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REVIEW ARTICLE

Carotid Body Tumor – radiological imaging and genetic assessment

Authors' Contribution:
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ABSTRACT: Carotid Body Tumor i.e. Paraganglioma is a challenging entity from the point of view of multidisciplinary diagnosis. The main treatment option, i.e. surgery, yields intraoperative risk related to cranial nerve palsy and vascular morbidity. Bifurcation of the common carotid artery, especially at the carotid body, is the place were head and neck paraganglioma is most frequently seen, i.e. in 60% of cases [15]. Indeed, the knowledge of genetic germline SDH mutations, which cause deregulation of hypoxia-induced factors, allows for better understanding of the tumor nature. It is recommended to conduct selective neck dissection in regions IIA, IIB, III to exclude malignant transformation and metastasis, due to malignant potential of carotid body tumors, especially in case of SDHB mutation. SDHD mutation is the main cause of hereditary HNPGLs. Computed tomography (CT), magnetic resonance imaging (MRI) and angiography allow for thorough assessment of paraganglioma extension. In large tumors embolization of the supplying artery under guidance of angiography may be considered. In case of carotid body tumor, differential diagnosis should include: carotid artery aneurysm, lymphadenopathy, Schwannoma of the hypoglossal nerve or accessory thyroid gland.

KEYWORDS: angiography, Carotid Body Tumor, computed tomography, germline mutations, magnetic resonance, paraganglioma

ABBREVIATIONS

CBT – Carotid Body Tumor
CT – Computed Tomography
ECA – External Carotid Artery
HNPGL – Head and Neck Paraganglioma
ICA – Internal Carotid Artery
MRI – Magnetic Resonance Imaging
US – Ultrasonography

INTRODUCTION

Approximately 30% of all PGLs are caused by germline mutations of genes associated with the mitochondrial succinate dehydrogenase complex (SDHD, SDHB, SDHC) and follow autosomal dominant inheritance [1]. Malignancy of Carotid Body Tumor (CBT) i.e. Paraganglioma is not defined by tumor size, hypervascularity, pleomorphism or mitotic figures, but by metastases in non-endocrine tissue [2, 3]. This is why in case of surgical treatment of carotid body tumor, ipsilateral lymphadenectomy (region IIA, IIB, III) is recommended to identify malignant tumors [4]. Presence of distant metastases and regional lymph nodes' alterations indicates malignancy [5].

According to Sanna et al. [4], postoperative screening for distant metastases comprises: CT scan of the thorax and abdomen, PET scan and scintigraphy (with octreotide). Preoperatively performed computed tomography imaging as well as magnetic resonance describes the level of internal and external carotid artery displacement. Carotid body tumors, as they increase in diameter, displace the internal carotid artery postero-laterally and the external carotid artery antero-medially. Arterial, vascular supply to the highly vascularized carotid body tumors, is via the ascending pharyngeal artery, however, lingual artery, superior thyroid artery and muscular branches of the occipital and vertebral arteries also take part [4].

EPIDEMIOLOGY, CLINICAL ASSESSMENT AND SHAMBLIN'S CLASSIFICATION

Carotid body tumors are the most common type of paraganglioma of the head and neck. They are usually diagnosed in females in the 4th to 5th decade of life. Typically, these tumors are located at the bifurcation of the common carotid artery as slow-growing rounded masses, splaying the internal and external carotid arteries. On palpation, carotid body tumor appears as a pulsating mass, movable only in horizontal i.e. cephalocaudal direction ("Fontaine sign") [6, 7]. However, a rare clinical manifestation is an abnormal position of the neck with increased tension, tightening of the broad neck muscle (Latin: *musculi colli*) and unilateral hearing impairment [8]. Malignant transformation has been reported in up to 36% of cases, however, it differs between the authors, e.g. ranges from 2% to 50% [6, 9]. Carotid body was described for the first time by Haller in 1743 [1]. The carotid body is a chemoreceptor organ, that mediates reflex hyperventilation during hypoxemia by the activation of the respiratory center. The afferent reflex from the carotid body is mediated by the glossopharyngeal nerve, a branch called the nerve of Hering. Annual growth rate of carotid body tumor is roughly 1–2 mm [10].

