Head-and-neck paragangliomas: An overview of 54 cases operated at a tertiary care center

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Abstract

Background: Head-and-neck paragangliomas (HNP's) are rare autonomic neoplasms associated with high morbidity and mortality. We aimed to study epidemiology, clinicopathological correlation, and management of HNP to assist clinicians in advocating the most appropriate therapy. **Materials and Methods:** Epidemiological parameters, including age and sex distribution, clinical presentation, tumor classification, familial predisposition, multicentricity, and treatment modalities adopted, were analyzed in this retrospective analysis of 54 patients of HNP. **Results:** Age ranged from 15 to 85 years, with a female preponderance. Among all HNP, carotid body tumor (CBT) (48.1%) was the most common, followed by Glomus Jugulare (24.1%). Majority of the patients presented with neck swelling associated with nerve palsies. A preoperative neurological deficit was most commonly observed with Glomus jugulotympanicum (68.4%). **Conclusion:** CBT is the largest and most common paraganglioma in our study. The familial occurrence warrants meticulous screening for multifocality. Tumor location, neurovascular involvement, malignant potential, and patient factors should guide the designing of management options.

Key words: Familial, multicentric, paraganglioma, radiotherapy, secretory, surgery

Introduction

Extra-adrenal paragangliomas arise from sympathoadrenal neuroendocrine system and are classified according to the primary site of origin[1] (carotid bifurcation, vagal or jugulotympanic, ciliary body, or larynx). Head-and-neck paragangliomas (HNPs) are rare, benign, parasympathetically innervated tumors, comprising of 0.03% of all human tumors, and <0.5% of all head-and-neck tumors, with an annual incidence of 0.001%. Of all the paragangliomas in the body, approximately 3% occur in the head-and-neck area.[2] Previous studies have estimated the incidence of HNP to be around 1 in 30,000 head-and-neck tumors.[3] Even though the majority of these are sporadic, a familial predisposition cannot be ruled out altogether.[4,5] Various studies report germline mutations of SDHB, SDHD, VHL, and RET to be involved in familial pheochromocytoma.[6] These tumors have an indolent course with a variable progressive growth pattern ranging from being asymptomatic and diagnosed incidentally on radiology to producing cranial nerve palsies and brainstem compression.

Although radiotherapy (RT) or stereotactic radiosurgery can be advocated in some patients of HNP, surgery still remains the mainstay of the treatment,[7] which is a challenge to the surgeon owing to the proximity of the tumor to important blood vessels and cranial nerves.

As both, the tumor growth as well as surgery can cause disabling loss of function, knowledge of the natural history of paragangliomas is of foremost importance when considering treatment strategies.[8,9] Glomus jugulotympanicum (GJT), if left untreated, is notorious for causing maximum morbidity among all HNPs, and if operated, leads to a two-fold increase in cranial nerve palsies.[10] Surgery for carotid body tumors (CBTs) results in cranial nerve impairment in as much as 10% of the cases.[11,12] Therefore, the risk of serious complications as a result of treatment remains an important factor in the treatment decision-making for individual patients and must be weighed against the natural course of these tumors.[13] According to the literature, no significant improvement in the life expectancy is achieved after surgery whereas the patients who undergo surgery develop the most complications.[13]

This study aims at being a useful survey to current data on the epidemiology and management of HNPs to assist clinicians in advising their patients on the most appropriate therapy.

Materials and Methods

This is a retrospective study analyzing 54 consecutive patients of HNP treated at a tertiary care center, over 5 years (2009–2013). The clinical history and examination along with specific radiological features guided us toward the clinical diagnosis of paraganglioma. The epidemiological parameters, including age and sex distribution, clinical presentation, tumor classification, familial predisposition, multicentricity, and treatment modalities adopted, were studied and analyzed in each case with a minimum follow-up of 10 months (mean follow-up of 24 months).

The treatment modalities adopted were either surgery alone or surgery supplemented with postoperative radiation, depending on the type of HNP, stage of disease, preoperative cranial nerve involvement, and proximity to various vital structures. Histopathological examination was done to confirm the diagnosis and to evaluate for the features of metastasis (intratumoral necrosis, high mitotic index, and nuclear pleomorphism along with capsular and vascular invasion).

The sequential follow-up was done monthly during the 1st year, 3 monthly in the 2nd year, and 6 monthly thereafter, including clinical evaluation and radiology, if and when required.

Results

Our study showed female preponderance (35:19) with age ranging from 15 to 85 years (mean 37 years), with majority (53.7%) presenting in their 3rd and 4th decades. Out of the total 54 patients, 51 (94.5%) had symptoms attributable to their disease, whereas three were diagnosed incidentally.

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CBT was the most prevalent type, comprising 48.1% of the total (26 patients), Glomus Jugulare (GJ) being second with 13 patients (24.1%), followed by Glomus tympanicum (GT) and Glomus vagale (GV) with six patients each (11.1%). In three patients, it was arising from the supraglottis (5.5%). Majority of the patients presented to us in the advanced stages (CBT-15/26 had Stage II, and 11/26 had Stage III whereas, in GJT, 5/19 had Stage B, 6/19 had Stage C, and 8/19 had Stage D).

