Paraganglioma of the Carotid Body: Treatment Strategy and SDH-gene Mutations

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WHAT THIS PAPER ADDS
This paper summarises our experience in the treatment of PGL, in particular the carotid body tumours and addresses clinical, surgical and genetic issues. In addition, we reviewed the literature and developed feasible strategies for both treatment and follow-up.

Objectives: The aim of the present study was to review treatment results in patients with paraganglioma (PGL) of the neck presenting as carotid body tumour, long-term follow-up and relevance of genetic testing for succinate dehydrogenase (SDH)-gene mutations.

Design: Retrospective analysis of prospectively collected data and prospective genetic analysis.

Materials and Methods: Over a 25-year period (1987–2011) 50 patients were operated for 63 PGLs of the neck. Pre-, intra- and postoperative findings were analysed. Sanger sequencing was performed for genetic testing of SDH-gene mutations (SDH B, SDHC and SDHD).

Results: Fifty patients underwent resection of 63 PGLs (62 benign, one malignant) without mortality. Eight patients underwent preoperative embolisation. Vascular surgical procedures were required in 15 operations (15/63 = 23.8%). Nerve lesions occurred after 13 operations (13/63 = 20.6%) and were associated with large tumours. A total of 44 patients are alive after a mean follow-up of 9.8 years.

In 40 patients 17 SDH-gene mutations were detected (17/40 = 42.5%): 14 SDHD mutations, two SDHB mutations and one rare SDHC mutation.

Conclusion: Surgery for PGL is recommended. All PGL patients should be screened for SDH mutations because it impacts the individual follow-up strategy. Whereas all PGL patients require annual ultrasound control, mutation carriers and family members with proven mutations should in addition be regularly examined by magnetic resonance imaging (MRI) of head, neck, thorax, abdomen and pelvis.

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Paragangliomas (PGLs) are extra-adrenal tumours originating from the neuro-ectoderm, occurring from the skull base to the pelvic floor. With an incidence of 0.03% of all tumours, they are extremely rare. In most cases (~50%) they are found in the head and neck region, especially as highly vascularised carotid body (CBT) or glomus tumours in 50%.

PGLs may also appear as adrenal tumours in the abdomen or as phaeochromocytoma. In the head and neck region, they are found at the jugular bulb, the vagal and tympanic nerve and the aortic glomus. Depending on their location, patients may notice a slowly growing, painless lateral neck mass, pulse-like sensations or voice changes. In the majority of cases the tumours are benign, but in up to 6% malignant. Malignancy in PGL is defined by the confirmation of metastases in non-neuro-ectoderm tissue such as lymph nodes.

The carotid body was first described by Haller in 1743 and functions as a receptor for blood pressure and oxygen. Chronic hypoxia can induce hypertrophy and the resulting lesions are referred to as non-heritable or sporadic tumours. Up to 30% of all PGLs are caused by germline mutations of genes associated with the mitochondrial succinate dehydrogenase complex (SDHD, SDHB, SDHC or SDHAF2) and follow autosomal dominant inheritance. The aim of this report is to summarise our clinical experience in patients with CBTs over the last 25 years. We focussed on preoperative management, surgical treatment, follow-up and genetic issues.
MATERIAL AND METHODS

Between 1987 and 2011 a total of 50 consecutive patients with PGL presented at the Department of Vascular Surgery at the Medical University Hospital Graz. Their clinical and operative data were collected prospectively in a special database (DataEase®) and analysed retrospectively.

For the present study all living patients were contacted and underwent follow-up with physical examination and ultrasound. After informed consent, a blood sample was taken for genetic testing on succinate dehydrogenase (SDH)-gene mutations. This was performed at the Institute for Human Genetics.

Sequencing was done by cycle sequencing using the ABI BigDye Terminator Cycle Sequencing Kit according to the supplier’s protocol and was analysed on an ABI3100 genetic analyser (both ABI). We sequenced all coding exons and flanking intronic sequences. Family counselling was offered if applicable.

The routine preoperative work-up in patients with suspected PGL consisted of careful family history, clinical examination, duplex ultrasound of the neck, computed tomography (CT) or magnetic resonance (MR) tomography, angiography (Fig. 4(a)) or MR angiography. The primary diagnostic procedure depended on the referring institution. The necessity of preoperative interventional embolisation was assessed by the operating surgeon and vascular radiologist. Every patient underwent surgery and postoperative follow-up with physical examination and duplex ultrasound once a year.

