The 2015 VHL Alliance Annual Conference was held in Rolling Hills, Illinois on Saturday, October 17, 2015. The agenda included eight scientific presentations and a talk on how to speak with children about genetic disorders. In addition, the meeting included an update from the VHLA Board Chair on the State of the VHLA, and two facilitated break-out sessions: one for VHL patients and one for family members and caregivers.

**Summaries of presentations are below.** Audiotapes and slides from most presentations may be viewed on the VHLA website vhl.org/about/resources/annual-meeting-presentations/.

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**Retinal Angiomas: Different Techniques for Treatment**

Michael P. Blair, MD, from the University of Chicago discussed retinal angiomas. VHL in the eyes is usually limited to two structures: the retina, and the optic nerve. The retina is a neural layer of tissue inside the back of the eye that senses light – similar to photographic film in a pre-digital camera. The optic nerve joins the retina near the center, and transmits images from the retina to the part of the brain that translates these signals into vision. A study at NIH found that 37% of people with VHL had hemangioblastomas in their eyes, but not all of these caused vision problems. VHL lesions located at the periphery of the retina need to be treated. Although they do not usually reduce vision at an early stage, as they grow they can leak fluid that can cause retinal detachment andblindness. A new “wide field” Fluorescein Angiography test allows the ophthalmologist to see the entire retina, instead of just the central section. With this improvement, fluorescein angiography becomes the first choice for locating even the smallest VHL lesion.

Small lesions are treated using a thermal laser. This treatment is non-invasive, but leaves a tiny scar on the retina where each lesion was ablated. Each scar causes a small blind spot, but these are not noticeable in the periphery. However, if the laser is used near the optic nerve or the macula (the center of the retina for sharp vision), there will be a noticeable loss of vision. Larger lesions require cryotherapy, a tissue freezing treatment. Anti-VEGF medications and radiation can also be used to treat some lesions as well.

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**Exocrine Pancreatic Insufficiency**

Christopher G. Chapman, MD, from the University of Chicago discussed pancreatic insufficiency. The operating pancreas has two functions: endocrine (e.g. secretion of insulin) and exocrine (e.g. secretion of lipase, protease, and amylase). In VHL, patients may develop exocrine pancreatic insufficiency (EPI) which reduces the ability to digest and absorb fats, starch and protein. VHL associated pancreatic lesions are primarily cysts, not tumors, but as they grow in number, they may block the delivery of the digestive enzymes to the intestine or replace normal, functioning pancreatic cells. Although symptoms of EPI do not occur until only about 10% of the exocrine function remains, patients may start to develop asymptomatic nutritional deficiencies...
even earlier. Symptoms to be aware of include cramping (bloating after meals), large amounts of gas, foul-smelling, floating, oily stools, incontinence, unexplained weight loss or bowel movements at night.

Michael B. Gluth, MD, from the University of Chicago gave an overview of ELSTs. Endolymphatic sac tumors (ELSTs) are benign, extremely rare tumors derived from the inner ear. Although they are benign and progress slowly, ELSTs destroy the bone surrounding inner ear and can grow into important structures such as the inner ear, facial nerve, and even into the brain compartment. There may be no symptoms until the inner ear is partly invaded and there is hearing loss. Sometimes this condition can be confused with another inner ear disease called Meniere’s disease due to similar symptoms of hearing loss, vertigo, and ringing in the ear.

In VHL, 10-15% of patients will have an ELST; 80% of these only affect one ear. These tumors are usually diagnosed between ages 20–40 and if all screening tests are normal up to age 45, an ELST is unlikely to develop. These tumors can be seen on a contrasted MRI. Current screening recommendations are to undergo a hearing evaluation every 2-3 years.

Surgery is the best treatment in most cases. Early surgery is best for several reasons: to possibly prevent hearing loss, to prevent facial nerve involvement, and to provide simpler surgery that may be done as an outpatient. The primary reason that surgery “fails” and there is a recurrence of the ELST is that dura adjacent to the ELST is not removed. ELST surgery for more extensive tumors requires a neurotologist (ear surgeon) and a neurosurgeon. Chemo and radiation therapy have not been studied in ELSTs. Following ELST surgery, it may be possible now or in the future to have a cochlear implant placed to restore hearing since the newer cochlear implants are much better suited for MRI. Newer cochlear implants are compatible with MRI tests with more limited distortion and will not majorly interfere with VHL screening.

