Von Hippel-Lindau Syndrome: Implications for Nursing Care

Suzanne M. Mahon, RN, DNSc, AOCN®, APNG, and Laura Waldman, MS, CGC

Von Hippel-Lindau syndrome (VHL) is an autosomal dominant inherited disorder characterized by the formation of both benign and malignant tumors and cysts in various parts of the body. Identification of individuals and families affected with this disorder is imperative to implement appropriate screening measures so as to detect complications early and to reduce the morbidity and mortality associated with the diagnosis.

Case Study 1

A 39-year-old man named S.E. had complete resection of two hemangioblastomas. The patient had other comorbidities including diabetes, obesity, and recurrent gastric ulcers. Subsequent testing demonstrated a 5 cm renal mass on the left kidney. S.E. underwent a left partial nephrectomy, which demonstrated clear cell renal cancer. After his surgery, S.E. was referred for genetic counseling and consideration of genetic testing.

The genetics professional constructed a pedigree for the patient. S.E.’s father had died at age 59 from high blood pressure and a stroke, and a fraternal twin brother had been successfully treated for a cerebellar hemangioblastoma two years prior. S.E. also had two younger sisters and three children, all of whom were in good health. S.E.’s mother died at age 59 from high blood pressure and recurrent gastric ulcer. S.E. was offered and S.E. tested positive for a deleterious VHL mutation. Subsequently, P.L.’s mother was 62 years old, had diabetes, and was obese. She was adopted at birth and had no information about her biologic family. P.L.’s father was 63 years old with no major health problems and no family history of malignancy. P.L. had two healthy siblings and no offspring. During his visit with the genetics professional, P.L. was questioned about any personal or family history of vision problems. He stated that he had been experiencing some blurry vision in his right eye. He was then referred to an ophthalmologist and was found to have a unilateral retinal angioma. Genetic testing of the VHL gene was performed and a deleterious mutation was detected, confirming the clinical diagnosis of VHL. Imaging was negative for renal cell carcinoma or additional hemangioblastomas. P.L.’s mother and father underwent genetic testing for the same mutation and both were found to be negative, as were his two siblings.

Pathophysiology

VHL is an inherited disorder characterized by the formation of both benign and malignant tumors and cysts in various parts of the body. Tumors may occur during young adulthood; however, the signs and symptoms of VHL can develop throughout life. VHL is an autosomal dominant hereditary cancer syndrome caused by mutations in the VHL tumor suppressor gene located on chromosome 3. VHL is estimated to occur in 1 of every 30,000–40,000 individuals (Lindor, McMaster, Lindor, & Greene, 2008).

VHL follows Knudson’s (1996) “two-hit” model for carcinogenesis. In inherited cases, the first hit is a VHL germline (inherited) mutation. The second hit is a somatic (acquired) mutation. Tumor formation requires mutations in both VHL alleles in the somatic tissue. Individuals with VHL have a predisposition for developing renal cell carcinomas, pheochromocytomas, central nervous system hemangioblastomas, retinal hemangioblastomas, endolymphatic sac tumors, and renal and pancreatic cysts (see Table 1). Genetic (DNA) testing for germline VHL mutations costs less than $1,000, often is covered by insurance, and is capable of detecting about 100% of all described VHL mutations (Frantzen, Links, & Giles, 2009; Kaelin, 2007). When the clinical diagnosis of VHL is confirmed by germline genetic testing, implementation of appropriate screening can significantly decrease a patient’s morbidity and mortality.

Table 1. Clinical Features of von Hippel-Lindau Syndrome: Occurrence and Age of Onset

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Average Age at Diagnosis (Years)</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal cell cancer (clear cell)</td>
<td>40 (16–69)</td>
<td>35–75</td>
</tr>
<tr>
<td>CNS hemangioblastomas</td>
<td>30</td>
<td>50–79</td>
</tr>
<tr>
<td>Retinal hemangioblastoma</td>
<td>21–28</td>
<td>70</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>25–34</td>
<td>3.5–17</td>
</tr>
<tr>
<td>Pancreatic islet cell carcinomas</td>
<td>24–35</td>
<td>7.5–25</td>
</tr>
<tr>
<td>Endolymphatic sac tumors</td>
<td>16–28</td>
<td>11–16</td>
</tr>
<tr>
<td>Epididymal cystadenoma</td>
<td>14–40</td>
<td>7–27</td>
</tr>
</tbody>
</table>

