Internal Carotid Artery Stenosis and Ipsilateral Subretinal Drusenoid Deposits

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Purpose. Subretinal drusenoid deposits (SDDs) in age-related macular degeneration (AMD) are strongly associated with vasculopathies such as myocardial infarction and ischemic stroke. This study evaluates ischemic stroke subjects for SDDs to determine whether ocular hypoperfusion from internal carotid artery (ICA) stenosis is associated with ipsilateral SDDs.

Methods. A cross-sectional study at Mount Sinai Hospital recruited 39 subjects with ischemic stroke (aged 52–90; 18 women, 21 men); 28 completed all study procedures. Computed tomography (CT) of the head and neck evaluated 54/56 ICAs for stenosis criteria: none (n = 33), mild (n = 12), moderate (n = 3), severe (n = 3), and complete (n = 3). Spectral-domain optical coherence tomography (SD-OCT) scans were read to consensus by two masked graders for soft drusen, SDDs and choroidal thickness (CTh; choroidal thinning = CTh < 250 µm). Univariate testing was done with Fisher's exact test. Multivariate logistic regression models tested age, gender, and ICA stenosis as covariates.

Results. Moderate or more ICA stenosis (≥50%–69%) was significantly associated with ipsilateral choroidal thinning ($P = 0.021$) and ipsilateral SDDs ($P = 0.005$); the latter were present distal to six of nine stenosed ICAs versus five of 33 normal ICAs. Mild ICA stenosis (≥1%–49%) was not significantly associated with ipsilateral SDDs. Multivariate regression found that older age ($P = 0.015$) and moderate or more ICA stenosis ($P = 0.011$) remained significant independent risks for ipsilateral SDDs.

Conclusions. At least moderate ICA stenosis (≥50%–69%) is strongly associated with ipsilateral SDDs and choroidal thinning, supporting downstream ophthalmic artery and choroidal hypoperfusion from ICA stenosis as the mechanism for SDD formation. SDDs may thus serve as sensitive biomarkers for ischemic stroke and other vascular diseases.

Keywords: age-related macular degeneration, subretinal drusenoid deposits (SDDs), optical coherence tomography, ischemic stroke, internal carotid artery stenosis

Cardiovascular disease (CVD) and stroke are the leading causes of death,[1] and age-related macular degeneration (AMD) is the leading cause of blindness in developed countries.[2] Despite sharing common risk factors such as cholesterol-containing lesions, large studies[3–5] and meta-analyses[6,7] have not shown consistent associations between these conditions.

The two main categories of lesions found in intermediate AMD (iAMD) are subretinal drusenoid deposits (SDDs) and soft drusen. SDDs are also known as reticular pseudodrusen. On spectral-domain optical coherence tomography (SD-OCT), SDDs are found above the retinal pigment epithelium (RPE). Soft drusen originate between the RPE and Bruch's membrane, elevating the RPE (Fig. 1).

Thomson et al.[8] have recently demonstrated that the aforementioned inconsistencies between AMD and vascular disease may be due to the fact that only one category of iAMD, SDDs, is associated with CVD and stroke. Other known associations with SDDs include female gender and older age.[9]

In a recent study of 200 iAMD subjects, Ledesma-Gil et al.[10] have further demonstrated that SDDs are strongly associated with three high-risk vascular disease (HRVD) categories within CVD and stroke: (1) myocardial dysfunction (congestive heart failure, myocardial infarction), (2) valvular heart disease, and (3) ischemic stroke/transient ischemic attack. These cardiovascular and neurovascular disorders pose a high risk for morbidity, mortality, and ophthalmic hypoperfusion, with decreased blood flow through the internal carotid artery (ICA), its ophthalmic artery (OA) branch, and the posterior ciliary arteries that emerge from the OA to supply the choroid.

