VHLA 2013 Annual Meeting
Ann Arbor, Michigan

Scientific Presentations

The 2013 VHL Alliance Annual Conference was held at the Ann Arbor Regent Hotel on Saturday, September 21, 2013.

The agenda included seve n scientific presentations (summarized below), a talk on the State of the VHLA, and two panel discussions with VHL patients regarding aspects of living with VHL and family and lifestyle decisions.

Videotapes and slides from the presentations may be viewed on the VHLA website: http://www.vhl.org/wordpress/patients-caregivers/get-involved/calendar-of-events-and-meetings/201-vhl-annual-family-meeting-ann-arbor/

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Monitoring the VHL Patient

Elena M. Stoffel, MD, MPH
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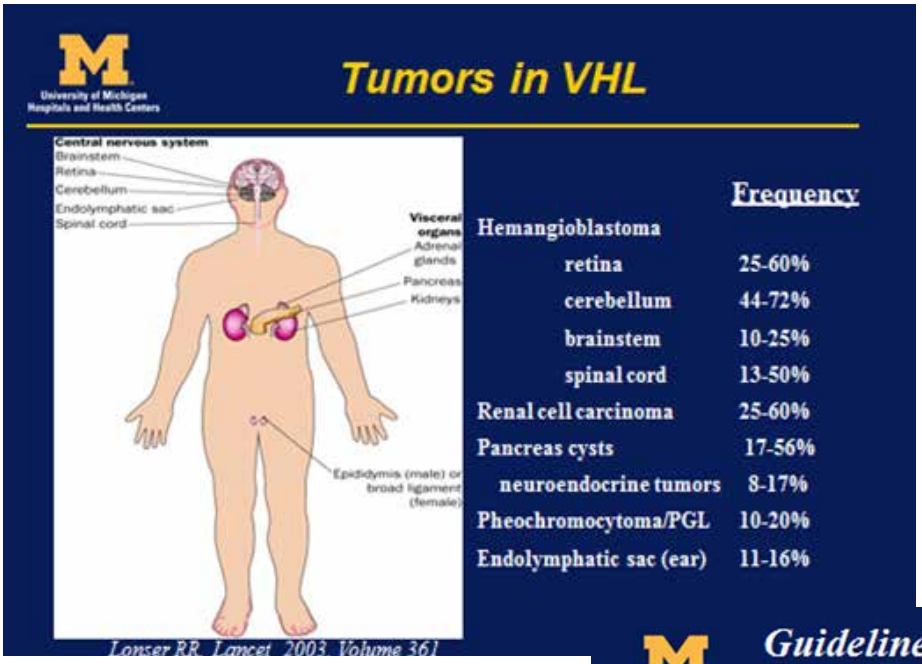
The VHL gene has a tumor suppressing function. A mutation in the gene causing inactivation of this function increases the likelihood that tumors will occur. In order for a tumor to grow, both copies of the VHL gene must be inactivated, therefore VHL disease gives tumors a head start. CNS tumors are one of the most prominent features.



There is a broad spectrum of disease in VHL; the disease does not always follow what is written in books.

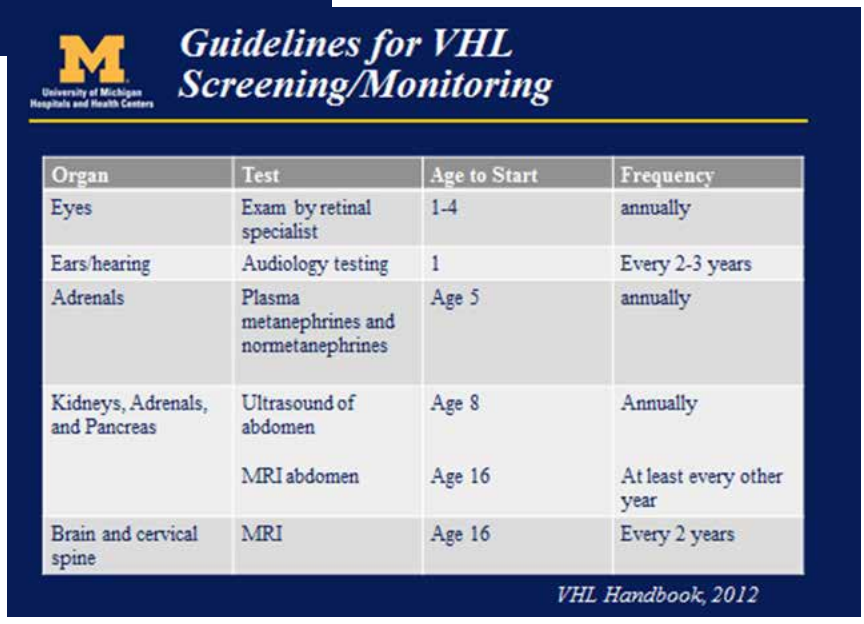
Different types of tumors are based on VHL mutations, but there are also differences based on other gene modi-fiers which impact the VHL phenotype. It has been shown that some differences in VHL tumors are based upon the VHL mutations, but there are probably other types of genes, unrelated to VHL, which modify risks for different types of cancer. Environment and lifestyle factors are also important in VHL tumor growth: a good example is smoking.

