



2016 ANNUAL MEETING SUMMARY OF PRESENTATIONS

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NEUROSURGERY: WHEN & HOW TO OPERATE

Ian McCutcheon, MD, Professor in Neurosurgery at the University of Texas MD Anderson Cancer Center, discussed 7 key challenges that a neurosurgeon faces when caring for a person with VHL manifestations in the Central Nervous System. Non-surgical treatments, including SRS (stereotactic radio surgery, delivering a focused dose of radiation to a specific area), may be available at some institutions, but Dr. McCutcheon focused on the surgical approaches.

1. Locations of these tumors are very sensitive. Find a surgeon with a lot of experience caring for VHL patients.
2. CNS tumors do not have a predictable pattern of growth so they must be monitored carefully. Following the screening guidelines is very important so you can identify tumors and plan a surgery when the patient is in good health instead of waiting for them to decline. Timing a surgery can be tricky. If a woman with VHL develops symptomatic hemangioblastomas when she is pregnant, it is still possible to care for her and her child. As Dr McCutcheon explained, "We don't tell people to have their pregnancy terminated because they have a hemangioblastoma."
3. A syrinx (fluid filled pocket that surrounds the tumor) can grow faster than the tumor and cause severe symptoms. You have to locate the tumor, sometimes comparatively much smaller, and remove it; once the tumor is gone the syrinx will regress. If you do not remove the tumor, the syrinx will continue to grow. When there are multiple tumors and only one cyst, it can be difficult to identify the tumor associated with the syrinx.
4. Hemangioblastomas are hyper-vascular. The bleeding can get much worse if the patient has tumors of the adrenal gland (pheochromocytomas and paragangliomas). These tumors must be sufficiently blocked or removed before neurosurgery.
5. Sometimes there are complex tumors in tricky places which can be difficult to leave or remove. In some of these cases, a surgeon may choose an operation that relieves symptoms without removing the tumor.
6. We do not strip out cysts, because this is dangerous for the patient. Sometimes a cyst can even be helpful. For example, a surgeon may opt to go through the cyst to access a tumor on the brain. This is "much more forgiving" in terms of recovery than going through brain to access the tumor.
7. We do not usually need shunt with hydrocephalus cases. Again, if we just remove the tumor (without first placing a shunt), the cyst will regress and the patient will heal.
8. Immediately after surgery, a patient may be in worse shape than before they entered. However, after long-term recovery, a patient's function often returns to their original state or (in some cases) improves from their original state. "The better the neurological condition of the patient is before surgery, the better the condition will be after surgery... and the more rapid and complete the recovery. Therefore, waiting for profound decline is unwise."

Dr. McCutcheon also shared this summary table which outlines some of the key factors that would influence a surgeon's decision "to operate or not to operate."

| Yes | No |
|---|--|
| Tumor is symptomatic (what a person feels depends on tumor location) | Tumor is small, asymptomatic |
| Tumor endangers function (patient still intact, but not for long) | Tumor is very large, the removal of which will surely harm the patient |
| Tumor prevents function (ie: teen who cannot play sports unless it is removed) | Patient has significant co-morbidities |
| Tumor causes hydrocephalus | Patient is not ready to accept surgery |

GENETIC ISSUES & CHALLENGES IN THE COORDINATION OF CARE

Julian A. Martinez-Agosto, MD, Associate Professor in Human Genetics at the University of California Los Angeles (UCLA) School of Medicine, discussed the benefits of multidisciplinary specialty clinics in providing optimal coordinated care for people with genetic conditions.

A gene contains a specific set of instructions which tell a protein how it should function. Sometimes, like in VHL, a variation (mutation) in a gene can cause a disease. For example, a small “mutation” in a cake recipe could result in using a CAP of sugar instead of a CUP of sugar. A properly functioning VHL gene makes a protein that alerts your cells when they need more oxygen. If the VHL gene is “broken” (mutated), cells think they are starving for oxygen and your body responds by producing more and more blood vessels (tumors).

A genetic disease can be inherited from a parent that has already has the mutation in their sperm or eggs and (except for mosaic cases) every other cell in their body. In 20% of people with VHL, the disease is acquired by a mutation that randomly occurs in one sperm or one egg. We call this a de novo case; the child will have VHL but the parents will not. Random gene deletions, like those that cause a de novo VHL mutation, occur more often in sperm than in eggs.

The multi-disciplinary clinic in which Dr. Martiz-Agosto participates helps people who have cancer predispositions. These clinics (and all other VHL Clinical Care Centers) are organized to improve testing, diagnosis, counseling, surveillance, and treatment for all affected family members. Their goal is to offer state-of-the-art coordinated care and also gather information to conduct research to help improve methods for other patients.

