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Article *in* Clinical Endocrinology · May 2024

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Received: 29 February 2024 | Revised: 2 April 2024 | Accepted: 25 April 2024

DOI: 10.1111/cen.15070

ORIGINAL ARTICLE

Genetics/MEN/Neuroendocrine tumours

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Clinical management and outcome of head and neck paragangliomas (HNPGLs): A single centre retrospective study

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Abstract

Context: Head and neck paragangliomas (HNPGLs) are rare, usually benign, slow-growing tumours arising from neural crest-derived tissue. Definitive management pathways for HNPGLs have yet to be clearly defined.

Objective: To review our experience of the clinical features and management of these tumours and to analyse outcomes of different treatment modalities.

Methods: Demographic and clinical data were obtained from The Northern Ireland Electronic Care Record (NIECR) as well from a prospectively maintained HNPGL database between January 2011 through December 2023.

Results: There were 87 patients; 50 females: 37 males with a mean age of 52.3 ± 14.2 years old (range 17–91 years old). 58.6% (n = 51) of patients had carotid body tumours, 25.2% (n = 22) glomus vagal tumours, 6.8% (n = 6) tumours in the middle ear, 2.2% (n = 2) in the parapharyngeal space and 1.1% (n = 1) in the sphenoid sinus. 5.7% (n = 5) of patients had multifocal disease. The mean tumour size at presentation was 3.2 ± 1.4 cm (range 0.5–6.9 cm). Pathogenic SDHD mutations were identified in 41.3% (n = 36), SDHB in 12.6% (n = 11), SDHC in 2.2% (n = 2) and SDHA in 1.1% (n = 1) of the patients. Overall treatment modalities included surgery alone in 51.7% (n = 45) of patients, radiotherapy in 14.9% (n = 13), observation in 28.7% (n = 25), and somatostatin analogue therapy with octreotide in 4.5% (n = 4) of patients. Factors associated with a significantly higher risk of recurrence included age over 60 years (p = .04), tumour size exceeding 2 cm (p = .03), positive SDHx variants (p = .01), and vagal and jugular tumours (p = .04).

Conclusion: The majority of our patients underwent initial surgical intervention and achieved disease stability. Our results suggest that carefully selected asymptomatic or medically unfit patients can be safely observed provided lifelong surveillance is maintained. We advocate for the establishment of a UK and Ireland national HNPGL

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registry, to delineate optimal management strategies for these rare tumours and improve long term outcomes.

KEYWORDS
clinical management, head and neck paragangliomas, outcomes, recurrence

1 | INTRODUCTION

Paragangliomas are rare neuroendocrine neoplasms derived from neural crest cells of the autonomic nervous system. Based on their anatomical location, paragangliomas are classified as extra-adrenal sympathetic paragangliomas, and head and neck paragangliomas (HNPGLs) of parasympathetic origin. HNPGLs account for up to 70% of extra-adrenal paragangliomas with an estimated prevalence of 1 per 30,000 population.[1,2]

Carotid body tumours (CBT) are the predominant subtype of HNPGLs comprising over 50% of cases. There has been a recent trend towards classifying these tumours into CBT and non CBT, given the different treatment modalities that are required.[3] Non CBT tumours are subdivided into vagal paragangliomas which are the next most common, while jugular paragangliomas arise at the jugular bulb with extension into the middle ear.[4] Glomus tympanicum tumours arise along the promontory in the middle ear. Other rare locations include the orbit, nasal cavity, and thyroid gland. HNPGLs typically cause symptoms by local mass effect and or by invasion of cranial nerves.

Malignancy is defined by metastatic spread and occurs in <10% of HNPGLs.[5] HNPGLs are usually non-secreting with ≤5% associated with catecholamines excess.[6] Plasma or 24 h urine catecholamines/metanephrines should be measured in all HNPGLs. If catecholamine excess is demonstrated, a detailed investigation is required to exclude the possibility of synchronous phaeochromocytomas or sympathetic PGLs. HNPGLs may be sporadic or due to germline mutations in Succinate Dehydrogenase (SDH) genes, particularly SDHD, SDHB, and SDHC.[7] SDHB variants confer a higher risk of metastatic disease. Therefore, genetic testing and counselling provide important diagnostic and prognostic guidance.