Genetic testing ensures everyone gets the care they need before manifestation of symptoms. Dr. Stoffel likes the screening grid in the *VHL Handbook*:

For example, annual eye exams need to begin in infancy and CNS monitoring should begin by age 16. Audiology testing and adrenal monitoring are also important. Testing may be required more often than the guidelines if there are symptoms to investigate. Pregnancy is also a time for closer monitoring because "everything grows." Dr. Stoffel recommends MRIs to spare radiation when possible for abdomen and pelvis screenings.

The challenge is when do we intervene in a VHL tumor? The threshold for intervention is often different for VHL patients. An example from gastroenterology is pancreatic cysts: there is a higher threshold for intervention for VHL patients than non-VHL patients.

Living with VHL requires a team approach: the VHL Alliance provides links between patients and MDs and among physicians in different specialties. Dr. Stoffel urges patient involvement in VHL research as this is how we will learn how best to manage VHL and find a cure.



VHL and the Central Nervous System: Panel Discussion

Moderator: Steve. E. Sullivan, MD
University of Michigan, Ann Arbor

Ghaus M. Malik, MD, Neurosurgeon
Henry Ford Hospital, Detroit

Ian E. McCutcheon, MD, Professor of Neurosurgery
University of Texas
MD Anderson Cancer Center, Houston

A 2006 study by NIH documented the natural history of CNS hemangioblastomas. The goal is as few operations as possible during the patient's life. Therefore, physicians base surgical decisions on symptoms, BUT watch for future problems.

VHL patients should have yearly scans. Tumors can remain dormant, but doctors must look at the location—some areas of the brain have more functions, meaning that even small tumors in sensitive areas need to be carefully watched. This is a key factor in determining when to operate.

Cysts can grow more rapidly than tumors, causing pressure and blocking fluid. Also, cysts and tumors located closer to surface of the brain may grow more quickly. Removing the tumor will usually shrink the surrounding cyst, so the cyst itself does not need to be removed.

Removing cerebellar tumors is lower risk. Tumors in the brainstem are much more difficult, but they must be removed once they become symptomatic. Physicians cannot wait to monitor brainstem tumors as they tend to begin on the surface, and then grow inward. Surgeons must be careful when removing tumor blood vessels to not remove blood supply to brainstem as this increases the possibility of a brainstem stroke.

Multiple tumors in the brain and spinal cord can make it difficult to decide which tumors are the sources of the symptoms. If the physician is not sure, the safest surgery is performed first. The cerebellum is a relatively safe area as one side can compensate for tissue removal from the other side.

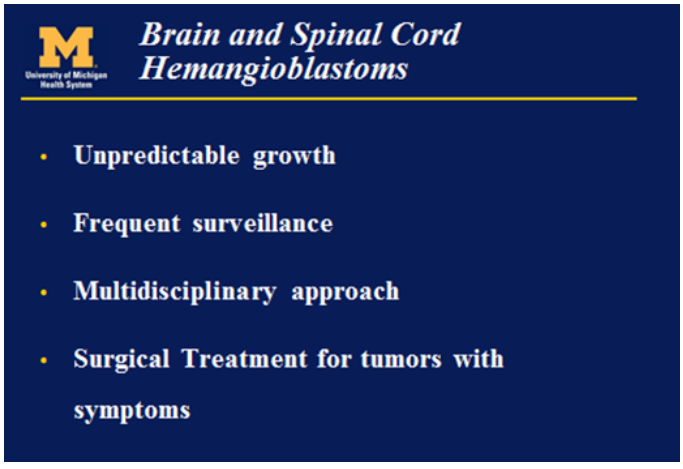
Changes associated with spinal cord tumors are not as rapid as with brain tumors. A higher location of a lesion in the spine causes more severe paralysis. The surgeon also needs to also look at the HISTORY of the symptoms: if arm problems begin before leg symptoms, the higher located tumor, even though it is smaller, is probably the more important tumor to remove.

If possible, the surgeon removes more than one tumor in a single operation. It is important to always look at the risk/benefit ratio for surgery vs. not operating. The approach is the same for all patient ages.

The most difficult challenge is several tumors all growing in one area of the spine. The surgeon usually removes multiple tumors at the same time. The job of the surgeon is to lay out the risks and benefits as known, explain to the patient and decide with the patient.

