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ORIGINAL ARTICLE

Investigation of Ocular Hemodynamics in Sturge-Weber Syndrome

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ABSTRACT

Purpose. Sturge-Weber syndrome (SWS) is a condition often associated with facial cutaneous angioma, vascular malformations in the brain, and ocular anomalies such as glaucoma. Reduced cerebral blood flow and ischemia have been well documented. Less is known about ocular blood flow despite the frequent associations between altered hemodynamics and the mechanisms underlying glaucomatous optic neuropathy. The aim of this research was to investigate retrobulbar hemodynamics in patients diagnosed with SWS.

Methods. The sample comprised 16 patients diagnosed with SWS and 16 age- and gender-matched normal control subjects. Four patients were diagnosed with both SWS and primary open-angle glaucoma (mean age 34.3 years; SD 26.9 years), three patients with both SWS and closed-angle glaucoma (mean age 23.3 years; SD 18.0 years), and nine patients with SWS and no glaucoma (mean age 17.2 years; SD 9.1 years). Systemic blood pressure and intraocular pressure were measured to determine the mean arterial pressure and ocular perfusion pressure. All patients and subjects underwent ultrasonography of the ophthalmic artery, central retinal artery, and short posterior ciliary arteries.

Results. No significant difference between groups for mean arterial pressure or ocular perfusion pressure ($p > 0.05$) was recorded. Participants diagnosed with SWS and primary open-angle glaucoma showed significantly reduced end-diastolic velocity (mean 0.036 m/s; SD 0.005 m/s) in their central retinal artery ($p = 0.016$) when compared against their age-matched normal controls (mean 0.054 m/s; SD 0.010 m/s). Participants diagnosed with SWS and no glaucoma also showed significantly reduced end-diastolic velocity (mean 0.038 m/s; SD 0.015 m/s) in their central retinal artery ($p = 0.046$) when compared against their age-matched normal controls (mean 0.054 m/s; SD 0.014 m/s).

Conclusions. Retrobulbar hemodynamics appear to be altered in participants diagnosed with SWS irrespective of their diagnosis of glaucoma. Further research is needed to ascertain whether there are any long-term consequences of such changes to ocular physiology.

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Key Words: Sturge-Weber syndrome, ocular blood flow, glaucoma

Sturge-Weber syndrome (SWS) is a rare neuro-oculocutaneous disorder of unknown incidence and cause. The patient often presents with a port wine stain (PWS) or nevus flammeus; neurological abnormalities include epilepsy, hemiparesis, and learning disabilities; ocular anomalies consist of glaucoma or vascular irregularities of the conjunctiva, episclera, choroid, and retina.[1–3] SWS is thought to occur during the first trimester of embryological development when the venous system divides into an external portion providing vascular support to the facial skin and scalp, a middle portion sustaining the meninges, and the deep portion that feeds and drains the brain.[4] A mutation of these embryological tissues at this early stage of development is postulated as one mechanism for the occurrence of SWS.[5]

Cerebral blood flow anomalies associated with SWS include an excessive layer of blood vessels on the surface of the brain (meningeal angiomas) ipsilateral to the PWS.[6] Brain imaging techniques have documented decreased glucose metabolism and hypoperfusion of the cortex underlying the angioma.[7,8] A reduction in arterial blood flow velocity has been recorded via transcranial Doppler sonography in the middle cerebral arteries in children with SWS.[9] In SWS, the brain region below the meningeal angioma often shows signs of progressive gliosis, atrophy, and calcification.[10] Neuroimaging studies have provided important insights into the pathology and progression of neurological injury. General consensus indicates that neurological deterioration of SWS is secondary to

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impaired blood flow in the brain and is exacerbated by the presence of seizures.[11] Significantly less is known about ocular blood flow in SWS despite the frequent associations between altered ocular blood flow responses, vascular dysregulation, and the mechanisms underlying glaucomatous optic neuropathy (GON).

The most frequent ophthalmic manifestation associated with SWS is glaucoma, which has a reported prevalence between 60 and 71%.[12,1] The risk significantly increases on the ipsilateral side of the face as the PWS, especially when the stain affects the upper eyelid.[1,13] Children presenting before 2 years of age have enlarged corneal diameters and an angle anomaly similar to that seen in congenital glaucoma resulting in significantly elevated intraocular pressure (IOP) and glaucoma.[1,13] Patients presenting in the late-onset group frequently have normal anterior chamber angle and raised episcleral venous pressure often accompanied with blood in Schlemm's canal.[1,13–15] Authors have postulated that raised episcleral venous pressure causes an obstruction to aqueous outflow in the venous drainage system resulting in open-angle glaucoma.