The management of HNPGLs requires a multidisciplinary approach addressing the genetic, surgical, radiotherapeutic, oncological, neurological and endocrinological aspects of these tumours. Complete surgical resection remains the treatment of choice for HNPGLs.[5,8] However, surgical resection can be challenging due to the highly vascular and infiltrative nature of these tumours. Cranial nerve deficits are estimated to occur in 20%–50% of patients after surgery.[9] Radiation therapy may be used as alternative or adjunctive treatment option for unresectable tumours and residual disease. The indolent growth pattern of HNPGLs has led to increasing interest in the possible virtue of initial observation strategies.[10] Other treatment options include stereotactic radiosurgery, permanent embolization, and medical therapy with somatostatin analogues.[11,12] Due to the rarity of HNPGLs, few studies have examined evolving strategies in diagnosis, management and clinical outcomes of these tumours.[13–15] In this study, we aimed to review our 12 years institutional experience in managing HNPGLs in a large regional tertiary referral centre, and to analyse the outcomes of different treatment modalities.

2 | METHODS

2.1 | Study design and data collection

This was a retrospective review of all patients diagnosed with HNPGLs in the Regional Centre for Endocrinology and Diabetes, Royal Victoria Hospital, Belfast between January 2011 through December 2023. Baseline clinical information was obtained from a prospectively maintained HNPGL database. All patients with a tissue diagnosis of HNPGLs in the Belfast Trust during the twelve years study period were included. Further clinical, radiological and laboratory data as well as outcomes were obtained from The Northern Ireland Electronic Care Record (NIECR). Data were collected on patient demographics, clinical presentation, imaging studies, genetic testing, functionality, treatment details, complications, and outcomes. Preoperative tumour size was determined based on maximal diameter on cross-sectional imaging. Available pathology was reviewed to confirm the diagnosis. Tumours were considered functional (catecholamines secreting) when patients had elevated urine metanephrines levels (twice our laboratory's reference range) on at least two occasions. Duration of clinical follow-up was defined as the time interval from the date of treatment (surgery or final dose of radiation) or first patient encounter (for patients undergoing observation only) to the last clinical evaluation or patient death. Serial follow-up imaging was reviewed to assess treatment response. Recurrence was defined as tumour regrowth after initial therapy requiring further intervention or as increased size of tumour for patients undergoing observation only. The latest follow-up visit was used to ascertain disease status.

The standard preoperative protocol for HNPGLs patients at our institution included:

A) Biochemical workup: 24-h urine collection for metanephrines, normetanephrine levels.
B) Imaging: CT/MRI neck with contrast, PET-CT, Octreotide scan (111In-pentetreotide) and Ga 68 Dotatate PET CT (in selected cases and via our Multidisciplinary assessment pathway).
C) Genetics: Referral to Regional Genetic Service for evaluation of clinically relevant mutations and family screening where indicated.
D) Multidisciplinary assessment: including Surgical (Vascular/ENT/Neurosurgery), Endocrinology, and Radiology input.

If required, complex cases were managed jointly with centres outside of Northern Ireland including London, Manchester or Birmingham. This may have involved consideration of novel therapies/adjunctive treatment or more complex surgery.

2.2 | Statistical analysis

Data were analysed using SPSS version 22.0. Continuous variables were reported as mean ± standard deviation or median (range) as appropriate. Categorical variables were reported as frequency (percentage). Fisher's exact or chi-square tests were used to analyse associations between categorical variables. Mann-Whitney U or unpaired *t*-tests compared continuous variables. P values < 0.05 were considered statistically significant.

2.3 | Ethical approval

The research project was approved within our institutional trust review board (within the audit department) of the Belfast Health and Social Care Trust (reference: 6622). Informed consent was not obtained because this study was of retrospective design and we used only deidentified clinic-pathologic information. Data were collected anonymously on a secure and password protected computer. Identifiers (unique patient health and care number) were held on a secure work-computer separately to the clinical data.

