

Bilateral pheochromocytoma as first manifestation of von Hippel-Lindau disease: a case report

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SUMMARY: Çatlı G, Abacı A, Neumann HCH, Altıncık A, Demir K, Böber E. Bilateral pheochromocytoma as first manifestation of von Hippel-Lindau disease: a case report. Turk J Pediatr 2012; 54: 532-535.

Von Hippel-Lindau syndrome is an autosomal dominant disorder that includes susceptibility to hemangioblastomas of the eyes and central nervous system, renal clear cell carcinoma, multiple pancreatic cysts, serous cystadenomas and pancreatic neuroendocrine tumors, pheochromocytoma, endolymphatic sac tumors, and cystadenomas of the epididymis and broad ligament.

We present a 16-year-old male who had been followed for having bilateral adrenal, and in addition, extraadrenal multifocal pheochromocytoma for six years. At the age of 16, he presented with bilateral retinal hemangioblastomas, which led to the diagnosis of von Hippel-Lindau disease type 2A confirmed by genetic analysis. The patient's mother also had bilateral adrenal pheochromocytoma with no other von Hippel Lindau-associated tumor. In children, pheochromocytoma may be the only and/or initial manifestation of the disease with delayed manifestations of the syndrome in other organs. Von Hippel-Lindau disease is a complex multidisciplinary disorder that requires well-coordinated medical care. Surveillance of these patients and asymptomatic relatives may prevent morbidity and mortality and improve long-term prognosis. Molecular analysis of the von Hippel-Lindau gene is useful for early diagnosis of the disease in individuals who do not yet fulfill the clinical diagnostic criteria and is instrumental in the management and follow-up of the affected family.

Key words: von Hippel-Lindau syndrome, pheochromocytoma, retinal hemangioblastoma.

Von Hippel-Lindau (VHL) disease is an autosomal dominantly inherited neoplastic syndrome characterized by hemangioblastomas of the retina, brain and spinal cord, renal clear cell carcinoma, pheochromocytoma, pancreatic neuroendocrine tumors, and endolymphatic sac tumors^{1,2}. Incidence of VHL syndrome is approximately 1 in 36,000 live births and its penetrance is over 90% by the age of 65³.

According to the diagnostic criteria, a diagnosis of VHL disease can be made by finding only a single VHL tumor, provided that a family history of VHL disease is present. On the other hand, approximately 20% of VHL disease cases are sporadic, and if there is no family history, presence of two VHL tumors is needed to diagnose the disease⁴. VHL

disease displays complex genotype-phenotype correlations and can be classified according to the absence (type 1) or presence (type 2) of pheochromocytoma. VHL type 2 is further divided into types 2A, 2B and 2C (5). Type 2A families manifest hemangioblastomas and pheochromocytoma with a lower risk of renal cell carcinoma (RCC) and families with type 2B manifest hemangioblastomas, RCC and pheochromocytoma, whereas families with specific VHL missense mutations in which pheochromocytoma is the only feature are designated as type 2C VHL disease⁴. The VHL gene is localized on the short arm of chromosome 3 with three exons coding for two isoforms of the protein. A wide variety of mutations have been described in more than

900 kindreds⁴. The type of the mutation differs between subtypes of the disease. Missense mutations usually confer better prognosis and are almost always responsible for VHL type 2, whereas deletions and nonsense mutations may be present as well as missense mutations in type 1 patients⁶. Molecular analysis of the VHL gene in patients and at-risk relatives allows early diagnosis of the disease and prevents morbidity and mortality. On the other hand, the identification of VHL gene mutations may also change the management and follow-up of the affected family.

We present a patient who was initially diagnosed as bilateral familial pheochromocytoma. During the follow-up, the emergence of retinal hemangioblastomas led to a diagnosis of VHL disease. We report this case to point out the importance of genetic analysis and careful follow-up of patients who are diagnosed with familial or bilateral pheochromocytoma.

Case Report

A 10-year-old boy was admitted to our hospital with complaints of headache and diplopia. On physical examination, he weighed 40 kg (75-90p), with a height of 142 cm (50-75p). His brachial blood pressure was 150/120 mmHg (95th percentile 123/81 mmHg). His mother had been operated for bilateral pheochromocytoma at the age of 23 and had not been under medical follow-up since then. Laboratory tests showed elevated 24-hour (h) urinary vanillylmandelic acid (VMA) (40 mg/day; normal value 1-11) and normetanephrine (>2000 µg/day), but normal metanephrine levels (143 µg/day). Abdominal magnetic resonance imaging (MRI) indicated the presence of multiple lesions in perivascular areas neighboring both adrenal glands. An iodine ¹²³ metaiodobenzylguanidine (MIBG) scan revealed multiple focal areas of increased uptake near the adrenal glands. After the preparation for operation, bilateral subtotal adrenalectomy including removal of the masses was performed. The diagnosis of bilateral pheochromocytoma was confirmed histologically and immunohistochemically. The patient remained asymptomatic with no laboratory or radiologic abnormalities for six years of follow-up. At the age of 16, the patient was referred to our clinic with visual defect in the left eye. Ophthalmologic

examination led to the diagnosis of bilateral retinal hemangiomas, and he underwent laser photocoagulation. Positive family history with bilateral pheochromocytoma and retinal hemangioma revealed the diagnosis of VHL disease. Cerebral, spinal MRI and abdominal computed tomography (CT) were normal.

