VITREOPAPILLARY ADHESION IN MACULAR DISEASES

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ABSTRACT

Purpose: The effect of vitreopapillary adhesion (VPA) in macular diseases is not understood. Spectral-domain optical coherence tomography/scanning laser ophthalmoscopy (SD-OCT/SLO) was used to identify VPA in macular holes, lamellar holes, macular pucker, and dry age-related macular degeneration (AMD).

Methods: Ultrasonography and SD-OCT/SLO were performed in 99 subjects: 17 with macular holes, 11 with lamellar holes, 28 with macular pucker, 15 with dry AMD, and 28 age-matched controls. Outcome measures were the presence of total posterior vitreous detachment (PVD) by ultrasound and the presence or absence of VPA and intraretinal cystoid spaces by SD-OCT/SLO.

Results: PVD was detected by ultrasound in 26 (92.9%) of 28 eyes with macular pucker, 6 (54.5%) of 11 eyes with lamellar holes (P = .01), and 4 (23.5%) of 17 eyes with macular holes (P = .000003). SD-OCT/SLO detected VPA in 15 (88.2%) of 17 eyes with macular holes, 11 (39.3%) of 28 age-matched controls (P = .002), 4 (36.4%) of 11 eyes with lamellar holes (P = .01), 4 (26.7%) of 15 eyes with dry AMD (P = .0008), and 5 (17.9%) of 28 eyes with macular pucker (P = .000005). Intraretinal cystoid spaces were present in 15 (100%) of 15 eyes with macular holes with VPA. In eyes with macular pucker, 4 (80%) of 5 with VPA had intraretinal cystoid spaces, but only 1 (4.3%) of 23 without VPA had intraretinal cystoid spaces (P = .001).

Conclusions: VPA was significantly more common in eyes with macular holes than in controls or eyes with dry AMD, lamellar holes, or macular pucker. Intraretinal cystoid spaces were found in all eyes with macular holes with VPA. When present in macular pucker, VPA was frequently associated with intraretinal cystoid spaces. Although these investigations do not study causation directly, VPA may have an important influence on the vectors of force at the vitreoretinal interface inducing cystoid spaces and holes.

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INTRODUCTION

Posterior vitreous detachment (PVD) usually results in innocuous separation of vitreous from retina. Anomalous PVD is the consequence of gel liquefaction without sufficient dehiscence at the vitreoretinal interface, causing a variety of untoward sequelae.[1] When anomalous PVD involves persistent adherence at the optic disc, vitreopapillary adhesion (VPA) can cause optic nerve dysfunction.[2-5] What is not known is whether VPA plays a role in macular diseases such as macular holes, macular pucker, and age-related macular degeneration (AMD). Furthermore, it is not known whether the presence or absence of VPA is associated with certain macular pathologies, such as intraretinal cystoid spaces. Indeed, while intraretinal cystoid spaces are known to occur in various maculopathies[6-13] and while localized perifoveal vitreous detachment may cause anterior traction, resulting in foveal cysts without macular hole formation or capillary leakage,[14] an association between VPA and cystoid spaces in these diseases has not yet been investigated.

It is plausible that persistent vitreous attachment to the optic disc can influence the vectors of force exerted by vitreous on the macula and might therefore play a role in macular diseases, especially macular holes. This study was therefore designed to test the hypothesis that VPA is more commonly found in full-thickness macular holes than in lamellar holes, macular pucker, dry AMD, and age-matched controls. It was also hypothesized that when present in macular holes and macular pucker, VPA would be more commonly associated with intraretinal cystoid spaces.

METHODS AND MATERIALS

The Institutional Review Board of St Joseph Hospital, Orange, California, approved the study, and informed consent was given by all participants. There were 99 subjects: 17 with macular holes, 11 with lamellar holes, 28 with macular pucker, 15 with dry AMD, and 28 normal controls. Controls were age-matched to eliminate any influence of aging. The mean ages in each group are listed in Table 1 along with statistical analyses demonstrating that there were no significant differences between the groups. There were also no statistically significant differences in the gender distributions between the various groups in this study.

All subjects were evaluated at the VMR Institute in Huntington Beach, California, between February 2007 and December 2008. Exclusion criteria were the presence of diabetic retinopathy, retinal detachment, intraocular inflammation, ocular trauma, and a history of vitreoretinal surgery. Ultrasonography and spectral-domain optical coherence tomography/scanning laser ophthalmoscopy (SD-OCT/SLO) were performed in all subjects.

ULTRASONOGRAPHY

The presence of a PVD was determined by high-gain, real-time ultrasonography (10-MHz probe; Quantel Medical Inc, Bozeman, Montana). A through-the-lid contact technique with both horizontal and vertical views was used, and the mobility of the posterior vitreous was examined during saccadic eye movements.

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TABLE 1. MEAN AGE OF EACH PARTICIPANT GROUP

		MH	CONTROL	LH	DRY AMD	MP
Mean Age		65.9±6.1	65.5±8.4	67±9.5	70.3±6.4	69.8±9.2
			Control	**LH**	**dry AMD**	**MP**
Age Comparison *P* value	**MH**		0.9	0.7	0.05	0.1
	Control			0.6	0.06	0.07
	LH				0.3	0.4
	Dry AMD					0.8
Gender Comparison *P* value	**MH**		0.54	0.25	0.28	0.12
	Control			0.48	0.52	0.28
	LH				1	1
	Dry AMD					1

AMD, age-related macular degeneration; LH, lamellar hole; MH, macular hole; MP, macular pucker.

