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High Altitude Head and Neck Paragangliomas: A First Sub-Himalayan Experience

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Abstract

Objectives. High-altitude natives have a high incidence of paragangliomas (PGL) of the head and neck, especially the carotid body tumor. The aim of this study is to describe the clinical presentation, pattern, altitude of residence, distribution, management, and follow-up of head and neck paragangliomas (HNPGL) in our sub-Himalayan population.

Study Design. Retrospective cohort study.

Setting. Academic tertiary care hospital.

Methods. Hospital records of 20 patients of HNPGL diagnosed from December 2017 to December 2021 were retrieved for analysis.

Results. Twenty patients with 23 HNPGL, with a mean age of 41.74 years were managed in our institute. The female-to-male ratio was 2.3: 1 and the mean follow-up was 29.95 months. Nine had carotid body (CBPGL), 7 had tympanic (TPGL), 2 had jugular (JPGL), and 2 had vagal paragangliomas (VPGL). Multiple PGL were seen in 4 patients (20%). Majority of cases (all CBPGL and 57.14% of TPGL) were residents of the high altitude, and the rest were from the low altitude. Fifteen patients (8 CBPGL, 7 TPGL) were operated. There were no major complications except in a patient with large carotid body tumor required anastomosis of carotid artery. Five patients received stereotactic radiotherapy, and 1 malignant PGL received chemoradiotherapy.

Conclusion. In this study, JPGL and VPGL are common at low altitudes, whereas carotid body and tympanic PGL were the most common tumor at high altitudes. Being a retrospective and study small sample size, a definite conclusion is not established, however, a genetic analysis and inclusion of a wider population in a future prospective study may establish the hypothesis.

Keywords

head and neck, high altitude, low altitude, paraganglioma, sub-Himalayan

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Paraganglia's are a chain of extra-adrenal neuroendocrine cells, derivative of neural crest, and are distributed along the branchial mesoderm in the head and neck region.[1] They are distributed along the cranial nerve, vessels, and may function as chemoreceptors.[2] Paragangliomas (PGL), are tumors of the paraganglia and are rare, and benign but highly vascular in nature. They constitute only 0.5% of all head and neck tumors and are frequently found in the carotid body, jugular foramen, vagus nerve, and middle ear.[3] These tumors are very slow growing in nature, and mean doubling time is around 4.2 years.[4] Yet, they are locally aggressive, can infiltrate the surrounding vital structures, and pose a threat to life during surgical excision. In the literature, various treatments have been described, including surgical excision, fractionated and stereotactic radiotherapy (SRT), and observation with serial imaging.[5]

Chronic hypoxia is a recognized causative factor for PGL and natives residing in high altitudes, and females are more prone to develop such tumors. Carotid body paragangliomas (CBPGL) incidence increases linearly with the increase in altitude and elevation gain, and natives of Quito, Mexico City, Peruvian, and Bolivian Andes have been at a high risk of developing such tumors.[6] Our institute is located in the Northwest of India, geographically a sub-Himalayan area, and caters for a population residing in altitudes ranging from 300 to

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7000 m above sea level. Therefore, our study cohort provides a unique population with people residing in both high as well low altitudes. At high altitudes, the prevalence of head and neck paragangliomas (HNPGL), may reach as high as 1 in 10 as compared to fewer than 1 in 500,000 at low altitudes.[4] There are only a few case series on high-altitude head and neck paragangliomas (HNPGL) till date,[6,7] and no study is reported from the sub-Himalayan area. Therefore, considering these evidences, we would like to present our case series of 20 patients of HNPGL, along with analyses of their demographic, clinical features, management, and distribution in terms of altitude and their management.

Materials and Methods

In this retrospective study, data of 20 patients of HNPGL managed in our department of Otolaryngology–Head and Neck Surgery between December 1, 2017, to December 31, 2021, were reviewed after obtaining ethical clearance from the Institutional ethical committee of Dr Rajendra Prashad Govt. Medical College Tanda on dated December 9, 2021. Patient data in terms of demography, altitude of inhabitant, tumor characteristics, clinical presentation, diagnostic evaluation, treatment, and follow-up were analyzed.

