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Case Report

Hereditary Pheochromocytoma as a Main Manifestation of von Hippel Lindau Disease (vHL) in Childhood – A Long-term Follow-up of 5 Patients with vHL from One Family

Pasternak-Pietrzak K et al. Long-term Follow-up of 5 Patients with vHL

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What is already known on this topic?
The presentation of many lesions associated with vHL occurs in the third and fourth decades of life, however, the age range of initial manifestations is wide and children are particularly vulnerable, being at risk of developing hemangioblastomas and pheochromocytoma that can remain clinically occult until symptoms become severe. There is a lack of data in the literature regarding the long-term care of patients with vHL diagnosed with pheochromocytoma in childhood.

What this study adds?
We present five patients with vHL from one family with PHEO as the main manifestation of the disease with a very long follow-up (47 yrs (Patient 1); 32 yrs. (Patient 2); 27 yrs. (Patient 3); 1,5 yr (Patient 4) and 0,7 yr (Patient 5), respectively from the 1st PHEO diagnosis), which is unique in the literature on pediatric population.

Abstract
Von Hippel-Lindau disease (vHL) is a hereditary, autosomal dominant syndrome manifested by a predisposition to the occurrence of benign and malignant neoplasms. The spectrum of vHL-related neoplasms includes: pheochromocytoma (PHEO), central nervous system and retinal hemangioblastomas, renal clear cell carcinoma, epididymal cystadenomas, pancreatic neuroendocrine tumors as well as visceral (renal and pancreatic) cysts. We report the family (5 patients) with genetically confirmed vHL in which every member had PHEO diagnosed during pediatric care. The presented family had a missense variant in the *VHL* gene (ex1 g.A451G gene, p. S80G) which is connected with an increased risk of PHEO. Performing screening laboratory and imaging tests in patients with genetically confirmed vHL disease can help to avoid the occurrence of disease symptoms and to perform an elective surgery in safe conditions. Due to the risk of coexisting pathologies and the complexity of the disease, patients with vHL require long-term care.
Keywords: von Hippel-Lindau syndrome, pheochromocytoma, adrenal paraganglioma, metanephrines

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Background
Von Hippel-Lindau disease (vHL) is a hereditary, autosomal dominant syndrome manifested by a predisposition to the occurrence of benign and malignant neoplasms. vHL is caused by a highly penetrating mutation in the *VHL* gene (3p25.3), a classic suppressor gene. The spectrum of vHL-related neoplasms includes: pheochromocytoma (PHEO), central nervous system (CNS) and retinal hemangioblastomas (HB), renal clear cell carcinoma (RCC), epididymal cystadenomas, pancreatic neuroendocrine tumours (NETs) as well as visceral (renal and pancreatic) cysts [1]. The prevalence of vHL is up to one in 36.000 [2]. The prevalence of PHEO in vHL is estimated at 15-30%, these are usually benign tumours [3]. We report the family with genetically confirmed vHL in which every member had PHEO diagnosed during paediatric care.
Case presentation
Genetic pedigree of patients has been presented in Figure 1.
Case report 1 (Patient 1 - a mother of Patient 2 and 3)

An 18-year-old woman underwent subtotal right adrenalectomy (no detailed medical documentation available from this period) and was diagnosed with PHEO, confirmed by histopathological examination. At the age of 21, she was admitted to the internal medicine department due to the recurrence of hypertension, tachycardia, subfebrile states, poor heat tolerance and weight loss of 10 kg within 6 months. Daily noradrenaline, metoxycatecholamines and vanillylmandelic acid (VMA) excretion were elevated (Table 1). Abdominal computed tomography (CT) showed a nodular mass of about 4.5 cm in diameter at the upper area of the left kidney. She was treated with labetalol and was referred to the surgical institute for surgical treatment. Left-sided adrenalectomy was performed. She was treated with hydrocortisone (HC) and fludrocortisone. Replacement therapy was discontinued after eight years, when normal adrenal function was shown. At the age of 58 the patient was cured due to an adrenal crisis and since then she was treated with HC and fludrocortisone. Three years later abdominal magnetic resonance imaging (MRI) showed a lesion in pancreas which was confirmed in somatostatin receptor scintigraphy (SRS) and positron emission tomography (PET). A biopsy was performed and the microscopic image supported NET (G2). Due to lack of patient's consent for the surgery, treatment with somatostatin analogue - lanreotide has been started. Currently, the 65- year-old patient is still under endocrinological care for adults.

