INTRODUCTION

The first edition of this national clinical guideline was published in 2002 after an extensive review of the international literature and the long standing Danish experience and praxis performed by a working group of Danish doctors and other specialists interested in vHL. The second revised edition came in 2005. Since then, Denmark has hosted “The 8th International Medical Symposium on von Hippel-Lindau disease”, Roskilde 2008, original Danish literature on vHL has been published [1-4], and the working group has been formalized as The Danish vHL Coordination group.

The present third edition of the clinical guideline is the result of a thorough revision. The diagnostic criteria have been changed: There is no longer a distinction between major and minor criteria, the analysis of catecholamines in urine has been replaced by analysis of plasma-metanephrines, recommendations regarding prophylactic screening for endolymphatic sac tumours (ELSTs) have been added, and prophylactic screening in families with an isolated case of central nervous system (CNS) hemangioblastoma are no longer recommended.

Many individuals predisposed to vHL have to take several days off from work to attend the screening examinations. For many this is inconvenient, and it may cause some to refrain from surveillance. It is an ambition of the working group to optimize the coordination of the screening examinations, for example by establishing interdisciplinary vHL clinics.

The working group behind the third edition of the clinical guideline comprised (in alphabetical order):

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TERMINOLOGY

The present report refers to the following categories of individuals:

- In relation to manifestations: Affected individuals, possibly affected individuals, and unaffected individuals.
- In relation to a family: At-risk individuals (1st degree relatives to an affected individual and/or mutation carrier, and his/her descendants, whose risk has not been clarified by predictive genetic testing).
- In relation to a pathogenic mutation: Mutation carriers.

DEFINITIONS

Von Hippel-Lindau disease (vHL) (OMIM number 193300) is a hereditary multi-organ tumour-disease. The prevalence is internationally reported to be between 1: 36,000 – 91,000 [5-8]. In Denmark the prevalence has been estimated to be 1:93,000. Predisposed individuals are at risk of developing multiple benign as well as malignant neoplasms, especially hemangioblastomas in the retina (von Hippel), in the cerebellum (Lindau), and renal cell carcinomas. Neoplasms also occur in other locations in the CNS, adrenal glands (pheochromocytomas), pancreas, the endolymphatic sac in the inner ear, and others (Table 1).

1 Based on numbers from [1].
### Typical VHL-associated manifestations

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Average age of onset (years)</th>
<th>References</th>
<th>Frequency of VHL patients with the manifestation (No. of vHL pts. of total no. of pts., range)</th>
<th>References</th>
<th>Frequency of VHL patients among patients with the manifestation (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinal hemangioblastoma</td>
<td>25-37</td>
<td>[16-18]</td>
<td>52% (1,716 of 3,294, range: 15-73%)</td>
<td>[1,6,7,9,16-32]</td>
<td>Median: 46% (N=145, range: 31-81%)</td>
<td>[32-35]</td>
</tr>
<tr>
<td>Cerebellar hemangioblastoma</td>
<td>29-30</td>
<td>[9,16, 36]</td>
<td>49% (786 of 1,598, range: 35-79%)</td>
<td>[1,6,9,16-19, 21,22,24-26, 27,32,36-48]</td>
<td>Median: 18.5 (N= 563, range: 4-57 %)*4</td>
<td>[33,39-43]</td>
</tr>
<tr>
<td>Spinal hemangioblastoma</td>
<td>33-54</td>
<td>[1,9,16]</td>
<td>27% (392 of 1,472, range: 7-53%)</td>
<td>[1,6,16,19, 21,22,26,27, 32,37,38,44]</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Brainstem hemangioblastoma</td>
<td>25-38</td>
<td>[1,38, 45]</td>
<td>16% (65 of 413, range 4-22 %)</td>
<td>[1,21,23,27,3 2,37,38]</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Cerebral hemangioblastoma</td>
<td>29 (N=1)</td>
<td>[1]</td>
<td>4% (26 of 586, range: 1-7%)</td>
<td>[1,19,26,32,3 8]</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>40-45</td>
<td>[9,16, 36]</td>
<td>30% (532 of 1,784, range: 5-86%)</td>
<td>[1,6,9,22- 29,31,36,37, 41,45]</td>
<td>&lt; 5 %</td>
<td>[27]</td>
</tr>
<tr>
<td>Renal cysts</td>
<td>34-39</td>
<td>[1,6,34]</td>
<td>42% (99 of 231, range: 10-89 %)</td>
<td>[1,22- 25,27,34,37, 41]</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>20-29</td>
<td>[9,16, 47]</td>
<td>16% (403 of 2,546, range: 0-32%)</td>
<td>[1,6,9,16, 19,22,24-26, 32,37,46,47]</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Pancreatic cysts</td>
<td>29-37</td>
<td>[1,6,34]</td>
<td>21% (178 of 831, range: 15-35 %)</td>
<td>[1,19,22- 25,27,29,37, 41,56]</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Pancreatic neuroendocrine tumour</td>
<td>32-38</td>
<td>[57-59]</td>
<td>10% (170 of 1,656, range: 1-17 %)</td>
<td>[1,24,28,29,3 7,56,58,59]</td>
<td>1 % (N= 101)</td>
<td>[60]</td>
</tr>
<tr>
<td>Endolymphatic sac tumour</td>
<td>22-40</td>
<td>[61-63]</td>
<td>11% (67 of 583, range: 3-16 %)</td>
<td>[3,22,25,32,3 7,61,63]</td>
<td>5-15 % (N= 74)</td>
<td>[64-66]</td>
</tr>
<tr>
<td>Epididymal cyst adenoma</td>
<td>24</td>
<td>[1]</td>
<td>25% (73 of 287, range 3-32 %)</td>
<td>[1,19,22,32]</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