Although a strong association between choriocapillaris (CC) hypoperfusion and SDDs has recently and definitively

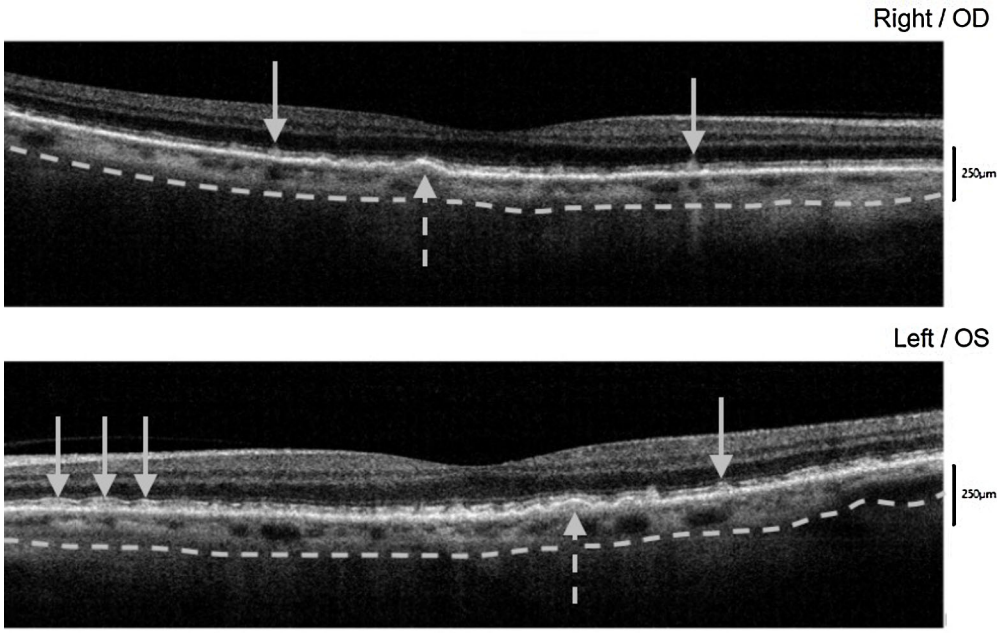

FIGURE 1. SD-OCT imaging of SDDs (*solid arrows*) and soft drusen (*dashed arrows*) in a patient with ischemic stroke and bilateral ICA stenosis on CT head and neck (100% stenosis of the right ICA, 50% stenosis of the left ICA). SDDs of Stages 1, 2 and 3 appear as hyperreflective material above the retinal pigment epithelium (RPE) and below, elevating and penetrating the EZ, respectively. Stage 1 SDDs are numerous in both scans. Three Stage 2 SDDs elevating the EZ are seen on the left in the scan of OS. A Stage 3 SDD penetrating the EZ is seen at the right in the scan of OD. Soft drusen are found below the RPE in both scans. The *gray dashed lines* demarcate the choroidal-scleral interface. This patient had at least moderate ICA stenosis, thin choroids (<250 µm), drusen, and SDDs bilaterally.

been demonstrated on SD-OCT angiography,[11] the mechanism of hypoperfusion remains to be proven. For instance, in the Alienor study, Chan et al.[12] showed that choroidal thinning in AMD preceded SDDs over three years. Although this does not prove that choroidal insufficiency causes SDD formation, it is unlikely that SDDs induce choroidal thinning.

To provide direct support for a hypoperfusion mechanism of SDD formation, we sought to identify whether SDDs were present in eyes ipsilateral to carotid artery disease in ischemic stroke subjects. The severity of right and left ICA stenosis was measured on CT head and neck and concurrently correlated with the presence of downstream SDDs in each ipsilateral eye on SD-OCTs.

ICA stenosis compromises blood flow through the ipsilateral OA, posterior ciliary arteries, choroid, and CC. Given that the choroid does not have autoregulation, as is afforded to the retinal circulation, compensatory modulation of choroidal blood flow downstream of ICA stenosis is unlikely.[13] We therefore hypothesize that ICA stenosis causes ipsilateral SDDs via CC insufficiency that in turn leads to RPE dysfunction and photoreceptor hypoxia, with damaged photoreceptors accumulating as SDDs. We further hypothesize an ipsilateral dose-response to the severity of ICA stenosis, with a greater incidence of SDDs and age-corrected choroidal thinning distal to more stenosed ICAs.

METHODS

This was a cross-sectional study of subjects diagnosed with ischemic stroke that were admitted to Mount Sinai Hospital between August 2022 and February 2023. The institutional review board (IRB) of the Icahn School of Medicine at Mount Sinai approved the study, IRB approval no. 22-00765, which adhered to the tenets of the Declaration of Helsinki.

Inclusion Criteria

Subjects were aged 52 to 90 years and diagnosed with ischemic stroke. All subjects had the capacity to sign informed consent and comply with study procedures.

