

Pathophysiology and management of glaucoma associated with phakomatoses

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Abstract

The phakomatoses, encephalotrigeminal angiomas (ETA; Sturge-Weber Syndrome), neurofibromatosis type I (NF1 or von Recklinghausen disease), Von Hippel-Lindau (VHL) disease, tuberous sclerosis (TSC), oculodermal melanocytosis (ODM), and phakomatosis pigmentovascularis are a group of neurocutaneous disorders that have characteristic systemic and ocular manifestations. Through many different mechanisms, they may cause glaucomatous damage of the optic nerve and subsequent vision loss varying from mild to severe. Glaucoma commonly affects patients with ETA (43-72%), orbito-facial NF1 (23-50%), and ODM (10%). Rarely, it may present as neovascular glaucoma in VHL and TSC. In ETA, glaucoma typically occurs ipsilateral to the port-wine stain, which is caused by a mutation in the *GNAQ* gene. Specifically, mechanical malformation of the anterior chamber angle and elevated episcleral venous pressure have been implicated as causes of glaucoma in ETA. In NF1, which is caused by a mutation in the *NF1* tumor suppressor gene, glaucoma commonly occurs ipsilateral to lid plexiform neurofibromas. Histological studies of eyes with NF1 have revealed direct anterior chamber infiltration by neurofibromas, secondary angle closure, fibrovascularization, and developmental angle abnormalities as mechanisms of glaucoma. Lastly, phakomatosis pigmentovascularis is a rare combination of ODM and port-wine stain. Affected patients are at very high risk of developing glaucoma.

Despite the many different mechanisms of glaucomatous damage, management follows similar principles as that for congenital glaucoma and primary open angle glaucoma. First-line therapy is topical intraocular pressure-lowering eye drops. Surgical management, including goniotomy, trabeculotomy, trabeculectomy, and tube shunt placement may be required for more severe cases.

Significance statement

The pathogenesis of glaucoma associated with the phakomatoses, encephalotrigeminal angiomas, neurofibromatosis type I, Von Hippel-Lindau disease, tuberous sclerosis, oculodermal melanocytosis, and phakomatosis pigmentovascularis is highly varied. Knowledge of the characteristics of glaucoma in these diseases will help diagnose and manage these patients.

Introduction

The phakomatoses are a group of rare multisystem disorders with characteristic ophthalmic and neurocutaneous manifestations. Although the term “phakomatosis” was coined by van der Hoeve in the early 1900’s due to similarities between neurofibromatosis and tuberous sclerosis, research in genetics and pathophysiology of disease has evolved the understanding of these diseases through the years. The group of conditions considered to be phakomatoses and their effects on the eye are heterogeneous. However, many result in glaucoma and subsequent vision loss.

Glaucoma is often associated with elevated intraocular pressure (IOP) and optic nerve damage. Intraocular aqueous humor is produced by the ciliary processes. The fluid exits the eye via either the pressure-dependent trabecular meshwork pathway or pressure-independent uveoscleral pathway. In the conventional pressure-dependent trabecular pathway, aqueous fluid flows around the pupil to the anterior chamber, then through the trabecular meshwork located in the anterior chamber angle to Schlemm’s canal, the episcleral veins, and the anterior ciliary and superior ophthalmic veins, which ultimately drain into the cavernous sinus. Obstruction or malformation in phakomatoses at any of these levels can result in elevation of IOP, resulting in glaucomatous damage.

In this article, we discuss the various types of glaucoma associated with the phakomatoses, including encephalotrigeminal angiomas, neurofibromatosis type I, Von Hippel-Lindau disease, tuberous sclerosis, oculodermal melanocytosis, and phakomatosis pigmentovascularis (Table 1). Although these phakomatoses result in glaucoma through a variety of different mechanisms, management follows similar principles and is aimed at decreasing IOP pharmacologically or surgically to preserve vision. We highlight the current literature on the pathogenesis of glaucoma in these phakomatoses and discuss the clinical approach to these patients.

Encephalotrigeminal angiomas (Sturge-Weber syndrome)

Clinical description

Encephalotrigeminal angiomas (ETA) is a congenital syndrome characterized by a facial capillary malformation (port-wine stain or nevus flammeus; Figure 1) that affects the skin in the distribution of the ophthalmic branch of the trigeminal nerve. It is associated with vascular malformation of the brain (leptomeningeal angioma) and/or the eye. Neurological symptoms often present in infancy with focal seizures and most affected individuals survive into adulthood with varying degrees of neurological impairment including epilepsy, hemiparesis, and cognitive impairment. Approximately 50% of patients show ocular involvement (Figure 2), usually ipsilateral to the port-wine stain, involving the eyelid, anterior chamber, cornea, choroid, and retina (Mantelli et al. 2016). Glaucoma develops in 30-70% of patients (Sujansky and Conradi 1995; Sullivan et al. 1992) and choroidal hemangiomas affect the posterior segment in 20-70% of cases (Mantelli et al. 2016; Witschel and Font 1976).