Case report 2 (Patient 2 - a mother of Patient 4 and 5)

A 13-year-old girl with a burdened family history (*VHL* mutation in her mother (Patient 1)) was admitted to the paediatric ward because of periodic increases of blood pressure (BP) with headaches for six months, excessive sweating and heart complaints (chest pain, palpitations) for the last two months. She was examined for tachycardia and elevated BP (up to 150/100 mmHg), which normalized after treatment with phenoxybenzamine and propranolol. Biochemically: elevated levels of noradrenaline, adrenaline and VMA in urine were found (Table 1). CT showed a large tumour measuring 4x4 cm in the central part of the right adrenal gland and a small nodule of about 1 cm in the lower part of the left adrenal gland. $^{131}I/^{123}I$-Metaiodobenzylguanidine (MIBG) scintigraphy revealed a large focus of tracer accumulation above the right kidney and a much smaller one on the left side. She was qualified for surgery. Right-sided adrenalectomy and subtotal left-sided adrenalectomy were performed. After surgery she developed symptoms of adrenal insufficiency and treatment with HC and fludrocortisone was started. The control tests (VMA in daily urine collection (DUC), catecholamines and metoxycatecholamines) **performed 45 days after surgery** were in the normal range. **Similarly like in the Patient 1, hormonal substitution with HC and fludrocortisone was not necessary after 13 months, the normal results of synthetic corticotropin test were documented earlier than in the Patient 1.** Due to the family history of PHEO (mother (Patient 1) and younger brother (Patient 3)), when the patient was 23 years old, all three family members underwent molecular tests - based on DNA analysis, a mutation in the *VHL* gene (*VHL*c.451 A/G) was found in every patient. At the age of 19 she completed endocrinological care at the Children's Memorial Health Institute (CMHI). Observation and research up to this point had not revealed other than PHEO vHL-related diseases. At the age of 35, abdominal CT showed a cystic-solid focal lesion 11x9 mm in the upper pole of the right kidney - suspicion of RCC. Wedge resection of the left kidney was performed - histopathologically - RCC G2. During intraoperative ultrasound, a focal lesion in the body of the pancreas was revealed, in endoscopic ultrasonography two solid, hypoechoic nodules were visualized in the head and body of the pancreas. The microscopic image of biopsy material suggested NET, which was confirmed after surgical removal of the lesions. At the age of 37, the patient was operated due to a spinal canal tumour - L3-L4 laminectomy was performed – histopathologically - HB. She also had laser photocoagulation due to retinal capillary HB. Moreover, at the age of 43 yrs, an endoscopic ultrasound revealed a few lesions in pancreas, the biopsy showed NET G1, which are under observation till now.

Case report 3 (Patient 3)

A patient with a positive family history (bilateral PHEO in his mother and sister) was under endocrinological care of CMHI since the age of 5. The patient, apart from sweating, had no symptoms. At the age of 5, the elevated values of noradrenaline and VMA in DUC were shown (Table 1). On the basis of extended hormonal and imaging (CT and MRI) diagnostics (Table 1), the boy was qualified for surgical treatment. At the age of 5.5, a complete resection of the left adrenal gland and removal of the right adrenal nodule was performed. **The normalization of catecholamines and metanephrines in DUC was confirmed 9 days after the surgery.**

