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Evaluation of Head and Neck Paragangliomas by Computed Tomography in Patients with Pheochromocytoma-Paraganglioma Syndromes

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A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Summary

Background: Hereditary head and neck paragangliomas (HNP) are very often associated with pheochromocytoma-paraganglioma syndromes, which are caused by mutations in genes encoding subunits of succinate dehydrogenase (*SDHx*) complex.

The aim of this study was to determine the frequency and location of HNP among SDHx carriers.

Material/Methods: A total of 72 patients with *SDHx* mutations underwent computed tomography examinations of the head and neck. HNP were present in 44 (61.1%) out of 72 patients (31 *SDHD*, 11 *SDHB*, 2 *SDHC*); 113 HNP were found; the most common were carotid paragangliomas (59) and vagal paragangliomas (27).

Results: The HNP were statistically more frequent in carriers of *SDHD* mutations compared to carriers of *SDHB* mutations (72.1% *vs.* 43.5%, p=0.033). Multiple tumors more often occurred in patients with *SDHD* mutations 26/31 (83.9%) than in patients with *SDHB* mutations 6/11 (54.5%) p=0.05.

There was a significant difference in the prevalence of carotid paragangliomas between patients with *SDHB* and *SDHD* mutations (7/11 [63.6%] *vs.* 30/31 [96.8%], respectively, p=0.004). Patients with *SDHD* mutations more often had carotid paragangliomas located on the left side than on the right side, as compared to *SDHB* mutations 25/31 (80.6%) *vs.* 4/11 (36.4%), p=0.006.

Conclusions: *SDHx* mutations predispose to multifocal and bilateral HNP. Carotid and vagal paragangliomas occurred most often.

Patients with *SDHD* mutations are characterized by higher frequency of HNP than patients with *SDHB* mutations, which is mainly driven by higher frequency of carotid body tumors in patients with *SDHD* mutations. No difference in the frequency of head and neck paragangliomas in other locations was found.

MeSH Keywords: Carotid Body Tumor • Head and Neck Neoplasms • Paraganglioma, Extra-Adrenal • Succinate Dehydrogenase

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Background

Head and neck paragangliomas (HNP) are rare vascular tumors accounting for less than 0.5% of all head and neck tumors [1]. They are highly vascular neoplasms, mostly benign, but clinical symptoms depend on their size and location. In general, HNP are characterized by a slow rate of growth and, potentially, they remain stable and clinically silent over years. These neuroectodermal tumors arise from a group of tissues (paraganglia) which migrate along the branchiomeric (of the branchial mesoderm) distribution in the head and neck region. Paragangliomas within the head and neck arise mainly from four primary sites: carotid bodies, common carotid artery bifurcation (carotid paragangliomas), jugular foramen (jugular paragangliomas), along the vagus nerve (vagal paragangliomas), and the tympanic branch of the ascending pharyngeal artery within the middle ear (tympanic paragangliomas). Other sites, including the paranasal sinuses, larynx, cervical sympathetic chain, parathyroid gland and thyroid gland are rare [2].

The majority of paragangliomas evolve sporadically, but one-third to one-half of cases have familial etiology [3,4].

Mutations in ten different genes connected with hereditary HNP were found [2].

Pheochromocytoma-paraganglioma (PGL) syndromes are associated with *SDHx* gene mutations, encoding the subunits of the succinate dehydrogenase enzyme complex, subunit D *(SDHD*), B (*SDHB)* and C (*SDHC*), (PGL type 1,4, and 3, respectively). Recently, germline mutations in two consecutive subunits of succinate dehydrogenase (*SDHA, SDHAF2*) have been found in patients with pheochromocytoma-paraganglioma syndrome [5]. HNP association with other genetic multisystemic disorders such as von Hippel-Lindau (*VHL*), transmembrane protein 127 (*TMEM 127*), neurofibromatosis type 1 (*NF1*), MYC-associated factor X (*MAX*), protooncogene *RET* occurs rarely [6–9].

Patients with hereditary syndromes are at a higher risk of having multifocal disease [10].

The aim of this study is to determine the frequency and location of HNP among SDHx carriers.

