SDHx mutation and the hereditary Head- and Neck-paraganglioma: what the radiologist should know

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Learning objectives

SDHx mutation is a recent discovery in Head- and Neck-paraganglioma (HNPGLs, once known as "glomus tumors") and genetic fields, showing its influence on imaging work-up and therapeutic approach. These pieces of knowledge are increasing over the years along with the emerging clinical value of techniques for genetic analyses.

Background

In 1903 Alfred Kohn used for the first time the word "paraganglion" to describe the microscopic structure of the Organs of Zuckerkandl and their similarity with the neural ganglia[1, 2]. The term "paraganglia" was later extended to other tiny cellular nests scattered throughout the body deriving from neural crest. These little structures are closely associated and connected with nervous autonomic system, being also distinguished in sympathetic and parasympathetic paraganglia according to their different histologic features and anatomical district, referring to the Glenner-Grimley classification[1, 3]. In the head and neck region both branchiomeric and vagal paraganglia, respectively in relation to cervical vessels and X cranial nerve, are connected to parasympathetic nervous system. Moreover, these paraganglia present nonchromaffin cells having a chemoreceptor-like function and therefore typically non-secreting catecholamines; other paraganglia are instead related to sympathetic system and formed by chromaffin cells similar to adrenal medulla, indeed, more typically with a secreting phenotype[4]. The term "paraganglioma" (PGL) refers more typically to tumors originating from extra-adrenal paraganglia[5, 6]. Conversely, adrenal medulla paraganglioma is more commonly labeled as "pheochromocytoma" (PHEO). Paragangliomas-pheochromocytomas (PPGLs) is a common wording to indicate both pheochromocytoma and/or paraganglioma tumours, which might potentially arise anywhere along the paravertebral axis from the base of the skull to the pelvis[5]. HNPGLs are less common than PHEO, respectively 1:3, but twice more frequent than other extra-adrenal PGLs[3]. *SDHx* germline mutations determine a predisposition in all carriers to develop PPGL tumours. Other hereditary syndromes associated with PPGLs are neurofibromatosis type 1 (NF1), von Hippel-Lindau (VHL) disease, multiple endocrine neoplasia type 2 (MEN2), determined by mutations in *NF1*, *VHL* and *RET* genes; less known germ-line mutations described are in genes *HIF2A*, *TMEM127*, *MAX* and *FH*[5, 7].

SDHx mutation

Succinate dehydrogenase (SDH) is a mitochondrial protein complex made by subunits SDHA, SDHB, SDHC and SDHD, which correspond to as many nuclear genes. The complex plays a role in Krebs cycle and in the mitochondrial respiratory chain, working with small soluble proteins encoded by SDHAF1 and SDHAF2 (or SDH5) genes. The wording *SDHx* generally refers to all these genes. SDH complex would seem to play a role in tumour suppression mainly through inducible factor control (HIF-#). Mutations in *SDHB*, *SDHC* and *SDHD* are found in HNPGLs and PHEO, with a higher unexplained malignancy in SDHB tumors[3, 5, 8]. A germline mutation in these genes is present in all patients with Carney-Stratakis syndrome, where paraganglioma is associated with gastrointestinal stromal tumours (GIST). The importance of this genetic mutation lies in the risk of the coexistence of multiple tumours, including other types such as renal cell carcinoma, pituitary and papillary thyroid tumors[6]. The germline mutations

in *SDHA*, *SDHB*, *SDHC*, *SDHD*, and *SDHAF2* genes are also responsible for the familial syndromes, relatively called PGL5, PGL4, PGL3, PGL1 and PGL2, which held responsible for 40% of all cases of hereditary PPGLs; the same mutations have been found in 12% of the apparently non-hereditary PPGLs[3, 5, 6]. The full spectrum of SDHx-related disease is still not clear. In our clinical experience, we found a patient with SDHB germline mutation and simultaneous carotid body paraganglioma in association with follicular lymphoma[9]. WHO defines malignant a paraganglioma only if distant metastases are found[5, 6]. Only 10% of PPGLs are malignant, but malignancy reaches 30-40% in some groups with higher risk [6, 10]. SDHB-related PGL represents 23% of all malignant paraganglioma, whereas SDHD is only 3%[3, 5]. In the future recognizing *SDHx* might permit us to use some molecular targeted therapy[3].

