Case report

The importance of genetic study and long-term management in patients with bilateral pheochromocytomas

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Abstract

Tumors secreting catecholamines, such as pheochromocytomas and paragangliomas, are rare and life-threatening, due to their complications. They can be sporadic or occur in genetic syndromes, such as von Hippel-Lindau in which pheochromocytomas are observed in 10 to 20%. We report a case of a 42 years old male, who was sent in 2016 to our department for neurological symptoms related to cerebellar and central vestibular syndromes. His medical history revealed that at 8 years old he was operated for a symptomatic bilateral pheochromocytoma discovered by adrenergic symptoms and high blood pressure. Cerebral MRI showed intra- and extra-axial, supra- and infratentorial lesions causing supratentorial hydrocephalus associated with leptomeningeal dissemination deemed to be hemangioblastomas. One year later the patient started complaining of chronic diarrhea. The abdominal CT revealed three pancreatic tumors with radiological signs of pancreatic neuroendocrine tumors (PNETs) and a 12 mm mesenteric nodule presenting as a homogenously and typical for NET. The largest PNET had intensive fixation on octreotide scintigraphy. The association of pheochromocytomas, hemangioblastoma and pancreatic neuroendocrine tumors highlighted the diagnosis of VHL syndrome. The family history proved positive in a sibling with bilateral pheochromocytoma in infancy, retinal hemangioblastomas and cerebral hemangioblastoma. Genetic testing would have been useful, but in our case, it was lacking due to poor socio-economic conditions of the patient and absence of genetic testing in public hospitals.

Keywords: *pheochromocytoma; pancreatic neuroendocrine tumors; von Hippel-Lindau*

Introduction

Pheochromocytomas and paragangliomas are rare tumors, characterized by catecholamine secretion and life-threatening due to complications. The most recent World Health Organization (WHO) classification uses the term pheochromocytoma only for intra-adrenal tumors, and paraganglioma for extra-adrenal manifestations [1], although behavior and prognosis of tumors arising from neural crest-derived tissue throughout the body are the same.

Pheochromocytomas/paragangliomas (PPGL) could be either sporadic or inherited. In familial forms, transmission is usually autosomal dominant. These tumors could be either isolated or integrated in genetic syndromes such as: multiple endocrine neoplasia type 2 or MEN2, neurofibromatosis type 1 or NF1 and von Hippel Lindau (VHL) (OMIM193300) [2].

VHL is an autosomal dominant disorder resulting from germline mutations in the VHL gene. VHL syndrome clinical features include

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the following: retinal (von Hippel) and cerebellar (Lindau) hemangioblastomas [3] and other multi-organ tumors such as paragangliomas and bilateral pheochromocytoma [2].

The overall incidence of pheochromocytomas in patients with VHL is 10–20%, but genotype–phenotype correlations are also important to consider. Patients with partial or complete VHL deletions (VHL type 1) have low risk of pheochromocytoma (6–9%), whereas patients with missense VHL mutations (VHL type 2) have a high (40–59%) risk of pheochromocytoma [4].

Usually, tumors in the VHL are multiple and bilateral, with adrenal tumors accounting for 50 to 70% of cases. Sympathetic extra-adrenal paragangliomas occur in 10 to 15% of cases. Malignant forms are less than 10% [5], but they tend to occur at a younger age (sometimes as the first manifestation) compared to the sporadic cases [6]. For this, genetic testing in young patients (below 30) is extremely useful to determine which individuals are harboring the mutated allele in the family. When genetic testing is lacking, the diagnosis is late and the prognosis is poor, as was the case for one family where 3 siblings have been operated on in their infancy for pheochromocytomas (two with bilateral forms).

Case report

A 42 year-old male, was admitted to our department for neurological symptoms. His medical history was rich, as at 8 years old he was operated for a symptomatic bilateral pheochromocytoma revealed by adrenergic symptoms and high blood pressure. During that period, he did not have access to genetic testing. However, clinical examination and morphological investigations excluded multiple endocrine neoplasias type 2 (MEN 2). After surgery his blood pressure normalized, catecholamines were normal and there were no signs of relapse on his adrenal computed tomography during the follow-up examinations.

The family history revealed that he has a second sibling also suffering from bilateral pheochromocytoma in his infancy, for which he underwent surgery. Thirty years later, he developed retinal and cerebellar hemangioblastomas.