Material and Methods

Patients

The patients with confirmed *SDHx* mutations by genetic testing entered the study.

This study consisted of 72 patients with *SDXs* mutations (36 men, 36 women, mean age 44±14.26 y, age range 13–74 yrs, 44 index cases, 28 relatives), 23 (31.9%) patients with *SDHB* mutations, 5 (6.9%) with *SDHC* mutations, and 44 (61.1%) with *SDHD* mutations.

Patients with the Polish Pheochromocytoma-Paraganglioma Registry were included in our study. All SDHx germline mutation carriers underwent screening work-up which included computed tomography (CT) of the head and neck.

Clinical characteristics of patients are present in Table 1.

All patients gave their informed consent before participating in the study. The study was approved by the local ethics committee.

Methods

Computed tomography (CT) examinations were performed with a dual source scanner (Somatom Definition or Somatom Flash, Siemens Medical Solution). Head and neck acquisition started after 40s of the contrast medium injection (80–100 mL at a rate of 3.5–4 mL/s) in order to obtain good opacification of both arterial and venous vessels.

The slice thickness was 1 mm, tube voltage was set at 80–120 kV, tube current 165–210 mA.

Contraindications to CT examination included renal insufficiency, hypersensitivity to iodine-containing contrast material and uncontrolled hyperthyroidism.

Soft tissue masses with intense enhancement after i.v. contrast administration in typical locations were recognized as paragangliomas [11].

The criterion for malignancy were metastases to lymph nodes or distant metastases.

The HNP were classified according to the location: carotid body paragangliomas (located in the common carotid artery bifurcation), jugular paragangliomas (located in the foramen jugular), tympanic paragangliomas (located in the middle ear cavity) and vagal paragangliomas (along the cervical portion of the vagus nerve). Carotid paragangliomas lead to splaying of the carotid arteries, while vagal paragangliomas cause an anterior displacement of the internal carotid artery [11].

Carotid body paragangliomas were classified according to the Shamblin criteria based on the involvement of the carotid vessels.

Class I – tumors are localized in the carotid bifurcation with splaying of arteries but the surrounding vessels remain intact.

Class II – tumors adhere to the carotid vessels or partially surround them.

Class III – large tumors encase the carotid vessels.

Statistical analysis

The data were analyzed using SPSS statistical analysis software version 12.0 (SPSS Inc., Chicago, IL, USA). Continuous variables are presented as mean ± standard deviation (SD) and compared using 2-tailed, unpaired Student's t-test. Fisher's test and/or Chi-square were used to test for differences in categorical variables. The 2-tailed probability value of $p<0.05$ was considered statistically significant.

Table 1. Clinical characteristics of patients.

