Visual Function in Pentosan Polysulfate Sodium Maculopathy

Riley J. Lyons,[1] Judy Brower,[2] and Nieraj Jain[2]

[1]Emory University School of Medicine, Atlanta, Georgia, United States
[2]Department of Ophthalmology, Emory University School of Medicine, Atlanta, Georgia, United States

Correspondence: Nieraj Jain, 1365B Clifton Road, N.E., Suite 2400, Atlanta, GA 30322, USA; nieraj.jain@emory.edu.

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Purpose. Individuals with pentosan polysulfate sodium (PPS) maculopathy commonly report symptoms of prolonged dark adaptation and difficulty reading. We hypothesize that PPS maculopathy causes degradation of visual function not fully captured with visual acuity testing.

Methods. Subjects with PPS maculopathy underwent multimodal evaluation of retinal structure and function. Structural changes were graded as moderate or advanced. Patient-reported visual function was assessed with the National Eye Institute Visual Function Questionnaire 39 (NEI-VFQ-39) and Low Luminance Questionnaire (LLQ). Objective functional evaluations included Early Treatment of Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA), Pelli–Robson contrast sensitivity, mesopic microperimetry, and dark adaptometry. Functional testing results were correlated with structural disease category.

Results. Thirteen patients (26 eyes), median age 62 years (range, 37–76), completed the study. Median ETDRS letter score was 82 (Snellen equivalent 20/25). Median NEI-VFQ-39 and LLQ composite scores were 65 (range, 33–88) and 41 (range, 20–92), respectively. Median contrast sensitivity was 1.65 (range, 0.15–1.95), and median mesopic microperimetry average thresholds and percent reduced thresholds were 26 decibels (range, 0.4–28.6) and 21.6% (range, 0–100%), respectively. Median rod intercept time was 14.1 minutes (range, 4.4–20.0). Eyes with advanced disease based on retinal structure had significantly worse retinal function for several testing modalities.

Conclusions. PPS maculopathy causes considerable visual function degradation that is not fully captured with BCVA testing. There was good correlation between other measures of visual function and disease severity. These findings deepen our concern regarding this patient safety issue.

Keywords: retina, maculopathy, pentosan polysulfate

Pentosan polysulfate sodium (PPS) is the only U.S. Food and Drug Administration-approved oral therapy for interstitial cystitis, a chronic pain syndrome affecting the bladder.[1,2] PPS was first approved for interstitial cystitis treatment in 1996, and it remains widely used today.[2] A recent study identified a novel vision-threatening maculopathy associated with long-term PPS use in six patients at a single center.[3]

Subsequent studies at multiple institutions have confirmed a strong association between long-term PPS use and the newly described maculopathy while also expanding our understanding of the phenotypic manifestations of this condition.[4–6] Fundus examination typically reveals nonspecific findings of macular pigment clumps amidst a background of yellowish subretinal deposits in early disease and retinal pigment epithelium (RPE) atrophy in late disease.[6] Multimodal fundus imaging demonstrates characteristic findings that localize disease to the RPE and RPE–photoreceptor interface and help differentiate this condition from other maculopathies such as age-related macular degeneration (AMD) and pattern dystrophy.[6–8] In particular, fundus autofluorescence (AF) imaging reveals a characteristic pattern of densely packed hypo- and hyper-autofluorescent spots that is typically centered on and involves the fovea and is highly symmetric between eyes.[9]

Visual acuity in PPS maculopathy is typically normal until late disease in the setting of RPE atrophy. In a retrospective study of 35 affected patients, median visual acuity was 20/25, and 86% of the eyes had a visual acuity of 20/40 or better.[6] However, patients with PPS maculopathy describe prominent visual symptoms with difficulty reading and challenges with performing other activities of daily living, particularly under dim and dynamic lighting conditions.[6] We hypothesize that PPS maculopathy leads to considerable degradation of macular function that has not been fully characterized by prior studies of this condition.

A more nuanced understanding of the functional impact of PPS maculopathy would be of value to clinicians and patients making decisions regarding PPS use, particularly when faced with the sometimes debilitating symptoms of interstitial cystitis. Through this cross-sectional study, we aim to comprehensively evaluate the functional impact of PPS

maculopathy with multimodal assessments of visual function. These findings will serve as baseline data for a multiyear prospective study of this condition. By exploring the functional impact of PPS maculopathy, we hope to gain a better understanding of the patient experience, and we may also identify novel endpoints for early disease detection and for monitoring disease progression.