Audience questions and responses:

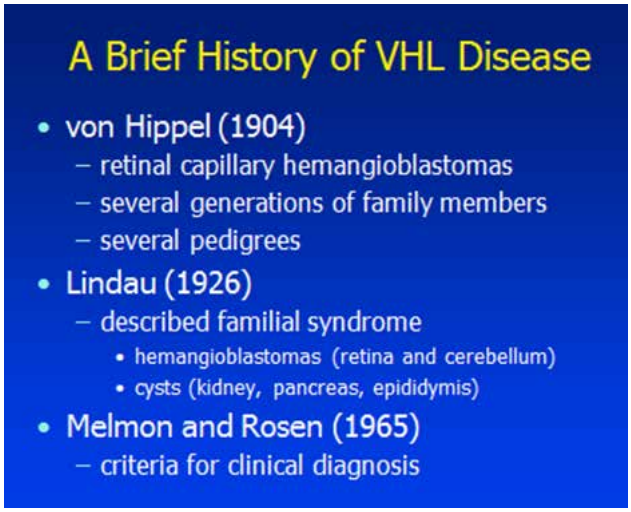
- Hemangioblastomas can grow off of nerve roots, not just the spinal cord. The panel has not come across any bone hemangioblastomas.
- Should radiation therapy be used as an adjunct? No, try not to use as it is not as effective, especially on slower-growing tumors. One does not want to sacrifice tissue function to kill tumors; it is a last, desperate measure. It does not work rapidly and the spine does not tolerate radiation well. Stereotactic radiosurgery is not recommended for CNS tumors. Radiation causes scarring that can make subsequent surgery more difficult.
- The panel does not screen every patient for metanephrines unless their history indicates pheochromo-cytomas. (Note: The *VHL Handbook* recommends screening all patients as 3-5% will have a "silent" pheo that reacts during surgery.)
- Doctors dread patients who cannot have MRIs at all, but scans can work without contrast. Clinical judgment can work when scans are not possible. It is possible to turn off pacemaker for an MRI, but this is rarely done. A CT myelogram can be used if there is a rod implanted in the spine.
- Why are VHL lesions not present in the cerebrum? The panel does not know, but has seen a few. (Note: these are called "supratentorial lesions" and are possible, though rare.) "Awake" surgery is only used for the cerebrum.
- There is no evidence that CNS tumors grow due to steroid use.
- How do you prevent blood clots after surgery? The panel uses subcutaneous heparin. There is no established timeframe; the concern is post-operative bleeding.



Ophthalmology Issues in VHL

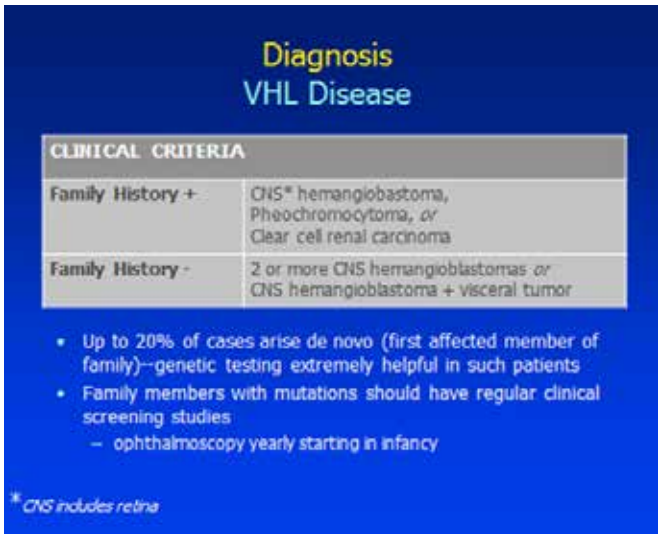
Mark W. Johnson, MD
Professor of Ophthalmology and Visual Sciences
Director of Retina Services, University of Michigan
Kellogg Eye Center, Ann Arbor

The eye allows the physician to see VHL directly on the retina—no imaging is required. Both von Hippel and Lindau (20 years later) saw retinal lesions, but Lindau connected them with lesions in other organs.



Ocular manifestations are often the first lesions found and lead to diagnosis. Up to 20% of VHL cases diagnosed are de novo mutations. Most lesions are in the periphery where they do not impact vision. Smaller lesions are easier to treat. As they grow, lesions develop prominent feeding and draining vessels, except when on the optic nerve, making them more difficult to detect there.