SD-OCT/SLO IMAGING

Fundus imaging was performed using the SD-OCT/SLO instrument (OPKO/Ophthalmic Technologies Inc, Toronto, Ontario). Longitudinal imaging was used to determine the presence of intraretinal cystoid spaces. Staging of macular holes and macular puckers was performed according to the Gass classifications.[15,16] Using the calibrated digital calipers of the SD-OCT/SLO software, macular hole diameters were measured (Figure 1) at four axes (45°, 90°, 135°, and 180°), and an average of the four measurements was computed for each eye and used for macular hole staging. Lamellar holes were diagnosed according to the criteria proposed by Haouchine and associates[17] and Witkin and associates.[18]

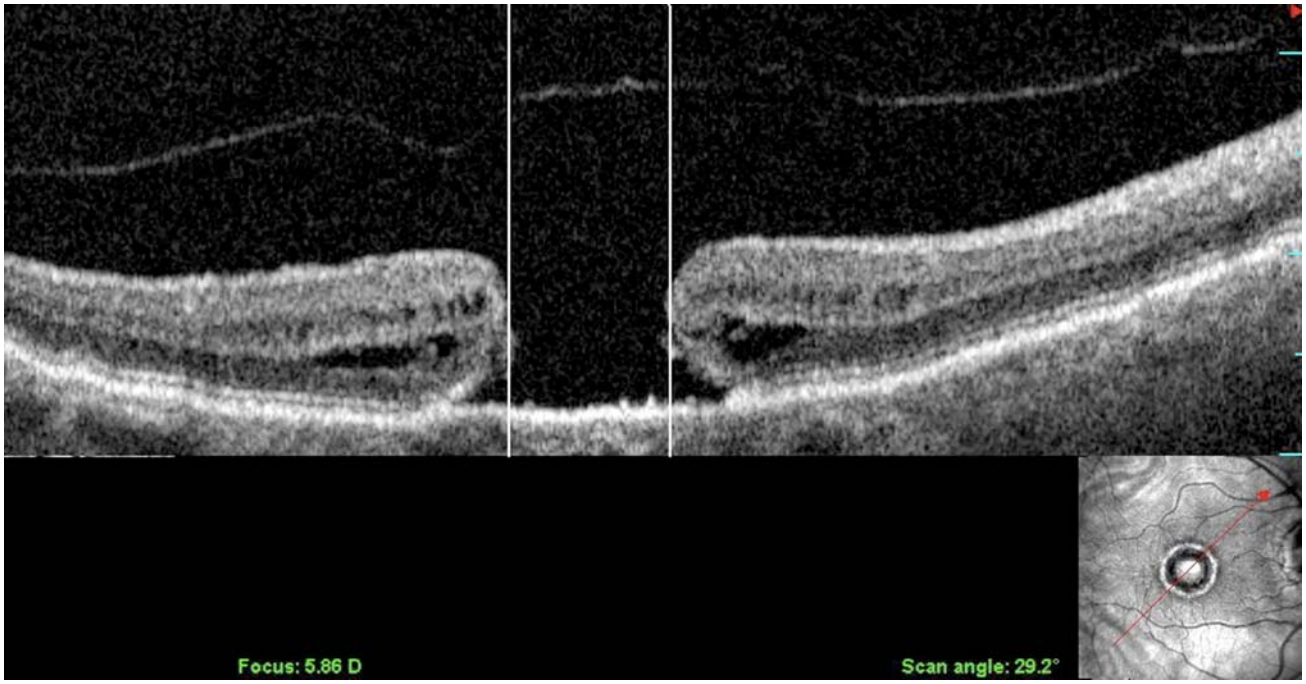

FIGURE 1

Longitudinal OCT/SLO scan (SLO image in lower righthand corner) illustrating the measurement of a stage 4 macular hole, determined by the distance between the vertical lines.

SD-OCT/SLO was used to evaluate the optic nerve head for VPA by obtaining images that centered the optic disc in the scanned field. The presence of VPA was established when a prominent vitreous membrane was found to be attached to the borders of the optic disc.

STATISTICAL ANALYSES

Two-sample *t* test assuming equal variance and Fisher exact test were used for the analyses. *P* values of .05 or less were considered statistically significant.

RESULTS

MACULAR HOLE

The clinical characteristics of this group are shown in Table 2. There were 17 eyes with full-thickness macular hole (5 men [29.4%], 12 women [70.6%]; average age, 65.9 ± 6.1 years). The diameter of the macular holes ranged from 205 to 1240 µm with a mean size of 485 µm. Based on the measurements of macular hole diameter and the presence or absence of vitreous attachment to the edge of the macular holes, 8 of 17 eyes (47.1 %) had stage 2 macular holes, 7 of 17 (41.2%) had stage 3 macular holes, and 2 of 17 (11.8%) had stage 4 macular holes. The macular hole stage was positively correlated with the macular hole diameter ($P < .001$).

TABLE 2. CLINICAL CHARACTERISTICS OF 17 EYES WITH MACULAR HOLE

AGE (yr)	SEX	BCVA	EYE	VPA
50	F	20/60-2	OD	Y
62	F	20/50+3	OD	Y
69	M	20/100-1	OD	Y
67	M	20/20-2	OS	Y
58	F	20/64-1	OD	Y
70	M	20/140-1	OS	Y
67	F	20/50-2	OS	Y
70	F	20/80+1	OS	Y
67	F	20/400	OS	Y
67	F	CF'8	OD	Y
64	F	20/100	OD	Y
60	M	20/400	OS	Y
76	F	20/140	OD	Y
65	F	20/100+2	OS	Y
67	F	20/400	OS	Y
75	M	20/140	OS	N
66	F	20/CF 4 feet	OD	N

BCVA, best-corrected visual acuity; CF, counting fingers; VPA, vitreopapillary adhesion; N, no; Y, yes.

PVD was detected by ultrasonography in 4 of 17 eyes (23.5%). VPA (Figure 2) was detected by SD-OCT/SLO in 15 of 17 eyes (88.2%). Intraretinal cystoid spaces surrounding the macular holes were found in 15 (100%) of 15 eyes with macular holes with VPA.