Materials and Methods

This single-center, cross-sectional study was reviewed and approved by the institutional review board of Emory University and adhered to the tenets of the Declaration of Helsinki. Written, informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization were obtained from all subjects participating in this study. Patient confidentiality was maintained according to HIPAA standards.

Patients of the Emory Eye Center with a diagnosis of PPS maculopathy were invited to participate. Diagnostic criteria for PPS maculopathy were based on fundus imaging findings as previously described.[4,6] Exclusion criteria included visually significant cataract (exceeding 1+ nuclear sclerosis) or any other ocular comorbidity that may impact visual function. Some study candidates have been included in prior retrospective studies on this disease. Patient demographics and detailed PPS exposure histories were collected during the study visit. Testing for the baseline visit reported herein was carried out over 2 days to mitigate against the potential for fatigue. Testing was performed at no cost to the subject, and funds were available for subjects to defray the cost of travel.

Functional Testing

Functional evaluations were performed prior to the ophthalmic exam and imaging. Early Treatment of Diabetic Retinopathy Study (ETDRS) refraction was performed prior to dilation by a study coordinator and best corrected ETDRS letter score was recorded for each eye. Pelli–Robson contrast sensitivity was performed using a standard chart presenting eight lines of letters with decreasing contrast. The chart was displayed at a standard luminance (60–120 candela per square meter) and placed 1 meter from the patient. Each eye was tested separately.

The National Eye Institute Visual Function Questionnaire 39 (NEI-VFQ-39) and Low Luminance Questionnaire (LLQ) were administered by the study coordinator. The NEI-VFQ-39 is a validated general vision functional assessment consisting of 39 vision-targeted questions evaluating function along 11 vision-related constructs.[10] Subjects receive scores for each of the 11 subscales, which are then averaged to create a composite score.[10] The LLQ was developed specifically to assess visual function under low luminance and at night for patients with age-related maculopathy.[11] The LLQ is a 32-item questionnaire with six subscales. Subscale scores were once again averaged to produce a composite score.[11] Both questionnaires are scored from 0 to 100, with higher scores representing better visual function.

Mesopic microperimetry testing was performed on each eye separately using the MAIA, an eye tracking, nonmydriatic microperimeter (CenterVue, Padova, Italy). Using a standard 10-2 testing grid with 37 loci, Goldman size III stimuli were presented for 200 ms against a background luminance of 4 apostilb along a 4-2 testing strategy. Average thresholds and percent reduced thresholds were recorded for each eye individually. Average thresholds represent the average retinal sensitivity (decibels, dB) along all testing loci. Percent reduced threshold indicates the amount of testing loci that recorded a sensitivity below 25 dB.

Dark adaptometry was performed separately on 23 eyes of 12 subjects with the AdaptDx Dark Adaptometer (MacuLogix, Hummelstown, PA, USA) as previously described.[12,13] Three eyes of two patients with BCVA < 20/100 were excluded. Corrective lenses were used to adjust for refractive error, and the non-testing eye was patched. This study assessed recovery of retinal sensitivity after a bleaching flash at a location 5° on the inferior visual meridian. The rod intercept time, which indicates the amount of time needed to recover and detect a threshold stimulus of 5×10^{-3} scotopic candelas per square meter located within the second half of rod-mediated dark adaptation, was recorded. Patients underwent a rapid testing protocol for each eye, which automatically terminated after 6.5 minutes. The testing protocol was amended mid-study to allow for an extended testing protocol in one or both eyes, as tolerated, of patients that did not recover within the 6.5-minute rapid test time frame. The extended testing protocol applied the same bleaching flash at the same location as the rapid test and terminated after 20 minutes. Scores were recorded as 20 if the rod intercept time exceeded the time limit. Results were determined to be valid if fixation error was less than 30%.

Structural Testing and Severity Grading

Dilated fundus examination was performed by an expert examiner (NJ). Color fundus photography (Optos California rg/af; Nikon Corp., Tokyo, Japan), ultra-widefield fundus autofluorescence (Optos California rg/af), and optical coherence tomography (Spectralis HRA+OCT; Heidelberg Engineering, Heidelberg, Germany) images were collected by ophthalmic photographers and then evaluated by an expert grader (NJ) masked with respect to all functional data except BCVA (Fig. 1). Disease severity was assessed using a previously described PPS maculopathy staging system that classifies cases into grade 1, 2, or 3 based on the extent of fundus involvement and presence of RPE atrophy.[6] Grade 3 includes the most advanced cases, with AF imaging demonstrating disease extending at least two disc diameters beyond the temporal vascular arcades or RPE atrophy involving the central fovea.[6]

Statistical Analysis

Descriptive statistics were used to summarize patient demographics, exposure histories, structural disease stage, and functional testing results. Functional testing results were compared across structural disease categories using a Mann–Whitney *U* test. Normative data from studies of demographically similar normal subjects and subjects with intermediate AMD are used for comparison (Supplementary Table S1).

