www.endocrinologia.org.mx PERMANYER Rev Mex Endocrinol Metab Nutr. 2022;9:116-124

REVISTA MEXICANA DE ENDOCRINOLOGÍA, METABOLISMO & NUTRICIÓN ORIGINAL ARTICLE

Head and Neck Paragangliomas are not so Rare after All: A Single-Center Experience in 3 Years

Los paragangliomas de cabeza y cuello no son tan raros: experiencia de un Centro en tres años

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ABSTRACT

Background: Paragangliomas in the head and neck (HNPGN) are usually non-functioning but associated with complications. Some of them are hereditary, but more studies are required to determine the need for genetic tests in our country. **Objective:** The objective of this study was to describe the characteristics HNPGN evaluated in the Hospital de Especialidades Centro Medico Nacional Siglo XXI from 2018 to 2021, and the number of candidates for genetic testing. **Materials and methods:** This study was a retrospective evaluation of files from patients with HNPGN during this period. Clinical data, laboratory, imaging, pathology, and treatment results were collected with a calculated sample size of 81. Non-parametric statistics (frequencies, medians, and interquartile ranges, U-Mann–Whitney tests, or Chi-square tests) were calculated using SPSS v 21.0 with a significant $p < 0.05$ and approved by the Institutional National Ethics Committee. **Results:** Two hundred and forty-six patients, 90.2% female, 28.5% were 50 years of age or younger, 19.1% had head tumors, 78.5% neck and 2.4% in multiple sites, 55.7% had hypertension and 20.7% were incidental, 38.6% were large or invasive, 2% were metastatic, 2% were associated with a specific syndrome, and 38.6% had factors associated with hereditary HNPGN. **Conclusions:** HNPGN are more common than expected, and 53.7% are candidates for genetic testing.

Keywords: Paraganglioma. Glomus. Head. Neck. Neuroendocrine.

RESUMEN

Antecedentes: Los paragangliomas de cabeza y cuello (HNPGN) suelen ser no funcionantes, pero se asocian a complicaciones serias. Muchos son hereditarios, pero se requieren estudios para determinar la necesidad de pruebas genéticas. **Objetivo:** Describir los HNPGN evaluados en el Hospital de Especialidades Centro Médico Nacional Siglo XXI desde 2018 a 2021 y cuántos requieren prueba genética. **Materiales y métodos:** Estudio retrospectivo de archivos HNPGN. Se registraron datos clínicos, laboratorio, imagen, patología y tratamientos con un cálculo de muestra de 81 pacientes. El análisis no paramétrico (frecuencias, medianas y rangos intercuartílicos, U de Mann-Whitney, chi cuadrada) se hizo con SPSS v 21.0 y una $p < 0.05$ se consideró como significativa. Fue aprobado por el Comité Nacional Institucional de Ética. **Resultados:** De 246 pacientes, el 90.2% fueron mujeres, el 28.5% < 50 años al diagnóstico, el 19.1% tuvieron tumores de cabeza, el 78.5% cuello y el 2.4% sitios múltiples, el 55.7% hipertensión y el 20.7% fueron incidentales, el 38.6% fueron grandes o invasores, el 2% metastásicos, el 2% sindrómicos y el 38.6% tuvieron factores para ser hereditarios. **Conclusiones:** Los HNPGN son más comunes de lo esperado en nuestro centro, un 53.7% son candidatos a pruebas genéticas.

Palabras clave: Paraganglioma. *Glomus*. Cabeza. Cuello. Neuroendocrino.

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Date of reception: 29-10-2021
Date of acceptance: 18-12-2021
DOI: 10.24875/RME.21000075
Available online: 01-09-2022
Rev Mex Endocrinol Metab Nutr. 2022;9:116-124

INTRODUCTION

Paragangliomas (PGNs) are uncommon neuroendocrine neoplasms derived from the autonomic nervous system ganglia[1]. They are also known as glomus tumors (tympanic, jugular, vagal, or carotid), chemodectomas, or chromaffin tumors, among other names[2]. Their variable clinical and biochemical features, as well as their ubiquity and nomenclature variations, have led to the conception that they are rare and unpredictable, but epidemiologically irrelevant[3]. However, recent publications conclude that pheochromocytomas (PHEO) and PGN are a spectrum of the same disease, that most tumors are biochemically undetectable with current laboratory test algorithms, but they are associated with serious comorbidities, 35% may be hereditary and a multidisciplinary approach is necessary to reduce the complications associated with their treatment[4]. Most of them are benign and isolated neoplasms, while a few are associated with other endocrine or non-endocrine neoplasias, metastasis, or local invasion.