High altitude over the sea level may lead to increased growth of carotid body tumor. The mechanism is as follows: glomus cells secrete endothelin-1, which induces stem cell-dependent carotid body hypertrophy for better acclimatization to chronic hypoxemia. The Shamblin's classification is used to accurately assess tumor – relationship with vessels and local invasion [1]. The Shamblin grades are as follows:

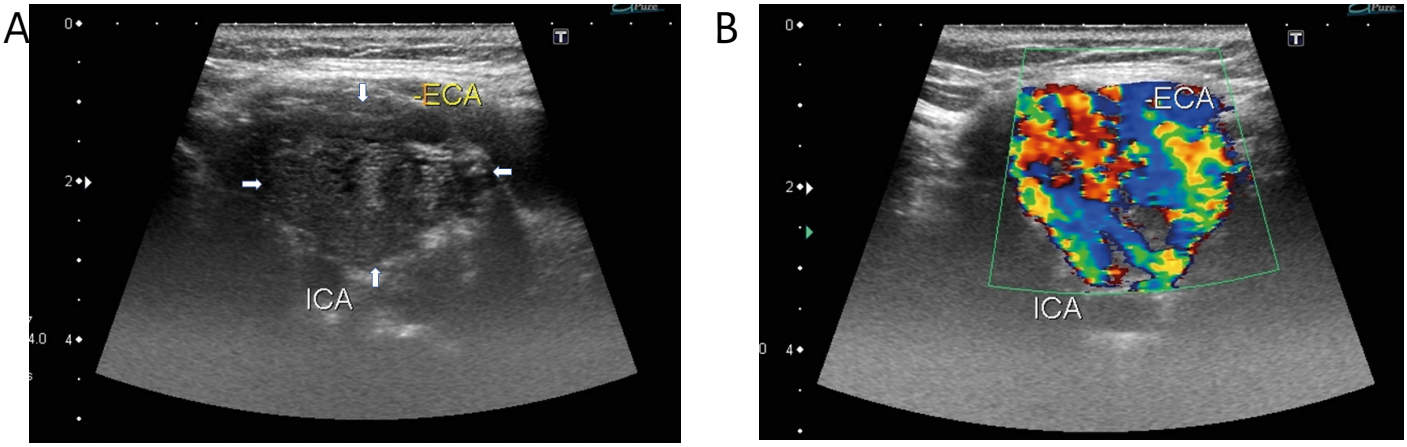

Fig. 1. Ultrasonography as an appropriate tool for an initial study of the neck. However, it has limitations in assessing tumors extending into the skull base. Images courtesy of TMS Diagnostyka, Bialystok, Poland.

- I grade – the tumor splays the carotid bifurcation, has a small attachment to the carotid vessels and can be easily resected;
- II grade – tumor involves carotid vessels partially;
- III grade – tumor encases carotid vessels completely.

In case of CBTs adherent or partially surrounding the carotid vessels (Shamblin class I/II) resection of the tumor in periadventitial plane has a lower risk of vascular morbidity and iatrogenic cranial nerve damage. Complete surgical resection is recommended even in Shamblin class III tumors, also in tumors of 3.5 cm maximum diameter and larger. Moreover, Fruhmann et al. [1] observed that cranial nerve resections were unpreventable in surgical removal of carotid body tumors measuring at least 3.5 cm and also collaboration with vascular surgeon is advisable because vascular reconstructions are indispensable in up to 25% of cases. Intraoperative hypersecretion of vasoactive substances is rare. Hormonal activity of a tumor should be assessed preoperatively. Results of biochemistry test decide whether adrenergic blockade has to be used. Dopamine metabolite 3-methoxytyramine is a biochemical marker which seems to be rarely elevated in HNPGLs. Also, urine metanephrines have to be measured. Elevations of metanephrines may indicate concurrent pheochromocytoma or thoraco-abdominal PGLs. In such a case, preoperative CT, MRI of the pelvis, abdomen, thorax should be performed to exclude suspicion of PGLs' multiplicity.