LAMELLAR HOLES

There were 11 eyes with lamellar holes (6 men [54.5%], 5 women [45.5%]; average age, 67 ± 9.5 years). The clinical characteristics of this group are shown in Table 3. PVD was detected by ultrasonography in 6 of 11 eyes (54.5%). SD-OCT/SLO imaging detected VPA (Figure 3) in 4 of 11 eyes (36.4%). No patients had both a PVD and VPA. Intraretinal cystoid spaces were detected in 3 of 4 eyes with VPA (75%). Of the 7 eyes without VPA, 3 of 7 (42.9%) had intraretinal cystoid spaces.

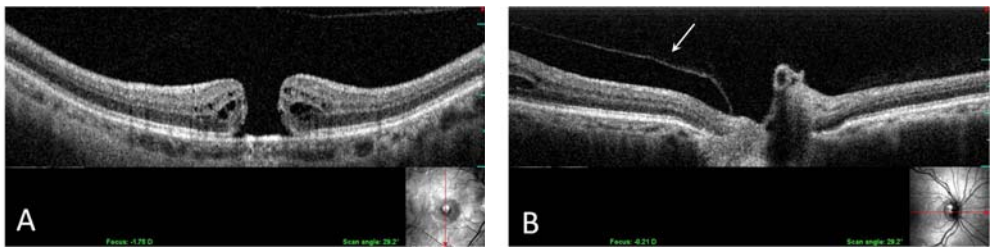

FIGURE 2

Longitudinal OCT/SLO image demonstrating a macular hole with the detachment of posterior vitreous cortex (A). The posterior vitreous cortex is attached to the optic disc (B).

TABLE 3. CLINICAL CHARACTERISTICS OF 11 EYES WITH LAMELLAR HOLE

AGE (yr)	SEX	BCVA	EYE	VPA
43	F	20/20	OS	Y
71	F	20/30	OD	Y
68	F	20/80	OD	Y
78	M	20/100	OS	Y
70	M	20/30-2	OD	N
72	M	20/50-2	OD	N
71	F	20/30	OD	N
60	F	20/25-3	OD	N
60	M	20/20-1	OD	N
72	M	20/60-2	OD	N
72	M	20/30-1	OD	N

BCVA, best-corrected visual acuity; VPA, vitreopapillary adhesion; F, female; M, male; N, no; Y, yes.

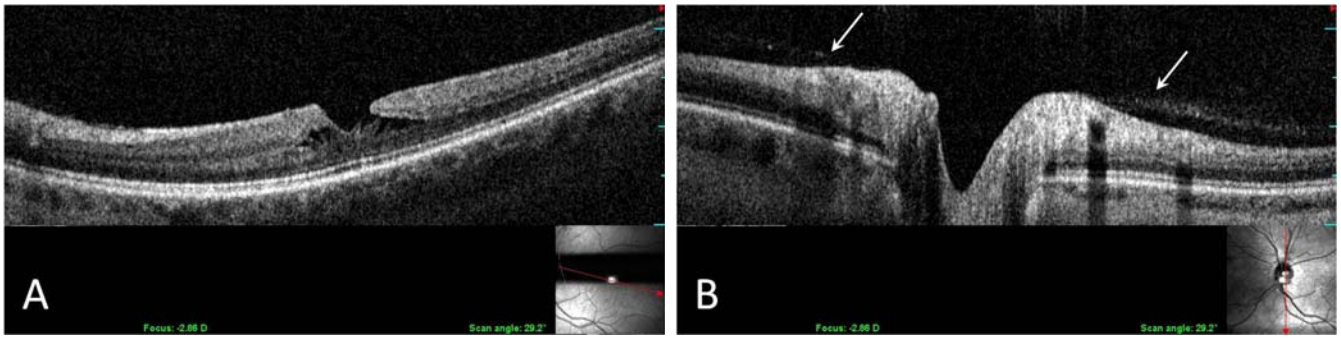

FIGURE 3

Longitudinal OCT-SLO imaging demonstrates a lamellar hole with intraretinal cysts (A). Vitreous adhesion is evident at the margins of the optic disc (B).

MACULAR PUCKER

There were 28 eyes (16 men [57.1%], 12 women [42.9%]; average age, 69.8 ± 9.2 years) with grade 2 macular pucker, which appeared as wrinkling of the macula with linear striae. The clinical characteristics of this group are shown in Table 4. Ultrasonography detected the presence of PVD in 26 of 28 eyes (92.9%). SD-OCT/SLO imaging identified VPA in 5 of 28 eyes (17.9%). Of the 5 eyes with macular pucker and VPA, intraretinal cysts (Figure 4) were present in 4 eyes (80%), as compared to only 1 (4.3%) of the 23 eyes with macular pucker but no VPA (P = .001).

TABLE 4. CLINICAL CHARACTERISTICS OF 28 EYES WITH MACULAR PUCKER

AGE (yr)	SEX	BCVA	EYE	VPA
89	M	20/26-3	OD	Y
61	F	20/50	OD	Y
64	F	20/140+1	OD	Y
84	M	20/140	OD	Y
67	M	20/30-1	OD	Y
70	M	20/50-2	OD	N
57	M	20/30+2	OD	N
71	M	20/25-1	OS	N
85	M	20/100-2	OS	N
82	M	20/100	OD	N

TABLE 4 (CONTINUED). CLINICAL CHARACTERISTICS OF 28 EYES WITH MACULAR PUCKER

AGE (yr)	SEX	BCVA	EYE	VPA
56	F	20/40	OS	N
73	M	20/32-2	OS	N
52	F	20/80	OD	N
77	F	20/60-1	OS	N
59	F	20/20-1	OS	N
67	M	20/80-1	OS	N
71	M	20/26+3	OD	N
67	M	20/40-1	OD	N
65	F	20/40-3	OD	N
79	M	20/60-2	OD	N
74	F	20/30	OS	N
75	M	20/30+1	OD	N
72	F	20/40-2	OS	N
59	M	20/40	OD	N
75	F	20/80	OD	N
69	M	20/60	OS	N
65	F	20/20	OS	N
69	F	20/50-1	OD	N

BCVA, best-corrected visual acuity; VPA, vitreopapillary adhesion; F, female; M, male; No, no; Y, yes.

