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Case report

Bilateral diffuse choroidal hemangioma in Sturge Weber syndrome: A case report highlighting the role of multimodal imaging and a brief review of the literature

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Abstract

Purpose: The purpose of this paper is to present a patient with bilateral choroidal hemangioma in Sturge-Weber syndrome (SWS) and highlight multimodal imaging techniques for early detection and management of ocular alterations.

Methods: A 37-year-old woman with diagnosis of SWS presented to our unit. The patient had been treated with pulsed dye laser for bilateral nevus flammeus and had right leptomenigeal angiomatosis. She had glaucoma, but ultrasound biomicroscopy did not show anterior chamber or ciliary body alterations.

Results: Enhanced depth imaging (EDI) spectral domain optical coherence tomography (SD-OCT) showed bilateral diffuse choroidal hemangiomas in both eyes with choroidal thickness above 1000 μm . B-scan ultrasound examination showed diffuse choroidal hemangioma in both eyes, with a choroidal thickness of 1.53 mm and 1.94 mm in the right and left eye (RE, LE), respectively. Peripapillary retinal nerve fiber evaluation showed thinning of the retinal nerve fiber layer in both eyes.

Conclusions: This report highlights multimodal imaging techniques for the critical assessment of patients with SWS, especially in rare cases with bilateral choroidal hemangioma of the choroid. Novel imaging modalities enable optimal management and follow-up of rare conditions, and our case adds further evidence to the existing literature.

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Keywords: Sturge Weber syndrome; Choroidal hemangioma; Spectral domain optical coherence tomography; Peripapillary retinal nerve fiber layer; Enhanced depth imaging

Introduction

Sturge-Weber syndrome (SWS) is a rare condition with an estimated incidence of 1 in 20,000 to 50,000 live births,

affecting male and female infants equally, and the clinical manifestations are usually reported as unilateral leptomenigeal angiomatosis associated with *ipsilateral* facial cutaneous vascular malformation, and ocular alterations.¹ Some authors have classified this syndrome as part of the phakomatoses due to the possible role of neural crest anomalies² while other authors prefer the term neuro-oculocutaneous disorder. Recently, a crucial role of somatic mosaic mutations in the *GNAQ* gene located on the long arm of chromosome 9 has been reported.³

The authors report no conflicts of interest.

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The first reports were by Schirmer and Sturge in 1860 and 1876, who described patients with bilateral nevus flammeus and monolateral glaucoma.^{4,5} However, bilateral manifestations of the syndrome are not common.⁶ Although leptomeningeal angiomatosis is usually ipsilateral to the nevus flammeus, in 1913, Oppenheim reported two cases of SWS where the involved cerebral hemisphere was contralateral to the facial nevus.⁷ Bilateral nevus flammeus is seen in 10–30% cases of SWS.⁸ The most common ocular manifestation, present in 50–70% of SWS patients, is glaucoma. Diffuse choroidal hemangiomas, observed as a bright red or red-orange color of the retina in contrast to the normal fellow eye, are typically unilateral and ipsilateral to the other manifestations of the syndrome and are observed in 23% of cases.⁹ Imaging techniques, used in the diagnosis of choroidal hemangioma are ultrasonography, indocyanine-green angiography, and enhanced depth imaging (EDI) spectral domain optical coherence tomography (SD-OCT). Contrast-enhanced magnetic resonance imaging (MRI) can also be used to investigate choroidal thickening.¹⁰ Bilateral choroidal hemangiomas are rare^{11–14} although recent investigation using EDI SD-OCT has shown increased choroidal thickness even in fellow eyes with a normal fundus appearance.^{15,16}

The present paper aims to highlight the role of multimodal imaging methods in the early diagnosis and management of the ocular manifestations of SWS with a case report of a patient with glaucoma and bilateral choroidal hemangiomas, diagnosed through EDI SD-OCT imaging.

Case report

We describe a 37-year-old woman with diagnosis of SWS. The patient had undergone MRI with Gadolinium administration, which revealed right leptomeningeal angiomatosis, right pial hemangioma, and choroid plexus hypertrophy. There were no evident focal signal alterations in the left hemisphere (Fig. 1). The patient received treatment for epilepsy with carbamazepine due to hypotonic crisis since the age of four.