Clinical geneticists advice all patients to undergo screening for germline mutations to assess postoperative recurrence or new occurrence of PGLs in other locations. Postoperative follow-up is strongly recommended for all CBT paraganglioma patients. Annual biochemical screening and MRI are advised for mutation carriers, especially SDHD. SDHD mutation is the main cause of hereditary HNPGLs.

RADIOLOGICAL IMAGING

Radiological imaging of the carotid body tumor plays pivotal role in the pre-operative diagnosis. It is of particular importance due to the contraindication to the carotid body tumor biopsy [11]. A high degree of vascularization carries a risk of life-threatening bleeding during biopsy of the carotid body tumor [11]. Ultrasound (US) examination may be the first method that accidentally detects a neck tumor. Typically, in US, carotid body tumor are relatively well-defined soft tissue masses, predominantly hypoechoic, in the bifurcation of the common carotid artery. In color and power Doppler these lesions appear hypervascular with multiple vascular channels inside.

Contrast-enhanced CT is a good method of paraganglioma detection. In CT, carotid body tumor is usually a homogeneously and vividly enhancing soft tissue mass seen at the carotid bifurcation with splaying of the ICA and ECA. With computed tomography angiography we can visualize the tumor being supplied by the branches of the external carotid artery. The need of contrast media and radiation dose limits the use of this method in a long-term observation.

Of huge importance is that MRI imaging is superior to CT because MRI does not expose patients to ionizing radiation and allows for accurately delineated soft tissue extension. In T2-weighted images PGL is always a hyperintense lesion. When large, in T1- and T2-weighted images the tumor has pathognomonic punctate regions called "salt and pepper" appearance. It is related to high-flow vascular voids within the tumor [2, 4]. Classic "salt and pepper effect" comprises low signal flow voids i.e. "pepper" and high signal foci of hemorrhage, i.e. "salt" [6].

As in CT, tumors on MR produce high signal intensity following gadolinium administration, due to contrast enhancement. The splayed and displaced carotid bifurcation appears in a typical 'Goblet deformity' [1, 12].

Digital subtraction angiography (DSA) is not necessary in diagnostic procedures, but it evaluates the supplying vessels the best. Angiographic evaluation with early arterial and venous phase is mandatory to assess tumor blood flow, tumor flow dynamics, displacement of major vessels – e.g. angiographic evaluation of jugulotympanic paragangioma assesses venous outflow of the contralateral and ipsilateral transverse sinus and jugular system, which have to be evaluated preoperatively. Piazza et al. [13] elicit that anatomical variation in the form of an absent or contralateral hypoplastic jugular system is a contraindication for surgical treatment of jugulotympanic paraganglioma because of increased risk of venous stroke after surgery [14, 13].

Due to the fact that paragangliomas show neuroendocrine features, scintigraphy with metaiodobenzylguanidine (MIBG) and octreoscan can be useful for assessing multiple lesions.

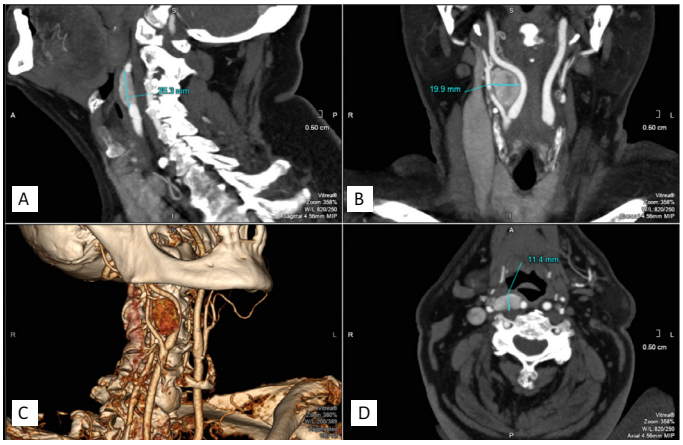

Fig. 2. Computed tomography angiography revealed hypervascular mass at the right common carotid artery (CCA) bifurcation splaying the internal (ICA) and external (ECA) carotid artery. It measures around 25 x 19 x 11 mm (HFxRLxAP). The right ICA is surrounded by the tumor less than in a half. The right ECA is only adherent to the tumor. Internal jugular vein (IJV), CCA and ICA are patent. A – sagittal, B – coronal, D – axial maximum intensity projections (MIP) reconstruction. C – 3-dimensional reconstruction.

