ASYMPTOMATIC CATECHOLAMINE-PRODUCING TUMOURS IN VON HIPPEL-LINDAU DISEASE

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Introduction

Von Hippel–Lindau Disease (VHLD) is an autosomal dominant neoplastic syndrome that results from a germline mutation in the tumoral supressor *VHL* gene (chromosome 3p25-26). VHLD incidence is about one in 36 000 live births.

Disease spectrum is characterized by the development of multiple cancers and cysts (Figure 1). A clear genotype-phenotype relation is present, allowing for a subtypes classification:

-Type 1: Retinal haemangioblastomas, CNS haemangioblastomas, renal cell carcinoma and pancreatic neoplasms and cysts

-Type 2A: Pheochromocytomas, retinal haemangioblastomas and CNS haemangioblastomas

-Type 2B: Pheochromocytomas, retinal haemangioblastomas, CNS haemangioblastomas, renal cell carcinoma and pancreatic neoplasms and cysts

-Type 2C: Pheochromocytoma only

Screening is mandatory for close relatives. (Figure 1).

Main lesions in VHLD	Mean age of onset (years)	Frequency (%)	Recommended screening test	Recommended screening intervals
Retinal haemangioblastomas	25 (1-67)	25-60%	Ophtalmoscopy	Since infancy (yearly)
Endolymphatic sac tumour	22(12-50)	10%	Audiological function tests; Inner ear MRI/CT	When clinically indicated
CNS haemangioblastomas	33 (13-72)	Up to 72%	MRI of craniospinal axis	11 years of age (early)
Renal cell carcinoma or cyst	39 (16-67)	25-60%	Abdomen US or RMI/ Abdomen CT	Respectively: Since 8 years/Since 18 years (yearly)
Pancreatic tumour or cyst	36 (5-70)	35-70%		
Phaeochromocytomas	30 (5-58)	10-20%	Plasma or 24h catecholamines and metanephrines	Since 2 years of age (yearly)

Figure 1: Main features of VHLD, age of onset, prevalence and recomended screening. CNS: Central Nervous System; MRI: Mangnetic Ressonance Imaging; CT: Computorized Tomography; US: Ultra Sound. Adapted from Lonser et at, *Lancet* 2003

Case Report

A Portuguese caucasian male aged 23 years old (identified as "A") Police officer was referred to the Endocrine Inpatient Department because of recent genetic diagnosis of VHLD during familiar screening.

His mother, the index case ("B"), and his aunt (mother's monozigotyc twin syster) identified as "C" were also diagnosed VHLD and shared the same mutation in *VHL* gene:

c.482G>A (p.Arg161Gln) in the exon 3 of VHL gene in heterozigoty

Patient A

Completely asymptomatic:
-Normal arterial pressure
-No anxiety nor vegetative paroxysms
-No visual disturbance
-No cardiovascular complaints
-No neurologic complaints

Unremarkable physical examination

Patient B

Previously diagnosed and treated of:

-**Bilateral pheochromocytoma** (Bilateral suprarenalectomy)
-**Retinal angiomas** (Photocoagulation)
-**Pancreatic cancer** (Pancreatectomy)

Medullar angiomas under surveillance

Patient C

Previously diagnosed and treated of:

-**Bilateral pheochromocytoma** (Bilateral suprarenalectomy)
-**Retinal angiomas** (Photocoagulation)
-**Breast cancer** (Mastectomy)

