CLINICAL REVIEW

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SYSTEMATIC SCREENING AND TREATMENT EVALUATION OF HEREDITARY NECK PARAGANGLIOMAS

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Accepted 19 January 2007
Published online 11 June 2007 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/hed.20638

Abstract: Familial paragangliomas of the neck are often bilateral and more aggressive than spontaneous forms. Tumors appear earlier (2nd–4th decade) often with diffuse, multifocal involvement. Without treatment, these tumors can lead to significant morbidity. Three families with *succinate dehydrogenase subunit D* (SDHD) germline mutations underwent clinical and genetic evaluation. Patients were screened using ultrasound and evaluated further with conventional and functional imaging. Tumors with a diameter >1.5 cm were surgically removed. Multicentric and bilateral tumors were detected in 9/13 (69%) and 8/13 (62%) patients, respectively. Surgical morbidity occurred in 64% of patients. Local recurrence was 57%, although this was lower in tumors with a diameter <2 cm. We recommend an algorithm for a systematic approach to the diagnosis, monitoring, and treatment of familial head and neck paragangliomas. Operative treatment in advanced stages often leads to unwanted morbidity, such that earlier detection and treatment of smaller tumors seems to be of benefit. ©2007 Wiley Periodicals, Inc. *Head Neck* **29:** 864–873, 2007

Keywords: carotid body tumor; familial; screening; genetics; surgery

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Presented at the International Vascular Workshop, Going, Austria on March 16, 2006.

Hereditary paragangliomas (PGLs) are neuroendocrine tumors that are often found in the head and neck (70%), most often presenting clinically as a carotid body tumor. Approximately 10% of PGLs are familial, although this may be an underestimation due to unaffected generations caused by genomic imprinting.[1,2] The most frequently involved head and neck sites are areas with neural crest derived autonomic tissue, such as the carotid body (glomus caroticum or chemodectoma), middle ear (glomus tympanicum), jugular bulb (glomus jugulare), and the vagus nerve (glomus vagale). Typically, these neoplasms are seen in the third to fifth decade as an asymptomatic neck mass. Familial tumors, however, have been shown to appear much earlier, with multicentric PGLs reported in up to 78% of patients.[3–5] Anatomic sites such as the retroperitoneum, adrenal gland, and vertebral column, may be involved; other sites such as the mediastinum, heart, and skin are less frequently involved. Rarely, extra-adrenal PGLs produce catecholamines (pheochromocytomas), although a vast majority of head and neck glomus tumors are hormonally inactive.

The transmission and inheritance pattern are important considerations in clinical evaluation, once hereditary PGLs are suspected. Genetic studies of familial patients with PGL show a linkage to chromosome 11q23 with germline mutations in the *succinate dehydrogenase subunit D* (SDHD) gene, described as PGL1, which codes for the small subunit of cytochrome b of succinate dehydrogenase of the oxygen-sensing mitochondrial complex II.[1,6,7] Another localization for SDHD mutations maps to 11q13 and is known as PGL2.[3,8] An inheritance pattern supporting genetic imprinting has been demonstrated in studies involving both PGL1 and PGL2.[1,9] More recently, PGL3 and PGL4 syndromes have been described, resulting from mutations in the SDHC gene at 1q21[10,11] and in the SDHB gene at 1p36,[12] respectively. The latter 2 syndromes (not involving SDHD) do not appear to follow a pattern of genomic imprinting and collectively account for less than 30% of familial patients.[12] In this report, we describe 3 Austrian PGL1 families with SDHD point mutations.

Glomus tumors are highly vascularized, and their intimate association with the carotid arteries lends themselves well to care and management initiated and maintained by a vascular clinic. Left untreated, nonchromaffin PGLs of the head and neck can lead to significant morbidity, including cranial nerve dysfunction, chemo- and baroreceptor dysfunction, carotid occlusion and cerebrovascular accident, malignant transformation, and other compressive symptoms caused by tumor enlargement. Although they are mostly benign, these neoplasms, nevertheless, show variable presentations with wide variability in growth rates. Malignant transformation (glomangiosarcoma) is difficult to establish due to the relative paucity of classic histological evidence for anaplastic mitotic changes, which would differentiate a benign from a malignant lesion.[13] Malignancy has been reported to vary from 5% to 10%, with only a few small patient series seen in the literature.[5,14–16]

Surgical results reported in the past have demonstrated a high rate of surgical morbidity after extirpation of carotid body and vagal PGLs.[5,17] The surgeon is therefore faced with the decision of when to recommend intervention versus a "wait and see" approach. The latter observational approach is certainly valid in some patients, given the slow-growing nature of these tumors and the consideration of possible surgical morbidity. Van der Mey et al[17] supported such an observational policy in skull base and bilateral glomus tumors because of the significantly increased morbidity.