TREATMENT

In large tumors preoperative embolization helps reduce blood loss during surgery. Preoperative embolization is not recommended in small tumors (less than 3 cm in diameter) as it can overweight its potential benefits. However, in large size tumors embolization of the ascending pharyngeal artery or occipital arteries may be considered. The results of embolization may be assessed by MRI with gadolinium contrast (24–48 hours after the embolization) e.g. T1W imaging with contrast detects avascular i.e. hypointense areas. Computed tomography scans with iodine contrast (24 hours after embolization) gives comparable results [6]. Also, preoperative angiographic balloon occlusion (BOT) test of ICA may be performed if the risk of intraoperative interruption of the ipsilateral common or internal carotid artery occurs [15, 6].

Surgical treatment is the only curative option for carotid body tumor – paraganglioma. Radiation seems to be an option when deleterious nerve damage is inevitable and in patients who refuse surgical treatment. However, the risk of development of malignant post-radiation tumor persists in young patients. "Wait and scan" strategy in case of carotid body tumor is advised to elderly patients who are free of PGL's symptoms but who suffer from other comorbidities. "Wait and scan" policy may be taken into consideration in selected cases and withhold surgical intervention. In the head and neck region, surgical resection of carotid body tumor also carries the risk of complications e.g. hypoglossal, accessory and vagus nerve paralysis or sympathetic nerve injury, [6] thus, tumor growth is an important factor in the "wait and scan" approach [16]. The most often chosen imaging modalities used in radiological "wait and scan" follow-up are computed tomography (CT) and magnetic resonance imaging (MRI) – both show avid contrast enhancement, although MRI size and morphology follow-up assessment does not require contrast media administration.

Surgical excision is recommended also in cases of catecholamine-secreting paragangliomas, as resistant to radiotherapy chief cells secrete granules containing catecholamines. Thus, the first option in the treatment of patients with catecholamine-secreting tumors is surgery. Only surgical excision leads to normalization of catecholamine levels and suppression of cardiovascular symptoms. Secreting paragangliomas are rare in the region of the head and neck, constituting approximately 3% to 5% [17].

GENETIC TESTING IN HEAD AND NECK PARAGANGLIOMA

Succinate dehydrogenase is a mitochondrial enzyme complex with an important role in oxidative phosphorylation and intracellular oxygen sensing and signaling. SDH is a part of the mitochondrial electron transport chain and catalyses the oxidation of succinate into fumarate in the Krebs cycle [18]. Within the succinate dehydrogenase complex, mutations in three genes: SDHD, SDHB, and SDHC occur [19]. Approximately 30% of all PGLs are caused by germline mutations of genes associated with the mitochondrial succinate dehydrogenase complex and follow autosomal dominant inheritance [1]. Martin et al. [20, 21] explained the pathogenesis of SDH mutations as follows: SDH mutations cause dysregulation of hypoxia, yielding a cellular response leading to paraganglia hypertrophy. Secondly, SDH mutations cause inactivation of some factors, such as prolyl hydroxylase Eg1N3, that mediate apoptosis in paraganglionic cells [20]. However, the cost of mutational screening at all 3 main SDH loci (SDHD, SDHB, SDHC) is high for the National Health Care System (roughly $ 2, 700 per patient) [19]. The majority of investigations highlight the necessity of genetic assessment in case of head and neck paragangliomas. Boedeker et al. [22] found a prevalence of SDHD mutations (45 cases) and SDHB mutations (13 cases) amongst 195 patients with head and neck paragangliomas. SDHD is the most common mutation, followed by SDHB and then SDHC. This is a meaningful information that SDH mutations are generally inherited in an autosomal dominant pattern.