Table 1 shows that among CBT, 96.1% (25 patients) presented with diffuse neck swelling whereas 46.1% (12 patients) presented with pain. A preoperative cranial nerve involvement was seen in six patients (23.1%) of CBT. In GJT, the most common presentation was cranial nerve involvement (13 patients, 68.4%), followed by ear discharge (57.9%), seen in 11 patients. Swelling was invariably seen in all the patients of GV, with cranial nerve deficit seen in two patients (33.3%). Overall preoperative cranial nerve involvement was present in 24 patients (44.4%), most commonly seen with GJT in 13 patients (54.1%) [Table 1].

In the present study, four patients (7.4%) had a secretory tumor (two of CBT and one each of GJT and SGL glomus). A positive family history was present in one patient (CBT) who also received postoperative RT. One of the patients with secretory tumor also showed multicentricity. Multicentricity was seen in five patients (9.2%). All of them had CBT, (four had Shamblin Class 3 and 1 had Shamblin Class 2), with an age range of 25 years to 35 years. Out of the five patients, two patients had concomitant GJ. A positive family history was seen in two patients whereas one patient showed a hypersecretory state. Preoperative cranial nerve deficit was seen in three patients. Four out of five patients with multicentricity required postoperative RT.

A positive family history was seen in three patients, all were CBT Shamblin Stage 3, with two patients having preoperative cranial nerve deficits. They all showed multicentricity, with one patient having hypersecretory state.

All the patients were subjected to surgical excision depending on the tumor location and extent. The decision of postoperative RT was based on the advanced stage of the disease, residual tumor, and proximity to vital structures.

Out of 54 patients of HNP, complete tumor excision could be achieved in 50 patients (92.6%) whereas four patients had residual tumor. Three of the four patients with residual tumor had GJT, and one patient had CBT. Residual tumor was more commonly seen with GJT (3/19–15.8%) than CBT (1/26–3.8%).

Light microscopic examination revealed that out of 54 patients, only two patients (3.7%) showed microscopic features of malignant potential in the form of high mitotic activity and capsular and vascular invasion. These two patients belonged to CBT Shamblin Stage 3 and GV.

Table 1: Paraganglioma symptoms

Symptoms	CBT	GJT	GV
Mass	25	4	6
Pain	12	10	1
Cranial nerve involved	6	13	2
Ear discharge	-	11	-
Decreased hearing	-	10	-
Hoarseness	6	4	2
Dysphagia	4	3	2

CBT=Carotid body tumors, GJT=Glomus jugulotympanicum, GV=Glomus vagale

A total of 24 patients had preoperative cranial nerve deficits. Out of the total of 30 patients with normal preoperative cranial nerve status, 17 patients (31.5%) developed cranial nerve deficits after surgical intervention. Postoperative cranial nerve involvement was more common in surgery for CBT (10 patients, 58.8%), as compared to the surgery for GV (7 patients, 41.2%).

In the present study, six patients received postoperative RT (11.1%) in the form of fractionated radiation. Out of the six patients, four had Shamblin Class 3 CBT, and two patients had GJT (one each in Fisch Class C and D). Five out of six patients received RT due to the presence of gross residual tumor after the surgery. One patient had a secretory tumor whereas three patients were diagnosed to have multicentric tumor. A positive family history was present in two patients receiving postoperative RT.

Discussion

Paragangliomas arise from small groups of neuroendocrine cells from the autonomic nervous system ganglia.[14] The parasympathetic paraganglia are primarily situated in the head-and-neck region, and less frequently in the thorax or pelvis whereas the sympathetic ones are mainly located along the sympathetic nerve chains bordering the vertebrae and in the pelvis. Parasympathetic paraganglia are usually nonchromaffin and nonsecretory when compared with their sympathetic counterparts.[14]

HNP are rare tumors, representing 0.012% of the total oncological surgical series (Lack *et al*. 1977), with an estimated annual clinical incidence of 1/100,000 patients (Baysal 2002). Erickson *et al*. in 2001 and Papaspyrou *et al*. in 2009 showed that HNP is most frequently diagnosed in middle-aged adults (mean age 41–47 years). A similar trend is seen in the present study also, with a mean age of 37 years, and around 53.7% of the patients presenting in their 3rd and 4th decades.

Among all paragangliomas, the CBT is the most common and the least frequent are those arising from vagus paraganglia (GV). Majority of the patients in our study had CBT (48.1%), followed by GJ (24.1%), with 11.1% each having GT and GV. The relative frequencies of these paragangliomas vary widely across different series, with Erickson *et al*. reporting 57% CBT, 30% GJT, and 13% GV in a large series of 204 HNPs in 2001.

