How Caregivers Cope When a Patient Does Not Comply

by Gary L. Wood, PsyD, VHL patient

The article “Who is Hiding from VHL?” in our Spring 2019 issue dealt with what does - and what does not – motivate VHL patients to take control of their health. Sometimes overlooked is the psychological effect on caregivers when a loved one will not comply with medical advice.

As a psychologist and von Hippel-Lindau patient, I strive to learn all I can about monitoring my health. I have tried to emphasize the importance of surveillance to my daughter and my young grandson who also have VHL. I particularly worry about my grandson’s future. Will he understand the need to have scans? Will he be motivated enough to stay on top of his VHL? I know I cannot control these things, only set an example and hope he will follow it.

When a loved one does not take their health seriously, the emotions can be complex. There may be sadness, resentment, worry, frustration, and anger. In my practice, I see some people who become so involved in the problems of others that they end up with their own health issues.

When you cannot change the behavior of someone you love, focus on your own wellbeing.

It can be difficult to recognize that we cannot control what another person chooses to do. Some people may attempt to cope by abusing alcohol or other substances when the emotions of caring for someone become overwhelming, says psychologist Angela M. McBride, PhD. “They may isolate themselves socially, for fear of burdening family and friends. But those are absolutely the wrong things to do. Exercise – even a short walk, yoga, or anything that gets the blood flowing – is valuable. Spending time with friends and family can help caregivers feel that they are not alone. Some people find it helpful to journal, while others may find creative activities like woodworking or painting improve their mood and enjoyment of life.”

We can learn from the story of a woman named Tracy Torma, 64, who watched with frustration as her husband Frank made unhealthy choices despite a family history of heart disease. Tracy’s experience echoes that of anyone who cares for a person who doesn’t follow health guidelines.

While not a VHL patient, Frank had a host of health issues. “Frank’s attitude was ‘what will be will be,’ and he lived his life on his own terms,” says Tracy. “He was a three-pack-a-day smoker and his favorite meal was a triple-meat cheeseburger.”

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In her early 50s, Tracy resolved to focus on her own health. As motivation, she signed up for a series of physical challenges: a 150-mile bike ride and a half Ironman event, 5k runs and sprint triathlons, completing all. “Meanwhile, Frank began experiencing major health issues, including sepsis, a broken hip, liver and heart blockages,” Tracy says. “Yet he wouldn’t change his habits, and died at age 64. It was very hard to watch, and I have to admit, I felt some resentment. I wish he had taken better care of himself. It makes me all the more determined to take better care of myself.”

“Know that it's okay to feel the way you do,” McBride assures caregivers. “It's also okay and necessary to take time to care for yourself. Caregivers tend to express guilt about doing this. I don’t see it as optional. If you don’t take care of yourself, you won’t have anything left to give.”

Join a VHL Alliance discussion group call. Visit vhl.org/support for more details

Your Input is Important to Us

VHL Clinical Care Centers (CCC) are designed to provide holistic, coordinated care for people with VHL. Your input is essential for helping them to provide quality care. We ask that you provide feedback (both positive and negative) at: vhl.org/CCCFeedback

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BOARD UPDATE

WELCOME VHLA’S NEWEST BOARD MEMBER

July 1st kicked off VHLA’s new fiscal year (FY20). We welcome Julie Woodruff as the newest member to the VHHA Board of Directors!

This year’s Executive Committee consists of: Doug Karle, Chair; Camron King, Vice Chair; Seth Horwitz, Treasurer; Jane Beasley, Secretary. Returning Board members are: Emily Billcheck, Gordon Cooke, Barbara Correll, Jennifer Galenkamp, Eric Jonasch, Stacy Lloyd, Mark Pallansch, Connie Rath, Soniya Sapre, Anna Waller, and Deanna Wickizer. For information on all board members, please visit vhl.org/about/people/board-of-directors.

Julie Woodruff was diagnosed with VHL 10 years ago. During the past twenty plus years, she has worked as a legal, regulatory, and policy professional providing guidance to government officials and policy makers in areas of appellate law, public utility regulation, and postsecondary higher education regulation. Julie has served as a board member and treasurer for the National Association of State Administrators and Supervisors of Private Schools. Prior to that, she served on the National Association of Regulatory Utility Commissioners Telecommunications Subcommittee.
When I first heard that there would be a VHL Family Education Day in New York City in April, I was intrigued, but didn’t know what to expect. After I cleared my calendar, I had to figure out how to get to Columbia University Medical Center from my home in northern Westchester, NY. Due to my VHL-related vision challenges, I no longer can drive long distances. I called the VHL Clinical Care Center at Columbia for public transportation directions, and Diana was so helpful. She also explained that the first half hour was a social meet-and-greet with refreshments, with the first presentation set for 9 am. That gave me a bit more time to get down to the conference. As is the case with so many VHLers, I have a caring husband who offered to drive me down to Columbia. I then planned to take the subway and Metro North back home later that afternoon. I like to be as independent as possible.