Findings and procedure details

Hereditary HNPGLs are linked to *SDHD* in >50% of cases, *SDHB* in 30% and *SDHC* in 15%. These do not affect all relatives, because of their low morbidity, symptoms and penetrance. HNPGLs usually are non-secreting (95%) and, for a third of them, the only blood biomarker is a dopamine metabolite called 3-methoxytyramine(3MT)[3, 8]. The main symptoms of HNPGLs depend from compression of neuro-vascular structures, potentially presenting an indolent neck mass or a pulsatile tinnitus/hypoacusia in case of jugular or tympanic tumors[3].

The Radiologist should know:

1) RADIOLOGICAL FEATURES OF PARAGANGLIOMAS(Fig.1), recognizing typical sites and appearance of PGLs on US, CT and MRI modalities[11].

2) CLASSIFICATION OF HNPGLs(Fig.2)

Classifications are commonly used to guide treatment, in fact the main role of imaging is to select patients who could benefit from curative surgical resection. Pre-operative embolization is suggested for jugular paragangliomas (JP) and carotid body paragangliomas (CBP), whereas in tympanic paragangliomas (TP) and vagal paraganglioma (VP) is not usually performed. Other therapeutic strategies consist in radiotherapy or observational approach in selected cases[12].

3) RISK OF SDHx GERMLINE MUTATION FOR METASTASIC AND SECONDARY TUMORS

If genetic status is known, the radiologist should accurately investigate the presence of metastasic/multicentric disease and secondary tumors in SDHx mutation carriers (especially GISTs and kidney tumors with *SDHB* mutation)[5]. The European Society of Endocrinology in 2016 recommended genetic testing in all patients with PPGL and screening for metastatic tumors by 18F-fluorodeoxyglucose-positron emission tomography (^{18}FDG-PET) in SDHB carriers[6]. Exposure to radiation should also be limited during the follow-up. Even though immunohistochemistry can give information on the occurrence of a mutation in *SDHx* genes, it could be difficult to interpret[5].

Nuclear Imaging results more sensible for diagnosis and is based on Scintigraphy, Single-photon emission computed tomography (SPECT) and Photon emission tomography (PET). This latter, commonly combined with CT scanning, shows the best results and employs several radiotracers:

- 68 Ga-labeled DOTA(0)-Tyr(3)-octreotide(^{68}Ga-DOTATATE PET) has a very high and selective affinity for PPGLs, both sporadic or hereditary, because these tumours present somatostatin receptor type 2 (SST2), especially HNPGLs[5, 7, 8].

- ^{18}FDG-PET sensitivity for metastatic disease is high in *SDHx*- and *VHL*- PPGLs[7, 13], becoming the first-line imaging modality in follow-up of patients with SDHB-related metastatic tumours and to monitor patients' response to therapy [7, 8].

- 18 F-fluorodihydroxyphenylalanine (^{18}F-FDOPA-PET) is sensitive for HNPGLs, independently from SDHx mutation[7, 8].

Over the years ^{68}Ga-DOTATATE PET/CT surpassed ^{18}F-FDOPA PET/CT as functional imaging modality of choice for PPGLs, particularly in sporadic and SDHB-related metastatic disease. ^{18}F-FDOPA PET/CT might still be superior in detecting PPGLs in somatic HIF2A gain-of-function mutation or for small PHEO with *SDHx* mutation. It is useful also for disease staging, differentiation between relapse and residual disease after surgery, selection of candidates for radiometabolic treatment (PRRT) with radionuclides (^{177}Lu,^{90}Y,^{111}In) and targeting molecules (DOTATATE, DOTANOC, DOTATOC)[7].

Iodine-123-metaiodobenzylguanidin (^{123}I-MIBG) is a structural guanethidine analogue similar to noradrenaline, very useful for pheochromocytoma, but it can miss extra-adrenal paragangliomas and metastases, particularly when associated with SDHx mutations[5, 13, 14].