All patients were referred to our institute with clinical suspicion of HNPGL. They were clinically examined and underwent computed tomography (CT) and magnetic resonance imaging (MRI) of the neck to confirm the diagnosis and for the staging of the tumor. In cases of suspected multiple PGL or metastasis, imaging of the chest and abdomen were also performed. The diagnosis and the size of the tumor was finalized on histopathology, however, in nonoperated cases, it was based on characteristic radiological findings and size was measured on MRI. Preoperatively, all patients had CT/MRI angiogram done to assess the feeding vessels. However, none of

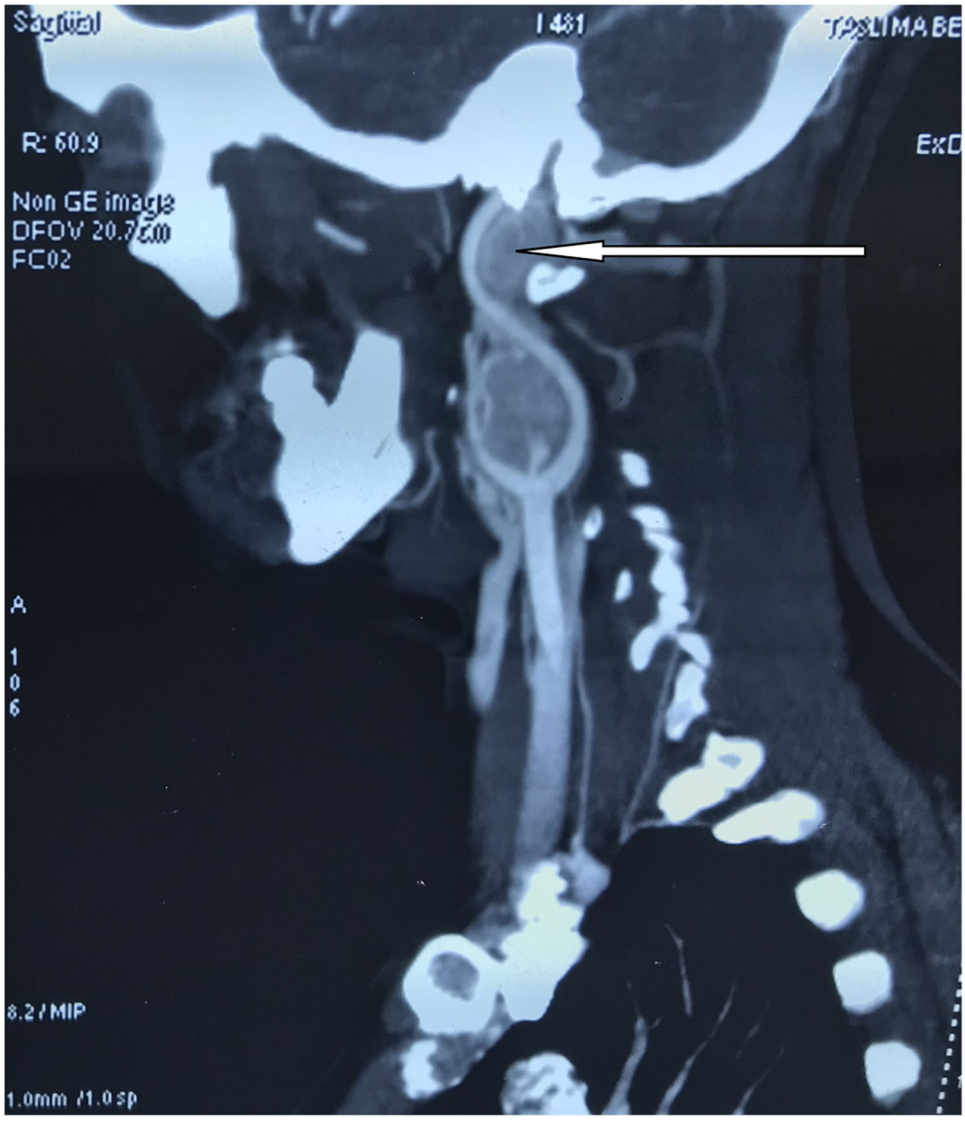

Figure 1. Contrast enhancing computed tomography of neck (saggital section) showing a bi-lobed carotid body paganglioma with encasement of carotids (Shamblin III) with superior extension to the base of skull (arrow).