Glaucoma in ETA shows a bimodal age of development with 60% developing congenital glaucoma within the first year of life and 15% developing glaucoma between the ages of 5 and 9, although development in adolescence and adulthood have also been reported (Sharan et al. 2009; Sujansky and Conradi 1995). The glaucoma is typically unilateral and affects the eye on the side of the port-wine stain. An extension of the port-wine stain from V1 into the V2 distribution confers a greater risk of glaucoma

(Sujansky and Conradi 1995). In a survey of 170 patients with craniofacial port-wine stains, only 21% of the 28 patients with unilateral V1 port-wine stain developed unilateral or bilateral glaucoma, compared to 43% of 63 patients with unilateral V1 and V2 port-wine stain and 72% of 17 patients with bilateral V1 and V2 port-wine stain (Sujansky and Conradi 1995). Patients typically have progressive glaucoma leading to progressive visual field loss, although a few cases of secondary acute angle closure from lens-induced pupillary block and posterior scleritis in patients with ETA have been reported (Lambiase et al. 2015; Maruyama et al. 2002). Infants with congenital glaucoma may have epiphora (tearing), photophobia (light sensitivity), and blepharospasm (abnormal eyelid contraction) with typical corneal changes, including haze, megalocornea (enlarged corneal diameter), and buphthalmos (enlarged ocular globe).

Genetics

ETA occurs sporadically in approximately 3 of every 1000 newborns and affects males and females of all races and ethnic backgrounds (Comi 2007). It is caused by a somatic mosaic activating mutation of the *GNAQ* gene, which leads to stimulation of cell proliferation and inhibition of apoptosis (Shirley et al. 2013). This genetic mutation is present in both syndromic and non-syndromic port-wine stains (Shirley et al. 2013). The *GNAQ* mutation has been identified within the blood vessels and connective tissues of port wine stains and absent in normal control skin adjacent to the port wine stains (Tan et al. 2016).

Pathophysiology

Glaucoma typically occurs ipsilateral to the port-wine stain in ETA. Histologically, port-wine stains consist of ectatic capillary-venous blood vessels in the dermis with decreased perivascular innervation (Rydh et al. 1991). The vessels lack sympathetic innervation with subsequent loss of vessel tone and progressive ectasia. Additionally, loss of sensory innervation may decrease release of neuropeptides at the peripheral site. The link between the *GNAQ* mutation, perivascular innervation, and port-wine stain in the pathogenesis of glaucoma has not been well-established.

The two main theories of the pathophysiology of glaucoma are malformation of the anterior chamber angle and increased episcleral venous pressure from the ectatic vasculature of the port-wine stain. As many of the anatomical abnormalities in ETA resemble findings in congenital glaucoma, malformation of the anterior chamber angle is likely responsible for early-onset glaucoma in ETA, whereas elevated episcleral venous pressure may play a greater role in later-onset glaucoma.

Mechanical malformation of the anterior chamber

Abnormal anterior chamber angle formation or angle dysgenesis leading to increased resistance to aqueous fluid outflow is partially responsible for glaucoma in ETA. On gonioscopy, an examination technique used to visualize the anterior chamber, iris processes covering angle structures and a poorly developed angle can be seen in glaucomatous eyes (Barkan 1957; Mwinula et al. 1994). Electron microscopy shows abnormal presence of blood vessels in the trabecular meshwork, excessive accumulation of extracellular matrix in the juxtacanalicular connective tissue, and abnormally well-formed basal lamina of the endothelial layer of Schlemm's canal suggesting angle dysgenesis (Mwinula et al. 1994). Other pathological findings include anterior insertion of the ciliary body and iris root into the trabecular meshwork (Christensen and Records 1979).

Increased episcleral venous pressure

Gonioscopy in patients with later-onset glaucoma often demonstrates normal angle structures, though blood may be seen in Schlemm's canal, which is a result of elevated episcleral venous pressure. In 1978, Phelps showed that patients with ETA had episcleral hemangiomas with blood reflux back into

Schlemm's canal and high episcleral venous pressure. His finding of elevated episcleral venous pressure in glaucomatous eyes in patients with ETA was supported by a 2012 study by Shiau et al. In 11 patients with ETA, Shiau et al. (2012) found that the mean episcleral venous pressure of 20.9 mmHg in glaucomatous eyes was statistically significantly higher than the 9.6 mmHg in the contralateral nonglaucomatous eyes. In patients with unilateral port-wine stain without glaucoma, there was no difference in mean episcleral venous pressure between the ipsilateral and contralateral eyes.