About a year after the surgery, the patient experienced periodic severe abdominal pain, increased sweating, periodic headaches and constipation (with normal BP). On the basis of biochemical and radiological tests (MIBG scintigraphy and MRI) the diagnosis of PHEO recurrence was established. When the patient was 6 years 8 months, a resection of the right adrenal nodule was performed. Four months later, the boy was readmitted due to abnormal, increased urinary catecholamines, without typical for PHEO clinical symptoms. After performing imaging tests (CT and scintigraphy), the existence of a recurrence in the projection of the right adrenal gland was confirmed and the boy was qualified for resection of the right adrenal gland. **The normalization of catecholamines and metanephrines in DUC was confirmed 10 days after the surgery.** At the age of 18, the patient was diagnosed with severe hyponatremia (minimal sodium concentration - 92 mmol/l), syndrome of inappropriate antidiuretic hormone secretion and hypothalamus tumour (hypothalamic HB). The patient underwent neurosurgical operation.

Similarly like in his sister (Patient 2), during routine screening examinations, HB of vertebral body Th3 was detected in MRI as well as retinal capillary HB in the left eye. CT scan performed at the age of 25 showed foci with strong contrast enhancement in the pancreas. SRS showed active pathology in the pancreatic lesion, and MIBG scintigraphy showed increased accumulation of radiotracer in the pelvic projection corresponding to a paraganglioma. The concentration of normetanephrine in the blood plasma was almost 3 times above normal range. A cytological and histological biopsy of the pancreatic lesion confirmed NET of the pancreas. Total pancreaticoduodenectomy, splenectomy and surgical treatment of a pelvic tumour (a paraganglioma) were performed. The patient is treated with insulin due to diabetes, he remains under the care of an adult endocrinology centre.

Case report 4 (Patient 4 - a daughter of Patient 2)

A 5-year-old girl (a daughter of Patient 2) with genetically confirmed vHL syndrome (mutation in the *VHL* ex1 g.A451G gene, p. S80G) was under endocrine care at CMHI due to the family history of vHL. She has been screened for vHL related diseases since then. At the age of 13, the result of noradrenaline in DUC was abnormal. In the control DUC elevated levels of noradrenaline and plasma normetanephrine were found with the normal plasma concentration of metanephrines (Table 1). Chromogranin A and NSE (neuron-specific enolase) level were normal. The ambulatory BP monitoring was normal. After imaging diagnostics (MIBG scintigraphy, SRS, MRI of the abdomen, Figure 2), the patient was qualified for laparoscopic removal of focal lesions in the right adrenal gland. Right-sided adrenalectomy was performed after 10 days preparation with a selective alpha-blocker. Postoperative studies **performed 7 days after surgery** showed a decrease in noradrenaline concentration in DUC (63 µg/24h (8.3-51)), **and slightly elevated normetanephrine concentration** (161.07 pg/ml (<137 pg/ml)). The control studies performed 3 months after the surgery revealed the increase of noradrenaline in 24-hour urine collection (161.3 µg/24h (8.3 – 51.1)) and normetanephrine in the blood serum (385.5 pg/ml (<137)). 2-deoxy-2-[fluorine-18]fluoro-D-glucose (^{18}F-FDG) PET showed the presence of metabolically active hyperplastic changes in the left adrenal gland. Doxazosin treatment was started. The patient was qualified for laparoscopic partial adrenalectomy of the left side, which was performed successfully. The control studies **performed 12 days, 4 and 12 months after the surgery** revealed normal results of catecholamines in DUC, plasma metanephrines, chromogranin A and NSE. The patient remains under constant endocrinological care.

Case report 5 (Patient 5 - a son of Patient 2)

