Michael G. Gorin, MD, PhD, Professor in Ophthalmology and Chief of the Division of Retinal Disorders and Ophthalmic Genetics at UCLA School of Medicine, discussed retinal lesions. Long term surveillance is critical because up to 70% of VHL patients will have retinal angiomas and the age of onset ranges from age 3 to 50+. Unless it is on the optic nerve, Dr Gorin suggests that “if you can see it, treat it.” There is no good strategy for observing retinal lesions away from the optic nerve. Early intervention preserves vision by preventing the angiomas from growing to a size where they leak behind the retina and cause a retinal detachment.

Larger lesions are definitely more difficult to treat. Here is a summary of treatment options which have been attempted.

- **External cryotherapy** is a painful treatment in which tumors are frozen in an uncontrolled way by applying a probe to the outside of the globe.
- **Endo-cryotherapy / intraoperative cryotherapy** is more controlled and has better outcomes, but it requires the probe to be applied directly to the tumors, for example, during a vitrectomy operation.
- **Radiation** is generally not a good option because VHL patients have a long time to live (⃣) during which the radiation treatment can cause ongoing damage to their retina.
- **Traditional argon laser** is relatively ineffective because the laser gets reflected off of larger tumors instead of penetrating / killing the tumor tissue.
- **Photodynamic therapy** uses special type of dye and an infrared laser to increase the uptake of laser into the tumor. While promising in theory, clinical outcomes are still variable and the dye is very expensive.
- **Anti-VEGF therapy** requires injections in the eye. While it has had some success in reducing tumor leakage, it does not kill or shrink the tumor.
- **Fluorescein-potentiated argon laser (FPAL)**, Dr. Gorin’s preferred method, requires the use of a blue-light laser. After giving a patient fluorescein dye (inexpensive), the angioma will “light up like a light-bulb” and absorb blue light, which enables the ophthalmologist to destroy the tumor with little damage to the surrounding tissue.

More work must be done to continue developing better treatments for retinal angiomas. Dr. Gorin was awarded the two-year $100,000 research grant from the VHL Alliance which he plans to use to develop two models to study VHL retinal lesions. The in vivo model (taking place in a living animal) will use a knockout mouse so angiomas can be studied in vivo to test safety and efficacy of new treatments before they are used in humans. The in vitro model (taking place outside the body) will use induced pluripotent progenitor cells made from skin or blood cells so we can better understand cell-cell interactions during angioma development. This research may help us to develop tools to better predict angioma development and to develop drugs to more effectively treat existing angiomas.
Surveillance and Treatment of Retinal Angiomas
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David Geffen School of Medicine - UCLA
September 24, 2016

Disclosures
- MBG is listed as a co-inventor of Susceptibility genes for age-related maculopathy (ARM) on chromosome 10q26.
- Assignee- University of Pittsburgh
- Licensee: Sequenom

Objectives of this talk
- Review the epidemiology of retinal angiomas and when does one start surveillance
- Describe the features of retinal angiomas and how they affect vision
- Consider the current treatment options for retinal angiomas
- Discuss the research needs that we have to consider to improve detection and treatment
- Consider potential strategies for new treatments
Epidemiology of VHL-related retinal angiomas

- Age of onset: as early as 3-4 years old reported
- Up to 70% of VHL patients will have retinal angiomas
- 14% of our patients with VHL had only retinal angiomas as their clinical finding
- Bilateral involvement can be seen in up to 50% of individuals
- One report states “25% of cases can have permanent visual loss of acuity less than 20/40 in one or both eyes”

Features of retinal angiomas

- 20% of lesions are less than 200 microns in diameter
- 20% of lesions are anterior to equator
- 14% of our patients with VHL had only retinal angiomas as their clinical finding
- Intraretinal, subretinal and peripapillary lesions

Small retinal angiomas:

- Often do not have feeder vessels
- Initially appear as flat, telangetastic lesions
- Can be mistaken for a hemorrhage or “large” microaneurysm
- Usually leak on fluorescein angiogram, but not always

Medium and large retinal angiomas
Peripapillary Angiomas
- Often have an atypical appearance
- May appear as a “segmental” blush to the disc
- Almost always leak on fluorescein angiogram

Macular subretinal angioma with overlying fibrosis and extensive exudation
- Relatively uncommon location and often the appearance can mislead clinicians

THE VHL AT-RISK PATIENT
- Indirect ophthalmoscopy (ie with 20 D lens) is insufficient
- Slit lamp biomicroscopy
  - with contact lens or indirect lens (60, 78, 90 D)
  - High magnification is necessary
- Fluorescein angioscopy/angiography
  - Extremely useful in the young patient or person who cannot cooperate for an extended examination.
  - Can often distinguish an angioma from other vascular lesion
  - Extremely sensitive (detects lesions otherwise overlooked)

THE VHL AT-RISK PATIENT
- Optos Angiography
  - is excellent at detecting peripheral lesions, and provides a photographic record
- Angioscopy requires special filters for indirect ophthalmoscope and direct involvement of the clinician. A real time examination with no permanent image record.
THE VHL PATIENT  
Clinical Objectives:
- Detect any hemangioblastomas that need to be treated, especially those that are vision- or eye-threatening

Indirect ophthalmoscopy alone may be adequate, though very small lesions will be overlooked. One should be able to detect any eye-threatening lesion. The disadvantage of only using indirect ophthalmoscopy is that very small lesions that can be easily treated will be missed.

