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

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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 branchiomeriС (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 yrs, 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 | Nonsense | 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 | Index | 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 | 53  | SDHD          | Exon 1, c.33C>A, p. C11X | Nonsense | Index | Yes | Yes |
| 16.     | Female | 71  | SDHC          | Exon 4, c.214C>T, p.R72C | Missense | Index | Yes | No |
| 17.     | Male   | 47  | SDHB          | Exon 7, c.689 G>T, p. R230L | Missense | Index | Yes | No |
| 18.     | Male   | 47  | SDHD          | Exon 3, c.274G>T, p.D92Y | Missense | Index | Yes | No |
| 19.     | Male   | 55  | SDHD          | Exon 1, c.33C>A, p. C11X | Nonsense | Index | Yes | No |
| 20.     | Male   | 49  | SDHD          | Exon 1, c.33C>A, p. C11X | Nonsense | Index | Yes | No |
| 21.     | Male   | 38  | SDHD          | Exon 1, c.33C>A, p. C11X | Nonsense | Index | Yes | No |
| 22.     | Female | 71  | SDHC          | Exon 4, c.214C>T, p.R72C | Missense | Index | Yes | No |
| 23.     | Female | 62  | SDHB          | Exon 6, c.574T>C, p.C192R | Missense | Relative | Yes | No |
| 24.     | Female | 70  | SDHB          | Exon 6, c.574T>C, p.C192R | Missense | Index | Yes | No |
| 25.     | Female | 33  | SDHD          | Exon 1, c.33C>A, p. C11X | Nonsense | Index | Yes | No |
| 26.     | Male   | 31  | SDHB          | Exon 6, c.587G>A, p.C196Y | Missense | Index | Yes | No |
| 27.     | Male   | 39  | SDHD          | Exon 2, c.112C>T, p.R38X, | Nonsense | Index | Yes | No |
| 28.     | Male   | 47  | SDHB          | Exon 5, c.530G>A, p.R177H | Missense | Index | Yes | No |
| 29.     | Male   | 26  | SDHB          | Exon 5, c.530G>A, p.R177H | Missense | Relative | Yes | No |
| 30.     | Female | 44  | SDHD          | Exon 1, c.33C>A, p. C11X | Nonsense | Index | Yes | No |
| 31.     | Female | 31  | SDHD          | Exon 1, c.33C>A, p. C11X | Nonsense | Index | Yes | No |
| 32.     | Female | 49  | SDHD          | Exon 3, c.274G>T, p.D92Y | Nonsense | Relative | Yes | No |
| 33.     | Male   | 34  | SDHD          | Exon 1, c.33C>A, p. C11X | Nonsense | Index | Yes | No |
| 34.     | Male   | 64  | SDHD          | Exon 1, c.33C>A, p. C11X | Nonsense | Index | Yes | Yes |
| 35.     | Male   | 59  | SDHD          | Exon 1, c.33C>A, p. C11X | Nonsense | Index | Yes | No |
| 36.     | Male   | 24  | SDHD          | Exon 1, c.33C>A, p. C11X | Nonsense | Index | Yes | No |
| 37.     | 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 type | Variants 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 | 23  | SDHD          | Exon 4, c.395C>G, p.S132X    | Nonsense | Index      | No   | No        |
| 43.     | Male   | 32  | SDHD          | Exon 1, c.33C>A, p. C11X    | Nonsense | Index      | No   | No        |
| 44.     | Male   | 59  | SDHC          | Exon 4, c.214C>T, p.R72C     | Nonsense | Relative   | No   | No        |
| 45.     | Male   | 70  | SDHD          | Exon 1, c.33C>A, p. C11X    | Nonsense | Relative   | No   | No        |
| 46.     | Male   | 74  | 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.     | Female | 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_88insCA, 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 | Relative   | 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  | SDHB          | 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.689G>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        |
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.

| Location                        | SDHB N=19 | SDHD N=90 | SDHC N=4 |
|---------------------------------|-----------|-----------|----------|
| Carotid paraganglioma          | 10        | 48        | 1        |
| Jugular paraganglioma          | 14        | 11        | 1        |
| Vagal paraganglioma            | 2         | 23        | 0        |
| Tympanic paraganglioma         | 1         | 8         | 0        |
| Other location                  | 2         | 2         | 0        |

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
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** | **SDHD** |
| **No. of patients** | **No. of patients** | **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 | | |
| Multifocal 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.
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.

Netterville 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 et al. [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, lungs and lymph nodes. Lee et al. reported that in the head and neck area vaginal 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 paragangliomas 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 a 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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