3 | RESULTS

A total of 87 patients were diagnosed with HNPGLs during the 12 years period. The mean age at diagnosis was 52.3 ± 14.2 years. There was a female preponderance, with 57.4% (*n* = 50) females compared to 42.6% (*n* = 37) males. The most common presenting symptoms were neck pain and or swelling in 32 (36.7%) patients, as an incidental finding in 25 (28.7%) patients, hearing impairment and tinnitus in 19 (21.8%) and cranial nerve involvement in 11 (12.6%) patients (Table 1).

Radiological investigation revealed 58.6% (*n* = 51) of tumours were localised to the carotid body, 25.2% (*n* = 22) were situated at the jugular foramen and along the vagal nerve, 6.8% (*n* = 6) in the middle ear, 2.2% (*n* = 2) in the para-pharyngeal space and 1.1% (*n* = 1) in the sphenoid sinus region, 5.7% (*n* = 5) patients had multifocal disease lesions (Figure 1). In 15 (17.2%) of those with carotid body tumours the tumours were bilateral.

The mean tumour size was 3.2 ± 1.4 cm (0.5–6.9 cm). 58.6% (*n* = 51) of tumours were >2 cm in maximal diameter while 41.3% (*n* = 36) were ≤2 cm.

There were 14.9% (*n* = 13) of patients were initially diagnosed as part of family genetic screening. Pathogenic SDHD variant was identified in 41.3% (*n* = 36), SDHB in 12.6% (*n* = 11) and SDHC in 2.2% (*n* = 2) and SDHA in 1.1% (*n* = 1) of patients. No genetic cause was found in 28.7% (*n* = 25). The genetic variants results were unknown in 13.7% (*n* = 12) of patients; 11 patients were still awaiting genetic testing and one patient had declined testing (Table 2). The vast majority were missense variants and there was no correlation with malignant tumour risk with the truncating variants.

All patients were screened with 24 h urinary metanephrines collection, all were negative with the exception of one patient who had a secretory carotid body tumour.

The treatment modalities included surgery alone in 51.7% (*n* = 45), radiotherapy (with or without initial surgery) in 14.9%

TABLE 1 Baseline demographic and clinical characteristics

Variable	Overall N (%)
Gender	
Male	37 (42.6%)
Female	50 (57.4%)
Age in years, mean (range)	52 years (17–91)
Presentation	
Swelling/pain	32 (36.7%)
Incidental	25 (28.7%)
Hearing impairment/tinnitus	19 (21.8%)
Cranial nerve involvement	11 (12.6%)
Tumour size	
>2 cm	51 (58.6%)
≤2 cm	36 (41.3%)
Secretory tumours	
Non secretory Secretory	86 (98.8%)
Secretory	1 (1.2%)
Bilateral CBT tumours*	15 (17.2%)

*CBT, Carotid body tumour.

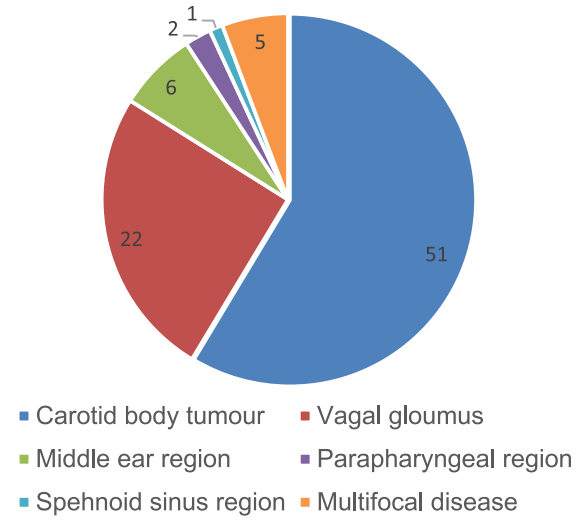

FIGURE 1 Number of tumours per anatomical site. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Genetic profile of patients tested