Due to the low number of patients in our cohort with grade 2 disease, grades 1 and 2 were combined into a "moderate" group that was compared to the grade 3 "advanced" group. Additionally, to account for inter-eye correlation of results with this symmetric disease process, functional testing scores for both eyes in each patient were averaged and treated as one data point when correlating functional scores with structural grade. Pearson

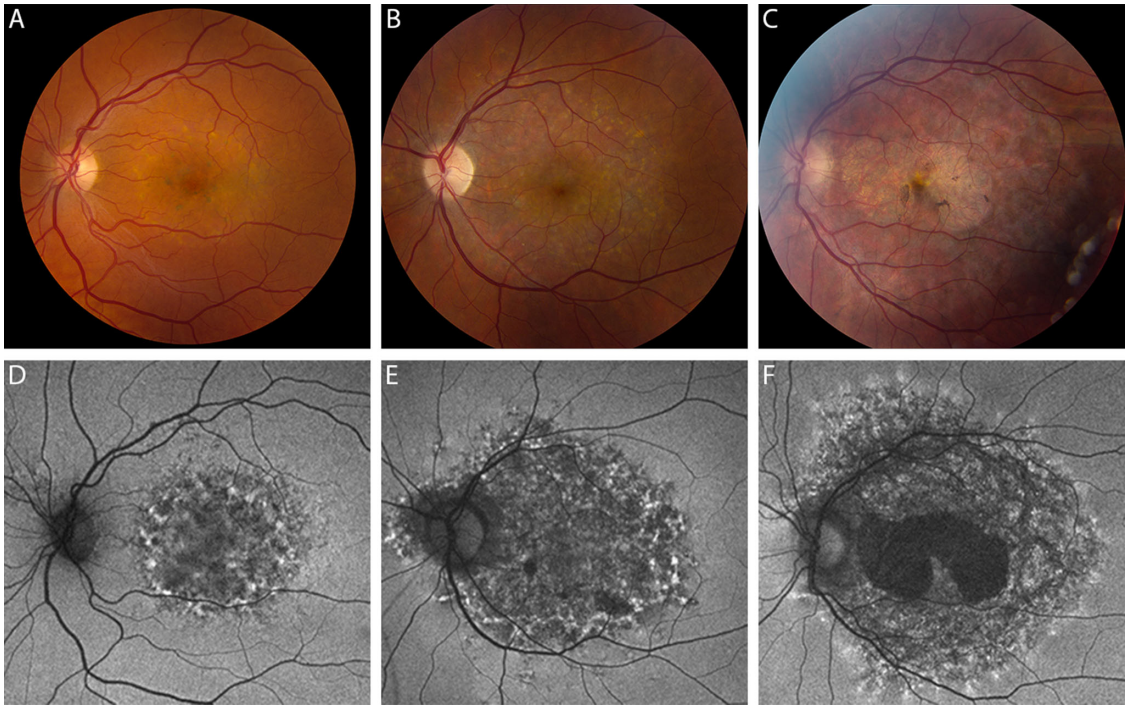

Figure 1. PPS maculopathy fundus images. Fundus images of the left eye of three subjects sorted by disease severity: a subject with grade 1 disease on the left (subject 13; **A**, **D**), a subject with grade 2 disease in the middle (subject 7; **B**, **E**), and a subject with grade 3 disease on the right (subject 1; **C**, **F**). (**A**–**C**) Color fundus photographs demonstrating that all eyes show macular pigmentary changes, including pigment clumps amidst a background of yellowish subretinal deposits in milder eyes and center-threatening retinal pigment epithelium atrophy in severe cases (**C**). (**D**–**F**) Fundus autofluorescence images demonstrating fairly well-delineated areas of irregular hyper- and hypoautofluorescence signal involving the posterior pole. Center-threatening retinal pigment epithelium atrophy can be noted in severe cases (**F**). Note that, due to the small study size, subjects classified as either grade 1 or grade 2 were combined into one analysis group for this study.

