Mohamed A Elmasry

Ophthalmology Department, Alexandria University Faculty of Medicine, Khartoum Square, Azarita, Alexandria 21526, Egypt
Correspondence to: Mohamed A Elmasry. Infront of 27 Maarouf Rasafi Street, Kafr Abdou, Roshdi, Alexandria 21500, Egypt. Moah384@gmail.com
Received: 2016-02-26 Accepted: 2016-06-29

Abstract

• AIM: To evaluate the vitreomacular interface in cases with wet age-related macular degeneration (AMD) and to compare them to eyes with dry AMD and normal eyes.

• METHODS: This was a cross-sectional comparative study that included 87 eyes with wet AMD, 42 eyes with dry AMD and 40 eyes without AMD as a control group. Optical coherence tomography (OCT) examination was performed for all patients to assess the vitreomacular interface.

• RESULTS: In the wet AMD group, 34.5% of cases had vitreomacular adhesion (VMA). Only 14.3% of dry AMD cases and 10% of control cases had VMA. There was a significant difference between the control group and the wet AMD group (*P*=0.004) as well as the dry and wet AMD group (*P*=0.017). There was also a significant difference between the incidence of VMA in patients with subretinal choroidal neovascularization (CNV, type 1) and intraretinal CNV (type 2 or type 3) (*P*=0.020).

• CONCLUSION: There is an association between posterior vitreous attachment and AMD. There is also an increased incidence of VMA with intra-retinal CNV.

• KEYWORDS: age-related macular degeneration; vitreomacular interface; optical coherence tomography; macula

DOI:10.18240/ijo.2017.02.11

El-Hifnawy MA, Ibrahim HA, Gomaa AR, Elmasry MA. The vitreomacular interface in different types of age-related macular degeneration. *Int J Ophthalmol* 2017;10(2):246-253

INTRODUCTION

Age-related macular degeneration (AMD) is a major cause of legal blindness in developed countries[1]. Genetic factors, ageing, ischemia and environmental factors are considered the main important etiological factors of AMD[2]. Despite intensive basic and clinical research, the pathogenesis and risk factors for AMD are incompletely characterized[3].

Recent studies have shown, using optical coherence tomography (OCT), that central attachment of the posterior hyaloid membrane to the retina, that is, the vitreomacular adhesion (VMA), is more frequently observed in exudative AMD than in control eyes[4-5], supporting the idea that there may be an association between VMA and exudative AMD. Different hypothesis have been formulated to explain the role of VMA in AMD, focusing on both mechanical and biochemical factors underlying the observed phenomenon[6]. Yet whether VMA is associated with an increased rate of progression to advanced AMD or a secondary phenomenon to the actual choroidal neovascularization (CNV) has yet to be determined.

There have been no reports that investigate the state of the vitreomacular interface in different subtypes of CNV. In addition, there have been limited studies that have studied this relationship in dry AMD and its different presentations[7]. The current study was conducted to determine the association of the posterior vitreous face and exudative AMD, focusing especially on the various CNV subtypes. The study also aimed at limiting confounding factors by excluding diabetics, pseudophakics and patients with previous intravitreal injections.

SUBJECTS AND METHODS

This study is a prospective non-interventional cross-sectional comparative study that was conducted at Main University Hospital, Alexandria, Egypt. The study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board. All study participants gave informed consent before enrollment.

The subjects consisted of consecutive patients who visited the Outpatient Retina Clinic at Alexandria Main University Hospital, Alexandria, Egypt between June 2012 and December 2014.

Eligibility criteria were: 1) age >50 years of age; 2) exudative and dry AMD proven by clinical examination, OCT examination and fluorescein angiography (FA); 3) control groups included a group of age-matched volunteers with no ocular pathology. Exclusion criteria were: 1) intraocular surgery including cataract surgery, IV injection or naïve lasers in the last 6mo; 2) diabetes mellitus; 3) myopia more than -6 D and hyperopia more than +6 D; 4) presence of active uveitis.

Patients with AMD underwent FA exam and fundus color photographs. OCT examination was done through a dilated pupil using commercially available Spectralis OCT Heidelberg engineering, Germany. A 5 Line Raster protocol was used in all patients. Additionally if the vitreomacular interface was not clearly visualized an additional macular cube 512×128 protocol was used. In all patients a 30 degree long scan was performed horizontally to cut through the macula all the way to the optic disc to help differentiate complete posterior vitreous detachment (PVD) from partial PVD.