*1 Age of onset: This is a review based on studies which have reported: The number of vHL patients/VHL mutation carriers with the specific VHL manifestation, the average age at diagnosis of the specific manifestation, and how the diagnosis of VHL was made. The ages given were rounded up to the nearest whole year. The published studies were of varying sizes. For each manifestation, the table gives data from the three studies with the largest number of patients. Average age of onset (years): The lowest to the highest reported average ages at diagnosis in the three included studies. N: The total number of vHL patients with the manifestation in the three studies used for the calculation. Range: The lowest – the highest age at diagnosis of the manifestation in the three studies used for the calculation. Please note that this range does not account for the extreme limits reported in smaller studies. *2 Frequency of the manifestation among vHL patients: This is a review based on studies of vHL patients which have reported: The number of vHL patients/VHL mutation carriers with the specific VHL manifestation, the total number of patients in the study, and how the diagnosis of VHL was made. Inclusion criteria for studies in this calculation: The study was based on observations in more than 5 vHL patients, and the diagnoses of VHL were either based on the patients fulfilling clinical diagnostic criteria or the patients were carrying a pathogenic mutation in VHL. Exclusion criteria for studies in this calculation: To avoid bias due to geno-phenotype correlations, we excluded studies with vHL patients selected based on a specific genotype or VHL patients selected based on the presence of a specific manifestation. Frequency of VHL patients with the manifestation: The percentage and total number of vHL patients with the manifestation (sum of all included studies) out of all vHL patients in the included studies (sum of all included studies). Range: The lowest - the highest frequency of the specific manifestation in all of the included studies. *3 Frequency of vHL patients with the manifestation: This is a review of studies of populations of patients with each specific VHL-associated manifestation that have reported the frequency of VHL among these patients (either based on the patients fulfilling clinical diagnostic criteria or the patients were carrying a pathogenic mutation in VHL). Frequency of VHL patients: The percentage of VHL patients among patients selected based on a specific VHL-associated manifestation (sum of all patients in the included studies). Range: The lowest - the highest frequency of vHL patients in all of the included studies. *4 Frequency of vHL patients among patients with CNS hemangioblastomas. *5 Frequency of VHL mutation carriers among patients with either a) sporadic pheochromocytoma, or b) familial pheochromocytoma. It should be noted that VHL-associated manifestations can occur in children; such cases are most commonly published in case reports and are therefore not included in the table [67-74].