Patient	Gender	Age	Gene mutation	Variants	Variants type	Index case/ relative	HNP	Malignant
1.	Female	52	SDHD	Exon 1, c.33C>A, p. C11X	Nonsense	Index	Yes	No
2.	Male	32	SDHD	Exon 1, c.33C>A, p. C11X	Nonsense	Index	Yes	No
3.	Male	25	SDHD	Exon 1, c.33C>A, p. C11X	Nonsense	Relative	Yes	No
4.	Male	22	SDHD	Exon2, c.112 C>T, p.R38X	Nonsense	Index	Yes	No
5.	Female	50	SDHD	Exon 1, c.33C>A, p. C11X	Nonsense	Index	Yes	Yes
6.	Male	40	SDHD	Exon 1, c.33C>A, p. C11X	Nonsense	Relative	Yes	No
7.	Male	25	SDHD	Exon 1, c.33C>A, p. C11X	Nonsense	Relative	Yes	No
8.	Male	25	SDHD	Exon 1, c.33C>A, p. C11X	Nonsense	Relative	Yes	No
9	Female	38	SDHD	Exon 1, c.33C>A, p. C11X	Nonsense	Index	Yes	No
10.	Female	46	SDHD	Exon 1, c.33C>A, p. C11X	Missense	Index	Yes	No
11.	Male	50	SDHB	Exon 5,c.530G>A, p.R177H	Missense	Index	Yes	No
12.	Male	43	SDHB	Exon 5,c.530G>A, p.R177H	Missense	Relative	Yes	No
13.	Male	55	SDHB	Exon 7, c.650G>T, p.R217L	Missense	Index	Yes	No
14.	Female	43	SDHD	Exon 1, c.33C>A, p. C11X	Nonsense	Index	Yes	No
15.	Female	30	SDHD	Exon 1, c.33C>A, p. C11X	Nonsense	Index	Yes	No
16.	Female	53	SDHD	Exon 1, c.33C>A, p. C11X	Nonsense	Index	Yes	Yes
17.	Female	71	SDHC	Exon 4, c.214C>T, p.R72C	Missense	Index	Yes	No
18.	Male	47	SDHB	Exon 7, c. 689 G>T, p. R230L	Missense	Index	Yes	Yes
19.	Male	47	SDHD	Exon 3, c.274G>T, p.D92Y	Missense	Index	Yes	No
20.	Male	55	SDHD	Exon 1, c.33C>A, p. C11X	Nonsense	Index	Yes	No
21.	Male	49	SDHD	Exon 1, c.33C>A, p. C11X	Nonsense	Index	Yes	No
22.	Male	38	SDHD	Exon 1, c.33C>A, p. C11X	Nonsense	Index	Yes	No
23.	Female	71	SDHC	Exon 4, c.214C>T, p.R72C	Missense	Index	Yes	No
24.	Female	62	SDHB	Exon 6, c.574T>C, p.C192R	Missense	Relative	Yes	No
25.	Female	70	SDHB	Exon 6, c.574T>C, p.C192R	Missense	Index	Yes	No
26.	Female	33	SDHD	Exon 1, c.33C>A, p. C11X	Nonsense	Index	Yes	No
27.	Male	31	SDHB	Exon 6, c.587G>A, p.C196Y	Missense	Index	Yes	No
28.	Male	39	SDHD	Exon 2 c.112C>T, p.R38X,	Nonsense	Index	Yes	No
29.	Male	47	SDHB	Exon 5,c.530G>A, p.R177H	Missense	Relative	Yes	No
30.	Male	26	SDHB	Exon 5,c.530G>A, p.R177H	Missense	Relative	Yes	No
31.	Female	44	SDHD	Exon 1, c.33C>A, p. C11X	Nonsense	Index	Yes	No
32.	Female	31	SDHD	Exon 1, c.33C>A, p. C11X	Nonsense	Index	Yes	No
33.	Female	49	SDHD	Exon 3, c.274G>T, p.D92Y	Nonsense	Relative	Yes	No
34.	Male	34	SDHD	Exon 1, c.33C>A, p. C11X	Nonsense	Index	Yes	No
35.	Male	64	SDHD	Exon 1, c.33C>A, p. C11X	Nonsense	Index	Yes	Yes
36.	Male	59	SDHD	Exon 1, c.33C>A, p. C11X	Nonsense	Index	Yes	No
37.	Male	24	SDHD	Exon 1, c.33C>A, p. C11X	Nonsense	Index	No	No
38.	Male	37	SDHB	Exon 3, c.268C>T, p. R90X	Nonsense	Index	Yes	Yes

Table 1 continued. Clinical characteristics of patients.

