CASE REPORT

JCRPE Journal of Clinical Research in Pediatric Endocrinology

DOI: 10.4274/jcrpe.galenos.2024.2024-2-1
J Clin Res Pediatr Endocrinol 2026;18(Suppl 1):12-19

Hereditary Pheochromocytoma as a Major Manifestation of von Hippel Lindau Disease (vHL) in Childhood: Long-term Follow-up of Five Patients with vHL from One Family

Katarzyna Pasternak-Pietrzak, Agata Kozłowska, Elżbieta Moszczyńska

The Children's Memorial Health Institute (CMHI), Department of Endocrinology and Diabetology, Warsaw, Poland

Cite this article as: Pasternak-Pietrzak K, Kozłowska A, Moszczyńska E. Hereditary pheochromocytoma as a major manifestation of von Hippel Lindau disease (vHL) in childhood: long-term follow-up of five patients with vHL from one family. J Clin Res Pediatr Endocrinol. 2026;18(Suppl 1):12-19

What is already known on this topic?

The presentation of many lesions associated with von Hippel-Lindau disease (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 (PHEO) that can remain clinically occult until symptoms become severe. There is a lack of published data regarding the long-term care of patients with vHL diagnosed with PHEO in childhood.

What this study adds?

We present five patients with vHL from one family with PHEO diagnosed in childhood. PHEO was the main manifestation of the disease and extensive follow-up data [47 yrs (Patient 1); 32 yrs (Patient 2); 27 yrs (Patient 3); 1.5 yrs (Patient 4) and 0.7 yrs (Patient 5), respectively] from the first PHEO diagnosis is available. This duration of follow-up data is unique in the literature concerning the pediatric vHL 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, and pancreatic neuroendocrine tumors, as well as visceral, especially renal and pancreatic, cysts. We report a single family including five 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 (exon 1, g.A451G, p.S80G) which has been connected with an increased risk of PHEO. Performing screening laboratory and imaging tests in patients with genetically confirmed vHL

Corresponding Author: Katarzyna Pasternak-Pietrzak, MD, PhD, The Children's Memorial Health Institute (CMHI), Department of Endocrinology and Diabetology, Warsaw, Poland
E-mail: k.pasternak-pietrzak@ipczd.pl **ORCID:** orcid.org/0000-0001-9602-5023
Conflict of interest: None declared.
Received: 17.04.2024 **Accepted:** 24.08.2024 **Epub:** 23.09.2024 **Publication Date:** 22.05.2026

may help to avoid the occurrence of disease symptoms and to perform elective surgery under 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

Introduction

Von Hippel-Lindau disease (vHL) is a hereditary, autosomal dominant syndrome manifested by a predisposition to the occurrence of benign and malignant neoplasms. It is caused by a highly penetrant mutation in the *VHL* gene (3p25.3), a classic example of a 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; and pancreatic neuroendocrine tumours (NETs), as well as visceral cysts especially affecting the renal system and pancreas (1). The prevalence of vHL is as high as 1:36,000 (2). The prevalence of PHEO in vHL is estimated at 15-30%; these are usually benign tumours (3). We report a single family with genetically confirmed vHL in which every member had PHEO diagnosed during pediatric care.

Case Report

Genetic pedigree of patients is shown in Figure 1.

Case 1

(Patient 1- the mother of Patients 2 and 3). An 18-year-old woman underwent subtotal right adrenalectomy. Unfortunately, there is no detailed medical documentation available from this period, but she was subsequently diagnosed with PHEO, confirmed by histopathological examination. At the age of 21 years, she was admitted to the internal medicine department due to the recurrence of hypertension, tachycardia, subfebrile episodes, poor heat tolerance and weight loss of 10 kg within six 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 evident. At the age of 58 yrs the patient was admitted due to an adrenal crisis and since then she has been treated with HC and fludrocortisone. Three years later abdominal magnetic resonance imaging (MRI) showed a lesion in her pancreas which was confirmed by somatostatin receptor scintigraphy (SRS) and positron emission tomography (PET). A biopsy was performed and the histopathology suggested a diagnosis of NET (G2). Due to lack of patient's consent for the surgery, treatment with somatostatin analogue (lanreotide) was started. Currently, she is 65 years old and continues under the care of adult endocrinology.