Head and neck PGN (HNPGN) comprise only 0.03% of all human tumors, and < 0.5% of all head-and-neck tumors, with an annual incidence of 0.001%, but the proportion of HNPGN varies between series and their diagnosis is skewed by the specialists evaluating them, but the most reported origin is usually the carotid body, where the classic clinical manifestation is a non-tender, insidious, mobile, and pulsatile neck mass. Some patients report local obstructive symptoms, as well as nerve palsies, vertigo and rarely, cerebrovascular events[5-7]. HNPGN in other locations are also associated with cranial nerve palsies, hearing, and equilibrium problems or local pain. In the head and neck, they are seldom related to the classical triad of PHEO, while thoracic or abdominal PGN may be more commonly related to headache, sweating, and heart palpitations[7]. PGN lack the Phenylethanolamine N-methyltransferase, the enzyme that transforms norepinephrine (NE) to epinephrine (E), which is mainly restricted to the adrenal medulla[8]. Dopamine is a precursor of both NE and E, transformed by Dopamine beta-hydroxylase. While all catecholamines are structurally similar, their potency, affinities for different tissue receptors, functions, and metabolic pathways differ greatly. NE acts mainly on alpha receptors and increases the heart rate, while E is relatively nonspecific for alpha- and beta-receptors, which elicit responses in metabolic pathways as well as cardiovascular responses[8]. An excess production of NE by a PGN may not be as evident as an E excess, unless great quantities are secreted to the bloodstream, usually in an episodic fashion[9]. PGN has been known to be efficient in terms of metabolizing their NE inside the tumor, but causing catecholamine crisis during anesthetic induction or tumor manipulation[10]. However, there is no current consensus as to the most appropriate perioperative management of clinically non-functioning PGN.

Recent advances in molecular and genetic testing show that 20-43% of PGN are hereditary[11]. Classical syndromes with PGN include Multiple Endocrine Neoplasia Type 2, neurofibromatosis Type 1 (NF1), and Von Hippel–Lindau (*VHL*). MEN Type 1 has also been related to these tumors and novel genes have been described in these tumors. Approximately 20% of hereditary PGN have been associated with germ line alterations of the succinate dehydrogenase complex genes (SDHx), which has created a new group of "PHEO/PGN syndrome." These genes relate to large, multicentric and functioning tumors in patients under 50 years of age, they are more frequently metastatic (2-23%) and show an autosomal dominant inheritance[12].

Even when they are still rare, studies show that hormonally active PGN is associated with an increased cardiovascular morbidity and mortality if left untreated, while autopsy studies suggest that 50% of all PGN are clinically unsuspected[12]. Increasing the awareness of neuroendocrine neoplasms and their long-term relevance for the patients is necessary to improve diagnostic and treatment algorithms[13]. At present, there is little information in our region regarding PGN, their characteristics and risk factors have not been described thoroughly. Considering that chronic hypoxia is a predisposing factor for HNPGN and that many Mexican cities are located at high altitudes, we speculate that head and neck PGN could be present in our population. Chronic obstructive pulmonary disease and obstructive sleep apnea and hypoxemia have also been described as predisposing factors that may be present in some patients.

Current guidelines suggest that only large, functioning or potentially malignant PGN require definitive treatments, such as surgery or radiotherapy[14], since a large proportion of patients report complications. Cranial nerve palsies are reported in more than 60% of the cases[15], neurological complications are present in 42% of the patients, but they are usually transient and cerebrovascular complications are detected in less than 2% and correlated with tumor size and carotid artery involvement[16]. Our hospital is a referral center for complicated cases. We aimed to evaluate the clinical characteristics at diagnosis in a limited time frame to analyze the need for specific management algorithms and genetic testing in our population.