The patient reported various sessions of pulsed dye laser treatment for bilateral nevus flammeus, but this was still slightly evident due to a deep purple coloration of the skin

both on the right side (first trigeminal branch) and the left side (first and second trigeminal branches) of the face with a small nodular angiomatous formation on the upper lid of the right eye (RE) (Fig. 2). The patient referred bilateral glaucoma since the age of 14 and was on topical medication consisting of brimonidine tid and dorzolamide/timolol bid in both eyes. Visual field examination, carried out previously, showed glaucomatous defects in both eyes left eye (LE) > RE.

Upon presentation to our retina center, best corrected visual acuity (BCVA) using the decimal chart was 1.0 in the RE and 0.7 in the LE. Slit-lamp examination revealed abnormal conjunctival vessels with increased conjunctival vascularity, particularly evident at the caruncle in both eyes (Fig. 3). Intraocular pressure was 16 and 19 mmHg on therapy in the RE and LE, respectively. Fundus examination with indirect ophthalmoscopy showed that in the LE, the optic nerve head was pale and excavated, choroidal striae were visible, and there was venous congestion of the left upper venous branch, and the fundus color was slightly darker (Fig. 4).

Ultrasound biomicroscopy did not show anterior chamber or ciliary body alterations. EDI SD-OCT showed bilateral diffuse choroidal hemangiomas in both eyes with choroidal thickness above 1000 μm . There were no structural alterations of the retinal layers but only a deformation of the retinal profile in the LE (Fig. 5). B-scan ultrasound examination showed diffuse choroidal hemangioma in both eyes, especially in the LE, with a choroidal thickness of 1.53 mm and 1.94 mm



Fig. 2. Small nodular angiomatous formation on the upper lid of the right eye (RE).

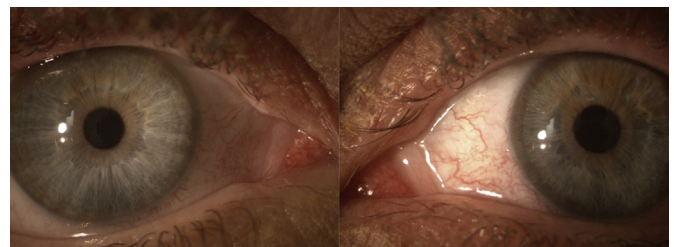


Fig. 3. Slit-lamp examination. Abnormal conjunctival vessels with increased conjunctival vascularity, particularly evident at the caruncle in both eyes.

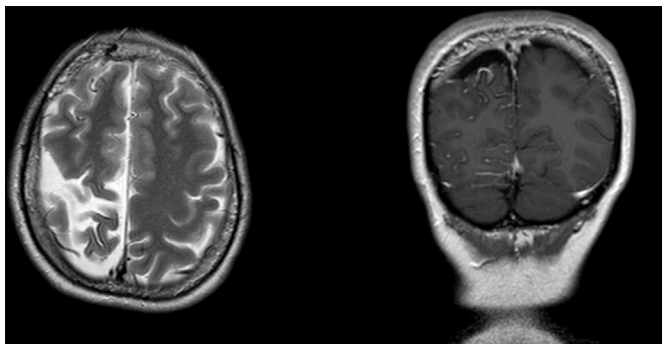


Fig. 1. Cerebral magnetic resonance imaging (MRI) performed with Gadolinium administration showing right leptomeningeal angiomatosis, a right pial hemangioma, and choroid plexus hypertrophy. There are no evident focal signal alterations in the left hemisphere.