TREATMENT OF RETINAL ANGIOMAS

What are the indications for treatment?
- Any lesion that is jeopardizing the retina due to hemorrhage or exudation
- Any lesion that could in the future jeopardize the retina that is readily treatable

Is a retinal angioma ever too small to treat?
- The smallest lesions are the easiest and most successful to treat.
- Very small lesions rarely have exudation or bleeding associated with direct treatment
- Easier to treat before there is blood or exudation from the lesion

When can one observe a lesion without treatment?
- Convenience for a limited time.
- Some angiomas can double in size within 6 months

If one is going to observe an angioma, what should be the criteria to stop watching and start treating?
- If the goal is to minimize retinal damage, why wait until the lesion leaks or bleeds?
- There are no good criteria for observation unless the patient and/or physician feel that the potential complications of treatment are comparable to the potential effects of the lesion.

When do you not treat a retinal angioma?
- Peripapillary angiomas have a different natural history than lesions in the retinal vasculature.
- They tend to be indolent and if there is no significant exudation or hemorrhage in the macula, they can be observed indefinitely.
- Exudation and hemorrhage are frequent side effects of treatment, thus macular damage is a consideration.
- Previous laser treatment trials of peripapillary angiomas indicated that laser was less successful than observation alone.
When do you not treat a retinal angioma?

- Concerns regarding exudative retinal detachments (RD) from the treatment of a hemangioblastoma are valid.
- However, a lesion capable of causing an exudative RD during treatment is one which can spontaneously cause an RD on its own.
- Successful closure is easier if one starts prior to a spontaneous hemorrhage and/or RD.
- Treatment is generally advised.

TREATMENT OF RETINAL ANGIOMAS

Large lesions: Cryotherapy
- Significant damage to surrounding tissue
- Works poorly if there is an exudative RD
- Can be painful and precipitate choroidal and exudative RDs
- Generally a single session

Radiation
- Used effectively in a number of cases
- Different methods are available
- Key issue is selective targeting and shielding eye structures to limit collateral damage
- Requires careful calculation and titration of dose

TREATMENT OF RETINAL ANGIOMAS

Large lesions: Traditional argon laser
- Relatively ineffective, poor uptake into lesions

Photodynamic therapy
- Excellent potential, but no clinical experience
- Very expensive dyes and specialized lasers
- Patients must avoid sunlight for several days after treatment.
- Multiple sessions are likely (based on experience with other retinal vascular lesions)
- Because dyes are activated by infrared lasers, tissue penetration is excellent compared to FPAL which relies on visible wavelengths.

TREATMENT OF RETINAL ANGIOMAS

Large lesions: Anti-VEGF therapy
- Limited clinical experience but initial clinical trial at NEI found no efficacy
- Might be useful as an adjunct therapy but unlikely to eliminate the need for tumor ablative approaches.
- Has been suggested that it might be a preventative agent even if it doesn’t cause regression of existing angiomas.
Large lesions:

**Fluorescein-potentiated argon laser (FPAL)**

- Easy to perform
- Can titrate the amount of treatment and distribute over multiple sessions.
- Uses a safe, inexpensive, readily available dye
- Primarily enhanced thermal effect by using the dye to absorb the blue/green laser light
- Works well on lesions with exudative detachment
- Limited efficacy if there is substantial blood in the vitreous or media opacities
- No photosensitization of the patient
  - Hard to find a laser with 480 nm transmission but can work with only 514 nm (green)
Patient #1

- 60 yo WM
  - Peripapillary hemangioma, OD
  - Initial visual acuity 20/100-
  - Normal vision and exam - OS
  - Workup for VHL (CNS and systemic) - negative

April 4, 2000

Treatment - Fluorescein-potentiated argon laser (FPAL)

- 3 cc of 10% fluorescein administered intravenously.
- Laser treatment with blue-green argon at 0.2-0.5 seconds, 200 micron spot, 0.2 watts and Mainster Standard Lens
- Initiate treatment within 30 seconds of completion of injection. Stop when vessels spasm or there is excessive leakage into the surrounding retinal tissue.
- Number of sessions: 5

June 8, 2000
July 20, 2000
Aug 31, 2000
April 17, 2001
Va: 20/50
Patient #2

- 25 yo WF
- Peripapillary hemangioma OD
- Visual acuity 20/25 with difficulty
- No lesions - OS
- Documented VHL lesions in brain and spine
- Treated with 5 sessions of FPAL from 5-17-01 through 9-13-01. Vision remained at 20/20-2.
- Visual acuity decreased to CF at 10 ft on 11-18-01. Recovered spontaneously to 20/40 by 1-10-02.
- Pt lost to follow up.