In our cohort, we demonstrate 3 separate familial patterns of relatively aggressive glomus caroticum, jugulare, and vagale tumors, with a high rate of recurrence and multicentricity. We therefore propose a multidisciplinary approach toward the management and diagnosis of hereditary glomus tumors that augments the screening protocol for PGL suggested by Bikhazi et al,[3] including ultrasound, molecular genetics, nuclear medicine imaging, and fusion of functional and conventional radiographic images. Recommendations for surgical and nonsurgical treatment of hereditary glomus tumors are also discussed.

MATERIALS AND METHODS

Patients. Three multigenerational families were evaluated in our multidisciplinary approach. Family A ($n = 8$) consists of 8 of 38 screened family members afflicted with head and neck PGLs. Patient data are listed in Table 1. The pedigree is outlined in Figure 1, pedigree A. The proband (patient no. 1) was a 43-year-old Austrian man, who presented with an asymptomatic neck mass at a health fair, where screening ultrasound led to the initial discovery of a right-sided 3.7- $\times$ 2.5-cm glomus caroticum tumor. Of this index patient's 12 living siblings, 6 others were identified with glomus tumors. The patient's father was also found to have bilateral caroticum tumors. Two sisters had previous surgical treatment for glomus tumors by other departments, and 1 other sister suffered from a thromboembolic stroke with ipsilateral carotid stenosis (patient no. 8). No familial pattern was identified prior to identification of the proband. There are 7 additional family members, all belonging to the subsequent generation (III), who test positive for a SDHD Y114C mutation originally described by Milunsky et al[18] and are currently free of tumorous growth. This point mutation was also isolated in all 8 affected family members.

Family B ($n = 2$) was discovered after the index patient (patient no. 9)—who had previously undergone surgery at an outside institution for PGLs on the right in 1993 and 1998—came to our institution for evaluation and treatment of recurrent bilateral glomus tumors. This family consists of 1 other affected sibling (patient no. 10), who was discovered to have a left-sided glomus caroticum tumor. Both siblings were found to have the germline R38X SDHD mutation, first described by Baysal et al,[6] that was also isolated in the

Table 1. Patient characteristics.

Patient no.	Sex	SDHD mutation type/family	Age at initial diagnosis, y	Glomus caroticum tumor(s)	Extra-carotid paraganglioma locations
1	M	Y114C / A	43	Bilateral*	Glomus jugulare, intracranial
2	M	Y114C / A	69	Bilateral*	?
3	F	Y114C / A	26	Bilateral*	Paraspinal
4	F	Y114C / A	45	Bilateral*	Glomus vagale and jugulare
5	F	Y114C / A	26	Right*	Paraspinal, paratracheal
6	F	Y114C / A	33	Left	–
7	F	Y114C / A	40	–	Glomus vagale
8	F	Y114C / A	48	Bilateral	–
9	F	R38X / B	18	Bilateral*	Kidney, adrenal gland, retroperitoneum, paraspinal
10	M	R38X / B	22	Left	–
11	F	Exon 3 / C	37	Bilateral	Paraaortal
12	F	Exon 3 / C	43	Left	Mediastinal / pulmonary
13	M	Exon 3 / C	39	Bilateral	–

Asterisk (*) indicates extension to the cranial base; "?" indicates unknown; "–" indicates none.

patients' father, who remains tumor-free (Figure 1, pedigree B).

Family C ($n = 3$) was discovered after the index patient (patient no. 11) and her sister (patient no. 12) came to our clinic in March of 2004 for further treatment of known glomus caroticum tumors in both patients. The index patient was a woman who previously underwent surgical extirpation of a left-sided glomus tumor in 1993 at the age of 37 and removal of a mediastinal PGL in the aortopulmonary window in January of 2004. At the time of arrival to our institution, she had an asymptomatic 2- $\times$ 2.3-cm glomus caroticum tumor on the right side. After establishment of a familial pattern, a glomus caroticum tumor was also discovered in the third direct sibling (patient no. 13). In addition, 2 other half-siblings were reported to have glomus tumor from the same father. The pedigree is outlined in Figure 1, pedigree C.