Gene	N (%)
SDHD	36 (41.3%)
SDHB	11 (12.6%)
SDHC	2 (2.2%)
SDHA	1 (1.1%)
Negative	25 (28.7%)
Unknown	12 (13.7%)

TABLE 3 Treatment modalities

Treatment	N (%)	Outcomes	N (%)
Surgery	45 (51.7%)	Stable disease Recurrence	35 (77.8%) 13 (22.2%)
Observation	25 (28.7%)	Stable disease	25 (100%)
Radiotherapy	13 (14.9%)	Stable disease Recurrence	10 (76.9%) 3 (23.1%)
Octreotide	4 (4.5%)	Stable disease	4 (100%)

(*n* = 13), observation in 28.7% (*n* = 25), and somatostatin analogue therapy with octreotide in 4.5% (*n* = 4) of patients (Table 3).

In this cohort, carotid body tumours were resected in 64.4% (*n* = 29) of those patients (*n* = 45) who underwent surgical intervention and 11 (37.9%) of these sustained a postoperative cranial nerve deficit. By contrast, vagal & jugular paragangliomas were resected in 26.6% (*n* = 12), 41.6% (*n* = 5) of whom sustained a postoperative cranial nerve deficit. Overall, six patients had postoperative vocal cord/s injury, four patients had 7th nerve palsy, two patients had 12th nerve injury, two patients had injury to the vagus nerve, and two patients developed sensorineural deafness. One patient developed E Coli septicaemia and hyponatraemia, and one patient had post operative bleeding and wound infection.

For patients (*n* = 13) who received radiotherapy, nine patients were treated with photon therapy and one patient with Proton Beam Therapy. For all 10 patients, the median dose delivered was 45 Gy in 25 fractions (Range 45–50.4 Gy in 25–30 fractions). Three patients had their radiotherapy elsewhere and radiotherapy details remained unknown.

The median follow-up was 5 years (range 1–8 years). At the last follow-up, 85.1% (*n* = 74) of patients had stable disease (*p* = .003) and did not require further intervention (Table 3). However, 14.2% (*n* = 13) experienced local disease recurrence requiring further intervention.

Factors associated with a significantly higher risk of recurrence included age over 60 years (*p* = .04), size exceeding 2 cm (*p* = .03), positive SDHx variants (*p* = .01), and vagal and jugular tumours (*p* = .04). There was one (1.1%) patient who died due to frailty and disease progression from a large extensive sphenoidal sinus PGL. There were three (3.4%) patients who had subsequently developed abdominal paraganglioma with successful surgical excision on most recent follow up.

4 | DISCUSSION

HNPGLs are rare complex tumours that necessitate a tailored management strategy based on individual patient, tumour location and genetic testing. The data presented represent a 12-year retrospective review of the management of 87 patients with these tumours in a large regional tertiary referral centre. The female predominance and mean age findings were consistent with previous reports.[16–18] Carotid body tumours were the most frequent (58.6%), followed by jugular and vagal paragangliomas (25.2%). This distribution was similar to the relative incidences reported in current literature,[15,16] 28.7% of patients were diagnosed incidentally and this highlights the value of early detection, as smaller tumours are more amenable to resection without surgical induced neurologic sequelae. Nonetheless, HNPGLs become clinically detectable due to mass effect or cranial nerve involvement, as evidenced by neck swelling and pain (36.7%) and hearing loss and tinnitus (21.8%) being the most common symptoms in this cohort. This is also consistent with previous reports and indicating the locally infiltrative nature of HNPGLs.[19,20]

Genetic analysis revealed SDHx variants in 57.4%, and this was higher than the known 30-40% prevalence of hereditary disease.[21–23] Hence, testing of all PGLs patients remains essential to diagnosis of hereditary disease, guides screening of family members, and predicts metastasis risk in SDHx carriers.[24,25] Catecholamine excess is very uncommon in head and neck paragangliomas. All tumours in this study were non-secretory except for one patient who had secretory sporadic CBT at initial diagnosis with no other detectable disease elsewhere. Hence, biochemical testing is crucial and still recommended at the time of diagnosis, but unlikely to be beneficial for routine follow-up, however genetic testing will also dictate the relevant need for this.[8]

