

Manifestations of Von Hippel Lindau Syndrome: A retrospective national review

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Abstract

Introduction

Von Hippel-Lindau disease (VHL) is a syndrome that is defined by variety of tumours, including; cerebellar haemangioblastomas, renal cell carcinomas, pheochromocytomas, pancreatic adenomas and ear, nose and throat (ENT) adenomas. This disease is often genetic and inherited in an autosomal dominant fashion, and can present in childhood, adolescence or in adult life. This study describes the presentation, natural history and manifestations of patients attending our institutions with this condition. We aim to highlight the importance of screening in diagnosing the manifestations of VHL.

Methods

A retrospective review was performed on all patients diagnosed with VHL and coded as such by the national Hospital Inpatient Enquiry Scheme (HIPE) at Beaumont Hospital Dublin and Cork University Hospital. This was performed over a 20 years period between 1989 and 2009. Age, sex, mode of presentation, presence or absence of end stage kidney disease (ESKD) and genotype were documented. Presence or absence of the characteristic tumours of VHL was also recorded, as were the initial presenting features of these tumours.

Results

Thirty-six patients were diagnosed with VHL. These patients ranged from 18 to 78 years old. Three patients were members of the Irish travelling community. The most frequent mode of presentation was altered neurological signs (40%), with a significant proportion presenting with haematuria (23%). Patients diagnosed prior to 1995 were more likely to have presented with significant complications of VHL, while those diagnosed after this time were more likely to have been diagnosed via screening. Genetic testing was performed on 17 patients; those who did not have genetic testing performed were more likely to have been diagnosed prior to the era of genetic testing. Thirty-one patients had received screening for complications of VHL including; renal cell carcinomas, CNS haemangioblastomas and pheochromocytomas. The patients who did not receive any screening presented with neurological symptoms.

Conclusion

Beaumont Hospital Dublin and Cork University Hospital are tertiary referral centres for nephrology, urology and neurosurgery and deals with a significant proportion of patients diagnosed with VHL in Ireland. This study highlights the significant burden of this illness, and emphasises the importance of screening for these renal/central nervous system (CNS) and ENT complications. This study also highlights the importance of family screening in diagnosing this condition.

Introduction

Von Hippel Lindau disease (VHL) is an autosomal dominant syndrome associated with a variety of tumours including; central nervous system haemangioblastomas, pheochromocytomas, renal cell carcinomas, retinal angioma and ear nose and throat (ENT) tumours¹.

VHL results primarily from a germline mutation in the VHL tumour suppressor gene on chromosome 3p25-26. It is most commonly familial (80%) however 20% of patients will present with a de novo mutation². The protein produced by this gene is involved in tumour suppression by targeting hypoxia inducible factor proteins (HIF) for destruction³. In VHL these HIF proteins accumulate and promote pathological growth via up-regulation of proteins involved in glucose metabolism, angiogenesis and mitogenesis⁴.

VHL affects 1 in 36,000 newborns worldwide⁵ and the Irish prevalence can be estimated at 1 in 80,000 people⁶. VHL can be broadly subclassified into VHL type 1 and type 2, based on the likelihood of developing pheochromocytoma⁷. Patients with VHL type 1 have a lower risk of developing pheochromocytoma, while those with type 2 have a higher risk of developing pheochromocytomas. Type 2 patients can be further sub-classified into type 2a, 2b and 2c. Type 2a patients have a low risk of developing renal cell carcinoma, while those with type 2b have a higher risk. Type 2c patients present with pheochromocytomas, without the other manifestations of VHL.

Patients present with manifestations of VHL in a variety of ways, however in the past ten to fifteen years, increasing numbers of patients are being diagnosed using genetic testing and screening protocols⁸.

One of the common clinical presentations of this illness is; painless haematuria secondary to underlying renal cell carcinoma. Renal cell carcinomas or multiple renal cysts have been described in 60-70% of patients with VHL. Renal cell carcinomas are less likely to be found before ages 20, however incidence increases with age thereafter.