5-year-old boy known to be a carrier of the *VHL* mutation in the *VHL* ex1 g.A451G gene, p. S80G has been under endocrine care since he was 4 years old. The genetic testing was performed due to vHL in his mother, uncle and sister. His laboratory tests were normal until the age of 5, when the results of catecholamines in DUC during routine check-up visits were significantly elevated (NA in DUC: 966.0 and 1248.5 µg/24h (normal range: 8.3-51.1)), plasma normetanephrine 5259.75 pg/ml (normal range 31-257), Table 1. Chromogranin A and NSE results were also above normal. Abdominal CT showed two focal, solid lesions in the left adrenal gland, with dimensions 22x23x23 mm and 14x14x15 mm with strong contrast enhancement. SRS revealed a lesion with a discreetly increased expression of receptors in the projection of the left adrenal gland. PET examination showed a polycyclic lesion in the left adrenal gland with pathological accumulation of [18]-FDG, the possibility of another lesion above (Figure 3). BP values were above 95 percentile. There were no significant signs of organ damage caused by hypertension. Doxazosin was added to the treatment in a gradually increased dose. In Holter ECG sinus tachycardia was diagnosed - propranolol at a dose of 3x5 mg/day was started. A partial left-sided adrenalectomy was performed laparoscopically. The control studies performed respectively: **3 weeks**, 3 months and 8 months after the surgery revealed normal results of catecholamines in DUC, plasma metanephrines, chromogranin A and NSE. The patient remains under constant endocrinological care.

In all patients postoperative histopathological examinations of the adrenal glands revealed a tumour corresponding to an adrenal paraganglioma (PHEO).

Discussion

A clinical diagnosis of vHL can be established in one of two situations: (1) in a patient with a family history of vHL and the presence of a CNS or retinal HB, PHEO, or RCC; or (2) in a simplex case (a patient with no family history) with 2 HB or 2 visceral tumours or one HB and one visceral tumour [4]. The gold standard for vHL diagnosis is identification of a pathogenic variant in the *VHL* gene, which confirms the clinical diagnosis [5].

The nomenclature and classifications of paragangliomas has changed. In the old classification there were: PHEO and paraganglioma: head and neck or sympathetic. In the new one there are: adrenal paraganglioma („PHEO"), sympathetic abdominal paraganglioma, sympathetic head and neck paraganglioma and parasympathetic paraganglioma [6].

The presentation of many lesions associated with vHL occurs in the third and fourth decades of life, however, the age range of initial manifestations is wide and children are particularly vulnerable, being at risk of developing HB and PHEO that can remain clinically occult until symptoms become severe [7, 8]. The lifetime risk of developing PHEO in patients with vHL is 10-25% [9]. Data about vHL manifestation in children and adolescents (such as age at first manifestation, manifestation frequencies, and types) are limited. Launbjerg K et al. evaluated 99 patients who had started surveillance before 18 years (37 Danish vHL patients and 62 international patients described in 15 articles) [10]. Seventy percent of patients developed manifestations before 18 years (median age at first manifestation: 12 years (range: 6–17 years)). The majority of manifestations were asymptomatic and only found because of surveillance. Thirty per cent (30 of 99) had developed more than one manifestation type; the most frequent were retinal (34%) and CNS (30%) HB. Eighteen percent of patients developed PHEO before the age of 18. In the family described in the presented article all patients were recognized with PHEO before the age of 18. The PHEO diagnosis was the first diagnosis related to vHL syndrome in all patients. Patient 3 had been recognised for HB of the hypothalamus at the age of 18, whereas all other vHL-related disorders were recognised in 3 other patients (Patient 1, Patient 2 and Patient 3) in their adulthood. The most common disease, apart from PHEO, was NET of the pancreas (Patient 1, Patient 2 and Patient 3), which was recognized in these patients at the age of 61, 43 and 25 years, respectively.

According to the available literature, the youngest patient with vHL was 2.75 years old at the moment of PHEO diagnosis, and the mean age of PHEO diagnosis in vHL patients is 27 years [9].

In the presented family the youngest patients (Patient 3 and Patient 5) were 5-year-old, and the oldest patient (Patient 1) at the moment of PHEO diagnosis was 18-year-old. Fugaru I. et al reported rapidly progressing PHEO in siblings, the diagnosis was at the age of 7 and 11, respectively [11]. In the cited article both brothers presented with large PHEOs, despite routine screening. The authors conclude that a more accelerated surveillance protocol may be adequate for vHL families with a high PHEO risk, which is typical for vHL patients with missense mutations.