The Shamblin classification was used to grade the tumour size, the tumour—vessel relationship and invasion. In group I the tumour is small and easily resected. Group II includes tumours adherent to or partially surrounding vessels. Group III consists of tumours surrounding or encasing the vessels.6

Routine follow-up consisted of clinical evaluation after 4–6 weeks, duplex ultrasound after 1 year and at 12-month intervals. CT or magnetic resonance imaging (MRI) was performed if new pathological findings occurred in ultrasound.

RESULTS

Between 1987 and 2011 a total of 50 patients (33 female, 17 male; mean age 54.5 years, range 17–80 years) underwent surgery for PGLs at our institution. A total of 37 patients presented with one unilateral tumour at the carotid bifurcation (15 on the left side, 22 on the right side), 10 were affected at two sites (nine patients bilateral at the carotid bifurcation, one patient in the tympanic cavity and contralateral at the carotid bifurcation). Three patients suffered from three tumours each. (Two of them had one tumour in the middle ear and two contralateral CBTs, the third patient had bilateral CBT’s and one recurrent tumour.) The patients with PGL in the middle ear were operated at the Ear, Nose, Throat (ENT) Department.

In total, there were 66 PGLs in the 50 patients: 63 PGLs presenting as CBTs (including one recurrent tumour) and three PGLs in the middle ear.

Applying the Shamblin classification, there were 13 tumours in group I, 28 in group II and 22 in group III.

Preoperative embolisation was performed in eight patients with a mean tumour diameter of 41.3 mm (range 20–55 mm) and a mean age of 54.9 years (range 31.8–78.8 years). This was to reduce tumour mass and blood flow. One patient suffered from ipsilateral transient ischaemic attack during the procedure so the embolisation was not completed due to neurologic symptoms.

The operative strategy consisted of a standard endarterectomy incision along the front border of the sternocleidomastoid muscle under general anaesthesia. The tumour was excised at the carotid bifurcation using proximal and distal vessel control (Fig. 1) and cross-clamping of the external carotid artery. Vascular reconstruction was performed as necessary. Ipsilateral lymphadenectomy completed the standard operative procedure. The mean age at first operation was 54.4 years (range 17–80 years).

Additional vascular procedures were required in 15 patients as shown in Table 1. Due to severe vessel kinking, the internal carotid artery was resected and reinserted in three patients. Two patients were treated by a venous interposition (reversed saphenous vein). In five patients, resection of the external carotid artery was required. In another two patients, ligation of the common carotid artery was necessary. Three patients sustained a ligation of the superior thyroid artery. An enlarged carotid body was an incidental finding in another patient during standard endarterectomy for carotid artery stenosis. Histology after complete resection showed a PGL.

Nerve palsies occurred after 13 operations (13/63 = 20.6%) (Table 1). In eight patients the vagal nerve was resected due to the in-growing tumour. In one patient the hypoglossal nerve could not be preserved. Two patients underwent combined resection of the superior laryngeal and the recurrent laryngeal nerve. In one patient the hypoglossal nerve was reconstructed successfully by microsurgery. In the 15 patients undergoing extended resections and additional vascular procedures, there was no higher incidence of nerve lesions (2/15 patients = 13.3%).

Figure 1. Intra-operative situs with spread bifurcation and paraganglioma (PGL, white arrow) partially resected. CCA Common – Carotid Artery; ECA — External Carotid Artery; ICA — Internal Carotid Artery; PGL — Paraganglioma.
Table 1. Nerve lesions and additional vascular procedures compared to maximal tumour diameter.

<table>
<thead>
<tr>
<th>Affected nerves and vascular procedures</th>
<th>Number</th>
<th>Tumour diameter 0–29 mm</th>
<th>30–59 mm</th>
<th>60–90 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vagal nerve</td>
<td>8</td>
<td>0</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Hypoglossal nerve</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Superior laryngeal nerve</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Recurrent laryngeal nerve</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Resection and reinsertion ICA</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Saphenous interposition ICA</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Ligation CCA</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Ligation STY</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Ligation ECA</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>


Postoperatively, no re-operation for bleeding or wound complications was required. A 68-year-old male patient suffered from postoperative ipsilateral transitory ischaemic attack (TIA) and was transferred to Neurology. Symptoms resolved completely within 24 hours with no persisting neurological deficit. Cranial CT scan showed no abnormality. Histological examination confirmed the diagnosis of paraganglioma in all cases. In 40 of our 50 patients genetic testing was conducted. Out of our tested patients, 17 (17/40 = 42.5%) showed germline mutations (Table 3). Of these, 14 had mutations in SDHD, two in SDHB and one in SDHC. These 17 patients with mutation were at a mean age of 45.2 (±18.2) years (range 17.2–75.7 years) at their first operation. Twelve out of these 17 patients presented with a second PGL (mean age 51.2 years), and three of them developed a third tumour (mean age 42 years). Patients with sporadic tumours were at a mean age of 59.4 (±14.6) (range 33.1–79.9 years); Mann–Whitney U Test (age mutation carriers/age sporadic tumours): p = 0.005.