CNS—central nervous system

Note. Based on information from Frantzen et al., 2009; Lindor et al., 2008.
**Commentary on the Cases**

Case 1 illustrates several red flags indicative of VHL. Hemangioblastomas are highly vascular, histologically benign tumors that occur in the cerebellum (80% of cases) and the spinal cord (20% of cases) (Farrell & Plotkin, 2007). In 50%–79% of patients with VHL, hemangioblastomas are the presenting symptom with an average age of onset of 30 years (Lindor et al., 2008). The presentation of two separate hemangioblastomas even in the absence of family history meets diagnostic criteria for VHL (see Figure 1). The fact that S.E.’s brother had a cerebellar hemangioblastoma also points toward VHL. In addition, the patient’s father’s history of high blood pressure and stroke may have been from an underlying pheochromocytoma estimated to occur in 3.5%–17% of patients with VHL. A pheochromocytoma is a tumor occurring in the adrenal gland tissue that results in the release of excessive epinephrine and norepinephrine causing an increase in heart rate, metabolism, and blood pressure. These pheochromocytomas rarely undergo malignant transformation (Lindor et al., 2008).

Clear cell renal carcinoma occurs in about 35%–75% of individuals with VHL (Lindor et al., 2008; Meister, Choyke, Anderson, & Patel, 2009). The clear cell renal cancers often are multiple and bilateral and may arise within complex cysts (Reed & Parekh, 2009). The mean age at diagnosis is 40 years. Early identification of renal cancers is critical because they account for 50% of the deaths in patients with VHL (Shehata et al., 2008).

Renal cancer treatment focuses on preserving renal function and limiting intervention until solid tumors reach 3 cm in diameter on imaging studies (Lindor et al., 2008; National Comprehensive Cancer Network, 2012). Larger tumors have a higher risk of invading and metastasizing, so they usually are surgically excised with a nephron-sparing nephrectomy aiming to preserve as much renal function as possible (García-Donas, Hernando, Romero, & Jara, 2011; Nguyen, Campbell, & Novick, 2008). Renal cysts also are commonly present, but the transition from a cyst to a solid lesion is thought to be relatively rare. Debate exists as to whether carcinoma in situ arises from the walls of complex cysts (Shehata et al., 2008). For that reason, cysts require careful follow-up and surgical management may be appropriate if a noted change in additional imaging is suggestive of cancer (Morrison, Donnelly, Atkinson, & Maxwell, 2010).

Patients who have sporadic renal cell cancer (i.e., do not have an inherited VHL mutation) often have acquired VHL gene mutations, indicating that inactivation of the VHL gene plays a role in the pathogenesis of renal cell cancer. Because sunitinib often is used to treat patients with sporadic renal cell carcinoma, this agent also has been used to treat patients with VHL (Jonasch et al., 2011). In patients with VHL, a significant response to sunitinib therapy was observed in renal cell cancer, but not in hemangioblastomas (Jonasch et al., 2011).

Case 2 illustrates a scenario in which the patient initially presented without the traditional syndromic red flags for VHL. Pheochromocytoma is a tumor of the paraganglial system. About one in three patients with pheochromocytoma carry a cancer-predisposing germline mutation in one of six different genes. These gene mutations cause distinct clinical syndromes including VHL; multiple endocrine neoplasia type 2; paraganglioma syndromes type 1, type 3, and type 4; and neurofibromatosis type 1 (Erfic et al., 2009). Clinical features associated with the presence of a germline mutation include young age at diagnosis, multifocal or bilateral disease, and extra-adrenal location. When a tumor type, such as pheochromocytoma, can be attributed to a mutation in any one of several genes, assessment for specific syndromic features in the patient or their family members is essential for determining which gene to test first. In this case, eliciting the history of vision problems with subsequent confirmation of a