Development of neurological signs or symptoms is another common presenting feature of VHL, secondary to CNS haemangioblastomas. Central nervous system haemangioblastomas occur in 60-80% of VHL patients, with a mean age at diagnosis of 29 years^{9, 10, 11}. CNS haemangioblastomas can be attributed to VHL disease in approximately 33% of cases.

Pheochromocytomas have been noted in 18-60% of VHL patient series^{12, 13}. These may present with the classical features of catecholamine excess, such as headache, hypertension or anxiety, however they are increasingly picked up using screening protocols. Pheochromocytomas in VHL patients are more likely to be extra adrenal and are less likely to have biochemical evidence of excess catecholamine production¹⁴.

Endolymphatic sac tumours of the middle ear (ELST) occur in approximately 10% of VHL patients¹⁵, and bilateral ELST's are considered pathognomonic of VHL.

We describe the presentation, natural history and manifestations of patients attending our institutions with this condition. Beaumont Hospital Dublin is a tertiary referral centre for neurosurgery, endocrinology, urology, transplantation and nephrology. Cork University Hospital is a tertiary referral centre for neurosurgery, endocrinology, nephrology and urology. We also focus on the importance of screening for complications in those patients. This study also aims to highlight the importance of family screening in diagnosing this illness.

Methods

This was a retrospective cohort study of all patients coded as having Von Hippel Lindau syndrome by the Hospital InPatient Enquiry system (HIPE) at Beaumont Hospital Dublin and Cork University Hospital. All patients who attended these institutions over the past twenty-five years were eligible for inclusion in the study. This was compared to national prevalence data on VHL as provided by the Economic of Social Research Institute (ESRI), Ireland.

Patients were defined as having VHL if they were noted to have a germline mutation in the VHL gene, however many of our patients were diagnosed with VHL prior to the era of genetic testing, and so the clinical definitions of VHL for those time periods were used. These definitions were based on the presence of two or more characteristic features of VHL, or one or more characteristic features with a positive family history¹⁶. Patients in Beaumont Hospital who were diagnosed with VHL based on the above findings were not routinely sent for genetic testing.

A standardized data collection protocol was subsequently formulated recording age, sex, mode of presentation and genotype. Features of VHL present in patients and whether they had developed end stage renal disease was also recorded. We specifically noted whether these patients received screening for complications of VHL. Data was collected on abnormalities of diagnostic imaging in these patients.

Results

Thirty-six patients with Von Hippel Lindau disease were identified in these institutions; 17 at Beaumont Hospital, and 19 in Cork University Hospital. Genotype information was available on four of the patients attending Beaumont Hospital and on thirteen of the patients in Cork University Hospital. The remaining 19 patients were diagnosed as having VHL on the basis of family history and the finding of characteristic VHL lesions.

Three main genotype abnormalities were noted in patients who had genetic testing performed. All had abnormalities of the VHL gene on chromosome 3, with 8 patients having a missense mutation at c.713G>A, exon 3;p.Arg167Gln. These patients all belonged to the same extended family and presented primarily with adrenal lesions. 3 patients had mutations at g.739delA,exon 3, again, these patients were members of the same family. The remaining genotype confirmed VHL patients had non-identical abnormalities of the VHL gene.

The majority of patients were of Irish ethnicity, with one from Eastern Europe. Three of the patients were members of the Irish Travelling Community. The age range of patients was 18-78 years old with a female predominant sex distribution. [Table 1]

The most common mode of presentation was with altered neurological signs, or symptoms (40%). Patients presented primarily with headaches or back pain, two patients initially presented with seizures. These presentations were secondary to CNS haemangioblastomas.

A significant proportion of patients presented with haematuria (23%). Ten patients developed renal cell carcinoma, which was bilateral in eight cases. [Figure 1] Six patients required bilateral nephrectomies, and developed end stage kidney disease (ESKD). All six patients commenced on haemodialysis when they developed ESKD, for a range of six months to five

years. Four of these patients subsequently received a deceased donor renal transplant, and became dialysis independent. One patient received a living unrelated kidney transplant.