TREATING THE KIDNEY: SURGERY VS. RADIO ABLATION

Steven Raman, MD, Director of Abdominal Imaging Fellowship at UCLA Health, discussed radio ablation as an alternative to surgical or pharmaceutical treatment for clear cell renal cell carcinoma (ccRCC). Since VHL is a very scan-based disease, he emphasizes the importance of having an expert reading the scans. One of his top interests is distinguishing benign from malignant kidney tumors *by scan*. While many specialists will say that this cannot be accomplished reliably, Dr. Raman argues that 80+% of the tumors can be characterized correctly because different tumors behave differently on the scan. Biopsies can be used to confirm the ~20% of tumors that cannot be confirmed by scan. By correctly characterizing tumors by scan, Dr. Raman can avoid over-treating benign tumors and begin treating malignant (cancerous) tumors even before they are small than 3 cm. Note: the “3 cm rule”—which states that surgery is only recommended for tumors larger than 3 cm—has been the consensus since the 1994 VHL International Medical Symposium.

Dr. Raman also prefers to avoid using surgery to treat the malignant tumors. Instead, he uses needles inserted into the skin without an incision to ablate or freeze the specific tumor. In some cases he can even avoid needles by using focused ultrasound. He shared a case study of one VHL patient under his care since 2004 who has responded very well to ablations. It was only in 2015 that his kidney function began suffering, and in September 2016 he was one month post-transplant. While these results cannot be guaranteed for all cases, Dr. Raman suggests that his use of ablation to treat kidney cancer holds promise for other VHL patients with ccRCC.

RETINA LESION DETECTION & TREATMENT

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.

ADRENAL ISSUES & SURGERY

Masha Livhits, MD, Endocrine Surgeon at UCLA School of Medicine, discussed detection and treatment of tumors of the adrenal gland. Pheochromocytomas occur inside the adrenal gland and paragangliomas occur outside. VHL patients are predisposed to develop these tumors which are often non-cancerous but produce too much adrenaline, the “fight or flight” hormone. Symptoms can be violent (panic attack), less obvious (elevated blood pressure), or non-existent.

Asymptomatic adrenal tumors are fairly common for VHL patients, so it is especially important to follow the screening recommendations. For example, under anesthesia for an unrelated surgery a “hidden” (undiagnosed / asymptomatic) adrenal tumor can create a life-threatening spike in blood-pressure. Patients who need anesthesia

and know they have an adrenal tumor can receive pre-operative medicines (α -blockers and sometimes β -blockers) to help prevent this crisis. Emergency surgeries without the proper pre-operative medicines should be avoided. Screening for VHL patients can include a blood test, 24-hour urine test, and various types of scans.

Once a patient is diagnosed with a pheo or a paraganglioma, it should be surgically removed even if it is asymptomatic. Again, pre-operative medications, which are taken for 2-3 weeks, are vital! α -blockers block adrenaline hormone and control blood pressure. They can also make patients tired and thirsty, so taking patients should use this time to re-hydrate. β -blockers are sometimes added if a patient's heart rate needs to be lowered. To operate on the right adrenal gland, the surgeon will have to mobilize the liver; on the left adrenal gland, the spleen must be mobilized. In the 1950s open adrenalectomies were considered the gold standard. In the 1990s, laparoscopic (entering through small incisions in the front) and retroperitoneal approaches (entering through small incisions in the back, fewer surrounding organs to manipulate) became available which dramatically decreased healing time. Open adrenalectomies, however, are still used if the surgeon is concerned about malignancy or if it too large. The latest technique preserves some of the adrenal cortex so patients can hopefully avoid being on steroid supplementation for the rest of their lives. Although this is promising, there is an increased risk of recurrence because the only way to ensure that all the tumor tissue is removed is to remove the whole adrenal gland.

UPDATE ON VHLA-FUNDED RESEARCH

Eric Jonasch, MD, Professor in Genitourinary Medical Oncology at the University of Texas MD Anderson Cancer Center discussed the most recent research projects to which the VHL Alliance has awarded grant funding. The goal is to advance our scientific understanding of VHL disease by

- 1) increasing our understanding of how VHL affects the cell;
- 2) permitting the creation of model systems that better mimic the organ involvement of VHL; and
- 3) developing improved screening and treatment approaches for people living with VHL.

VHLA grants come in two sizes: a one-year \$25,000 pilot grant and a two-year \$100,000 research grant. Each research proposal is evaluated on rationale, approach, and significance.

2014 Pilot Grant Awardee: Dr. Danny Segal, Tel-Aviv University

Dr. Segal's team is trying to see if readily available materials like the amino acid arginine can be used to help refold misfolded VHL. This is especially promising because 1/3 of all VHL mutations are point mutations which mean they only have one error to fix.

2014 Full Grant Awardee: Dr. Othon Iliopoulos, Massachusetts General Hospital

Dr. Iliopoulos' team uses zebrafish with VHL to screen drugs that may help treat people with VHL. Zebrafish with the VHL gene deleted display a number of VHL lesions similar to those seen in people. Since these tiny fish are relatively transparent, you can actually "see" the effect that potential drugs have on the VHL manifestations.

2015 Pilot Grant Awardee: Dr. Horst-Shrivers, University Medical Center in Groningen, Netherlands

Dr. Horst-Shrivers' team is trying to understand if hormones produced by pheochromocytomas can be reliably measured in saliva. If successful, this would enable VHL patients to screen for pheos using a "spit in cup" method instead of the 24-hour urine test or the blood test which requires you to rest for 30 minutes before the blood draw.