The type of AMD was classified into dry and wet AMD. Wet AMD was classified primarily based on OCT criteria using a modification of the classification first proposed by Gass[8] and then by Freund *et al*[9]. The previous classification described three distinct types of CNV; type 1 where the CNV is mainly sub-retinal pigment epithelium (RPE), type 2 where the CNV is above the RPE in the subretinal space and type 3 which describes intraretinal neovascularization or retinal angiomatous proliferation (RAP). We used a slight modification to the Freund classification to categorize our cases into sub-retinal choroidal neovascularization (SR-CNV) and intraretinal choroidal neovascularization (IR-CNV). Sub-retinal type is associated mainly with subretinal fluid and very rarely intr-aretinal fluid and conforms to type 1 CNV categorized by Freund *et al*[9]. The intraretinal type describes a CNV that disrupts the RPE or any case where there is no clear delineation between the CNV and inner retina. It is more frequently associated with intraretinal fluid and incorporates both type 2 and type 3 CNV. The lesions were also classified according to the presence or absence of any fluid activity into active or inactive based on a combined analysis of their OCTs and FA. The reason for the modified criteria is our inability to perform indocyanine green angiography (ICGA) early in the course of the study to diagnose type 3 CNV and any possible diagnosis based on FA and OCT criteria would probably be inaccurate. For mixed lesions, the CNV was classified based on the predominant CNV subtype. The vitreomacular interface was classified into vitreomacular traction (VMT), VMA and no VMA based on the VMT study group classification[10]. An illustration of the different CNV subtypes and vitreomacular interfaces can be seen in Figure 1.

Statistical Analysis Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. Qualitative data were described using number and percent. Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Comparison between different groups regarding categorical variables was tested using Chi-square test. When more than 20% of the cells have expected count less than 5, correction for Chi-square was conducted using Monte Carlo correction. The distributions of quantitative variables were tested for normality. If it reveals normal data distribution, parametric tests was applied. If the data were abnormally distributed, non-parametric tests were used. For normally distributed data, comparison between more than two populations were analyzed with the *F*-test (ANOVA). For abnormally distributed data, Kruskal-Wallis test was used to compare between different groups and pair wise comparison was assessed using Mann-Whitney *U* test. Significance of the obtained results was judged at the 5% level.

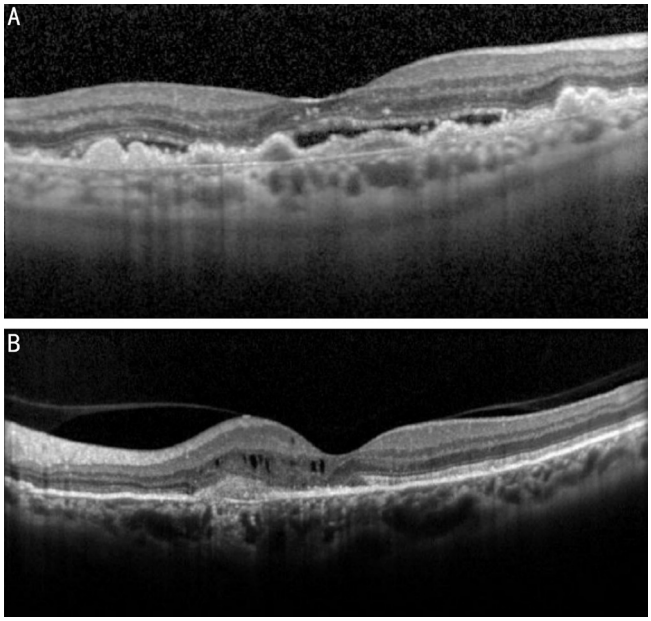

Figure 1 Figure illustrating the vitreomacular interface in different types of wet AMD A: Type 1 CNV with subretinal fluid and no VMA, probably a PVD; B: Type 2 CNV with intraretinal fluid with VMA.

RESULTS

Demographic and Clinical Data A total of 169 eyes were included in this study. The study included 42 eyes with dry AMD, 87 eyes with wet AMD and 40 control eyes. Table 1 summarizes the demographic data for the different groups. There was no significant difference in age and sex between all three groups. Similarly there was no significant difference between the 3 groups with respect to intraocular pressure (IOP) and spherical equivalent. However, the visual acuity was significantly worse in the wet AMD group (1.3 logMAR) compared to the dry AMD group (0.4 logMAR) and to the control group (0.1 logMAR) (Tables 1, 2).

Both the wet AMD group and the dry AMD group were categorized based on their characteristics. In the wet AMD group (Table 3) 68 cases were active whereas 19 cases did not show any signs of fluid activity whether by FA or by OCT. In addition there were 44 cases with subretinal CNV and 43 cases with intraretinal CNV. In eyes classified as having dry AMD 30 patients had drusen and/or pigmentary abnormalities and 12 patients had geographic atrophy.