Lesions can appear at any age. They can spontaneously regress, but generally keep growing slowly, eventually causing vision loss through secondary complications:

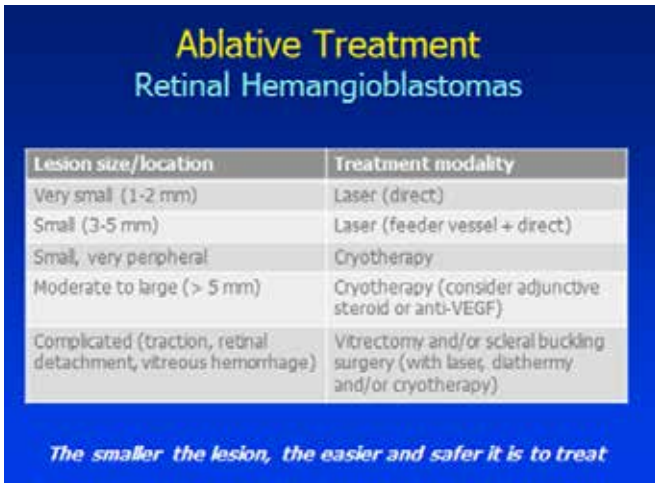


retinal edema, lipid exudates, fibrosis, retinal detachment, bleeding, or neovascular glaucoma. The National Eye Institute (NEI—Wong 2008) study found that 38% of VHL patients have eye lesions, but even so, 77% have 20/20 vision and only 5.7% were legally blind.

VHL is diagnosed based upon clinical appearance; there is no definitive diagnostic tool. Fluorescein angiography is commonly used to highlight feeding vessels and tumors. It can find subtle lesions and delineate the size of lesions. Optical coherence tomography can show retinal swelling.

Treatment:

Small lesions: use laser (can treat feeder artery first). Cryotherapy is easier in the periphery; it is also used for larger lesions along with Anti-VEGF to reduce leakage. Surgical treatments are used for more extensive lesions or detachments, etc.



Dr. Johnson recommends that all peripheral lesions be treated because it is so low risk. Scars will be seen on the retina following treatment, each causing a tiny blind spot that is usually imperceptible to the patient. Optic nerve hemangioblastomas are among the most challenging. There are always a few of these shown at Ophthalmology meetings, but there are no good answers. Photodynamic therapy has had mixed results.

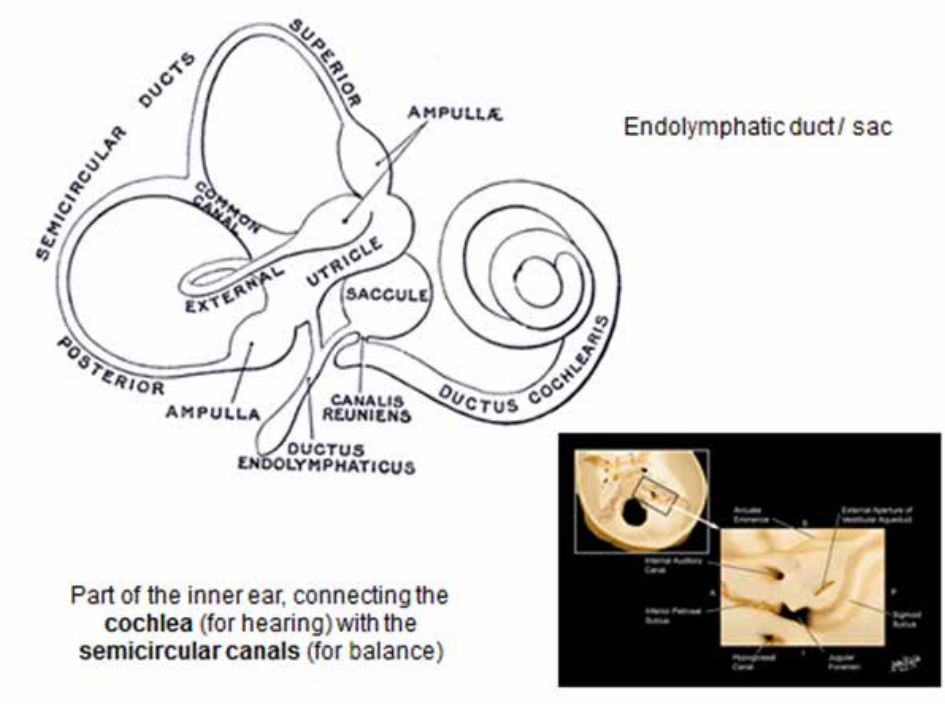
Are there any drug treatments? Anti-VEGF can decrease tumor leakage, but does not change tumor size, so it is an inadequate treatment on its own. Eylea (aflibercept) is an anti-VEGF agent that can be used if everything else has been tried, but it is not expected to be a long-term treatment. Sequential, low-intensity laser may be an option.

Dr. Johnson thinks that lesions in older patients may have less potential for growth, but there is no definitive data. There is no modification of the screening regimen during puberty.

