Hemangioblastoma diagnosis and surveillance in von Hippel–Lindau disease: a consensus statement

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OBJECTIVE  Hemangioblastomas are a frequent underlying cause of neurological morbidity and death in patients with von Hippel–Lindau disease (VHL). Although these benign tumors can cause significant neurological debility when undetected and untreated, unified evidence-based surveillance recommendations for VHL patients have not been established. To develop consensus recommendations, the VHL Alliance established an expert committee, named the International VHL Surveillance Guidelines Consortium, to define surveillance recommendations.

METHODS  The Central Nervous System (CNS) Hemangioblastoma Subcommittee of the Guidelines Consortium was formed as a multidisciplinary team of experts in the diagnosis and management of hemangioblastomas. Recommendations were formulated using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) and National Comprehensive Cancer Network Categories of Evidence and Consensus categorization after a comprehensive literature review.

RESULTS  Published studies (n = 49) that discussed age at onset, MRI frequency, natural history of VHL, and the risks and benefits of surveillance were analyzed. Based on this analysis, the authors recommend that clinical evaluation (yearly) be used as the primary screening tool for hemangioblastomas in VHL. The subcommittee suggests that screening be performed between the ages of 11 and 65 years, or with the onset of symptoms, for synchronicity with other testing regimens in VHL. The subcommittee also recommends that baseline MRI be first performed at the age of 11 years (suggested 2B, level of evidence D) or after identification of neurological symptoms or signs (if earlier) and continue every 2 years (recommended 2A, level of evidence A).

CONCLUSIONS  The CNS Hemangioblastoma Subcommittee of the International VHL Surveillance Guidelines Consortium here proposes guidelines that aim to increase the early detection of VHL-associated hemangioblastomas to reduce their morbidity and mortality.

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KEYWORDS  hemangioblastoma; magnetic resonance imaging; surveillance; von Hippel–Lindau disease; oncology

CENTRAL nervous system (CNS) hemangioblastomas are the most common tumor type in von Hippel–Lindau disease (VHL). Approximately 60%–80% of patients with VHL will harbor a CNS hemangioblastoma. Symptomatic hemangioblastomas are the initial manifestation of VHL symptoms in 40% of patients (Table 1).1–3 CNS hemangioblastomas are histologically benign; however, they can cause significant morbidity due to mass effect and are the cause of death in approximately half of patients with VHL.1–3 The presence of CNS hemangioblastomas has been found to be a greater risk factor in the overall mortality of VHL patients than the presence of renal cell carcinoma.4 A significant number of VHL patients (40%) will develop multiple CNS hemangioblastomas. Indeed, a previous investigation revealed that patients with VHL have a median of 8 CNS hemangioblastomas per patient (range 1–33 tumors per patient).1

CNS hemangioblastomas are distributed in the cerebellum (45%), brainstem (7%), spinal cord (36%), and cauda equina (11%).1,5–8 Rarer manifestations include hemangioblastomas of the supratentorial brain (1%), nerve roots (0.3%), pituitary stalk,3 optic nerve,6 and peripheral nerves11–13 (Fig. 1). Disseminated leptomeningeal hemangioblastomatosis is rarely seen.14 Patients with VHL may
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**TABLE 1. Studies reporting the incidence of CNS hemangioblastomas in VHL**

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Patients</th>
<th>% of Patients w/ VHL-Associated HBs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maddock et al., 1996</td>
<td>83</td>
<td>34.9%</td>
</tr>
<tr>
<td>Poulsen et al., 2010</td>
<td>54</td>
<td>53.7%</td>
</tr>
<tr>
<td>Kanno et al., 2013</td>
<td>294</td>
<td>68.1%</td>
</tr>
<tr>
<td>Lonser et al., 2014; Huntoon &amp; Lonser, 2014</td>
<td>250</td>
<td>75.0%</td>
</tr>
</tbody>
</table>

HB = hemangioblastoma.