Vitreomacular Interface The vitreomacular interface was studied in the different groups as illustrated in Tables 4, 5. The

Table 1 Comparison between the studied groups according to demographic data *n* (%)

Parameters	Control (*n*=40)	Dry AMD (*n*=42)	Wet AMD (*n*=87)	Test of significance	*P*
Sex				χ^2=1.444	
M	27 (67.5)	31 (73.8)	55 (63.2)		0.486
F	13 (32.5)	11 (26.2)	32 (36.8)		
Age					
Min-max	51.0-78.0	50.0-82.0	50.0-74.0		
$\bar{x} \pm s$	61.53±6.63	63.98±9.82	63.52±5.37	*F*=1.487	0.229
Median	60.0	64.0	65.0		

χ^2: Chi-square test; *F*: *F*-test (ANOVA).

Table 2 Comparison between the studied groups according to different clinical parameters

Clinical parameters	Control (*n*=40)	Dry AMD (*n*=35)	Wet AMD (*n*=87)	Test of significance	*P*
Intraocular pressure					
Min-max	9.0-22.0	10.0-19.0	10.0-19.0		
$\bar{x} \pm s$	14.40±3.87	13.54±2.06	13.67±2.07	*F*=1.283	0.280
Median	14.0	13.0	14.0		
Spherical equivalent					
Min-max	-2.0 to +5.0	-3.0 to +4.0	-4.25 to +4.0		
$\bar{x} \pm s$	0.84±1.67	0.74±1.87	0.66±1.71	$^{KW}\chi^2$=0.153	0.927
Median	0.75	1.0	1.0		
Visual acuity					
$\bar{x} \pm s$	0.11±0.07	0.61±0.54	1.31±0.65	$^{KW}\chi^2$=101.028[a]	<0.001[a]
Median	0.10	0.40	1.30		
		P_1<0.001[a], P_2<0.001[a], P_3<0.001[a]			

[a]Statistically significant at $P<0.05$; P_1: *P* value for Mann-Whitney *U* test for comparison between control and dry AMD group; P_2: *P* value for Mann-Whitney *U* test for comparison between control and wet AMD group; P_3: *P* value for Mann-Whitney *U* test for comparison between dry AMD and wet AMD group. $^{KW}\chi^2$: Chi-square for Kruskal-Wallis test; *F*: *F*-test (ANOVA).

Table 3 Distribution of the studied cases according to wet AMD characteristics in wet AMD group *n*=87

Parameters	*n*	%
CNV activity (OCT&FA)		
Active	68	78.2
Not active	19	21.8
CNV type (OCT)		
Subretinal CNV (type 1)	44	50.6
Intraretinal CNV (types 2 and 3)	43	49.4

OCT: Optical coherence tomography; FA: Fluorescein angiography; CNV: Choroidal neovascularization.

incidence of VMA was higher in cases of wet AMD (34.5%) compared to cases with dry AMD (14.3%) and control cases (10%). There was a statistically significant difference between the wet AMD group and the control group (RR 5.80; 95%CI, 2.245-14.983; *P*=0.000). In addition there was a statistically significant difference between the wet AMD group and the dry AMD group (*P*=0.017). However no difference was found between the control and dry AMD groups (RR 1.200; 95%CI, 0.366-3.932, *P*=0.763).

Table 6 shows the relation between VMA and different wet AMD characteristics. No differences were seen between the active and non-active CNV groups. There was a statistically significant difference in the prevalence of VMA in cases with intraretinal CNV (66.7%) compared to cases with subretinal CNV (33.3%).

DISCUSSION

Vitreous changes that occur with aging have been previously described by Sebag[11-12]. PVD occurs due to age related vitreous liquefaction and weakening of the peripheral vitreoretinal adhesions so that by the eight decade 63% of patients have a demonstrable PVD[13]. Several large population based studies have verified the role of cigarette smoking, genetics, age and diet in the development of AMD. In addition the age-related eye disease study (AREDS) study demonstrated that unilateral large drusen, multiple bilateral intermediate drusen or a CNV in the contralateral eye are all risk factors for the development of severe or advanced AMD[14-17]. However, differences in phenotype and grading of AMD in both eyes cannot be explained by environmental and genetic factors alone. A paired eye study showed that 24.4% of patients had wet AMD in only one eye and no signs of AMD or wet AMD in the fellow eye [18]. Additional ocular conditions, including the position of the posterior vitreous cortex, may be responsible for this difference, besides time-related differences in disease onset.