The disease is inherited in an autosomal dominant manner, and is caused by mutation in the tumour suppressor gene VHL on chromosome 3. The penetrance of a mutation in the VHL gene is close to 100% at the age of 65 years (Table 2) [5,6,9,10].
Diagnosing vHL on clinical criteria can be difficult. When considering the diagnosis vHL in an affected individual without affected relatives ("an isolated case"), the age of onset should be included in the considerations. In some cases, differential diagnosis vHL in an affected individual without affected relatives should be considered in all individuals with an endolymphatic sac tumour.

**IN WHICH INDIVIDUALS SHOULD VHL BE SUSPECTED?**

- The prevalence of ELST is about 13% among Danish VHL mutation carriers. Symptoms of ELSTs can be hearing loss, tinnitus, dizziness, or facial paresis.
- The risk of epididymis cyst adenomas appear to be high in VHL patients; incidence figures of 10-60% have been reported, and in many cases the cysts occurred bilaterally. However, several authors agree that neither epididymis cyst adenomas nor renal cysts should be included in the clinical diagnostic criteria for VHL due to their high frequency in the general population.
- The age limits are due to lack of reference intervals for younger individuals.
- The hearing examination should consist of: A) Pure tone audiometry: Screening audiometry (classifying the individuals hearing ability as "within/outside normal hearing limits") and B) Speech audiometry: Determination of Speech Reception Threshold (SRT) and Speech Discrimination test. C) Impedance audiometry: Tympanometry and stapedial reflex determination (both contra- and ipsilateral reflexes).

**RECOMMENDATIONS FOR THE WORK-UP OF AN INDIVIDUAL SUSPECTED OF VHL**

1. Interview about VHL-associated symptoms and neurological examination
2. Ophthalmoscopy in dilation
3. Plasma-metanephrine and plasma-normetanephrine (if the individual is ≥ 5 years of age) and plasma-chromogranin A (if the individual is ≥ 18 years of age)
4. MRI of the entire CNS (the craniospinal axis), kidneys, pancreas, and liver
5. Hearing examination in a department of audiology

VHL manifestations which are part of the clinical diagnostic criteria:
1. The retina: Hemangioblastoma
2. The cerebellum, the medulla oblongata, or the spinal cord: Hemangioblastoma
3. The inner ear: Endolymphatic sac tumour (ELST)
4. The kidneys: Renal cell carcinoma
5. Pheochromocytoma, paraganglioma, and/or glomus tumour
6. The pancreas: Neuroendocrine neoplasms and/or multiple cysts

Some VHL manifestations are so common in the general population that they are not a part of the clinical diagnostic criteria; but they can help to support the diagnosis of VHL (kidney cysts, papillary cystadenoma in the epididymis, papillary cystadenoma of the broad uterine ligament). Other rarer locations for cysts, cystadenomas, angiomas, hemangiomas, and hemangioblastomas are the cerebrum, liver, the spleen, the lungs, the skin, the ovaries, and the bones.

**CLINICAL CLASSIFICATION**

Two main classic VHL phenotypes based on the occurrence of pheochromocytoma and renal cell carcinoma in the family, have been described. These two phenotypes can be further subclassified, see Table 3 [11-14]. At present (2013), identical recommendations for surveillance are given in all families with VHL, irrespectively of the subtype.

**TABLE 2**

Age-related cumulative frequency of diagnosis of first VHL-associated manifestation

<table>
<thead>
<tr>
<th>Ages (years)</th>
<th>Cumulative frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>N= Number of VHL patients/VHL mutation carriers included. The differences between the two countries are most likely due to differences between the materials: In the British study only clinically affected VHL patients with unknown mutation status were included (some could therefore represent sporadic cases of VHL associated manifestations). Also, data from both deceased and living VHL patients was included. In the Danish study, only living VHL mutation carriers were included.</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.02</td>
</tr>
<tr>
<td>15</td>
<td>0.19</td>
</tr>
<tr>
<td>25</td>
<td>0.52</td>
</tr>
<tr>
<td>35</td>
<td>0.78</td>
</tr>
<tr>
<td>45</td>
<td>0.91</td>
</tr>
<tr>
<td>55</td>
<td>0.96</td>
</tr>
<tr>
<td>65</td>
<td>0.99</td>
</tr>
<tr>
<td>70+</td>
<td>1.00</td>
</tr>
</tbody>
</table>