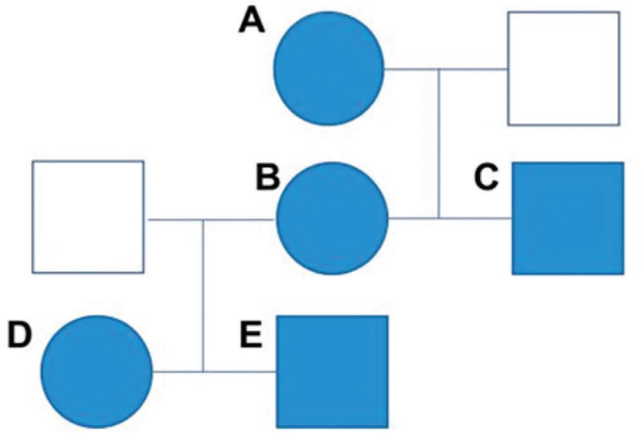

Figure 1. Genetic pedigree of patients. A) Patient 1, B) Patient 2, C) Patient 3, D) Patient 4, E) Patient 5

Case 2

(Patient 2- the mother of Patients 4 and 5). A 13-year-old girl with a confirmed family history of vHL (*VHL* mutation in her mother, Patient 1) was admitted to the pediatric ward because of periodic increases in blood pressure (BP) with headaches for six months, excessive sweating and cardiac symptoms (chest pain, palpitations) for the last two months. She was investigated for tachycardia and elevated blood pressure (up to 150/100 mmHg), which normalized after treatment with phenoxybenzamine and propranolol. Biochemically, she had elevated levels of noradrenaline, adrenaline and VMA in urine (Table 1). CT showed a large tumor 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 eligible 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 monitoring tests [VMA in daily urine collection (DUC), catecholamines and metoxycatecholamines] performed 45 days after surgery were in the normal range. Similarly to her mother, Patient 1, replacement with HC and fludrocortisone was not necessary after 13 months, and normal results of a

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 µg/d (↑)	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 narrow hypoechoic rim measuring 5x3.6x3cm in the right adrenal area		Normal	-	Two solid, abnormal masses between the 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 25x24x21 mm) 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 7 mm	Progression of the previously described nodules in the left adrenal gland (the largest ones 14x12x12 mm and 8x7x7 mm, other small ones up to 5 mm)	
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.

Table 1. Continued

	Patient 1	Patient 2	Patient 3	Patient 4		Patient 5
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

PHEO: pheochromocytoma, NA: noradrenaline, DUC: daily urine collection, VMA: vanillylmandelic acid, MRI: magnetic resonance imaging, SRS: somatostatin receptor scintigraphy, MIBG: $^{131}I/^{123}I$-Metaiodobenzylguanidine, 18F-FDG PET/CT: fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography

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. DNA analysis showed a mutation in the *VHL* gene (*VHLc*.451 A/G) which was present in all three patients. At the age of 19 years she completed endocrinological care at the Children's Memorial Health Institute (CMHI). Observation and investigation up to this point had not revealed any other problems apart from PHEO in terms of vHL-related diseases. At the age of 35 years, abdominal CT showed a cystic-solid focal lesion 11x9 mm in the upper pole of the right kidney which was suspicious for RCC. Wedge resection of the left kidney was performed and histopathology reported RCC G2. During intraoperative ultrasound, a focal lesion in the body of the pancreas was also identified. On endoscopic ultrasonography, two solid, hypoechoic nodules were visualized in the head and body of the pancreas. The histopathology of biopsy material suggested NET, which was confirmed after surgical removal of the lesions. At the age of 37 years, the patient was operated due to a spinal canal tumor and an L3-L4 laminectomy was performed. Once again, histopathology reported HB. She also had laser photocoagulation due to retinal capillary HB. Moreover, at the age of 43 years, an endoscopic ultrasound revealed some new lesions in her pancreas, the biopsy showed NET G1, and these are currently under observation.