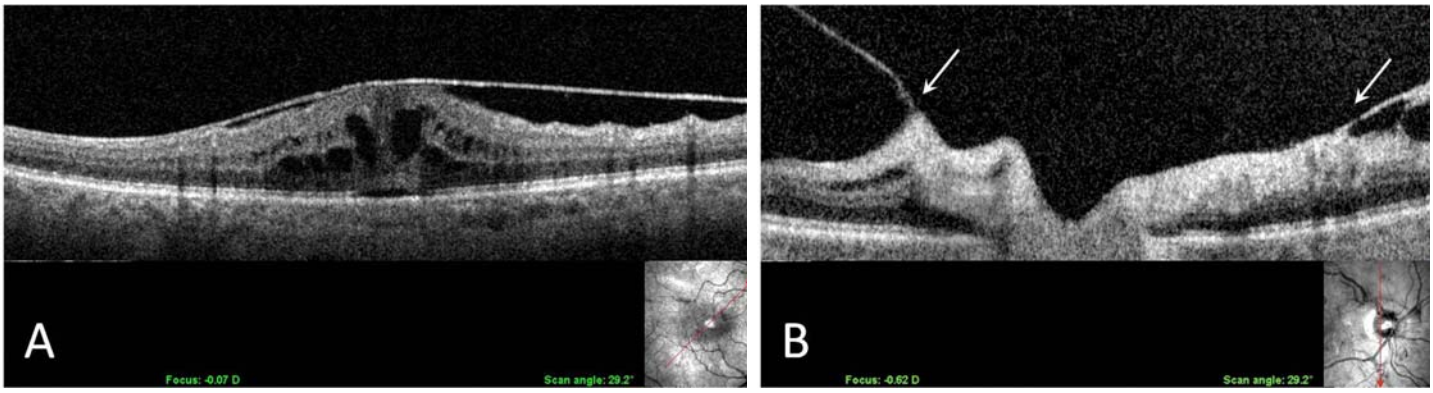

FIGURE 4

Longitudinal OCT-SLO imaging demonstrates a macular pucker with intraretinal cystoid spaces (A) and vitreopapillary adhesion to both sides of the optic disc (B).

DRY AMD

There were 15 eyes (8 men [53.3%], 7 women [46.7%]; average age, 70.3 ± 6.4 years) with dry AMD. The clinical characteristics of this group are shown in Table 5. SD-OCT/SLO imaging detected VPA in 4 of 15 eyes (26.7%).

AGE-MATCHED CONTROLS

There were 28 age-matched eyes (11 men [39.3%], 17 women [60.7%]; average age, 65.5 ± 8.4 years). The clinical characteristics of this group are shown in Table 6. SD-OCT/SLO imaging detected VPA in 11 of 28 eyes (39.3%).

TABLE 5. CLINICAL CHARACTERISTICS OF 15 EYES WITH DRY AMD

AGE (yr)	SEX	BCVA	EYE	VPA
65	M	20/30+3	OS	Y
68	F	20/25+2	OD	Y
71	F	20/50	OS	Y
76	F	NA	OD	Y
52	M	20/20-2	OD	N
67	M	20/25+2	OD	N
68	F	20/40	OS	N
70	M	20/30+2	OS	N
70	F	20/80-2	OD	N
72	F	20/40-1	OD	N
72	M	20/25-2	OS	N
72	F	20/40-2	OD	N
77	M	20/30-2	OD	N
77	M	20/25	OD	N
78	M	20/40	OD	N

AMD, age-related macular degeneration; BCVA, best-corrected visual acuity; VPA, vitreopapillary adhesion; F, female; M, male; OD, right eye; OS, left eye; N, no; Y, yes.

TABLE 6. CLINICAL CHARACTERISTICS OF 28 AGE-MATCHED CONTROL EYES

AGE (yr)	SEX	EYE	VPA
54	F	OD	Y
56	M	OD	Y
56	M	OD	Y
59	F	OD	Y
61	M	OD	Y
63	F	OD	Y
65	M	OD	Y
70	F	OD	Y
70	F	OD	Y
79	F	OD	Y
53	F	OD	Y
58	F	OD	N
59	F	OD	N
60	F	OD	N
61	F	OD	N
62	M	OD	N
63	M	OD	N
64	F	OD	N
64	F	OS	N
65	M	OD	N
65	F	OD	N
68	M	OD	N

TABLE 6 (CONTINUED). CLINICAL CHARACTERISTICS OF 28 AGE -MATCHED CONTROL EYES

AGE (yr)	SEX	EYE	VPA
69	M	OD	N
71	F	OD	N
72	F	OD	N
78	F	OD	N
83	M	OD	N
86	M	OD	N

VPA, vitreopapillary adhesion; M, male; F, female; OD, right eye; OS, left eye; N, no; Y, yes.

DISCUSSION

This study found that vitreopapillary adhesion (VPA) is far more prevalent in full-thickness macular holes (88.2%) than age-matched controls (39.3%; *P* = .002), lamellar holes (36.4%, *P* = .01), dry AMD (26.7%, *P* = .0008), and macular pucker (17.9%, *P* = .000005) (Figure 5). Thus, while VPA is important in some optic neuropathies,[2-5] as well as in various ischemic retinopathies, such as proliferative diabetic vitreoretinopathy,[19] the results of this study suggest that VPA is also important in macular holes. These observations with SD-OCT/SLO imaging confirm the ultrasonography findings of Van Newkirk and colleagues,[20] who detected vitreous attachment to the peripapillary retina in 65 of 65 patients (100%) with stage 3 macular holes and pseudo-opercula. Thus, VPA may be causally associated with macular holes.

