European Journal of Ophthalmology / Vol. 18 no. 2, 2008 / pp. 172-176

Color Doppler imaging of retrobulbar hemodynamics in Sturge-Weber syndrome–associated glaucoma

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PURPOSE. *Sturge-Weber syndrome (SWS) is frequently associated with early onset glaucoma in the eye on the same side as the facial angioma. The exact cause of glaucoma in SWS is poorly understood and difficult to treat. The purpose of this study is to investigate the ocular hemodynamics of children with SWS-associated glaucoma using color Doppler imaging techniques.*

METHODS. *This is a prospective study of 10 pediatric patients with unilateral SWS-associated glaucoma. Color Doppler imaging was used to measure the peak systolic velocity and the end diastolic velocity of both the ophthalmic and central retinal arteries in the glaucomatous eye compared to the fellow healthy eye.*

RESULTS. *Twenty eyes of 10 children with SWS (6 boys) with unilateral glaucoma were included in the prospective study. The mean age of the 10 participants was 5.5 years. When compared to their contralateral normal eyes, the glaucomatous eyes had greater CDR ($p<0.001$) and a myopic shift ($p=0.04$). No significant differences were found in the measurements of ocular blood flow velocities of the ophthalmic and central retinal arteries.*

CONCLUSIONS. *Vascular pathology has been proposed to play a role in SWS glaucoma etiology. The authors did not find arterial retrobulbar blood flow differences between the glaucomatous and the fellow normal eye. Since the primary vascular anomaly in patients with SWS is in the venous plexus, a bigger prospective trial is warranted in order to better understand and treat children with SWS glaucoma. (Eur J Ophthalmol 2008; 18: 172-6)*

KEY WORDS. *Sturge-Weber syndrome, Early onset glaucoma, Color Doppler imaging*

Accepted: September 20, 2007

INTRODUCTION

Sturge-Weber syndrome (SWS) is a rare congenital disorder with an estimated incidence of 1 per 50,000 live births, which is characterized by a triad of cutaneous facial angioma, leptomeningeal angioma, and ocular manifestations. Glaucoma, in association with vascular malformations of the conjunctiva, episclera, choroid, and retina, is the most frequently observed ocular complication (1, 2). Prior studies have reported a 42 to 85% incidence of secondary glaucoma in patients with SWS (3-6). This association is most common in patients with facial port-wine stain (nevus flammeus) involving the periocular skin, particularly the upper and/or lower eyelids (3-5, 7).

Several mechanisms have been proposed for SWS-associated glaucoma but none has been proven conclusively. These theories include incomplete cleavage of the anterior chamber angle (8), increased episcleral venous pressure (4, 9), and premature aging of the trabecular meshwork (8). Given the known presence of vascular anomalies involving the eye, particularly angiomas of the upper eyelid skin, a vascular etiology would seem the most plausible mechanism.

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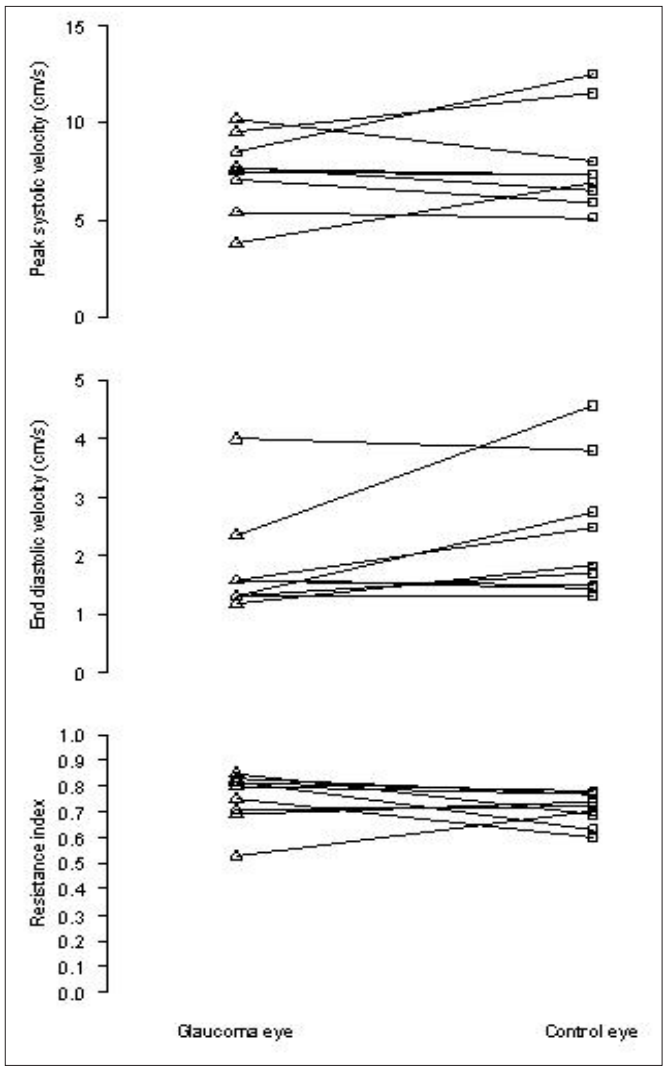