Patient	Gender	Age	Gene mutation	Variants	Variants type	Index case/ relative	HNP	Malignant
39.	Male	28	SDHB	Exon 6, c. 574 T>C, p. C192R	Missense	Index	Yes	Yes
40.	Male	43	SDHD	Exon 1, c.33C>A, p. C11X	Nonsense	Index	Yes	No
41.	Female	46	SDHD	Exon 1, c.33C>A, p. C11X	Nonsense	Index	Yes	No
42.	Female	45	SDHD	Exon 1, c.33C>A, p. C11X	Nonsense	Relative	No	No
43.	Female	23	SDHD	Exon 4 c.395C>G, p.S132X	Nonsense	Index	No	No
44.	Male	32	SDHD	Exon 1, c.33C>A, p. C11X	Nonsense	Relative	No	No
45.	Male	59	SDHC	Exon 4, c.214C>T, p.R72C	Missense	Relative	No	No
46.	Male	70	SDHD	Exon 1, c.33C>A, p. C11X	Nonsense	Relative	No	No
47.	Female	35	SDHD	Exon 1, c.33C>A, p. C11X	Nonsense	Index	No	No
48.	Male	66	SDHD	Exon 1, c.33C>A, p. C11X	Nonsense	Relative	No	No
49.	Male	74	SDHB	Exon 5,c.530G>A, p.R177H	Missense	Relative	No	No
50.	Female	33	SDHB	Exon 5,c.530G>A, p.R177H	Missense	Relative	No	No
51.	Male	43	SDHB	Exon 7, c.650G>T, p.R217L	Missense	Relative	No	No
52.	Male	56	SDHB	Exon 7, c.650G>T, p.R217L	Missense	Relative	No	No
53.	Male	63	SDHD	Exon 1, c.33C>A, p. C11X	Nonsense	Relative	No	No
54.	Female	63	SDHB	Exon 2, c.87_88insCAG, p.Ala29_ Gln30insProfsX63	Frameshift	Index	No	No
55.	Female	38	SDHD	Exon 1, c.33C>A, p. C11X	Nonsense	Index	No	No
56.	Female	61	SDHB	Exon 6, c.574T>C, p.C192R	Missense	Relative	No	No
57.	Female	50	SDHB	Exon 6, c.587G>A, p.C196Y	Missense	Relative	No	No
58.	Female	34	SDHB	Exon 6, c.587G>A, p.C196Y	Missense	Index	No	No
59.	Male	30	SDHD	Exon 1, c.33C>A, p. C11X	Nonsense	Relative	No	No
60.	Female	23	SDHD	Exon 4 c.395C>G, p.S132X	Nonsense	Index	No	No
61.	Female	45	SDHD	Exon 1 deletion	Large deletion	Index	No	No
62.	Female	29	SDHD	Exon 1, c.33C>A, p. C11X	Nonsense	Relative	Yes	No
63.	Female	61	SDHD	exon2 c.112C>T,p.R38X	Nonsense	Index	Yes	No
64.	Female	40	SDHB	Exon 1 deletion	Large deletion	Index	No	Yes
65.	Male	64	SDHD	Exon 1, c.33C>A, p. C11X	Nonsense	Index	Yes	No
66.	Female	13	SDHB	Exon 7, c. 689 G>T, p. R230L	Missense	Relative	No	No
67.	Male	53	SDHC	Exon 3, c.78-2A>G, p.splicesite alteration	Splicesite	Relative	No	No
68.	Male	28	SDHC	Exon 3, c.78-2A>G, p.splicesite alteration	Splicesite	Relative	No	No
69.	Female	37	SDHD	Exon 1, c.33C>A, p. C11X	Nonsense	Relative	No	No
70.	Female	45	SDHB	Exon 5,c.530G>A, p.R177H	Missense	Index	No	No
71.	Male	43	SDHD	Exon2, c.123C>T, p.R38X	Nonsense	Index	Yes	No
72.	Female	27	SDHB	Exon 6, c.587G>A, p.C196Y	Missense	Relative	No	No

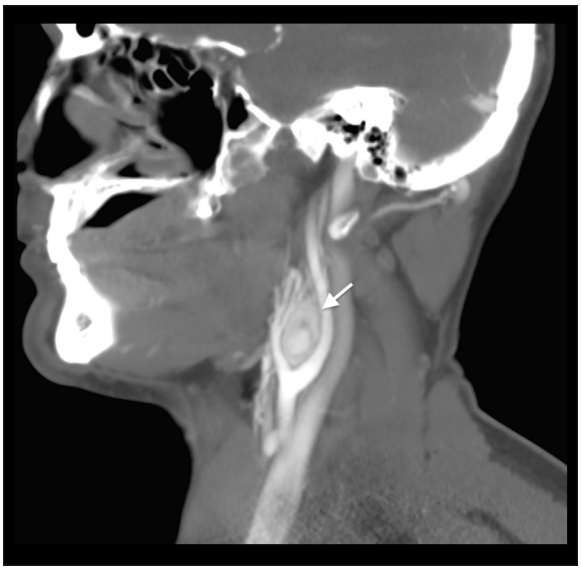

Figure 1. Carotid paraganglioma in a 32-year-old man with *SDHD* mutation. Contrast-enhanced CT, sagittal view, MIP reconstruction shows an intensely-enhancing mass in the left carotid bifurcation (arrow).