Screening and Surveillance. Carotid duplex ultrasound was used in all cases as a screening tool to direct further imaging. A modified screening algorithm was developed based on the protocol from Bikhazi et al[3] and is outlined in Figure 2.

Genetic analysis was performed by the Molecular Genetics Laboratory of St. Anna Children's Hospital in Vienna, Austria, and by the Department of Human Genetics, University of Pittsburgh, in conjunction with genetic counseling provided by the Department of Human Genetics of the Medical University Innsbruck. Blood samples and shock-frozen biopsy specimens were obtained from Innsbruck and sent to Vienna and Pittsburgh for analysis.

Glomus tumors, like many neuroendocrine tumors, express specific type-2 receptors for somatostatin, thus enabling the use of radioactive tracers for in vivo functional imaging.[19,20] Nuclear imaging was carried out using a 111In-labeled tetra-azacyclododecane tetra-acetic acid-octreotide (DOTA-octreotide) preparation, the methods for which will be described in detail in a future report. Whole-body planar imaging using a double-head camera system as well as a single photon emission CT (SPECT) was then carried out. Nuclear images were also obtained as an initial baseline study for all paternally inherited mutation-positive SDHD patients.

Patients were initially followed up at 3, 6, and 12 months postoperatively. Both SPECT and duplex sonography were employed for postsurgical follow-up. If recurrence, signs of new lesions, or mass effect were suggested, CT was obtained and fused with SPECT images with the use of an individual mattress mold for fixation. After the first postoperative year, patients were then followed on a yearly basis with carotid ultrasound. If multicentric foci were initially detected, follow-up nuclear imaging every 2 years was additionally employed.

For tumor-negative patients who tested positive for a SDHD gene mutation inherited paternally, yearly clinical examination and surveillance screening with Doppler duplex carotid ultrasound was started with the patient's 18th birthday, since previous studies support an exceedingly rare incidence of such tumors in pediatric patients.[21]