**TABLE 2. Previously recommended surveillance strategies for hemangioblastoma in VHL**

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Age to Start Surveillance (yrs)</th>
<th>Neurological Exam</th>
<th>Age to Start Brain Imaging (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binderup et al., 2013</td>
<td>5</td>
<td>Every yr</td>
<td>8</td>
</tr>
<tr>
<td>VHL Alliance, 2016</td>
<td>5</td>
<td>Every yr</td>
<td>16</td>
</tr>
<tr>
<td>Rednam et al., 2017</td>
<td>5</td>
<td>Every yr</td>
<td>8</td>
</tr>
</tbody>
</table>

CNS hemangioblastomas. Neither is used to refer to clinical assessments or imaging ordered as part of the workup of new neurological or other signs or symptoms, as part of surgical planning, or as postoperative follow-up. In practice, throughout this article, the term “screening” refers to detecting new hemangioblastomas and “surveillance” for identifying any changes in the patient’s hemangioblastomas.

MRI (with and without contrast) surveillance coupled with clinical history and examination can reduce VHL-associated morbidity and mortality. Early detection of hemangioblastomas allows for longitudinal monitoring with imaging and examination findings. This can potentially reduce morbidity by balancing conservative observation with the need for resection of growing or symptomatic hemangioblastomas. To minimize the neurological impact of craniospinal hemangioblastomas in VHL, patients are counseled on early warning signs and symptoms of progressive symptom-forming hemangioblastomas. Resection at early development of symptoms and signs supports maintaining best possible function over a lifetime while minimizing or eliminating unnecessary resection. Recent studies have shown that VHL patients who have extensive surgical histories do not demonstrate an increased risk of impaired functionality and cumulative surgical morbidity, particularly with regard to cerebellar hemangioblastomas.

**Methods**

**Creation and Scope of the CNS Subcommittee of the International VHL Surveillance Guidelines Consortium**

Several surveillance guidelines have been proposed for VHL-associated CNS hemangioblastomas (Table 2). Guidelines on updated literature can improve hemangioblastoma diagnosis and optimize management of CNS hemangioblastomas in patients with VHL. The majority of surveillance guidelines for CNS hemangioblastomas in patients with VHL have been part of systemic guidelines. Historically, these were established by a panel of experts based on expert opinion and generally included one or only a handful of experts per organ system. The VHL Alliance established the International VHL Surveillance Guidelines Consortium to evaluate the existing literature regarding screening and surveillance for each organ system. The goals of this consortium would include 1) creation of a dedicated committee of multiple subject-matter experts for each organ system (with additional input from experts in radiology, pediatrics, anesthesia, and other disciplines); 2) creation of guidelines based on system-
TABLE 3. Level of evidence defined by GRADE criteria

<table>
<thead>
<tr>
<th>Code</th>
<th>Level of Evidence</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>High</td>
<td>Further research is unlikely to change our confidence in the estimate of effect</td>
</tr>
<tr>
<td>B</td>
<td>Moderate</td>
<td>Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate</td>
</tr>
<tr>
<td>C</td>
<td>Low</td>
<td>Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate</td>
</tr>
<tr>
<td>D</td>
<td>Very low</td>
<td>Any estimate of effect is very uncertain</td>
</tr>
</tbody>
</table>


atic review of the existing literature; 3) the grading of the strength of evidence underlying each recommendation; 4) generation of very specific and detailed guidelines for the specialist in each field; and 5) creation of more general guidelines for the physician tasked with managing overall surveillance for the patient. The general surveillance guidelines created by the consortium for all organ systems intended for the primary physician managing the patient with VHL can be found on the VHL Alliance website.18 The present article lists the detailed guidelines created by the CNS Subcommittee specifically for the neurological/neurosurgical community.