Exclusion Criteria

Hemorrhagic stroke. History of previously diagnosed AMD, other retinal degenerations, or retinal vascular diseases such as diabetic retinopathy. Subjects with the following were excluded after enrollment: absent CT head and neck on chart review, CT head and neck without assigned ICA stenosis criteria, feeble state precluding OCT scanning, inadequate OCT quality, and coincident pathology that precluded evaluation of SDDs.

Neurovascular Data

Patient charts were reviewed to evaluate CT head and neck and obtain bilateral ICA stenosis status. Two stenosis criteria have been defined by the North American Symptomatic Carotid Endarterectomy Trial (NASCET): 30-69% moderate (medium-grade) and 70–99% severe (high-grade).[14] The six criteria for carotid stenosis as used in the Mount Sinai Hospital electronic medical record are essentially refinements of the established NASCET criteria: 0% = normal, 1%–49% = mild, 50%–69% = moderate, 70%–89% = severe, 90%–99% = critical, 100% = complete. All CT scans were performed during the corresponding admission.

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Demographic and Systemic Clinical Data

Chart review was done on 28 ischemic stroke subjects to obtain age, gender, and history of hypertension or diabetes.

Ophthalmic Imaging and Data

All subjects underwent bilateral SD-OCT at the bedside during their inpatient admission using an Optovue Eye Scan (Visionix, Pont-de-l'Arche, France). For each eye, these scans were read to consensus by two expert masked graders (R.T.S., G.L.) for drusen (Y/N), as well as SDDs (Y/N) and SDD staging (1, 2, or 3) by published criteria.[15] SDD presence was defined as Stage 1 or greater, with Stage 1 defined as hyperreflective material between the ellipsoid zone (EZ) and underlying RPE; Stage 2, such material elevating the EZ; and Stage 3, such material penetrating the EZ. Choroidal thickness (CTh) was examined on a subfoveal scan, and choroidal thinning (Y/N) was defined as CTh < 250 µm. Soft drusen presence (Y/N) was defined by the presence of hyper-reflective material beneath and elevating the RPE (Fig. 1).

On SD-OCT scans read as positive for SDDs, an SDD score was assigned as follows. The SDD load was quantified on five representative B scans, one through the fovea and the other four approximately 500 and 1000 µm above and below the fovea, respectively. Each Stage 2 and 3 SDD was scored as 1 individually on each B scan, and stage 1 SDDs were counted as a single binary value of 1 if stage 1 SDDs were present anywhere in the B scan, and 0 otherwise. The SDD score then assigned to each B scan was the sum of scores for each SDD stage; the score for the entire SD-OCT scan was the sum of scores for the five B scans studied for that scan. SD-OCT scans read as negative for SDDs were assigned a score of 0. For each category of ICA stenosis, the SDD scores for the ipsilateral SD-OCT scans for that category were reported as total, mean, median, and range.

Statistics

Ipsilateral ICA stenosis (none, mild, moderate, severe, critical, complete), older age (age ≥ 70), gender, hypertension (Y/N), and diabetes (Y/N) were the categorical variables tested as risks for ipsilateral SDD presence. Age was also tested as a continuous variable by *t* testing. Univariate testing was done by Fisher's exact test. Multivariate logistic regression analysis was performed on all variables of univariate significance.

Results

Patient Selection, ICA Selection, Demographics, and Clinical Characteristics

A total of 39 subjects with ischemic stroke were recruited into this cross-sectional study. Six did not have CT scans of the head and neck on chart review, four were too feeble for OCT scanning, and one had inadequate OCT quality. These 11 subjects were excluded, leaving 28 study participants. Two ICAs without assigned stenosis criteria were excluded, leaving 28 subjects and 54 ICA/ipsilateral eye pairs with no missing data for analysis.

The associations of demographic and systemic clinical characteristics with ipsilateral SDDs were significant only for female gender and older age (≥70 years), not for hypertension or diabetes. In males, SDDs were present distal to 2/25 ICAs versus 12/29 ICAs in females ($P = 0.006$, Fisher exact test). In older subjects, SDDs were present distal to 12/28 ICAs versus 2/26 ICAs in younger subjects ($P = 0.005$, Fisher exact test). The mean ages for eight subjects with SDDs versus 20 subjects without SDDs were 78 and 66 years, respectively ($P = 4.98 \times 10^{-4}$, one-tailed *t* test).