Therapeutic Approach. Once PGL was established by means of a combined diagnostic

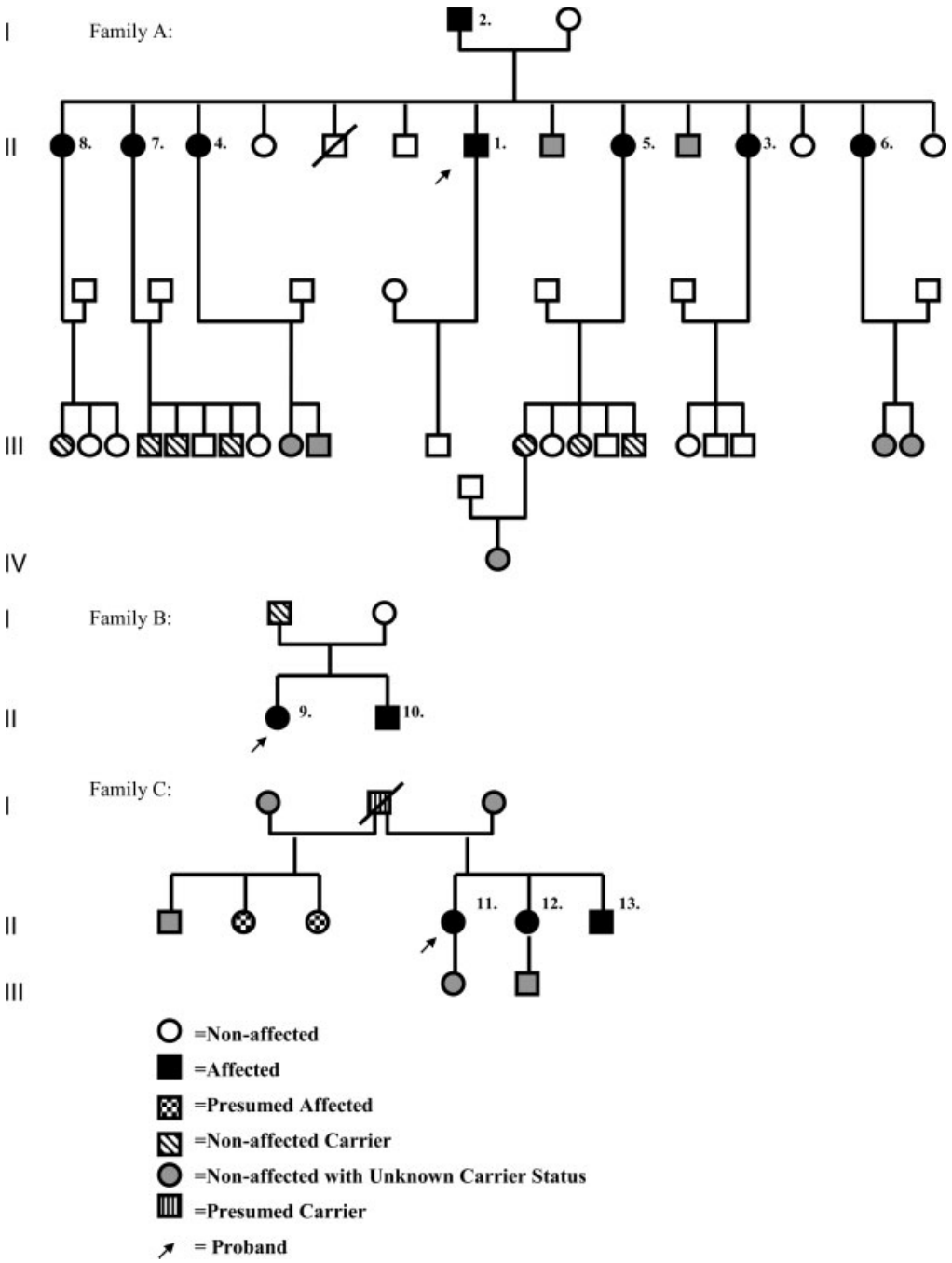

FIGURE 1. Multi-generational pedigrees for families A, B, and C. Numbers correspond to patient numbers in Table 1. Roman numerals in the left margin designate generations.

approach (as described earlier) cases were discussed in interdisciplinary conferences. These discussions focused on the therapeutic options with respect to tumor morphology and the individual patient's history. Surgical extirpation of glomus tumors of size greater than 1.5 cm in any dimension was recommended in all cases, since this was felt to be significant with regard to possible future morbidity, especially in the setting of relatively rapid recurrence exhibited in other family members.

Informed consent was obtained, and nonsurgical options and possible surgical morbidity was discussed with each patient. Eight of the 13 patients were elected for surgery. Presurgical and postsurgical sonographic and otolaryngo-