In the analysis by Libutti et al. of 389 patients with vHL the mean age of diagnosis of NET of pancreas was 35 years and the youngest patient was 16 years old at the moment of diagnosis [12]. In the family presented in this article the youngest patients with NET of pancreas diagnosis was 25 years old.

vHL is a result of pathogenic variants in the *VHL* gene [5]. About 80% of patients with vHL disease have an affected parent, and about 20% result from a *de novo* pathogenic variant [5]. In the presented patients the mutations came from an affected parent (however, there is no data about parents of Patient 1). Clinically, vHL is subdivided into five subtypes based on tumour spectrum as well as mutation type [13]. **Clinical manifestation of type I are: retinal angioma, CNS HB, RCC, pancreatic NETs. Type IB is characterised by the occurrence of retinal angioma, CNS HB, pancreatic NETs (the risk for PHEO and RCC is low). In type IIA PHEO, retinal angioma, CNS HB occur, the risk for RCC is low.**

In type IIB and IIC the risk of PHEO is high. Moreover, the occurrence of retinal angioma, CNS HB, pancreatic cysts, pancreatic NETs, RCC is characteristic for type IIB and the occurrence of CNS HB for type IIC (pancreatic NETs are rare in type IIC) [13].

The type of variant in the *VHL* gene accounts for differences in PHEO risk, with a strong genotype – phenotype correlation [14]. Truncating variants or exon deletions in the *VHL* gene are identified among individuals with vHL type I and are associated with a relatively low risk of PHEO [14]. In contrast, vHL type II is associated with missense variants that generally do not affect the protein structure and are associated with a relatively higher risk of PHEO [14]. **Interestingly, missense mutations that cause amino-acid changes on the surface of VHL gene product (pVHL) appear to have a higher risk for PHEO than missense mutations occurring deep within the protein. Surface missense mutations also appear to have a higher risk for PHEO than deletions, nonsense and frameshift mutations [15]. Germline mutations that lead to a truncated pVHL are associated with a 40% higher risk of developing RCC comparing to patients with germline missense mutations [16]. An earlier onset of CNS HB in patients with a truncating variant was described, while missense variants predispose for an earlier onset of PPGL [17].**

The presented family had a missense variant in the *VHL* gene (ex1 g.A451G gene, p. S80G) and in every patient PHEO occurred before their adulthood. In four patients (Patient 1,2,3 and 4) PHEO was bilateral, the last patient (Patient 5) is the youngest in this family (6-years-old at the moment of the last follow-up) and he is at high risk of developing PHEO in the contralateral adrenal gland.

Screening strategies for PHEO and other tumours in patients with a *VHL* mutation include an annual clinical examination and an annual determination of urinary or plasma methoxycatecholamines. However, there are different recommendations for paediatric screening procedures, including the age at which screening should begin, the conditions under which imaging is performed, and the frequency of these examinations. Table S1 summarizes recommendations for screening patients with vHL from the VHL Alliance consensus panel consisting of clinicians covering all fields of expertise involved in the management of vHL (see Supplementary Material, Table S1) [18].

Based on the fact that patients with type 2 vHL have an increased risk of PHEO, biochemical screening with plasma-free metanephrines for children harbouring *VHL* missense pathogenic variant has been proposed to start immediately after genetic diagnosis and not only after 5 years old [19]. The presented patients' history confirms this recommendation.

Conclusions

Performing screening laboratory tests and imaging tests in patients with genetically confirmed vHL can help avoid the occurrence of disease symptoms and to perform an elective surgery in safe conditions. Due to the risk of coexisting pathologies and the complexity of the disease, as well as for monitoring small asymptomatic lesions for evidence of progression, patients with vHL require long-term care.