the patients underwent Digital subtraction angiography and embolization. A 24-hour urinary vanillyl mandelic acid and metanephrine level were routinely done pre-operatively in all to rule out the secretary tumors.

Our cohort comprised 20 patients with a mean age of 41.7 years (age range between 19 and 60 years). The female-to-male ratio was 2.3:1. The final diagnosis in terms of the numbers of patients was CBPGL (n = 9), tympanic paragangliomas (TPGL) (n = 7), jugular paragangliomas (JPGL) (n = 2), and vagal paragangliomas (VPGL) (n = 2). The biochemical analysis did not show features of secretory PGL. Majority of patients (n = 13; 65%) were from high altitude. All CBPGL and 57.14% of TPGL were from high-altitude regions, whereas the remaining 3 TPGL, JPGL, and VPGL were from low-altitude regions.

The mean altitude of CBPGL patients was 2680 meters (range 2130-4440), and painless upper neck swelling was the main presenting symptom, however, malignant patient presented with pain and hypoglossal nerve palsy. Female-to male ratio was 3.5:1, and the mean age was 39 years (range from 21 to 60 years). Tumor was right side in 5 patients, and in 3 patients it was left side, and 1 had a bilateral tumor. According to the Shamblin classification, the majority (n = 6) had stage II, 1 had stage I and 3 patients had stage III tumors (**Figure 1**). Eight tumors were excised by transcervical approach, and average size of the tumor was $3.3 \times 2.56 \times 3.06$ cm (**Figure 2**). The malignant tumor, diagnosed on cervical lymph node biopsy, received 3 cycles of chemotherapy (Cisplatin, Etoposide), and 15 fraction of radiotherapy. There were no observed major complications, for example, cranial nerve palsy, hemiplegia, and so on, however, in a patient with a bilateral tumor, during excision of the larger tumor there was a tear in the vessel which required carotid anastomosis. The smaller tumor was followed up with serial imaging. The average follow-up period was 28.55 months (ranging from 10 to 48 months).

The next most common tumor was TPGL (n = 7), with a mean age of 50.11 years (range between 19 and 60 years). The female-to-male ratio was 3.5:1. In terms of altitude, 4 patients were from the high-altitude regions, while 3 were an inhabitant of low-altitude regions. The tumor was commonly seen on left side (n = 6), while 1 had it on the right side. According to the Glasscock-Jackson staging system, 2 patients had stage II, 1 stage III, and 4 had stage IV tumors (**Figure 3**). All were operated by transmastoid approach and the average size of the tumor on histopathology was $1.1 \times 1.5 \times 1.1$ cm. The average follow-up was 32 months (ranging from 16 to 50 months). One patient had a recurrence after 1 year of surgery and as it was anterior to internal carotid artery, she was given SRT.

Both of the JPGL patients were females from low-altitude regions, had stage 3 disease as per the Glasscock-Jackson staging system, and 1 patient had bilateral tumors. Both of these patients were treated with SRT