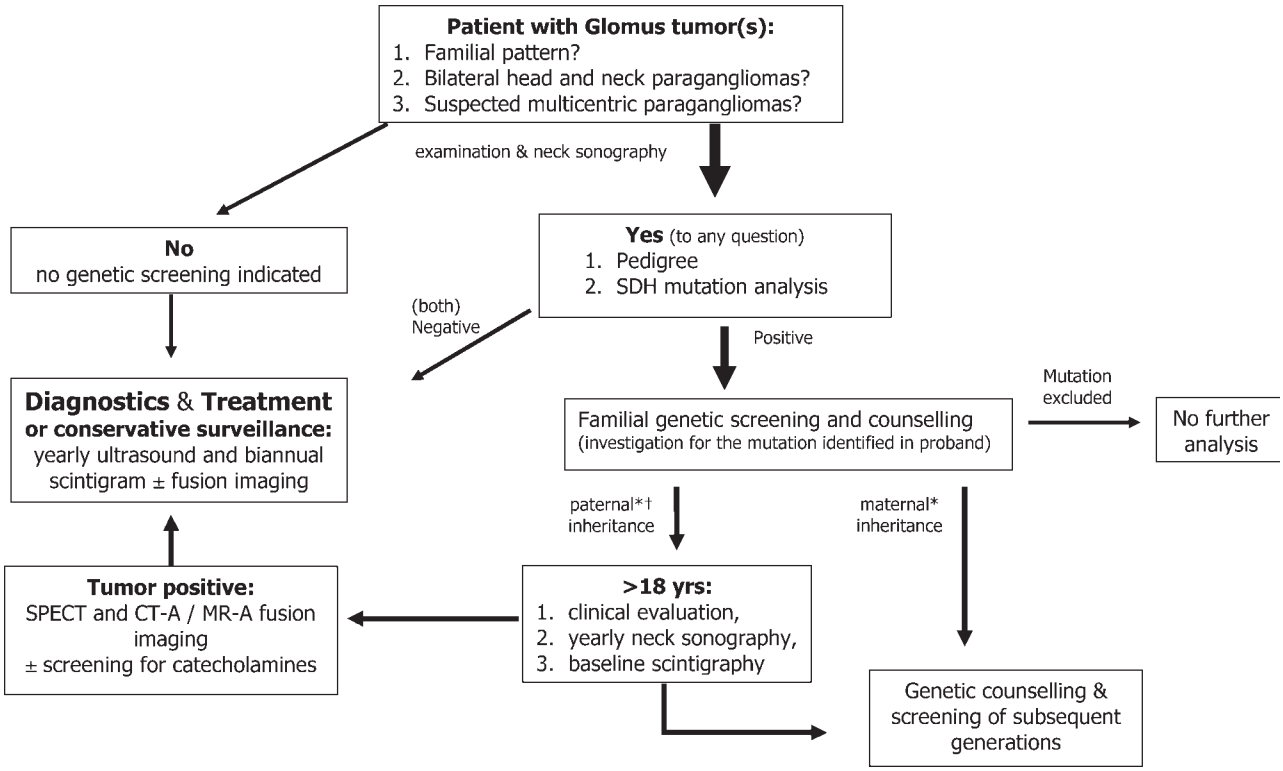

FIGURE 2. Recommended screening algorithm for suspected cases of familial head and neck paragangliomas. *Indicates for *succinate dehydrogenase subunit D* (SDHD) mutations only due to imprinting. †Indicates plan of action for all other non-SDHD genomic mutations.

logic examinations were obtained to monitor carotid flow dynamics and cranial nerve function, respectively. In the case of large glomus caroticum tumors (any dimension >3 cm), initial treatment by means of endoluminal tumor embolization with alcohol-histacryl was recommended prior to surgery, to reduce intraoperative tumor hemorrhage. In 2 patients, external beam radiation (EBR) was administered prior to operative therapy.

Surgery was performed under general anesthesia by means of longitudinal incision along the anterior border of the sternocleidomastoid muscle. Particular attention was paid to intraoperative blood pressure monitoring. The carotid sheath was opened, and the tumor was accessed after gradual preparation of the carotid bifurcation in a caudal to cranial fashion. The deep layer of the lateral neck compartment and the retropharyngeal space were explored, if necessary. Standard microdissection techniques were employed in order to preserve carotid anatomy and avoid nerve lesions. Cross-clamping of the carotid arteries was not necessary for tumor excision. Fusion images were sometimes used intraoperatively to aid dissection and tumor localization.

RESULTS

Screening Protocol. A modified screening algorithm based on the protocol for PGL suggested by Bikhazi et al[3] was developed and is outlined in Figure 2. We based our genetic screening criteria on the evidence that multifocality and bilateral neck paragangliomas (PG) have been shown to be predictive of hereditary PGL.[12,22] Specifically, previous studies report metachronous multifocality in 55% to 78%[5,17,23–25] and bilaterality in 60%[24] patients with PGL1. Once a pedigree was established, SDHD mutation analysis was first performed only in the index patient, and, if positive, familial genetic screening was initiated. We did not screen for other SDH mutations in this cohort.

Genetics. Multigenerational pedigrees are outlined in Figure 1. In Family A, SDHD gene mutation analysis showed a single base substitution (A to G) of codon 144 of exon 4, predicting a tyrosine to cysteine change of the protein (Y114C) in the index patient. Upon screening the family for this missense mutation, a total of 15 of 46 family

members tested positive (Figure 1). Several individuals in the third generation inherited the SDHD Y114C mutation from their mothers, but remain tumor-free, consistent with the previously described inheritance pattern for PGL1 involving imprinting of the maternal SDHD allele.[1]

In Family B, SDHD gene analysis revealed a nonsense mutation leading to an early stop codon (R38X). The imprinting rule can be supported in this case by the nonaffected father "re-activating" the dormant mutation (during spermatogenesis) for the subsequent generation. Family B (patient nos. 9 and 10) also demonstrated an earlier age of diagnosis—on average 20 versus 41 years—with widely disseminated tumor burden demonstrated at a very early age (18 years) in patient no. 9.

SDHD analysis of Family C revealed a deletion involving exon 3; further investigation and mutation analysis is forthcoming.