The suggestion that altered hemodynamic responses might play a role in the mechanism underlying GON is somewhat unsurprising. Over the years, different theories have been put forward to explain some of pathological consequences underlying GON. The mechanical hypothesis states that increased IOP causes stretching of the laminar beams and damage to retinal ganglion cells leading to GON. The mechanical theory in isolation however does not explain why GON continues to progress for some patients despite significant reduction of their IOP.[16] Neither does it explain normal tension glaucoma where patients with normal IOP develop glaucomatous disks and visual field defects nor ocular hypertension where patients with IOPs more than 21 mm Hg present without any clinically detectable damage. These factors have led many researchers to propose a vascular theory which states that vascular insufficiency and ischemia might be another important risk factor associated with GON. The purpose of this research was therefore to investigate ocular hemodynamic responses of patients diagnosed with SWS.

METHODS

Sixteen participants with a confirmed diagnosis of SWS and their age- and gender-matched normal controls were enrolled in the study. Inclusion criteria consisted of a distance refractive error no greater than ±6.00 D of sphere or ±2.0 D of astigmatism. Age-matched normal controls did not have any systemic pathology which would have interfered with their circulation. Participants diagnosed with SWS did not have any other systemic pathology that would have interfered with their circulation. All participants were informed of the procedure and written informed consent was taken. Research attended to the tenets of the Declaration of Helsinki.

All participants attended for one visit at Aston University Day Hospital where the following investigations were carried out on both eyes. Visual acuity was measured via logMAR acuity charts. Fundus images were recorded using a non-mydriatic fundus camera (Topcon NW-200). IOP was determined using the Nidek NT-1000 non-contact tonometer. Systemic systolic blood pressure and diastolic blood pressure was measured three times using an automated sphygmomanometer (A&D Company limited, Tokyo, Japan). For each participant, anterior chamber angles and anterior chamber depth were measured by the Pentacam (PTC, Oculus Inc., Wetzlar, Germany). Angle images were captured using the horizontal liner scan protocol (from 3-o'clock to 9-o'clock direction) following the protocol recommended by Hong et al.[17]

The Sequoia 512 Color Doppler Imaging (CDI) System (Siemens AG Medical Solutions, Erlangen, Germany) was used to obtain blood velocity and resistance measurements for the ophthalmic artery, central retinal artery (CRA), and short posterior ciliary arteries. Peak systolic velocity (PSV), end-diastolic velocity (EDV), and resistivity index (RI) were recorded for each of the examined vessels. Participants were placed in a supine position with their head tilted upward approximately 30°. A 7.5 MHz linear phased array transducer (Siemens Sonoline Sienna, Erlangen, Germany) was gently applied to their closed upper eyelid after resting for a period of 15 min. To determine the Doppler flow angle, the proximal and distal portions of the vessels were both imaged. The same sonographer was used to perform all measurements.

The systemic features associated with SWS are presented in Table 1. Six out of a potential 16 participants (37.5%) had complete trisymptomatic SWS with cutaneous angiomatosis, leptomeningeal angiomatosis, and ocular involvement. The other 62.5% presented with either incomplete bisymptomatic or monosymptomatic SWS. For the SWS participants, the diagnosis of glaucoma or no glaucoma was based on each participant's own clinician who was independent of this study. The criteria used to establish a diagnosis would have varied between participants as some had been diagnosed decades before in their early infancy. Participant 13 was diagnosed with bilateral glaucoma shortly after she was born and had surgery on both eyes in her early infancy; this fact probably explains why her cup disc ratios were small. The Pentacam (PTC, Oculus Inc.) was used to categorize participants as primary open-angle glaucoma (POAG) or closed-angle glaucoma (CAG). An accurate scan for participant 9 or participant 13, or 16 was not possible; however from their history, including age of onset, it appears likely that all participants had an angle anomaly[1,13] and were therefore classified as having CAG. Consequently, four participants were diagnosed with both SWS and POAG (mean age 34.3 years; SD 26.9 years), three participants with both SWS and CAG (mean age 23.3 years; SD 18.0 years), and nine participants (53%) with SWS presented without glaucoma (mean age 17.2 years; SD 9.1 years). No attempt was made to wash out participants from their topical glaucoma medication. Other ocular features included strabismus (18.8%) and retinal detachment (6.3%). All participants diagnosed with glaucoma also had a PWS affecting their upper eyelid, and the two participants with bilateral glaucoma had a bilateral port wine stain on both upper eye lids. Not everyone diagnosed with glaucoma was diagnosed with epilepsy.