9 patients presented with features of catecholamine excess, and were found to have pheochromocytomas (25%). One patient presented via the ophthalmology department with visual loss.

8 (22%) Patients were diagnosed with VHL through family screening alone.

Screening was undertaken in 31 of the 36 patients in our cohort. This primarily consisted of renal imaging, and screening to identify neurological and endocrinological complications of VHL.

Renal screening consisted of yearly or two yearly renal ultrasonography. Five patients did not receive any renal screening in our institution. The patients who did not receive any renal screening presented with neurological symptoms. They were discharged to their local hospital for further screening, but declined to re attend.

CNS and endocrinological screening involved all patients receiving Magnetic Resonance Imaging (MRI) Brain scans and either Computerized Tomography (CT) Abdomen scans or MR adrenal scans every three to five years. Urinary catecholamine collection was performed in approximately half of our patients group.

It was noted that screening of some form was more likely to be used from 1994 onwards, and that patients diagnosed with VHL after this time were more likely to have been diagnosed via a screening program.

Discussion

We report on a specific cohort of patients with VHL disease who attend our institutions, and document the range of manifestations of this illness observed in these patients.

As noted above, our institutions consist of tertiary referral centres for nephrology, endocrinology, urology/transplantation and neurosurgery. It is expected that the population of patients seen in our study would be representative of patients with VHL disease nationally.

The prevalence of VHL disease internationally is one per 36,000 newborns. The Irish national prevalence of this disease can be estimated at 1 per 80,000 using admission/discharge statistics from the ESRI and national HIPE system. This system estimates that there are 38-42 patients with VHL living in the Republic of Ireland. Based on this data, slightly under ninety percent these patients attend our institutions.

If Ireland was to have a rate of VHL similar to that described by Joerger et al¹, then we would have over one hundred patients attending our institutions with this condition. It is possible that we are underestimating our population burden of VHL, however the above study may also not apply to our relatively homogenous population.

The patients described in our group had similar rates of ESKD to those described in other studies, however our group had a higher rate of transplantation. This reflects our high rate of cadaveric renal transplantation per head of population, with a rate of approximately 140-160 transplants per year in the Republic of Ireland¹⁷.

It is noted that genotype information was available on under half of our patients. This reflects differing practices between institutions, and also underline the fact that a significant proportion of our patients were diagnosed with VHL before genetic testing was widely

available. From an academic perspective it would be useful to genotype all our current VHL patients.

We noted that a significant majority of patients had renal pathology diagnosed, highlighting the significant burden of renal illness in these patients. This highlights the importance of renal screening. It was noted that of the five patients who did not have renal screening performed in our institutions, initially presented with neurological complications. These patients were to have renal screening performed in their local hospital. This emphasises the importance of referring patients who initially present with neurological or endocrinological complications of VHL for renal diagnostic imaging, or to a urologist/nephrologist for review. This would also allow for family screening to take place, if deemed appropriate.

An increasing numbers of patients were diagnosed with the complications of VHL via screening of family members over the past 20 years. This highlights the benefits of a standardized screening program, and further supports implementation of an institutional or national screening protocol for patients with genetic confirmation of VHL. It also supports the introduction of a family screening protocol for relatives of patients with VHL.

We recommend annual renal/abdominal MRI examinations for all patients with known VHL and for all patients with a positive family history of VHL. This will identify renal cell carcinoma and pheochromocytoma.

CNS screening needs to be considered in different situations, i.e. relatives of VHL patients with known germline mutations, versus relatives of patients with no known mutation. We also need to consider how the screening of asymptomatic CNS haemangioblastomas and ELST's may alter the natural history of these lesions.