Glaucoma monitoring and treatment

Glaucoma screening should begin at birth for patients with craniofacial port-wine stain, due to the potential for congenital glaucoma and severe visual outcomes if left untreated. The effect of laser treatment of a port-wine stain on IOP has not been well-established (Quan et al. 2010) and successful cosmetic laser treatment of a port-wine stain may mask its existence. The port-wine stain might not become evident until later in childhood, as its color may change as the child matures, so screening examinations should begin as soon as the port-wine stain is diagnosed. Routine slit lamp examination is necessary to monitor for glaucoma, but infants and young children may require examination under general anesthesia. In addition to IOP measurement, measurements of axial length and corneal diameter, which increase with elevated IOP, are also used to monitor disease in children. Glaucomatous damage in the optic nerve head can be monitored with optical coherence tomography.

Individuals with port-wine stains remain at risk for glaucoma due to elevated episcleral venous pressure throughout their lives, so all patients should receive annual screening eye exams. In adults, visual field analysis in addition to IOP measurement is fundamental in evaluating glaucomatous progression. It can, however, be challenging to perform in patients with intellectual disabilities. The visual field must be interpreted with caution, as patients with ETA may also have visual field defects due to diffuse choroidal hemangiomas or homonymous hemianopia secondary to occipital involvement of leptomeningeal angioma (Koenraads et al. 2016).

Due to the rarity of ETA, evidence for treatment comes from small case series with variable results. Medical therapy with topical eye drops are frequently used in adjunct or as first line therapy to lower IOP in glaucoma in both childhood and adult-onset cases. Aqueous suppressants, such as β -blockers, adrenergic agonists, and carbonic anhydrase inhibitors are typically preferred in congenital glaucoma. Brimonidine, an α -2 agonist, is contraindicated in children under 2 years old and should be used with caution in children due to the potential for central nervous system (CNS) toxicity. Latanoprost, a prostaglandin analogue that acts by increasing uveoscleral outflow, was successful in stabilizing ocular parameters, such as IOP, corneal diameter, cup to disc ratios, and refractive status in 7 of 14 children at 12 months in a study by Ong et al. (2003) and effective in decreasing IOP in 2 of 6 eyes in a study by Yang et al. (1998). Other topical IOP-lowering agents have not been systematically studied. Systemic propranolol, also used to reduce hemangiomas associated with ETA, was ineffective in decreasing IOP in 3 of 4 children studied by Wygnanski-Jaffe et al. (2015).

When medical treatment is insufficient in controlling glaucoma, surgical treatment can be offered. In early-onset glaucoma in ETA, angle procedures might be effective in controlling IOP. The type of angle surgery performed can be variable and goniotomy and trabeculotomy, which work by mechanically disrupting the anterior chamber angle structures, are often preferred as the initial surgical procedure for congenital glaucoma in children with ETA due to lower risk of adverse effects compared to filtering or tube surgery. Better IOP control can be obtained by repeating the procedure, as initial goniotomy is only successful for a median of 8 months and trabeculotomy for 21 months in children younger than 4 years old with ETA (Iwach et al. 1990). Olsen et al. (1998) reported IOP control in 67% (10/15) of eyes after

one or more goniotomy or trabeculotomy procedures followed for a median of 5.4 years. Earlier diagnosis of glaucoma and surgery at a median age of 3 months may afford a better success rate with a single trabeculotomy (Wu et al. 2017). Due to high risk of failure with single procedures, combined procedures, such as trabeculotomy-trabeculectomy have been proposed as the first-line approach in infants and children with ETA (Mandal 1999; Mantelli et al. 2016; Sood et al. 2017).

Filtering and tube surgeries are the next line of treatment and work by bypassing the trabecular meshwork and redirecting outflow of aqueous humor out of the eye via an ostium (filtering trabeculectomy) or tube shunt. The Ahmed glaucoma valve implant, a type of tube shunt with a unidirectional valve, was studied in ETA by Hamush et al. (1999) and was found to achieve lowering of IOP to <21 mmHg (normal 10-21 mmHg) in 79% of the 11 eyes (10 patients) studied and followed for a mean of 2.5 years. There may be an increased risk of intraoperative choroidal effusions and expulsive suprachoroidal hemorrhage in patients with ETA due to a sudden change in the IOP gradient when the eye is opened based on case reports and small case series (Bellows et al. 1979; Christensen and Records 1979), but the risk can be mitigated with techniques that prevent sudden lowering of IOP during surgery and in the post-operative period. No intraoperative choroidal effusion, choroidal detachment, or choroidal hemorrhage occurred in a retrospective case series of 17 patients who underwent glaucoma filtering surgery without prophylactic posterior sclerotomy by Eibschitz-Tsimhoni et al. (2003) or in the study by Hamush et al. (1999) where patients received an Ahmed glaucoma valve.

Other potential interventions include cyclodestructive procedures to destroy the ciliary body epithelium and decrease aqueous production.