Normal age-matched controls had their history, visual acuity, fundus examination, and IOP measured by a clinician to ensure nil ocular pathology. One eye per subject was selected for statistical analysis. Mean arterial pressure was calculated from the formula: mean arterial pressure = diastolic pressure + 1/3 (systolic pressure − diastolic pressure). Ocular perfusion pressure was calculated from the formula: ocular perfusion pressure = 2/3 (mean arterial blood pressure − IOP). RI was calculated from the formula: RI = (PSV − EDV)/PSV.

TABLE 1.
Features of Sturge-Weber population

Participant number	Visual acuity RE	Glaucoma RE	ACA RE	ACD RE	Cup/disc RE	Visual acuity LE	Glaucoma LE	ACA LE	ACD LE	Cup/disc LE	Glaucoma medication	Epilepsy	Facial PWS
1	0.16	Yes (POAG)	37.63	2.99	0.5	0.10	No	28.95	2.63	0.3	Timolol	No	Yes
2	0.04	No	43.05	3.19	0.3	0.02	No	40.73	3.17	0.3	—	Yes	No
3	0.20	No	48	3.07	0.2	0.08	No	48.07	3.09	0.2	—	Yes	Yes
4	0.32	No	35.95	2.84	0.4	0.08	No	35.17	2.53	0.3	—	Yes	Yes
5	0.28	Yes (POAG)	54.6	4.08	0.8	0.22	No	Z	Z	0.2	Lantanoprost	Yes	Yes
6	0.1	No	37	2.84	0.2	NPL	No	Z	Z	Z	—	Yes	Yes
7	0.00	No	39.23	3.46	0.4	0.04	Yes (POAG)	42.5	3.77	0.7	Timolol	No	Yes
8	0.04	No	41.9	3.07	0.5	0.02	No	41.9	3.05	0.5	—	Yes	No
9	0.36	Yes (CAG)	Z	Z	0.6	0.80	Yes (CAG)	Z	Z	0.7	—	Yes	Yes
10	0.80	Yes (POAG)	41.8	3.67	0.7	0.14	No	38.3	3.20	0.6	Lantanoprost	Yes	Yes
11	0.02	No	39.62	3.39	0.3	0.14	No	33.8	3.21	0.2	—	Yes	Yes
12	0.06	No	42.3	3.38	0.2	0.02	No	38.75	3.36	0.2	—	Yes	No
13	0.44	Yes (CAG)	Z	Z	0.2	0.44	Yes (CAG)	Z	Z	0.3	Lantanoprost	Yes	Yes
14	0.08	No	Z	Z	0.4	0.18	No	Z	Z	0.5	—	Yes	Yes
15	0.0	No	39.05	2.81	0.2	0.0	No	35.1	2.69	0.2	—	Yes	Yes
16	NPL	Yes (CAG)	Z	Z	Z	0.22	No	40.75	3.28	0.2	—	Yes	Yes

RE, right eye; LE, left eye; Z, reading not possible; NPL, nil perception of light; ACA, anterior chamber angle; ACD, anterior chamber depth.

Statistical Analysis

As age and gender are known to effect blood flow, each participant diagnosed with SWS was age- and gender-matched to a normal healthy control. An independent t-test was then carried out on SWS participants with any type of glaucoma (CAG and POAG) in either eye (bilateral or unilateral) using one affected eye ($n = 6$) vs. their age- and gender-matched normal control. The eye chosen for analysis was randomized between participants for those with CAG. In addition, an independent t-test was carried out on SWS participants with POAG in either eye (bilateral or unilateral) using one affected eye ($n = 4$) vs. their age- and gender-matched normal control. Participant 16 could not be used in any blood flow analysis as the eye with glaucoma was necrotic. An independent t-test was also carried on SWS and no glaucoma in either eye ($n = 9$) vs. their age- and gender-matched normal control. The eye chosen for analysis was randomized between participants with the exception of participant 6 where the right eye was chosen due to a retinal detachment in their left eye. To carry out a comparison between participants diagnosed with SWS and glaucoma ($n = 6$) vs. participants diagnosed with SWS and no glaucoma ($n = 9$), a one-way analysis of variance was carried out for both the right eyes and left eyes using age as a covariate for each of the blood flow parameters as it was impossible to match this group in terms of age.