Systematic Review and Evaluation of the Evidence

Recommendations were developed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) guidelines as a framework.17 To formulate surveillance recommendations, specific problems were identified related to hemangioblastoma diagnosis and are reviewed herein. Specifically, the utility of various screening and surveillance modalities for detection of hemangioblastoma(s), patient age at presentation of hemangioblastoma in VHL, and testing burden were analyzed in detail. A comprehensive PubMed literature review was performed using the search terms “hemangioblastoma,” “von Hippel-Lindau,” and “VHL.” GRADE criteria were used to evaluate the level of evidence related to each problem (Table 3).17

These data were then used to develop recommendations that were reviewed by the International VHL Surveillance Guidelines Consortium. When possible, and when the evidence did not contradict it, we attempted to harmonize the testing schedules among the various organ systems to facilitate care for patients. The degree of consensus within the CNS Guidelines Subcommittee was then categorized for each recommendation (Table 4).

For ease of interpretation, recommendations were then differentiated as either “recommended” (category 1 or 2A) or “suggested” (category 2B or 3) based on the level of evidence. Final recommendations including all organ systems were then made available publicly for reference by VHL patients and providers.25

Diagnostic Considerations

Clinical Features

A large prospective natural history study demonstrated that the majority (> 90%) of hemangioblastomas found on imaging do not produce symptoms.1 However, when neurological symptoms and signs are present, they are often due to the mass effect related to hemangioblastoma and/or a peritumoral cyst or edema that is related to their anatomical location. Symptoms and signs most frequently associated with brainstem hemangioblastomas include headache (83%), singultus (67%), nausea/vomiting (50%), dysphagia (42%), cough (25%), and paresthesia (25%). Hemangioblastomas arising in the cerebellum often produce symptoms and signs, including headaches (77%), gait ataxia (57%), nausea/vomiting (19%), vertigo (18%), speech difficulties (15%), and dysmetria (11%).1 Spinal cord hemangioblastomas most often cause symptoms/signs including hypesthesia (83%), weakness (65%), gait ataxia (65%), hyperreflexia (52%), and pain (17%) (Table 5).19

Magnetic Resonance Imaging

MRI with gadolinium is the most sensitive and specific imaging modality for detecting and monitoring changes in CNS hemangioblastomas.16 Hemangioblastomas are high-ly vascular intraxial tumors that vividly and discretely enhance on T1-weighted MRI sequences. Hemangioblastomas can have several morphological patterns, including peritumoral cyst/syringomyelia with a small mural nodule, solid mass with a central intratumoral cyst, tumor with peritumoral edema, or solid tumor without a cystic component. Cystic fluid surrounding the nodule is usually hypointense on T1-weighted images and hyperintense on FLAIR or T2-weighted sequences. Similar to peritumoral cysts, hemangioblastomas often have associated peritumoral edema that is best detected as a hyperintense signal on FLAIR and/or T2-weighted sequences.20 The mural nodule is isointense on unenhanced T1-weighted images and demonstrates high signal on T2-weighted MR sequences.21 Hemangioblastomas often have associated in-
TABLE 5. Frequency of signs and symptoms of patients with hemangioblastoma who underwent resection based on location

<table>
<thead>
<tr>
<th>Location</th>
<th>Signs &amp; Symptoms*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brainstem</td>
<td>Headache (63%), singultus (67%), nausea/vomiting (50%), dysphagia (42%), cough (25%), paresthesia (25%)</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>Headaches (77%), gait ataxia (57%), nausea/vomiting (19%), vertigo (18%), speech difficulties (15%), dysmetria (11%)</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>Hypoesthesia (83%), weakness (65%), gait ataxia (65%), hyperreflexia (52%), pain (17%)</td>
</tr>
</tbody>
</table>

Data are from Lonser et al. J Neurosurg. 2014;120(5):1055–1062.1

ternal or peripheral serpentine signal voids that represent tumor-associated vessels. MRI can reliably detect small hemangioblastomas (≥ 2 mm in diameter), and usage of the Freiburg protocol can aid in detecting small nodules and distinguish these from vessels. The Freiburg protocol includes a sagittal T1-weighted contrast-enhanced cranial sequence with fat saturation and 1-mm3 isotropic voxels (4 minutes 53 seconds), followed by sagittal T1-weighted 3-mm-thick slices of the upper and lower spine (4 minutes 45 seconds each). Additionally, new protocols for VHL surveillance have allowed for a whole-body scan in 35 minutes, and contrast for the abdominal portion was sufficient to detect CNS hemangioblastomas while limiting the gadolinium dosing.