**TABLE 3**

Clinical classification of VHL phenotypes

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Frequency of manifestation</th>
<th>Most common mutation type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 A</td>
<td>Low</td>
<td>Mutations leading to total loss of the biological activity of pVHL</td>
</tr>
<tr>
<td>B</td>
<td>Low</td>
<td>Missense mutations allowing a residual activity of pVHL</td>
</tr>
<tr>
<td>Type 2 A</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>High (no other manifestations)</td>
<td></td>
</tr>
</tbody>
</table>

**DIAGNOSTIC CRITERIA**

With these reservations and distinctions in mind, the clinical diagnostic criteria can be stated as follows:

- An individual has VHL if the criteria in either 1 or 2, or both are fulfilled:
  1. The individual has at least two of the manifestations stated below
  2. The individual has at least one of the manifestations stated below, and a pathogenic mutation in VHL or at least one first-degree relative with VHL.
6) Referral to a department of clinical genetics for a genetic work-up, including recording the family history and mutation analysis

SURVEILLANCE PROGRAM FOR AFFECTED INDIVIDUALS, POSSIBLY AFFECTED INDIVIDUAL, AT-RISK INDIVIDUALS, AND MUTATION CARRIERS

The examinations should as far as possible be performed by medical specialists with a special interest and experience in vHL. It is valuable that one of the involved professionals takes the responsibility of being the contact person/clinical coordinator. This person is typically the neurosurgeon, the ophthalmologist, or the clinical geneticist, but can in principle be any doctor with experience in vHL, who can refer to and coordinate the many surveillance examinations and who will take care of the communication with the patient.

To facilitate the coordination and especially for patients' own use, a mobile chart can be ordered at: mlbi@sund.ku.dk or www.vhl.dk.

RECOMMENDED SURVEILLANCE

From 0 to 4 years of age:
- Annual clinical examination by a paediatrician
- Annual ophthalmoscopy in dilation

From 5 to 14 years of age:
- Annual clinical examination by a paediatrician
- Annual ophthalmoscopy in dilation
- Annual plasma-metanephrine and plasma-normetanephrine
- Annual hearing examination in a department of audiology
- 1 x Magnetic Resonance Imaging (MRI) scan of the CNS and 1 x Ultra Sound (US) of the abdomen (kidneys, adrenal glands, pancreas, liver) – optimally in the age interval 8-14 years of age.
- Every second year: MRI scan of the abdomen (kidneys, adrenal glands, pancreas, liver)

The recommendations apply for organs in which the individual does not have any manifestations. Once an organ becomes affected, a specific follow-up program for this organ will be composed. Besides the routine surveillance examinations, symptoms which occur in between these, will naturally lead to a new targeted examination. Any positive findings should lead to referral to a relevant specialist.