Surgery. Results of the 14 separate operative cases (in 9 patients), including operative morbidity and functional outcomes, are summarized in both Tables 2 and 3. Of the 8 family members in Family A who developed tumors, 7 patients were operated upon by our department between 1999 and 2002. In Families B and C ($n = 5$), only patient no. 10 was treated surgically in 2002. Three patients (4 operations) were previously treated outside our department between 1977 and 1998. Radical tumor extirpation was the operative goal in all patients, although in 5 patients subradical excision was performed due to local invasion into vital structures and high cranial extension. All tumors were histologically consistent with PGLs of a benign nature, with low mitotic activity and regressive changes. Resection edges were found to be tumor-free in 9/14 patients. A recurrence-free period of at least 2.5 years was only achieved in 6 (43%) operative patients (Table 3).

Systemic multifocality of tumors was seen in 7/13 patients (Table 1). Paraspinal malignant conversion with vertebral body erosions is possible in 3 of these patients because of local invasiveness. Paraspinal or vertebral body needle biopsy was not routinely obtained, however, owing to the high risk of significant bleeding with such tumors. These 7 patients with systemic multifocal tumor involvement were referred for additional treatment with radioisotope therapy, and further surgery was abandoned. Owing to the latency time needed to see effects of a radionuclide therapy, these results will be deferred for a later communication.

DISCUSSION

Glomus tumors are notoriously difficult to dissect, given their intrinsic vascularity and their proximity to the internal and external carotid arteries. This may present problems with incomplete resection, difficulties with intraoperative hemostasis, and postoperative bleeding. Moreover, the relationship of glomus tumors to multiple cranial nerves often makes careful microdissection necessary, since normal nerve anatomy can be disturbed through tumorous ingrowth. Local traction on these nerves during surgery can lead to temporary or permanent nerve palsy as well. Reports in the literature describe postoperative cranial or peripheral nerve dysfunction in cervical PGLs to range from 20% to 50% and even up to 90% in vagal body tumor excisions, with no proven significant improvement in these figures over the past 70 years.[17,26]

Very few studies dealing with long-term surgical results of glomus tumor extirpation have been published in the past. One such series of 108 patients (Van der May et al[17])—in which 50% of patients were familial tumors—casts doubt on whether the natural course of the disease is positively altered, and thus an overall reduction of morbidity is achieved by surgery. In the conclusion by these authors, the removal of solitary tumors should be considered to prevent future morbidity, although it was suggested that bilateral and skull base tumors should be monitored more conservatively. We feel that the results of our series support these statements. These authors also pessimistically concluded that overall survival could not be improved by any treatment modality available at the time of publication.

The results of our systematic approach to familial glomus tumors suggest that early detection and regular surveillance are the keys to overall lifetime reduction of tumor load and morbidity. Delayed detection was likely associated with advanced tumor size (>2 cm in any dimension), local nerve invasion, encasement of both the internal and external carotid arteries (Shamblin group III), and disseminated extracarotid involvement. Larger tumors also showed a tendency to expand longitudinally, often as multiple, discrete tumors along the internal carotid artery toward the skull base, which suggests glomus jugulare involvement. This fact was associated with incomplete resection, and locally recurrent tumors had a higher percentage of skull base involvement (63% vs 17% in nonrecurrent tumors, Table 3). Larger tumor size also appeared to be associated with

Table 2. Familial paraganglioma treatment results.

	Surgical extirpation	Max. tumor diameter, cm	Max. tumor length, cm	Other therapies	Surgical complications		Local recurrence, y
					Functional outcomes	Permanent CN lesions	
Patient 1	1999 (L)*	3	3.5†	EBR, coiling	Mild Horner syndrome	Recurrent n. paresis	1
	1999 (R)*	2.8	4†	EBR, coiling	Temporary Horner syndrome	None	1
	2000 (R)*,‡	2.5	3†	r.i.	Mild dysphagia	CN XII and sup. laryngeal n. paresis	0.5
Patient 3	*1988 (R)*	2.5	3	None	Mild dysphagia	CN XII paresis	None
	2002 (L)*,‡	1.2	4.8†	EBR, r.i.	Severe dysphagia (requiring temporary PEG tube)	CN IX & XII paresis	1.5
Patient 4	2002 (R)*,‡	1.6 cm	6†	Coiling, r.i.	Mild temporary dysphonia and dysphagia	Recurrent n. paresis	None
Patient 5	*1997 (L)*	Unknown	Unknown	EBR		CN XII paresis	None
Patient 6	2001 (L)	1.5	2	None	None	None	None
Patient 7	2002 (R)§	1	2	None	Mild permanent dysphonia	CN X paralysis	None
Patient 8	2000 (R)	2.5	3	None	Moderate permanent dysphonia	CN X paralysis, CN XII paresis	2.5
	2001 (L)‡	1.8	2.2	Coiling, r.i.	None	None	1
Patient 9	*1993 (R)*	Unknown	Unknown	EBR	None	None	5
	1998 (R)	4	5†	EBR, r.i.	None	None	4
Patient 10	2002 (L)	1.7	3.5	None	None	None	None