Fig. 1 - *Color Doppler imaging measurements of the central retinal artery in each of ten SWS individuals. Measurements include peak systolic velocity, end diastolic velocity and resistance index. Each line denotes an individual from the sample with the glaucomatous eye represented by a triangle and the control eye by a square. No significant differences in any ocular blood flow parameters were found between glaucomatous and control eyes.*

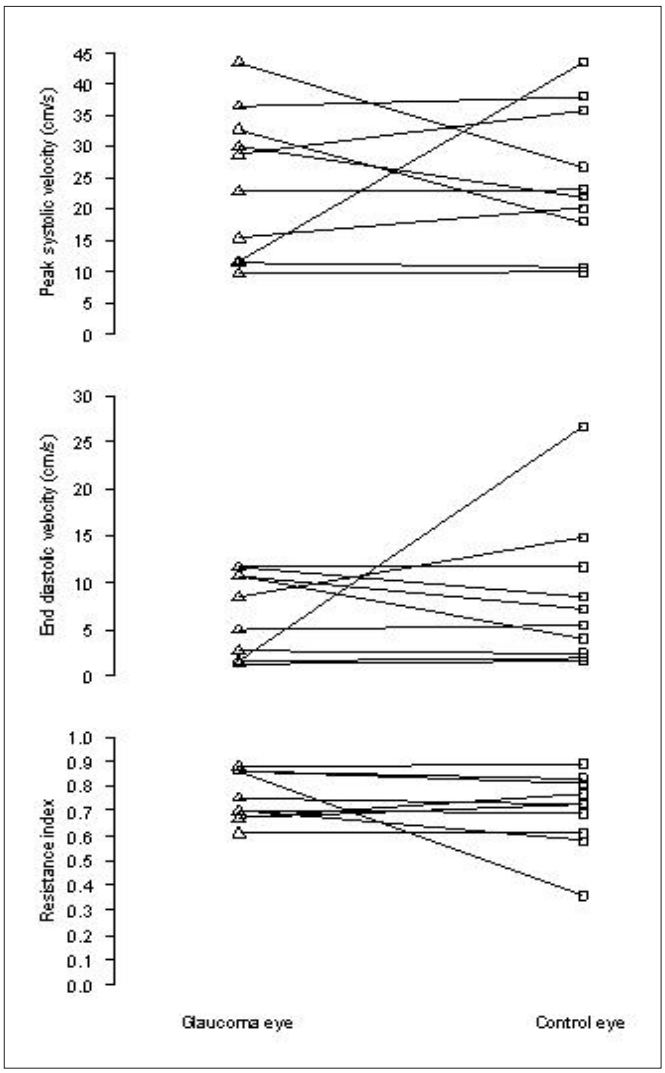

Fig. 2 - *Color Doppler imaging measurements of the ophthalmic artery in each of ten SWS individuals. Measurements include peak systolic velocity, end diastolic velocity and resistance index. Each line denotes an individual from the sample with the glaucomatous eye represented by a triangle and the control eye by a square. No significant differences in any ocular blood flow parameters were found.*

To our knowledge, the relationship of retrobulbar hemodynamics in patients with SWS unilateral glaucoma between the affected side and the unaffected contralateral side has not been evaluated. The purpose of this study is to measure the ocular hemodynamics of specific blood vessels in the eyes of patients with SWS. This information might be beneficial in understanding the role of ocular hemodynamics in such patients.

METHODS

This was a prospective study of 10 consecutive pediatric patients with unilateral SWS-associated glaucoma presenting to the Riley Hospital for Children at Indiana University, Indianapolis. The study was approved by the Indiana University–Purdue University Indianapolis and Clarian Health Partners Institutional Review Board in accordance with HIPAA guidelines.