Raymon Grogan, MS, FACS, and Colleen Majewski, MD, from the University of Chicago spoke about VHL-related adrenal tumors VHL tumors in the adrenal glands form in the medulla, the middle part of the gland and can produce adrenaline at random times. Pheochromocytomas (pheos) in VHL are rarely malignant (3%). Similar tumors called paragangliomas (paras) can also form outside of the adrenal glands, along the parasympathetic nerves in the head and neck or along the sympathetic nerves in the chest, abdomen, and pelvis. Paragangliomas in the chest, abdomen, and pelvis are more likely to produce excess adrenaline. VHL-related adrenal tumors are most commonly first diagnosed between ages 12–25 and approximately 10-20% of VHL patients will develop a pheo or para, with pheos being 80% of VHL cases.

Diagnosis of a pheo or para can be challenging as not all produce symptoms and many medications can interfere with testing. Ideally, testing should be done in an outpatient clinic as many patients find hospitals stressful. CT and MRI can be used to locate and confirm pheos and paras. Surgery is the best treatment, but if surgery is not possible, high adrenaline levels must be treated with medications. Radiosurgery is used in a few patients. Life-long follow-up is needed, even if both adrenal glands are removed, to detect recurrent or metastatic disease.
Gopal N. Gupta, MD, from Loyola University in Chicago from NIH presented information about VHL and the kidneys. Management of tumors in the kidneys and adrenal glands in VHL is very different from management of the same tumors in patients without VHL. In the kidneys, the goal is to maintain kidney function while avoiding metastatic disease. In the adrenals, removal of pheochromocytomas (pheos) takes precedence over maintenance of adrenal function as a long-term effect of pheos is damage to the heart. Regular screening and monitoring of any lesions is key to successful management in both organs. MRI has the highest quality images, followed by CT, and finally by ultrasound.

Tumors are often referred to by their cancer stage. VHL tumors should remain at Stage 1 prior to removal. Stage 1 is defined as less than or equal to 7cm diameter that has not spread to other organs. A stage 1 tumor in the kidney has a 5-year survival rate of 96%. With VHL tumors, we are even more careful, removing them once they reach 3cm. Pheos should be removed as soon as possible.

Tumors in the kidney are encased in a thin rim of fibrous tissue called a “pseudo capsule”. The pseudo capsule allows minimally invasive removal of the kidney tumor using robotic surgery. Standard, open surgery is still preferred if there are a number of tumors and cysts in order to minimize the number of separate surgeries required. An experienced surgeon is needed because partial nephrectomies are more complicated than removing the entire kidney. In the adrenal glands, partial adrenalectomies should also be used whenever possible.

Dr. Eric Jonasch from MD Anderson Cancer Center spoke the latest in VHL research. The goal of the VHL Alliance funded research is to be talking about effective treatments beyond surgery in 10–15 years. In order to find a cure, many layers of research are required. The process is like peeling an onion: the knowledge gained in one project suggests new projects that were not even thought of previously. The VHL gene was identified in 1993; now we are looking at how specific VHL mutations affect cellular function. We are learning that VHL is not just about HIF (Hypoxia Inducible Factor), but also about how a cell sees its neighbors and how it interacts with tumor cells, blood vessels, and connective tissue. Questions that need to be answered include: Can the VHL protein be fixed? Can we directly kill the VHL mutated tumor cells?; Can the immune system be used to stop tumor growth?

Research funded in fiscal year 2015 included two exciting projects. The first, A novel chemical chaperone for treating the VHL cancer syndrome, looked at the possibility of repairing the full-sized VHL proteins that occur in VHL missense mutations (over 1/3 of VHL mutations). An amino acid, Arginine, is showing positive results in cell lines. The second project, Zebrafish Based Discovery of VHL Disease Targeting Drugs, was funded for two years and is testing 25,000 chemical compounds that have “drug-like” properties in zebrafish with VHL.

Two new research projects are being funded in fiscal year 2016. The first is Dr. van der Horst-Schrivers’ new process for testing for pheochromocytomas (pheos) using a saliva sample. This will be an exciting advance in both ease and accuracy over the current blood and urine tests. The second is Dr. Frew’s mouse model of renal cell carcinoma to test a recently developed, promising treatment. The information as well as the new mouse model are important steps in our quest for discovering an approvable therapy.

Finally, the VHL Alliance is continuing the Cancer in our Genes International Patient Databank. This VHL patient registry resulted from the 2012 VHL International Medical Symposium in response to the top unmet research needs for VHL: detailed natural history of the disease, genotype/phenotype.
correlations, impact of lifestyle, and impact of geographical location. This registry is unique and does not duplicate the information for any registry you may already be enrolled in. Data security has been approved by an Institutional Review Board and your information is kept confidential. Your participation in the Databank is a critical part of finding and measuring the success of VHL treatments.