There is one family with SDHD, a father and two daughters, expressing the same mutation (c.95C>G). The one recurrent tumour occurred unilaterally in one daughter 5 years after resection of bilateral PGL. It was diagnosed by routine follow-up via ultrasound and confirmed by MR tomography. This family was operated for eight PGLs in total. No further family relations were detected.

Mutation carriers were screened for phaeochromocytoma but none was found in each case. In addition to routine clinical yearly follow-up all patients were contacted for additional follow-up and genetic testing. After a mean follow-up time of 9.8 years (range 1–25 years) 44 patients are alive (44/50 = 88%). One patient with recurrent tumour underwent secondary resection 6 years after the first operation. One female patient, operated in 1988, suffered from a malignant PGL at the age of 52, but was lost at follow-up. Five patients died due to reasons other than the PGL between 3 and 13 years postoperatively. One patient moved abroad and could not be followed up with genetic testing, but could be personally interviewed by telephone. Another three patients declined genetic testing.

**DISCUSSION**

In patients presenting with swelling at the lateral neck, cranial nerve palsies, voice changes or auditory defects, a PGL of the neck should be included in the differential diagnosis. Careful evaluation of family history regarding tumours is important. Every patient should undergo precise clinical examination on both sides of the neck. Imaging procedures, which include a mandatory ultrasound of soft tissue and vessels of the neck, and MR tomography including angiography should be performed. In ultrasound the tumours appear as a homogeneously hypoechoic mass (Fig. 2), and in Doppler ultrasound imaging a multidirectional hypervascularity is the discerning feature (Fig. 3).

Due to contrast medium enhancement, the tumours give high intensive signal in MR angiography. Especially in the T2-weighted images, the spread and displaced carotid bifurcation appears in a typical ‘goblet deformity’ (Fig. 3).

CT can be useful in special questions such as relevant bony erosions or punctate calcification in the tumour. To reduce radiation exposure and improve soft-tissue visualisation, MR tomography plus angiography should be preferred to CT.

The clinical value of embolisation is discussed controversially in the literature. It can be considered in large tumours, because hypervascularity can be challenging during surgery. The effect of embolisation is shown in Fig. 4(a) and (b).

The risk for neurologic complications such as transient ischaemic attack (TIA) or stroke caused by angiography or embolisation is considerable. In our series one of eight patients (12.5%) developed neurologic complications during surgery. The effect of embolisation is shown in Fig. 4(a) and (b).
embolisation. This is comparable to Schick et al. (3/22 = 13.6%) and Persky et al. (6/47 = 12.8).11,12 In large tumours the operative resection can be facilitated by preoperative embolisation. In our institution the indication for embolisation is currently discussed between the interventional radiologist and the surgeon in each patient individually and performed one day before the operation now in patients with tumours of 3.5 cm maximum diameter and larger.

Complete surgical excision is the aim of any operative procedure for PGL and is the only curative option.9 Radiation for stopping tumour growth can be discussed in patients with poor health and high risk for anaesthesia, patients with Shamblin group IV tumours where nerve injuries seem to be unavoidable, also in patients declining operation. The risk for nerve palsies seems to be lower than that in operation, but there is still a risk especially in younger patients for development of a malignant tumour post radiation.9 Operation after radiation can be more challenging because of soft-tissue alteration and scarring. This may cause more nerve palsies than operation without radiation. Tumour doubling time is very slow and lies between 4 and 14 years; hence conservative treatment, such as a wait-and-see strategy, can also be discussed in elderly patients, who are free of PGL symptoms but do have other co-morbidities.

Our results showed that the incidence of additional vascular procedures or nerve lesions was significantly lower in mutation carriers (Table 2). This can be partly explained by the early diagnosis of the contralateral PGL in patients with SDH mutation. This contralateral PGL in our practice was operated upon early, explaining the significantly different Shamblin classification status between the two groups.

Residual tumour masses can continue to grow and may cause symptoms again. Ipsilateral lymphadenectomy should be performed simultaneously to identify malignant tumours. In these tumours malignancy is not defined by tumour size, pleomorphism, hypercellularity or mitotic figures, but by metastases in non-neuroendocrine tissue.8 To reduce intra-operative bleeding, temporary clamping or ligation of the external carotid artery may be required. The larger the tumour the more the risk for inevitable nerve lesions or additional vascular procedures increases during the operation.2 In our group nerve resections were unpreventable in tumours measuring at least 3.5 cm. Therefore early diagnosis and surgery at tumour diameters < 3 cm are recommended. Treatment in specialised centres with availability of a vascular surgeon is advisable because the incidence of vascular reconstructions is more than 25%.

