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Association between Visual Function and Subretinal Drusenoid Deposits in Normal and Early Age-Related Macular Degeneration Eyes

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Abstract

Purpose—To examine the association between subretinal drusenoid deposits (SDD) identified by multimodal retinal imaging and visual function in older eyes with normal macular health or in the earliest phases of age-related macular degeneration (AMD).

Methods—AMD status for each eye was defined according to the AREDS 9-step classification system (normal=step 1, early AMD=steps 2–4) based on color fundus photographs. Visual functions measured were best-corrected photopic visual acuity, contrast sensitivity, and light sensitivity, mesopic visual acuity, low luminance deficit, and rod-mediated dark adaptation. SDD were identified through multi-modal imaging (color fundus photographs, infrared reflectance and fundus autofluorescence images, spectral-domain optical coherence tomography).

Results—The sample included 1,202 eyes (958 eyes with normal health, 244 eyes with early AMD). In normal eyes SDD were not associated with any visual function evaluated. In eyes with early AMD, dark adaptation was markedly delayed in eyes with SDD versus no SDD (4-minute delay on average), $p=0.0213$. However this association diminished after age adjustment, $p=0.2645$. Other visual functions in early AMD eyes were not associated with SDD.

Conclusion—In a study specifically focused on eyes in normal macular health and in the earliest phases of AMD, early AMD eyes with SDD have slower dark adaptation, largely attributable to

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the older ages of eyes with SDD; they did not exhibit deficits in other visual functions. SDD in older eyes in normal macular health are not associated with any visual functions evaluated.

Keywords

age-related macular degeneration; aging; dark adaptation; subretinal drusenoid deposits; visual function

Subretinal drusenoid deposits (SDD), the leading histologic correlate for reticular pseudodrusen, are space-filling extracellular lesions distinct from drusen due to their location, differential cholesterol content, and independently-conferred risk for age-related macular degeneration (AMD) progression.¹⁻⁴ Recently we showed with multi-modal imaging that SDD are present in 23% of older adults in normal macular health and 52% of those with early AMD, usually appearing as sparse lesions not forming a distinctive pattern.⁵ Furthermore, our prospective study has shown that SDD presence in *normal eyes* doubles their risk for incident early AMD three years later.⁶ Histology and adaptive optics assisted imaging show that these lesions exert a stage-specific effect on photoreceptor structure.^{4, 7}

A growing body of work has documented that SDD increase the risk for visual deficits, which has been documented under a wide range of ambient lighting conditions, including scotopic (rod-mediated), photopic (cone-mediated), and mesopic (both rod and cone-mediated) conditions. Impairments have been reported for light sensitivity as assessed by microperimetry,⁸⁻¹⁰ low luminance visual acuity,¹¹ delayed rod mediated dark adaptation,^{12, 13} contrast sensitivity,⁹ and electrophysiological implicit times as measured by multifocal electroretinogram.^{14, 15} These visual effects could be attributable to direct toxicity of the lesions contacting photoreceptors, increased diffusion distance in the subretinal space, and/or a diffuse dysregulation of retinoid processing, among other processes. All of these effects would be superimposed on a transport barrier already present in the subjacent RPE and Bruch's membrane, which could also impair visual function.¹⁶ These studies focused on patients seen in retinal referral clinics where tested cohorts were dominated by patients at intermediate AMD or worse.

A novel question for understanding the significance of SDD is whether these lesions also accentuate visual functional deficits in normal older eyes, and in those in the earliest phases of AMD. Although earlier work documented an association between SDD and exacerbated visual functional deficits as compared to eyes without SDD, literature to date has not specifically focused on the impact of SDD on visual function in normal retinal aging or on very early AMD as defined by gold standard definitions of AMD. Here we examine the association between SDD identified by multimodal retinal imaging and several aspects of visual function in a very large sample of older eyes in normal macular health and those with early AMD.