Images for this section:

ULTRASOUND (US) in case of neck PGLs	Iso-hypoechoic mass mostly ovoid, homogeneous and well-defined At Color Doppler the mass results markedly hypervascular
COMPUTED TOMOGRAPHY (CT)	Intense arterial wash-in with early wash-out. Sometimes it may appear disomogeneous because of intratumoral haemorragic and trombotic phenomena. CT imaging is excellent for evaluation of osseous involvement, especially of temporal bone in JP. CT angiography can help in the pre-operative surgical assessment of tumour, including vessel anomalies that may complicate the intervention.
MAGNETIC RESONANCE IMAGING (MRI)	Low to intermediate signal intensity on T1- and protondensity-weighted sequences and a high signal intensity on T2-weighted images. Sometimes a "salt-and-pepper" pattern is recognizable, with the salt representing the hyperintense haemorrhagic areas (or slow flow) and tumour matrix, whereas the pepper representing the high flow in the intratumoural vessels and corresponds to areas of flow void as punctate or serpentine hypointense foci. After administering paramagnetic contrast medium, the lesions show high vascularization. Diffusion weighted imaging (DWI) may also be useful. In HNPGLs, MRI is generally preferred to other radiological techniques.

[9, 11, 12]

Fig. 1: Radiological features of Paraganglioma

SHAMBLIN CLASSIFICATION FOR CAROTID BODY PARAGANGLIOMA (CBP)		
CBP arises at the bifurcation of carotid arteries - 60% of HNPGLs - 40% SDHx		**FIRST-LINE THERAPY**
Class I	CBP adherent to the adventitia of the artery	RESECTION
Class II	CBP partially encircles the artery	RESECTION
Class III	CBP encircles or encompasses the artery	RADIOTHERAPY **SDHB+→ RESECTION**

NETTERVILLE CLASSIFICATION FOR VAGAL PARAGANGLIOMA (VP)		
along the course of the vagus nerve, below the jugular foramen and behind the mandible. It might extend to the jugular foramen or extend to the carotid bifurcation. - 5% OF HNPGLs - 30% SDHx		
A	VP confined to the neck	RADIOTHERAPY? **SDHB+ → RESECTION**
B	VP extended to jugular foramen	RADIOTHERAPY **SDHB+ → RESECTION?**
C	VP extended beyond the jugular foramen, with or without intracranial invasion	RADIOTHERAPY **SDHB+→ RESECTION?**

The displacement of internal and external carotid body can help distinguishing CBP from VP: the VPs usually move anteriorly both the carotid vessels and backward the jugular vein [11, 12].

[8, 12, 14]

FISCH CLASSIFICATION FOR SKULL BASE PARAGANGLIOMA			
A	**TP (Tympanic PGL)** arising from the cochlear promontory, confined to the tympanic cavity -6% of HNPGLs -rarely SDHx	along tympanic plexus on promontory	RESECTION
B		invasion of hypotympanon; cortical bone over jugular bulb intact	RESECTION
C1	**JP (Jugular PGL)** associated with the adventitia of the jugular bulb, expanding from the jugular foramen along pneumatized portions of the temporal bone -23% of HNPGLs -25% SDHx	erosion of carotid foramen	Debated, but RADIOTHERAPY is preferred because of the high risk of complications and recurrences after surgery. **SDHB+→ RESECTION?**
C2		destruction of carotid canal	
C3		invasion of carotid canal; foramen lacerum intact	
C4		Invasion of foramen lacerum and cavernous sinus	
De ½	D classification cannot be apart from C classification.	intracranial extension, no infiltration of interarachnoidal space. According to the displacement of dura: • De1 5 <2 cm • De2 5 >2 cm	
Di 1/2/3	D classification cannot be apart from C classification.	intracranial and intradural extension, Di1–Di3 according to depth of invasion into posterior fossa: • Di1 5 <2 cm • Di2 5 2 -4 cm • Di3 5 >4 cm	**Di1/2 →**RESECTION involving ENT specialist and neurosurgeon **Di3 →** RADIOTHERAPY
Glasscock/Jackson classification is another classification used to describe TPs and JPs			

The multidisciplinary assessment of the patient (age, comorbidities, genetic status) and of the tumour (dimension, catecholamine secretion, multicentric disease, mass effect and growing rate) should be considered in the therapeutic choice. "Wait and see" strategy is common in asymptomatic tumours, furthermore it permits to observe their growth before an operative strategy.
Before surgery, a preoperative embolization should be considered in JPs or larger CBPs and VPs. Metastatic disease can be treated with PRRT.