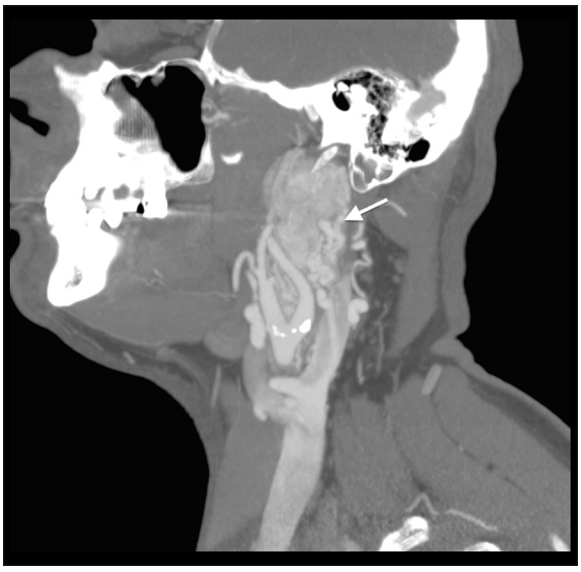

Figure 2. Vagal paraganglioma in a 47-year-old man with *SDHB* mutation. Contrast-enhanced CT, MIP reconstruction, sagittal view shows an enhancing mass (arrow) causing displacement of the internal carotid artery anteriorly.

Table 2. The number and locations of paragangliomas in patients with *SDHx* mutations.

	Carotid paraganglioma	Jugular paraganglioma	Vagal paraganglioma	Tympanic paraganglioma	Other location
HNP N=113	59 (52.21%)	14 (12.38%)	27 (23.89%)	11 (9.7%)	2 (1.8%)
SDHB N=19	10	2	4	1	2
SDHD N=90	48	11	23	8	0
SDHC N=4	1	1	0	2	0

Results

HNP were present in 44 (61.1%) out of 72 patients (31 *SDHD*, 11 *SDHB*, 2 *SDHC*).

One hundred and thirteen paragangliomas were found in 44 patients; the most common locations were: the carotid bifurcation (59 paragangliomas, Figure 1) and along the vagal nerve (27 paragangliomas, Figure 2). Moreover, 14 jugular paragangliomas and 11 tympanic paragangliomas were found. In one case, a paraganglioma was located in the thyroid and, in one case in soft tissues of the neck. Table 2 shows the number and locations of paragangliomas in patients with *SDHx* mutations.

The mean dimension of all HNP was 17.9±10.8 mm (dimension range 3–48 mm). The mean dimension of carotid paragangliomas was 17.8±11.1 mm (range 4–42 mm), the jugular paragangliomas 21.6±6.3 mm (range 10–35 mm), vagal paragangliomas 19.6±12.0 (range 6–48 mm) and tympanic paraganglioma 6.7±2.3 mm (range 3–10 mm).

Multiple paragangliomas were found in 34 (77.2%) patients and in 87.5% of them they were located bilaterally.

Seventeen patients underwent surgeries.

Intracranial invasion with the involvement of the jugular foramen and destruction was observed in 12 cases (3 *SDHB*, 8 *SDHD*, 1 *SDHC*).

According to Shamblin classification, we assessed 47 carotid paragangliomas; 27 (57.4%) were classified as class I, 13 (27.7%) as class II and 7 (4.9%) as class III, the mean dimension in class I was 12.8±5.5 mm, in class II 13.4±9.8 mm, and in class III 29.6±13.6 mm.

We compared HNP of patients with *SDHB* and *SDHD* mutations.

There were no statistical differences in gender distribution and mean age between both groups. HNP were statistically more prevalent among *SDHD* compared with those with *SDHB* mutations (72.1% *vs.* 43.5%, p=0.033).