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Table 1. Laboratory and imaging tests before PHEO surgery

	Patient 1	Patient 2	Patient 3	Patient 4		Patient 5
age at the moment of PHEO surgery [yrs]	21 (date of left adrenalectomy)	13	5.5	13 yrs 10 mo (date of right adrenalectomy)	14 yrs 3 mo (date of left adrenalectomy)	5
NA in DUC [µg/d]	1749 (↑)	1127 (↑)	606 (N: <44)	121.5 (N: 8.3-51)	161.3 (N: 8.3-51)	1248.5 (N: 8.3-51.1)
A in DUC [µg/d]	normal	37.7 (↑)	normal	4.1 (N: 1.3-14.5)	5.7 (N: 1.3-14.5)	
VMA in DUC	25.2 mg/d (↑)	16.6 mg/d (↑)	14.7 mg/d (↑)	5.2 (2-5.2)	4.5 (2-5.2)	
Normetanephrine in plasma	3000	3465 µg/d (↑)	1890 µg/d (↑)	295 pg/ml (N: <137)	385.5 pg/ml (N: <137)	5259.75 pg/ml (N: 31-257)
Metanephrine in plasma				27.17 pg/ml (N <75)	10.75 pg/ml (N <75)	
Abdominal ultrasonography	-	a heterogeneous, hyperechoic mass with a		normal	-	two solid, abnormal masses between the

		narrow hypoechoic rim measuring 5x3.6x3cm in the right adrenal area				tail of the pancreas and the left kidney without any connection, size 20x20x25mm and 12x9.5x14.5 mm.
Abdominal CT	At the upper pole of the left kidney there is a nodular mass with a diameter of approximately 4.5 cm. Density measurement shows greater tumor saturation in the marginal layers and less in the central part.	a large tumor measuring 4x4 cm with necrosis in the central part of the right adrenal gland and a small nodule of about 1 cm in the lower part of the left adrenal gland	quite large, medium shape, with quite uneven averages	-	-	two focal, solid lesions in the left adrenal gland, with dimensions 22x23x23 mm and 14x14x15 mm with strong contrast enhancement
MRI of the abdomen	-		a nodule (size 25x24x21mm) emerging from the lower part of the left adrenal gland; in the part of the right adrenal gland a nodule of similar morphology, measuring about 9x7 mm	A lesion in the upper part of the right adrenal gland approx. 11x 9 mm ax x 13 mm cc, and in the lower part, size 5 mm, also within the left adrenal gland, small nodules with features of contrast enhancement, size up to 7mm	Progression of the previously described nodules in the left adrenal gland (the largest ones 14x12x12mm and 8x7x7mm, other small ones up to 5mm)	
SRS	-			The scintigraphic image shows no signs of changes with increased expression of somatostatin receptors	-	A lesion with a discreetly increased expression of receptors in the projection of the left adrenal gland somatostatins.
MIBG scintigraphy	-	a large focus of tracer accumulation above the right kidney and a much smaller one on the left side.		In the projection of the right adrenal gland, a focus of abnormal increased tracer accumulation. No increased tracer accumulation in the left adrenal gland	-	

18F-FDG PET/CT	-				Presence of metabolically active changes in the left adrenal gland - of a hyperplastic nature, in other areas there are no signs of hyperplastic changes	A polycyclic lesion in the left adrenal gland with pathological accumulation of [18]-FDG, the possibility of another lesion above

NA - noradrenaline, DUC - daily urine collection, VMA - vanillylmandelic acid, MIBG - $^{131}I/^{123}I$-Metaiodobenzylguanidine

Recommendations for screening patients with vHL from the VHL Alliance consensus panel [14]:

Surveillance Modality (Tumors being screened)	**AGE[1]**						**Pregnancy[11]**
	<5 years	**Beginning at age 5y**	**Beginning at age 11y**	**Beginning at age 15y**	**Beginning at age 30y**	**Beginning at age 65y[1]**	
History and Physical Examination[2]	Yearly from age 1 year	Yearly	Yearly	Yearly	Yearly	Yearly	Prior to conception[11]
Blood Pressure and Pulse (Pheochromocytomas/paragangliomas)	Yearly from age 2 years	Yearly	Yearly	Yearly	Yearly	Yearly	Prior to conceptionr[11]
Dilated Eye Examination[3] (Retinal Hemangioblastomas)	Every 6-12 months, beginning before age 1 year	Every 6-12 months	Every 6-12 months	Every 6-12 months	Yearly	Yearly	Prior to conception, then Every 6-12 months[11]
Metanephrines[4] (Pheochromocytomas/paragangliomas)	——	Yearly	Yearly	Yearly	Yearly	Stop routine[1]	Prior to conception[11]
MRI Brain and Spine w/wo Contrast[5,6,7] (CNS Hemangioblastomas)	——	——	Every 2 years[8]	Every 2 years[8]	Every 2 years[8]	Stop routine[1]	Prior to conception[11]
Audiogram (Endolymphatic sac tumors)	——	——	Every 2 years	Every 2 years	Every 2 years	Stop routine[1]	——
MRI Abdomen w/wo Contrast[5,6,7] (Renal cell carcinomas, Pheochromocytomas/paragangliomas, Pancreatic neuroendocrine tumors/cysts)	——	——	——	Every 2 years[9]	Every 2 years[9]	Stop routine[1]	Prior to conception[11]
MRI Internal Auditory Canal[10] (Endolymphatic sac tumors)	——	——	——	Once	——	——	No specific changes