ICA Stenosis and Associations With Downstream Ipsilateral Retinal Pathology

Twelve subjects had ICA stenosis, three with unilateral and nine with bilateral carotid disease (21 stenosed ICAs in total). The 54 ICAs that were analyzed include 21 stenosed ICAs and 33 nonstenosed ICAs, categorized by Icahn School of Medicine at Mount Sinai criteria: none (n = 33), mild (n = 12), and moderate or more ICA stenosis (n = 9), with none referring to no ICA stenosis. The nine ICAs in the moderate or more category had moderate (n = 3), severe (n = 3), critical (n = 0), and complete (n = 3) stenosis.

ICA stenosis was significantly associated with ipsilateral SDDs, as illustrated in Table. For moderate or more ICA stenosis (≥50%), ipsilateral SDDs were found distal to 6/9 stenosed ICAs vs 5/33 normal ICAs ($P = 0.005$, Fisher exact test, OR 11.2, 95% CI 2.1–60.2). Figure 2 demonstrates the CTA and SD-OCT of a case of severe ICA stenosis with ipsilateral SDDs and choroidal thinning.

Breaking down the moderate or more ICA stenosis group into its three subcategories – moderate (50–69%), severe (70–89%) and complete (100%), ipsilateral SDDs were found distal to the following: 3/3 moderately stenosed ICAs versus 5/33 normal ICAs ($P = 0.008$, Fisher exact test), 1/3 severely stenosed ICAs versus 5/33 normal ICAs ($P = 0.431$, Fisher

Table. ICA Stenosis Versus Downstream Ipsilateral Pathology (SDDs, Choroidal Thinning, Soft Drusen)

		Ipsilateral SDDs		Ipsilateral Choroidal Thinning (CTh < 250 µm)		Ipsilateral Soft Drusen	
	ICAs (n)	Yes	No	Yes	No	Yes	No
Mild ICA stenosis (1%–49%)	12	3	9	3	9	2	10
None	33	5	28	13	20	7	26
P value		0.661		0.491		1.000	
Moderate or more ICA stenosis (≥50%–69%)	9	6	3	8	1	5	4
None	33	5	28	13	20	7	26
P value		**0.005**		**0.021**		0.090	

Bolded *P* values indicate statistically significant associations by Fisher exact test.