RESULTS

No significant difference was found for age, systolic pressure, diastolic pressure, mean arterial pressure, or ocular perfusion pressure between either participants diagnosed with SWS and glaucoma and between participants diagnosed with SWS without glaucoma vs. their age-matched controls ($p > 0.05$) (Table 2). The only parameter to reach statistically significant differences between participants diagnosed with SWS and glaucoma (both CAG and POAG) vs. their age-matched normal controls was IOP ($p = 0.017$) (see Table 2). Inspection of the raw data reveals that all those diagnosed with SWS and glaucoma consistently had higher IOPs (mean = 20.567 mm Hg, SD = 6.767 mm Hg) when compared against their age-matched normal controls (mean = 12.45 mm Hg, SD = 1.553 mm Hg) (see Fig. 1). A non-significant trend was found in the ocular blood flow in the CRA EDV between participants diagnosed with SWS and glaucoma (both CAG and POAG) vs. their age-matched normal controls ($p = 0.056$). However, when only those participants diagnosed with SWS and POAG were compared against their age-matched normal controls, this difference reached statistical significance ($p = 0.016$). Inspection of the raw data (see Fig. 2) reveals that all those diagnosed with SWS and POAG consistently had lower blood flow velocities in their central retinal arteries (mean 0.036 m/s, SD 0.005 m/s) when compared against their age-matched normal controls (mean 0.054, SD 0.010). However, there was no difference in ocular perfusion pressure ($p > 0.05$).

An independent t-test also revealed that the only hemodynamic parameters to reach statistically significant differences between participants diagnosed with SWS and no glaucoma in either eye vs. their age-matched normal controls was CRA EDV ($p = 0.046$) and CRA RI ($p = 0.040$). Inspection of the raw data (Fig. 3) again reveals that with the exception of one participant, all those diagnosed with SWS and no glaucoma consistently had lower blood flow velocities and higher RI in their central retinal arteries (mean 0.038 m/s, SD 0.015 m/s; mean 0.673, SD 0.092) when compared against their age-matched normal controls (mean 0.054 m/s, SD 0.014 m/s; mean 0.582, SD 0.080). Again, there was no difference in ocular perfusion pressure ($p > 0.05$) (Table 3).

Finally, with the exception of IOP in the right eye ($p = 0.001$), no significant difference between any parameter and participants diagnosed with SWS and glaucoma vs. participants diag-

TABLE 2.
Characteristics of the SWS patients with and without glaucoma and their age-matched normal controls: standard deviation in parentheses

	SWS with glaucoma (any type)	Age-matched normal control	p	SWS with POAG	Age-matched normal control	p	SWS without glaucoma	Age-matched normal control	p
Age	27.2 (23.6)	27.2 (22.8)	>0.05	34.3 (26.9)	34.3 (25.9)	>0.05	17.2 (9.1)	17.7 (7.6)	>0.05
Systolic pressure (mm Hg)	116.5 (12.8)	109.5 (27.3)	>0.05	117.5 (16.1)	119.3 (29.2)	>0.05	103.6 (17.1)	115.3 (8.9)	>0.05
Diastolic pressure (mm Hg)	69.5 (8.8)	68 (14.3)	>0.05	67.3 (9.6)	70.5 (12.9)	>0.05	63.8 (7.1)	64.4 (9.4)	>0.05
Mean arterial pressure	85.2 (8)	81.8 (16.9)	>0.05	84 (9.4)	86.8 (17.4)	>0.05	77 (10)	81.4 (7.5)	>0.05
Ocular perfusion pressure	43.1 (8)	46.3 (11)	>0.05	42.9 (8.4)	49.7 (11.3)	>0.05	42.9 (6.9)	45.4 (7.3)	>0.05
Intraocular pressure	20.6 (6.8)	12.5 (1.6)	0.017	19.7 (6.9)	12.3 (1.7)	>0.05	12.9 (3.4)	13.2 (4.3)	>0.05