Once I checked into the conference, I knew I had made the right decision to attend. I immediately felt welcomed and valued. Even though I have chatted on the phone with Josh and others on the VHLA team, as well as VHL patients, I have never actually met someone else with VHL in person. For me, meeting other people with VHL was empowering and liberating. Truly, I felt that I belonged at that conference.

As we (about 50 patients and caregivers) checked in, we each received a folder with the event’s program and other useful handouts. The program included biographical sketches of the six doctors who would present. It was great to read a bit about the doctors before they gave their 20-minute presentations. Each speaker addressed a different aspect of VHL and its manifestations, using well prepared PowerPoint slides that could be viewed on two wide screens in the room.

I particularly was impressed with conference’s facilitator, Dr. Wendy Chung (CCCC sponsor), who kept the program running smoothly. I found her presentation on “Reproductive Genetics and Family Planning” fascinating. I related most to the presentation by Dr. John Chabot on pancreatic lesions, as well as the presentation by Dr. James McKiernan on kidney manifestations, since those are the VHL areas that most affect me.

It was wonderful to see how well the Columbia doctors worked together to provide their VHL patients with such quality care. (The medical center where I have been a patient has given me very good surgical care, but I am seen in isolation, not as a VHL-affected patient.) During the question-and-answer session, one woman spoke passionately about how these wonderful Columbia doctors have cared for her and her family for nearly 20 years. I myself was very moved by her gracious thanks. Other attendees asked thoughtful questions which were answered thoroughly with respect. We were all grateful that these fine doctors gave up their Saturday to provide us with such an informative conference.

During the lunch break, we all had a chance to converse with one another as we ate. Then we came together for a group discussion where we sat in a circle. We were asked to write short thoughts about VHL and/or the conference on slips of paper, which Diana collected in a basket. Each of us randomly selected a slip and read it to the group, for further discussion, before the conference concluded, and then we said our goodbyes.

As I walked to the subway, I chatted with a couple who told me about a Coffee Against Cancer event they were hosting for May VHL Awareness Month. Interestingly enough, as I stood on the subway platform waiting for the A train, another woman from the conference recognized me. We chatted all the way until her stop on 59th street. Truly, the NYC VHL Education Day on April 27th was a bonding experience!

To get involved at your Clinical Care Center or to help arrange a similar event, please contact Josh Mann at josh.mann@vhl.org.
HEMANGIOBLASTOMAS ARE DIFFERENT THAN OTHER BRAIN TUMORS

by Gautam U. Mehta, MD, House Clinic
Los Angeles, CA

Brain tumors have been in the popular news a lot lately. Several celebrities have recently been diagnosed and treated. Likewise, high-profile research programs like the Biden Cancer Initiative have started in the last decade. In VHL, a brain tumor diagnosis is very common (up to 70% of individuals). The tumors – hemangioblastomas – that occur in VHL, are unique in several ways, which we will discuss here.

About a third of all hemangioblastomas occur in patients with VHL. The location of these tumors is different from most brain tumors, which are often found near the top of the brain in the cerebral hemispheres. Hemangioblastoma are often found near the base of the brain in the cerebellum and brainstem. There are genetic differences as well. Hemangioblastomas develop because of mutations on chromosome 3, which are unique to this type of brain tumor.

Hemangioblastomas are benign tumors, which means they are not cancerous like the ones that affected Senators John McCain and Ted Kennedy. However, even though they are not malignant, they still are challenging to manage and treat. The strategies for treating hemangioblastomas are similar to those used for other benign brain tumors. Usually doctors will observe these tumors and only treat them if they start to grow or cause symptoms. In VHL, this is especially important since individuals can have multiple tumors and it is usually not feasible, or even safe, to treat every tumor. Therefore, in VHL, we usually only treat tumors when they cause symptoms (e.g. headache, weakness, numbness).

When patients do develop symptoms, the best treatment option is usually surgery. Hemangioblastomas can be very tough to remove because they can occur in critical locations such as the brainstem, which connects the brain and the spinal cord and controls basic functions like breathing and swallowing. These tumors can also bleed a lot if not removed correctly. These challenges highlight the importance of choosing an experienced surgeon.