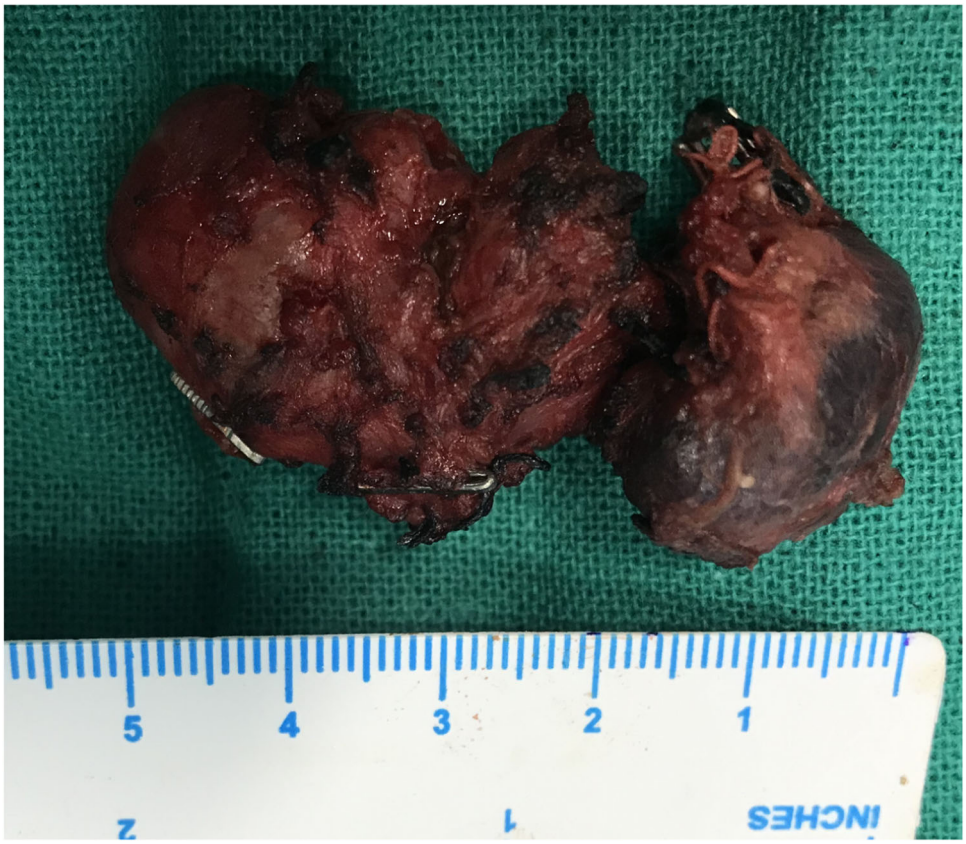

Figure 2. Excised specimen of the same patient showing a bi-lobed tumor of size of 5.2 cm.

and had stable disease on serial radiography till a follow-up period of 36 months.

Both Vagal PGL patients were residents of low-altitude regions, both were on the left side and the average volume of the tumor was 72 × 44 × 31 cc. Of these, 1 patient had a simultaneous CP tumor, while the second patient refused for the surgery, and therefore, both patients were given SRT. Both of these patients have been doing well, with no progression of disease during the average follow-up of 14 months.

Discussion

There are only a few epidemiological studies adequately studying the association of the PGL with altitude, ethnicity, and genetics.[8] Chronic hypoxic condition at high altitude is known to cause hyperplasia of carotid body cells, and there is an increased incidence of CBPG in these regions. The Himalayan have some of the highest mountain ranges in the world, and a large population inhabits the sub-Himalayan area, but to date, there are no studies on HNPGL from the region. Only a few studies are reported in the literature are from North and South America.[6,7]

Recently Leung et al on the met-regression analysis found that with every 500 m increase in elevation, the incidence proportion of PGL increases by 0.31 cases per 100,000 population.[9] Our state is situated in the northern India, a sub-Himalayan area that has an elevation ranging from 350 to 4500 m above sea level, providing a unique population with both low and high-altitude inhabitants. The high altitude in terms of HNPGL described in the literature, is an altitude of 2000 m or more.[7]