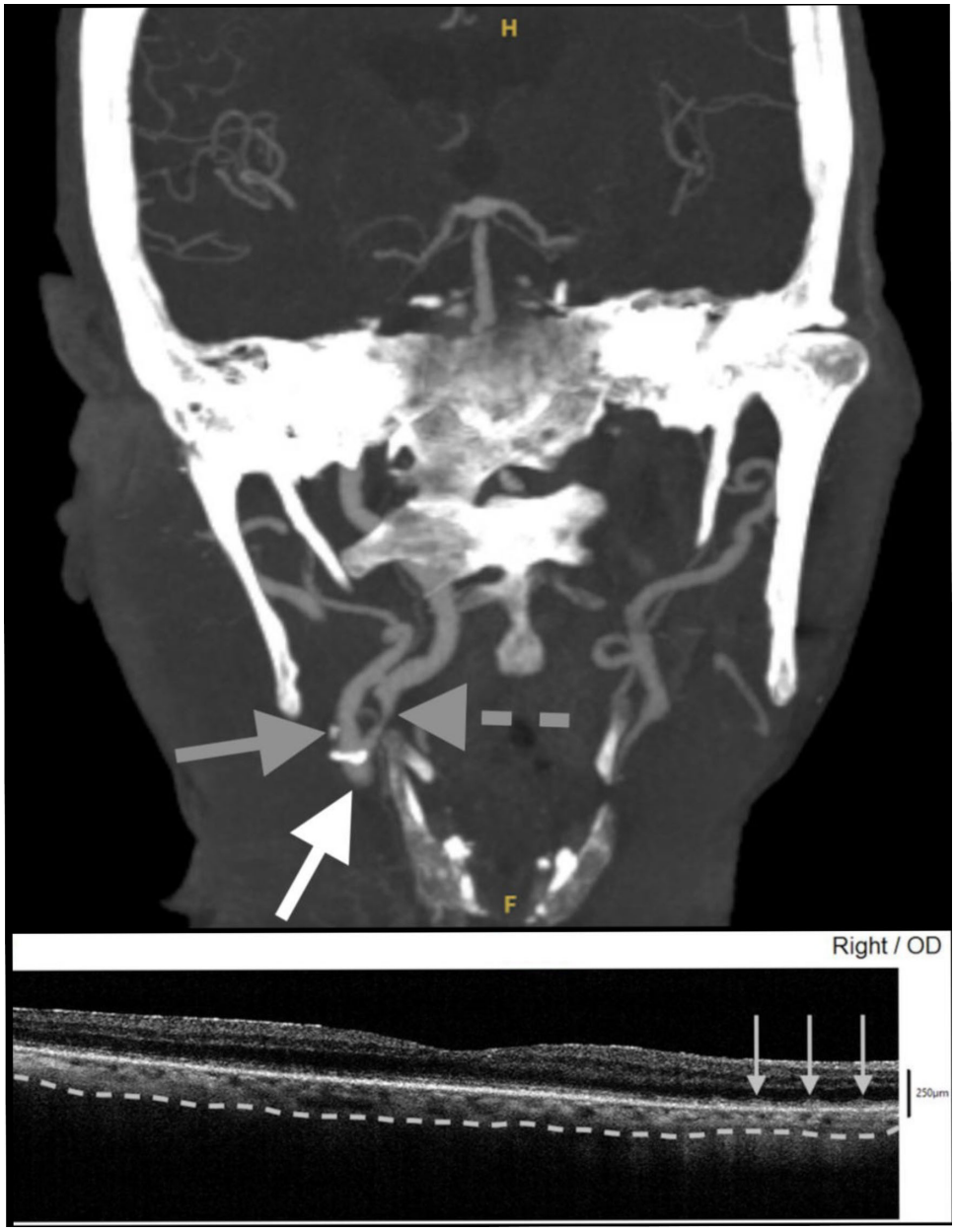

Figure 2. *Top image*: CT angiography head and neck of a patient with bilateral ICA stenosis. Severe (70%-89%) right ICA stenosis is shown. Complete (100%) left ICA stenosis is demonstrated in another CT section (not shown). The right common carotid artery (*white arrow*) bifurcates into the right external carotid artery (*solid gray arrow*) and right ICA (*dashed gray arrow*). The *dashed arrow* points to the exact location of right ICA stenosis. Per neurovascular expert (M.D.), this image was windowed to distinguish between bone and contrast enhancement. Window width (WW) and window level (WL) were adjusted to 1133 and 395 Hounsfield units (HU), respectively. *Bottom image*: SD-OCT of the same patient's right eye demonstrating stage 2 and 3 SDDs (*gray arrows*), which elevate and penetrate the EZ. The interdigitation zone (IZ) is not visualized throughout and is replaced by granular material (stage 1 SDDs) in some places. The *gray dashed lines* demarcate the choroidal-scleral interface and demonstrate CTh (<250 µm). SD-OCT of this patient's left eye, not depicted, also showed stage 2 SDDs and choroidal thinning.

exact test), and 2/3 completely stenosed ICAs versus 5/33 normal ICAs ($P = 0.090$, Fisher exact test).

The moderate or more ICA stenosis group was also broken down by laterality. SDDs in the right eye were found distal to 2/4 right-sided stenosed ICAs versus 4/17 right-sided normal ICAs ($P = 0.544$, Fisher exact test). SDDs in the left eye were found distal to 4/5 left-sided stenosed ICAs versus 1/16 normal ICAs ($P = 0.004$, Fisher exact test). Mild ICA stenosis (1%–49%) was not significantly associated with ipsilateral SDDs, which were found distal to 3/12 stenosed ICAs versus 5/33 normal ICAs ($P = 0.661$, Fisher exact test).

Moderate or more ICA stenosis was also significantly associated with ipsilateral choroidal thinning, which was present distal to 8/9 stenosed ICAs versus 13/33 normal ICAs ($P = 0.021$, Fisher exact test; OR = 12.3; 95% CI, 1.4–110). Breaking down the moderate or more ICA stenosis group into its three subcategories (moderate, severe, and complete), choroidal thinning was found distal to the following: 3/3 moderately stenosed ICAs versus 5/33 normal ICAs

($P = 0.078$, Fisher exact test), 2/3 severely stenosed ICAs versus 5/33 normal ICAs ($P = 0.559$, Fisher exact test), and 3/3 completely stenosed ICAs versus 5/33 normal ICAs ($P = 0.078$, Fisher exact test). Moderate or more ICA stenosis was not significantly associated with ipsilateral soft drusen, which were present distal to 5/9 stenosed ICAs versus 7/33 normal ICAs ($P = 0.090$, Fisher exact test). Mild ICA stenosis was not significantly associated with ipsilateral choroidal thinning or soft drusen ($P = 0.491$ and $P = 1.000$, respectively, Fisher exact test).