Neurofibromatosis Type I (von Recklinghausen disease)

Clinical description

Individuals with neurofibromatosis type I (NF1) are prone to developing benign or malignant tumors of the peripheral nervous system. Neurofibromatosis type II is not associated with glaucoma. The most common tumor in adults with NF1 is a neurofibroma, a benign neural tumor consisting of proliferating Schwann cells, fibroblasts, and perineural cells that envelop the axons of peripheral nerves. Neurofibromas can be superficial (dermal) or diffuse and involving multiple nerves (plexiform). Neurologically, 30-65% of affected patients have learning disabilities and patients may have sensory or motor deficits from CNS tumors or neurofibromas involving spinal nerve roots or major peripheral nerves (Friedman 2002). Characteristic dermatologic features are café-au-lait spots and axillary freckling.

Ocular manifestations include iris Lisch nodules, optic nerve gliomas, and neurofibromas involving the periocular, intraocular, and orbital tissues (Figure 3). Glaucoma is estimated to affect 23-50% of patients with NF1 and ipsilateral lid plexiform neurofibromas (Morales et al. 2009). Glaucoma is typically unilateral and diagnosed from birth to 3 years, although diagnosis in childhood and adolescence have been described (Edward et al. 2012; Morales et al. 2009).

Genetics

NF1 is inherited in an autosomal dominant fashion with 100% penetrance by adulthood, variable expressivity, and prevalence of 1 in 2,000 to 5,000 (Huson et al. 1989; Rasmussen and Friedman 2000). An estimated 50% of NF1 cases result from new mutations (Huson et al. 1989; Rasmussen and Friedman 2000). NF1 is caused by mutations in the tumor suppressor gene *NF1* on chromosome 17, which result in increased cellular proliferation causing tumor formation (Rasmussen and Friedman 2000). The gene product, neurofibromin, is an intracellular protein that acts as a negative regulator of the RAS oncogene

(Rasmussen and Friedman 2000). Abnormal neurofibromin leads to sustained RAS signaling and activation of the RAS-MAPK pathway, which may lead to tumor formation (Ratner and Miller 2015).

A few clinically significant genotype-phenotype correlations have been reported in NF1 (Kehrer-Sawatzki et al. 2017). A more severe phenotype resulting in many neurofibromas early in life has been associated with *NF1* microdeletions, which are large deletions encompassing the *NF1* gene and its flanking regions. A single amino acid *NF1* deletion (c.2970_2972del [p.Met992del]) presents with a milder phenotype and affected individuals have multiple café-au-lait spots, but no external neurofibromas. *NF1* missense mutations affecting arginine at position 1809 are associated with developmental delays, pulmonic stenosis, and Noonan-like features, but no external neurofibromas. Although glaucoma in NF1 is associated with an ipsilateral upper eyelid plexiform neurofibroma, whether glaucoma is more common in genotypes resulting in more neurofibromas has not been studied.

Pathophysiology

The main recognized mechanisms for pathogenesis of glaucoma in NF1 include (1) direct infiltration of the anterior chamber angle by neurofibromas, (2) secondary angle closure resulting from neurofibromatous thickening of the ciliary body and choroid, (3) fibrovascularization leading to synechial angle closure and neovascular glaucoma, and (4) developmental angle abnormalities (Edward et al. 2012). Glaucoma in NF1 is likely the result of a combination of these mechanisms, as the same eye may have multiple findings on pathology (Edward et al. 2012).

Direct angle infiltration by neurofibromas

Obstruction of aqueous outflow through the anterior chamber angle by neurofibromatous tissue in the angle is supported by gonioscopic findings of light brown tissue obscuring angle structures and angle infiltration with diffuse uveal neurofibromas on pathology (Edward et al. 2012; Grant and Walton 1968).

Secondary angle closure from infiltration of anterior chamber angle by neurofibromas

Infiltration of uveal neurofibromas into the ciliary body and its processes was observed in the pathology of all 5 enucleated eyes with intractable glaucoma by Edward et al. (2012) with subsequent anterior displacement of the ciliary processes in the majority of the eyes examined (Figure 4). Clinically, anterior displacement of the ciliary processes due to neurofibromatous thickening can be demonstrated by ultrasound biomicroscopy (Edward et al. 2012; Morales et al. 2009). All 5 eyes in the study by Edward et al. (2012) also had endothelial overgrowth resulting in ectropion uvea (presence of iris pigment epithelium, which is normally only on the posterior iris surface, that is dragged onto the anterior iris surface; Figure 5). However, the role of angle endothelialization in glaucoma remains unclear, as lack of peripheral anterior synechiae in the presence of endothelial overgrowth covering the angle was observed.