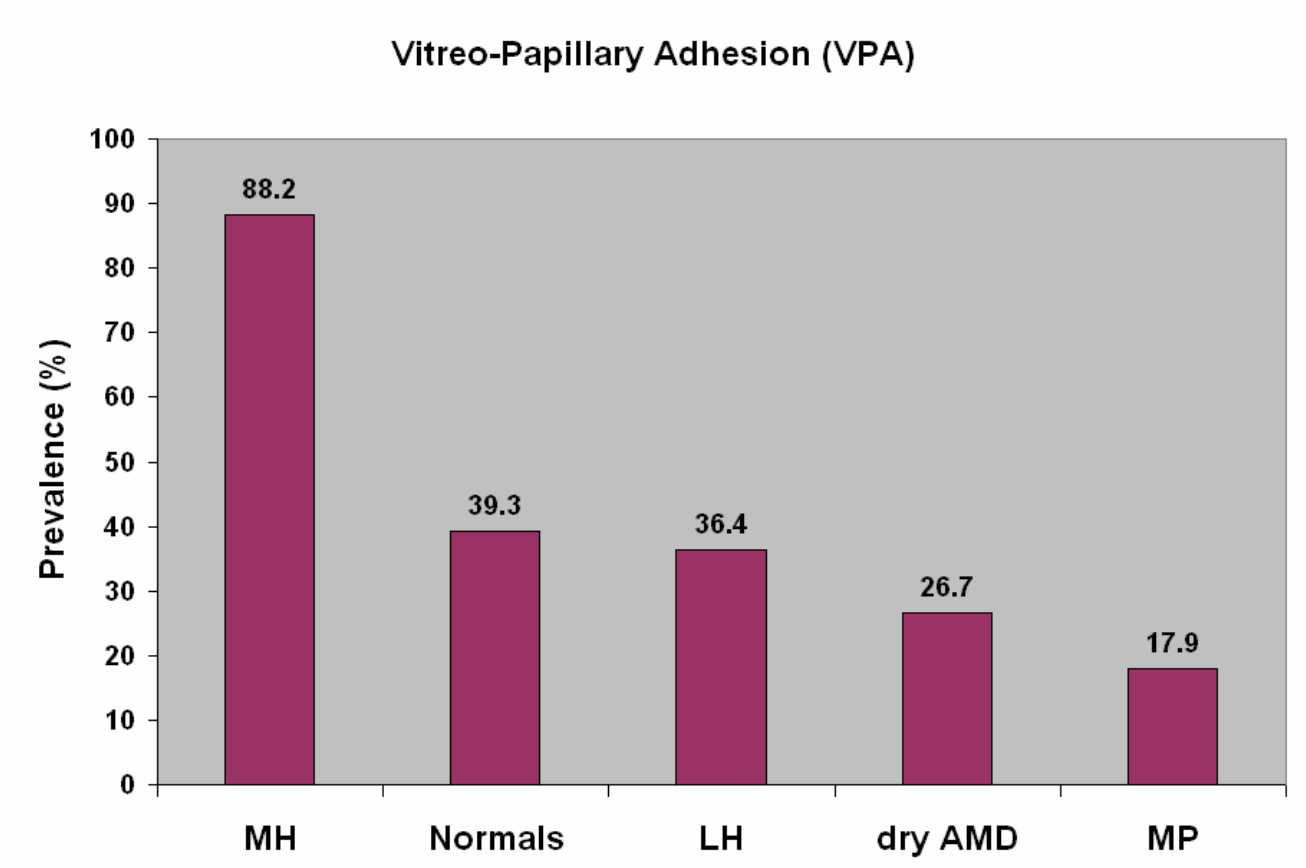

FIGURE 5

Vitreopapillary adhesion (VPA) was found most prevalent in macular hole (MH) (88.2%) compared to age-matched controls (39.3%; *P* = .002), lamellar hole (LH) (36.4%, *P* = .01), dry age-related macular degeneration (AMD) (26.7%, *P* = .0008), and macular pucker (MP) (17.9%, *P* = .000005), suggesting that VPA may be causally associated with MH..

The possible pathogenic mechanism by which VPA contributes to macular hole formation could involve anomalous PVD and vitreoschisis,[21] which has been implicated in the pathophysiology of both macular hole and macular pucker.[22,23] Following anomalous PVD with vitreoschisis, the outer layer of the split posterior vitreous cortex remains attached to the macula. Inward (centripetal) tangential traction by the outer layer of the split posterior vitreous cortex likely throws the underlying retina into folds, resulting in macular pucker. If, however, vitreous is still attached to the optic disc, the vectors of force would be different, resulting in outward (centrifugal) tangential traction that induces central retinal dehiscence and a macular hole. Indeed, papillofoveal traction has previously been implicated in the pathogenesis of macular holes.[24] Hence, while anomalous PVD may be the initial event, the presence or absence of VPA may influence the subsequent course and vectors of traction, especially in the presence of a perifoveal vitreous detachment.[25]

The results of this study suggest that in the absence of VPA, a macular pucker is more likely to be present, since VPA was detected in only 17.9% of macular pucker cases. In the presence of VPA, a macular hole is more likely to develop, since VPA was detected in 88.2% of macular hole cases (P = .000005), while lamellar hole possibly represents an intermediate stage in these events. In fact, previous studies[6] have suggested that lamellar holes represent an "abortive" process of macular hole formation and that foveal pseudocysts with partial PVD become lamellar holes if the base is preserved and full-thickness macular holes if the outer retinal layer is disrupted.[8] It is plausible that the vectors of force that result from VPA also contribute to the perifoveal vitreous detachment that Johnson and associates[25] have proposed as the primary pathogenic event in macular hole formation. What's more, intraretinal cystoid spaces may also be caused by VPA, since cysts were found more frequently in macular pucker with VPA (4 of 5, 80%) than macular pucker without VPA (1 of 23, 4.3%; P < .001). Figure 6 demonstrates that this is also the case in macular holes and lamellar holes, where VPA is highly associated with intraretinal cystoid spaces, whereas eyes without VPA have a low prevalence of cystoid spaces.