Postoperative monitoring for hypertensive episodes is recommended. Baroreceptor failure syndrome (BFS) was described by Toma and Netterville and found in 16%.13,14 It might occur in patients after bilateral resection of the glomus caroticum with postoperative acute hypertension and tachycardia. After operation, none of our patient had blood pressure above 160 mmHg; no further medication was necessary.

### Table 2. Differences between sporadic tumours and tumours in mutation carriers.

<table>
<thead>
<tr>
<th>Tumour species</th>
<th>Mutation carrier [n = 32]</th>
<th>Sporadic tumours [n = 34]</th>
<th>Sign</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Size</td>
<td>31 ± 10.6</td>
<td></td>
<td>35.1 ± 16.7</td>
</tr>
<tr>
<td>Embolisation</td>
<td>2</td>
<td>6.3</td>
<td>6</td>
</tr>
<tr>
<td>Vascular Procedures</td>
<td>5</td>
<td>15.6</td>
<td>10</td>
</tr>
<tr>
<td>Nerve lesions</td>
<td>4</td>
<td>12.5</td>
<td>9</td>
</tr>
<tr>
<td>Shamblin A</td>
<td>10</td>
<td>31.3</td>
<td>4</td>
</tr>
<tr>
<td>Shamblin B</td>
<td>16</td>
<td>50</td>
<td>13</td>
</tr>
<tr>
<td>Shamblin C</td>
<td>6</td>
<td>18.8</td>
<td>17</td>
</tr>
</tbody>
</table>

Size: mean value ± standard deviation; *clinically significant.
At confirmation of a PGL by the pathologist, we strongly recommend genetic testing. Standard clinical predictors, such as positive family history, preceding pheochromocytoma, multiple or malignant tumours or age at diagnosis of <40 years may not always be reliable, because individuals with germline mutations may also present as clinically sporadic appearing PGL.9,13 Our results confirm these observations because 4 of the 17 mutation carriers had none of the aforementioned clinical predictors although the mutation carrier age at first operation differed significantly from patients with sporadic tumours. Previously made cost calculations will have to be reconsidered with the emerging introduction of next-generation sequencing technologies into the clinic.13

Previous studies showed that it is possible to find patients subgroups according to clinical features, family history and special predictors with a high probability of germline mutations, for example, young man with bilateral tumours.15 On the other hand there are reports that up to 30% of apparently sporadic PGL are caused by germline mutations.16 Therefore we will continue to test all our patients.

In order of frequency, SDHD mutation should be tested first, followed by SDHB and SDHC. Hereditary cases can also be seen in von Hippel—Lindau disease, multiple endocrine neoplasia type 2 (MEN 2) or neurofibromatosis.9 Additional genetic testing for these syndromes and for SDHAF2 needs to be discussed in patients with negative results for SDHD, SDHB and SDHC mutation analysis. Parallel to the developments in genetic testing, also immunohistochemical methods advanced clearly as described by Barletta and van Nederveen.17,18 Applied to the tumour samples from the operation, patients with an immunohistochemical negative result for SDH mutation would not need to be subjected to extensive genetic testing. Currently the implementation of these immunohistochemical methods is structured at our centre in cooperation with the department for pathology.

In every patient individual follow-up should be planned, as suggested in the recent review by Boedeker.9 For patients with sporadic PGL we recommend regular follow-up with clinical examination and ultrasound of the neck, primarily every year and in the case of inconspicuous results of the ultrasound every 5 years.

Mutation carriers should undergo closer regular check-up with ultrasound and additional MR angiography scans of the head and neck region, the thorax, the abdomen and the pelvis because these tumours can occur everywhere at the vegetative nervous system.9 The ideal follow-up protocol is currently under discussion and depends on the result of genetic testing. In the most frequent mutation (SDHD) complete MR imaging for patients every year is discussed.9,19 In SDHB, Collins recommended a follow-up strategy with SDHB radionucleotide screening by 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) with baseline screen and annually repeated surveillance screening supplemented by annual MR imaging.19

**CONCLUSION**

Early detection of CBTs is beneficial for the operative outcome and can prevent intra-operative nerve lesions.20 Diagnosis can be reached by ultrasound or MR angiography. Resection should be performed whenever possible and by a surgeon who is familiar with the head and neck region and has the technical options for vascular reconstruction. Regular follow-ups and genetic analysis are mandatory. Genetic counselling and examination in families of mutation carriers are advisable to detect PGL early and prevent extended resection in large tumours.
CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

REFERENCES