By the age of 42, he complained of neurological symptoms related to cerebellar and central vestibular syndromes. Cerebral MRI showed intra- and extra-axial, supra- and infratentorial lesions causing supratentorial hydrocephalus associated to leptomeningeal dissemination deemed to be hemangioblastomas. The largest lesion, for which he underwent neurosurgery, was located in the left cerebello-protuberancial area, and measured 37x45x33mm (Figure 1).

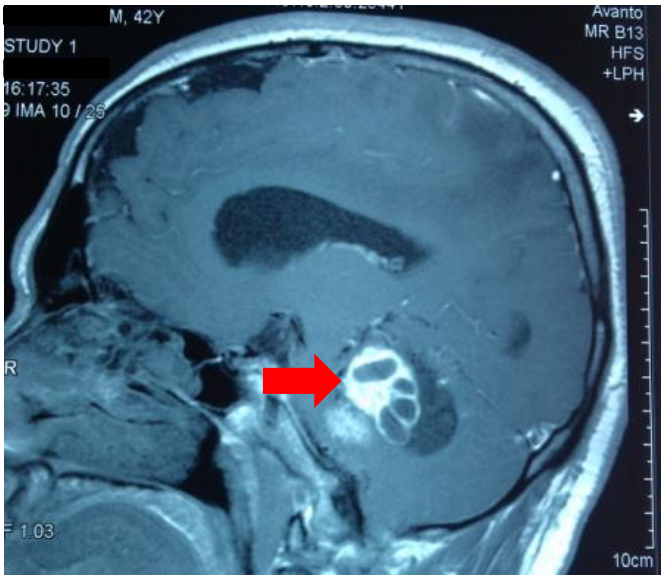

Fig. 1. Cerebral MRI- cerebellar cystic mass corresponding to the hemangioblastoma

Pathological examination confirmed the diagnosis of cerebellar hemangioblastoma.

For the second supratentorial intra-axial tumor, the neurosurgeons decided on a "wait and see" approach. Fortunately, there were no leptomeningeal metastases in the case of our patient.

One year later, the patient started complaining of chronic diarrhea. Abdominal CT revealed three pancreatic tumors with radiological signs of pancreatic neuro-endocrine tumors (PNETs), and a 12 mm mesenteric nodule manifesting as a homogenous typical for neuro-endocrine tumor (NET). The largest PNET had intensive fixation in octreotide scintigraphy (Figure 2). The abdominal MRI revealed just two PNETs. Nonsurgical management for PNET was recommended for the patient, because he presented the following good prognosis criteria: tumors size less than 3 cm, stable tumor for at least 9 months on follow-up.