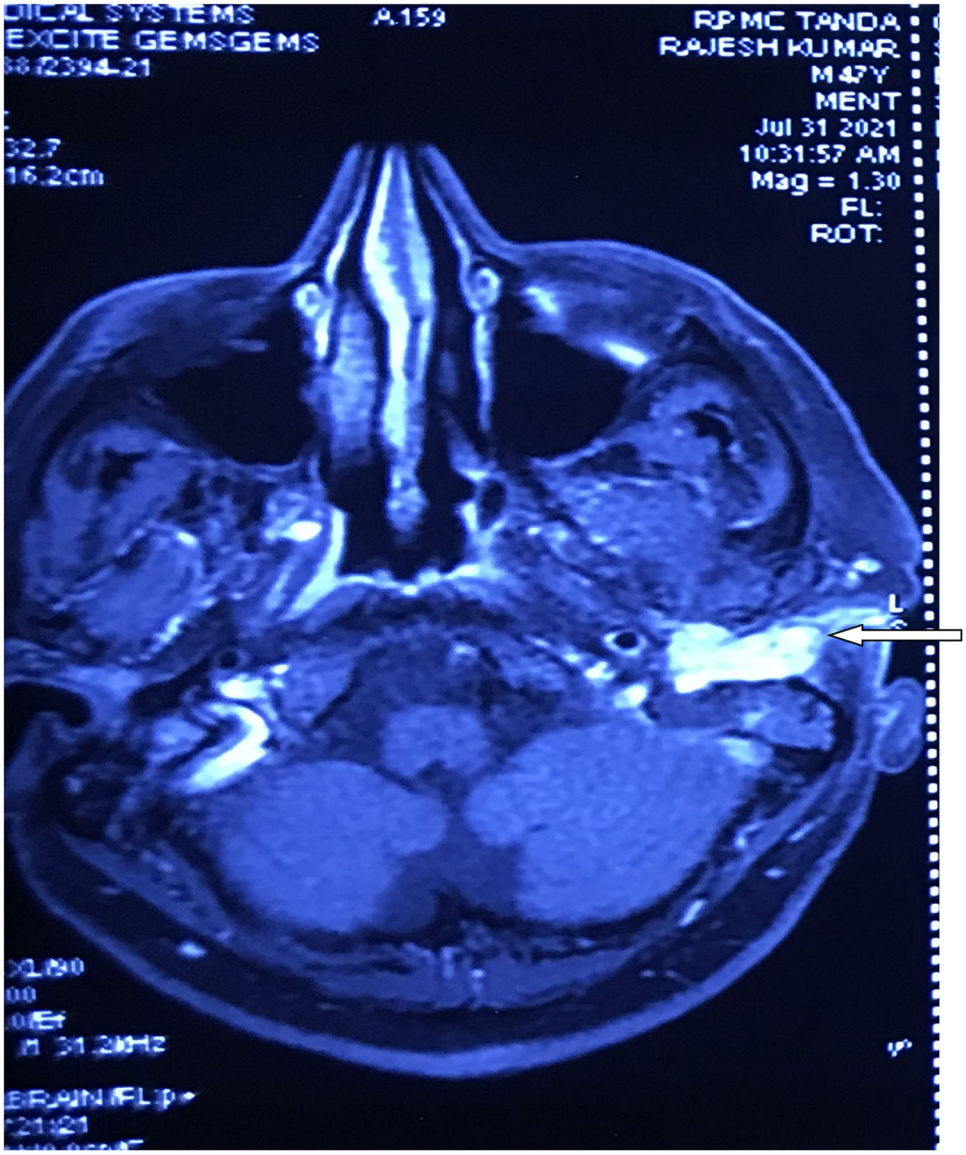

Figure 3. Contrast magnetic resonance imaging (axial section) showing a contrast enhancing mass in left middle ear, mastoid, and filling the left external auditory canal (open arrow).

The most common tumor seen in our series was CBPGL (n = 9), and all these patients were an inhabitant of the high-altitude throughout their lifetime with an average altitude of 2680 m. There was a female preponderance, with female-to male ratio of 3.5:1 which was lower than the 8.3:1 described by Rodriguez-Cuevas et al.[10] An early age of presentation in CBPGL, 39 years observed in our series is also significantly lower than 49 years described by Hector et al in 1986.[7] A likely explanation of this observed difference because there has been a lot of improvement and innovation in the field of radiology in the last 20 years, so the facility of ultrasound/CT is easily available even in remote areas.