The SWS glaucoma diagnosis was made based on the characteristic neurocutaneous morphology along with elevated intraocular pressure (IOP), enlargement of the cup to disk ratio (CDR), and evidence of previous glaucoma medication or surgery. IOP was measured with the Tono-Pen (Mentor). Bilateral cases were excluded from the study. At the examination date, the following variables were recorded: age, gender, neurologic involvement, laterality, the refractive error, the presence of choroidal angioma, IOP, and visual acuity (VA) in both eyes. With the patient in the supine position, the same experienced examiner performed color Doppler imaging (CDI) measurements of both eyes. A Siemens Quantum 2000 CDI system (Siemens Quantum, Issaquah, WA) with a 7.5 MHz linear probe was utilized. This technique has been described in detail previously (10, 11). In brief, samples of pulsed-Doppler signal from within a 0.2 x 0.2 mm sample area were analyzed to calculate blood velocities in the specific retrobulbar vasculature. Blood flow velocities and resistive indices were measured in the ophthalmic (OA) and central retinal (CRA) arteries. In each vessel, peak systolic velocity (PSV) and end diastolic velocity (EDV) were determined, and Pourcelot's resistance index was calculated by (RI) = (PSV – EDV)/PSV. Examination of the short posterior ciliary arteries was not included in this study as they are extremely hard to image in young children. It would also require them to remain still for an extended period which would not be a realistic expectation in this study group.

A two-sided, paired *t*-test was used to compare the CDI measurements of the glaucomatous eye to the control eye. A paired *t*-test was also used to compare the characteristics of the glaucomatous and the control eye. A 95% confidence interval was estimated for the mean of the difference between the glaucomatous eye and the control eye. Summary data are presented as mean (standard deviation). A p value of <0.05 was considered statistically significant.

RESULTS

Twenty eyes of 10 children with SWS (6 boys) with unilateral glaucoma were included in the prospective study. The mean age of the 10 participants was 5.5 years (SD 4.9; range 0.5, 17.3). Five patients had glaucoma in their right eye and five in their left. The subject characteristics (IOP, laterality, CDR, refraction, and logMar VA) are listed in Table I. When compared

TABLE I - CHARACTERISTICS OF GLAUCOMATOUS AND CONTROL EYES

	Glaucoma	Control	Difference	95% CI	p Value
IOP, mm Hg	20.8 (6.8)	16.8 (4.1)	4.0	–1.4, 9.4	0.128
LogMAR VA, n=7	0.20 (0.20)	0.07 (0.11)	0.13	–0.04, 0.29	0.108
CDR, n=9	0.42 (0.17)	0.19 (0.11)	0.23	0.15, 0.30	<0.001
Refraction, diopters	0.33 (1.91)	1.89 (2.61)	–1.56	–3.05, –0.06	0.043

IOP = Intraocular pressure; VA = Visual acuity; CDR = Cup to disk ratio

TABLE II - COLOR DOPPLER IMAGING MEASURES

	Glaucoma	Control	Difference	95% CI	p Value
CRA-PSV, n=9	7.5 (2.0)	7.9 (2.5)	–0.4	–2.0, 1.2	0.574
CRA-EDV, n=9	1.8 (0.9)	2.4 (1.1)	–0.6	–1.2, 0.1	0.07
CRA-RI, n=9	0.75 (0.10)	0.71 (0.06)	0.04	–0.04, 0.13	0.288
OA-PSV	24.2 (11.9)	24.7 (11.3)	–0.5	–10.3, 9.2	0.902
OA-EDV	6.6 (4.5)	8.5 (7.7)	–1.9	–8.2, 4.4	0.514
OA-RI	0.76 (0.10)	0.70 (0.15)	0.06	–0.06, 0.18	0.316

CRA = Central retinal artery; PSV = Peak systolic velocity; EDV = End diastolic velocity; RI = Pourcelot's resistance index; OA = Ophthalmic artery

to their contralateral normal eyes, the glaucomatous eyes had greater CDR ($p<0.001$) and a myopic shift ($p=0.04$). The differences in IOP ($p=0.12$) and decreased VA ($p=0.108$) between the glaucomatous eye and the fellow eye did not reach statistical significance.

No significant differences were found in the measurements of ocular blood flow (OBF) velocities of the OA and CRA. Table II presents the CDI blood flow measurements. Figures 1 and 2 show the CDI-CRA and CDI-OA graphic plots, respectively. Each line represents an individual subject and shows the CDI values for the glaucomatous (Δ) and control eye (□).