Surgical Management of Angiomas

- Becoming a better option with large lesions rather than dealing with the effects of cryotherapy and massive exudation.
- Intraoperative cryo to the lesion directly and better surgical control
- Excision of membranes that are creating retinal traction
- Removal of vitreous and scaffolding for fibrovascular proliferation and future retinal detachment
- Use of silicon oil to maintain the attachment of the retina
  - This only works when the lesion is truly destroyed otherwise leakage will still cause a shallow detachment and proliferative changes
  - Some use steroids and anti-VEGF meds during the postsurgical period to reduce exudation

What is holding us back from better treatments for retinal angiomas

- There are essentially no large clinical trials that have assessed treatment
  - The condition is relatively rare
  - The size, location and number of angiomas as well as associated factors such as exudation, hemorrhage and retinal detachment make a standardized ablation therapy challenging
  - New treatments are done on only a few individuals and most innovations currently rely on existing medications that are being used for other conditions.
  - Treatments intended to prevent or retard angiomas are difficult to assess because of the variable natural history.
What is holding us back from better treatments for retinal angiomas

- We need an animal model for VHL-related retinal angiomas
  - Though there is a mouse that has a modified VHL gene that can be selectively turned off in specific tissues, it has never been used to recreate the condition that triggers angioma formation in the eye.
  - With such a model we could test both the safety and efficacy of new treatments before human exposure.
  - Greatly expand our ability to look at preventive treatments and those that can inhibit angioma growth.

What is holding us back from better treatments for retinal angiomas

- We need in vitro system for studying the biology and rapid testing of new medications.
  - We need cell lines that represent both the vascular endothelial cells that proliferate and the potential cell types that are referred to as the stromal cells which trigger the process because of the loss of VHL expression.
  - Unlike the in vivo animal model, an in vitro system lets us better study cell-cell interactions that trigger angioma formation and find pathways that are altered by the loss of VHL expression.
  - Can be used to rapidly screen new drugs for the effect on suppressing the development and growth of angiomas.

What is holding us back from better treatments for retinal angiomas

- We need in vitro system for studying the biology and diversity of the effects of the VHL gene.
  - Cells derived from VHL patients (such as induced progenitor cells made from skin or blood samples) could provide a means of understanding why some patients develop numerous retinal angiomas while other individuals have only isolated angiomas.
  - These cells could be used in a similar fashion as the genetically engineered cells that allow us to turn on and off the VHL genes on demand.

Potential strategies for new treatments

- Intraocular gene therapy to restore VHL expression in cells which have lost expression of both of the VHL genes.
  - We could develop and test drugs to be delivered chronically in the eye to block the activation of the pathways that are activated by the loss of VHL expression.
  - We could develop drugs and delivery methods that would allow us to selectively release those drugs within the angiomas by using focused laser light.
Potential strategies for new treatments

- Some potential agents:
  - Honokiol, a biphenolic phytochemical extracted from the Magnolia genus, is a potent inhibitor of the HIF pathway. Suggested by in vitro studies. Not used in humans.
  - Interferon 2 alpha (IFN-2α) has been tried in a small series with positive results. No clinical trials.
  - SU5416 (semaxanib), is a potent and selective inhibitor of the Fk-1/KDR receptor tyrosine kinase (VEGR-receptor). One patient had regression of retinal angioma (treated systemically).
  - Vatalanib is a potent inhibitor of VEGF-receptor tyrosine kinases. A phase II open-label study of oral, continuous, once daily vatalanib - Novartis – 11 patients – study completed several years ago – no results given.

Potential strategies for new treatments

- We could develop drugs and delivery methods that would allow us to selectively release those drugs within the angiomas by using focused laser light.

- We could develop tools to better predict when the eye is vulnerable to fibrovascular proliferation, even when the angiomas look quiescent.

Potential strategies for new treatments

- Sunitinib – oral agent, 3 clinical trials (one stopped because of lack of recruitment). One study (Pfizer) completed with 15 subjects and no improvement of angiomas (CNS or retina). Suggested that FGFR-blocking agents might be useful for angiomas.

- Pazopanib, a small molecule multi-receptor tyrosine kinase inhibitor – used for CNS lesions in a single refractory case.

- Thalidomide – powerful anti-angiogenic agent and affects other pathways. A few case reports with positive results. No clinical trials.

- Propanolol – in vitro evidence for possible effect. Multiple case reports of efficacy for non-VHL, capillary infantile and some adult hemangiomas.

Potential strategies for new treatments

- This talk is dedicated to the memories of two physicians who dedicated their careers to the patients and families with VHL.
  - Michelle Filling-Katz, MD (NIH)
  - Samuel Fisherman, MD (Pittsburgh)

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