Medullar angiomas under surveillance

Patients D, E and F

Asymptomatic

Negative for *VHL* gene mutation

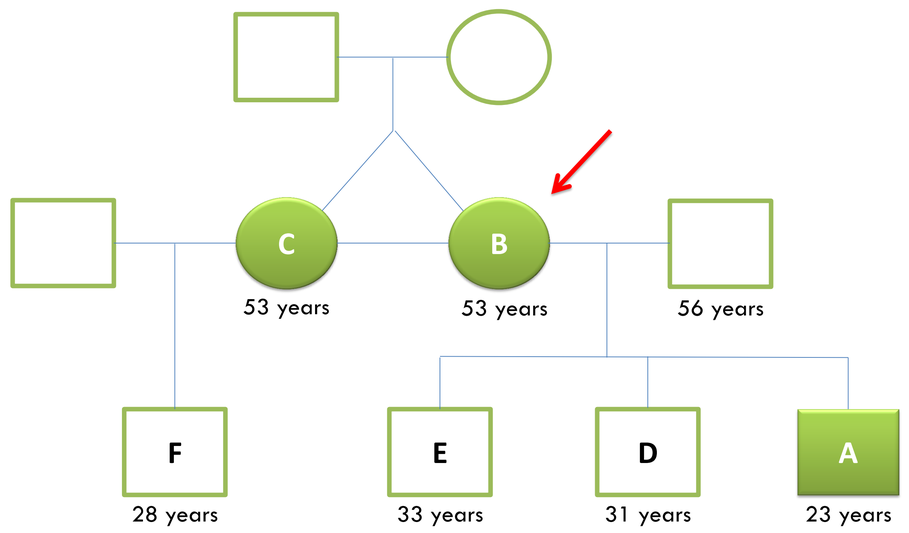

Figure 2: Patient's Family Tree. Filled figures represent affected members. All of them were identified mutation c.482G>A (p.Arg161Gln) in the exon 3 of *VHL* gene in heterozigoty.

Complementary diagnostic tests

Parameter	value	Reference values (RV)
Hemoglobin	15	13-17,5 g/dL
Leucocit count	9,07	4-11x10^9/L
Glucose	88	70-110 mg/dL
Creatinine	0,87	0,7-1,3 mg/dL
AST	19	0-34 U/L
ALT	18	10-49 U/L
NSE	**34,4**	0-16,3 ug/L
Urinary adrenaline	9,9	0,6-19,9 ug/24h
Urinary noradrenaline	**142,4**	15-80 ug/24h
Urinary dopamine	265,7	64,8-399 ug/24h
Urinary metanephrine	147,7	74-297ug/24h
Urinary normetanephrine	**969**	105-354ug/24h

Table 1: Basal analytic evaluation. Thyroid, parathyroid, , corticosuprarenal, gonadic and pituitary disfunction were also excluded

Parameter	0h	3h	RV
Plasmatic adrenaline	**138,2**	29,2	<100 pg/mL
Plasmatic noradrenaline	**658,6**	388,8	<600 pg/mL
Plasmatic dopamine	**101,4**	84,8	<100 pg/mL
Plamatic metanephrine	<20	20	<90 pg/mL
Plasmatic normetanephrine	**200**	71	<180 pg/Ml

Table 2: Clonidine test. Results before and after administration on 300mg of clonidine p.o..

Adrenal CT-scan

-Nodular solid lesion centered inside the right adrenal, with 25mm of higher diameter, with well defined borders. This lesion hyperfixates at 60 seconds (137HU atenuation) and has 51% calculated washout. The mass probably corresponds to a pheochromocytoma.

-Solid lesion on the L3 right paravertebral aspect, with 3x1,5cm. This lesion strongly but heterogeneously hyperfixates the contrast, probably corresponding to a paraganglioma

-Two millimetric nodular hypodense lesions in the left kidney's inferior pole, probably corresponding to cortical cysts.

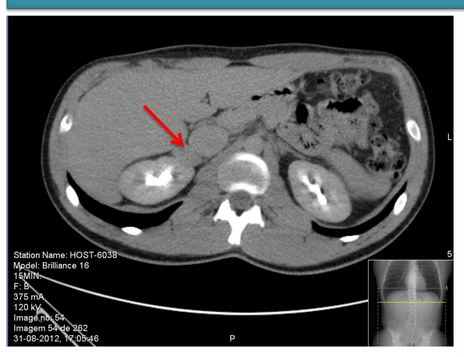

Figure 3: Adrenal CT scan demonstrating the right adrenal mass, corresponding to a pheochromocytoma (red arrow).

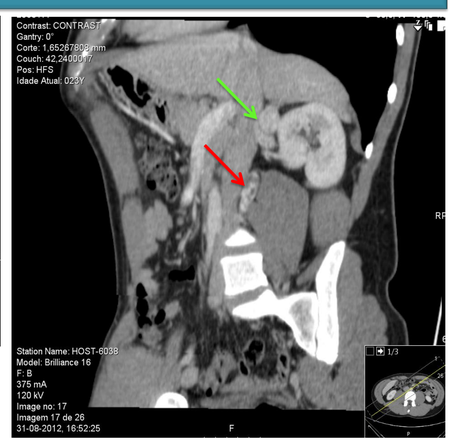

Figure 4: Abdominopelvic CT scan demonstrating the right adrenal pheochromocytoma (green arrow) and the right paraganglioma (red arrow).