Surgical resection is not usually recommended for asymptomatic haemangioblastomas as natural history studies have demonstrated variable rates of growth, with some lesions remaining static over many years,¹⁸. However close clinical correlation is paid to asymptomatic cystic haemangioblastomas and spinal haemangioblastomas as these lesions are associated with developing oedema, and these groups appear to have a higher incidence of developing symptoms and in some cases may require intervention.

Baseline craniospinal MRIs and audiometry should be performed during adolescence if VHL is suspected, or in those with a positive family history. Imaging should be performed earlier if symptoms are present.

Thereafter, patients continue with screening depending on the findings found on baseline MRI. If no abnormalities are seen, patients should receive an annual detailed neurological exam, and audiometry every 3-5 years until age 65.

Patients who are noted to have an abnormality on initial MRI should be referred to a neurosurgeon for further management. Asymptomatic patients are managed thereafter depending on the location and appearance of the lesions. Certain patients will continue to have annual detailed neurological examinations, while those with cystic lesions may be considered for more frequent surveillance or for surgical intervention.

If an ELST is noted on initial baseline MRI, joint discussions need to be undertaken with neurosurgery and otorhinolaryngology, as these lesions tend to be locally aggressive and can lead to hearing loss. Similarly, if deterioration in hearing is noted at audiometry patient should be referred for cranial imaging.

We conclude that screening should be considered for patients and relatives of patients with known VHL mutations and for all patients and relatives of patients with a clinical diagnosis of VHL.

This should follow an amended version of the Massachusetts General Hospital screening protocol, including initial baseline Magnetic Resonance Imaging (MRI) brain, MRI adrenals, Renal ultrasonography, 24 hour catecholamine collection and ophthalmology assessment [Figure 2].

Tables*Table 1*

	No. (%)
Sex	
Male	15(42%)
Female	21(58%)
Age Group	
<18	0(0%)
18-49	22(61%)
50-64	11(30%)
>65	3(9%)
Ethnicity	
Irish	32(88%)
Eastern European	1(3%)
Irish Traveler	3(8%)
Complications of VHL	
CNS lesion	17(47%)
Renal cell carcinoma	10(27%)
Phaeochromocytoma	9(25%)

Baseline patient characteristics

Figure 1
Von Hippel Lindau Disease
Screening Guidelines

Who should be referred?

Any patient with

- Family history of VHL

- Any patient with two or more of the following
 - Haemoangioblastoma
 - Renal cell carcinoma
 - Pheochromocytoma
 - Endolymphatic sac tumour
 - Pancreatic cystadenoma
 - Pancreatic neuroendocrine tumour
 - Epididymal/adnexal cystadenoma

- Any patient with one or more
 - CNS haemangioblastomas
 - Pheochromocytoma
 - Endolymphatic sac tumour
 - Epididymal papillary cystadenoma

- Any patient with
 - Renal cell carcinoma diagnosed <40years old
 - Multiple renal cell ca
 - >1 pancreatic cystadenoma
 - >1 pancreatic neuroendocrine tumour

These patients should be seen in the out patient department and referred to the National Centre for Medical Genetics, Crumlin for genetic testing +/- genotyping

Screening protocol

Patients aged 12 to 21 years old:

Annual 24-hour urine collection for catecholamines
(Adrenaline/noradrenaline/metanephrin/normetanephrin/DOPA)

Initial baseline MR Adrenal glands/renal tract

Initial baseline MRI Brain/Spinal cord

Annual ophthalmoscopy until age 5, every 6 months thereafter

Patients aged over 21 years old

Annual urine collection for catecholamines

Annual renal ultrasound, looking for renal cell carcinoma

Annual detailed neurological examination

Six monthly ophthalmoscopy

Referral to ENT surgeons for baseline ear, nose and throat exam, including audiometry every 3 -5 years

Addendum

Screening frequency may be altered depending on individual patients.

References:

Created using a revised version of the Massachusetts General Hospital screening protocol for Von Hippel Lindau Disease. The VHL clinic at MGH.

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Figure 1
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