Synechial angle closure and neovascular glaucoma

Formation of peripheral anterior synechiae with adhesions of the iris root to the trabecular meshwork may occur due to adherence of peripheral Lisch nodules in the angle region, as well as proliferation of a fibrovascular membrane from iris neovascularization. Iris neovascularization and subsequent neovascular glaucoma occur secondary to retinal vasoproliferative lesions or extensive retinal ischemia. In NF1, a few cases of neovascular glaucoma driven by vascular endothelial growth factor (VEGF) have been described in the literature (Al Freihi et al. 2013; Pichi et al. 2013). A variety of posterior segment vascular abnormalities and tumors, including retinal ischemia, vasoproliferative tumors, hamartomas, hemangiomas, and the neurofibromas themselves, may serve as stimuli for VEGF production in NF1 (Al Freihi et al. 2013; Destro 1991; Kotsuji-Maruyama et al. 2002; Shields et al. 2014).

Formation of secondary peripheral anterior synechiae also occurs as a result of repeated increases of IOP, which can worsen pre-existing glaucoma (Grant and Walton 1968; Payne et al. 2003). It should be noted that synechial angle closure due to adherence of peripheral Lisch nodules in the angle region may also be observed on gonioscopy in NF1 patients without glaucoma (Morales et al. 2009; Quaranta et al. 2004).

Developmental angle abnormalities

Compressed or absent trabecular meshwork, absent Schlemm's canal, and anterior iris insertion have been found in some pathology specimens of NF1 patients with glaucoma (Edward et al. 2012). In a study of 42 eyes of 42 patients ranging from 1 to 18 years old with NF1 mostly without glaucoma (only 3 eyes had glaucoma), 69% had mild anteriorization of the iris insertion and abundant basal iris processes on gonioscopy compared to controls (Quaranta et al. 2004). These findings suggest that anomalous development of the iridocorneal angle may be present in a large number of NF1 patients and glaucoma development is the result of multiple factors.

Glaucoma monitoring and treatment

NF1 patients, particularly those with ectropion uvea, should be closely monitored for glaucoma development (Edward et al. 2012; Ritch et al. 1984). The American Academy of Pediatrics (2008) recommends annual eye examination from ages 1 to 7, followed by complete eye examinations every 2 years screening for glaucoma, in addition to optic pathway gliomas. The visual prognosis in eyes with glaucoma is poor and of the 13 patients with glaucoma studied by Morales et al. (2009), all required glaucoma surgery and one third had either enucleation or evisceration of the affected globe, which is typically done once a blind eye becomes uncontrollably painful. Measurement of globe enlargement, which is typically severe with axial lengths ranging from 26 to 36 mm (mean 29.8 ± 4.1 mm vs. 25.6 ± 2.0 mm in patients with orbito-facial NF1 without glaucoma), can be used in conjunction with previously discussed glaucoma monitoring tools for infants and children (Morales et al. 2009).

Evidence-based guidelines for the management of glaucoma in this population does not exist. Since the glaucoma typically occurs in early childhood, treatment is often the same as that in congenital glaucoma as previously discussed. Goniotomy or trabeculotomy are preferred as initial surgical therapy when angle anomalies similar to primary congenital glaucoma are seen. Glaucoma surgery in these cases can be challenging due to cloudy corneas precluding a clear view for the ab interno goniotomy approach, in which case the ab externo trabeculotomy approach must be performed. If they fail, trabeculectomy with or without adjunctive antifibrosis therapy, glaucoma drainage devices, or cyclodestructive procedures may be used. Trabeculectomy frequently fails due to presumed endothelial growth over the filtration site, similar to that seen with iridocorneal endothelial syndrome, so a glaucoma drainage device or cyclodestructive procedure might be preferred. Glaucoma drainage devices are preferred in buphthalmic eyes with thinned scleras, or when there is conjunctival scarring due to previous filtering surgeries (Colas-Tomas et al. 2010).

Although the majority of NF1-associated glaucoma presents in children, adults should continue to have regular eye examinations to screen for glaucoma in addition to retinal vasoproliferative lesions or extensive retinal ischemia that could lead to neovascular glaucoma if left untreated.

Von Hippel-Lindau disease

Clinical description

Von Hippel-Lindau (VHL) is a multisystem neoplastic syndrome that leads to the development of benign or malignant tumors or cysts. Symptoms typically develop in the second through fourth decades of life. Affected individuals might develop craniospinal hemangioblastomas, renal cell carcinomas or cysts, pheochromocytomas, and pancreatic tumors or cysts (Lonser et al. 2003). Without screening, median survival in VHL complications was less than 50 years of age due to complications linked to renal cell carcinomas and CNS hemangioblastomas, but improved surveillance and treatment has improved prognosis of this disease (Lonser et al. 2003).