Table 4 Comparison between the studied groups according to VMA *n* (%)

Parameters	Control (*n*=40)	Dry AMD (*n*=42)	Wet AMD (*n*=87)	χ^2	*P*
VMA or no VMA					
VMA	4 (10.0)	6 (14.3)	30 (34.5)	11.815[a]	0.003[a]
No VMA	36 (90.0)	36 (85.7)	57 (65.5)		
Sig. bet. Grps	$^{FE}P_1$=0.738, $^{\chi2}P_2$=0.004[a], $^{\chi2}P_3$=0.017[a]				

VMA: Vitreomacular adhesion; AMD: Age-related macular degeneration; χ^2: Chi-square test; FE: Fisher exact test; P_1: *P* value for comparing between control and dry AMD group; P_2: *P* value for comparing between control and wet AMD group; P_3: *P* value for comparing between dry AMD and wet AMD group. [a]Statistically significant at $P<0.05$.

Table 5 Analysis of complete posterior vitreous detachment and VMA in wet and dry AMD

Vitreomacular interface	Variable	Risk ratio	95%CI		*P*
			Lower bound	Upper bound	
VMA	Dry AMD	1.200	0.366	3.932	0.763
	Wet AMD	5.800	2.245	14.983	<0.001[a]
	Control	1			Reference
No VMA	Dry AMD	1.029	0.646	1.638	0.906
	Wet AMD	1.657	1.089	2.521	0.018[a]
	Control	1			Reference

VMA: Vitreomacular adhesion; AMD: Age-related macular degeneration. [a]Statistically significant at $P<0.05$.

Table 6 Relation between VMA and wet AMD characteristics *n* (%)

CNV activity	VMA (*n*=30)	No VMA (*n*=57)	χ^2	*P*
CNV activity (OCT&FA)				
Active	23 (76.7)	45 (78.9)	0.060	0.807
Not active	7 (23.3)	12 (21.1)		
CNV type (OCT)				
Subretinal (type 1)	10 (33.3)	34 (59.6)	5.445[a]	0.020[a]
Intraretinal (types 2 and 3)	20 (66.7)	23 (40.0)		

VMA: Vitreomacular adhesion; AMD: Age-related macular degeneration; OCT: Optical coherence tomography; FA: Fluorescein angiography; χ^2: Chi-square test; FE: Fisher exact test; [a]Statistically significant at $P<0.05$.

In our study we categorized patients into three groups; normal eyes, eyes with wet AMD and eyes with dry AMD. The percentage of VMA in the control group was 10%, 14.3% in the dry AMD group and 34.5% percent in the wet AMD group. The percentage of VMA in cases of exudative AMD was significantly higher than in cases of dry AMD and the control group. These results are similar to other studies that measured the association between VMA and AMD. Six studies of AMD detailed the prevalence of VMA[4,7,18-21]. A summary of the different studies and their comparison to the present study can be found in Table 7. These studies specifically studied the interaction between the vitreomacular interface and AMD and usually included a control group, such as the unaffected fellow eye or eyes with dry AMD. A Meta-analysis that grouped these studies together showed that the overall prevalence of VMA in patients with wet AMD was 22.6% (*n*=654), 9.5% (*n*=327) in dry AMD, and 7.7% (*n*=261) in unaffected control eyes. The rate of VMA was higher than controls in each of these reports[22]. The study also showed that eyes with wet AMD were 2.15 times more likely to have VMA than controls (95% CI, 1.34-3.48; *P*=0.002). In addition compared to the dry AMD group they were 2.54 times more likely to have VMA, but this difference was not significant (95%CI, 0.88-7.36; *P*=0.09).

Our study also showed no relationship between VMA and dry AMD. When compared to the control group the incidence of VMA was the same. A subgroup analysis of early dry AMD (drusen) and more advanced AMD (geographic atrophy) failed to show any significant difference between them in terms of VMA. There were two previous controlled studies that studied VMA in cases of dry AMD: one showed an increased prevalence of VMA[21] and the other a reduced prevalence[4]. A Meta-analysis[22] of both studies combined showed that the likelihood of having VMA was 1.23 times that of controls, but this difference was not statistically significant (95% CI, 0.74-2.36; *P*=0.53).