Rimas V. Lukas, MD, from the University of Chicago spoke about the central nervous system. VHL can result in progressive central nervous system (CNS) hemangioblastomas which although benign, may cause significant symptoms. The median age at which CNS hemangioblastomas are first diagnosed is 20–30 years. Most tumors do not cause symptoms prior to diagnosis. Usually the tumors may grow in a stepwise pattern. Tumors may also develop cysts which occupy space and can compress adjacent tissue. CNS hemangioblastomas occur in 60–90% of VHL patients and approximately half of these patients have lesions in 2 or more regions. The location of current lesions does not predict that there will be more lesions in the same region. Less than 1% of VHL lesions are located in the cerebral cortex; most are in the cerebellum, brain stem, spinal cord, or spinal nerve roots.

Surgery is often a mainstay of treatment of CNS hemangioblastoma. Surgery can often completely remove the tumor. Treatment decisions are often made on an individualized basis and take into account the size of the tumor, the size of the associated cyst, the rate of growth, the tumor's location, the prior treatments administered, and a patient's other medical conditions. Another focal therapy which can be utilized for treating CNS hemangioblastomas is stereotactic radiosurgery (SRS). This is often employed when surgery is not the ideal option. SRS provides good short-term control. However, at 15 years about half of patients with CNS hemangioblastomas treated with SRS will have local growth of tumor. There is not yet a systemic therapy (an oral or IV medication) that has proven successful for treating VHL hemangioblastomas.

Sarah Nielsen, MS, CGC, Genetic Counselor from the University of Chicago, discussed the basics of VHL. VHL disease was first recognized in the retina of the eye by Dr. Eugene von Hippel, a German ophthalmologist, in 1904. Then, in 1927, a Swedish pathologist, Dr. Arvid Lindau, found hemangioblastomas in the brain and spinal cord and realized that they were linked to the retinal lesions discovered by Dr. von Hippel. However, the disease was not called VHL until 1964.

VHL has been in the news since an Associated Press story came out in 2007 about the possible role of the McCoy family's pheos (due to VHL) in the multi-generation Hatfield and McCoy feud. A character with VHL has also appeared in the TV series “Grey's Anatomy.”

VHL is usually first diagnosed at around age 25, and there are about 125 new cases per year in the US. Initial symptoms that may lead to diagnosis include headaches, problems with balance and walking, dizziness, weakness of the arms or legs, vision problems, or high blood pressure. VHL can affect different organs, even within the same family. VHL can cause tumors (both benign and malignant), hemangioblastomas, and cysts in up to 10 different areas of the body. Hemangioblastomas are the most common VHL lesion and occur in 60–80% of patients. The most common tumor that can become malignant in VHL is renal cell carcinoma, which occurs in 25–45% of people with VHL.

The genetic cause of VHL was discovered in 1993 and research has since found over 500 different VHL mutations. 80% of people with VHL have an inherited mutation from one of their parents and every blood relative with VHL will have the same mutation. Once a person has been identified with a VHL mutation, or has clinical signs of VHL, it is important to follow the recommended screening guidelines to manage any VHL lesions at an early stage. Your VHL Clinical Care Center can make it easier to maintain a regular screening schedule.
Talking to Children about Genetic Disorders

Ken Onel, MD, of the University of Chicago, and Lindsay Rhodes, MS, CGC, of Genedx, Gaithersburg, MD, spoke about communicating with children about VHL. VHL is one of the inherited diseases for which it is appropriate to perform genetic testing in children: the results will guide the child's health management. Genetic testing may be “diagnostic” to find the cause of specific clinical findings, or “pre-symptomatic” to test a healthy child for the presence of an already known familial mutation. Special considerations apply when testing minor children and there is no single approach for every family. The child may not be part of the initial discussion if too young, or if the family wants to prolong childhood and protect the child from knowledge of the disease. Family experience with VHL will also be a factor. However, it is important never to assume that just because a child has family members with VHL, that child knows about VHL. Frequently, what a child imagines is far worse than reality, and so, it is critical for family members and medical professionals to assess a child's understanding and share facts in a developmentally appropriate manner. Additionally, another possible consequence of having multiple family members with VHL is “screening fatigue,” because of the lifelong commitment to screening required of each affected individual. It is important to follow the suggested screening schedule for each family member, both to successfully manage VHL, and to instill a good example for each child to follow as an adult.

Researchers have found from studies with both parents and children, that keeping discussions of VHL informal and gradually adding to the child's knowledge of VHL over time is the most effective approach. Learning all of the details about VHL at once can be overwhelming. Gradual learning results in children who feel that they had always known about VHL. VHL becomes part of the shared family identity. Children generally want to learn about VHL between 6–10 years of age, and almost always ask questions by age 14. In cases where parents avoided discussion of VHL, children were often reluctant to ask questions as a way of protecting their parents from distressing conversations, and this could affect healthy parent-child relationships. The child's healthcare provider can facilitate parent-child communication during visits, and parents can meet privately with a genetic counselor to ask questions and practice how to communicate VHL information to their children. No parent we have worked with has regretted being open and honest with their children about VHL.