Finally, what does the future hold for treating hemangioblastomas? Ideally, there will be effective medical therapies that will help individuals with VHL avoid surgery. It is important to note that because the gene mutation and mechanism of tumor development are unique in VHL, research for other types of brain tumors may not be relevant to hemangioblastomas. Furthermore, drugs that are effective for other brain tumors may not be effective for hemangioblastomas. Conversely, drugs that are effective for other tumors in VHL, may work for hemangioblastomas. A great example of this is the drug pazopanib, which was recently studied in VHL. This drug showed an effect in body tumors (kidney, pancreas tumors) as well as a small subset of hemangioblastomas. VHL researchers are continuing to look for a medication that could be effective against body tumors and hemangioblastomas.

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The Implications of HIF2α Inhibitors in VHL

by Alexa L. Werner, SPT, VHL Family Member & Eric Jonasch, MD, VHLA Board Member, Chair of Clinical Advisory Council and Research Council

One of the key ways that the human body reacts to low oxygen state (hypoxia) is through the production of hypoxia inducible factor or HIF. This factor has several effects including the creation of new blood vessels (angiogenesis) and the formation of new red blood cells through the increased formation of erythropoietin (EPO) in the liver and kidneys (1). There are multiple subunits of this factor including HIF1α and HIF2α.

HIF1α and HIF2α appear to have slightly different roles in adapting the body to hypoxia. For instance, HIF1α appears to be more tied to the pathways that increase the body’s ability to convert energy from its storage form into energy that can be used by the body. It also works as a tumor suppressor (2). On the other hand, HIF2α seems to play a larger role in the formation of new blood vessels (angiogenesis), which can promote tumor growth. Considering this information, the tendency may be to think that turning off HIF2α can prevent tumors from developing. The main concern with this, is that HIF2α is needed to produce EPO, see figure (1).

The VHL gene carries the code for the VHL protein (pVHL). In turn, pVHL provides the instructional information for the creation of a protein that works with other proteins to make a complex called the VCB-CUL2 complex. This complex maintains normal function of cells through selective destruction of proteins that are no longer needed or damaged. An important target of the VCB-CUL2 complex is HIF, particularly HIF2α (1, 3).

In von Hippel-Lindau disease (VHL), pVHL is not functional or is not produced. This results in the VCB-CUL2 complex being inactive leading to increased amounts of HIF in the body (2). This in turn, causes angiogenesis, which can feed cancer growth. If this process can be stopped, it may cause the cancer to either die or, at least, stop growing and spreading through the body.

Drugs, such as Pfizer’s sunitinib (Sutent) and Novartis’ pazopanib (Votrient) are designed to prevent the angiogenesis process caused by the absence of functioning pVHL. Both of these agents are FDA approved to treat metastatic renal cell carcinoma (RCC). Small clinical trials have been performed to test each in their effectiveness for limiting VHL manifestations. Sunitinib was found to have a significant response (33%) for RCC with no impact on hemangioblastomas (4). On the other, pazopanib demonstrated a 42% overall response rate (50% for kidney) with similar results in the pancreas. A small response was also seen in hemangioblastomas including retinal lesions (5).

A clinical trial is currently underway testing a new drug, PT2977 specifically targets HIF2α. While all involved sites are being followed, this Phase 2 trial is designed to test the effect of PT2977 on VHL renal tumors. It remains to be seen whether or not this drug is effective in this setting. In early phase clinical trials in patients with metastatic RCC, the drug was found to be well-tolerated and showed signs of response in metastases (6). The hope is that this drug will provide the potency and tolerability needed for patients with VHL disease.

The views expressed here are those of the author and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the U.S. Government.

References:
**THE FDA DRUG APPROVAL PROCESS FOR SERIOUS MEDICAL CONDITIONS**

*by Charles Carter, PharmD, Campbell University, Buies Creek, NC*

All new drugs must demonstrate that the benefits of using the drug outweigh the potential risks. This is commonly referred to as a favorable, or positive, benefit-risk ratio. This is the premise for the long and detailed clinical development of new drugs. Drug approval is a multi-year process, but fortunately, there are procedures that speed up the availability of drugs designed to treat serious diseases. This is particularly true when the drug is the first available treatment option or if the drug has advantages over existing treatments. The Food and Drug Administration (FDA) has four processes to making such drugs available more rapidly:

1. Fast Track Process
2. Breakthrough Therapy Designation
3. Accelerated Approval
4. Priority Review

**Fast Track Process**

The Fast Track process is designed to facilitate the drug development, accelerate the FDA review of drugs for serious conditions, and fill an unmet medical need. Determining whether a medical condition is serious is based on whether the drug impacts survival, day-to-day functioning, or the likelihood the condition will become more serious if untreated. If the drug in development is designed to treat a condition where no current therapy exists, or has significant advantages over existing therapies, the unmet medical need requirement is fulfilled.