Endolymphatic Sac Tumors and VHL

Ian E. McCutcheon, MD, ***Professor of Neurosurgery***
University of Texas
MD Anderson Cancer Center, Houston

These tumors are still relatively unknown even to neurosurgery residents. The endolymphatic sac (ELS) connects the cochlea (hearing) with the semicircular canals (balance). ELS function may involve pressure equalization. This means that ELS tumors (ELSTs) can cause both hearing and balance problems.

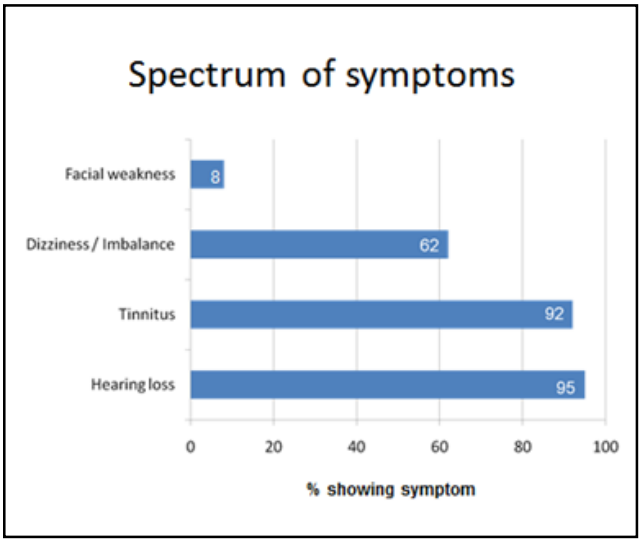


ELSTs are rare in the general population: 2/3 are not associated with VHL. 11-16% of VHL patients have ELSTs: 30% are bilateral, and they generally occur at a younger age than in the general population. Unlike ELSTs, papillary cystadenomas have lots of blood vessels. ELSTs can invade both bone and dura and other tumors are possible in the area. A MRI is good for showing the tumor; a CT scan will show bone loss.

The mean age of onset is 22 years old and is the tumor is usually unilateral. The duration of hearing loss (for 95% of patients) at diagnosis is 3–6 months. Also, 92% of patients with ELSTs have tinnitus. If both VHL and tinnitus occur, the doctor should suspect ELST; bleeding can indicate a tumor (12% of ELSTs are found this way). A regular brain scan of VHL patients with hearing loss will show no ELSTs in 60% of cases; thin sections through the inner ear and petrous bone are required to see the ELST.

Once lost, hearing usually does not return due to cochlear disruption or 8th nerve damage. Menières Disease is similar, but is due to excess endolymphatic fluid, making the treatment is very different. Patient histories indicate that 43% of ELSTs have sudden hearing loss; others lose hearing in gradual stuttering steps over a year or more.

Surgery is the best option. Radiosurgery should be saved for a tumor that cannot be accessed. Different approaches are taken depending upon whether hearing is present or not. Bone will be missing following surgery (this space can be filled with fat from another part of the body). The ELST tumor rarely recurs (unless part of the tumor is left behind).



Treatment

- First-line treatment: **SURGERY**
- Radiosurgery can be considered but experience is almost non-existent
  - reported in several cases of recurrence, but follow-up inadequate
- Must remove dura, endolymphatic sac, and involved portion of endolymphatic duct
- Visible tumor with intact hearing: operate to preserve hearing
- Visible tumor and pt deaf: operate to help other symptoms *or* to protect brainstem

Evaluation and Treatment of Kidney Tumors

Moderator: J. Stuart Wolf, Jr., MD, FACS
University of Michigan, Ann Arbor

Elaine M. Caoili, MD
Professor of Radiology: Abdominal Imaging
University of Michigan Health System, Ann Arbor

Khaled S. Hafez, MD
Professor of Urology
University of Michigan Urology Center, Ann Arbor

W. Marston Linehan, MD
Chief of Urologic Surgery and the Urologic Oncology Branch
Center for Cancer Research at the National Cancer Institute
National Institutes of Health, Bethesda

There are pros and cons to each type of imaging: ultrasound, MRI, and CT; the panel prefers MRI or CT scans for renal tumors. A balance is needed between sparing the kidneys and avoiding metastasis with the goal to preserve the kidneys for the patient's entire life.

The largest tumors generally spared are less than 3 cm, but there are exceptions. Dr. Linehan's group also looks at location and growth rate. NIH has not lost a single patient to metastatic kidney cancer to date when this approach is followed. The location of tumors is also an important factor as is solid vs. non-solid.

Robotic surgery has a number of benefits for patients, however, open surgery is still recommended for for centrally located lesions, for very large tumors or when there are a large number of tumors to remove. Dr. Linehan's group has removed over 70 tumors from a single kidney. VHL shows 3 types of tumors: solid, cysts, and "mixed." The 3 cm refers to solid tumors. Ultrasound is sometimes used to determine how "solid" a tumor is. The physician must also check VHL patients for CNS and pancreatic lesions and pheochromocytomas prior to surgery.

