Case Report

Two Childhood Pheochromocytoma Cases Due to Von Hippel-Lindau Disease, One Associated with Pancreatic Neuroendocrine Tumor; A Rare Manifestation

Short Running Title: Pheochromocytoma cases as first manifestation of VHL

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What is already known in this topic?
In childhood, pheochromocytomas (PCC) are mostly due to genetic causes in which von Hippel Lindau (VHL) disease is the most frequent disorder and may be the only and/or initial manifestation of the disease with delayed manifestations of the syndrome in other organs.

What this study adds:
We report two cases of VHL disease presented with PCC. In second case, pancreatic neuroendocrine tumor (PNET), a very rare manifestation of VHL disease, developed during follow-up. To best of our knowledge, this is the second case in literature, presenting with combination of PNET and PCC in childhood.

Abstract
(VHL) disease is an autosomal dominantly inherited disorder characterized by hemangioblastomas of retina and central nervous system (CNS); renal cysts, clear cell carcinoma; PCC; endolymphatic sac tumors; cystadenomas of the epididymis in males, broad ligament of uterus in females; pancreatic cysts, cystadenomas and neuroendocrine tumors. We here report two cases of VHL disease presented with PCC as the first manifestation. Hemangioblastoma of CNS in the first case and PNET in the second case developed during follow-up and led to the diagnosis of VHL disease. Genetic analyses of cases revealed p.Arg161Gln (c.482G>A) and p.Leu129Pro(c.386T>G) heterozygous missense mutation in VHL gene, respectively. In children, PCC may be the only and/or initial manifestation of the disease with delayed manifestations of the syndrome in other organs. PNET is a very rare manifestation of VHL disease. To best of our knowledge, this is the second case in literature, presenting with combination of PNET and bilateral PCC as components of childhood VHL disease. Pediatric patients diagnosed with PCC should be investigated for the genetic causes especially for VHL.

Keywords: von Hippel-Lindau syndrome, pheochromocytoma, pancreatic neuroendocrine tumor, hemangioblastoma
**Introduction**

VHL disease is an autosomal dominantly inherited caused by a germline mutation in the VHL tumor supressor gene and characterized by hemangioblastomas of retina and central nervous system; renal cysts, clear cell carcinoma; PCCs; endolymphatic sac tumors; cystadenoas of the epididymis in males, broad ligament of uterus in females; pancreatic cysts, cystadenomas and neuroendocrine tumors (1,2). Incidence of VHL disease is estimated at 2-3 cases per 100,000 population (3). If family history of VHL disease is present, a diagnosis of VHL disease can be made by finding only a single VHL tumor. On the other hand, approximately 20% of VHL disease cases are sporadic and presence of two VHL tumors is necessary to diagnose the disease if there is no family history (4).

PCCs are uncommon neuroendocrine tumors that arise from chromaffin cells of the adrenal medulla and produce excessive amounts of catecholamines, which are responsible for hypertensive surges, palpitations, headache, and diaphoresis(5). PCCs are rare in childhood but represent a curable cause of hypertension and must be considered in the differential diagnosis of hypertension. Compared with adults, children with PCCs have a higher incidence of bilateral adrenal tumors, extraadrenal tumors, and multiple tumors(6). Although most PCCs are sporadic, more than 25% of cases are associated with an inherited mutation and this ratio can be as high as 55% if diagnosed before 18 years of age (7).

In childhood, PCCs are mostly due to genetic causes in which VHL disease is the most frequent disorder(8). PCCs in VHL disease tend to be seen in younger ages, are often multiple and may be extra-adrenal (9-10).

We here describe two cases of VHL disease, who presented with PCC as the first manifestation. Hemangioblastoma of CNS in the first case and PNET in the second case developed during follow-up and led the diagnosis of VHL disease.