Retinal capillary hemangioma (RCH; Figure 6) is the most frequent and earliest manifestation of VHL disease and is seen in more than 60% of patients with up to half of patients having bilateral involvement (Carr and Noble 1980; Singh et al. 2001). Left untreated by laser or cryotherapy, RCHs may progressively enlarge, resulting in retinal exudation, retinal detachment, vitreous hemorrhage, and retinal neovascularization. Neovascularization of the iris with subsequent neovascular glaucoma is rare, but has been reported (Chen et al. 2015; Gaudric et al. 2011). Iris neovascularization was reported in only 2% of eyes with RCHs, but was present in 4 of 25 eyes blind from previous ocular angiomatosis in a study by Webster et al. (1999).

Genetics

VHL is inherited in an autosomal dominant fashion with high penetrance in 90% of patients by the age of 65 and affects approximately 1 in 35,000 individuals (Kaelin 2002; Lonser et al. 2003). Approximately 20% of cases arise from *de novo* mutations (Varshney et al. 2017). VHL results from a mutation in the tumor suppressor *VHL* gene on chromosome 3. The α -domain of the normal VHL protein interacts with elongin B/C, Cul2, and Rbx1 to form the ubiquitin ligase complex, while the β -domain binds to the transcription factor hypoxia inducible factor (HIF) (Mettu et al. 2010). Disruption of the VHL protein leads to dysregulated accumulation of HIF, which then directs overproduction of growth factors including VEGF that contribute to tumor formation.

Although the genotype-phenotype correlation of glaucoma in VHL has not specifically been studied, phenotypes for more aggressive RCHs would be expected to increase the risk of glaucoma. In a study of 890 VHL patients, 335 of whom had RCHs by Wong et al. (2007), prevalence of RCHs was lowest and ocular involvement least severe (defined by retinal detachment, massive subretinal exudation, and phthisical changes preventing visualization of the retina) in patients with complete deletion of the VHL protein compared to those with amino-acid substitutions and protein-truncating mutations. A further study by Mettu et al. (2010) revealed that mutations in the α -domain were significantly associated with a higher prevalence of RCHs compared with β -domain mutations. There was no effect of missense mutation position on present/severe ocular involvement.

Pathophysiology

Neovascular glaucoma in VHL is an end-stage consequence of aggressive RCHs. Neovascularization is driven by VEGF, which is present in high concentrations in the anterior chamber of VHL patients compared to unaffected subjects (Los et al. 1997). VEGF was also present on immunostaining at the corneal surface and within the hemangioblastoma of an enucleated eye with neovascular glaucoma and VHL (Chen et al. 2015).

Glaucoma monitoring and treatment

Neovascular glaucoma in VHL is treated similarly to neovascular glaucoma due to other causes, as there are few studies examining neovascular glaucoma specifically in VHL, due to its rarity. First line of

treatment of neovascular glaucoma due to all causes is complete panretinal photocoagulation and control of IOP and inflammation (Sivak-Callcott et al. 2001). Topical IOP-lowering agents, such as β -blockers, α -agonists, and topical and oral carbonic anhydrase inhibitors work by suppressing aqueous production. Prostaglandin analogues may be used empirically, but may have limited efficacy due to impaired access to the uveoscleral route. Topical atropine may be used for cycloplegia and inflammation may be treated with topical corticosteroids. Pilocarpine and other anticholinergic agents are contraindicated due to potential to increase inflammation, cause miosis, and worsen synechial angle closure (Sivak-Callcott et al. 2001).

Few small studies have shown that intravitreal anti-VEGF agents may lead to rapid regression of anterior chamber neovascularization due to all causes with a corresponding short-term decrease in IOP (Aref 2016; Kim et al. 2015; Vasudev et al. 2009). However, long-term IOP reduction with anti-VEGF agents has not yet been proven. Medical therapy alone is typically insufficient in managing neovascular glaucoma. Although surgical intervention to prevent glaucomatous progression may be performed, neovascular glaucoma in VHL it is typically an end-stage consequence of aggressive retinal hemangiomas, so affected eyes have poor visual potential secondary to retinal disease. Comfort, rather than visual preservation, is the goal in these cases. Five eyes in a study of 23 eyes with severe RCHs that underwent vitreoretinal surgery by Gaudric et al. (2011) for severe exudative of tractional retinal detachment developed neovascular glaucoma due to aggressive RCHs. Neovascular glaucoma developed 4 to 10 years postoperatively despite multiple additional sessions of photocoagulation. Four eyes, which had no light perception vision prior to onset of neovascular glaucoma, ultimately underwent enucleation. Prevention of neovascular glaucoma in VHL, therefore, relies on treatment of underlying retinal hemangiomas to promote regression.