There was a significant difference in the prevalence of carotid paragangliomas between patients with *SDHB* and *SDHD* mutations (7/11 [63.6%] *vs.* 30/31 [96.8%], respectively, p=0.004). Patients with *SDHD* mutations more often had carotid paragangliomas located on the left side than on

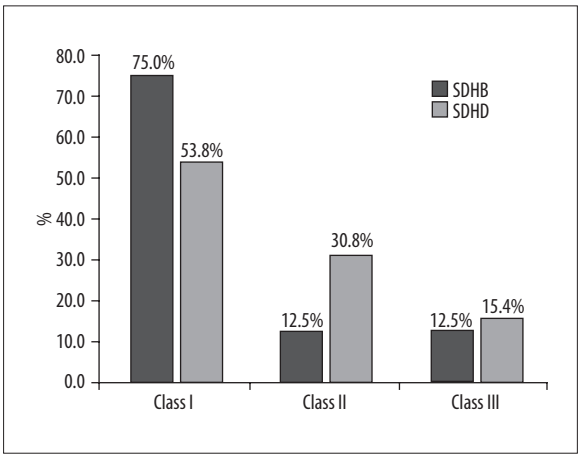

Figure 3. Comparison of carotid paragangliomas according Shamblin classification in patients with *SDHB* and *SDHD* mutations.

the right side as compared with *SDHB* mutations (25/31 *vs.* 4/11, p=0.006), but in both groups the prevalence of bilateral localization of carotid paragangliomas was similar (15/30 [50.0%] *vs.* 3/7 [42.9%], respectively, p=NS).

No statistical difference between both groups of *SDHx* mutations in the Shamblin classification was found (Figure 3).

No marked differences between the prevalence of vagal, jugular and tympanic paragangliomas in terms of *SDHB* and *SDHD* mutations were found. The comparison of patients with *SDHB* and *SDHD* mutations is shown in Table 3.

Multiple tumors occurred in 32 patients, 6 out of 11 (54.5%) carriers with SDHB and 26 out of 31(83.9%) with *SDHD* mutations, p=0.05. Patients with *SDHD* mutations statistically more often revealed bilateral localization of HNP, 25/31 (80.6%) *vs.* 5/11 (45.5%) with *SDHB*, p=0.03.

Out of 72 patients with *SDHx* mutations, 7 patients (4 with *SDHB* and 3 with *SDHD* gene mutations) had a malignant disease with distant metastases to bones, liver, lungs and lymph nodes, and 6 of them had head and neck paragangliomas (Figure 4A–4D). The carotid paragangliomas in patients with malignancy were in advanced stage (Shamblin classes II and III) compared to benign paragangliomas.

Discussion

Among 72 patients with confirmed *SDHx* mutations we found HNP in 44 (61.1%) patients. The most common locations were carotid bifurcations and along the vagal nerves; moreover, paragangliomas were very often multifocal and bilateral.

HNP are uncommon tumors, which may occur sporadically or be associated with hereditary syndromes.

HNP are mostly benign, slowly enlarging tumors. Because of their location they may cause mass-effect symptoms with blood vessel and neural involvement, so early detection of paragangliomas may be crucial to increase the chance of cure with a lower morbidity rate. Different types of paragangliomas are connected with different clinical symptoms and prognosis. High tumor and skull-base involvement may cause nerve dysfunction after operation, therefore knowledge of the most frequent locations and differentiation with *SDHx*-related HNP may be clinically useful.

The most common mutation in our group was *SDHD* (61.1%), the rarest was *SDHC* (6.9%), which is in agreement with other authors [12–15]. The average age of patients in all group was 44±14.26 yrs, in groups of *SDHB* and *SDHD* mutations the mean age was similar. Head and neck paragangliomas were statistically more prevalent among *SDHD* mutation carriers (72.1%) compared with *SDHB* mutation carriers (43.5%), like in other studies [16,17].

Table 3. Comparison of patients with *SDHB* and *SDHD* mutations.