Methods

This study utilized data from the baseline visit of the Alabama Study on Early Age-Related Macular Degeneration (ALSTAR) study.^{17, 18} Eligible persons were (1) 60 years old, (2) in normal macular health (grade 1) or in the early stages of AMD (grades 2 – 4) in the

AREDS 9-step classification system,¹⁹ which is based on 3-field color photographs graded by trained and masked evaluators; and (3) free of other ocular diseases. This study was approved by the Institutional Review Board of the University of Alabama at Birmingham and followed the tenets of the Declaration of Helsinki. Written informed consent was obtained from participants after the nature and purpose of the study was described.

Eyes were examined for the presence of SDD using color fundus photographs (450 plus camera, Carl Zeiss Meditec, Dublin, CA), infrared reflectance (IR) and 488 nm-excitation autofluorescence (AF) images, and spectral-domain optical coherence tomography (SD-OCT) volumes. SD-OCT, IR, and AF images were captured on the Spectralis HRA + OCT (Heidelberg Engineering, Heidelberg, Germany). The SDD identification process has been described in detail elsewhere⁵ and is summarized here. To assess retinal images for the presence of SDD in SD-OCT, IR, and AF images, we used Heidelberg Eye Explorer (HEYEX version 1.6.4.0 with Spectralis Viewing Module 5.3.2.0, Heidelberg Engineering, Heidelberg, Germany). To assess color fundus photographs we used OphthaVision (version 3.50, Escalon Medical Corp., Ardmore PA). SD-OCT volumes of macula and optic nerve head (ONH) were included. B-scans of the macula volumes were horizontally oriented and centered over the fovea across an area of $20^{\circ} \times 15^{\circ}$ (5.7×4.2 mm), as reported by the software. B-scans of the ONH volumes were radially oriented and centered over ONH within a circular area 20° (5.8 ± 0.1 mm) in diameter. Automatic real-time averaging was set between 8 and 18 for both volumes. SD-OCT was graded for presence of SDD first, followed by the grading of the three *en face* imaging modalities. Our criteria for SDD at the eye level required identification on 1 *en face* modality and OCT or on 2 *en face* modalities in the absence of OCT findings (called strict criteria).⁵ Because of the many normal eyes in our study population, our criterion included sparse or solitary lesions not discernable as a pattern, in the context of multimodal imaging.

Visual function measurements were carried out for each eye unless otherwise noted below. Best-corrected visual acuity was assessed by the Electronic Visual Acuity tester²⁰ (EVA; JAEB Center, Tampa FL) under photopic conditions (100 cd/m^2) and expressed as the logarithm of the minimum angle resolvable (logMAR). Low luminance visual acuity was also assessed using the EVA with participants viewing letters through a 1.5 log unit neutral density filter, which reduced background luminance to 3.16 cd/m^2 (mesopic conditions). To determine how much logMAR decreased under conditions of the lower light level as compared to the photopic (100 cd/m^2) assessment, we defined a decrease in visual acuity under low luminance by the increase in logMAR. This measure has been referred to as the “low luminance deficit”.^{21, 22} Contrast sensitivity was estimated by the Pelli-Robson chart²³ (Precision Vision, La Salle, IL) with mean luminance of 100 cd/m^2 , the letter-by-letter scoring method²⁴ and expressed as logarithm of sensitivity. Light sensitivity in the macula was assessed using the Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin, CA). The 24-2 SITA standard protocol was used following the instrument’s recommended testing procedure for a white stimulus on a white background. Macular light sensitivity was defined as the average sensitivity (in dB) of 16 targets falling within the region $9^{\circ} \times 9^{\circ}$ grid centered on the fovea. Rod-mediated dark adaptation was measured psychophysically using the AdaptDx (MacuLogix, Hummelstown, PA), using a procedure described in detail previously¹⁷ and summarized here. The procedure began with a photobleach (0.25 ms

duration, 58,000 scotopic cd/m² s intensity; equivalent ~83% bleach). The 4°-diameter flash was centered at 5° on the inferior vertical meridian (i.e. superior to the fovea on the retina). The test target for measuring light sensitivity was also placed at this position. Fifteen seconds after bleach offset, threshold measurement for a 2° diameter, 500 nm circular target began and continued at 30-second intervals for 20 minutes. Speed of dark adaptation was characterized by the rod-intercept time, defined as the duration (minutes) required for a sensitivity value of 5.0×10^{-3} scotopic cd/m² (3.0 log units of attenuation of the stimulus), which is in the latter half of the second component of rod recovery.²⁵ A higher value for rod-intercept time indicates slower dark adaptation. Dark adaptation was measured in one eye only because of time constraints in the protocol. The eye with better visual acuity was selected for testing. Dark adaptation data were missing for 79 participants due to fixation instability during testing (n=78) or equipment technical problems (n=1).