Complete surgical resection remains the standard treatment for HNPGLs. The majority of our patients (51.7%) had initial surgical intervention. Patients who had surgical treatment had either observed rapid growth of their tumour size or increase in symptomatology. One patient had surgery because of a secreting tumour. Postoperative cranial nerve injury occurred in 35% of patients. Other studies report rates of more than 50% following resection,[15] this highlights the difficult balance between achieving gross total resection and the preservation of neurological function. Multiple studies have reported much higher morbidity, particularly with vagal and jugular paragangliomas where postoperative cranial neuropathies occur in over 50% of patients,[2,15] therefore surgery is now reserved for selected cases such as rapidly progressive or symptomatic tumours. The elderly and medically unfit are preferentially managed with observation or radiotherapy.[26]

Medical therapy with somatostatin analogues may allow for tumour control while avoiding surgical morbidity but requires further

study. Somatostatin analogues like octreotide are gaining favour for refractory paragangliomas, but supporting data remains sparse.[27] In our cohort, 16 patients had Octreotide positive disease on their uptake scan. Four of these patients, with recurrent tumours not amenable to re-resection, were managed medically with monthly octreotide injections. These patients achieved tumour stabilisation without additional growth over 2 years follow-up. This was consistent with previous case series reported in 2013 by Van Hulsteijn et al.[11] Ongoing clinical trials will provide higher-quality evidence regarding their efficacy.[28]

In the last few years, molecular targeted therapies have been used in treating progressive and metastatic PGLs. Sunitinib is the only therapeutic option which has been investigated in a randomised placebo-controlled clinical trial. It is clinically used as a main therapeutic option for the treatment of progressive and metastatic PGLs. Some combination therapies such as temozolomide/Olaparib or cabozantinib/atezolizumab, are currently being evaluated in clinical trials.[29] It is expected that advances in such molecular targeted therapies will play a critical role in the future treatment of these tumours.

In our experience, 33% of tumours were managed conservatively with observation or octreotide medical therapy. This is higher compared to some published case series, where surgical intervention rates exceeding 85% have been reported.[30] After a median of 5-year follow-up, tumour recurrence developed in 14% of the study population. This is comparable to prior data reporting 10%–15% recurrence rates.[6,31] Age over 60 years, tumour size exceeding 2 cm, positive genetic variants, and vagal and jugular locations were significantly associated with recurrence. The need for annual lifelong follow-up has been suggested given that late recurrences are possible and caution is warranted while monitoring elderly patients, large tumours, hereditary cases, and jugular HNPGLs.[32]

The limitations of this study include the retrospective design and small sample size. Also, details of surgical resection were unavailable in some. Detailed histopathology information were unavailable. 3-Methoxytyramine (3-MT) results testing was not part of our diagnostic pathway protocol. Nonetheless, the study provides useful real-world data on multimodality management and insights into current management and outcomes that will further guide clinicians caring for patients with HNPGLs. There has been a recent trend towards establishing dedicated paraganglioma clinics to facilitate the management and follow of these patients and we are planning to establish this dedicated clinic locally.

5 | CONCLUSION

HNPGLs are rare complex tumours requiring individualised management based on patient factors and tumour characteristics. The majority of our patients underwent initial surgical intervention and achieved disease stability. Age, large tumours >2 cm, positive genetic variants, and vagal/jugular locations were associated with significantly higher recurrence risk in our cohort. Carefully selected asymptomatic or medically unfit patients can be safely observed provided lifelong surveillance is maintained. The role of newer adjunctive therapies for those with recurrence/disease progression merit further study in multi-centre trials. We advocate for the establishment of a UK and Ireland national HNPGL registry, to delineate optimal management strategies for these rare tumours and improve long term outcomes.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data of this study are available on request from the corresponding author. The data are not publicly available due to ethical restrictions.

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How to cite this article: Darrat M, Lau L, Leonard C, et al. Clinical management and outcome of head and neck paragangliomas (HNPGLs): a single centre retrospective study. *Clin Endocrinol*. 2024;1-6. doi:10.1111/cen.15070

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