	SDHB No. of patients 11	SDHD No. of patients 31	p
Age (years)	45±15.3	42.25±12.8	0.43
Male	9 (81.8%)	16 (51.6%)	0.069
Carotid PGL	7 (63.6%)	30 (96.8%)	0.004
Jugular PGL	2 (18.2%)	9 (29%)	0.48
Vagal PGL	3 (27.3%)	14 (45.2%)	0.29
Tympanic PGL	1 (9.1%)	7 (22.6%)	0.32
Other PGL	2		
Mulitifocal HNP	6 (54.5%)	26 (83.9)	0.05
Bilateral HNP	5 (45.5%)	25 (80.6%)	0.026

P<0.05 significant; No. – number.

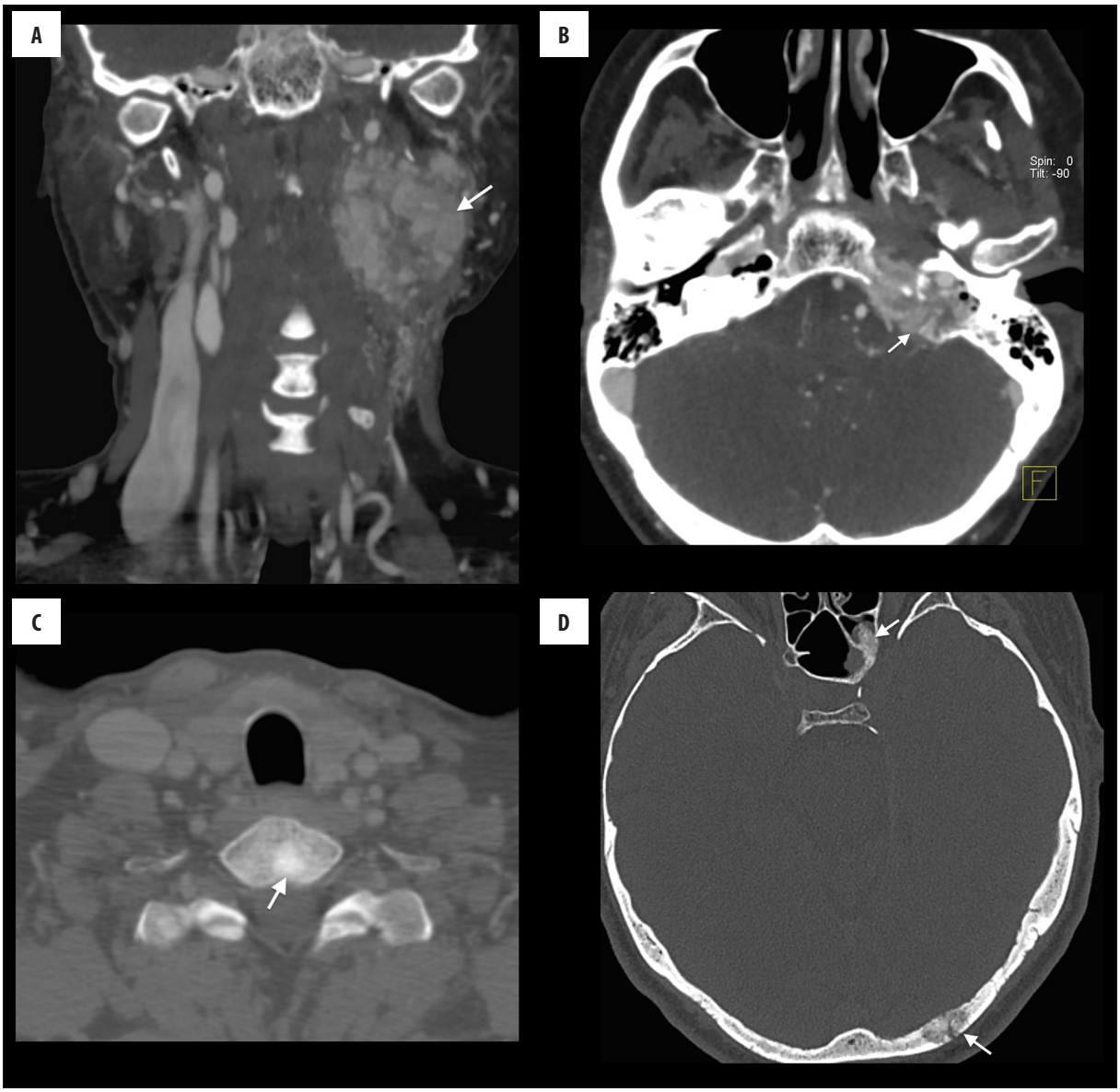

Figure 4. A 37-year-old man with malignancy *SDHB* mutation. (**A, B**) Contrast-enhanced CT, a-coronal, b-axial view, showing well-enhanced tumor mass extending from the carotid bifurcation to the left tympanum (arrows). (**C, D**) CT, axial views show osteoblastic metastases to the thoracic vertebrae and to the left occipital and sphenoid bones (arrows).

The majority of paragangliomas in the current study, like in other studies, were located in the carotid bifurcation [18,19]. In our study, carotid paragangliomas significantly more commonly occurred in patients with *SDHD* mutations and were more often located on the left side. The Shamblin classification of carotid paragangliomas is still in use and some authors have shown a good correlation with surgical complications and outcomes [20–22]. Morbidity related to surgical resection (postoperative neurovascular complications) for Shamblin type III carotid body tumors is higher than for type I and II [23].

The majority of carotid paragangliomas in our study were classified as group I, but in patients with malignant carotid paragangliomas, they were in advanced stage (Shamblin classes II and III) compared to benign paragangliomas.

Ericson et al. reported that the second most common location of HNP was the jugular bulb, the least frequent were vagal paragangliomas, which represent less than 5% of all HNP [9,24–26]. In our study, vagal paragangliomas were more frequent than jugular and tympanic paragangliomas and they represented 23.89% of all paragangliomas.

Nettervile et al. reported intracranial extension in 22% of vagal paragangliomas and in case of extension through the jugular foramen the vagal paraganglioma may cause the same symptoms as jugular paraganglioma [25]. The resection of vagal and jugular paragangliomas is related to a higher morbidity compared with carotid paragangliomas [27].

Paragangliomas have a tendency to occur multifocally, especially in familial lesions [27,28]. Reports about