Statistical analysis

Age and AMD status were described for the overall sample and compared between those eyes with and without SDD using generalized estimating equations (GEE) to account for the within-person correlation that occurs when two eyes from the same person are included. For each visual function, linear regression models using GEE were used to compare mean values between those eyes with and without SDD. Adjusted models accounted for the potentially confounding effects of age. The model was repeated only among those with AMD and among those with normal macular health. $p < 0.05$ was considered statistically significant.

Results

The sample consisted of 1,202 eyes. Eyes were from a participant sample that was 63.9% women and 96.1% white of non-Hispanic origin. They averaged 69.4 years old and ranged from 60 to 92 years (Table 1). Those eyes with SDD were from persons who were older on average by approximately 2 years. SDD was present in 25.0% (n=300 of 1202) of the overall sample judged by the strict criteria, with SDD prevalence being higher in those eyes with early AMD (47.1%) than in those in normal macular health (19.3%). These prevalence values at the eye level differ very slightly from our separately reported prevalence values at the person level for older normal adults and those with early AMD using information from both eyes.⁵ Of 300 eyes meeting strict criteria for SDD presence, 286 met criteria by OCT and one *en face* modality, and 14 met criteria with two *en face* modalities only. Of 902 eyes without SDD, 245 had SDD on OCT that was not seen on an *en face* modality, and in 657 eyes viewed by OCT, lesions were questionable or non-detectable.

Table 2 summarizes the visual function results for the overall sample with respect to SDD presence or absence. SDD presence was not associated with visual functions evaluated with the exception of dark adaptation. The mean rod intercept time in the total sample was on average approximately 3 minutes longer in eyes with SDD as compared to eyes with no SDD ($p = 0.0019$; age-adjusted, $p = 0.0511$). When analyses were restricted to normal eyes only (Table 3), SDD were not associated with any visual functions, even dark adaptation. The rod-intercept time was very similar for eyes in normal macular health with and without SDD (11.6 versus 11.1 minutes, $p = 0.4805$; age-adjusted, $p = 0.8772$). When analyses were

restricted to early AMD eyes only, SDD presence was not associated with any visual functions evaluated with the exception of slowed dark adaptation ($p = 0.0213$). Rod intercept time averaged 16.9 minutes in early AMD eyes with SDD and 12.7 minutes in eyes. This association between rod intercept time and SDD was no longer statistically significant after age-adjustment ($p = 0.2645$).

Figures 1 and 2 display representative retinal imaging and dark adaptation results, respectively, for 4 eyes, 2 normal and 2 early AMD, to demonstrate the impact of SDD on dark adaptation. Figure 1 shows IR reflectance images and SD-OCT B-scans, one without SDD (Figure 1A) and one with SDD (Figure 1B). As is common in older eyes with healthy maculas and in eyes with AMD,²⁶ the SDD in Figure 1B is located closer to the optic nerve head than the fovea. These two older adults in normal macular health, regardless of their SDD status, have similarly fast time courses of sensitivity recovery, as compared to eyes with early AMD (Figure 2). Figure 1C&D shows images of two eyes at AREDS step 2 indicating early AMD. While both eyes have slow dark adaptation as compared to normal eyes, the eye with SDD (Figure 1D) is dramatically slowed. Even after 20 minutes, the eye with early AMD with SDD still had exhibited little recovery of sensitivity.