<table>
<thead>
<tr>
<th>TABLE 4</th>
<th>Differential diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manifestation and differential diagnoses</td>
<td>Mode of inheritance<em>1: gene(s)/ etiology</em>2</td>
</tr>
<tr>
<td>Kidney cancer</td>
<td>Bilateral kidney cancer</td>
</tr>
<tr>
<td>Hereditary leiomyomatosis with kidney cancer</td>
<td>AD: FH</td>
</tr>
<tr>
<td>Hereditary papillary type 1 kidney cancer</td>
<td>AD: MET</td>
</tr>
<tr>
<td>Hereditary kidney cancer with the chromosomal translocation 3:8 (13;8)</td>
<td></td>
</tr>
<tr>
<td>Lynch syndrome</td>
<td>AD: MLH1, MSH2, MSH6, PMS2</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>AD: TSC1, TSC2</td>
</tr>
<tr>
<td>Cowden syndrome</td>
<td>AD: PTEN</td>
</tr>
<tr>
<td>Sickle cell anemia, heterozygotes</td>
<td>AD: HBB</td>
</tr>
<tr>
<td>Beckwith-Wiedemann syndrome</td>
<td>Sporadic: IGF2, CDKN1C AD: CDKN1C (paternally imprinted)</td>
</tr>
<tr>
<td>Hereditary paraganglioma/pheochromocytoma (PGL4)</td>
<td>AD: SDHB</td>
</tr>
<tr>
<td>Pheochromocytoma/Paragangliomas</td>
<td></td>
</tr>
<tr>
<td>Multiple Endocrine Neoplasia ( MEN) 1</td>
<td>AD: MEN1</td>
</tr>
<tr>
<td>Multiple Endocrine Neoplasia ( MEN) 2</td>
<td>AD: RET</td>
</tr>
<tr>
<td>Hereditary paraganglioma/pheochromocytoma (PGL1-4)</td>
<td>AD: SDHD, SDHAF2, SDHC, SDHB, SDHD and possibly SDHAF2 are imprinted, the penetrance is low if inherited from the mother</td>
</tr>
<tr>
<td>Neurofibromatosis type 1</td>
<td>AD: NF1</td>
</tr>
</tbody>
</table>
Multiple Endocrine Neoplasia (MEN) 4
- AD: CDKN1B and possibly other CDKN genes
- *MEN1 like*

Paraganglioma and gastric stromal sarcoma (Carney-Stratakis)
- AD: SDHB, SDHC, SDHD. SDHD are imprinted, see above
- Paragangliomas, gastric stromal sarcoma

Carney triade
- Multifactorial etiology?
- Gastric epithelioid leiomyosarcomas, pulmonary chondromas, and extradrenal paragangliomas, etc.

Kidney cysts
- Autosomal Dominant Polycystic Kidney (ADPKD)
  - AD: PKD1, PKD2
  - Polycystic kidneys, hypertension, liver fibrosis

- Autosomal Recessive Polycystic Kidney (ARPKD)
  - AR: PKHD1
  - Polycystic kidneys, liver fibrosis

- Renal cysts and diabetes (RCAD) syndrome
  - AD: HNF-1beta
  - Polycystic kidneys, diabetes, early onset gout, malformations of the uterus

- Multicystic kidney
  - Often sporadic
  - Unilateral cystic kidney

*1: AD: Autosomal dominant; AR: Autosomal recessive; Imprinting: The expression depends on whether the mutated gene is inherited from the patient’s father or mother.
*2: Not all mutations can be detected: For many of the conditions there is genetic heterogeneity and the disease-causing mutation(s) can be found in other genes. Also, there is pleiotropy for many of the mentioned genes. Therefore, detection of a mutation can support a clinical diagnosis, but absence of a detectable mutation cannot be used to exclude a diagnosis for which there is a clinical basis.

THE GENE: VHL

VHL is a tumour suppressor gene located on chromosome 3 in the region p25-26. VHL is a small gene covering 14,443 base pairs. The gene has three exons coding for a protein of 213 amino acids. VHL encodes a protein, pvHL, which is produced in two forms, an 18 kDa and a 30 kDa protein. The main action of the VHL protein is believed to be its E3 ubiquitin ligase activity that leads to specific target proteins, HIFs (Hypoxia Inducible Factors), being ‘marked’ for degradation [15].

Tumourigenesis is explained by Knudson’s two hit hypothesis which proposes mutation in both alleles of a tumour suppressor gene. In most tumours in VHL patients, both alleles of VHL are mutated. The “first” of these mutated alleles is also present in healthy cells of the individual, whereas the “second” mutated allele is present in the neoplastic cells of the tumour, only.

Most often the first mutated allele is present in all cells of the individual, either because the individual has inherited the mutated allele, or because the allele was mutated in the oocyte, the spermatozoon, or the zygote (de novo mutation). In some cases of de novo mutation, however, the mutation occurred after the zygote stage. In that case, some cells of the individual carry the mutated gene and other cells do not carry the mutated gene (mosaicism). An individual that is mosaic for a mutated VHL gene may have a milder phenotype than usual. If the mutated gene is not present in blood cells, it may be overlooked in mutation screening. Offspring of an individual who is mosaic can inherit the mutated gene.