hereditary paragangliomas indicate that 10-50% of patients have multiple tumors [26]. In our report, the prevalence of multifocal tumor was higher (77.2%) and 87.5% of them were located bilaterally.

In our study, patients with *SDHD* mutation significantly more commonly had multifocal paragangliomas than patients with *SDHB* mutations, as in the study by Neumann [16], 26 patients out of 31 with *SDHD* mutations in the present study had multifocal paragangliomas compared with 6 out of 11 patients with *SDHB* mutations [16]. The treatment of a multicentric disease is more complicated than in case of solitary paragangliomas [27].

Paragangliomas are mainly benign but some cases of malignant tumors have also been described. Several authors reported that the risk of malignance is higher in SDHB than in *SDHD* mutations [16,28].

In our study, unlike in other studies, the prevalence of malignancy in both groups (*SDHB* and *SDHD)* was similar [16,28].

Seven patients were diagnosed with a malignant disease with metastases to bones, liver, lung and lymph nodes. Lee et al. reported that in the head and neck area vagal paragangliomas were the most common (16–19%), the next location was carotid body paragangliomas (approximately 6%) followed by jugulotympanic paragangliomas (2–4%) [29]. In our study, patients with malignancies had multifocal head and neck paragangliomas, mostly located in different regions, while carotid paraganliomas were found in 4 patients, and vagal paragangliomas in 3 patients.

The carotid paragangliomas in patients with malignancy were in advanced stage (Shamblin classes II and III) compared to benign paragangliomas.

The optimal management of HNP depends on size, location, involvement of neurovascular structures, malignancy and multifocal locations [24]; therefore, early recognition is important.

Conclusions

SDHx mutations predispose to multifocal and bilateral HNP. Carotid and vagal paragangliomas occurred most often.

Patients with *SDHD* mutations are characterized by higher frequency of head and neck paragangliomas than patients with *SDHB* mutations which is mainly caused by a higher frequency of carotid body tumors in patients with *SDHD* mutations. No difference in the frequency of head and neck paragangliomas in other locations was found.

Conflict of Interest

The authors declare that they have no conflict of interest.

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