Case 3

(Patient 3). A patient with a positive family history (bilateral PHEO in his mother and sister) was under endocrinological care at CMHI from the age of five years. The patient, apart from sweating, had no symptoms. However, at the age of five years, biochemistry reported elevated values of noradrenaline and VMA in DUC (Table 1). On the basis of extended hormonal and imaging (CT and MRI) diagnostics (Table 1), this boy was eligible for surgical treatment. At the age of 5.5 years, a complete resection of the left adrenal gland and removal of a right adrenal nodule was performed. The normalization of catecholamines and metanephrines in the urine was biochemically confirmed nine days after this surgery.

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

Similar to his sister (Patient 2), during routine screening examinations, HB of the T3 vertebral body was detected

on MRI, as well as a retinal capillary HB in the left eye. A CT scan performed at the age of 25 years 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 three-fold greater than the upper limit of normal. A cytological and histological biopsy of the pancreatic lesion confirmed NET of the pancreas. Total pancreaticoduodenectomy, splenectomy and surgical treatment of a pelvic paraganglioma were performed. The patient is currently treated with insulin due to diabetes and he remains under the care of an adult endocrinology centre.

Case 4

(Patient 4- a daughter of Patient 2). A 5-year-old girl, the daughter of Patient 2, with genetically confirmed vHL (same mutation in the *VHL* ex1 g.A451G, p.S80G) was under endocrine care at CMHI because of the strong family history of vHL. She has been screened for vHL-related diseases since the age of five years. At the age of 13 years, 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 neuron-specific enolase (NSE) levels were normal., and ambulatory BP monitoring were within normal limits. Ambulatory BP monitoring was normal. After imaging diagnostics (MIBG scintigraphy, SRS, MRI of the abdomen, see Figure 2), laparoscopic removal of focal lesions in the right adrenal gland was planned. Right-sided adrenalectomy was performed after 10 days preparation with a selective alpha-blocker. Postoperative studies performed seven days after surgery showed a decrease in noradrenaline concentration in DUC of 63 µg/24 h (NR 8.3-51), and slightly elevated normetanephrine concentration of 161.07 pg/mL (NR<137 pg/mL). The follow-up studies performed three months after surgery revealed an increase of noradrenaline in 24-hour urine collection of 161.3 µg/24 h (NR 8.3-51.1) and normetanephrine in blood serum of 385.5 pg/mL (NR<137 pg/mL). Imaging with 2-deoxy-2-[fluorine-18]fluoro-D-glucose PET showed the presence of metabolically active hyperplastic changes in the left adrenal gland. Doxazosin treatment was started. The patient underwent laparoscopic partial adrenalectomy of the left side, which was performed successfully. Follow-up studies performed 12 days, and at four 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 5

(Patient 5- a son of Patient 2). A 5-year-old boy, known to be a carrier of the *VHL* mutation (g.A451G, p.S80G) was under endocrine from the age of 4 years. Genetic testing was performed due to vHL in his mother, uncle and sister. His laboratory tests were normal until the age of five years, when the results of catecholamines in DUC during routine follow-up were significantly elevated with noradrenaline in DUC of 966.0 and 1248.5 µg/24 h (NR 8.3-51.1, plasma normetanephrine 5259.75 pg/mL (NR 31-257 pg/mL) (Table 1). Chromogranin A and NSE results were also raised. Abdominal CT showed two focal, solid lesions in the left adrenal gland, with dimensions of 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 multilobulated lesion in the left adrenal gland with pathological accumulation of [18]-fluoro-D-glucose and the possibility of another lesion above (Figure 3). BP values were above the 95th percentile. There were no significant signs of organ damage caused by hypertension. Doxazosin was added to the treatment in a gradually increasing dose. On Holter electrocardiogram, sinus tachycardia was diagnosed and propranolol at a dose of 3x5 mg/day was started. A partial left-sided adrenalectomy was performed laparoscopically. Follow-up studies performed at three weeks, three months and eight months after the surgery revealed normal results for catecholamines in DUC, plasma metanephrines, chromogranin A and NSE. The patient remains under constant endocrinological care.

In all five patients postoperative histopathological examination of the adrenal glands revealed a tumor corresponding to an adrenal paraganglioma (PHEO).