**Case 1**

Twelve years old boy was admitted with the complaints of weight loss, hot flush, palpitation and diaphoresis for one month. He was the first child of nonconsanguineous parents. His birth history was unremarkable. His family history was uninformant for tumor occurence. On physical examination, he weighed 43kg (-0,28 SD), with a height of 150 cm (-0,48 SD). His blood pressure was 140/100 mmHg (95p 123/81 mmHg), heart rate was 115 per minute. General examination was otherwise normal. Laboratory tests showed an elevated 24-hour (h) urinary vanillylmandelic acid (VMA) level (115 mg/day; normal value <15 mg/day). An abdominal ultrasound revealed solid lesions, 27x35 mm at the right adrenal gland and 37x75 mm at the left adrenal gland. Abdominal magnetic resonance imaging (MRI) showed bilateral adrenal masses compatible with PCC. Bilateral subtotal adrenalectomy including removal of the masses was performed and the diagnosis of bilateral PCC was confirmed histologically. The patient remained asymptomatic with no laboratory or radiologic abnormalities for five years of follow-up. At the age of 17, he presented with the complaint of headache. Cranial MRI demonstrated a lesion of 1 cm diameter, located in the left frontal lobe. Positron Emission Tomography revealed a lesion of increased FDG uptake in the right adrenal gland, compatible with recurrence, and hypometabolic, hypodense focus in the left frontal lobe (Figure 1). Cranial mass was excised and hemangioblastoma was diagnosed histologically. Adrenalectomy was performed for the lesion in the right adrenal gland and recurrence of PCC was confirmed. Coexistence of PCC and cranial hemangioblastoma suggested the diagnosis of VHL disease and previously reported heterozygous missense mutation c.482G>A (p. Arg161Gln) in the VHL gene was detected.

**Case 2**

Ten years old girl presented with intermittent fever for one month. Her birth history was unremarkable. She was the fourth child of nonconsanguineous parents. Her family history was uninformant for tumor occurence. Physical examination revealed blood pressure of 160/100 mmHg (95p 120/79 mmHg), and heart rate of 110 beat per minute. Laboratory tests showed elevated 24-hour urinary VMA level of 83 mg/day. Abdominal MRI revealed 44x33 mm, well circumscribed mass with necrotic core in the left adrenal gland. Subtotal adrenalectomy was performed and histologic examination showed that the tumor was PCC. In the two years of follow-up, 20x19x12 mm mass in the right adrenal gland was detected in abdominal MRI. PET-CT with 68 Ga- DOTATATE showed increased uptake in the right adrenal gland and 11x10 mm nodular lesion in corpus of the pancreas.
Tumoral masses in the adrenal gland and pancreas were removed. Histologic investigation of adrenal and pancreas specimens confirmed the diagnosis of PCC and PNET (WHO grade 3) respectively. One year later, a 8x7 mm lesion in pancreas, compatible with recurrence, was observed in abdominal MRI. Same lesion was confirmed with 68 Ga-DOTATATE PET-CT. Splenectomy and subtotal pancreatectomy were performed for removal of the lesion. Histologic examination was reported as neuroendocrine tumor. Bilateral PCC with PNET suggested the diagnosis of VHL disease. Molecular genetic analysis of the VHL gene revealed a heterozygous missense mutation c. 386 T>G (p.Leu129Pro) which was previously described. No additional VHL tumor developed during follow up.

The two patients are being followed up according to the pediatric screening protocol recommended for the child carrying a VHL mutation (11).

**Genetic Analysis**

Molecular DNA was isolated from a 200μl blood sample using the QIAamp DNA Blood Mini QIAcube Kit with a QIAcube instrument (QIAGEN, Hilden, Germany) according to the manufacturer's specifications. The full coding sequences, including the 5' untranslated region (UTR) and the 3' UTR of the VHL gene (OMIM*608537), were amplified and sequenced. PCR products were purified using ExoSAP-IT (GE Healthcare, Little Chalfont, UK). The PCR fragments were sequenced by using the BigDye terminator V3.1 Cycle Sequencing ready reaction system (Applied Biosystems, Foster City, CA, USA) according to the manufacturer’s instructions. Sequence analysis was performed on an ABI Prism 3100-Avant DNA sequencer (Applied Biosystems).