The OCT findings in our study showed that a localized vitreous adhesion is associated with a high incidence of CNV. A subgroup analysis of our cases showed a significantly higher percentage of VMA with cases having intraretinal CNV as opposed to subretinal CNV. The intraretinal CNV also had a significantly worse VA. The paper by Mojana *et al*[21] had previously shown a higher incidence of VMA in cases with

Table 7 Summary of previous studies looking at the vitreomacular interface in cases of wet AMD

Study	Study design	Patients	Demographics	Vitreomacular interface	Other
Krebs *et al*[4], 2007	Prospective observational case series	163 eyes from 82 subjects (50 eyes with exudative AMD, 57 with nonexudative AMD and 56 control eyes)	Mean age was 74y (range 55-89y)	Partial PVD seen on OCT was present in 36% of eyes with exudative AMD compared with 7% of eyes with nonexudative AMD (P<0.001) and 11% of control eyes (P=0.002)	The location of the persistent adhesion was always in the foveal region non-exudative and control eyes. In the exudative AMD group it was in the fovea in 15/50 eyes, all of them with subfoveal CNV
Mojana *et al*[21], 2008	Retrospective, observational, case-control, interventional case series	170 eyes of 94 patients (61 with exudative AMD, 59 with non exudative and 50 control eyes)	Average age 79 for patients with exudative, 75 for patients with non exudative AMD and 72 in the control group	Hyaloid adhesion was present in 27.8% of patients with exudative AMD, 25.4% of patients with non exudative AMD and 16% of control eyes	Both exudative and nonexudative AMD were significantly more likely to have VMA (OR 6.3 exudative *vs* control and 3.2 (P=0.0012) for nonexudative *vs* control (P=0.014) Minimally classic lesion showed higher incidence of VMA than classic lesions (OR 7.7; P=0.0077) and occult (OR 7.0; P=0.0327)
Robison *et al*[20], 2009	Retrospective observational case series	29 treatment naïve patients with active (wet AMD) in one eye and active nonexudative (dry) AMD who were compared to 10 previously untreated patients with end stage geographic atrophy in one eye and end stage fibrotic disciform scar in the other eye.	Subjects with active AMD, the mean age was 79.4 Group with end stage AMD, the mean age was 85.1	PVD in eyes with nonexudative AMD was 20 (69%) of 29, compared with 6 (21%) of 29 with active exudative AMD VMA was present in 38% of eyes with exudative AMD and 10% of eyes with nonexudative AMD (P=0.08)	Pseudophakia was present in 52% of eyes with active exudative AMD No significant difference between presence and absence of VMA in eyes with disciform scar and geographic atrophy
Lee *et al*[18], 2009	Retrospective observational case series Paired eye study	502 eyes from 251 consecutive patients with wet AMD in one eye and the fellow eyes had dry AMD in 182 eyes and no AMD in 69 eyes.	Mean age 68y	Eyes with exudative AMD (18.7%) had a significantly higher incidence of VMA than fellow eyes (P=0.007)	In the VMA group classic type CNV occurred in 38% and occult CNV occurred in 52% of patients. There was no significant difference between both subtypes (P=0.968)
Nomura *et al*[7], 2011	Retrospective observational, case control study	378 eyes from 302 subjects (132 with typical AMD, 126 with PCV and 120 control eyes)	Age in typical AMD was 75.3 PCV was 72 Control eyes was 71.3	In typical AMD VMA tended to be higher 12.2% in typical AMD compared to 7% in control eyes (P=0.099) In PCV eyes VMA as 8.3%, same as control eyes (P=0.615)	In a paired eye study in eyes with typical AMD; VMA was observed in 7 eyes (17.5%) with wet AMD and 3 (7.5%) fellow eyes In the paired eye study eyes with PCV had similar VMA as their fellow eyes (P=0.67)
Waldstein *et al*[23], 2012	Prospective 4y	49 patients with AREDS category 4 AMD	Mean age of patients was 74.8 (range 58-88.5) Pseudophakic (8%)	18% of eyes (9 of 49) showed VMA 33% of eyes that had VMA developed CNV. In patients with no VMA the percentage of patients developing CNV was 38%. There was no significant difference between both groups	37% of eyes developed CNV during the 4 year interval. Occult CNV developed in 56% of cases, RPA in 11%, minimally classic CNV in 28% and hemorrhagic CNV in 6%
Present study, 2015	Retrospective, observational study	40 control eyes, 42 dry AMD eyes and 87 wet AMD eyes	No pseudophakics Mean age was 64 in dry AMD cases, 63.5 in wet AMD cases and 61.5 in control group	10% VMA in control eyes, 14.3% in dry AMD eyes and 34.5% in wet AMD eyes	No significant difference with regards to activity Increased incidence of VMA in mixed, type 2 and type 3 CNV

AMD: Age-related macular degeneration; CNV: Choroidal neovascularization; VMA: Vitreomacular adhesion; PVD: Posterior vitreous detachment; AREDS: Age related eye disease study; PCV: Polypoidal choroidal vasculopathy; RAP: Retinal angiomatous proliferation.

minimally classic lesions compared to occult and classic CNVs. A paper studying AMD in Japanese patients showed that eyes with typical AMD have less PVD than controls but that the frequency of PVD was not different between the polypoidal choroidal vasculopathy (PCV) eyes and the control eyes[7]. Of importance, Freund *et al*[9], considered that PCV might be considered as a variant of type 1 CNV and therefore our results obtained for subretinal or type 1 CNV could have been influenced by the presence of PCV.