Discussion

A clinical diagnosis of vHL can be established in one of two ways. These are: (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 two HB or two visceral tumours or one HB and one visceral tumor (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 classification 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 often occurs in the third and fourth decades of life, but 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 regarding vHL manifestation in

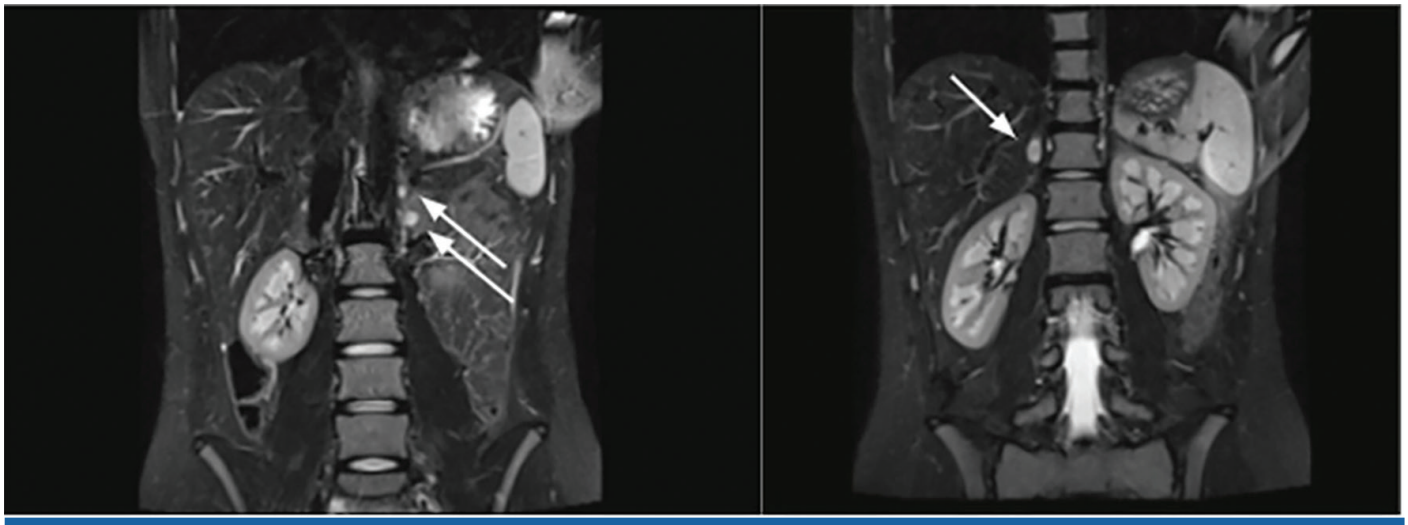

Figure 2. MRI of the abdomen, Patient 4- a lesion in the upper part of the right adrenal gland (arrow) approx. 11x 9 mm ax x 13 mm cc, and in the lower part, size 5 mm, also within the left adrenal gland, small nodules with features of contrast enhancement, size up to 7 mm
MRI: magnetic resonance imaging

children and adolescents, including age at first manifestation, manifestation frequencies, and types, are limited. Launbjerg et al. (10) evaluated 99 patients who had started surveillance before 18 years of age, including 37 Danish vHL patients and 62 international patients described in 15 articles). Seventy percent of patients developed manifestations before 18 years, with a median (range) age at first manifestation of 12 (6-17) years. The majority of manifestations were asymptomatic and only detected because of vHL surveillance. Thirty per cent (30 of 99) had developed more than one manifestation type, with the most frequent being retinal (34%) and CNS (30%) HBs. Eighteen percent of patients developed PHEO before the age of 18 years. In the family described in the presented article all patients were diagnosed with PHEO before the age of 18 years and this diagnosis was the first related to vHL syndrome in all patients. Patient 3 had hypothalamic HB at the age of 18 years, whereas all other vHL-related disorders, excluding PHEO, were recognised in three other patients (Patient 1, Patient 2 and Patient 3) in adulthood. The most common manifestation, apart from PHEO, was NET of the pancreas (Patient 1, Patient 2 and Patient 3), which was diagnosed in these patients at the ages of 61, 43 and 25 years, respectively.

The youngest reported patient with vHL was 2.75 years old at diagnosis of PHEO, 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 five years old, and the oldest patient (Patient 1) was 18 years old at the time of PHEO diagnosis. Fugaru et al. (11) reported rapidly progressing PHEO in siblings, and diagnosis was made at the ages of 7 and 11 years, respectively. In the cited article both brothers presented with large PHEOs, despite routine screening.