Table 1. Subject Demographics, Pentosan Polysulfate Exposure, and Disease Severity Grade

Subject No.	Age	Sex	Race	Height (m)	Mass (kg)	BMI (kg/m^2)	Lens Status	Smoking History	Duration of PPS Intake (mo)	Cumulative PPS Exposure (kg)	Duration Since Stopping PPS (mo)	Severity Grade
1	38	F	White	1.6	97.5	38.1	Phakic	Never	168	2.04	7.5	3
2	66	F	White	1.7	64.4	22.3	Phakic	Never	258	1.57	18.6	3
3	65	F	White	1.6	67.1	26.2	Pseudophakic	Never	89	0.84	0.0	3
4	68	F	White	1.6	71.2	27.8	Phakic	Never	239	2.18	6.9	3
5	63	F	White	1.5	65.3	29.0	Pseudophakic	Never	204	2.48	5.6	1
6	44	F	White	1.5	59	26.2	Phakic	Never	36	0.44	47.4	1
7	48	F	White	1.6	90.7	35.4	Phakic	Never	168	2.04	9.9	2
8	62	F	White	1.6	52.2	20.4	Phakic	Never	144	1.31	13.8	3
9	54	F	White	1.7	61	21.1	Phakic	Never	220	2.68	1.6	2
10	37	F	African American	1.5	49.9	22.2	Phakic	Never	108	0.99	137.8	3
11	72	F	White	1.8	62.6	19.3	Pseudophakic	Never	262	3.19	20.5	3
12	76	M	White	1.7	77.1	26.7	Pseudophakic	7 pack/y	237	2.85	0.0	1
13	51	F	White	1.8	81.6	25.2	Phakic	Never	77	0.70	65.4	1

correlation coefficients were calculated to determine the degree of correlation between patients' right and left eyes. Statistical analysis was performed using SAS University Edition (SAS Institute, Inc., Cary, NC, USA).

Results

Fourteen subjects (28 eyes) were enrolled in the study, but one enrolled subject was excluded from all analyses due to an incidental finding of an optic neuropathy at the baseline visit; therefore, 13 subjects (26 eyes) were included for analysis. Median age at enrollment was 62 years (range, 37–76). Twelve participants were female (92.3%), and 12 were white (92.3%) (Table 1).

The median duration of PPS intake was 168 months (range, 36–262), and the median cumulative PPS exposure was 2.04 kg (range, 0.44–3.19). All patients reported having discontinued PPS prior to the study visit at a median of 9.9 months (range, 0–137.8) prior. The median patient height was 1.6 meters (range, 1.5–1.8), median weight was 65.3 kg

Table 2. Functional Test Results by Subject

Subject		ETDRS Letter Score	NEI-VFQ-39 Composite Score	LLQ Composite Score	Contrast Sensitivity	Microperimetry Average Threshold (dB)	Microperimetry Percent Reduced Threshold (%)	Dark Adaptometry Rod Intercept Time (min)
1	OD	86	33	29	1.65	13.1	67.6	>20
	OS	83			1.35	10.5	75.7	>6.5*
2	OD	64	47	20	0.9	8.1	100	>20
	OS	12			0.15	Incomplete	Incomplete	—†
3	OD	79	50	30	1.05	8.6	100	>6.5*
	OS	81			1.2	11	100	>6.5*
4	OD	76	69	44	1.65	26.8	16.2	>6.5*
	OS	80			1.65	26.3	29.7	>6.5*
5	OD	75	78	38	1.65	25.9	18.9	>6.5*
	OS	81			1.5	27.2	0	14.3
6	OD	85	65	37	1.65	28.1	18.9	5.7
	OS	86			1.65	27.9	10.8	3.4
7	OD	88	88	92	1.65	27.5	2.7	5.7
	OS	91			1.65	26.2	13.5	5.9
8	OD	79	53	33	1.5	25.1	29.7	>6.5*
	OS	85			1.65	24.8	27	14
9	OD	90	76	43	1.65	26	16.2	>20
	OS	90			1.85	21.4	29.7	13.2
10	OD	83	74	54	1.65	25.2	51.4	>20
	OS	80			1.65	26.1	21.6	>20
11	OD	31	50	41	0.75	0.4	100	—†
	OS	24			0.9	3.4	100	—†
12	OD	87	65	58	1.8	27.2	13.5	5.6
	OS	89			1.95	28.6	5.4	3.3
13	OD	77	84	66	1.65	28.2	2.7	4.7
	OS	84			1.65	28.4	2.7	5.2

* Indicates eyes that warranted but did not undergo the extended testing protocol.
† Indicates subject was excluded from test due to best corrected visual acuity < 20/100.