Type 2 CNV as classified by Freund describes a CNV complex that is located above the RPE complex and invades the inner retina[9]. It is a more aggressive and visually debilitating

subtype as compared to type 1 which is localized in the sub-RPE space. Although no explanation has been described in previous literature we hypothesize that the inflammatory and ischemic changes induced by the VMA favor the development of this severe variant. It is also possible that these changes span the entire length of the retina (inner and outer) and therefore explain the intraretinal invasion. However, we did not identify any cases of type 3 CNV or RAP. Confirmation is usually based on ICGA studies which were not available at our facility and we relied mainly on FA and OCT. There is a possibility that some of our type 2 cases were in fact RAP and further studies are needed to study the vitreomacular interface with regards to this subtype of wet AMD. We also did not include a separate group for cases with a mixed pathology and classified cases based on the predominant CNV type. It is our belief that cases with mixed lesions behave based on the predominant pathology which in turn would affect the interaction with the vitreomacular interface.

Our study also failed to show any significant difference between the activity of the CNV and VMA. A previous study by Robison *et al*[20] showed that PVD is highly associated with nonexudative AMD whereas VMA is related strongly to exudative AMD. He hypothesized that the VMA was inducing active VEGF secretion and continued activity of the CNV. Therefore the VMA was acting as a pro-angiogenic factor. Perhaps these differences could be explained by differences in baseline criteria where the mean age was 63.5 and 64 in our study compared to 79.4 and 85.1 in the study by Robison *et al*[20], in the active and inactive groups respectively. The older age group in the non-active group could explain the higher percentage of PVD. Another difference was the number of cases. His study also included 15 pseudophakics in the active group and 12 in the non-active group whereas our study excluded pseudophakics. He also used both eyes for some of his patients whereas we only used one.

Sebag *et al*[24] recently proposed a unifying concept of vitreo-retinal diseases. The anomalous attachment of the vitreous could, in theory, exert a tractional effect. He postulated that this pathogenic mechanism is the initiating event in diseases such as retinal tears and detachments, macular holes and pucker, and advanced proliferative diabetic vitreoretinopathy. The results of our study as other studies suggest that in eyes with AMD, anomalous PVD could be a significant risk factor for progression from nonexudative to exudative forms of AMD. Whether this is a causal relationship or an association is yet to be determined.

There are several proposed mechanisms of how a VMA might induce the progression of AMD. It might be due to a chronic low grade inflammation that is induced by the mild traction leading to the development of advanced AMD[25-27]. This theory might also partially explain the presence of a higher percentage of VMA in patients with intraretinal CNV whereby the inflammation induces of trans-retinal weakening allowing the subretinal CNV to penetrate into the inner retina. It might also be the other way around whereby the intraretinal CNV creates a trans-retinal inflammation that prevents the posterior vitreous from detaching. Another possible theory is that the presence of an attached posterior vitreous leads to a state of hypoxia and decreased nutrition which in turn leads to increased progression of AMD. In addition, it might also result in the entrapment of several cytokines including vascular endothelial growth factor that might lead to the development of CNV. This might also explain why patients with wet AMD and VMA respond less to anti-VEGF drugs and require more injections because of the combined effect of a higher concentration of cytokines and because of the inability of the drug from reaching adequate concentrations at the macular area. Recent analysis from the EXCITE study showed that patients with VMA that developed a PVD showed better response than patients with sustained VMA[28-31]. Sebag and Hageman[32] emphasized that there are many embryologic, molecular, and structural similarities between the Bruch membrane and the internal limiting lamina of the retina, and thus it is likely patients who have VMA also have a weakened Bruch's membrane that not only allows for the progression to wet AMD but also allows for the development of intraretinal CNV.

However despite the wealth of information, the exact contribution of vitreoretinal adhesion in the macula remains uncertain, and future investigations should explore the exact nature of these events. It will also be important to prove causality and that the VMA is the inciting factor and not a secondary adhesion because of the inflammatory state induced by the CNV. Perhaps the emergence of pharmacologic vitreolysis[33-35] to induce a PVD can help answer these questions and help elucidate its role as a prophylactic medication to protect against exudative AMD.