Fig. 2: Classifications of the Head and Neck Paragangliomas.

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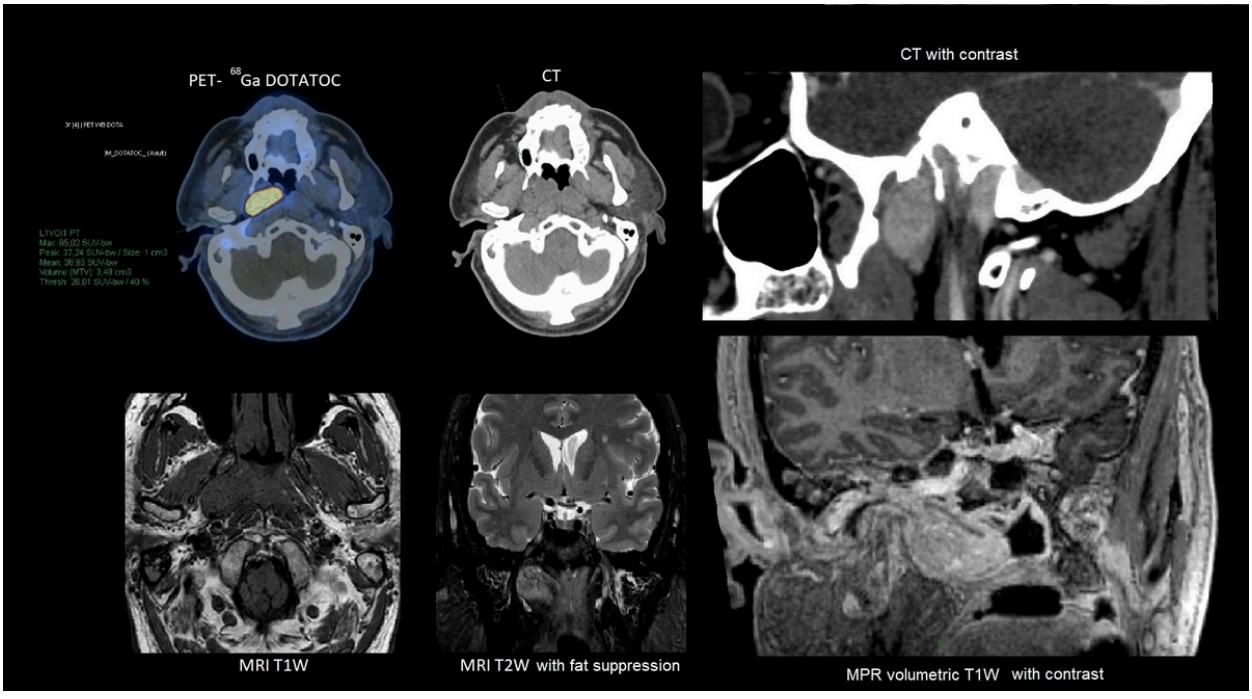

Fig. 3: PET-68Ga-DOTATOC, CT and MRI images with MPR reconstructions in both CT and MRI with contrast that show the appearance of a jugulotympanicum paraganglioma, indeed involving the jugular fossa and the middle ear with an uncommon extension to the nasopharynx through the Eustachian tube.