(range, 49.9–97.5), and median body mass index (BMI) was 26.2 kg/m^2 (range, 19.3–38.1) (Table 1).

All subjects received an identical disease severity grade between their right and left eyes. In total, four, two, and seven patients received structural severity grades of 1, 2, and 3, respectively (Table 1). We determined the correlation of functional testing results between patients' right and left eyes and found high inter-eye correlation. Pearson correlation coefficients for ETDRS letter score, contrast sensitivity, microperimetry average threshold, and microperimetry percent reduced threshold were 0.82 ($P < 0.01$), 0.85 ($P < 0.01$), 0.97 ($P < 0.01$), and 0.93 ($P < 0.01$), respectively.

Functional Evaluation

The median ETDRS letter score was 82 (Snellen equivalent 20/25; range, 12–91). Four eyes of two patients had ETDRS letter scores worse than 70 (Snellen equivalent 20/40). The median NEI-VFQ-39 composite score was 65 (range, 33–88), and the median LLQ composite score was 41 (range, 20–92). Median contrast sensitivity was 1.65 (range, 0.15–1.95). Median microperimetry average threshold and percent reduced thresholds were 26 dB (range, 0.4–28.6) and 21.6% (range, 0–100), respectively (Table 2). Median microperimetry average thresholds were 10.5 dB (range, 0.4–26.0) and 27.0 dB (range, 24.8–28.6) among eyes with and without RPE atrophy, respectively (Table 2).

Subscale analysis of NEI-VFQ-39 results demonstrated that patients scored lowest on general vision questions related to mental health (mean ± SD, 48 ± 24) and role difficulties (53 ± 20) (Supplementary Table S2). The LLQ subscale analysis revealed that patients scored lowest on low luminance vision questions related to driving (27 ± 26) and general dim lighting (43 ± 19) (Supplementary Table S3).

Rapid dark adaptometry testing was performed on 23 eyes of 12 subjects. Three eyes were excluded due to BCVA < 20/100. Fifteen of 23 eyes had a rod intercept time exceeding 6.5 minutes on the rapid test. Extended dark adaptometry testing was performed on eight eyes out of the 15 eyes that warranted extended testing. Five of these eyes had rod intercept times exceeding the 20-minute limit (Table 2). The median rod intercept time of subjects in this study was 14.1 minutes (range, 4.4–20.0). Functional testing did not demonstrate a dose–response relationship between cumulative PPS exposure and visual dysfunction for any testing modality (Supplementary Fig. S1).

Structure–Function Correlation

There were no significant differences in patient demographics or PPS exposure histories when comparing subjects with moderate versus advanced disease (Table 3). Visual function scores were significantly different between the moderate and advanced severity groups for the NEI-VFQ-39 composite score (median, 77 vs. 50; $P = 0.01$), contrast

Table 3. Subject Demographics and Clinical Characteristics by Disease Severity

Demographics and Clinical Characteristics	Disease Severity		P^*
	Moderate ($n = 6$)	Advanced ($n = 7$)	
Age (y), mean (SD)	56 (12)	58 (15)	0.73
Sex, female, *n* (%)	5 (83)	7 (100)	0.46
Race, *n* (%)			>0.99
White	6 (100)	6 (86)	
African American	0 (0)	1 (14)	
Height (m), mean (SD)	1.6 (0.1)	1.6 (0.1)	>0.99
Weight (kg), mean (SD)	72.5 (12.7)	66.4 (15.7)	0.53
BMI (kg/m^2), mean (SD)	27.3 (4.8)	25.1 (6.5)	0.39
Lens status, *n* (%)			>0.99
Phakic	4 (67)	5 (71)	
Pseudophakic	2 (33)	2 (29)	
Smoking history, *n* (%)			0.46
None	5 (83)	7 (100)	
Former	1 (17)	0 (0)	
Duration of PPS intake (mo), mean (SD)	157 (82.1)	181 (72.1)	0.47
Cumulative PPS exposure (kg), mean (SD)	1.87 (1.04)	1.73 (0.81)	0.86
Duration since stopping PPS (mo), mean (SD)	21.6 (27.7)	29.3 (48.4)	0.66

* *P* values for continuous variables are based on Mann–Whitney *U* test; *P* values for categorical variables are based on Fisher's exact test.

sensitivity (median, 1.65 vs. 1.50; $P = 0.02$), microperimetry average threshold (median, 27.4dB vs. 11.8 dB; $P = 0.02$), and percent reduced thresholds (median, 9.5% vs. 71.7%; $P < 0.01$) (Table 4; Supplementary Fig. S2). ETDRS letter score (median, 87 vs. 80; $P = 0.06$) and LLQ composite score (median, 50 vs. 33; $P = 0.07$) were not significantly different among subjects with moderate versus advanced disease, respectively (Table 4; Supplementary Fig. S2). Comparisons could not be made for dark adaptometry due to low sample size.