The most common presentation of HNP in the lower part of the neck (CBTs and some GV) is painless, sometimes pulsatile, neck masses. With further growth, they may involve the lower CNs, leading to speech and swallowing deficits, and rarely aspiration (Miller *et al*. 2000, Offergeld *et al*. 2012). The present study shows a preoperative cranial nerve involvement in 44.44%, with maximum in GJT (54.1%). According to various studies done by Powell *et al*. in 1992, Netterville *et al*. in 1998, Sajid *et al*. in 2007, and Neskey *et al*. in 2011, preoperative cranial nerve deficit is most commonly observed with GJT (39%–40%), followed by GV (25%–36%), and less so in CBT (4%–22%).

The presence of distant metastases is an only indicator to ascertain malignancy. Our study demonstrates the malignant incidence to be around 3.7%, which is in accordance with the studies done by Manolidis *et al*. in 1999 and Jafri *et al*. in 2013 showing the incidence of malignancy in HNP to be around 3%–5%, with a lower risk for CBTs and GJT (2%–6%) and a higher risk (16%) for GV (Kahn 1976, Kloppel 2003).

In progressive tumors, the median doubling time (Td) of paragangliomas was 4.2 years, as compared with malignant neoplasms (Td of 100 days or 0.27 years), emphasizing on the extremely slow growth rate of these tumors.[15] The variation in the growth rate of paragangliomas is remarkable; varying between 0.6 and 21.5 years.[13] Several studies have suggested a "wait and watch" policy for HNPs, depending on patient age, hearing status in contralateral ear, and bilateral tumors.[16-21]

Taking into consideration the relatively mild natural history of HNP, a long follow-up duration is required before reaching to a concrete conclusion about the efficacy of various treatment modalities. Surgery still remains the mainstay of the treatment for paragangliomas. It may be combined with RT either external-beam RT or stereotactic radiosurgery. The respective roles of chemotherapy and peptide receptor radionuclide therapy are still debatable.

Overall, gross total resection (GTR) is achievable in 90%–97% of the cases of HNP, with a low surgical mortality rate (0%–2.7%).[14] According to Gaylis *et al*. in 1987 and Ma *et al*. in 2009, complete surgical resection is possible in 85%–100% cases of CBTs with low recurrence rates but high postoperative complications due to the high vascularity and proximity to essential neurovascular structures. Surgery is most challenging for GJT as posterolateral skull base exploration is required. Most studies have shown a GTR of 59%–96%, with a mortality rate of 0%–5%. The probability of surgical cure in GV is also very high, with a GTR of 92.3%–100%, and a low mortality rate of 0%–2.7%.[14] In the present study, the GTR is around 92.6%, with maximum residual tumor seen in cases of GJT (15.8%), followed by CBT (3.8%).

The surgery for CBT is associated with varying complications such as transient ischemic attack (TIA) or stroke. Anand *et al*. after analyzing the postoperative outcome of 1181 patients in 1995, showed the cumulative incidence of TIA to be around 6.3%, which was much lower in the recent studies done by Sajid *et al*. in 2007, Makeieff *et al*. in 2008, and Ma *et al*. in 2009 (0%–4.8%). The incidence of internal carotid artery injury ranges from 10% to 23%, and vessel reconstruction leads to significantly lower stroke and mortality rates versus ligation (Anand *et al*. 1995 and Plukker *et al*. 2001).

Immediate postoperative cranial nerve deficits in the form of lower cranial nerve palsies and Horner's syndrome are common, ranging between 19% and 50%; however, a permanent deficit is less common (1% and 18%), due to progressive slow rehabilitation (Persky *et al*. 2002, Sajid *et al*. 2007, and Makeieff *et al*. 2008). According to Luna-Ortiz *et al*. in 2005, advanced cases (Shamblin Classes II and III) were associated with higher rates of permanent neurological deficit (38%). As the Shamblin classification is significantly correlated with postoperative complications such as intraoperative blood loss and vascular reconstruction need, early detection is essential for safe management.

For the majority of HNP, complete remission is the most desirable outcome, and surgery is the mainstay method to achieve this outcome. However, for tumors with an indolent natural course of disease, it is of prime importance to minimize the posttreatment morbidity, and thus therapies offering local control with fewer adverse effects, such as RT, can sometimes be preferred.

Conclusion

HNPs rarely release catecholamines to produce a hypersecretory syndrome (<10%) making their early detection difficult. Symptomatology depends on the specific location of the tumor, with the mass effect being the most common presentation. CBT is the largest and most common HNP in our study (48%). The familial occurrence of the tumor warrants meticulous screening for multifocality. As the majority of HNPs have a very low growth rate, the management options are guided by several parameters such as tumor location, neurovascular involvement, malignant potential, and nonetheless, patient factors. It still remains a challenge for every physician, especially in cases of multiple paragangliomas or tumors, in an advanced stage. Although surgical resection remains the treatment of choice, slow growth and multifocality of HNPs may justify less aggressive treatment strategies following a "wait and scan" policy.

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Conflicts of interest

There are no conflicts of interest.

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