Nine of the 10 children were receiving antiglaucoma medications. Four were using Cosopt®, two Betoptic® 0.25, two Timoptic XE®, and one was on the combination of Cosopt® and Lumigan®. Due to the variety of medication classes there was no drug effect reported on any of the vessels measured.

DISCUSSION

Ocular disease in SWS manifests as glaucoma and vascular malformations of the conjunctiva, episclera, choroid, and retina, with unilateral glaucoma being the most common ophthalmic complication (12, 13). Because medical treatment frequently fails to control IOP in SWS-associated glaucoma (12, 14, 15), surgical intervention is often required. Complications such as expulsive choroidal hemorrhage and choroidal effusion make surgical correction difficult and might be attributed to the fragility of choroidal vessels in SWS with or without presence of a choroidal hemangioma (16).

The exact mechanism of glaucoma in patients with SWS remains unclear. It has, however, been suggested that anterior chamber dysgenesis (8), elevated episcleral venous pressure (4, 9), and premature aging of the trabecular network (8) are involved. Clinical studies have demonstrated that certain patients with open angle glaucoma have reduced OBF, which may be of primary vascular origin or secondary to IOP elevation (17, 18). Ischemia and apoptosis are considered to be involved in the pathophysiology of glaucomatous optic neuropathy.

Vascular abnormalities in SWS are well documented. The proposed underlying pathogenesis of SWS is failure of the embryonal vascular plexus to regress during the ninth week of gestation, resulting in angiomatosis of related tissues (2). The hallmark intracranial vascular anomaly is leptomeningeal angiomatosis, mostly involving the occipital and posterior parietal lobes (1). Clinical neurological findings associated with SWS include seizures, transient strokelike neurologic deficits, behavioral problems, and headaches (1). Patients with SWS demonstrate an abnormality of the cerebral venous system: few superficial cortical veins, enlargement of the deep medullary veins and choroid plexus (19). Calcifications in meningeal arteries and cortical veins are also common, and the laminar cortical necrosis that occasionally accompanies these calcifications suggests ischemic damage due to leptomeningeal venous stasis (1).

SWS angioma is a slow flow lesion with venous stasis (20). Studies suggest that complex molecular interactions contribute to the abnormal development and function of blood vessels in SWS and propose that the neurologic deterioration is likely secondary to impaired blood flow to the brain and is worsened by the presence of seizures (21). Transcranial Doppler flow velocities of the middle cerebral artery performed on three infants with SWS demonstrated reduced flow velocities in the affected hemisphere when compared to the normal contralateral side. This impairment of flow velocity worsened during clinical seizure activity (22).

CDI of the retrobulbar vasculature has proven to be a useful, reliable, and repeatable tool in several ophthalmologic diseases (11, 23, 24). Various studies using CDI readings comparing glaucoma patients with controls have demonstrated reduced OBF velocities in the OA, CRA, and posterior ciliary arteries (PCA) (25-27).

We did not find any significant differences in the measurements of blood flow velocities of the OA and the CRA in the affected glaucomatous eye compared with the fellow eye. Our data suggest that either 1) the hemodynamic changes seen in SWS are confined to the cerebral and not the ocular circulation or 2) the vascular differences are not measured in the retrobulbar circulation but rather may be relevant to the retina or choroid. Another possibility is that the vascular pathology is confined to the retrobulbar venous system, which was not evaluated in this study. Future studies utilizing Heidelberg retinal tomography of the retinal vasculature and fluorescein angiography might address these issues.

Our study has several limitations including its small sample size, lack of CDI measurements for the posterior ciliary arteries and the retrobulbar venous sys-

tem, and inability to exclude patients from the study who have undergone previous glaucoma surgeries. A bigger prospective trial is warranted in order to better understand and treat SWS glaucoma.

ACKNOWLEDGEMENTS

Supported in part by grants from Research to Prevent Blindness Inc., New York, NY, to the Indiana University Department of Ophthalmology and from the Indiana Lions Foundation. Dr. Neely is the recipient of a Research to Prevent Blindness grant.

The authors report no proprietary interest.