SDHB-related sympathetic paragangliomas (sPGL) occur in extra-adrenal tissue and according to Neuman et al. [23] are characterized by a strong tendency for metastatic spread. However, Hes et al. [24] showed a low penetrance of SDHB mutation in a large paraganglioma family. Also, Heesterman et al. [25] revealed in their clinical study only 12% of SDHB mutations responsible for asymptomatic head and neck tumors, which confirms the low penetrance of mutation, despite the malignant potential [25]. Malignant PGL is a kind of tumor which presents metastatic lesions in the lymph nodes, bone, lung and liver, that is in the tissues where chromaffin is normally absent. Neumann et al. [23] found among 32 patients with SDHB-associated PGL adrenal pheochromocytoma, extra-adrenal abdominal or thoracic sympathetic paraganglioma, head and neck paraganglioma in 28%, 59%, and 31% respectively. Moreover, 28% had multifocal tumors.

According to Amar et al. [26], SDHB mutation is a valuable predictor of mortality, i.e. in a group of 54 patients with malignant sympathetic paraganglioma, a 5-year probability of survival was roughly 36% in SDHB mutation carriers in comparison to 67% in the patients who did not express SDHB mutation. Moreover, according to Ricketts et al. [27], SDHB mutations are associated with renal cell carcinomas of early onset. Aggressive tumor behavior means young age of onset, metastatic disease at presentation, hypersecretion of catecholamines. Standard treatment for a potentially malignant carotid body tumor-PGL is resection of the primary tumor and neck dissection [2]. The problem appears in case of bilateral carotid body tumors,

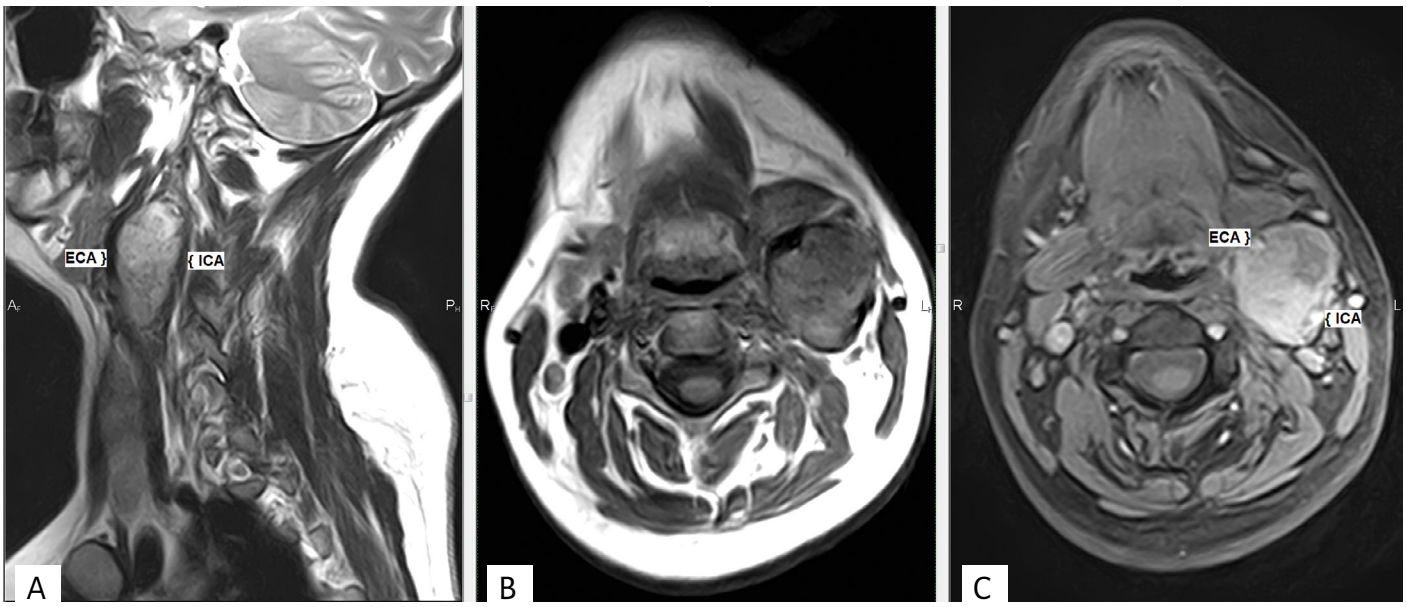

Fig. 3. MRI as the third step in confirmation of carotid body tumor.

treated with surgery, leading to baroreceptor function loss, and thus labile refractory hypertension, headache, and tachycardia. According to Sanna et al. [28], long-term treatment with Clonidine is advised. Clonidine is a medication for baroreflex failure because it acts as a central agonist to alpha-2 receptors resulting in decreased norepinephrine release [29].