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**Figure 1. Indications for Referral for von Hippel-Lindau (VHL) Genetic Testing**

**Note.** Based on information from Franzzen et al., 2009; Lindor et al., 2008.

- Two or more central nervous system (CNS) or retinal hemangioblastomas. No additional family history is needed.
- A single CNS or retinal hemangioblastoma with one of the following:
  - Multiple renal, pancreatic, or hepatic cysts
  - Pheochromocytoma
  - Clear cell renal cancer
  - Endolymphatic sac tumor
  - Papillary cystadenoma of the epididymis or broad ligament
  - Neuroendocrine tumor (pancreas)
- Definite family history of a VHL tumor with one of the following in the individual:
  - CNS or retinal hemangioblastoma
  - Multiple renal, pancreatic, or hepatic cysts
  - Adrenal or extra-adrenal pheochromocytoma
  - Renal cancer prior to age 60
  - Epididymal or broad ligament cystadenoma
- A known VHL mutation in the family

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**Figure 2. Routine Evaluation of Individuals With Confirmed or Clinically Suspected von Hippel-Lindau Syndrome**

**Note.** Based on information from Franzzen et al., 2009; Lindor et al., 2008; Teplick et al., 2011.

- Annual ophthalmologic examination (start at age 5)
- Annual physical examination, including blood pressure (pheochromocytoma), and neurologic evaluation for signs of cerebellar or spinal cord lesions starting at age 5
- Imaging of the central nervous system and the spinal cord by magnetic resonance imaging (MRI) with gadolinium starting at around age 11
- Audiologic evaluation for hearing loss associated with endolymphatic sac tumors
- Annual complete blood count seeking evidence of polycythemia (caused by erythropoietin secretion from renal cysts and cerebellar hemangioblastoma)
- Annual urinalysis to check for microscopic hematuria and abnormalities
- Annual ultrasound imaging of the kidneys and pancreas, beginning no later than age 16. MRI (in children) or computed tomography (in adults) should be performed to evaluate any abnormalities detected by ultrasound.
retinal angioma served to determine the order of genetic testing. In some cases, the approach is not always as clear.

Retinal angiomas occur in about 70% of individuals with VHL. They are benign, slow-growing lesions capable, over time, of causing significant visual abnormalities (Wong & Chew, 2008). Treatment is accomplished by laser photocoagulation, cryotherapy, photodynamic therapy, radiation, or surgical excision. The efficacy and choice of treatment are influenced by location of the angioma.

Case 2 most likely represents a de novo (i.e., was not inherited from a parent) VHL gene mutation that occurred in the proband—the first person seeking genetic testing in this family—as no family members had VHL-related tumors. This was confirmed when P.L.’s parents tested negative for the VHL mutation. If neither parent has VHL, the chances of P.L.’s siblings having VHL is small but still somewhat increased because of the possibility of parental germline mosaicism. In other words, a parent can have a mixture (mosaic) of cells in which the majority of cells (blood or skin cells) have the normal VHL gene but some of the germ (sperm or egg) cells have a VHL mutation—that is why testing was offered to P.L.’s siblings. Because VHL tumors can manifest early, screening can begin as early as age 5 (Teplick, Kowalski, Biegel, & Nichols, 2011). For this reason, testing was offered to the offspring of those who tested positive so screening could be appropriately implemented.

### Nursing Considerations

Understanding the variable presentation of VHL is important when extracting family history information. Recognition of VHL in patients presenting with the constellation of benign and malignant tumors associated with VHL is imperative to ensure appropriate monitoring for associated malignancies as well as benign conditions. When VHL is suspected, the family should be referred to a genetics professional for evaluation and testing. By age 25, most affected individuals have a detectable lesion of some type (Coleman, 2008).

Nurses should pay attention to any history of particularly unusual tumors and refer for genetic counseling promptly. Both of the families in the case studies will benefit from the identification of other at-risk members as appropriate screening measures can be implemented (see Figure 3). In addition, assessing the family’s perception of the diagnosis and providing education to correct any misconceptions is important (see Figure 3). With these steps, the mortality from complications associated with VHL tumors will ultimately be reduced and quality of life for these families will improve.