Multivariate logistic regression was performed on the three categorical variables that had univariate significance with ipsilateral SDDs: age (<70/≥70), gender (male/female), and ICA stenosis (moderate or more/none). Age ($P = 0.015$) and moderate or more ICA stenosis ($P = 0.011$) remained independent, significant risks for ipsilateral SDDs. Only female gender trended toward significance ($P = 0.061$).

SDD Scores on Ipsilateral SD-OCT Scans

By ICA stenosis grade, the total SDD scores and statistics were as follows:

1. Stenosis grade None (n = 33): total SDD score 59, mean 1.79, median 0, range 0–25
2. Stenosis grade Mild (n = 12): total SDD score 22, mean 2.08, median 0, range 0–10
3. Stenosis grade Moderate or more (n = 9): total SDD score 71, mean 7.89. median 11, range 0–32.

None of the data were normally distributed. Notable outliers were present in the data for ICA stenosis grade None. Subject 22 had ICA stenosis grade None bilaterally. The SDD scores for OD and OS were 15 and 25, respectively, compared to the group mean of 1.79, median 0.

Discussion

We have previously shown that three categories of HRVDs are associated with SDDs: (1) myocardial dysfunction (congestive heart failure and myocardial infarction), (2) valvular heart disease, and (3) internal carotid artery pathology (ischemic stroke/transient ischemic attack).[10] The common postulated mechanism for SDD formation in all categories is associated choroidal hypoperfusion. In this study, we solely recruited patients with one of these entities, ischemic stroke with ICA stenosis, to evaluate whether carotid artery disease is significantly associated with ipsilateral choroidal thinning and SDDs.

Moderate or more ICA stenosis (≥50%) was strongly associated with downstream ipsilateral SDDs, even after controlling for older age, female gender, diabetes, and hypertension. Mild ICA stenosis (1%–49%) was not. Mild ICA stenosis was not. This pathophysiological dose response to the severity of ICA stenosis, coupled with ipsilateral choroidal thinning distal to moderately or more stenosed ICAs, strongly supports ocular hypoperfusion from compromised OA blood flow and downstream CC insufficiency as the likely mechanism for SDD formation in cases of ICA stenosis.

SDDs were also quantitated in each SD-OCT scan with a combined score from five representative B scans. The mean SDD scores in the ICA stenosis groups of None, Mild and Moderate or more followed trends similar to those of the associations of SDDs with these groups. The mean scores in the None and Mild groups were both near 2, whereas that of the moderate or more was nearly 8. However, these data were not normally distributed, and the means do not tell the whole story. In particular, there were 2 clear SDD score outliers in the no ICA stenosis group, 15 and 25, from the 2 eyes of same patient. Our perfusion paradigm would suggest, but we cannot prove, that another hypoxia driver, not ICA stenosis, was also present bilaterally, perhaps cardiac disease in this vasculopathic patient. This should serve as an important reminder. Although the two ICA vascular systems in an individual are essentially independent of each other, they will both be dependent in a similar manner on systemic disease external to the carotids. The other important point here is whether ICA stenosis of any particular degree should be expected to correspond to CC insufficiency or SDD formation of some degree. We have measured general trends of evidence supporting the principle, but there surely must be significant, biological variability between individuals to these responses. This was demonstrated in the individual SDD scores.

Our paradigm is consistent with the physiology of oxygen consumption in the eye. SDDs form above the RPE (Fig. 1) in the photoreceptor (PR) layer. PRs have the greatest oxygen demand per unit mass in the body,[16] whereas the choroid, which supplies the CC and PRs, receives the highest perfusion per unit mass in the body.[17] Thus the structures most vulnerable to hypoxia from CC insufficiency are PRs. We hypothesize that CC insufficiency from systemic vascular diseases (e.g., ischemic stroke with ICA stenosis) produces a hypoxic insult to PRs, resulting in SDDs. Given that SDDs are found in the photoreceptor layer, they may be the byproduct of damaged PRs; however, the precise mechanism has yet to be elucidated.