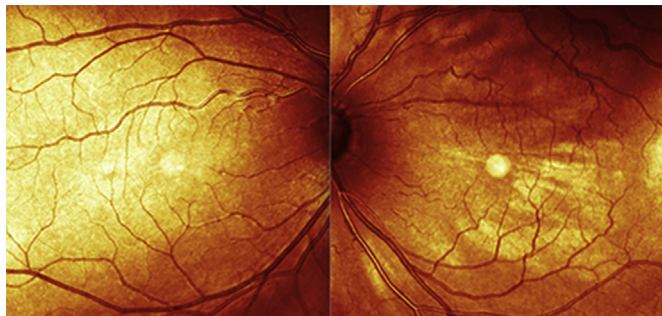


Fig. 4. Color photography of the fundus oculi. There is only a mild difference of color between the two eyes. In the left eye (LE), there is evident venous congestion of the left upper venous branch.

in the RE and LE, respectively (Fig. 6). Peripapillary retinal nerve fiber evaluation showed thinning of the retinal nerve fiber layer in both eyes, which was more severe in the LE (Fig. 7).

Discussion

A review of the literature suggests that the pathogenesis of the angiomas in SWS is still not completely understood. Some authors have suggested that it is related to altered

innervation of perivascular vessels due to neural crest cell abnormalities as it is hypothesized that altered vasomotor regulation leads to the formation of phakomas and the nevus flammeus; indeed, co-existence of more than one phakomatosis in the same individual has also been reported.^{17–23} Other theories suggest persistence of primordial sinusoidal vascular channels or dysplasia of the emissary veins in the peripheral intracranial circulation resulting in increased retrograde venous pressure within the communicating vessels and the superficial venous plexus of the skin.¹ Recent research showed somatic mosaic mutations in the *GNAQ* gene located on the long arm of chromosome 9, which could account for the angiomatosis.³

Clinically, nevus flammeus occurring in the ophthalmic division of the trigeminal nerve, especially with upper eyelid involvement, carries the highest risk of association with SWS. A recent investigation suggests that the risk for SWS appears not to be determined by the dermatome but rather by embryonic vascular placodes.²⁴ Leptomeningeal angiomas in SWS is characterized by enlarged and tortuous vessels with thin walls of the parietal and occipital lobes. Thrombi are a frequent event in these vessels together with hypoxia due to microcirculatory alterations.²⁵ Seizures affect 70–90% of patients by 3 years of age²⁶; in 50–60% of patients mental

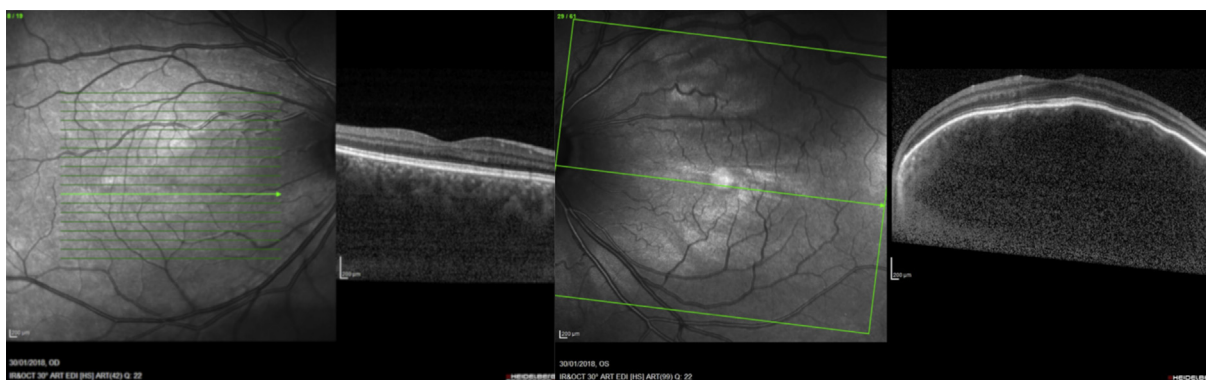


Fig. 5. Enhanced depth imaging (EDI) spectral domain optical coherence tomography (SD-OCT) shows bilateral diffuse choroidal thickening, more marked in the left eye (LE) with a dome-shaped macular profile. There are no structural alterations of the retinal layers.



Fig. 6. B-scan ultrasound examination. Diffuse choroidal hemangioma in both eyes, especially in the left eye (LE). Choroidal thickness of 1.53 mm and 1.94 mm in the right eye (RE) and LE, respectively.