The findings in dry AMD are of interest insofar as recent studies[26-29] have shown that vitreomacular adhesion is a risk factor for choroidal neovascularization and exudative AMD. The absence of VPA in the overwhelming majority (73.3%) of eyes with dry AMD in the study reported herein corroborates these previous reports that found the presence of a total PVD was highly associated with the dry form of AMD. Thus, PVD without VPA was the most common finding in this present group of subjects. Future studies should explore the relationship between VPA and exudative AMD by establishing whether certain subtypes of wet AMD are more commonly associated with VPA.

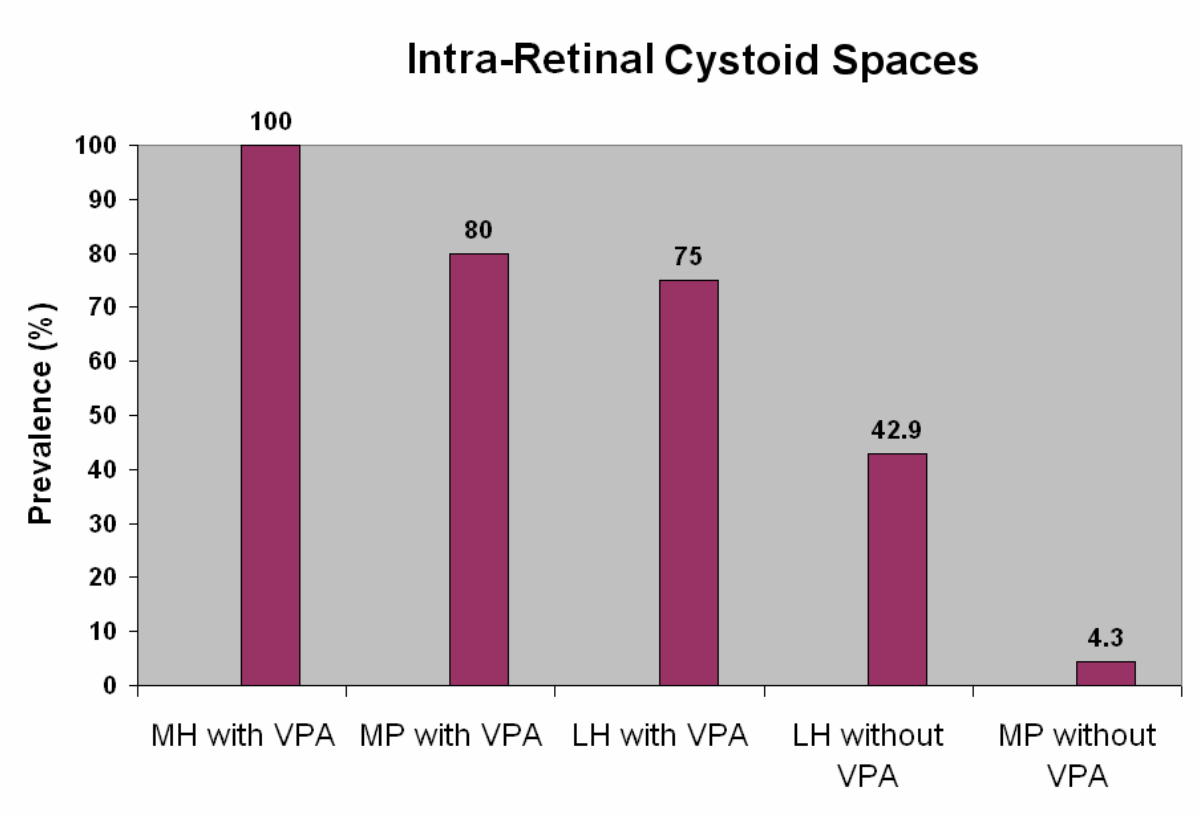

FIGURE 6

Intraretinal cystoid spaces are more prevalent in eyes with vitreopapillary adhesion (VPA). In macular holes (MH) with VPA, 100% of eyes had cysts. In macular pucker (MP) with VPA, 80% of eyes had intraretinal cystoid spaces. Lamellar holes (LH) with VPA had cysts in 75% of eyes, whereas cysts were present in only 42.9% of LH without VPA. MP without VPA had cysts in only 1 of 23 eyes (4.3%).

In conclusion, the present findings support the hypothesis that VPA is significantly more common in full-thickness macular holes than in controls, dry AMD, lamellar holes, and macular pucker. When present in macular holes and macular pucker, VPA is very highly associated with intraretinal cystoid spaces. VPA is also far more common in macular pucker and macular holes with cysts, as compared to lamellar holes and macular pucker without cysts. Thus, while VPA is known to play a role in certain papillopathies[2-5] and in diabetic vitreoretinopathy,[3,19] the present study suggests that VPA is also important in certain vitreomaculopathies.

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PEER DISCUSSION

DR. MYLAN R. VAN NEWKIRK: Like the authors, I have been on a quest to understand the "invisible" vitreous. Unlike the black holes of our universe, the vitreous has long been known to exist. However, both have proven challenging to study. The superb clarity of the images from the combined optical coherence tomography and scanning laser ophthalmoscopy (OCT/SLO) reported in this interesting paper will improve our understanding of vitreoretinal disorders.