Ablation vs. surgery

Percutaneous radiofrequency (heat) and cryoablation options use a needle through the skin, and are, therefore, minimally invasive. Open surgery, including laparoscopic and robotic, allows removal of adjacent tissue and multiple tumor removal. Ablation can cause scarring and can make it more difficult to go back in for additional surgeries. The ablative therapies can potentially also destroys nephrons, so care must be taken when this approach is undertaken in a patient who is at risk for multiple recurrent renal tumors.

In most cases, in patients at risk for multifocal tumors, ablative therapy is recommended for patients who are not suitable candidates for surgery. Therefore, for younger patients in otherwise good health, the recommendation is to use only open, laparoscopic, or robotic surgery.

Update on VHL Research and Clinical Trials

W. Marston Linehan, MD
Chief of Urologic Surgery and the Urologic Oncology Branch
Center for Cancer Research at the National Cancer Institute
National Institutes of Health, Bethesda

Kidney cancer (clear cell) affects over 200,000 worldwide annually and 100,000 will die of this disease. Historically, 81% with advanced kidney cancer die within 2 years. This is one of the few cancers where the incidence within the US population is growing.

Kidney cancer is not a single disease, it is made up of a number of different types of cancer, each with a different histology, a different clinical course, responding differently to therapy and caused by different genes. Researchers started by looking at sporadic kidney cancer and found that part of chromosome 3 was lost. Although the 3p loss region in clear cell carcinoma was mapped, given the scientific tools available at the time, it was not possible to find the clear cell kidney cancer gene by studying sporadic (non-familial) kidney cancer. Investigators turned to the work of Dr. Alfred Knudson, whose work provide the foundation for their studies which led to the identification of the VHL gene. VHL turned out to be the classic example Knudson model. Dr. Linehan and his colleagues' goal was to bring families in and see who was affected and who was not. They then performed linkage analysis and physical mapping and identified the VHL gene on chromosome 3. They also found that VHL patients can develop up to 600 clear cell tumors per kidney and that on average, it can take about 25 years for a kidney tumor to grow to 2 cm. While many of the tumors less than 3 cm are cancers, Dr. Linehan has seen metastatic tumors from VHL kidney tumors larger than 4 cm.

Dr. Linehan and his colleagues have been doing nephron-sparing enucleation kidney surgery since the mid-80s. Dr. Linehan's group generally follows the criteria of 3 cm size, and considers both growth rate and location.

Using this method of tumor evaluation, this group has detected no metastatic cancer from kidney tumors smaller than 3 cm. Dr. Linehan's group often uses robotic surgery to remove VHL-associated kidney tumors.

The VHL gene is on the short arm of chromosome 3. For patients with VHL, 2/3 have an intragenic change and 1/3 have complete or partial deletion or a splicing defect. VHL is a 2-hit gene, meaning that you need only one unaltered copy of the VHL gene per cell. Scientists studying clear cell kidney cancer have found that there is significant genomic heterogeneity in large kidney tumors, and scientists are working to understand how these findings can help us understand the mechanism behind tumor initiation, growth and metastasis... http://www.nejm.org/doi/full/10.1056/NEJMoa1113205#t=articleDiscussion).

There is intense interest in expanding our knowledge of the genetic basis of kidney cancer. The Cancer Genome Atlas is a federally funded project in which a large number of tumors, including clear cell, chromophobe and papillary kidney cancers, are undergoing intense study to identify the genetic basis of this disease. It is hoped that this will provide the foundation for the development of effective forms of therapy for all patients with this disease.

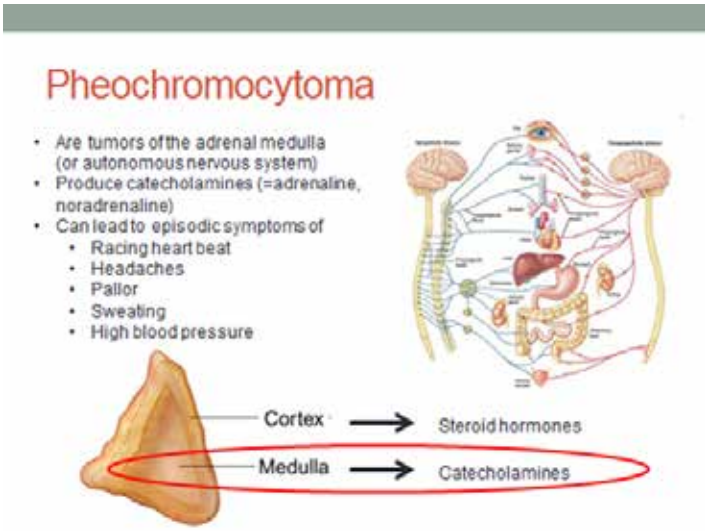
VHL and the Adrenals and Pancreas

Tobias Else, MD
Clinical Lecturer, Endocrinology & Diabetes
Department of Internal Medicine
University of Michigan Health System, Ann Arbor

Organ functions:

The adrenal glands regulate blood pressure, salt balance, and stress response. An insufficiency results in Addison's disease and the patient requires hormone replacement therapy. The pancreas regulates blood glucose levels and provides enzymes for digestion. Diabetes is the primary disease resulting from disruption of pancreatic function.