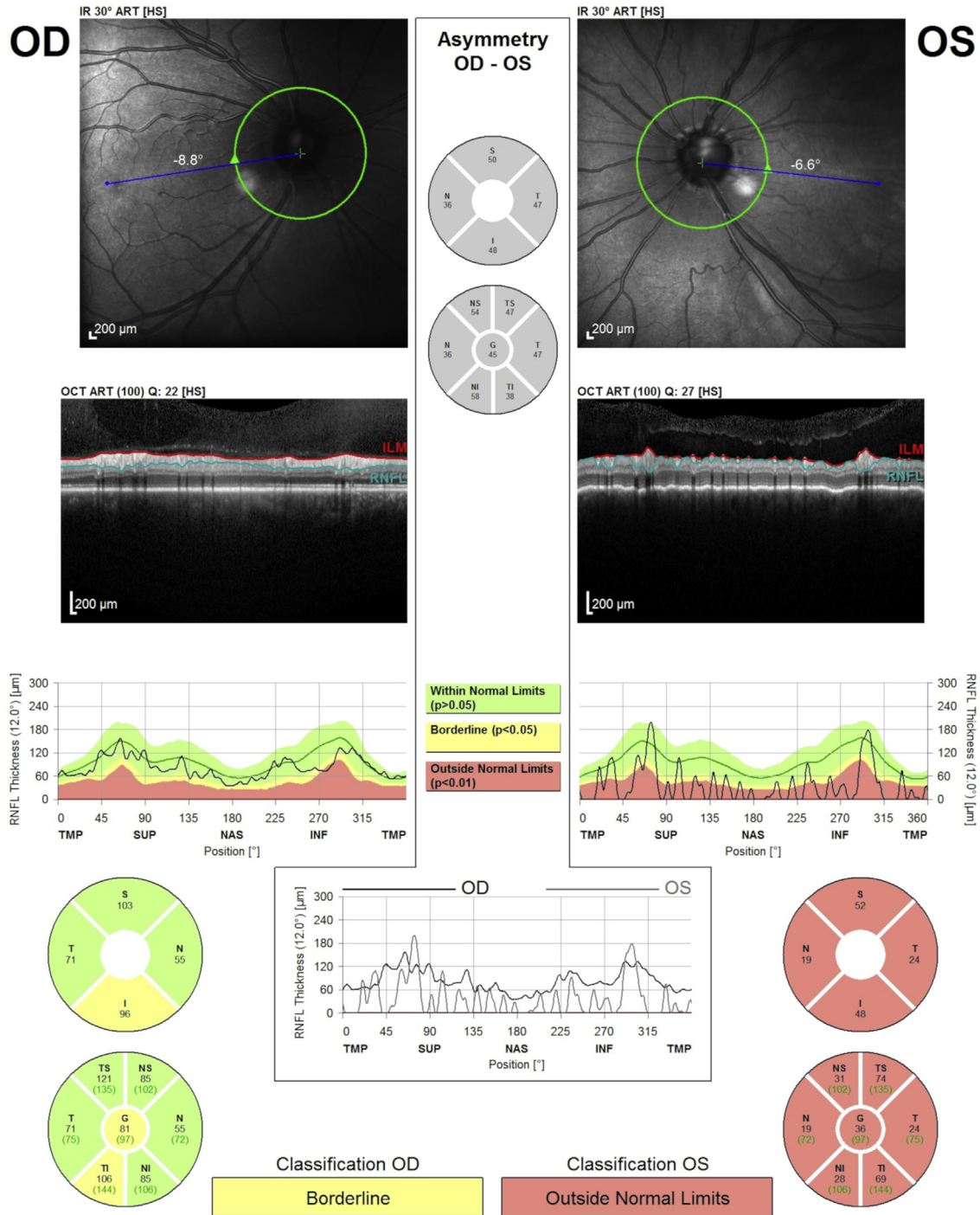


Fig. 7. Spectral domain optical coherence tomography (SD-OCT) of the optic nerve. Scans show abnormal peripapillary retinal nerve fiber thickness in both eyes but more pronounced in the left eye (LE).

