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Review article

Genetic pheochromocytoma/paraganglioma– A review

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ABSTRACT

The prevalence of pheochromcytoma in hypertensive patients is less than 1%.Most PHEOs occur sporadically, but a substantial proportion may be associated with germ line mutations of genes predisposing to the development of familial syndromes like multiple endocrine neoplasia(MEN),Von-Hippel Lindau(VHL) disease,neurofibromatosis type 1 (NF-1), familial paraganglioma/pheochromocytoma (PGL/PHEO) related to genetic mutation encoding the mitochondrial protein succinate dehdrogenase sub units(SDH-BCD) .Screening for genetic mutation is imperative as it may add more on management and surveillance of this patients .This review summarize the relevant data related to this fascinating clinical entity.

1. Introduction

Pheochromocytomas are catecholamine secreting tumors arising from chromaffin cells of adrenal medulla. However, 9-23% of this tumors originate from extra adrenal sympathetic or parasympathetic ganglions ,referred as extradarenal PHEOs or PGLs With the advent of genetic testing ,it is clear that ,about 30% of cases develop due to germ line mutations in any of the susceptible genes (Neumann et al., 2002, Amar et al., 2005, Pacak et al., 2007). Even patients with apparently sporadic PHEOs may harbor germ line mutations .patients with this familial syndromes are prone to develop other tumors associated with specific mutations. Beyond a single tumor, expression of this mutations may explore a broader clinical picture.

2. Genetic pheos/pgls

The common genetic mutations related to Pheochromocytomas and paragangliomas are RETprotooncogene,VHL,Neurifibromin and SDH sub units- BDC, responsible for the formation of multiple endocrine neoplasia(MEN-2), Von-Hippel Lindau disease(VHL), neurofibromatosis (NaF-1) and familial pheochromocytomas and paragangliomas respectively .Their clinical ,biochemical picture ,tumor location and susceptibility to develop malignant lesions are shown in the Table 1.

Table 1
Genetic syndromes and their characteristics.

Syndrome	Mutated gene	Type of tumor	Main secretion	malignancy	bilateral	Extra adrenal
MEN -2A and 2B	RET proto oncogene	pheo40-50%.PGL-rare	metanephrine	3%-5%	++	_
VHL	VHL gene	Pheos-10-20%,PGL 5%	Normetanehrine	<5%	+++	+/-
NF-1	Neurofibromini	Pheo<5%	Metanehrine/normetanehrine	10%	+/-	+/-
FamilaialPHEOs/PGLS	SDHD	Head&neck	Parasympathetic	Rare	+	+++
	SDHB	PGL	<5% catcholamine	40%	+	+++
	SDHC	Abdominal	Normetanehrine	Rare	+	+++
	SDHAF2	PGL	Parasympathetic	rare	+	+++
		Head& neck PGL	Parasympathetic			
		Head &neck PGL				

2.1. Associated components

Patients with MEN-2A are prone to develop medullary thyroid cancer (MTC- 95%) and hyperparathyroidism(35%) and MEN-2B group may develop aggressive MTC, mucosal neuromas ,thick corneal nerves ,intestinal ganglioneuromas and marfanoid habitus (Gagel et al., 1988, Brandi et al., 2001). Family members of this kindred should have genetic testing for RET mutation, and if found to carry mutation should offer prophylactic thyroidectomy.Carriers of VHL 2mutation are predisposed to develop multicentric haemangioblastoma in the retina, cerebellum and spine, clear renal cell carcinoma, cystic lesions in the pancreas, kidney, cystadnomas in the epididymis and broad ligament, nonfunctional neuroendocrine tumors of pancreas (Choyke et al., 1995) and endolymphatic sacs. In patients with VHL, the major risk of life is the development of renal cell cancer, and even simple renal cyst is considered as premalignant and their removal is advisable. Based on its clinical expression, VHL disease is subdivided into 4 subtypes (Koch et al 2002,Hes et al., 2003) –depicted in Table 2.

Table 2
VHL Mutations and their characteristics.