In all cases, the second mutated allele in a tumour underwent mutation in a somatic cell. Thus, the second mutated allele is not heritable.

Among the mutations identified in Danish VHL patients, approximately 1/3 are point mutations, approximately 1/3 are large genomic rearrangements, while nonsense mutations, frameshift mutations, in frame insertions, and intronic mutations account for the last fraction [4].

GENETIC WORK-UP AND COUNSELLING

An individual suspected of VHL is referred to the local department of clinical genetics. The department will check with the VHL database if the family of the individual has already been evaluated. If this is not the case, a full genetic work-up of the family will be performed.

A full genetic work-up has four main components: a) the medical history, b) clinical examination, c) the family history, and d) the mutation screening.

a) The medical history is obtained by interviewing the patient and reviewing medical records from the relevant departments.

b) If some of the recommended clinical examinations have not been performed, these will be arranged by the clinical geneticist.

c) The family history is obtained by interviewing the patient referred. Data on affected relatives are supplemented by reviewing their medical records etc. If relevant, the patient is asked to collect additional information about the family by interviewing (older) relatives etc. In some cases, affected relatives are contacted, via the patient, in order to supplement the clinical investigations of these. The information collected is documented in a pedigree.

d) Blood samples are obtained to screen the VHL gene for mutations. Standard mutation screening includes sequencing of coding exons and exon-intron boundaries, and analysing for deletions and duplications of the gene using MLPA (Multiplex Ligation-dependent Probe Amplification). Due to the possibility of mosaicism, blood samples from an affected individual with an affected parent are preferred. When a mutation is detected, this is evaluated in order to determine if it is pathogenic and to determine the likelihood that this mutation is responsible for the diseases in the family. A pathogenic mutation can be detected in the majority of VHL families with multiple affected relatives.

When the disease-causing mutation in a family is identified, predictive genetic testing is offered to at-risk individuals in that family.

As there is a risk of developing VHL manifestations in childhood, and as the recommended surveillance program is burdensome, predictive genetic testing is recommended to all relatives, including children. The genetic testing is carried out in accordance with guidelines for predictive testing, including recommendation of genetic counselling before and after the test. Once the disease-causing mutation in the family is known, prenatal testing can be performed on cells obtained by chorionic villus sampling that is performed in the 10-11 weeks’ gestation, or as preimplantation genetic diagnosis.

If mutation screening does not detect a mutation, relevant alternative diagnoses should be considered, see Table 4. If this leaves vHL as the most likely diagnosis, and the individual analysed is the first affected in the family, mutation screening should be repeated on DNA from other tissue types. Preferably a biopsy from a VHL manifestation should be analysed. Screening of fresh or frozen tissue is advocated, as mutation screening of DNA from formalin-fixed tissues is much more laborious and less successful than the screening of DNA from unfixed tissue. Another possibility is to repeat the mutation screening on blood samples from children of the affected individual. In some cases, it may be useful to supplement with mutation screening using other methods, for
example chromosome analyses, arrayCGH (Comparative Genomic Hybridization), SNP (Single Nucleotide Polymorphism) array, etc.

In families where all relevant mutation screenings have been performed and no disease-causing mutation has been identified, and where the diagnosis vHL is likely even after considering differential diagnoses, all affected family members and all first-degree relatives to affected individuals are referred to the surveillance program. When unaffected first-degree relatives have children, they are invited to the department of clinical genetics in order to evaluate the likelihood that their children will benefit from surveillance.

As early as possible during the genetic work-up, the clinical geneticist discusses the following topics with the patient(s):

- The nature of the hereditary predisposition suspected in the family
- The possibility of surveillance, if the diagnosis vHL is confirmed (see "Surveillance program for affected individuals, possibly affected individuals, at-risk individuals and mutation carriers")
- The importance of being aware of a hereditary predisposition in relation to the possibility of taking out insurance, pension etc.
- The possibility of stigma in the labour market and elsewhere
- The potential conflict between the desire to keep information about oneself confidential, and the fact that one shares one’s genes with one’s relatives.