retardation can develop and other neurological manifestations include hemiparesis, stroke episodes, hemianopia, and hemiatrophy.²⁷ A characteristic radiological feature is the typical gyriform parietal and occipital calcifications present in about 90% of cases (infants may present no or minimal calcifications) where MRI provides better identification with respect to computerized tomography. In order to assess the extension of vascular alterations the imaging method of choice is MRI with contrast.² Electroencephalography can suggest a greater

likelihood of cerebral cortical involvement of SWS.²⁸ Repeat imaging is warranted in patients with suspected SWS or those with intractable cryptogenic epilepsy because some imaging features of SWS may only become manifest over time.²⁹

Glaucoma, affects approximately 70% of SWS patients.^{30,31} According to a bimodal theory, approximately 60% of SWS patients develop glaucoma in infancy due to anterior chamber anomalies,^{26,30–34} and 40% develop glaucoma in childhood or early adulthood caused by elevated episcleral

venous pressure, possibly due to the presence of episcleral hemangioma and arterio-venous shunts.³³ Tanwar et al. reported a casual relationship between CYP1B1 mutations and glaucoma in patients with SWS presenting with gyral calcification, buphthalmos, and early onset glaucoma, presuming that the vascular malformation-induced venous engorgement induced by the syndrome is just additive and secondary to CYP1B1 mutation.³⁴ Glaucoma tends to almost always be ipsilateral to the nevus flammeus³³ and the risk is highest when the alteration involves both the eyelids with respect to involvement of the upper lid only: 72% vs. 21%, respectively.²⁹

The role of ultrasound biomicroscopy is fundamental in the evaluation of the structures of the anterior chamber, angle, and ciliary body, especially in the evaluation of silent vascular alterations of the ciliary body. Furthermore, the examination is non-invasive and can be performed on young children. Ultrasound biomicroscopy and clinical examination in SWS have shown supraciliary effusion and dilated superficial and intrascleral vessels promoting the assumption of raised episcleral venous pressure in the pathogenetic mechanism of glaucoma.^{2,35} Although rare, Maruyama et al. described a patient diagnosed with angle-closure glaucoma³⁶ as the consequence of ciliary body effusion, anterior displacement of the iridolenticular diaphragm and reduction of anterior chamber angle amplitude. As leptomenigeal angiomatosis can frequently lead to epilepsy, treatment with topiramate should be avoided in these patients due to the associated risk of ciliary body effusion.³⁷

Visual field defects are detected with perimetry, but recently, peripapillary retinal nerve layer and macular ganglion cell layer evaluation with optical coherence tomography has been established as a reliable non-invasive measure of anterior visual pathway integrity in a variety of conditions including glaucoma, multiple sclerosis, and optic neuropathy.^{38–45} This is a rapid and non-invasive method to enable precocious evaluation of glaucomatous damage in patients with SWS. Furthermore, in children and patients who can not collaborate, the hand-held OCT has been suggested as a valid alternative.⁴²

Diffuse choroidal hemangioma are benign vascular tumors,^{45–47} and in the SWS, these diffuse forms may also have localized areas of excessive thickening simulating circumscribed choroidal hemangiomas.¹⁴ Ultrasonography can be used to confirm or make a diagnosis; B-scans are notable for solid highly echogenic lesions with diffuse choroidal thickening, and A-scans exhibit high internal reflectivity.⁴⁸ Diffuse choroidal hemangiomas or choroidal thickening are not always readily observed with ophthalmoscopy, especially if the condition is bilateral. Diagnosis is made through observing a difference of color of the fundus, and this can be very difficult to evaluate in children who can not always collaborate during meticulous examination. Indocyanine green angiography can show the extension, vascularity, and arterio-venous shunts of choroidal alterations; however, this is an invasive method due to the use of a dye, and is almost impossible to perform in young or uncooperative patients.⁴⁹

Griffiths et al. used MRI and identified choroidal hemangioma as sickle-shaped enhanced regions, thickest over the posterior portion of the globe and thinner toward the ciliary body.¹⁰