Discussion

Even though 19.3% of the eyes in normal macular health in our sample had SDD, these eyes were not more likely to have abnormal dark adaptation than eyes without SDD. Eyes in normal macular health (grade 1) by the AREDS 9-step grading system do not have moderate or substantial drusen coverage (i.e., they had drusen area $< 125 \mu\text{m}$) nor do they have pigmentary abnormalities. We previously showed in a study based on these same eyes that SDD lesions in eyes in normal macular health tend to be single or sparsely distributed, not forming the patterns familiar in eyes with intermediate AMD.⁵ Our data suggest that SDD in this early manifestation, combined with the absence of moderate to substantial drusen coverage and pigmentary abnormalities, may be insufficient to impede the time-course of dark adaptation. Rather than engendering dark adaptation delays, the significance of SDD in eyes with normal macular health for AMD progression may be that they serve as a structural marker for future emergence of early AMD. In fact, recently we showed that SDD in normal eyes doubles the risk for incident early AMD three years later.⁶ Slowed dark adaptation may require further pathological steps beyond the mere appearance of SDD, such as their expansion and resulting confluence,^{27, 28} plus perturbation of RPE cell bodies in addition to the apical processes.²⁹ Within this framework, the presence of SDD remains an important signature not only as phenotypic entities in AMD patients currently in normal macular health, but potentially as a biomarker for increased risk for future visual decline in patients currently in normal macular health, an issue deserving of further investigation.

Although the presence of SDD in early AMD was associated with dramatically slowed dark adaptation (on average a 4-minute increase in the time rod photoreceptors needed to recover sensitivity following photopigment bleaching), this association is largely attributable to the fact that SDD is more likely to be found in older eyes.⁵ Dark adaptation slows in the later decades of life even in the absence of AMD.³⁰ Our finding is a reminder that the biological aging process itself is a powerful platform and the strongest risk factor identified to date for

the development of early AMD lesions and their functional manifestation. Our finding that the association between SDD and dark adaptation is largely attributable to aging in our cohort does not conflict with findings reported by Flamendorf et al.,¹² who found an association between SDD and dark adaptation in AMD independent of age, because of important differences in the two study populations. Flamendorf¹² focused on a broad range of AMD disease severity including eyes with intermediate AMD and whose fellow eye could have advanced AMD. In contrast, our AMD eyes were all at early AMD (AREDS grade 2–4 in the 9-step classification system¹⁹), with only 5% of fellow eyes with intermediate AMD and 0.4% of fellow eyes with advanced disease (geographic atrophy or choroidal neovascularization).

Results from this study are striking in that the many aspects of visual function assessed in this study bore no relationship to SDD in eyes in normal macular health or early AMD. Visual acuity, contrast sensitivity, and light sensitivity testing were all performed under photopic conditions and thus are cone-mediated. Cone density, including that in the fovea, remains remarkably stable during the aging process,³¹ and the cone photoreceptor mosaic is well preserved in early and intermediate AMD.³² From this perspective, it is not surprising that these cone-mediated functional tests were insensitive to SDD presence in normal and early AMD eyes. With respect to the null associations between SDD and low luminance acuity and the low luminance deficit, these foveal tests are performed under mesopic conditions. While foveal acuity under mesopic conditions relies on cones, rod photoreceptors also have a role through rod-cone coupling and the operation of surround mechanisms in retinal circuitry. Since the spatial density of macular rods is decreased in aging and AMD,^{31, 32} and the topography of SDD overall corresponds closely to the topography of rods in aging⁵ and in AMD,²⁶ one might expect mesopic tests to uncover SDD associated deficits. Yet our data show that these tests were insensitive to the presence of SDD in normal and early AMD eyes. However, mesopic and scotopic testing may be more likely to uncover SDD-associated visual dysfunction when test targets are positioned in retinal areas where rods are most numerous. Alternatively, a strong association between rod-mediated vision and SDD may not become manifest till later stages of AMD when photoreceptor health is more severely disturbed.