Discussion

Initial studies on PPS maculopathy described patients with prominent visual symptoms despite relatively spared visual acuities. Clinicians have subsequently encountered challenging decisions regarding how to balance the threat of poorly characterized vision loss associated with PPS use against the morbidity associated with interstitial cystitis. In this cross-sectional study, our comprehensive functional assessment of subjects with PPS maculopathy provides a more complete picture of the extent of visual disability in this condition. Our findings demonstrate that these patients do indeed perform poorly on numerous tests of visual function, particularly those evaluating patient reported outcomes, even in the setting of normal visual acuity. By many metrics, PPS maculopathy results in visual dysfunction comparable to intermediate or advanced AMD.

The median ETDRS letter score among all subjects in this study was 82 (Snellen equivalent 20/25). Only four eyes of two subjects had ETDRS letter scores less than 70 (Snellen equivalent 20/40), each case associated with center-involving RPE atrophy. Yet, patient-reported outcomes through the NEI-VFQ-39 demonstrated median composite scores in both moderate (median, 77; range, 65–88) and advanced (median, 50; range, 33–74) severity groups that were worse than those reported for intermediate AMD (89 ± 0.62).[14] The advanced severity group NEI-VFQ-39 composite scores in the present study were even worse than those previously reported in patients with geographic atrophy surveyed using the 25-item National Eye Institute Visual Function Questionnaire (61.7 ± 16.3).[15] The NEI-VFQ-39 subscale scores in the present study were particularly low for mental health and role difficulties.

The LLQ median composite score of 41 in this study is the lowest reported by any study using this instrument. A prior study examining LLQ scores among patients with AMD reported median composite scores of 76 (range, 29–97) in a cohort of patients with intermediate AMD and a median composite score of 94 (range, 79–99) in the healthy control cohort.[16] LLQ scores in the present study were low across all domains, but particularly profound under the subscales for driving, general dim lighting, and extreme lighting. Importantly, it is unclear how our subjects' other co-morbidities, such as their underlying interstitial cystitis diagnosis, may influence these measures of vision-related quality of life.

Contrast sensitivity does not appear to be markedly impaired among most patients with PPS maculopathy. The median Pelli–Robson contrast sensitivity score (1.65; range, 0.15–1.95) was not markedly lower than values reported in normal subjects of a similar age (1.72 ± 0.08).[17] However, contrast sensitivity testing in our cohort did demonstrate a significant difference between those patients with moderate (median, 1.65; range, 1.58–1.88) versus advanced (median, 1.50; range, 0.53–1.65) disease, indicating that impaired contrast sensitivity testing may serve as a marker for late-stage disease. Two subjects with advanced disease demonstrating significant RPE atrophy in this cohort scored less than 0.90.

Microperimetry demonstrated that mean retinal sensitivity was slightly below normal for the moderate severity group (median, 27.4 dB; range, 23.7–28.3) and clearly worse than normal for the advanced severity group (median, 11.8 dB; range, 1.9–26.6). By comparison, a study of AMD demonstrated a median sensitivity of 25.3 dB (range, 17.9–30.6) among subjects with intermediate AMD and 27.7 dB (range, 14.4–31.3) among subjects with healthy eyes.[18] Abnormal results in the present study were primarily driven by areas of RPE atrophy, as has been seen with conventional static perimetry studies in this condition (Fig. 2).[3] Notably, this test was administered under mesopic conditions. Results of other functional studies