Creaneoencephalic and spinal MRI

Morphologic and sinal anomaly lateral and anterior to the spine, at the level of L3 and intersomatic adjacent spaces. This lesion is T1 hipointense and T2 hyperintense, and has cystic-necrotic areas. Sinal intensification (of solid type) after contrast bolus. It probably corresponds to a paraganglioma.

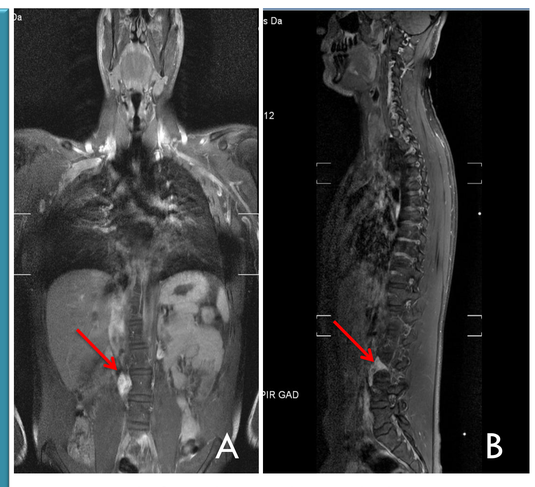

Figure 5: RMI T2 ponderation showing the hyperintense sinal anterior and laterally to L4 (red arrow).

Ophtalmologic Examination

Uneventful

MIBG scintigraphy:

Right adrenal hyperfixation sugestive of pheochromocytoma

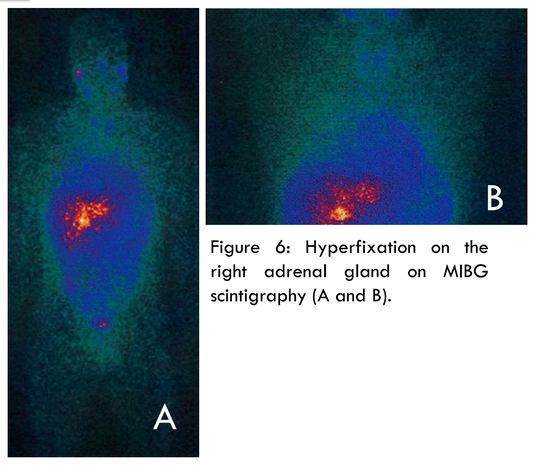

Figure 6: Hyperfixation on the right adrenal gland on MIBG scintigraphy (A and B).

Discussion and Conclusion

Ten to 20% of pheochromocytomas are familiar; VHLD is one of such hereditary syndromes. The VHLD-associated pheochromocytomas present in younger patients and are often multiple or bilateral.

We describe the clinical case of a young male diagnosed VHLD during genetic screening. Although completely asymptomatic and without analytic evidence of autonomous catecholamine production, a pheochromocytoma and a paraganglioma were diagnosed on morphologic and functional images. Despite the apparent non secretory nature of the lesions, presurgical preparation with α-blockers, ev normal saline and β-blockers was performed. The patient was submitted to right Aqrenalectomy, as well as excision of th pararaquidian lesion, and anatomopathologic examination confirmed the initial suspicion of RIGHT ADRENAL Pheochromocytoma and RIGHT LUMBAR PARAGANGLIOMA. No other components of the VHLD were found, namely brain, retinal, pancreatic or renal lesions.

Genetic testing allows for the early identification of VHLD patients, after one index case. As reported, these subjects may be asymptomatic although it is more uncommon that lesions would reach such dimensions and still remain non secretory and clinically silent. Also despite the same genetic abnormality, the phenotype was different from other affected relatives, and gender may be a relevant factor. Close follow up is justified given the complex and variable presentation that may become life threatening.

Bibliography: (1) Williams Textbook of Endocrinology; Melmed S, Plonsky K, Larsen P; Sounders Elsevier; 12th edition, 2011; (2) Lonser R, Glenn G, Walther M, *et al.* Von Hippel-Lindau Disease. *Lancet* 2003; 361: 2059–67; (3) Baghai M, Thompson G, Young W, *et al.* Pheochromocytoma and Paraganglioma in von Hippel-Lindau Disease. *Arch Surg.* 2002; 137:682-689

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