Abdolrahimzadeh et al. conducted a study with SD-OCT to assess choroidal thickness in SWS and reported extreme choroidal thickening in eyes with diffuse hemangioma but also choroidal thickening in the apparently unaffected fellow eyes.¹⁶ This was also shown by Arora et al. in a case series.¹⁵ Furthermore, the outer retina layers were shown to be thinner in SWS patients with choroidal hemangioma.¹⁶ Indeed, the choroid is fundamental for retinal tropism and choroidal thickness changes have been implicated in retinal layer alterations, especially of the outer retinal layers.^{41,50–52} A recent article reported the association of choroidal hemangioma in SWS with small white dot-shaped “micro-drusen-like” alterations of the retina,⁵³ and a further study with the recently developed OCT angiography may hold promising results.^{54,55}

Choroidal hemangiomas are usually asymptomatic throughout childhood. However, in adolescence or adulthood, the choroid can further increase in thickness and complications such as subretinal hemorrhage, serous retinal detachment, cystoid macular edema, and macular neuroepithelium detachment can arise and lead to severe vision loss.⁵⁶

Bilateral choroidal hemangiomas are considered a rare finding. The few reported cases in the literature are almost always described with complications such as exudative retinal detachment and/or hyperplastic retinal pigment epithelium alterations. These complications might have facilitated the diagnosis of the presence of bilateral choroidal hemangiomas, which could otherwise have been overlooked. Amirikia et al. presented a report of a six-year-old male with spontaneously involuted left cerebral angioma, ipsilateral nevus flammeus involving the left forehead, and diffuse choroidal hemangiomas in both eyes. However, in this case the patient had diffuse choroidal hemangiomas with the classic « tomato ketchup » appearance, overlying exudative retinal detachments and hyperplastic retinal pigment epithelium alterations with subsequent progressive visual loss.⁵⁷ Lindsey et al. reported a case of two patients who presented with the rare combination of bilateral diffuse choroidal hemangiomas and bilateral facial nevus flammeus. In one eye of one patient, an associated serous retinal detachment was a complication.¹³ Anand reported a case of a 15-year-old patient with bilateral SWS, associated retinal detachments in both eyes, and choroidal thickening in both eyes (5.2 and 5.6 mm).⁵⁸ Griffiths et al. conducted a study using contrast-MRI for cerebral and ocular imaging in children with SWS. In this study, four of fifteen patients had bilateral SWS with bilateral choroidal hemangiomas recognized at funduscopy, and three cases where bilateral abnormality was only revealed with MRI.¹⁰ Bilateral choroidal hemangioma were reported by Scott et al. who described an 8-year-old girl with bilateral facial nevus flammeus and exudative detachment with underlying choroidal hemangioma in both eyes confirmed with subsequent B-scan ultrasonography, that measured the choroidal thickness as 8 and 6 mm in the RE and LE, respectively.⁵⁹

The question has been raised as to whether obliteration of the facial nevus flammeus with laser treatment may exacerbate intraocular pressure by reducing alternative outflows channels, resulting in an increased pressure gradient through the cavernous sinus, thereby decreasing episcleral venous outflow and exacerbating ocular hypertension.^{26,60} However, laser treatment in the ocular region does not appear to adversely affect eye pressure,⁶¹ and in a retrospective cohort study, Sharan et al. did not find evidence to suggest that laser treatment of the nevus flammeus causes glaucoma or that it can worsen a preexisting ocular hypertension or glaucoma.⁶²

Treatment of glaucoma is commonly with topical therapy, such as timolol and latanoprost, which respectively decrease fluid production and increase fluid outflow in the eye.⁴³ Glaucoma in SWS can be difficult to treat even with combinations of ophthalmic medication, and if medical management is unsuccessful, various surgical approaches have been performed such as goniotomy and trabeculotomy in congenital forms, and filtering surgery such as trabeculectomy, and trabeculotomy-trabeculectomy and posterior lip sclerotomy in older patients. The Ahmed valve and Molteno tube have been used with variable results.^{44,63} The major complication of surgical intervention stems from the risks of relieving the eye pressure too quickly which can result in retinal hemorrhage.⁶¹