Table 4. Averaged Test Results and Structure–Function Correlation

	Structural Group			Normative Values		
Functional Test	**All Subjects (Eyes Averaged)**	**Moderate Disease Severity**	**Advanced Disease Severity**	**Healthy Controls**	**Intermediate AMD**	***P* (Moderate vs. Advanced Disease)**
ETDRS letter score						0.06
n	13	6	7	21	47	
Mean (SD)	76 (20)	85 (5)	67 (24)	83.81 (4.45)[17]	81.30 (5.67)[17]	
Minimum, median, maximum	28, 82, 90	78, 87, 90	28, 80, 85	73, 84, 90[17]	64, 83, 92[17]	
NEI-VFQ-39						0.01*
n	13	6	7	909	1125	
Mean (SD)	64 (16)	76 (10)	54 (14)	92 (0.61)[13]	89 (0.62)[13]	
Minimum, median, maximum	33, 65, 88	65, 77, 88	33, 50, 74	—	—	
LLQ						0.07
n	13	6	7	21	47	
Mean (SD)	45 (19)	56 (21)	36 (11)	91.4 (6.5)[15]	75.8 (16.7)[15]	
Minimum, median, maximum	20, 41, 92	37, 50, 92	20, 33, 54	79, 94, 99[15]	29, 76, 97[15]	
Contrast sensitivity						0.02*
n	13	6	7	22		
Mean (SD)	1.46 (0.39)	1.69 (0.11)	1.26 (0.45)	1.72 (0.08)[16]	—†	
Minimum, median, maximum	0.53, 1.65, 1.88	1.58, 1.65, 1.88	0.53, 1.50, 1.65	—	—	0.02*
Microperimetry average threshold (dB)						
n	13	6	7	20	47	
Mean (SD)	20.8 (9.3)	26.9 (1.7)	15.5 (10)	27.02 (3.63)[17]	25.20 (3.17)[17]	
Minimum, median, maximum	1.9, 25.7, 28.3	23.7, 27.4, 28.3	1.9, 11.8, 26.6	14.4, 27.7, 31.3[17]	17.9, 25.3, 30.6[17]	
Microperimetry percent reduced threshold (%)						<0.01*
n	13	6	7	20	47	
Mean (SD)	40.5 (38.1)	11.3 (6.9)	65.6 (35.7)	15.40 (25.61)[17]	42.32 (35.11)[17]	
Minimum, median, maximum	2.7, 23.0, 100.0	2.7, 9.5, 23.0	23.0, 71.7, 100.0	0.0, 2.7, 94.6[17]	0.0, 37.8, 100.0[17]	
Dark adaptometry rod intercept time (min)						NA
n	10	6	4	21	38	
Mean (SD)	12.5 (6.8)	8.4 (5.5)	18.5 (3.0)	6.20 (5.20)[17]	13.18 (6.40)[17]	
Minimum, median, maximum	4.4, 14.1, 20.0	4.4, 5.3, 16.6	14.0, 20.0, 20.0	1.1, 4.2, 18.4[17]	1.7, 13.3, 20.0[17]	

P values are based on Mann–Whitney *U* test.
* Statistically significant result.
† Reference data could not be located.

suggest that scotopic microperimetry may provide a more sensitive measure of retinal dysfunction in this disease.

Dark adaptometry testing yielded a range of findings that did not confirm our hypothesis that it would be a highly sensitive modality for detection of PPS maculopathy. The majority (65%) of eyes had rod intercept times exceeding the 6.5-minute threshold set for detection of early AMD.[12,13] Some eyes, even in the absence of RPE atrophy, had rod intercept times exceeding the 20-minute limit set for extended dark adaptometry testing on this device. Indeed, the median rod intercept time of subjects in this study of 14.1 minutes (range, 4.4–20.0) was similar to that observed in a study of AMD that reported a median rod intercept time of 13.3 minutes (range, 1.7–20.0) among subjects with intermediate AMD and 4.2 minutes (range, 1.1–18.4) among healthy controls.[18]

Although many subjects with PPS maculopathy do have objective confirmation of dark adaptation abnormalities, eight eyes of four subjects, all classified as moderate in severity, had rod intercept times under the 6.5-minute threshold. These included eyes with fundus imaging demonstrating disease involvement 5° above the fovea, which was the locus of dark adaptometry testing in this protocol. Taken together, these findings suggest that, although dark adaptometry provides important insights into the visual dysfunction in PPS maculopathy, this particular testing protocol with