Surveillance Considerations

Imaging Over a Lifetime

CNS hemangioblastoma detection in patients with VHL was dependent on symptoms, resulting in a mean age of onset of 30 to 32 years (Table 6). Rarely, case reports and selected studies have identified patients younger than 10 years of age with VHL-associated hemangioblastomas (Table 6). In a natural history study of patients with confirmed VHL, all of whom underwent surveillance MRI, the majority developed new CNS hemangioblastomas in the 4-year study period at a mean incidence of 0.4 ± 0.4 new tumors/patient/year (median 0.3 tumors). However, after the age of 65 years, only 14% of patients with VHL will develop a new hemangioblastoma. The reduced identification of new tumor development in these older patients may be influenced by multifactorial issues (decreased surveillance imaging in this patient population, lost to follow-up, and/or death).

Frequency of Surveillance and Testing Burden

Patients with VHL routinely undergo MRI of multiple organ systems for surveillance on a scheduled basis. The rate of intercurrent CNS manifestations was 7% when MRI of the craniospinal axis was performed biennially and 3% when performed annually. However, the benefits of routine MR surveillance need to be weighed against factors including the duration of the studies, risks of sedation (in the pediatric population), nephrogenic systemic fibrosis associated with gadolinium (in renal impairment associated with one or more renal cell carcinoma and/or prior multiple nephrectomies), and gadolinium accumulation.

Specific Recommendations

1) MRI of the Entire Craniospinal Axis Should Be Performed Every 2 Years for Surveillance of Hemangioblastomas in Patients With VHL (recommended 2A, level of evidence A)

MRI of the craniospinal axis is the cornerstone of identification and surveillance of hemangioblastomas. A history and comprehensive neurological examination delineate which of the lesion(s) may be symptomatic and require intervention. In patients who have quiescent disease (stable hemangioblastomas) and are asymptomatic, we recommend that MRI of the craniospinal axis be performed every 2 years or earlier if symptoms arise. Patients with progressive hemangioblastomas or enlarging peritumoral cysts may require more frequent MRI to guide management. Development of new CNS-related signs or symptoms during the interval period should trigger MRI. Surveillance after treatment with surgery or radiosurgery of VHL-associated hemangioblastomas is dictated by clinical necessity until a return to routine surveillance paradigm is plausible.

2) MRI Prior to a Planned Pregnancy (recommended 2A, level of evidence B)

Previously, anecdotal reports, case reports, and small studies have described the effect of pregnancy on hemangioblastoma development and progression with conflicting results. One prospective study included 36 consecutive female patients with VHL, 9 (25%) of whom became pregnant over the course of the study. The authors found that pregnancy was not associated with increased hemangioblastoma or peritumoral cyst development or progression. While this is the only prospective study examining hemangioblastoma development during pregnancy, it was limited by a small sample size and a potential selection bias, as patients who became pregnant may have had milder CNS disease burden. Similar results were found in a retrospective study that included 17 female patients with VHL who had completed 30 pregnancies. The authors found that the manifestation rates in women's pregnant intervals were lower compared with their age-matched control cohort's nonpregnant intervals. This lower manifestation rate during pregnancy may also be a product of women foregoing and/or postponing routine surveillance MRI. Anecdotal case reports have described occasional dramatic increase in the cysts or edema associated with hemangioblastomas during pregnancy; however, such in-
creases are infrequent and can be difficult to interpret, as they often occur in the aftermath of missed surveillance imaging.25,36

Consistent follow-up during pregnancy may not be feasible. Consequently, we recommend that surveillance MRI with contrast be performed prior to a planned pregnancy to characterize hemangioblastoma and/or hemangioblastoma-associated cysts before conception. If a patient becomes symptomatic while pregnant, MRI of the neuroaxis can be obtained without contrast if the clinician suspects a developing hemangioblastoma and/or associated cyst.37 Furthermore, if a CNS hemangioblastoma becomes symptomatic during pregnancy, tumor resection can be performed safely with careful maternal and fetal monitoring.38