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**RECENT DEVELOPMENTS IN VHL-RELATED RESEARCH**

*by Amit Tirosh, MD, VHL Clinical Care Center Sponsor, Sheba Medical Center*

We recently made another step towards practicing true precision medicine in VHL. Wang et al. (Frontiers in Genetics 2019) characterized telomere length, an important structure at the end of the chromosomes, in a large number of relatives with VHL, to try and understand the variable manifestations of members from the same families. The researchers reported that children had VHL-manifestations earlier in life compared to their parents, and also showed that the telomere length became shorter in subsequent generations. These fascinating findings may explain the heterogeneity we see between VHL patients. Another pivotal work, by Minervini and colleagues, studied the association between genetic alterations in the *VHL* gene, their effect(s) on the encoded protein function, and the association between these alterations and the clinical manifestations of the patients (PLoS Comput. Biol. 2019). The authors defined five groups of structural abnormalities, and were able to associate the clinical manifestations with each of the genetic subgroups. Two studies have shown the importance of identifying the genetic cause for tumors. The first shows the improved surveillance and even survival of patients with pheochromocytomas, when their genetic predisposition gene alteration was known (Buffet et al., JCEM 2019). The second study emphasized the importance of identifying carriers of *VHL* gene mutations, to improve active surveillance of renal cell carcinoma (Hong et al., Oncol Lett 2019). An exciting work by Flores et al. (JCEM 2019) has shown that genetic changes, that presumably do not change the encoded protein (“silent” mutation), can lead to major genetic alterations, and to VHL and hereditary pheochromocytoma.

Finally, a clinical study from the NIH clinical protocol for VHL surveillance, has shown a potential applicability for 68Ga-DOTATATE PET/CT in VHL surveillance. PET/CT is an imaging modality that combines anatomical imaging (CT) with functional imaging based on molecular targets. In this case, 68Ga-DOTATATE targets somatostatin receptors on the tumors cell-surfaces. Shell et al. (Eur J of Radiology 2019) reported a sensitivity and specificity of 80% and 90%, respectively, for detecting multiple types of VHL-related lesions, using this one scan. These preliminary data, comparing CT, MRI and 68Ga-DOTATATE PET/CT scans of 36 patients, suggest a potential role for this modality, using one whole-body scan in VHL. (https://www.practiceupdate.com/c/85744/48/14)
The drug developer must request the Fast Track designation. The request can be made at any time during the development process and the FDA will review and make a decision within sixty days.

**Breakthrough Therapy Designation**

The Breakthrough Therapy designation is a process designed to accelerate the development and review of drugs for a serious condition where preliminary clinical evidence indicates a substantial improvement over available therapy on a clinically significant endpoint(s). The drug’s preliminary clinical evidence should show a clear advantage over available therapies on clinically significant endpoints, such as irreversible morbidity or mortality, or on symptoms that represent serious consequences of the disease.

The drug developer requests Breakthrough Therapy designation but the FDA may suggest submitting a request after reviewing preliminary clinical evidence. Ideally, a designation request should be requested prior to the end-of-Phase-2 meetings.

A drug that receives Breakthrough Therapy designation receives all the Fast Track designation benefits and intensive guidance on an efficient drug development program.

**Accelerated Approval**

In 1992, the FDA instituted the Accelerated Approval regulations. In 2012, Congress passed the Food and Drug Administration Safety Innovations Act (FDASIA), which allowed the FDA to base Accelerated Approval for drugs for serious conditions that fill an unmet medical need on available therapies on clinically significant endpoints, such as irreversible morbidity or mortality, or on symptoms that represent serious consequences of the disease.

The drug developer requests Breakthrough Therapy designation but the FDA may suggest submitting a request after reviewing preliminary clinical evidence. Ideally, a designation request should be requested prior to the end-of-Phase-2 meetings.

A drug that receives Breakthrough Therapy designation receives all the Fast Track designation benefits and intensive guidance on an efficient drug development program.

**Priority Review**

In 1992, under the Prescription Drug User Fee Act (PDUFA), the FDA agreed to goals for improving the drug review time and created a two-tiered system of review times – Standard Review and Priority Review. A Priority Review designation means the FDA will take action on an application within 6 months as compared to 10 months under Standard Review.

The Priority Review designation directs FDA attention and resources to the evaluation of drugs that would be significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions when compared to standard applications.

The drug developer may expressly request Priority Review. If granted Priority Review status, there is no impact on the clinical development requirements nor the scientific/medical standard for approval or the quality of evidence necessary.

**Summary**

Drug effectiveness is based on predefined output measures. Several processes are currently in place to ensure new drugs get to patients as soon as possible. Several of the processes to speed development and accelerate the review processes are relatively new, within the last 10 years. This is particularly important for emerging products designed to treat serious medical conditions.

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