2015 Full Grant Awardee: Dr. Ian J. Frew, University of Zurich

Dr. Frew's team is using a mouse model to test drugs that may be able to treat clear cell renal cell carcinoma (ccRCC), a type of kidney cancer that frequently affects VHL patients. This research will be used to guide new trials in people with VHL or other patients with noninherited ccRCC.

2016 Pilot Grant Awardee: Dr. Raymond Kim, University of Toronto

Dr. Kim will head the international VHL-IT Sharing International Consortium (VISIon) with the goal of developing a more efficient approach to collect information on VHL mutations and the way that VHL manifests in these individuals. This will help us better understand genotype-phenotype patterns (ie: which mutations cause which manifestations).

2016 Full Grant Awardee: Dr. Michael Gorin, University of California Los Angeles

Dr. Gorin will work on developing two new models to study VHL retinal lesions. One model will use inducible pluripotent stem cells. This means that undifferentiated somatic cells (ie: undifferentiated skin cells, blood cells) can be trained to act as a cell in the eye. The other model involves a VHL knockout mouse which will allow us to better understand how retinal hemangiomas form and develop new strategies for blocking the formation of these retinal tumors.

CGIP: Cancer in our Genes International Patient Databank

This gives VHL patients an opportunity to contribute their own information. With more people participating longitudinally, we can better understand the natural history of the disease. One finding from the databank already is that the dry mouth, canker sores, and other oral health issues are seen at a higher incidence in VHL patients than they are in the general population. For more information, go to: vhl.org/databank

We anticipate that these talented investigators will help move the field of VHL research forward substantially in the next few years.

LIVING WITH CHRONIC PAIN

Jakun Ing, MD, MPH, Assistant Clinical Professor in Anesthesiology and Pain Management at UCLA School of Medicine discussed chronic pain management for patients with VHL. Pain can arise from VHL manifestations themselves (ie: back pain from kidney cancer) or from treatments (ie: pain associated with brain surgery recovery). Since VHL patients may have multiple causes of pain, it is important to use a regiment that treats multiple causes, not just one. This is a summary of different drug classes and considerations, for example regarding kidney health, that may be especially important for VHL patients.

| Class of drug | Example | Considerations |
|-------------------------|--------------------------------------|--|
| Opioids | Hydrocodone, fentanyl | Require good liver and kidney function; can cause dependence (addiction) |
| NSAIDs | Ibuprofen (Advil, Motrin) | Can cause kidney injury |
| Anticonvulsants | Gabapentin | Must decrease dose in patients with kidney problems |
| Acetaminophen | (Tylenol) | Unclear how much is "safe" for a patient in liver failure |
| Antidepressants | Duloxetine (Cymbalta) | Often an off-label treatment for pain |
| Muscle Relaxants | Baclofen, cyclobenzaprine (Flexeril) | Can be especially helpful post-surgery |

Non-pharmacological therapies such as physical therapy, aqua therapy, acupuncture, and others may also be good options. Talk with your care team to see what portfolio of therapies might be best for you.

CHILDBEARING OPTIONS

Candace Clark Trinchieri, an ambassador for RESOLVE – The National Infertility Association, considers herself a reluctant expert on childbearing options. After having multiple failed experiences utilizing multiple artificial reproductive technologies, she was delighted to become a mother through adoption. She acknowledged the concern that couples with VHL may have regarding the 50% chance of passing VHL on to their children and highlighted these family building options that couples may wish to consider.

Adoption

Within adoption, there are options to consider. Candace encouraged people to think about cultural differences when deciding on a domestic or international adoption: “if you would not date someone from a particular country, you should not adopt a child from that country.” She also expressed her preference for open adoption with an analogy to a cookie jar: if the cookie jar is on top of the fridge and out of reach, her son will constantly seek it, but if the jar is accessible, he can reach it as he is ready. For example, if her son asks about his birth mother, he and Candace can immediately face-time with his birth mother so he can speak directly to her.

Donors and surrogates

A donor is someone who gives a gamete (egg, sperm) or embryo. VHL couples may be interested in seeking donations that are free from a VHL mutation. A surrogate mother gestates a pregnancy for another woman. A woman with VHL may seek this option to avoid exacerbating VHL tumor growth with pregnancy. (NOTE: there is conflicting research about the effect that pregnancy has on VHL tumor growth rate.) Be sure to reference the laws regarding donors and surrogates, since the legal parental role that these individuals have vary by state / country.

IVF with PGD (in vitro fertilization with preimplantation genetic diagnosis)

A woman must take medications that ripen multiple eggs for extraction. After the sperm is collected from the man (typically a non-surgical procedure) the eggs are fertilized in a petri dish. After a few days, doctors can test each embryo for VHL and then implant only the embryos that do not have VHL. PGD is very accurate, but the couple will still be strongly encouraged (often required) to have a prenatal test (ie: amniocentesis) to confirm the baby does not have VHL or other genetic abnormality.

Living child-free

Wading through these child-bearing choices can be its own emotional rollercoaster. As you consider the multiple options available, remember that living child-free may also be an option you wish to consider. For example, some people with VHL have decided to use their “parenting” energy to become more active members of their community.