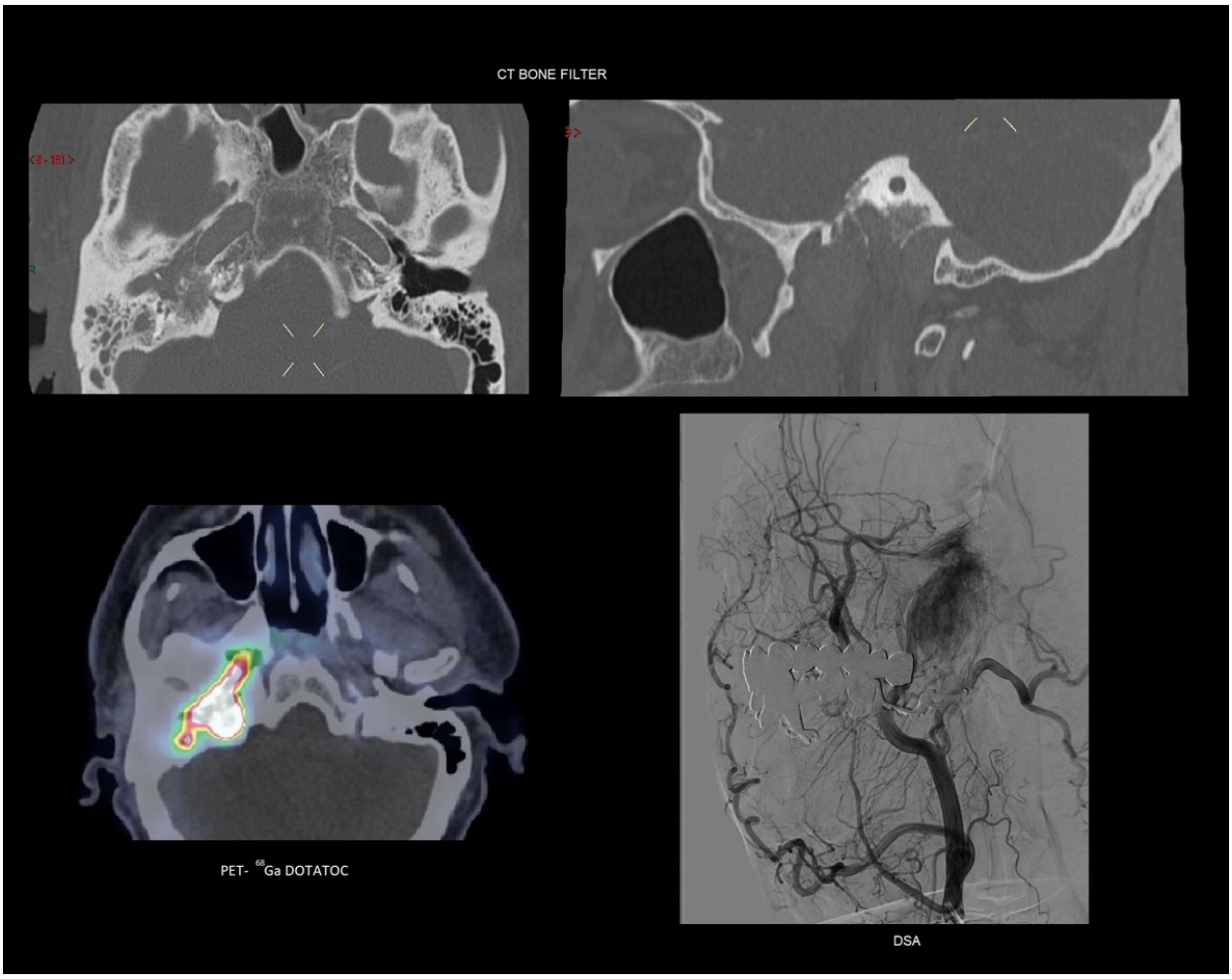

Fig. 4: In the upper CT images, the same patient with a jugulotympanicum paraganglioma determining the bone erosion of the temporal bone between the jugular and the carotid foramina. In the bottom left scan, PET-68Ga-DOTATOC\CT confirms that the resorption phenomena are partially due to the bone infiltration of the tumor. In the bottom-right corner, the image presents an angiogram of the right external carotid artery feeding the large hypervascularized mass of the paraganglioma.

Conclusion

A multidisciplinary clinical evaluation focused on the specific case is always mandatory in HNPGLs, guided by multimodality imaging. *SDHx* mutation should always be investigated in case of PPGLs and considered to establish the therapeutical strategy.

Personal information and conflict of interest

M. Giganti; Ferrara/IT - nothing to disclose L. Perrucci; Ferrara/IT - nothing to disclose L. Marchetti; Ferrara/IT - nothing to disclose R. Galeotti; Ferrara (FE)/IT - nothing to disclose

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