The link between carotid artery hypoperfusion and choroidal insufficiency is further supported by carotid endarterectomy resulting in increased ipsilateral subfoveal choroidal thickness and volume in neurovascular patients with clinically significant ICA stenosis.[18,19] We have shown that even moderate ICA stenosis is associated with ipsilateral choroidal thinning and SDDs, so carotid endarterectomy to improve ipsilateral choroidal perfusion could be investigated as a possible benefit to these patients with the SDD form of AMD.

Systemic vascular diseases besides ischemic stroke have also been linked to SDDs. Heart diseases in general are an important recently discovered association.[8,10] Coronary artery disease in particular was associated several years ago with SDDs[15] and with generalized choroidal thinning.[20] The choroidal thinning has also been associated with CC insufficiency[21] demonstrated by OCTA in such cases.

It is also important to note that although coronary artery disease, ICA stenosis, and other vascular disorders have been associated with choroidal thinning and downstream SDDs, thin choroids are not independently related to SDDs. There is no significant SDD presence in populations with high myopia, who have choroidal thinning in the absence of vascular disease. In CVD, we posit that the thinned choroid results from hypoperfusion, while in high myopia, choroidal thinning results from elongation of the globe. Thus, whereas hypoperfusion, not myopia, contributes to SDD formation, choroidal thinning may be associated with either.

Recent research suggests that the link between ocular hypoperfusion and SDD patterns can be modeled as a Turing pattern.[22] Named after mathematician Alan Turing, Turing patterns are complex patterns in nature (e.g., zebra stripes)

that may form as the result of a two-component diffusion system with an activator and competing inhibitor. By modeling such a reaction-diffusion system and varying the strength of the reaction kinetics (activator), Young et al.[22] generated topographic images consistent with all SDD morphologies (dot, reticular, confluent). If SDDs are thus viewed as Turing patterns, our findings are compatible with competition between an activator (ocular ischemia) and an intrinsic, variable inhibitor.

Not only does the association between HRVD (e.g., ICA stenosis) and SDDs support a hypoperfusion mechanism for SDD formation, it also helps explain why these lesions are disproportionately found in females later in life.[15,23,24] In this cross-sectional study of 28 subjects with ischemic stroke, females had a greater incidence of SDDs than their male counterparts. Women with HRVD tend to outlive age-matched males,[1] which may explain the preponderance of women with SDDs in later years.

This study has several limitations. All subjects were recruited from an inpatient ward at a hospital, which may have contributed to a selection bias toward more severe HRVD cases. Studies from both inpatient and outpatient populations would allow us to better characterize the impact of HRVD on SDD prevalence. Larger sample sizes in future studies are needed to replicate these results and would help determine the benefit of screening neurovascular patients for SDDs. Last, although SD-OCT angiography is needed to directly show ipsilateral CC insufficiency and was not obtained in the study, prior literature has shown that SDDs are associated with CC insufficiency on OCTA.[11] Hence, the significant presence of SDDs and choroidal thinning ipsilateral to moderately or more stenosed ICAs strongly supports coexistent ipsilateral CC insufficiency in this study.

Strengths of this cross-sectional study include well-defined inclusion criteria and strict subject selection, as well as high-quality imaging: CT head and neck for ICA stenosis, and SD-OCT for drusen, SDDs, and CTh. SD-OCT scans were read to consensus by two masked expert graders. The significant associations identified herein between moderate to complete ICA stenosis and ipsilateral SDDs build on the recently identified strong association between stroke and SDDs[10] and support a vascular mechanism of SDD formation. As postulated by that recent study, our findings similarly lend support to a larger role for SDDs as biomarkers of ischemic stroke and other coexistent high-risk vascular diseases.

In summary, this study provides strong support for the hypothesis that SDDs are driven by systemic vascular disorders that compromise ophthalmic and choroidal perfusion. It is in fact the first study to demonstrate a significant association between increasing severity of ICA stenosis and ipsilateral SDDs, suggesting a vascular mechanism for SDD pathophysiology. Further research is warranted to determine whether using OCT to detect SDDs could serve as an inexpensive mass-screening tool for HRVD that can prompt life-saving vascular evaluation.

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