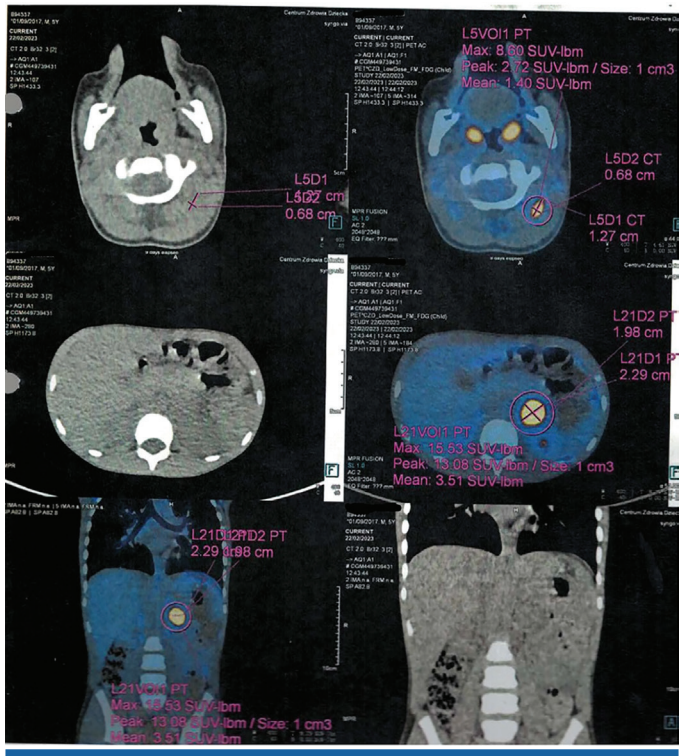

Figure 3. PET, Patient 5. A polycyclic lesion in the left adrenal gland with dimensions 22x20 mm with pathological accumulation of [18]-FDG (SUV_{max} FDG=13.4), above: the possibility of another lesion of dimensions 13x11 mm (SUV_{max} FDG=13.4)
PET: positron emission tomography, [18]-FDG: fluorine-18 fluorodeoxyglucose, SUV_{max}: maximum standardized uptake value

The authors concluded that a more frequent surveillance protocol may be appropriate for vHL families with a high risk of PHEO, which is typical for vHL patients with missense mutations.

In the analysis by Libutti et al. (12) of 389 patients with vHL the mean age of diagnosis of pancreatic NET was 35 years and the youngest patient was 16 years old at the time of diagnosis. In the family presented in this article, the youngest patients was 25 years old when NET of pancreas was diagnosed.

vHL results from pathogenic variants in the *VHL* gene (5). About 80% of patients with vHL have an affected parent, and about 20% result from a *de novo* pathogenic variant (5). The mutations were inherited from an affected parent in the patients presented (but there is no data about the parents of Patient 1).

Clinically, vHL is subdivided into five subtypes based on tumor spectrum, as well as mutation type (7). Clinical manifestation of type I are: retinal angioma, CNS HB, RCC, pancreatic NETs. Type IB is characterized by the occurrence of retinal angioma, CNS HB, and pancreatic NETs while the risk for PHEO and RCC is low.

In type IIA PHEO, retinal angioma and CNS HB occur, while 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, and RCC is characteristic for type IIB and the occurrence of CNS HB is characteristic for type IIC although pancreatic NETs are rare in type IIC (7).

The type of variant in the *VHL* gene accounts for differences in PHEO risk, with a strong genotype-phenotype correlation (13). Truncating variants or exon deletions in the *VHL* gene are reported among individuals with vHL type I and are associated with a relatively low risk of PHEO (13). 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 (13). Interestingly, missense mutations that cause amino-acid changes on the surface of the *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, non-sense and frameshift mutations (14). Germline mutations that lead to a truncated pVHL are associated with a 40% higher risk of developing RCC compared to patients with germline missense mutations (15). An earlier onset of CNS HB in patients with a truncating variants has been described, while missense variants predispose for an earlier onset of parasympathetic paraganglioma (PPGL) (16).