1. Beginning at age 65, routine laboratory and radiologic screening for patients who have never had specific VHL manifestations may cease. With the exception of routine physical examination and ophthalmologic assessment, this applies to all other routine screening/surveillance tests in asymptomatic patients. However, patients presenting with signs/symptoms should be evaluated with appropriate testing/imaging regardless of age.

2. Age-appropriate history and physical examination to include: Neurologic examination, auditory and vestibuloneural questions and testing, visual symptoms, catecholamine excess symptom assessment (headaches, palpitations, diaphoresis, hyperactivity, anxiety, polyuria, abdominal pain).

3. Dilated, in-person eye examination including ophthalmoscopy to occur every 6-12 months based on quality of examination obtained (especially in a child) and perceived adherence to follow-up. Consider examination under anesthesia in young children in whom a detailed eye examination cannot be adequately obtained in the clinic. Consider including ultrawidefield photography and ultrawidefield fluorescein angiography, but these should not replace a dilated eye examination with a specialist with experience in retinal manifestations of VHL.

4. Plasma free metanephrines (preferred, due to its higher sensitivity) or fractionated 24-hour urinary free metanephrines.

5. Use macrocyclic/class II gadolinium-based contrast agents. MRI of the neuroaxis may be obtained at the same time as MRI abdomen, and may be performed under a single long anesthesia event, especially in children. However, both the neuroaxis protocol and the abdominal protocols

should be obtained consecutively. It is NOT recommended to evaluate the spine solely using an abdominal protocol MRI, nor is it recommended to evaluate the abdominal organs solely using a neuroaxis protocol. See footnote #6 and #7 for how to combine these protocols.

6. Based on contraindications (metallic implants, renal failure, etc.), the following order of imaging priority applies: MRI (with and without contrast) > MRI (without contrast) > CT (with contrast) > CT (without contrast) > US (kidneys, adrenals and pancreas only) > Endoscopic US (pancreas only). See also footnote #5 and #7.

7. Timing of contrast administration when imaging multiple organ systems together should be as follows: Obtain non-contrasted images of CNS and abdomen first, then give contrast using a power injector and perform multi-phase contrast-enhanced imaging of the abdomen including pancreas and kidneys during the late arterial phase and delayed venous phases. Then late post-contrast imaging of neuroaxis. See also footnote #5 and #6.

8. If no CNS hemangioblastomas, continue routine surveillance every 2 years. If hemangioblastomas are present and there is an increase in hemangioblastoma size, or if the patient has associated symptoms, scans should be yearly (or more frequently), as appropriate (or referred to neurosurgery).

9. If no renal lesions present on initial scan, continue routine surveillance every 2years. If small tumors (< 3 cm) found, reimage initially with MRI every 3-6 months to determine stability. Once stability has been determined over 3 consecutive scans, consider extending to every 2 years. If renal mass is > 3 cm, consider a referral to a urologist (preferably familiar with the care of VHL).

10. High-resolution (1mm slice thickness) magnetic resonance imaging of the internal auditory canal. This baseline MRI of the internal auditory canal should be obtained after age 15 years (once the temporal bones have matured), and it should be added onto the MRI of the neuroaxis conducted between ages 15-20 years.