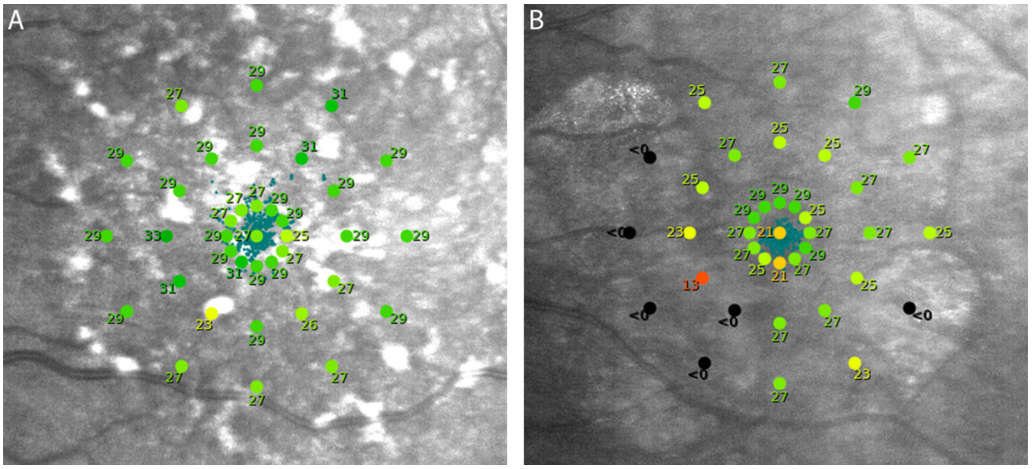

Figure 2. Macular sensitivity for two patients with differing disease severity. (**A**) Mesopic microperimetry demonstrated mildly subnormal sensitivities in a subject without RPE atrophy (subject 13). (**B**) In a subject with patchy paracentral atrophy (subject 9), microperimetry demonstrated deep scotomata associated with atrophy but only mildly subnormal sensitivity in areas outside of atrophy.

the 6.5-minute rod intercept time threshold is not likely to be a sensitive screening approach.

When comparing functional data to structural severity grades, there was a trend for worse visual function among subjects with advanced disease for all measures of visual function. This difference was statistically significant for the NEI-VFQ-39, Pelli–Robson contrast sensitivity, and microperimetry metrics. The lack of significant differences among other testing modalities may be a reflection of the limited power of this small study.

We did not identify a dose–response relationship between visual dysfunction and cumulative PPS exposure; however, this study evaluated a small and select group of subjects with high exposures and documented PPS maculopathy. We do believe that a larger study of all PPS users would identify such a relationship.[5,19] Future studies should continue to evaluate other individual differences with testing results to detect any risk factors for vision loss from PPS maculopathy. The mechanism for PPS toxicity is not well understood, and further research into the mechanism of PPS toxicity may aid in identifying risk factors for disease occurrence and progression.

Of note, the baseline results reported herein form the foundation for a prospective, longitudinal study of this condition. Our findings of prominent visual dysfunction in PPS maculopathy are especially troubling given recent retrospective studies demonstrating continued disease progression after PPS cessation.[20,21] The ongoing prospective study promises to add valuable data regarding the long-term impact of this condition and may identify risk factors for disease progression.

Study Limitations

The primary limitation of this study is the small sample size, which limits our ability to detect differences in visual function between disease severity groups. Perhaps a larger study would provide sufficient statistical power to detect additional structure–function correlations. However, although small relative to studies of common ocular diseases, this is the first comprehensive functional assessment of this recently described condition. The functional deficits described in the present study suggest additional areas for further research. For example, future studies should incorporate a test of reading performance. Additionally, standardized use of extended dark adaptometry testing protocols across a range of disease severities would provide a more complete understanding of the impact of PPS maculopathy on dark adaptation.

Another limitation of our study is the lack of a control group. We included historical normative data and results from studies on nonexudative AMD to provide context for our results. Finally, our cohort consists of patients seen at a tertiary referral center who were motivated to complete the lengthy evaluations involved in this study. This may bias our sample toward those with relatively severe disease.

Conclusions

This cross-sectional study confirms our hypothesis that PPS maculopathy is associated with considerable visual function impairment that is not adequately recognized by conventional visual acuity testing. Both subjective and objective testing modalities demonstrated visual dysfunction comparable to or worse than previously reported results in studies on AMD, with patient-reported outcomes demonstrating particularly profound impairment. Functional testing findings correlated with structural disease severity as assessed by fundus imaging.

These findings provide valuable guidance for providers and patients weighing the risks of PPS maculopathy against those of potentially uncontrolled interstitial cystitis. The results demonstrating worsening visual function across several testing modalities in more advanced disease are particularly troubling given reports that PPS maculopathy may continue to progress even after drug cessation.[20,21] Testing results from several subjects with center-involving RPE atrophy in the present study highlight the potentially profound impact of advanced disease.

Prescribers should discuss the risks associated with PPS use with their patients and implement the lowest necessary dose and duration of therapy. Patients diagnosed with PPS maculopathy should consider alternative therapies. Further longitudinal study of this cohort will provide additional

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insights into the long-term disease course after drug cessation and will inform screening guidelines and disease monitoring strategies.

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