MATERIALS AND METHODS

We reviewed the medical files of the patients that were evaluated at least once for a HNPGN from January 1, 2018, to September 30, 2021, in the Hospital de Especialidades Centro Medico Nacional Siglo XXI of the Mexican Institute of Social Security, which is a referral center for the surgical management these neoplasms from Mexico City and most of the Southeast of Mexico. The main data were gathered from their diagnosis to their last evaluation, using the available information in the file. In each center, the patients were evaluated by different specialties according to their specific characteristics and diagnosis and the laboratory and imaging tests performed were indicated by their treating physicians. This is a transversal, retrospective analysis of the data generated during the normal procedures performed during their evaluation. We collected data regarding the clinical, biochemical, and imaging evaluations, the patients' comorbidities, treatment modalities, and status at last evaluation. The protocol was evaluated and authorized by the National Scientific and Ethics Committee of the National Institute of Social Security. According to the reported incidences in the international literature, we were expecting to find 13 new cases per year of chromaffin tumors in all sites, although the frequency of HNPGN may vary in different series, but we aimed to describe also all the patients that were treated during these years even when their diagnosed was not done in that year. We calculated a sample size of 81 patients according to the epidemiology of the neoplasias and the fact that the patients are referred from the southeast and central Mexico.

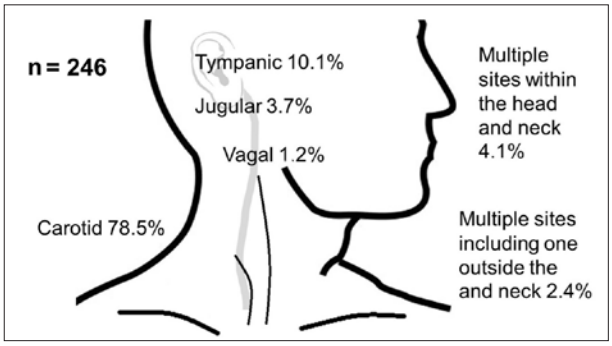

Figure 1. Location and frequency of the head and neck paragangliomas in this series.

Descriptive data are expressed according to the type of variable using nonparametric data. We used frequencies for the categorical variables and medians and interquartile ranges (IQR) for the numeric variables. Comparisons were performed using Chi-squared or U-Mann–Whitney. We analyzed the data using SPSS 21.0, with $p < 0.05$ as a cutoff for significance.

RESULTS

From 265 evaluated cases with chromaffin tumors, 246 were HNPGN (83.4% of the detected cases). A total of 114 cases were diagnosed *de novo* during the study period (43%) and the other had been diagnosed years before, 44 cases were diagnosed in 2018, 38 in 2019, 19 in 2020, 13 cases in 2021. The median follow-up since diagnosis was 3 years (IQR 1-5).

The patients evaluated during the study period were mostly female (90.2%), the median age at diagnosis was 58 years (IQR 48-67), but 30.1% were 50 years of age or younger; 93.3% of the patients were born and lived in cities above 2000 m above the sea level.

The location of the tumors was: 19.1% had head tumors (jugular, tympanic, and vagal), 78.5% neck (carotid), and 2.4% in multiple sites outside head and neck (Fig. 1).

Table 1. Main characteristics of the patients according to location of the tumor. Data is presented in frequencies (%) or median (interquartile ranges)

Characteristic	Head (n = 47) (%)	Neck (n = 193) (%)	p
Age at diagnosis (years)	47 (38-57)	53 (45-63)	0.004
< 50 years old	42.6%	24.9%	0.016
Female	83.0	91.7	0.074
Anxiety	14.9	17.6	0.656
Sweating	0	6.7	0.078
Pain in the location of the tumor	27.7	26.4	0.864
Dysphagia	8.5	4.1	0.218
Dysphonia	4.3	4.7	0.905
Dysarthria	2.1	1.0	0.546
Cerebrovascular event	0	1.6	0.318
Hypoacusia	91.5	8.3	< 0.001
Otorrhea	14.9	1.0	< 0.001
Palpitations	6.4	11.4	0.313
Pallor	0	4.1	0.156
Cranial nerve palsy	31.9	6.7	< 0.001
Otic plenitude	44.7	1.0	< 0.001
Tremor	0	3.6	0.185
Tinnitus	25.5	5.2	< 0.001
Tumor was visible at physical examination	36.2	75.1	< 0.001
Vertigo/dizziness	36.2	18.3	0.008
Cardiovascular symptoms			
Hypertension	44.7	58.5	0.086
Secondary or difficult to control hypertension	19.1	18.1	0.958
Hypertension before 30 years of age	15.8	3.6	0.169
Hypotension	17.0	26.7	0.039
Heart disease (any type)	14.9	25.9	0.112
Dilated cardiomyopathy	2.1	7.3	0.018
Hypertensive cardiomyopathy	12.8	14.0	0.827
Younger than 50 years old at the onset of heart disease	0	14.9	0.406
Chronic lung disease	8.5	15.5	0.215
Glucose metabolism abnormalities	45.7	65.3	0.020
Diabetes	28.3	29.0	
Pre-diabetes	17.4	36.3	
Body mass index (kg/m^2)	27.5 (25.0-30.6)	28.1 (25.1-32.3)	0.371
Obesity (30 kg/m^2 or more)	31.9	37.7	0.461