11. “Prior” indicates that this surveillance testing should ideally be performed prior to any planned conception, if possible. MRIs performed during pregnancy should be without contrast.

Figure 1. Genetic pedigree of patients A - Patient 1, B - Patient 2, C - Patient 3, D - Patient 4, E - Patient 5

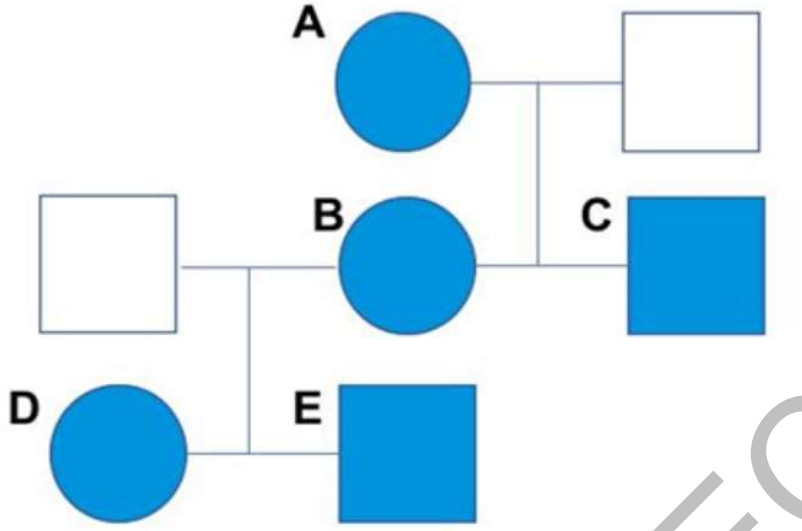

Figure 2. MRI of the abdomen, Patient 4 - a lesion in the upper part of the right adrenal gland (arrow) approx. 11x 9mm ax x 13 mm cc, and in the lower part, size 5 mm, also within the left adrenal gland, small nodules with features of contrast enhancement, size up to 7mm

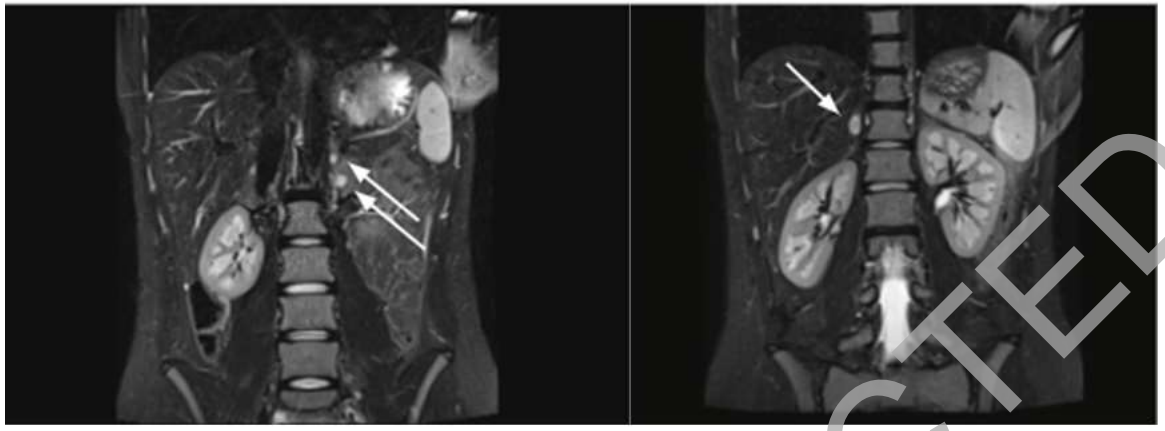

Figure 3. PET, Patient 5. A polycyclic lesion in the left adrenal gland with dimensions 22x20 mm with pathological accumulation of [18]-FDG (SUV max. FDG = 13,4), above: the possibility of another lesion of dimensions 13x11mm (SUV max FDG=13,4)