I learned a great deal about the elusive posterior hyaloid membrane (PHM) or posterior cortical vitreous in young diabetic eyes and macular hole patients during pars plana vitrectomy with the late R G Michels in October 1990 and from doing ultrasound on macular hole patients of the late J Donald M Gass in 1991.[1] I remember vividly in June of 1995 when Dr Gass held the Hee and associates article, Optical Coherence Tomography of Macular Holes. *Ophthalmology* 1995; 102: 748-756 and he asked me, "Is this what you have been trying to show with B-scan?" In 1996, I began to collaborate with Mark W. Johnson after we discovered at ARVO that we shared similar findings and thoughts regarding macular holes.[2] Dr Johnson's 2005 AOS thesis provides an excellent discussion of this topic.

In this report the authors compared the vitreo-papillary adhesion (VPA) in macular holes, macular pucker, age-related macular degeneration and age matched controls. These data showing 88.2% of VPA in macular hole patients is consistent with my experience. I will focus my discussion on these findings and the suggested role of VPA in macular hole formation. This report suggests that the observed VPA and vitreoschisis with anomalous PVD is a possible mechanism for macular hole formation.

While many theories have been advanced for macular hole formation, the mechanism of retinal hole formation as proposed by Okun in 1960 has consensus support in the ophthalmic community.[3] This illustration shown is taken from the Ryan 4th Edition text on Retina, Volume III by C. P. Wilkinson on page 1954.

I suggest that the mechanism of macular hole formation is similar to that proposed by Okun for most other retinal tears. I suggest the VPA provides a fulcrum for macular hole formation as does the vitreous base for peripheral retinal hole formation. The elevated PHM by partial and complete PVD functions as the lever. The other essential element is the vitreoretinal adhesion which varies in size and location. The presence of the small focal vitreo-macular adhesion (VMA) is well documented and its degree is critical but poorly understood. While most peripheral retinal tears are associated with a complete PVD, some peripheral retinal holes have a partial vitreous detachment. Significant evidence shows that idiopathic macular holes begin as a partial perifoveal elevation of the PHM by liquefied vitreous. It is essential for the PHM to be elevated from the retina to induce sufficient traction at areas of vitreo-retinal adhesion. Retinal tears result when traction exceeds the resistance of the retina.

The configuration of the retinal tear of the macula observed in (9 of 9) stage 2 macular holes reported by Hee et al and Chauhan[4] and associates with OCT, were all hinged nasally toward the VPA. Similar findings were observed by Johnson and myself with biomicroscopy, OCT and in surgery. Our echographic studies showed greater elevation of the PHM temporal to the Stage 1, 2,and 3 macular holes which should deliver greater traction on the temporal edge of the macula. (Unpublished data) The rapid transformation and the small size of most cases of stage 2 macular holes to stage 3 has reduced the opportunity to visualize the micro-horseshoe tear seen in stage 2 holes.

Questions for Authors. How do you differentiate folds in detached PHM from vitreoschisis? Have you compared through the lid ultrasound images with direct globe application of probe?

I strongly recommend to these authors a future study of data regarding the visualization frequency and degree of perifoveal PHM separation[1,2] or discrete linear signal (DLS) as described by Chauhan in patients with macular hole and lamellar macular holes.[4]

I would like to thank the authors and the program committee for allowing me to leisurely review this excellent manuscript and anticipate more excellent research from this team.

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DR. ALAN H. FRIEDMAN: No financial conflicts of interest .We performed histopathologic studies on approximately 400 vitrectomy specimens every year. In the vast majority of cases where the surgeon has peeled a membrane from the surface of the retina, our histopathology and immunochemistry examination showed that these membranes are glial in origin. Some years ago George Wise and I studied the histopathology of enucleated eyes when the clinical examination demonstrated an epiretinal membrane. We showed breaks in the inner limiting membrane in through which glial astrocytes grew out of the retina and proliferated on the surface. I believe that a similar mechanism is present here and to invoke the vitreous as the causative agent is perhaps only part of the answer. I also believe that there really are not "cysts" in the retina. Cysts are epithelial lined structures, rather they are cystoid spaces. John Marshall has shown that these cystoid spaces in spectral domain studies are one continuous space rather than a multitude of small ones. Thank you.

DR. HANS E. GROSSNIKLAUS: No financial conflicts of interest. To elaborate a little bit on Alan's comment. We examine many vitreous specimens in our lab and we did a study with Rick Spaide that was published a few months ago. Our study showed that if you look at patients with vitreomacular traction syndrome and harvest specimens from the posterior hyaloid, there are cells growing from breaks in the retina onto the posterior hyaloid. When you are proposing a tractional force mechanism, I suspect some of these cells undergo myofibroblastic differentiation, so they contain actin filaments, like smooth muscle to some extent. That is not unusual around the optic nerve, too. So I was just wondering what Dr. Sebag's comments are regarding cellular proliferations on the posterior hyaloid. Is there a possible component around the peripapillary traction adhesions?