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REFERENCES

1. Kristin A, Thomas-Sohl KA, Vaslow DF, et al. Sturge-Weber syndrome: a review. Pediatr Neurol 2004; 30: 303-10.
2. Di Rocco C, Tamburrini G. Sturge-Weber syndrome. Childs Nerv Syst 2006; 22: 909-21.
3. Van Emelen C, Goethals M, Dralands L, et al. Treatment of glaucoma in children with Sturge-Weber syndrome. J Pediatr Ophthalmol Strabismus 2000; 37: 29-34.
4. Phelps CD. The pathogenesis of glaucoma in Sturge-Weber syndrome. Ophthalmology 1978; 85: 276-86.
5. Awad AH, Mullaney PB, Al-Mesfer S, et al. Glaucoma in Sturge-Weber syndrome. J AAPOS 1999; 3: 4045.
6. Jorgensen JS, Guthoff R. [Sturge-Weber syndrome: glaucoma with elevated episcleral venous pressure]. Klin Monatsbl Augenheilkd 1987; 191: 275-8.
7. Sullivan TJ, Clarke MP, Morin JD. The ocular manifestations of the Sturge-Weber syndrome. J Pediatr Ophthalmol Strabismus 1992; 29: 349-56.
8. Cibis GW, Tripathi RC, Tripathi BJ. Glaucoma in Sturge-Weber syndrome. Ophthalmology 1984; 91: 1061-71.
9. Kranemann CF, Pavlin CJ, Trope GE. Ultrasound biomicroscopy in Sturge-Weber associated glaucoma. Am J Ophthalmol 1998; 125: 119-21.
10. Lieb WE, Cohen SM, Merton DA, et al. Color Doppler imaging of the eye and orbit: technique and normal vascular anatomy. Arch Ophthalmol 1991; 109: 527-31.
11. Williamson TH, Harris A. Color Doppler ultrasound imaging of the eye and orbit. Surv Ophthalmol 1996; 40: 255-67.
12. Van Emelen C, Goethals M, Dralands L, et al. Treatment of glaucoma in children with Sturge-Weber syndrome. J Pediatr Ophthalmol Strabismus 2000; 37: 29-34.
13. Sujansky E, Conradi S. Sturge-Weber syndrome. Age of onset of seizures and glaucoma and the prognosis for affected children. J Child Neurol 1995; 10: 49-58.
14. Audren F, Abitbol O, Dureau P, et al. Non-penetrating deep sclerectomy for glaucoma associated with Sturge-Weber syndrome. Acta Ophthalmol Scand 2006; 84: 656-60.
15. Awad AH, Mullaney PB, Al-Mesfer S, et al. Glaucoma in Sturge-Weber syndrome. J AAPOS 1999; 3: 40-5.
16. Bellows AR, Chylack LT Jr, Epstein DL, et al. Choroidal effusion during glaucoma surgery in patients with prominent episcleral vessels. Arch Ophthalmol 1979; 97: 493-7.
17. Rojanapongpun P, Drance SM, Morrison BJ. Ophthalmic artery flow velocity in glaucomatous and normal subjects. Br J Ophthalmol 1993; 77: 25-9.
18. Butt Z, McKillop G., O'Brien C, et al. Measurement of ocular blood flow velocity using color Doppler imaging in low tension glaucoma. Eye 1995; 9: 29-33.
19. Probst FP. Vascular morphology and angiographic flow patterns in Sturge-Weber angiomatosis: facts, thoughts and suggestions. Neuroradiology 1980; 20: 73-8.
20. Comi AM. Advances in Sturge-Weber syndrome. Curr Opin Neurol 2006; 19: 124-8.
21. Comi AM. Pathophysiology of Sturge-Weber syndrome. J Child Neurol 2003; 18: 509-16.
22. Aylett SE, Neville BGR, Cross JH, et al. Sturge-Weber syndrome: cerebral haemodynamics during seizure activity. Dev Med Child Neurol 1999; 41: 480-5.
23. Harris A, Kagemann L, Cioffi GA. Assessment of human ocular hemodynamics. Surv Ophthalmol 1998; 42: 509-33.
24. Harris A, Williamson TH, Martin B, et al. Test/retest reproducibility of color Doppler imaging assessment of blood flow velocity in orbital vessels. J Glaucoma 1995; 4: 281-6.
25. Galassi F, Nuzzaci G, Sodi A, et al. Color Doppler imaging in evaluation of optic nerve blood supply in normal and glaucomatous subjects. Int Ophthalmol 1992; 16: 273-6.
26. Akarsu C, Bigili MY. Color Doppler imaging in ocular hypertension and open angle glaucoma. Graefes Arch Clin Exp Ophthalmol 2004; 242: 129.
27. Birinci H, Danaci M, Oge I, et al. Ocular blood flow in healthy and primary open angle glaucoma eyes. Ophthalmologica 2002; 216: 434-7.