Abbreviations: L, left; EBR, external beam radiation; n, nerve; R, right; r.i., radioisotope therapy; CN, cranial nerve.
Note: Surgically treated PGL patients from Table 1 are included in this table. Other treatment modalities utilized either adjunctively or following surgical intervention are listed in the fifth column. Patients no. 2 and 11–13 either refused treatment or are undergoing close surveillance with or without radioisotope therapy. Italics in the second column indicate operations performed outside of our institution.
**Indicates probable incomplete resection.*
†Indicates tumors near or adjacent to the skull base.
‡Indicates multiple turmors in sequence.
§Indicates glomus vagale tumor.

Table 3. Outcomes of recurrent versus nonrecurrent paragangliomas.

	Recurrence, $n = 8$	Nonrecurrence, $n = 6$
Average diameter, cm*	2.5	1.8
Average length, cm*	3.6	3.3
Diameter < 2 cm*	2/6 (33)	4/6 (67)
Diameter ≥ 2 cm*	5/6 (83)	1/6 (17)
Skull base involvement	5/8 (63)	1/6 (17)
Systemic multifocality	6/8 (75)	2/6 (33)

Note: Outcomes following surgical extirpation of carotid body and vagal glomus tumors based on local recurrence or nonrecurrence of the tumor within 2.5 years in paraganglioma patients. Values represent number of cases (%) except as otherwise indicated.
The asterisk (*) indicates that 2/14 cases were not figured into the calculations due to a lack of accurate measurement data.

incomplete resection and increased recurrence rates, as demonstrated in Table 3, in which 83% of patients with local recurrence had tumor diameters $\geq$2 cm (vs 17% in the nonrecurrence group).

Multicentric, extra-carotid PGLs were demonstrated in 54% (7/13) of the patients seen in our series. The locations included glomus jugulare and vagale tumors, paratracheal, para-aortal, mediastinal, adrenal, and paraspinal tumors with local bony invasion into the vertebral bodies. There appears to be an association with local tumor recurrence and increased multifocality (75% vs 33% in nonrecurrent tumors as outlined in Table 3). Because of this overall high rate of unpredictable multicentricity in PGL, we recommend the combination of whole-body scintigraphy and conventional CT or MRI performed at regular intervals.

Given that tumor recurrence following resection was found in 4/9 patients (44%) or after 8/14 operations (57%) in this population, surgical extirpation was not always felt to have been beneficial, given the high rate of morbidity due to cranial nerve lesions. Similar findings are also reflected in the recommendations of Nora et al.[27] The postoperative functional outcomes included mild to moderate dysphonia ($n = 3$), mild to severe dysphagia ($n = 4$), and Horner's syndrome ($n = 1$) in 8/14 (57%) patients, displaying mild to moderate permanent cranial nerve deficits detected on repeat neurologic testing (Table 2). Owing to the high rate of surgical morbidity in this population of familial PGLs, which is also displayed in other cohorts,[17,26] we cannot support routine surgical intervention on asymptomatic tumors, especially those with advanced size. Our experience correlates advanced size with a tumor diameter >2 cm and/or extension of the tumor to the vicinity of the cranial base.