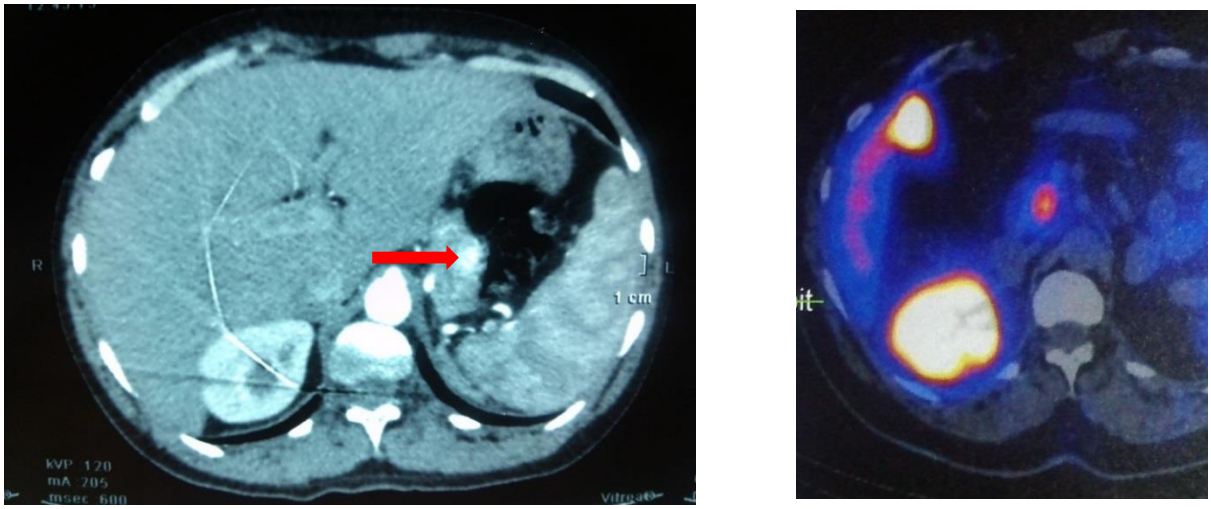

Fig. 2. A) Abdominal CT- the red arrow shows the corporeal PNET, B) Octreotid scintigraphy- intense fixation of corporeal PNET

Chromogranin values were increased: 118.7ng/ml (Normal ranges: 20-115ng/ml) with no evidence of relapsing pheochromocytoma.

Ophthalmological examination revealed signs of retinal hemangioblastoma (Figure 3).

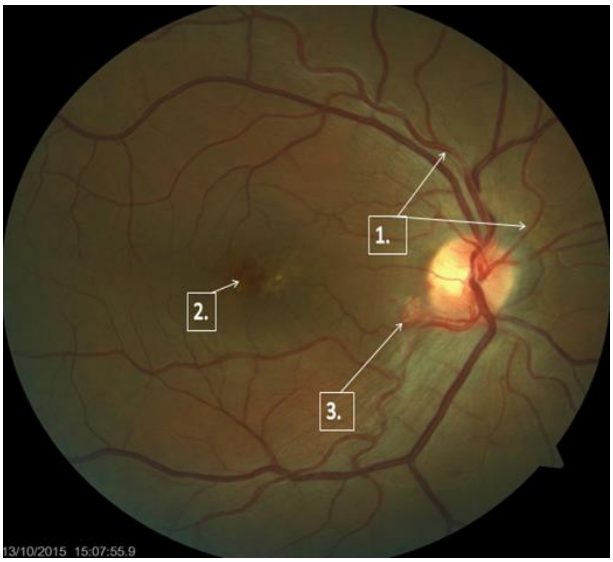

Fig. 3. Right eye fundus showing: vascular tortuosity (1), macular edema (2) and peri-papillary new retinal vessel (3), probable hemangioblastoma.

Therefore, the clinical diagnosis of VHL was made for three members of the family, however genetic testing was lacking due to poor socioeconomical conditions of our patient.

Discussions

The importance of genetic studies in such families consists in finding useful information to improve the clinical outcome, demography and prognosis in these rare cases. It was reported that SDHD p.Cys11X mutation is associated with paraganglioma tumors of the skull base, neck, thorax, and retroperitoneum, arising in the first four decades, and rarely associated with malignancy [7].

Furthermore, genetic testing importance motivates researchers to identify novel gene mutations that can better describe the clinical outcome. In a study report, in a Chinese family a c.464T>A mutation of the VHL gene was found in three patients with hemangioblastoma. These new findings highlight the diversity of the gene defects observed in VHL syndrome [8].

Von Hippel Lindau (VHL) syndrome is an inherited disease due to the germline mutation of the VHL gene, which is located on the short arm of chromosome 3 (3p26-25) [9].

VHL gene is a tumor suppressor with a coding sequence of 639 nucleotides on three exons. It induces production of VHL protein responsible for proteomic degradation of hypoxia-inducible factors (HIFs) that regulate negatively the production of angiogenic factors including vascular endothelial and platelet-derived growth factors (VEGF and PDGF). When the VHL gene is mutated, proteomic degradation of HIFs is altered. Increased HIFs lead to overproduction of VEGF and PDGF responsible for VHL syndrome. That one is characterized by highly vascularized tumors such as pheochromocytomas, hemangioblastomas, and retinoblastomas [10].

Regarding neuro-endocrine tumors (NET), patients with VHL disease have an increased risk of up to 20% for developing such tumors [11].

Pancreatic cysts (simple cysts - 47% of cases and serous cystadenomas - 11% of cases), representing benign lesions, can be present in up to 70% of VHL syndrome cases. Furthermore, in 4 to 15% of cases there were reported pancreatic NETs (PNETs) with malignant potential. Therefore, surgical treatment may be required in some cases. However, the pancreatic cysts often do not influence the outcome of most VHL syndrome patients [12].