DNA extraction, polymerase chain reaction and direct sequencing of exons 1 to 3 revealed a mutation in exon 3 of the VHL gene (c.695 G>A), both in the patient and his mother, which resulted in the amino acid change R161Q.

The patient's mother was evaluated by ophthalmologic examination and no abnormalities were found. She underwent cerebral and spinal MRI and abdominal CT to investigate any possible VHL tumors, and no tumor was detected.

Discussion

Pheochromocytoma is a rare tumor, with an incidence of 2-8 cases per million per year⁷. Approximately 10-20% of cases are diagnosed during childhood at an average age of 11. The prevalence of pheochromocytoma is 1% among hypertensive adolescents. In comparison with adults, childhood pheochromocytoma is associated with sustained hypertension rather than hypertensive attacks with the classical triad of palpitation, headache and excess sweating⁸. Although most pheochromocytomas are sporadic, up to 25% of cases are associated with familial cancer syndromes such as neurofibromatosis type 1 (NF1 gene), multiple endocrine neoplasia type 2 (MEN2) (RET gene), VHL syndrome (VHL gene) and paraganglioma syndrome types 1, 3 and 4 (SDHD, SDHC, SDHB genes)⁷. Recently, two new susceptibility genes, the TMEM127 gene and MAX gene, without homology to other functional classes, have been described^{9,10}.

Familial pheochromocytomas are often multifocal and frequently bilateral. Finding of multicentric tumors is highly suggestive of familial disease and is more common in childhood presentations¹¹. The patient in the current report was a 10-year-old boy who was initially diagnosed as familial, bilateral and multicentric pheochromocytoma presenting with intractable hypertension. At follow-up, the emergence of bilateral retinal hemangiomas

led to the diagnosis of VHL disease.

Von Hippel-Lindau (VHL) disease is propounded to account for about 50% of patients with apparently isolated familial pheochromocytoma¹². In childhood and adolescence, pheochromocytoma may be the only initial manifestation of VHL disease with delayed manifestations of the syndrome in the eye, central nervous system (CNS) or other organs⁶. Patients with VHL type 1 are characterized with retinal and CNS hemangioblastomas and RCC but not pheochromocytoma. They usually have truncating mutations and large deletions exceeding an exon. Pheochromocytomas are the hallmark of VHL type 2, and nearly all mutations associated with pheochromocytoma are of missense type. VHL type 2 can be classified as 2A, 2B and 2C. VHL type 2A has a lower risk of RCC, while VHL type 2B manifests RCC more commonly (70%). Patients with pheochromocytoma alone are classified as VHL type 2C⁵. In our patient, the presence of pheochromocytoma, negative family history for RCC and the result of mutation analysis suggested VHL type 2A. The patient's mother was investigated for additional VHL tumors, but no tumors other than the known bilateral adrenal pheochromocytoma were detected. She was thus considered as having VHL type 2C. Since the same mutation may cause two different subtypes, it may be suggested that the classification of VHL disease is most helpful for research studies and is less useful for clinical management. Langrehr et al.¹³ reported a 12-year-old girl with c.605 G>A mutation in exon 3 of the VHL gene resulting in neuroendocrine tumor of the pancreas and bilateral adrenal pheochromocytomas. According to an unpublished registry data from Neumann (n.d.), of the 10 cases with the identical mutation in exon 3 of the VHL gene (c.695 G>A, amino acid p.R161Q), all had pheochromocytoma, four had CNS tumors, four had pancreatic neuroendocrine tumors, three had retinal angiomas, and one had renal carcinoma. No endolymphatic sac tumor or epididymal/broad ligament tumor was detected.

Pheochromocytomas associated with VHL syndrome exhibit a clearly and constantly noradrenergic pattern, with the concentrations of 98% norepinephrine and 1.5% epinephrine of the total catecholamine content¹⁴. The patient

in the present report was diagnosed upon the elevated 24-h urinary normetanephrine and VMA levels. His 24-h urinary metanephrine level was normal, compatible with the literature.

Several demographic and clinical features have been associated with a germ-line mutation in patients with pheochromocytoma. According to a recent algorithm for the genetic diagnosis of patients with pheochromocytoma, patients of young age, with multifocal disease, extraadrenal location, and malignancy should be genetically tested¹⁵. Identifying a VHL mutation may provide early diagnosis of other manifestations and may facilitate definition of the disease risk in other family members.

In conclusion, VHL disease should be considered in children and adolescents with familial, bilateral and multifocal pheochromocytoma, even in individuals who do not yet satisfy the clinical diagnostic criteria. Surveillance of VHL patients and asymptomatic relatives facilitates the prevention of morbidity and mortality and may improve long-term prognosis. Thus, all patients with VHL disease and at-risk relatives should be included in routine screening programs beginning from childhood.

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