The presented family had a missense variant in the *VHL* gene (exon 1 g.A451G, p.S80G) and in every patient PHEO occurred before adulthood. In four patients (Patients 1, 2, 3 and 4) PHEO was bilateral, the last patient (Patient 5) is the youngest in this family (6-years-old at the time 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* mutations include an annual clinical examination and an annual determination of urinary or plasma methoxycatecholamines. However, there are different recommendations for pediatric 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 (17).

Given that patients with type II vHL have an increased risk of PHEO, biochemical screening with plasma-free metanephrines in children harboring *VHL* missense pathogenic variant has been proposed to start immediately after genetic diagnosis, rather than after 5 years old (18). The presented patients' history supports this recommendation.

Conclusion

Performing screening laboratory tests and imaging tests in patients with genetically confirmed vHL may help avoid the occurrence of disease symptoms and enable the performance of elective rather than emergency surgery. Due to the risk of coexisting pathologies and the complexity of the disease, patients with vHL require long-term care including monitoring of small asymptomatic lesions for evidence of progression.

Ethics

Informed Consent: Informed consent for publication was obtained from the patient's parents.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Katarzyna Pasternak-Pietrzak, Agata Kozłowska, Elżbieta Moszczyńska, Concept: Katarzyna Pasternak-Pietrzak, Agata Kozłowska, Elżbieta Moszczyńska, Design: Katarzyna Pasternak-Pietrzak, Agata Kozłowska, Elżbieta Moszczyńska, Data Collection or Processing: Katarzyna Pasternak-Pietrzak, Agata Kozłowska, Elżbieta Moszczyńska, Analysis or Interpretation: Katarzyna Pasternak-Pietrzak, Agata Kozłowska, Elżbieta Moszczyńska, Literature Search: Katarzyna Pasternak-Pietrzak, Writing: Katarzyna Pasternak-Pietrzak, Agata Kozłowska, Elżbieta Moszczyńska.

Financial Disclosure: The authors declared that this study received no financial support.

Supplementary Table: https://d2v96fxpocvxx.cloudfront.net/cf9d60d6-523c-458a-a2e6-78728d3ffbb0/content-images/a4e359fe-79fe-42d6-b84a-1a8dacc90252.pdf