Bilateral CBPGL was seen in 1 patient (11.11%) which is high compared to the 5% described by Hector et al in their article on high-altitude carotid body tumors from the Mexico region. Complications were seen in 1 patient (11.11%) which is significantly less than the complications rate of 34% reported by Hector et al.[7] Again this may be due to advancements in the surgical techniques and better operating facilities available these days facility that was available 20 or 30 years back. We preferred nasotracheal intubation in large carotid body tumors (>5 cm), and in tumor with high extension toward the base of the skull. This maneuver facilitates subluxation of the mandible anteriorly, which is helpful in increased exposure to the tumor.[11] A vascular surgeon always accompanies CBPGL surgeries, so that in the event of injury to the carotid artery, immediate assessment of the extent of the injury could be done, and repair or anastomosed as required.

There is no prior study depicting the distribution of TPGL in terms of altitude to date. Singh et al[12] reported a prevalence of 11.11% in their series of 54 patients from a tertiary care hospital in our country. However, their study did not consider any mention of or incorporate a correlation of the tumor with an altitude of the patient's inhabitancy. Our series it was observed as the second most common HNPGL, representing 35% of all the cases. Also in terms of the altitude, this tumor was more common in the high-altitude natives (57.14%). TPGL patients in terms of high and low altitude were comparable, that is, average age at diagnosis was 44 and 53.33 years, female-to male ratio of 4:0 and 1:2, and symptoms duration of 9 versus 18 months, and none of these were statistically significant ($P < .05$). The average size of these tumors was 1.15 × 1.5 × 1.1 cm, making them the smallest