3) Clinicians Can Cease Additional Routine Asymptomatic Screening Imaging for Patients Beyond the Age of 65 Years if They Have Not Developed a Hemangioblastoma Previously (suggested 2B, level of evidence C)

Patients older than 65 years of age appear to have a lower likelihood of developing symptomatic hemangioblastomas.39,40 In a large natural history study from the National Institutes of Health, the development of hemangioblastomas was associated with younger age.1 For patients older than 65 years of age who are asymptomatic and have never developed a hemangioblastoma previously, it is reasonable to consider stopping routine surveillance MRI. The development of symptoms and other individual patient factors may support ad hoc MRI after the age of 65 years.

This was the one age and guideline where the recommendation was affected by an attempt to harmonize and synchronize the guideline with those of the other organ systems (e.g., ophthalmology, renal). While we felt that the literature supported ceasing the routine surveillance of asymptomatic patients older than 65 years who did not have a history of CNS hemangioblastomas, it was not definitive from the literature as to whether this age should be 60 years, 65 years, or some age in between. Since the data for other VHL manifestations supported ceasing imaging for those organ systems at age 65 years, we adopted this specific age for CNS MRI as well.

4) Surveillance MRI for Hemangioblastoma Should Start at the Age of 11 Years in Patients With VHL (suggested 2B, level of evidence D)

For approximately 40% of patients with VHL, the initial disease manifestation is a symptomatic CNS hemangioblastoma.9,10 To identify the at-risk population in patients with VHL, we analyzed published population-based studies that examined initial identification of hemangioblastomas on MRI.2,10,11 These studies revealed that the great majority of first hemangioblastomas (those within 2 standard deviations of the mean) will present between the ages of 11 and 65 years.2,10,11 While case reports describe children with VHL who developed CNS hemangioblastomas as early as 8 years of age,14,15,26 all of these tumors were asymptomatic and did not require treatment. Moreover, a small series in which children were followed up showed that at the age of 10 years, 8% of patients with VHL harbored hemangioblastomas, but all were asymptomatic.27

Given the risks and burden of imaging, the committee resolved that the benefit of identifying this small group of very young (<11 years old) asymptomatic patients was outweighed by the impact of additional testing and difficulty in performing imaging. Based on these findings, in the first decade of life, we support a detailed, annual age-appropriate history and comprehensive neurological examination to screen for signs and symptoms in lieu of MRI. To develop a coherent and congruent set of screening guidelines for the multiple systems affected by VHL, we recommend imaging-based surveillance and screening for hemangioblastomas to be performed between the ages of 11 and 65 years in patients with VHL, including annual clinical examinations and MRI of the neuroaxis every 2 years. However, clinical screening can be initiated at an earlier age or done more frequently, based on clinical concern.

Conclusions

MRI-based screening and surveillance of asymptomatic patients should commence at age 11 years and conclude in most patients at the age of 65 years. The report of neurological symptoms or identification of hemangioblastoma-associated signs may significantly modify the frequency of MRI-based surveillance. When imaging is difficult to perform or when it has low routine diagnostic value (in patients <11 years, during pregnancy, and in patients >65 years of age), clinical findings should dictate the necessity of MRI-based evaluation. The general surveillance guidelines created by the consortium for all organ systems intended for the primary physician managing the patient with VHL can be found on the VHL Alliance website.18

Acknowledgments

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References


References


References


References


References


Disclosures
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions
Conception and design: Huntoon, Daniels, Asthagiri. Acquisition of data: Huntoon. Analysis and interpretation of data: Huntoon, McCutcheon, Asthagiri. Drafting the article: Huntoon, Shepard, Lukas, McCutcheon, Asthagiri. Critically revising the article: Huntoon, Lukas, McCutcheon, Daniels, Asthagiri. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Huntoon.

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