References

1. Chittiboina P, Lonser RR. Von Hippel-Lindau disease. Handb Clin Neurol. 2015;132:139-156.
2. Binderup ML, Galanakis M, Budtz-Jørgensen E, Kosteljanetz M, Luise Bisgaard M. Prevalence, birth incidence, and penetrance of von Hippel-Lindau disease (vHL) in Denmark. Eur J Hum Genet. 2017;25:301-307. Epub 2016 Dec 14
3. Feletti A, Anglani M, Scarpa B, Schiavi F, Boaretto F, Zovato S, Taschin E, Gardi M, Zanoletti E, Piermarocchi S, Murgia A, Pavesi G, Opocher G. Von Hippel-Lindau disease: an evaluation of natural history and functional disability. Neuro Oncol. 2016;18:1011-1020. Epub 2016 Jan 12
4. Lonser RR, Glenn GM, Walther M, Chew EY, Libutti SK, Linehan WM, Oldfield EH. von Hippel-Lindau disease. Lancet. 2003;361:2059-2067.
5. Nielsen SM, Rhodes L, Blanco I, Chung WK, Eng C, Maher ER, Richard S, Giles RH. Von Hippel-Lindau disease: genetics and role of genetic counseling in a multiple neoplasia syndrome. J Clin Oncol. 2016;34:2172-2181. Epub 2016 Apr 25
6. Mete O, Asa SL, Gill AJ, Kimura N, de Krijger RR, Tischler A. Overview of the 2022 WHO Classification of paragangliomas and pheochromocytomas. Endocr Pathol. 2022;33:90-114. Epub 2022 Mar 13
7. Rednam SP, Erez A, Druker H, Janeway KA, Kamihara J, Kohlmann WK, Nathanson KL, States LJ, Tomlinson GE, Villani A, Voss SD, Schiffman JD, Wasserman JD. Von Hippel-Lindau and hereditary pheochromocytoma/paraganglioma syndromes: clinical features, genetics, and surveillance recommendations in childhood. Clin Cancer Res. 2017;23:e68-e75.
8. Bausch B, Wellner U, Peyre M, Boedeker CC, Hes FJ, Anglani M, de Campos JM, Kanno H, Maher ER, Krauss T, Sansó G, Barontini M, Letizia C, Hader C, Schiavi F, Zanoletti E, Suárez C, Offergeld C, Malinoc A, Zschiedrich S, Glasker S, Bobin S, Sterkers O, Ba Huy PT, Giraud S, Links T, Eng C, Opocher G, Richard S, Neumann HP; International Endolymphatic Sac Tumor (ELST) Consortium. Characterization of endolymphatic sac tumors and von Hippel-Lindau disease in the international endolymphatic sac tumor registry. Head Neck. 2016;38 Suppl 1:E673-E679. Epub 2015 Jul 14
9. Sovinz P, Urban C, Uhrig S, Stepan V, Lackner H, Schwinger W, Benesch M, Moser A, Spuller E, Speicher MR. Pheochromocytoma in a 2.75-year-old-girl with a germline von Hippel-Lindau mutation Q164R. Am J Med Genet A. 2010;152A:1752-1755.
10. Launbjerg K, Bache I, Galanakis M, Bisgaard ML, Binderup MLM. von Hippel-Lindau development in children and adolescents. Am J Med Genet A. 2017;173:2381-2394. Epub 2017 Jun 26
11. Fugaru I, Goudie C, Capolicchio JP. Von Hippel-Lindau disease and rapidly progressing pheochromocytomas in siblings. Fam Cancer. 2022;21:229-233. Epub 2021 Apr 20
12. Libutti SK, Choyke PL, Alexander HR, Glenn G, Bartlett DL, Zbar B, Lubensky I, McKee SA, Maher ER, Linehan WM, Walther MM. Clinical and genetic analysis of patients with pancreatic neuroendocrine tumors associated with von Hippel-Lindau disease. Surgery. 2000;128:1022-1027;discussion 1027-1028.
13. Nordstrom-O'Brien M, van der Luijt RB, van Rooijen E, van den Ouweland AM, Majoor-Krakauer DF, Lolkema MP, van Brussel A, Voest EE, Giles RH. Genetic analysis of von Hippel-Lindau disease. Hum Mutat. 2010;31:521-537.
14. Ong KR, Woodward ER, Killick P, Lim C, Macdonald F, Maher ER. Genotype-phenotype correlations in von Hippel-Lindau disease. Hum Mutat. 2007;28:143-149.
15. Gallou C, Chauveau D, Richard S, Joly D, Giraud S, Olschwang S, Martin N, Saquet C, Chrétien Y, Méjean A, Correas JM, Benoît G, Colombeau P, Grünfeld JP, Junien C, Béroud C. Genotype-phenotype correlation in von Hippel-Lindau families with renal lesions. Hum Mutat. 2004;24:215-224.
16. Salama Y, Albanyan S, Szybowska M, Bullivant G, Gallinger B, Giles RH, Asa S, Badduke C, Chiorean A, Druker H, Ezzat S, Hannah-Shmouni F, Hernandez KG, Inglese C, Jani P, Kaur Y, Krema H, Krimus L, Laperriere N, Lichner Z, Mete O, Sit M, Zadeh G, Jewett MAS, Malkin D, Stockley T, Wasserman JD, Xu W, Schachter NF, Kim RH. Comprehensive characterization of a Canadian cohort of von Hippel-Lindau disease patients. Clin Genet. 2019;96:461-467. Epub 2019 Aug 6
17. The VHL Alliance -- https://www.vhl.org/ (Accessed on June 29, 2020).
18. Fagundes GFC, Petenuci J, Lourenco DM Jr, Trarbach EB, Pereira MAA, Correa D'Eur JE, Hoff AO, Lerario AM, Zerbini MCN, Siqueira S, Yamauchi F, Srougi V, Tanno FY, Chambo JL, Latronico AC, Mendonca BB, Fragoso MCBV, Almeida MQ. New insights into pheochromocytoma surveillance of young patients with *VHL* missense mutations. J Endocr Soc. 2019;3:1682-1692.