A major strength of our study is that single and sparse lesions (i.e., not in a pattern) were evaluated, in the context of multimodal imaging, and the presence of one lesion by itself did not define SDD presence in an eye. By adhering to the SDD nomenclature, we are less dependent on seeing a pattern as might be required for reticular pseudodrusen. There were enough correspondences of en face images with OCTs that we felt secure in our designations for the baseline and 3-year follow-up visit described herein. Also, absent ultrastructural data on SDD precursors, our working pathogenic model for SDD formation allows lesions to arise one at a time, rather than in a pattern, and most plausibly in retinal areas where advanced disease will be found. Other data from the ALSTAR cohort provided support for these decision rules. First was the striking correspondence of SDD lesions with the high density of rod photoreceptors in the perifovea,⁵ and encircling the optic nerve head, as similarly described for intermediate AMD.²⁶ Second was the two-fold risk for incident AMD in AREDS1 (normal) eyes with SDD by our criteria in this cohort.⁶

Other strengths of this study include a very large study sample of eyes ($N = 1,202$), many times larger than in previous work on SDD and visual function in AMD.^{8–15} The ALSTAR study^{17, 33, 34} was specifically designed to focus on the transition from normal macular aging to early AMD, an issue that has been largely unexplored in the literature. Unlike earlier research, this study focused on eyes in normal macular health and those in the earliest phases of AMD; previous studies on SDD and visual function were either directed at eyes with AMD regardless of disease severity or with intermediate and advanced disease. Previous research has suggested that male gender and cardiovascular disease increase the likelihood of SDD,^{35, 36} however, adjustment for these variables in our study did not change results. A limitation of our analyses is that they are cross-sectional and thus we cannot discern the temporal relationship between SDD and visual dysfunction in early AMD or normal macular health. Our sample of early AMD eyes ($N = 244$) was much smaller than our sample of eyes in normal macular health ($N = 858$), although still much larger than other studies on SDD and visual function in AMD.

In conclusion, in contrast to several reports that SDD are associated with an exacerbation of visual dysfunction in AMD as compared to eyes with no SDD,^{8–11, 14, 15} SDD in eyes in normal macular health do not appear to cause visual disturbances, at least as assessed by the visual function tests administered in this study. Eyes in normal macular health with SDD versus no SDD had similar distributions of photopic acuity, mesopic acuity, low luminance deficit, photopic contrast sensitivity, photopic light sensitivity, and rod-mediated dark adaptation, as did eyes in the early stages of AMD with and without SDD. Yet eyes with early AMD had delayed dark adaptation, however, this deficit appeared to be largely attributable to the advanced age of SDD eyes as compared to eyes with no SDD. Nevertheless, patients in normal macular health and early AMD who have SDD warrant observation due to their increased risk for incident early AMD and its progression.^{6, 37–40}

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Summary statement

Eyes in the earliest phase of AMD with SDD have slower dark adaptation than early AMD eyes without SDD, largely attributable to the more advanced age of these patients.

Figure 1. Multimodal imaging of eyes with and without subretinal drusenoid deposits, with different dark adaptation functions

A – D. Green lines on IR reflectance images show the location of corresponding SD-OCT scans. Curves for rod-mediated dark adaptation (RMDA) in these eyes are shown in Figure 2. **A.** Participant with healthy macula (AREDS grade 1) and lacking detectable subretinal drusenoid deposits (SDD), with rod intercept time (RIT) in minutes. **B.** Participant with macula considered normal (AREDS grade 1) and peripapillary SDD seen by IR and SD-OCT (arrows). **C.** Participant with early AMD (AREDS grade 2) and lacking detectable

SDD. **D.** Participant with early AMD (AREDS grade 2) and multiple SDD seen by IR and SD-OCT (arrows). Both participants with normal maculae (**A,B**) have normal RMDA, while both participants with early AMD (**C,D**) have delayed DA (defined as a RIT > 12.3). However, the eye with early AMD in the presence of SDD shows severely delayed RMDA: sensitivity was still not recovered after 20 minutes post-bleach, compared to the eye with early AMD and no SDD that had RIT of 16 minutes.

Figure 2. Dark adaptation functions for four eyes shown in Figure 1

The time course of recovery of log light sensitivity following photo-bleach offset is plotted over time for 20 minutes. The eye in normal macular health with no SDD (age 60) and the eye in normal macular health with SDD (age 73) had similar recovery functions, as indicated by their similar rod intercept times (shown by color-coded arrows on the x-axis). The eye with early AMD with no SDD (age 79) had slower recovery than the eyes in normal macular health. The eye with early AMD with SDD (age 78) exhibited little sensitivity recovery even after 20 minutes.