Type 1-VHL	Loss of VHL function–prone to develop hemangiblastoma/renal cell tumor, not at risk foe PHEOs
Type 2 VHL	
A	Prone to develop PHEO and hemangioblastoma ,low risk for renal cell cancer
B	PHEO and hemangioblastoma, high risk for renal cell cancer
C	Only PHEO ,no hemangioblastoma or renal cell cancer

Neurofibromatosis is presented with café-au-lait spots, cutaneous neurofibroma, optic glioma, axillary or inguinal feeckles, dysplasia of the sphenoid bone(Gutmann et al 1997). Familial PHEO/PGL is caused by the mutation in three of the four genes encoding succinate dehydrogenase sub units-SDHB-PGL4, SDHD-PGL-1, and SDHC-PGL3. They have a proclivity to develop sympathetic or parasympathetic tumors extending from neck to pelvis with or without adrenal pheochromocytoma.SDHD mutation is characterized by head and neck parasympathetic paraganglioma (glomus tumors) and less frequently with sympathetic PGLs and PHEOs (Baysal at el 2002,Benn at el 2006).Patients with SDHB is mainly come with sympathetic extra adrenal PHEOs (Brouwers at el., 2006, Timen at el., 2007) in the abdomen,mediastinum or pelvis and more likely to be malignant(Neumann at el., 2007). They are at increased risk for renal cell carcinoma and papillary thyroid cancer(Schiavi at el 2005).SDHC mutation is characterized by benign head and neck parasympathetic PGLS (Schiavi at el., 2005).

2.2.1. Genetic testing

Despite a high figure of unsuspected germ line mutations, genetic testing is restricted to patients who fulfill certain clinical criteria (Gimenz -Roqupo et al., 2006, Pacak et al., 2007). It is strongly recommended for extra adrenal PHEOs, multicentric, malignant tumors, family history of such tumors ,clinical presentation with other tumor components and presentation at a younger age (<50 years). All genetic PHEOs are inherited in an autosomal dominant manner. In kindred with SDHD mutation only paternal transmission of mutant gene cause susceptibility to PHEOs and PGLs and this phenomenon is known as maternal imprinting (Baysal et al 2002). The life time risk of developing PGLs in patients with this familial syndromes is around 1000% by the age of 70 years (Benn et al., 2006). The genetic PHEO patients require life time surveillance for tumor recurrence and the development of other tumor components.

2.2.2. Diagnosis

Although, a diverse clinical manifestation can be seen based on the variations of hormone secretion, generally they present with paroxysmal or sustained headache, palpitation, hypertension etc. Parasympathetic tumors usually come with local mass effect, cranial nerve dysfunction and only a small proportion (5%) is hyper functional. Biochemical diagnosis is made by raised plasma or 24 urine metanephrines level. A high level of chromogranin A (CgA) in patients with normal renal function, further support the diagnosis (Herbomez et al., 2007). Anatomical localization of the tumor by CT/MRI, followed by functional imaging using 123Iodine MIBG scan, PET scan or octreotide scan is required. Metastatic and malignant tumors are better detected by octreo scan compared with MIBG scan (87 vs 57%)(Vander Harst et al., 2001), possibly due to decreased expression of cell membrane nor epinephrine transporter.

2.2.3. Management

Definitive management is surgery. Patient should be prepared properly before surgery. Adequate control of hypertension using Alfa and beta receptor blockers, hydration including blood transfusion are important preoperative management steps (Takahashi et al 1985). As this tumor can recur, a long term follow up is required especially with genetic PHEOs /PGLs(Amar et al 2005).Patients with genetic PHEOs should be appropriately screened for associated tumor components and malignancy .Plasma or 24 urine metanephrine and chromogranin A are used to screened for any tumor recurrence.

3. Conclusion

It is well known that ,a significant percentage of patients with sporadic PHEOs and PGLS may have germ line mutation, predisposing to the development of a more generalized disease .It is worth doing genetic screening] in selected patients as it may reveal a broad disease spectrum. A Multidisciplinary team approach, involving clinical geneticist ,interventional radiologist, nuclear medicine, endocrine and oncology surgeon ,oncologist and last but not least ,endocrinologist is appropriate. The challenge is to have a tangible genetic testing, combination with appropriate imaging to confirm the presence of lesion and its secretory profile.

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