Earliest manifestations of VHL syndrome involve central nervous system lesions such as hemangioblastomas and retinal hemangioblastomas, resulting in vision loss and other neurological symptoms [13].

Similar to pancreatic cysts, pheochromocytomas can occur in VHL syndrome and are frequently bilateral tumors. Their manifestations can be present at 5 years old or earlier. The teenage years are the earliest time when renal tumors have been noted. However, peak clinical manifestations are present in the 4th decade. Moreover, kidney tumors can be diagnosed by screening or on presence of hematuria [10].

The positive diagnosis of VHL syndrome is based on genetics testing which should be systematic in all bilateral pheochromocytomas. In absence of genetic testing, only presence of all arguments (hemangioblastomas and PNET) can lead to VHL syndrome diagnosis, but the last one is usually delayed as in our case. Children who had surgery for pheochromocytomas should have a long-term screening in order to diagnose other tumors. The presence of bilateral pheochromocytoma in childhood should always bring into discussion other differential diagnosis of VHL syndrome, MEN2 or neurofibromatosis type1.

Pheochromocytoma screening includes yearly clinical examination. Abdomen ultrasound should be initiated in childhood. After 20 years of age, abdomen CT or MRIs should be done yearly. It seems there is no advantage in performing biochemical studies in order to look for subclinical pheochromocytoma, so plasma or urine analysis of catecholamines and their metabolites in mutated carriers are not mandatory [6].

Once the diagnosis of VHL is made, testing is extremely useful to determine which individuals are harboring the mutated allele in the family. For these individuals,

recommendations for screening are empiric. Nowadays, the screening is recommended for VHL family individuals that have not been tested. In our case, genetic testing was not performed due to low socio-economic conditions, and to the fact that it is not available in public hospitals.

As treatment, symptomatic pheochromocytomas and large tumors should be operated. In our case, the chromogranin A, a marker for malignant pheochromocytoma, was slightly above the normal superior interval and without release of pheochromocytoma. Thus, monitoring was recommended at 3 and 6 months. However, it is unclear if surgery is necessary in clinically silent lesions found in screening tests.

Neuroendocrine tumors medical treatment (alone and with radionuclide therapy) in VHL syndrome is the same as for sporadic cases [5].

Upon newly diagnosing hemangioblastoma patients should be screened for VHL, including ophthalmological complete examination and investigations for renal and pancreatic lesions [14]. In our case personal and family medical history added to presence of cerebral hemangioblastoma argued for VHL syndrome diagnosis.

Medical treatment includes various pharmacological agents, such as Thalidomide (for hemangioblastoma in cases without VHL) [15]. In a recent phase II study, an open-label study from the PREDIR VHL, Sunitinib was used in patients with genetically-confirmed advanced VHL disease (oral sunitinib, 50 mg/day for 28 days then a 2-week rest period) leading to a limited benefit, however it had better efficacy against metastatic renal cell carcinoma than in other VHL-related lesions [16].

In the case of abnormal kidneys, 25 to 60% of patients with VHL mutations can develop some of the following illnesses: cystic renal cell carcinomas (often bilateral and multifocal) or renal tumors and/or cysts. Multiple or bilateral tumors or early age of onset of clear cell renal cell carcinoma (associated with constitutional chromosome 3 translocations) should raise concern for the familial forms associated with VHL syndrome [10, 17]. Thus, screening for renal tumors in individuals affected by VHL are required starting with the age of 18, by performing axial imaging (CT or MRI) yearly [10].

In a retrospective cohort study including all families with VHL syndrome, conducted in Denmark it was concluded that the survival rate was improved over time, the risk of death associated with VHL syndrome has decreased but the main cause of death is still CNS hemangioblastomas [18].

Conclusions

The presence of classical retinal (von Hippel) and cerebellar (Lindau) hemangioblastomas associated with PNETs and NET, along with the familial bilateral pheochromocytomas make the described case a situation of a familial type 2 VHL syndrome. Children who benefited from surgery of pheochromocytomas should have a long-term screening in order to diagnose other tumors early. VHL syndrome requires a multidisciplinary approach for the diagnosis and for the treatment at the best moment of all the tumors and lesions.

Consent

Written informed consent was obtained from the patient for publication of this case report.

Competing interests

The authors declare that they have no competing interests.

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