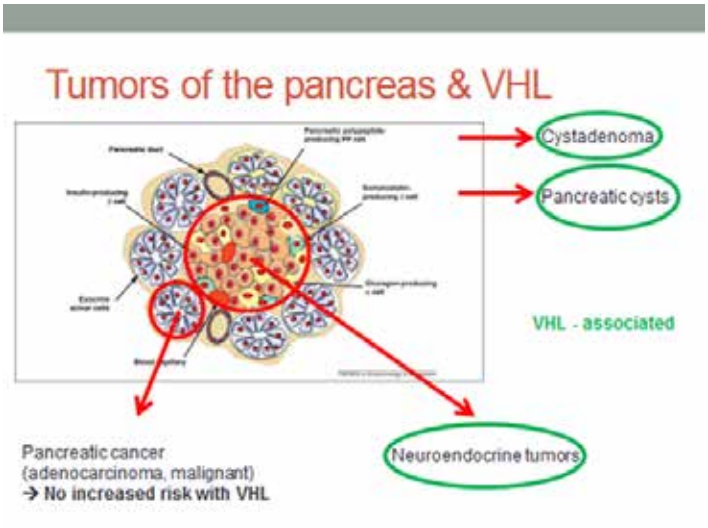
Pheochromocytomas are only in the adrenal medulla.



Pheos may be more likely to occur in some VHL families, but all VHL patients should be checked as about 20% might develop one. Tumors can be bilateral, occur at any age, and can be the only manifestation of VHL. There are usually no symptoms until the tumor reaches about 2 cm.

It is very important to screen for pheos before any type of surgery. Patients with pheos require use of Alpha and possibly Beta blockers prior to surgery; touching the tumor during surgery can lead to release of norepinephrine, dangerously raising blood pressure.

In the pancreas, neuroendocrine tumors (NETs) are "silent" (non-hormone producing) in VHL. NETs (islet cell tumors are NETs) occur in 10-20% of VHL patients, but up to 10% are malignant. NETs are rarely symptomatic. Diagnosis most often occurs between ages 30 and 50 years. Cysts and cystadenomas are commonly found in VHL. These tumors do not develop into cancer. There is no increase in the risk of adenocarcinomas of the pancreas with VHL. This is the malignant pancreatic cancer.



The extent of surgery for NETs depends upon location and size (>3cm). Surgeons are careful with 2-3cm tumors and must individualize therapy to preserve pancreatic function while treating any symptoms. Medications can be used for metastatic disease (octreotide, sunitinib), but larger studies including VHL patients need to evaluate the overall effectiveness. It is important to remember that both NETs and pheos start as "benign" lesions, only becoming metastatic as they grow.

Genetics and Childhood Issues

Moderators: Victoria Raymond, MS, CGC
Instructor, Department of Internal Medicine and Lead Genetic Counselor, Cancer Genetics
University of Michigan, Ann Arbor

Jessica Everett, MS, CGC
Genetic Counselor/Clinic Coordinator, Cancer Genetics
University of Michigan, Ann Arbor

Gayun Chan-Smutko, MS, CGC
Senior Genetic Counselor, Center for Cancer Risk Assessment
Massachusetts General Hospital, Boston

Panelists: Danielle K., Jeff Y, Andrea B.

"Genetics and Childhood Issues" was led by three genetic counselors: Victoria Raymond, Jessica Everett, and Gayun Chan-Smutko. The panelists were Danielle K., her brother, Jeff Y., and Andrea B. All three panelists were not diagnosed until they were adults. Danielle and Jeff grew up seeing their mother experience VHL brain and spine tumors. Andrea was the first person in her family diagnosed with VHL. The panelists discussed how to inform children (their own or younger siblings) about VHL. Children can have a range of reactions from anger at the parent who passed along VHL to anxiety about the uncertainty of symptoms associated with VHL. The moderators recommended using the VHL *Handbook Kid's Edition* to help children develop a vocabulary about VHL. It is also important to recognize that each child may want to receive information in a different way, but the kid's handbook is a good tool as the parent can read and discuss with the child or let the child read alone and then come to you with questions.