The goal of treatment of choroidal hemangiomas is to induce involution of the hemangioma, with reduction of subretinal and intraretinal fluid and minimal disruption of neurosensory retina. The decision to treat choroidal hemangiomas should be based on visual acuity potential and extent of detachment. Management of choroidal hemangiomas can be very challenging and therapeutic options may be limited because both circumscribed and diffuse tumors often involve juxtapapillary and subfoveal locations. Surgery carries an increased risk of hemorrhage secondary to abnormal dilated episcleral and choroidal vasculature. These lesions have been treated with photocoagulation,⁶⁴ external beam therapy,⁶⁴ stereotactic radiotherapy,⁶⁵ radiation therapy,⁶⁵ proton beam radiotherapy,⁶⁶ plaque radiotherapy,^{64,67} transpupillary thermotherapy,⁶⁸ and more recently photodynamic therapy (PDT) with verteporfin.⁶⁹ Laser photocoagulation usually leads to poor visual acuity, high rate of recurrent subretinal exudates requiring more photocoagulation, and high rate of retinal detachment. It can also lead to irreversible formation of scotoma when treating hemangiomas close to the optic disc or macula. Radiotherapy can be administered via fractionated lens sparing technique on a linear accelerator, episcleral plaque therapy, proton beam, or stereotactic radiotherapy. It is the method of choice when hemangiomas are close to the macula, are extensive, and when bullous subretinal fluid is present, which precludes PDT or photocoagulation. External beam radiotherapy is usually indicated when there is a lack of response to laser photocoagulation. In case of bilateral diffuse hemangiomas, bilateral parallel opposing portals can be used. Clinical improvement is achieved months following the first application, but recurrence frequently occurs. Furthermore, repeated applications can induce several complications like cataract, neuropathy, and radiation retinopathy.⁷⁰ A potential carcinogenic effect should be also considered. Episcleral plaque

therapy is usually limited to circumscribed choroidal hemangiomas. In this method there are no late complication such as retinopathy or papillopathy; however, the disadvantages include having to carry out two surgical procedures, brachytherapy, and the removal of the plaques under anesthesia. Proton beam radiotherapy allows homogenous irradiation. The drawbacks are that it is expensive, not easily available, and has late side effects on the anterior segment of the eye. Stereotactic radiotherapy can be used to treat posteriorly located circumscribed choroidal hemangiomas, using lens sparing external beam radiotherapy with linear accelerators. Recent reports showed successfully treated patients with transpupillary thermotherapy but only with small, localized tumors that may need repeated applications. PDT allows for selective occlusion of vascular structures by photochemical destruction of vascular endothelial cells. Barbazetto and Schmidt-Erfurth treated two patients with large choroidal hemangioma of the posterior pole, achieving complete resolution of serous retinal detachment and improved visual acuity. No systemic side effects were reported.⁷¹ Later, Kjeka and Krohn performed this therapy achieving similar results.⁷² Intravitreal anti-vascular endothelial growth factor (VEGF) treatment has recently been used in numerous pathologies^{73–75} and showed good results in one case of exudative detachment in SWS using pegaptanib.⁷⁶ However, the basis of genetic alterations in vascular tumors can cause a continuous production of VEGF and lead to unsuccessful results with anti-VEGF therapy.⁷⁷

SWS is a rare syndrome that can have a severe impact on visual acuity. Some features of this pathology can be undiagnosed without the aid of multimodal imaging. Anterior chamber anomalies can be detected with ultrasound biomicroscopy in order to better evaluate the management strategy for glaucoma. Furthermore, early glaucomatous damage can be shown with SD-OCT by evaluating the peripapillary retinal nerve fiber layer and macular ganglion cell layer. Bilateral diffuse choroidal hemangiomas are rarely observed, especially with a major involvement of the side opposite to the cerebral hemangioma. Since a relatively similar color of the fundus between the two eyes can hide the presence of choroidal hemangioma, bilateral imaging with EDI SD-OCT, and B-scan ultrasonography of the choroid is fundamental as diffuse choroidal hemangioma can lead to complications later in life with a significant impairment of vision.

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