Table 1

Characteristics of eyes in the study sample overall and by SDD status

Variable	Overall (N=1202)	SDD (N=300)	No SDD (N=902)	P value
Age, years, n (%)				
60–69	717 (59.7)	141 (47.0)	576 (63.9)	
70–79	420 (34.9)	124 (41.3)	296 (32.8)	
80–89	64 (5.3)	34 (11.3)	30 (3.3)	
90	1 (0.1)	1 (0.3)	0 (0.0)	
Mean (SD)	69.2 (6.0)	70.9 (6.4)	68.7 (5.8)	< 0.001
AMD presence and severity, n (%)				
Normal	958 (79.7)	185 (19.3)	773 (80.7)	< 0.001
Early AMD	244 (20.3)	115 (47.1)	129 (52.9)	

Table 2

Visual function stratified by SDD presence versus absence for the total sample

Visual function	N eyes	All eyes				P value	Age-adjusted P value
		SDD		No SDD			
		M	SD	M	SD		
Visual acuity, logMAR	1202	0.056 (20/22)	0.13	0.043 (20/22)	0.13	0.1964	0.7029
Low luminance acuity	1202	0.362 (20/46)	0.12	0.353 (20/45)	0.13	0.3464	0.9702
Low luminance deficit	1202	0.307 (0.11)		0.310 (0.10)		0.6566	0.6118
Contrast sensitivity, log sensitivity	1202	1.60 (0.10)		1.61 (0.10)		0.0479	0.4359
Light sensitivity, dB <i>I</i>	1195	30.29 (1.63)		30.51 (1.98)		0.1232	0.7013
Rod-mediated dark adaptation, rod-intercept time, minutes ²	547	14.1 (9.3)		11.4 (6.4)		0.0019	0.0511

M, mean; SD, standard deviation

¹N=1195; 7 participants did not complete light sensitivity measurements.

²N=547; only one eye of each participant was evaluated. In addition, data were missing for 57 eyes because participant was unable to complete the test (56) or equipment failure (1).

Table 3

Visual function stratified by SDD presence versus absence stratified by those in normal macular health and early AMD

Visual function	Eyes in normal macular health				P value	Age-adjusted P value	Eyes with early AMD				P value	Age-adjusted P value
	SDD (N=185)		No SDD (N=773)				SDD (N=115)		No SDD (N=129)			
	M	SD	M	SD			M	SD	M	SD		
Visual acuity, logMAR	0.044 (20/22)	0.12	0.041 (20/22)	0.13	0.7832	0.8879	0.074 (20/24)	0.13	0.055 (20/23)	0.13	0.2983	0.7614
Low luminance acuity	0.354 (20/45)	0.12	0.352 (20/45)	0.13	0.8260	0.8567	0.375 (20/47)	0.13	0.363 (20/46)	0.14	0.4787	0.7984
Low luminance deficit	0.310 (0.10)		0.310 (0.10)		0.9540	0.9558	0.301 (0.12)		0.307 (0.11)		0.6706	0.5181
Contrast sensitivity, log sensitivity	1.60 (0.09)		1.61 (0.10)		0.0979	0.2692	1.59 (0.11)		1.60 (0.11)		0.4493	0.6924
Light sensitivity, dB /	30.27 (1.71)		30.52 (2.01)		0.1276	0.3051	30.34 (1.48)		30.43 (1.79)		0.7015	0.3760
Rod-mediated dark adaptation, rod-intercept time, minutes ²	11.6 (4.6)		11.1 (5.9)		0.4805	0.8772	16.9 (12.0)		12.7 (8.3)		0.0213	0.2645

M, mean; SD, standard deviation

¹ N= 1195; 7 participants did not complete light sensitivity measurements.

² N=547; only one eye of each participant was evaluated. In addition, data were missing for 57 eyes because participant was unable to complete the test (56) or equipment failure (1).