The patient(s) is (are) advised to pass on a brief version of this information to his/her relatives, along with an invitation to consult a department of clinical genetics for more details. Often the clinical geneticist helps by writing a letter to the index patient, designed so that it is suitable to pass on to relatives.

POSSIBLY AFFECTED INDIVIDUALS

The gravest consequence of missing the diagnosis of vHL is the risk of the individual developing asymptomatic renal cell carcinoma, as this is the only vHL-associated manifestation with considerable risk of lethal outcome. In an individual, who a) was suspected of having vHL based on a single vHL-manifestation, b) underwent the diagnostic investigations described in "Recommendations for the work-up of an individual suspected of vHL" without having additional vHL manifestations detected, c) was without a family history, and d) had no mutation detected in VHL, the risk of developing renal cell carcinoma due to vHL can be approximated to be less than 0.5 per cent.\(^7\)

\(^7\) Our approximation of this risk is based on the following worst case scenario assumptions:
1) The probability that a single vHL-associated manifestation is caused by vHL and is not a sporadic manifestation, is assumed to be 50%.
2) The probability that a vHL patient has no family history with vHL equals the probability of a de novo mutation in VHL, which is 25% \([79]\).
3) The probability that a de novo mutation is not detected due to mosaicism is 5% \([79]\).
4) Among vHL patients, the frequency of renal cell carcinoma is about 30% (see Table 1).

The approximated risk that an individual with a single vHL-manifestation, no family history with vHL, and no mutation detected in VHL will develop renal cell carcinoma due to vHL is 0.30 x 0.50 x 0.25 x 0.05/(0.50 x 0.25 x 0.05 + 0.50) = 0.0037

Accordingly, such an individual is not recommended to undergo surveillance, but is invited to contact the department of clinical genetics immediately if he/she should experience vHL-associated symptoms in the future. However, children of the individual should be offered genetic counselling and possibly mutation screening; see "Genetic work-up and counselling".

It might be indicated to refer certain families to a renewed risk assessment at the department of clinical genetics some years after the initial genetic work-up. This may for instance be the case in families, in which the diagnosis vHL has been established but no disease-causing mutation has been identified, and in which surveillance programs for family members at-risk has been conducted without positive findings after repeated examinations.

REGISTRATION

The vHL Coordination group decided in May 2012 to establish a nationwide database, the vHL database, comprising individuals diagnosed with vHL, relatives to individuals diagnosed with vHL, and also individuals examined for vHL. The database has been notified to the Danish Data Protection Agency without remarks and it is regulated according to the directions stated May 5 2012 by the vHL Coordination group. The address of the database is: Department of Cellular and Molecular Medicine (ICMM), Panum Institute, University of Copenhagen.

The database is designated to be a treatment instrument and diagnostic instrument, but also a research tool. The database will comprise information about the individual’s civil registration number, name, disease status, family code, family relation, manifestations, results of molecular diagnosis, and also the doctor(s) responsible for the clinical surveillance and genetic counselling.

The database is based on previously collected material from multiple sources and will continuously be updated in corporation with the departments of clinical genetics, other clinical departments, and the molecular genetics laboratories.

In April 2013 the vHL database comprised approximately 2,800 live and deceased individuals from a little more than 150 families. Of these, 84 were registered as harbouring a mutation in the VHL gene and 270 individuals as having a least one vHL-associated manifestation. It is estimated that the disease is likely to be under-diagnosed in Denmark since the prevalence of diagnosed cases is approximately one third of the prevalence reported in thoroughly analysed, comparable regions \([1, 5-8]\).