DR. JERRY SEBAG: In the refined discussion of Dr. Van Newkirk, he raised two questions and proposed one hypothesis. The question regarding ultrasonography was whether we perform through-the-lid techniques only or whether we compare those to direct contact. The answer is that we did not do direct contact. All of our studies with ultrasound were done through the lid, but we felt that using the same technique in all of our groups would eliminate any variability. Furthermore, we did not rely upon ultrasound to draw our conclusions, only the OCT-SLO findings. The question of whether vitreoschisis is an imaging artifact can be answered in three ways. There is an anatomic predisposition, there are clinical findings, and there are also histopathologic findings suggesting that vitreoschisis is real. Greg Hageman taught us that in the vitreo-retinal interface of monkeys there are lamellae at the outer posterior vitreous cortex right in front of the internal limiting lamina of the retina. These are potential cleavage plains. In Vienna, Carl Glittenberg and Susanne Binder have used spectral domain OCT to corroborate these findings in humans where we see lamellae in the outer vitreous anterior to the retina. This represents an anatomic predisposition for splitting at the vitreo-retinal interface leaving a layer of vitreous attached to the retina. Clinically, vitreoschisis has been detected in proliferative diabetic retinopathy using ultrasound. Dr. Ron Green at the University of Southern California has demonstrated that in 20% of patients with proliferative diabetic retinopathy you can see the inner and outer layers of a vitreoschisis cavity and sometimes blood can fill the center of the vitreoschisis cavity. When the blood cells settle to the bottom of the cavity, you get the typical pre-retinal, boat shaped hemorrhage. Histopathologic studies done at Moorfields Eye Hospital in London found vitreoschisis in 80% of patients who had proliferative diabetic retinopathy. We employed combined OCT-SLO to study proliferative diabetic retinopathy and were able to identify splits in the posterior cortex which when they rejoined have the configuration of a lambda sign. Interestingly, the point at which the inner and outer layers of the vitreoschisis meet is always the point where the retina is tented, implying that that is where maximum traction is exerted. Two years ago I presented before this body our findings using combined OCT-SLO in patients with macular pucker and fully 19 out of 44, or nearly half, were found to have vitreoschisis. In 45 patients with macular holes we were able to identify images very similar to what was shown to you by Dr. Van Newkirk who used ultrasound to identify a membrane anterior to the retina. Thanks to the high resolution of the combined OCT-SLO, however, you can see there is a second membrane, consistent with vitreoschisis, which we found in 53% of individuals with macular holes. In addition to the histopathologic evidence of vitreoschisis in proliferative diabetic retinopathy, histopathology of vitreoschisis in macular pucker is also available. This is a patient with macular pucker with evidence of vitreoschisis on OCT-SLO who I took to surgery. The excised tissue was studied histopathologically and demonstrated that there is a split in the posterior vitreous cortex with a lambda sign very similar to what we saw on combined OCT–SLO. In summary, I believe that the anatomic predispositions, as well as the significant amount of clinical findings, coupled with this clinico-pathologic correlation strongly support the concept of vitreoschisis.

Regarding another comment of my esteemed colleague Dr. Van Newkirk, I do not entirely agree that macular holes are similar to retinal tears because if they were, then a simple vitrectomy with air fluid exchange would suffice as therapy. Our surgical experience has shown that we have to do relatively aggressive membrane dissection to successfully close macular holes. The studies I presented at the AOS two years ago provide evidence that what we are dissecting is probably the outer (posterior) layer of the vitreoschisis cavity. Removal of this membrane is more important than any other aspect of the surgery, since studies have shown that when using various dyes, so-called chromodissection, there is an increased closure rate of macular holes. All this points to the importance of vitreoschisis in the pathogenesis of macular holes. The study I presented today suggests that vitreo-papillary adhesion is also important in the pathogenesis of macular holes and macular pucker. The different clinical courses of these two pathologies could result

in part from differences in the location of the vitreoschisis split. If the vitreoschisis splits anterior to the hyalocytes, and if there is persistent vitreopapillary adhesion, which is uncommon, there is likely to be a macular pucker with cysts. If however, the vitreoschisis split occurs anterior to the hyalocytes without vitreo-papillary adhesion, which is far more common, the likely result is a macular pucker without cysts. If the split occurs posterior to the hyalocytes with persistent vitreo-papillary adhesion, then a full-thickness macular hole results, whereas vitreoschisis posterior to the hyalocytes without vitreo-papillary adhesion will most likely cause a lamellar macular hole.

Dr. Friedman asks whether cells of retinal glial origin can play a role. I agree that they do play a role in the macular pucker cases because those are hyper-cellular membranes with various cell types including glial cells. Macular hole membranes are much thinner than macular pucker and they are hypocellular, so I doubt that glial cells play an important role in macular holes. However, in answer to both Dr. Friedman and Dr. Grossniklaus we do not believe that these cells are the primary problem in vitreo-maculopathies, but rather the hyalocytes are the initiators of the cascade of events that may ultimately involve glial cells. Hyalocytes are mononuclear phagocytes that reside in a single cell layer in the posterior vitreous cortex about 50 microns anterior to the retina. As members of the reticular endothelial system, hyalocytes are sentinel cells whose job is to signal the body when something goes wrong. A vitreoschisis split anterior to the level in which hyalocytes reside will leave them attached to the retina where they will recruit monocytes from the circulation, as well as other cells, such as glial cells from the retina, and some RPE cells. It is a fairly nonspecific response, but that is what the inflammatory reaction is throughout the body. Consequently we see glial cells in these membranes. As Dr. Friedman and others have suggested, there may be breaks in the retina as well, but it is not necessary for breaks to be present for glial cells migration. Many cells have the capacity to produce matrix metalloproteinases that enable migration. It is furthermore very difficult to understand the exact sequence of pathogenetic events just by looking at the endstage result of histopathology and determining exactly the early stages of the condition. Thus, while these cells likely play a role in pathophysiology, it is later in the sequence of events. Hyalocytes, on the other hand, are important in both early and late stages, the latter with regard to the contractile features of vitreo-retinal membranes. Studies have indeed shown that hyalocytes have the capacity to induce membrane contraction in later stages of disease that may also be important in proliferative vitreo-retinopathy. It is our working hypothesis that the earliest stages of vitreo-maculopathy pathogenesis involve anomalous PVD and vitreoschisis, as was presented two years ago, and vitreo-papillary adhesion, as we presented this morning. Thank you.