There was also a discussion of when parents should talk to their children with VHL about the child's plans to have a family: the panelists thought that early teens would be appropriate. A genetic counselor can be helpful in explaining options to teens and young adults. Jeff, for example, was not upset when he learned that he had VHL at age 10. However, he wanted his own children to be genetically tested as early as possible. Danielle's son was angry upon learning his VHL diagnosis (also at age 10) and did not understand the long-term course of VHL. He wants to have his own family and is optimistic about a cure being available when that time comes. Andrea also wants a family and is confident about future treatments.

Finally, the panelists spoke about how they decided with whom and when to share their VHL diagnosis. It was generally agreed to share only with whom you are close and when the time feels right. Most were concerned about making friends feel bad if they revealed VHL. All agreed, however, that it would be important for someone with whom they are in a serious relationship to know.

The moderators concluded with the family planning choices they present as genetic counselors.: (1) have a child and then test for VHL; (2) conduct pre-natal testing (amniocentesis or a new non-invasive test coming soon); (3) pre-implantation genetic diagnosis, then only implant non-affected embryos; (4) donor gametes (eggs or sperm); and (5) adoption.

The Emotional Roller Coaster

Moderator: Wendy Uhlmann, MS, CGC
Clinical Associate Professor
Department of Human Genetics and Department of Internal Medicine
University of Michigan, Ann Arbor

Panelists: Amber M., Shawn M., and Molly O.

"The Emotional Roller Coaster," was moderated by Wendy Uhlmann and the panelists were Amber M., Shawn M., and Molly O. Amber is the first person in her family diagnosed with VHL; she was found to have VHL after symptoms of severe back pain. Molly learned that she had VHL at age 10 through genetic testing which was per-formed shortly after her mother learned that her own VHL was not just an eye disease. Shawn's father had died from VHL when Shawn was 10. When he learned that he also had VHL following a MRI to diagnose neck pain; he first felt that VHL was like a death sentence.

All three panelists have yearly scans as recommended. Annual screening causes stress, but all agreed that it is necessary. The annual trip for scans and tests can be made into a "fun" day by including a special meal or shopping in the city where the medical center is located.

Each feels that it is important to go to the specialists that they feel are the best for management and treatment of VHL, even if this means a long drive. All agree that a positive relationship between the doctor and patient is key to monitoring this disease. That being said, there are times when a doctor may leave a given institution or retire. Needing to develop a relationship with a new doctor can also be stressful.

The panelists, as adults in their childbearing years, were asked about the decision to have children. Amber had her daughter following her diagnosis with VHL. Her daughter tested negative, but Amber felt she "did not want to push her luck," and adopted her son. Molly and her husband were not interested in having children, so VHL was not a factor. Shawn felt that he has been fortunate with the course to his VHL disease, but did not know if his children would be so lucky. He also did not want his children to grow up with an absent father due to hospitalizations. Therefore, he decided not to have any children, biological or adopted.

The panelists all agreed that VHL follows an up and down course. Shawn's brother just passed away from VHL this year, but Shawn feels that his brother was a pioneer in the treatments that benefit other with VHL today. A friend even pointed out that VHL allowed Shawn to say "goodbye" to both his father and brother -something that not everyone has an opportunity to do.

In the cases where scans or testing reveal the need for surgery, the panelists again had to face the emotional rollercoaster. Shawn feels that the first consideration is whether or not to have the recommended surgery. He stated that he acts as his own advocate and views himself as the client seeking out the best doctors. For example, when his local doctor recommended surgery, he sought out the best doctors although they were a 6 hour drive away and also got a 3rd opinion from NIH. Only then, did he feel comfortable having the surgery. His rec-ommendation is not to wait for symptoms which may necessitate emergency surgery. Shawn views VHL as a similar type of challenge to the marathons he runs as a "VHL Warrior."

Molly has the mindset that there will be no changes in her VHL lesions after a few good years. Changes are always difficult to deal with whether in herself or her mother. She always hopes to avoid another surgery. She has found that researching her disease and getting multiple opinions when she "hears something scary or that doesn't sound right" helps her to feel better about the decisions she makes in her own care. Another concern is that her kidneys will last long enough to avoid being on dialysis.

Amber has learned not to associate every physical symptom with VHL. She has gotten to know her body and can differentiate between "normal headaches" and "VHL headaches." Amber always tries to enjoy the present and lives year-to-year. Involvement with the VHL Alliance, including attendance at the annual meeting, allows her to ask questions and meet others with VHL.

Shawn concluded the discussion by stating that he used to hide his VHL "difference," but has now "come out" with his running and website. The small rural community he lives in has rallied behind him. Shawn again emphasized that you need to be your own advocate because you and your family deserve the best. Make the change in your mental view of VHL and get in the best physical shape to combat VHL. This way, you are not letting VHL control your life. Molly added that it is good to post positive messages on VHL social media sites, and Amber said the social media sites show that you are not alone and to allow others to help you.