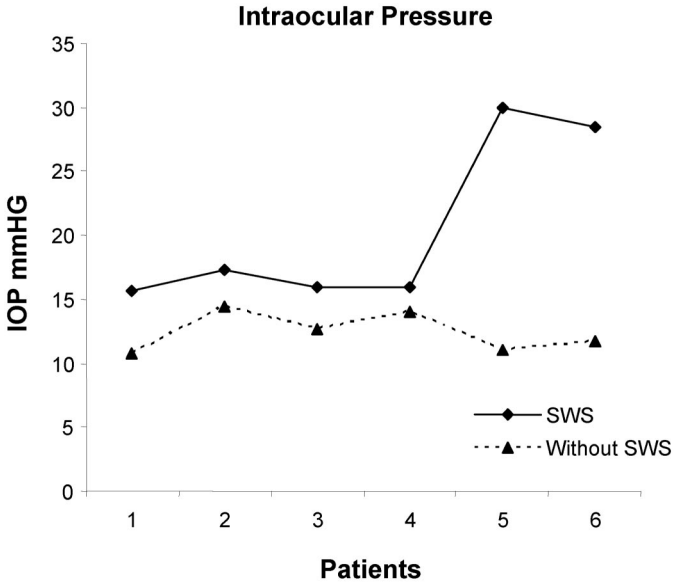

FIGURE 1.
Differences between IOP in participants diagnosed with SWS and glaucoma any type (POAG and CAG) compared with their age-matched normal controls.

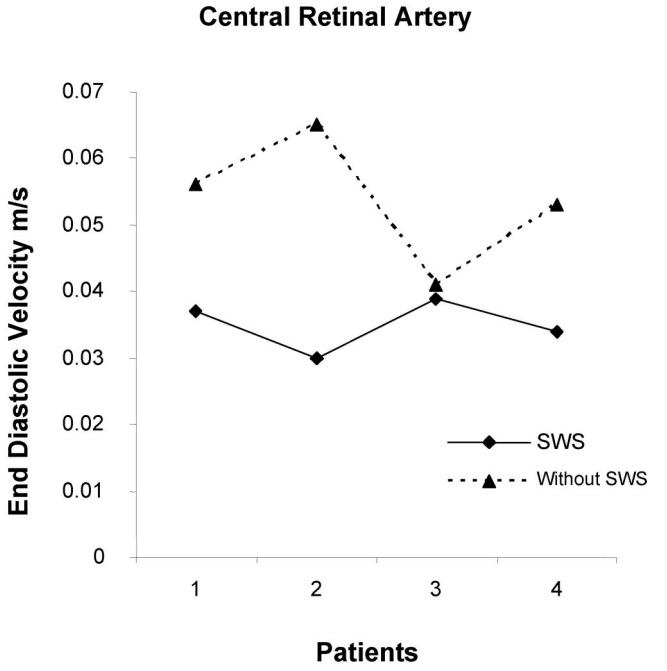

FIGURE 2.
Differences between CRA EDV in participants diagnosed with SWS and POAG compared with their age-matched normal controls.

nosed with SWS and no glaucoma was found using a one-way analysis of variance for either their right or left eyes using age as covariate.

DISCUSSION

Color Doppler measurements revealed reduced blood flow velocities in participants diagnosed with both SWS and POAG compared against normal healthy age- and gender-matched controls despite there being no influence of mean arterial pressure or ocular perfusion pressure. The presence of glaucoma with SWS may result from diminished perfusion, increased IOP, defective autoregulation, or a combination of these. In addition, these participants were receiving anti-glaucoma medication at the time which may have interfered with their retrobulbar CDI measurements.[18]

The findings that end-diastolic velocity was reduced in the CRA of participants diagnosed with SWS and POAG, when compared against age-matched normal controls, are consistent with earlier research. Previous researchers documented reduced blood flow responses in both POAG and pseudoexfoliative participants measured via pulsatile ocular blood flow,[19] laser Doppler flowmetry,[20] Heidelberg retinal flowmetry,[19] and CDI.[21–23] Reduced blood flow velocity has also been documented in participants diagnosed with POAG when responses were compared against age-matched ocular hypertension participants with a similar level of untreated IOP.[21] The authors felt that the higher blood flow velocities found in ocular hypertensive participants implied that these participants had better vascular autoregulation which ultimately protected these participants from GON. Piltz-