ADDRESSES

GENETIC WORK-UP AND COUNSELLING

- Department of Clinical Genetics, Odense University Hospital, 5000 Odense
- Department of Clinical Genetics, Rigshospitalet 4062, 2100 Copenhagen Ø
- Department of Clinical Genetics, Vejle Hospital, 7100 Vejle
- Department of Clinical Genetics, Aarhus University Hospital, Skejby, 8200 Århus N
- Department of Clinical Genetics, Aalborg University Hospital, 9000 Aalborg

THE ASSOCIATION OF VON HIPPEL-LINDAU PATIENTS AND THEIR RELATIVES

Webpage: www.vhl.dk, E-mail: info@vhl.dk
ABBREVIATIONS

AD: Autosomal dominant
AR: Autosomal recessive
CGH: Comparative Genomic Hybridization
CNS: Central Nervous System
CT: Computed Tomography
DNA: Deoxyribonucleic acid
ELST: Endolymphatic sac tumour
HIF: Hypoxia Inducible Factor
MEN: Multiple Endocrine Neoplasia
MLPA: Multiplex Ligation-dependent Probe Amplification
MRI: Magnetic Resonance Imaging
RCC: Renal Cell Carcinoma
SNP: Single Nucleotide Polymorphism
SRT: Speech Reception Threshold
US: Ultra Sound
VHL: von Hippel-Lindau disease
VHL: the von Hippel-Lindau gene

SUMMARY

These clinical guidelines outline the criteria and recommendations for diagnostic and genetic work-up of families suspected of von Hippel-Lindau disease (vHL), as well as recommendations for prophylactic surveillance for vHL patients. The guideline has been composed by the Danish Coordination Group for vHL, which is comprised of Danish doctors and specialists interested in vHL. The recommendations are based on longstanding clinical experience, Danish original research, and extensive review of the international literature.

vHL is a hereditary multi-tumour disease caused by germline mutations in the VHL gene. vHL is inherited in an autosomal dominant manner. Predisposed individuals are advised to undergo prophylactic examinations, as they are at lifelong risk of developing multiple cysts and tumours, especially in the cerebellum, the spinal cord, the retina (hemangioblastomas), the kidneys (renal cell carcinoma), the adrenal glands (pheochromocytoma), the pancreas, as well as in other organs. As many different organs can be affected, several medical specialties often take part in both diagnosis and treatment of manifestations. vHL should be suspected in individuals with a family history of the disease, and/or in individuals with a vHL-associated manifestation; i.e. a hemangioblastoma in the retina or the central nervous system, familial or bilateral pheochromocytomas, familial, multiple, or early onset renal cell carcinomas, and in individuals with an endolymphatic sac tumour in the inner ear.

Individuals suspected of vHL should be referred to a department of clinical genetics for genetic work-up and counselling as well as have a clinical work-up to identify any undiagnosed vHL-associated manifestations. This guideline describes the elements of the clinical diagnostic work-up, as well as the genetic work-up, counselling, and mutation screening.

Individuals who are affected with vHL, individuals at-risk of vHL, and VHL-mutation carriers are advised to follow the surveillance program which consists of regular prophylactic examinations relevant to different age groups. The examinations are recommended to start in infancy with annual paediatric examinations and ophthalmoscopy until the age of 5 years. From 5 to 14 years, annual plasma-metanephrine and plasma-normetanephrine tests, as well as annual hearing examinations are added. Also, an MRI (Magnetic Resonance Imaging) examination of the CNS and abdomen should be done between the ages of 8 and 14 years. After the age of 15 years, individuals should be referred to: a) annual ophthalmoscopy in dilation, b) annual neurological examination, c) every two years: MRIs of the CNS, including the inner ear, d) annual ultrasound/MRI of the abdomen, e) annual plasma-metanephrine, plasma-normetanephrine, and plasma-chromogranin A tests, and f) annual hearing examination at a department of audiology. It is advised that one doctor takes on the responsibility of coordination of and referral to the many examinations, and the communication with the patient. To facilitate the coordination, and especially for the patients’ own use, a mobile chart can be used.

In 2012, the Danish vHL Coordination Group established a national vHL database comprising individuals with vHL and their relatives, as well as individuals examined for vHL. The database is designated to be a treatment and diagnostic instrument, as well as a tool in future vHL research in Denmark.

REFERENCES


51. Brauch H, Hoepner W, Jahnig H et al. Sporadic pheochromocytomas are rarely associated with germline mutations in the VHL tumour suppressor gene or the ret protooncogene. J Clin Endocrinol Metab 1997;82:4101-4