**Discussion**

PCC is an exceptionally rare neoplasm in children, accounting for 1% of pediatric hypertensive patients (12). Approximately 10-20% of PCC are found in the pediatric population (13). In comparison with adults, childhood PCC is associated with sustained hypertension rather than hypertensive attacks with the classical triad of palpitation, headache and sweating (14). Episodic tachycardia, sweating and hot flush, the classic symptoms of PCC, accompanied by sustained hypertension were present in the first case. However, in the second case, the only symptom was intermittent fever. Sustained hypertension was detected in physical examination.

PCCs are seen both sporadically and in association with a number of familial cancer syndromes such as VHL disease, multiple endocrine neoplasia type 2, paraganglioma syndromes type 1,3 and 4, and rarely neurofibromatosis type (13). Family history was insignificant for familial cancer syndromes in both cases. Even in patients with apparently sporadic PCCs, up to 25% will have unsuspected germline mutations. Younger age and multifocal tumors as in our patients are significantly associated with the presence of mutation. Genetic testing may detect patients at risk for other associated tumors (15). The delayed diagnosis of VHL disease was made after the occurrence of cranial hemangioblastoma in the first case and PNET in the second case.

In childhood and adolescence, PCC may be the only initial manifestation of VHL disease with delayed manifestations of the syndrome in the eye, CNS or other organs (16). VHL disease is classified into four subtypes, type 1 without PCC, and type 2A, 2B and 2C having risk of development of PCC. Patients with type 2A have a low risk of renal cell carcinoma (RCC) while type 2B patients have a high risk of RCC. VHL type 2C confers an increased risk of PCCs without other manifestations of the disease. In type 1 families, deletions in the VHL gene are often detected, whereas in type 2 disease, missense mutations are most often encountered. In our cases, presence of PCC and the missense mutations in VHL gene suggested VHL type 2. Mutation found in the first patient, c.482G>A (p. Arg161Gln), is also known to be associated with RCC (17,18). However in the present time our patient does not have RCC.

Involvement of the pancreas in VHL disease has been observed in 25% to 70% of the cases. In most of the cases, pancreatic changes are characterized by benign cysts (19). In VHL disease neuroendocrine tumors of the pancreas and PCCs are observed in 8% to 17%, and 10%-20% of the patients respectively (20). The association of neuroendocrine tumors of the pancreas with PCCs are in 12% of the patients with VHL disease (21). Pancreatic tumors rarely occur during childhood (22). The mean age at presentation for neuroendocrine tumours is 35 year(20). In our second case, PNET as a component of VHL was detected at the age of twelve years, two years after diagnosis of PCC.

Langrehr et al. (23) reported a 12-year-old girl with c.695 G>A mutation in exon 3 of the VHL gene.
resulting in neuroendocrine tumor of the pancreas and bilateral adrenal PCC. To best of our knowledge, this is the second youngest case in literature, presenting with combination of PNET and bilateral PCC as components of childhood VHL disease.

**Conclusion**

Here we have presented two childhood cases of VHL disease with bilateral PCC and an additional tumor namely PNET and cranial hemangioblastoma diagnosed after two and five years following initial diagnosis of PCC respectively. The combination of PCC and PNET is seemingly reported for the second time in the literature with respect to childhood VHL disease. Meticulous follow-up and early genetic testing in PCC may facilitate the prevention of morbidity and mortality and may improve long term prognosis in VHL disease.

**References**


**Fig 1:** Positron Emission Tomography imaging showing increased FDG uptake in the right adrenal gland, compatible with recurrence, and hypometabolic, hypodense focus in the left frontal lobe
Fig 2: PET-CT imaging showing increased uptake in the right adrenal gland and 11x10 mm nodular lesion in corpus of the pancreas