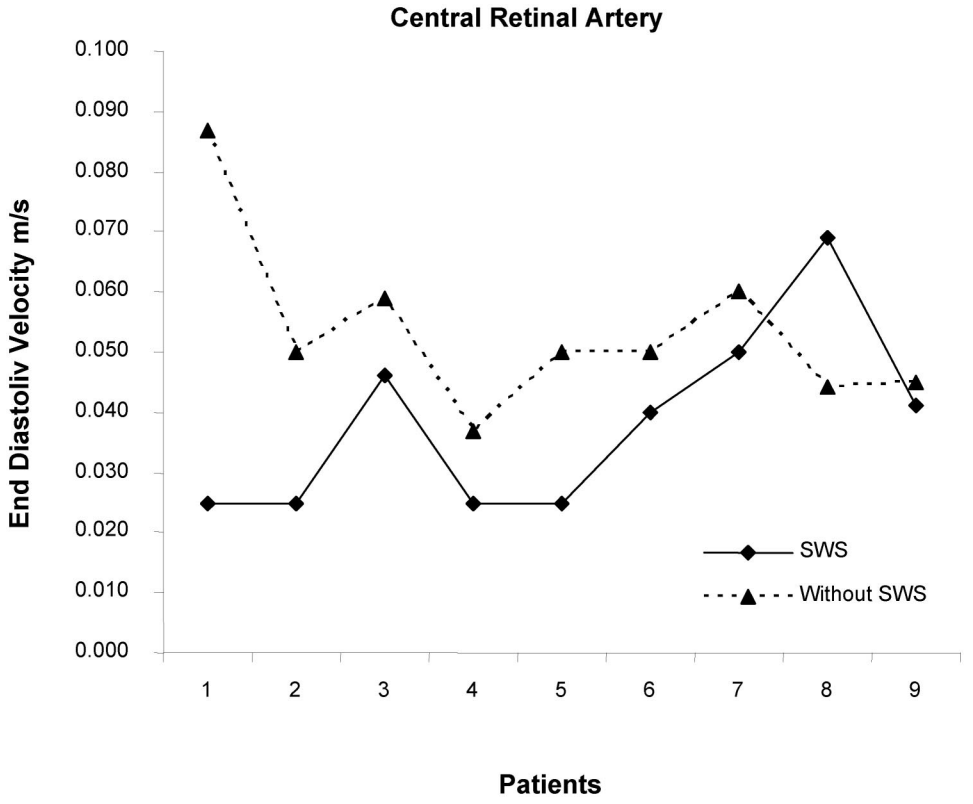

FIGURE 3.
Differences between CRA EDV in participants diagnosed with SWS and no glaucoma compared with their age-matched normal controls.

Seymour et al.[20] discovered reduced ocular blood flow in POAG suspect participants without any manifest visual field defects. The reduction in blood flow was similar to participants with confirmed POAG and manifest visual field loss. This suggests that, at the very least, a reduction of ocular blood flow occurs early on in the glaucomatous process and is not solely reduced because of neuronal loss, as the magnitude did not significantly change between the two groups of participants. A reduction in ocular blood flow has also been reported in participants diagnosed with glaucoma who showed progressive visual field loss when they were compared against glaucoma participants whose visual fields were stable.[24–26] The authors concluded that altered blood flow represented a primary risk for disease progression.