Our study also has several drawbacks. The small number of patients that were used, the lack of ICGA to help identify cases of PCV and RAP, the fact that many patients presented in advanced stages of the disease despite never receiving any treatments and the phakic nature of several of our patients who had significant cataracts that made imaging difficult. Despite these drawbacks there were certain factors that gave strength to this study namely the stringent selection criteria and the presence of a large control group. Patients with a previous history of intravitreal injections or intraocular surgery were excluded to remove confounding factors that might be responsible for inducing a PVD and in turn affect the disease course and pathogenesis.

In summary, compared with large epidemiologic studies examining risk factors of severe AMD like cigarette smoking, hereditary factors, large drusen, and pigmentary changes, the

number of participants was small in the current study. The largest meta-analysis dealing with this topic had a pooled number of 155 cases[22]. However, even in this small group, we found a significant correlation between vitreoretinal adhesion and wet AMD. We further found a correlation with intraretinal CNV. Further studies with more participants observed longitudinally over a longer period are required to validate our observations about the importance of vitreoretinal adhesion as a potential risk factor for exudative AMD. It is necessary to determine whether an attached posterior vitreous cortex is indeed a pathogenic factor or whether it is only an association. Furthermore, by correlating the findings with other known risk factors, future studies may help elucidate which of the several theories proposed above may explain the observations of this study.

ACKNOWLEDGEMENTS

Conflicts of Interest: El-Hifnawy MA, None; **Ibrahim HA,** None; **Gomaa AR,** None; **Elmasry MA,** None.

REFERENCES

1 Congdon N, O'Colmain B, Klaver CC, Klein R, Muñoz B, Friedman DS, Kempen J, Taylor HR, Mitchell P. Causes and prevalence of visual impairment among adults in the United States. *Arch Ophthalmol* 2004;122(4):477-485.

2 Spaide RF, Armstrong D, Browne R. Continuing medical education review: choroidal neovascularization in age-related macular degeneration-what is the cause? *Retina* 2003;23(5):595-614.

3 Nowak JZ. Age-related macular degeneration (AMD): pathogenesis and therapy. *Pharmacol Rep* 2006;58(3):353-363.

4 Krebs I, Brannath W, Glittenberg C, Zeiler F, Sebag J, Binder S. Posterior vitreomacular adhesion: a potential risk factor for exudative age-related macular degeneration? *Am J Ophthalmol* 2007;144(5):741-746.

5 Quaranta-El Maftouhi M, Mauget-Faÿsse M. Anomalous vitreoretinal adhesions in patients with exudative age-related macular degeneration: an OCT study. *Eur J Ophthalmol* 2006;16(1):134-137.

6 Ondeş F, Yilmaz G, Acar MA, Unlü N, Kocaoğlan H, Arsan AK. Role of the vitreous in age-related macular degeneration. *Jpn J Ophthalmol* 2000;44(1):91-93.

7 Nomura Y, Ueta T, Iriyama A, Inoue Y, Obata R, Tamaki Y, Yamaguchi T, Yanagi Y. Vitreomacular interface in typical exudative age-related macular degeneration and polypoidal choroidal vasculopathy. *Ophthalmology* 2011;118(5):853-859.

8 Gass JD. Biomicroscopic and histopathologic considerations regarding the feasibility of surgical excision of subfoveal neovascular membranes. *Am J Ophthalmol* 1994;118(3):285-298.

9 Freund KB, Zweifel SA, Engelbert M. Do we need a new classification for choroidal neovascularization in age-related macular degeneration? *Retina* 2010;30(9):1333-1349.

10 Duker JS, Kaiser PK, Binder S, de Smet MD, Gaudric A, Reichel E, Sadda SR, Sebag J, Spaide RF, Stalmans P. The International Vitreomacular Traction Study Group classification of vitreomacular adhesion, traction, and macular hole. *Ophthalmology* 2013;120(12):2611-2619.

11 Sebag J. Age-related changes in human vitreous structure. *Graefes Arch Clin Exp Ophthalmol* 1987;225(2):89-93.

12 Sebag J. Age-related differences in the human vitreoretinal interface. *Arch Ophthalmol* 1991;109(7):966-971.

13 Foos RY. Posterior vitreous detachment. *Trans Am Acad Ophthalmol Otolaryngol* 1972;76(2):480-497.

14 Clemons TE, Milton RC, Klein R, Seddon JM, Ferris FL 3rd, Age-Related Eye Disease Study Research Group. Risk factors for the incidence of Advanced Age-Related Macular Degeneration in the Age-Related Eye Disease Study (AREDS) AREDS report no.19. *Ophthalmology* 2005;112 (4):533-539.

15 Chakravarthy U, Augood C, Bentham G C, de Jong P T V M, Rahu M, Seland J, Soubrane G, Tomazzoli L, Topouzis F, Vingerling JR, Vioque J, Young IS, Fletcher AE. Cigarette smoking and age-related maculardegeneration in the EUREYE Study. *Ophthalmology* 2007;114(6):1157-1163.