Unfortunately, many of the tumors were diagnosed in more advanced stages (Shamblin groups II and III). Patient no. 8, for example, already experienced an ipsilateral stroke at the age of 48 prior to surgical intervention, secondary to local compression and high-grade internal carotid artery stenosis with superimposed intimal fibrosis. Several other cases demonstrated infiltration of surrounding structures and enveloping nerves and the carotid arteries, making complete resection difficult or impossible. In 6 patients, EBR to the neck already administered by outside institutions prior to our surgical management appeared to produce excessive soft tissue scar formation. For these reasons, subradical resection was sometimes unavoidable, and this set the stage for recurrence of the tumor in 8/14 operations, with a mean recurrence time of 2.1 years. We also propose that the use of intraoperative neuromonitoring in cases of local infiltration may further reduce the occurrence of peripheral nerve lesions during glomus tumor extirpation, although supporting data is lacking.

Genetic evaluation for SDH gene mutations is highly advocated for all patients seen with neck PGs with a positive family history, bilateral neck PGs, or a suspicion for multicentric PG tumor burden, in order to establish the transmission pattern and guide future surveillance (Figure 2). Younger patients with PGs may also warrant the initiation of genetic screening, although a definitive age cut-off for such a recommendation has not been established. Once a mutation is detected, a pedigree should be formed, and all first-degree relatives of the proband should be offered genetic screening and counseling. Genomic imprinting with mutations in the SDHD gene, as described in previous studies involving PGL and SDHD mutations,[1,9] is present in all 3 of the Austrian families. Given the autosomal dominant transmission, asymptomatic carriers of a mutated SDHD gene inherited paternally should undergo careful screening at regimented time intervals. On the other hand, patients who inherited an SDHD mutation maternally do not require long-term surveillance due to the imprinting phenomenon. We currently recommend yearly surveillance with carotid duplex-Doppler ultrasound for carriers over the age of 18 years, given the rare incidence of such tumors in pediatric patients.[21] This age was also used as a cut-off point in other studies,[24] although in the case of patient no. 9, even earlier screening would

have been warranted, given the findings of bilateral neck PGLs by the age of 18 years.

The 2 patients in our cohort with the R38X nonsense mutation (Family B) were diagnosed at a significantly earlier age compared with the other 2 families. This supports previous evidence from a larger study that nonsense mutations indeed are associated with earlier age of diagnosis (by 8.3 years) and earlier onset of symptoms (by 8.5 years) than those with missense mutations.[28] The same study also suggests that higher altitudes (>400 m above sea level) significantly impact the development of multiple tumors in genetically susceptible individuals because of hypothesized hypoxic stimulation of the carotid body. It is also interesting to note in our cohort the possible correlation between the relatively high rate of tumor multiplicity (77%) and the fact that the patients lived at relatively high altitudes ranging from 600 to 1300 m.

A multidisciplinary approach is crucial for appropriate detection, screening, treatment, and management of glomus tumors. In addition to requiring the vascular or head and neck surgeon, these tumors often require teamwork with several other specialists from radiology, nuclear medicine, neurology, and genetics. For future generations in our cohort that are genetically predisposed by means of inheritance through their father, we believe that our diagnostic and treatment approach will prove to be beneficial. This will be facilitated by genetic evaluation, early detection, and precision in surveillance. As diagnostic measures continue to be refined and tomographic detail improved in 3 dimensions, such tumors will possibly be able to be better targeted for radical resection before infiltration into vital structures or local compressive symptoms occur. Moreover, in addition to fractionated radiotherapy, other nonsurgical therapeutic options are available today, such as radionuclide therapy or radiosurgery with gamma knife. The effectiveness of these nonsurgical techniques is still under evaluation, but these techniques may offer an alternative to surgery to reduce overall tumor load and prevent further growth with minimal associated therapeutic morbidity.

CONCLUSIONS

Familial PGs present a challenge to the surgeon due to frequent invasion into local neural structures and overall poor therapeutic results reported in the past.[17] We therefore propose a systematic, multidisciplinary approach and algorithm for the diagnosis, monitoring, and treatment of familial head and neck PGs for the long-term reduction of morbidity. Surgically, we advocate a less aggressive approach in patients with large tumors and high cranial extension, those with multifocal disease, and those with bilateral neck tumors due to high surgical morbidity and recurrence rates. Ideally, with the use of regularly scheduled follow-up using multiple radiologic modalities and scintigraphy, tumors can be detected earlier and selectively targeted for overall better tumor management and care.

Acknowledgments. We acknowledge the contributions of Dr. Andreas Weinhäusel, formerly of the Molecular Genetics Laboratory of St. Anna Children's Hospital in Vienna, and Dr. Bora Baysal of the University of Pittsburgh School of Medicine for genetic analysis.

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