Tuberous Sclerosis

Clinical description

Tuberous Sclerosis (TSC) is characterized by hamartomas of the heart, kidney, brain, skin, and eyes. Retinal astrocytic hamartomas (Figure 7), occurring in about 50% of patients, are the most common ocular finding in TSC (Nyboer et al. 1976). Typically, retinal astrocytic hamartomas in TSC are relatively stationary with little potential for aggressive behavior (Zimmer-Galler and Robertson 1995). However, in rare cases, they can progressively grow and cause complications, including neovascular glaucoma (Shields et al. 2004; Zimmer-Galler and Robertson 1995). Shields et al. (2004) described 4 young children with TSC who developed growth of an aggressive juxtapapillary astrocytic hamartoma with secondary exudative retinal detachment and neovascular glaucoma that ultimately led to blind, painful eyes necessitating enucleation between the ages of 1 and 14.

Genetics

TSC is an autosomal dominant disorder with near complete penetrance resulting from mutations in the tumor-suppressing genes tuberous sclerosis-1 (*TSC1*) on chromosome 9q34 or tuberous sclerosis-2 (*TSC2*) on chromosome 16p13 (Consortium 1993; van Slegtenhorst et al. 1997). Two-thirds of cases are *de novo* events. The incidence of TSC is estimated to be 1 in 6,000 to 10,000 (Kwiatkowski 1994). Mutations in the *TSC2* gene are more frequent than mutations in the *TSC1* gene in patients with retinal findings (Aronow et al. 2012). However, specific genotypes corresponding to aggressive retinal astrocytic hamartomas that may lead to glaucoma have not been identified.

Pathophysiology

Neovascular glaucoma in TSC is a late complication of astrocytic hamartoma growth with secondary non-rhegmatogenous retinal detachment. Saito et al. (2010) demonstrated high intravitreal VEGF concentration in an eye with retinal hamartoma, suggesting that VEGF secreted by retinal hamartomas could drive neovascularization. Histopathologic examination of enucleated eyes reveals iris neovascularization, ectropion uvea, and peripheral anterior synechiae occluding the angle and leading to neovascular glaucoma (Eagle 2000; Shields et al. 2004). Hamartomas of the iris and ciliary epithelium have also been described on histopathology and may be clinically visible (Eagle 2000). However, they have not been implicated in glaucoma in TSC.

Glaucoma monitoring and treatment

Like VHL, neovascular glaucoma in TSC is a late complication occurring in eyes of limited visual potential. Although treatment for the neovascular glaucoma may be offered as previously described, prognosis is poor and the cases described in the literature have frequently necessitated enucleation for blind, painful eyes. TSC patients with neovascular glaucoma are typically young children (compared to adults with neovascular glaucoma in VHL), about 50% of whom have bilateral retinal astrocytomas (Robertson 1991). Interestingly, of 3 patients with bilateral retinal astrocytomas who necessitated enucleation in the series by Shields et al. (2004), only one of the contralateral tumors demonstrated progressive growth and its complications. Nonetheless, these children need lifelong monitoring and protection of the contralateral eye.

Oculodermal melanocytosis (nevus of Ota)

Clinical description

Oculodermal melanocytosis (ODM) is characterized by unilateral or bilateral brown or blue discoloration on the facial skin innervated by the trigeminal nerve (Lavaju and Mahat 2015). It is typically noted at birth. Ipsilateral orbital tissues may also be affected and melanocytosis may extend beyond the orbit to involve meninges and brain. Malignant melanoma of the uveal tract, skin, orbit, and CNS may be associated with ODM with a higher risk among Caucasians (Singh et al. 1998).

In addition to skin hyperpigmentation, the conjunctiva, episclera (Figure 8), cornea, iris, and anterior lens surface, choroid, and optic nerve head can show melanocytosis or pigmentation (Teekhasaene 1990). Roughly 10% (20/194) patients with an average age of 30 years old with ODM studied by Teekhasaene et al. (1990) had elevated IOP, usually unilateral and ipsilateral to the hyperpigmentation. Three (15%) patients had congenital glaucoma (2 of whom also had Klippel-Trenaunay-Weber syndrome), 7 (35%) patients had ocular hypertension, 2 (10%) patients had open angle glaucoma, 5 (25%) patients had open angle glaucoma associated with ipsilateral uveitis, and 3 (15%) patients had bilateral angle closure glaucoma. The angle closure glaucoma was presumed to be coincidental due to bilaterality and the higher incidence of primary angle closure in Asian patients.

Genetics

ODM affects 0.02 to 0.8% of Asians with a female to male ratio of about 5:1 and is rarely present in Caucasian populations (Nam et al. 2017; Plateroti et al. 2017). Although no genetic or inheritance pattern has been identified, a positive family history of ODM was noted in 14 of 194 patients studied and two fraternal twins were affected in opposite eyes (Teekhasaene 1990).