16 Francis PJ, George S, Schultz DW, Rosner B, Hamon S, Ott J, Weleber RG, Klein ML, Seddon JM. The LOC387715 gene, smoking, body mass index, environmental associations with advanced age-related macular degeneration. *Hum Hered* 2007;63(3-4):212-218.

17 Risk factors associated with age-related macular degeneration. A case-control study in the age-related eye disease study: Age-Related Eye Disease Study Report Number 3. *Ophthalmology* 2000;107(12):2224-2232.

18 Lee SJ, Lee CS, Koh HJ. Posterior vitreomacular adhesion and risk of exudative age-related macular degeneration: paired eye study. *Am J Ophthalmol* 2009;147(4):621-626.e1.

19 Lee SJ, Koh HJ. Effects of vitreomacular adhesion on anti-vascular endothelial growth factor treatment for exudative age-related macular degeneration. *Ophthalmology* 2011;118(1):101-110.

20 Robison CD, Krebs I, Binder S, Barbazetto IA, Kotsolis AI, Yannuzzi LA, Sadun AA, Sebag J. Vitreomacular adhesion in active and end-stage age-related macular degeneration. *Am J Ophthalmol* 2009;148(1):79-82.e2.

21 Mojana F, Cheng L, Bartsch DU, Silva GA, Kozak I, Nigam N, Freeman WR. The role of abnormal vitreomacular adhesion in age-related macular degeneration: spectral optical coherence tomography and surgical results. *Am J Ophthalmol* 2008;146(2):218-227.

22 Jackson TL, Nicod E, Angelis A, Grimaccia F, Prevost AT, Simpson AR, Kanavos P. Vitreous attachment in age-related macular degeneration, diabetic macular edema, and retinal vein occlusion: a systematic review and metaanalysis. *Retina* 2013;33(6):1099-1108.

23 Waldstein SM, Sponer U, Simader C, Sacu S, Schmidt-Erfurth U. Influence of vitreomacular adhesion on the development of exudative age-related macular degeneration: 4-year results of a longitudinal study. *Retina* 2012;32(3):424-433.

24 Sebag J. Anomalous posterior vitreous detachment: a unifying concept in vitreo-retinal disease. *Graefes Arch Clin Exp Ophthalmol* 2004;242 (8):690-698.

25 Anderson DH, Mullins RF, Hageman GS, Johnson LV. A role for local inflammation in the formation of drusen in the aging eye. *Am J Ophthalmol* 2002;134(3):411-431.

26 Donoso LA, Kim D, Frost A, Callahan A, Hageman G. The role of inflammation in the pathogenesis of age-related macular degeneration. *Surv Ophthalmol* 2006;51(2):137-152.

27 Zarbin MA. Current concepts in the pathogenesis of age-related macular degeneration. *Arch Ophthalmol* 2004;122(4):598-614.

28 Mayr-Sponer U, Waldstein SM, Kundi M, Ritter M, Golbaz I, Heiling U, Papp A, Simader C, Schmidt-ErfurthU. Influence of the vitreomacular interface on outcomes of ranibizumab therapy in neovascular age-related macular degeneration. *Ophthalmology* 2013;120(12):2620-2629.

29 Ciulla TA, Cuilla TA, Ying GS, Maguire MG, Martin DF, Jaffe GJ, Grunwald JE, Daniel E, Toth CA. Influence of the vitreomacular interface on treatment outcomes in the comparison of age-related macular degeneration treatments trials. *Ophthalmology* 2015;122(6):1203-1211.

30 Houston SK 3rd, Rayess N, Cohen MN, Ho AC, Regillo CD. Influence of vitreomacular interface on anti-vascular endothelial growth factor therapy using treat and extend treatment protocol for age-related macular degeneration (Vintrex). *Retina* 2015;35(9):1757-1764.

31 McKibbin MA, Suter CA, Willis TA. The influence of vitreomacular adhesion on outcomes after aflibercept therapy for neovascular age-related macular degeneration. *Retina* 2015;35(10):1951-1956.

32 Sebag J, Hageman GS. Interfaces. *Eur J Ophthalmol* 2000;10(1):1-3.

33 Sebag J. Molecular biology of pharmacologic vitreolysis. *Trans Am Ophthalmol Soc* 2005;103:473-494.

34 Sebag J. Is pharmacologic vitreolysis brewing? *Retina* 2002;22(1):1-3.

35 Sebag J. Pharmacologic vitreolysis. *Retina* 1998;18(1):1-3.