SDHC mutations are a kind of rare germline mutations which may be concomitant with carotid body tumor (CBT) paragangliomas. Clinical behavior of sympathetic paragangliomas in SDHC mutation carriers is similar to benign sporadic sympathetic paragangliomas (sPGL) [15].

SDHD mutations are related to multifocal head and neck paragangliomas, such as bilateral carotid body tumors (CBTs) which explains the necessity of thorough examinations in follow-ups and indispensable Magnetic Resonance Imaging (MRI) of the head and neck. SDHD mutation carriers also develop benign paragangliomas (PGL) [30, 18]. The incidence of malignancy is decreased in mutated SDHD gene carriers compared to mutated SDHB gene carriers [13]. According to Heestermann et al. [25], the penetrance of SDHD-related paraganglioma is influenced by genomic imprinting. There is almost a complete absence of disease following maternal transmission i.e. transmission of the SDHD mutation via the maternal line is therefore not considered to be a risk for paragangliomas. Incomplete penetrance is observed in paternal transmission (43–100%) [31, 25]. However, Heesterman et al. [25] revealed in their study of asymptomatic SDHD mutations carriers that a high number of occult head and neck paragangliomas and even multiple tumors may stay undetected. According to Schiavi et al. [32, 18], in the European-American registry of patients with paraganglioma (PGL), the prevalence of SDH mutations was roughly 10% in 371 patients with sporadic sympathetic paragangliomas and approximately 28% among 121 patients with head and neck paragangliomas. Thus, genetic testing in head and neck paragangliomas (HNPGL) e.g. carotid body tumors, can have profound implications for patients and their family counseling. According to Sridhara et al. [19] testing for SDHD and secondly for SDHB mutations is recommended in all patients suspected of a hereditary HNPGL and also those with younger age, multiple tumors, carotid body tumors and positive family history. Moreover, the most common hereditary syndromes involving paraganglioma and pheochromocytoma include multiple endocrine neoplasia type 2, von Hippel-Lindau disease and neurofibromatosis type 1 [19]. Mutations of RET, NF1 and VHL were also registered in rare cases of head and neck paragangliomas [33]. Therefore, testing for a genetic alteration at the VHL and Ret foci in cases of HNPGL is not recommended as a routine procedure but can be considered if family history suggests such a syndrome [19].

Follow-up of patients harbouring SDH germinal mutations is the matter of considerable debate up to date. Collins [34] proposed a strategy in SDHB mutation carriers to perform radionucleotide screening by 18-F fluorodeoxyglucose positron emission tomography (18F-FDG-PET) and annual MR imaging. According to Jasperson et al. [35] study, whole body MRI for SDH-related tumors has a higher sensitivity than biochemical testing (catecholamines, metanephrines) in patients undergoing screening due to their SDHB or SDHC mutations. Annual screening was performed in 37 SDH carriers, with MR imaging of the area from the skull base to the pelvis. Six new tumors were diagnosed in five patients i.e. paragangliomas of the organ of Zuckerkandl, renal cell carcinoma and in the region of the head and neck three cases of carotid body tumors. Complete annual MR imaging for patients harboring SDHD mutation is firmly recommended. Moreover, whole-body MRI reduces radiation exposure as compared to computed tomography scan (CT).

CONCLUSIONS

Patients with Carotid Body Tumor-Paraganglioma should be tested for germline mutations, first at the SDHD locus and then the SDHB locus which decreases the cost of genetic evaluation and gives a predictive value. Since patients harboring SDHD mutations, which are associated with multifocal tumors (e.g. bilateral carotid body tumors in the head and neck region) and SDHB mutations associated with the occurrence of malignant tumors, need screening, there is a strong recommendation to perform annual physical examinations with imaging e.g. MRI with gadolinium contrast.

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