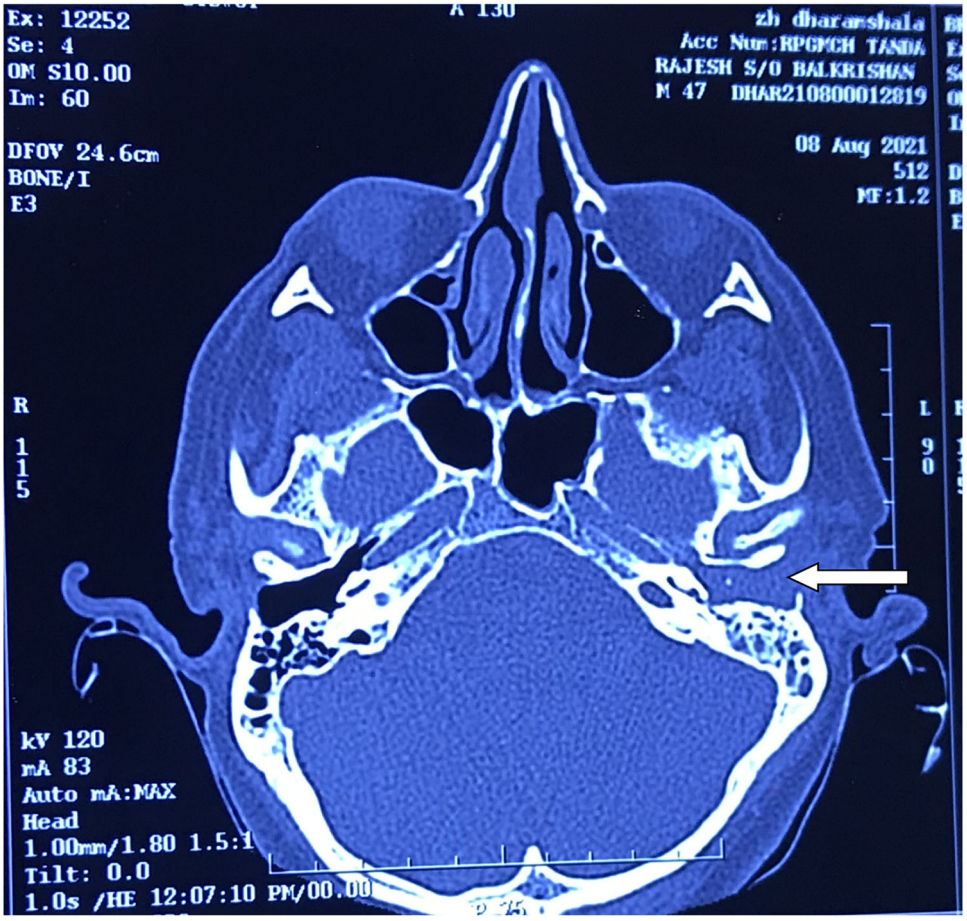

Figure 4. Preoperative high-resolution computed tomography of temporal bone showing soft tissue density in left middle ear and external auditory canal (open white arrow).

among HNPGL subtypes in the series. The presenting symptoms were tinnitus, hearing loss, and bleeding. The majority of patients (n = 4) had IV (**Figure 4**), 1 stage III, and 2 stage II tumors as per the Glasscock-Jackson staging system. There was a female preponderance with female-to-male ratio of 3.5:1. In all of these tumors were excised by the transmastoid approach. There were no observed postoperative complications. One patient from (a high altitude) had a recurrence of the tumor after 1 year of surgery and subsequently underwent SRT radiofrequency ablation as the tumor was anterior to the internal carotid artery.

Two patients JPGL and VPGL presented at an average age of 57.5 and 22.5 years, respectively. One of each subtype (50%) were having multiple PGL. They were not operated on and were instead offered/treated with SRT. Preoperative cranial nerve palsy (CNP) is a common feature of these tumors and was seen in 67.5% of the patients in a series described by Singh et al.[12] Further, surgical excision can also lead to CNP in as high as 42.4% of the cases.[12] In the contrary, CNP was not observed in any of our patients preoperatively or after treatment. Radiotherapy has been advocated as first-line therapy for PGL as it has fewer complications and high local control.[13] However, it can lead to malignant transformation of the tumor, and radiation-induced complications such as osteoradionecrosis, cranial nerve injury, and direct brain injury.

Nadia et al in 2020, first identified succinate dehydrogenase (SDH) mutation in 2 patients of high-altitude PGL, and such tumors had an aggressive course with recurrence within 2 months of excision.[14] However, as the genetic analysis was not carried out in our series, which is a routine preoperative investigation in the western set-up, and hence we cannot comment on the role or influence of genetic mutations in tumor pathogenesis or characteristics in our cohort. In our future studies, an analysis of genetic status in HNPGL, by assessing SDH mutation by immuno-histochemistry will be carried out. Its results in our cohorts may enable us better clarity on this topic.

The fact that our case series included 20 cases of HNPGL presented in a single institute in over 4 years, indicates that it is frequent, and may have a relatively higher prevalence in our area region. Furthermore, this number might still be under-represented, as some of such patients directly seek treatment from higher institutes outside our state, leading to selection bias. Hence these cases in our series might be just the tip of an iceberg and a proper population-based survey may identify more numbers of cases.

This study being a descriptive retrospective study has its limitations and a definite conclusion cannot be established between altitude and distribution of HNPGL, a further prospective study will be more informative. Other limitations are small sample size and only few prior studies in the literature.

Conclusion

HNPGL though a rare tumor, has a relatively higher prevalence/more common in high-altitude sub-Himalayan area. The CBPGL is the commonest subtype, followed by tympanic PGL in our region. A prospective study with a larger sample size by including patients from a larger area of our state along with the genetic study of all patients and their family members may help in better delineation of this relationship.

Author Contributions

Sudesh Kumar, conceptualization, data collection, drafting work; **Niraj Gupta**, data curation, final approval; **Priyanka Thakur**, analysis of data, writing and revision; **Nitin Gupta**, drafting work; **Anita Bodh**, revision of manuscript.

Disclosures

Competing interests: None.

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