Pathophysiology

Glaucoma in ODM is usually open angle and thought to arise from direct infiltration of the trabecular meshwork by accumulated melanocytes with hyperpigmentation of the iridocorneal angle in the eye ipsilateral to the dermal lesion on gonioscopy (Teekhasaene et al. 1990). Few case reports have demonstrated heavy asymmetric trabecular meshwork pigmentation in glaucomatous eyes ipsilateral to the ODM (Khawly 1995; Liu and Ball 1991). However, other studies have found that degree and extent of angle pigmentation do not clinically correlate with the presence or degree of IOP elevation, indicating that other factors likely also contribute to glaucoma development in these patients (Teekhasaene et al. 1990). Accumulation of melanocytes in the trabecular meshwork and outer wall of Schlemm's canal has been observed on electron microscopy of glaucomatous eyes with ODM (Teekhasaene et al. 1990). The ipsilateral nature of uveitis to the ODM in the study by Teekasaene et al. (1990) suggests that a relationship between pigmentation and autoimmune disorders and the uveitis itself may contribute to the glaucoma.

Glaucoma monitoring and treatment

Individuals with ODM should be regularly monitored for glaucoma. Treatment should be appropriate for the type of glaucoma and patient age. Typically, patients have open angle glaucoma presenting in adolescence to adulthood and are managed similarly to juvenile glaucoma or primary open angle glaucoma. If uveitis is present, it should be treated with corticosteroids. Topical IOP-lowering drops, such as β -blockers, α -agonists, prostaglandin analogues, and carbonic anhydrase inhibitors are typically first-line therapy if not otherwise contraindicated (Araie et al. 2002). It is unknown whether laser trabeculoplasty, an office-based procedure where short bursts of laser energy are applied to pigmented trabecular meshwork cells to improve aqueous outflow and lower IOP in open angle glaucoma, is effective. Filtering or tube surgery is indicated when there is any progression of optic nerve head damage and/or visual field damage taking into consideration the high rate of trabeculectomy failure in younger patients and East Asian patients (Araie et al. 2002).

Phakomatosis pigmentovascularis

Phakomatosis pigmentovascularis is a combination of ETA and ODM. It is a rare condition that has been primarily described in case series in Asian patients with cutaneous lesions that have vascular and melanocytic features. These patients are at high risk of developing congenital glaucoma, particularly when there are vascular malformations and melanocytosis covering 360° of the episclera (Teekhasaene and Ritch 1997).

Conclusion

The phakomatoses ETA, NF1, VHL, TSC, ODM, and phakomatosis pigmentovascularis may cause glaucoma through a variety of different mechanisms. All patients with these diseases need lifelong ophthalmic examinations to screen for glaucoma and various other ocular manifestations. Once glaucoma is diagnosed, management follows similar principles to that of primary glaucoma, beginning with topical IOP-lowering eyedrops. Congenital glaucoma and severe cases refractory to first-line treatment frequently require rapid escalation to surgical therapies, which may include goniotomy, trabeculotomy, trabeculectomy, tube shunt implantation, and diode cyclophotocoagulation. These treatments are often based on experiences in primary childhood glaucoma and need to be further studied systematically when applied to patients with phakomatoses.

Study of these phakomatoses is limited by the rare nature of these diseases, paucity of histological specimens, and small numbers of patients in many series. Further research is needed to elucidate the pathophysiology of glaucoma in these diseases in order to better screen patients and design successful targeted treatments. Better understanding of the genotype-phenotype correlations of these diseases will allow physicians to better counsel patients, screen for diseases, and recommend effective therapies.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

Role of Authors

Conceptualization, D.P.E., T.S.V.; *Investigation*, A.T.T.; *Resources*, J.D.B. and D.M.; *Writing - Original Draft*, A.T.T.; *Writing - Review & Editing*, D.P.E., T.S.V.; *Visualization*, A.A.; *Supervision*, D.P.E., T.S.V.

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Figure Legends

Figure 1. V1 and V2 port-wine stain in a patient with encephalotrigeminal angiomatosis.

Figure 2. Dilatation of scleral vessel in encephalotrigeminal angiomatosis.

Figure 3. Plexiform neurofibroma in the right upper eyelid (a) and Lisch nodules (arrowheads) on the iris (b).

Figure 4. (a) Pathology slide of ectropion uvea and closed angle. Note dragging of the iris pigment epithelium on to the iris surface (arrow) by a PAS positive membrane (endothelialization) on the iris surface (black arrowhead). Note angle closure due to infiltration of neurofibroma (*) and angle endothelialization (white arrowhead). (PAS Stain; composite photograph; original magnification x 2.5)

(b) The angle at high magnification showing anteriorly displaced ciliary processes (arrow) secondary to neurofibroma infiltration resulting in a pseudo anterior chamber angle (arrowhead). (PAS; original magnification x 10)

Figure 5. Clinical ectropion uvea (arrow) along the iris border in neurofibromatosis type I.

Figure 6. Retinal capillary hemangiomas in Von Hippel Lindau disease.

Figure 7. Retinal astrocytic hamartoma in tuberous sclerosis.

Figure 8. Episcleral and inferior eyelid hyperpigmentation in oculodermal melanocytosis.