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### References


Clinical Highlights: von Hippel-Lindau Syndrome

Background

Von Hippel-Lindau (VHL) syndrome is an autosomal dominant genetic disorder that oncology nurses may encounter in their practice. It occurs in an estimated 1 of every 30,000–40,000 people (Lindor, McMaster, Lindor, & Greene, 2008). The manifestations of VHL are many, including hemangio- and endolymphatic sac tumors. Because of the potential for great variability in the clinical presentation of VHL, patients may initially present with only one ostensible manifestation of the disease. Therefore, referral for genetic evaluation and testing is appropriate even for individuals with a single VHL-related tumor, regardless of family history.

Genetic Testing Considerations

Genetic testing is complicated by the fact that some VHL-associated tumors can be caused by mutations in non-VHL genes. A careful review of family and medical history is necessary to help prioritize the order of genetic testing strategy and reduce testing costs. Genetic testing must involve careful discussion of the many factors and ramifications that come into play and should be performed by a trained genetics professional (Coleman, 2008). Nurses should be familiar with VHL-associated tumors to facilitate and educate patients on the importance of genetic evaluation and testing since early detection and screening can help decrease morbidity and mortality.

Genetics

VHL disease is an autosomal dominantly inherited disorder caused by mutations in the VHL tumor suppressor gene located on chromosome 3 (Lindor et al., 2008). VHL is associated with nearly complete penetrance by age 65 (almost all individuals with a mutation in the VHL gene will have some manifestation of the disease by that time). However, for many, the manifestations will be much earlier—leading to genetic testing in children. About 80% of individuals with VHL have an affected parent, whereas about 20% of cases result from a new (de novo) mutation in the VHL gene. In de novo cases, neither parent has VHL but VHL results either from (a) a new mutation that occurred in the single egg or sperm involved in that person’s conception or (b) a new postconception mutation that occurred early in embryogenesis. Given that 20% of cases are de novo, the absence of affected parents or other family members does not exclude the possibility of VHL. All children of an affected parent (regardless of whether their VHL is inherited or de novo) have a 50% chance of inheriting the VHL gene mutation and developing the disease.

Implications for Nursing

VHL syndrome is a diagnosis that should be considered in any individual who presents with a VHL-related tumor. Once a diagnosis of VHL is made, nurses should educate affected individuals about symptoms that require prompt reporting. Symptoms of brain tumors may include headaches, difficulties with balance or ambulation, and weakness. Elevated blood pressure could be associated with a pheochromocytoma, particularly if the onset is sudden and severe. Eye tumors may present with blurred vision or other visual changes. Renal tumors may manifest as back pain or hematuria.

It also is important to assess the family’s perception of the diagnosis and provide education to correct any misconceptions. Healthcare professionals should provide education, support, and encouragement regarding the best approach to prevent or detect disease early and ultimately decrease the morbidity and mortality associated with the VHL diagnosis. The surveillance plan requires careful coordination so that patients and families are completely clear about what tests will be needed, who will order them and report the results, who will be providing follow-up care, and what symptoms should be reported promptly.

Family members may experience fear and anxiety and may be overwhelmed by the diagnosis. The current average life expectancy is estimated to be 52.5 years (Wilding et al., 2012). This life expectancy has improved since the early 2000s because of improved early diagnosis and treatment methods. However, more research on detection and management is needed, particularly in people with early identification of a mutation (García-Donas, Hernando, Romero, & Jara, 2011). Compassionate care combined with honest information understandable at age-appropriate levels is important. Children will need developmentally appropriate information that should be expanded on as they grow so that these individuals can learn to manage the diagnosis. Affected families should be managed by specialists with experience in dealing with VHL. Genetics professionals usually facilitate genetic testing and often coordinate follow-up care. They can assist parents who may experience feelings of guilt if a genetic mutation was passed to their child. Encouraging patients to verbalize feelings and concerns is important to facilitate adjustment and manage problems promptly. For those with significant psychosocial distress, a referral to a counselor may be beneficial.

References