For the SWS participants, the diagnosis of glaucoma or no glaucoma was based on each participant's own clinician who was independent of this study. The criteria used to establish a diagnosis would have varied between participants as some had been diagnosed decades before in their early infancy. All participants diagnosed with SWS and no glaucoma had a normal fundus examination and IOP on the day ocular blood flow was measured, which was consistent with their own clinician's findings. The study has the limitation that visual fields were not measured during this visit as 10 of the participants were children and 2 adults had significant learning disabilities. Without this information, there is a small possibility that some of the participants may have been diagnosed incorrectly. It is however interesting to note that ocular blood flow was altered in participants with SWS and was independent of their diagnosis of glaucoma (Figs. 2 and 3). This finding suggests that blood flow is not solely impaired in the cortex and indicates that there might be a systemic reduction in hemodynamic responses linked to SWS. Our research implies that ocular blood flow velocities are reduced in the CRA of SWS participants without glaucoma ($p = 0.046$). Previous research suggests that this group of participants might be at increased risk to GON in later years, therefore longitudinal monitoring of their ocular health is probably advisable. Ocular blood flow has previously been measured in SWS participants diagnosed with unilateral glaucoma using CDI.[27] The authors reported that vascular alterations in the eye played no role in the development of glaucoma as no significant difference was found between the ocular blood flow in the glaucomatous eye when it was compared against their normal contralateral eye. They concluded that hemodynamic alterations were either purely cerebral in origin or possibly limited to either the retina or choroid, which was not measured during the course of their investigation. This study, however, was possibly limited by their chosen methodology. Altered hemodynamic responses might have been masked by a bilateral/systemic reduction in ocular blood flow particularly if the reduction was quite symmetric in nature. In this study, a one-way analysis of variance revealed that there was no significant difference in blood flow velocity measurements between participants diagnosed with SWS and no glaucoma vs. participants diagnosed with SWS and glaucoma because the blood flow was reduced in both groups of participants. The suggestion that blood flow responses are reduced bilaterally in participants diagnosed with glaucoma is unsurprising when considered in light of other documented research.[28] Fontana et al.[28] documented statistically lower blood flow responses in normal tension glaucoma in both the eye with visual field loss ($p < 0.001$) and the eye without visual field loss ($p = 0.01$) when compared with a group of normal healthy controls. They concluded that circulatory abnormalities were associated with asymmetric onset of visual

TABLE 3.
Ocular blood flow characteristics of the SWS patients and without glaucoma and their age-matched normal controls measured by CDI

	Ocular blood flow characteristics (CDI)					
	SWS with any type of glaucoma (POAG and CAG)		SWS with POAG		SWS without glaucoma	
	Mean	SD	Mean	SD	Mean	SD
OA (PSV m/s)						
SWS	0.523	0.111	0.523	0.137	0.489	0.090
Normal	0.430	0.106	0.398	0.059	0.466	0.106
OA (EDV m/s)						
SWS	0.173	0.055	0.165	0.044	0.123	0.021
Normal	0.128	0.045	0.114	0.044	0.118	0.045
OA (RI)						
SWS	0.672	0.078	0.692	0.042	0.743	0.057
Normal	0.708	0.067	0.720	0.083	0.749	0.071
CRA (PSV m/s)						
SWS	0.111	0.030	0.106	0.035	0.115	0.018
Normal	0.133	0.022	0.138	0.023	0.127	0.014
CRA (EDV m/s)						
SWS	0.040	0.01	0.036	0.005	0.038	0.015
Normal	0.052	0.008	0.054	0.010	0.054	0.014
CRA (RI)						
SWS	0.612	0.105	0.633	0.116	0.673	0.092
Normal	0.608	0.029	0.608	0.033	0.582	0.080
SPCAs (PSV m/s)						
SWS	0.121	0.013	0.115	0.012	0.217	0.212
Normal	0.268	0.300	0.332	0.359	0.239	0.305
SPCAs (EDV m/s)						
SWS	0.056	0.015	0.050	0.014	0.092	0.062
Normal	0.069	0.021	0.068	0.027	0.123	0.161
SPCAs (RI)						
SWS	0.542	0.103	0.575	0.114	0.530	0.100
Normal	0.410	0.170	0.364	0.202	0.500	0.109

CRA, central retinal artery; OA, ophthalmic artery; SPCAs, short posterior ciliary arteries.

field loss as the eye with the established field loss was documented to have lower blood flow responses when compared with the normal contralateral eye. These findings therefore appear to add further support to the suggestion that altered ocular blood flow plays a role in the development of GON and that blood flow is reduced bilaterally.

In conclusion, this work appears to suggest that ocular blood flow velocity might also be reduced in participants diagnosed with SWS without any sign of GON. Our results highlight the importance of carrying out longitudinal research on a group of participants diagnosed with SWS who have reduced blood flow velocities and no GON to establish whether vascular alterations play a significant role in the development of GON.

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