The most common symptoms at presentation were compressive, while blood pressure abnormalities or clear adrenergic signs were less frequent. In 20.7%, the tumor was an incidental imaging finding. Main characteristics per tumor site are shown in table 1, only the cases where single tumors were diagnosed, and data were available, which are shown.

BIOCHEMICAL EVALUATION

Only 67 patients (27.2%) were subjected to biochemical testing before surgery. Hormonal testing varied widely regarding the test type and normal laboratory ranges. Urinary metanephrines were the

Table 2. Biochemical tests performed on the patients. Patients were considered to have an elevated result if it was above the upper limit of normal, expressed in percentage. The number of patients tested for each parameter are expressed in parenthesis). Chromogranin A cannot be measured in urine and is therefore reported as Not applicable

Test	% of cases with elevated test in PLASMA (number of patients tested)	% of cases with elevated test in the 24 h URINE collection (number of patients tested)
Adrenaline	23.1 (n = 13)	0 (n = 23)
Noradrenaline	7.7 (n = 13)	0 (n = 21)
Dopamine	28.6 (n = 14)	33.3 (n = 21)
Total catecholamines	2.6 (n = 39)	2.6 (n = 39)
Vanillylmandelic acid	0 (n = 2)	0 (n = 1)
Metanephrines	5 (n = 40)	2.6 (n = 39)
Normetanephrines	0 (n = 2)	0 (n = 1)
Chromogranin A	0 (n = 4)	Not applicable

most requested tests. Results are expressed as an index, calculated from the division of the patients' result divided by the upper limit of normal (ULN) of the test to standardize the results. The percentage of patients that had an elevated catecholamine result is expressed in table 2.

In most of the cases with elevated catecholamines, the value was mildly higher than the ULN. Even in the patients with severe or secondary hypertension, the numbers were usually low, however, they were tested using their usual antihypertensive drugs. One patient had an elevated plasma dopamine 3 times above the ULN, with plasma metanephrines and adrenaline in the ULN, while all the urinary tests were negative. The only patient that had both plasma catecholamines and plasma noradrenaline 3 times above the ULN had one additional PGN in the abdomen and metastasis to the right femur, she had been operated for a pheochromocytoma 15 years earlier, these tests were performed after an observed hypertensive crisis since all previous tests had been negative.

HIGH-RISK TUMORS

Patients were analyzed for predictive factors for a hereditary tumor, metastasis, recurrence, or persistence or complications during procedures, young age (< 50 years old at diagnosis) represented 28.5% of our population. Bilateral tumors (right and left in the same autonomic ganglia) were present in 11.8% of the cases; multicentric tumors (in different ganglia) were present in 0.8%, 11% of the patients reported having family members with neoplasias of the head, neck, breast, pancreas, kidney, lung, and other gastrointestinal organs, but the histologic type diagnosis was not available. One patient had a family member with abdominal PGN, other thymus tumor and two papillary thyroid cancer.

Malignant tumors, defined as metastatic disease, were reported in only 2% of the cases. Positive peritumoral ganglia were present in most cases and one patient had a femoral metastasis and a pathologic fracture; however, 11 cases of the head PGN invaded local structures in imaging.

In the imaging results, large or invasive tumors are considered to have high risk. PGN in the neck were 5 cm or larger in 17.7% of the cases with a median cephalocaudal length of 5.7 cm (IQR 5.1-6.8), 43.7% surrounded one carotid artery and 38.4% surrounded both. The data for tumor size or invasion in other sites were limited.

At present, reasons to have a genetic test when a PGN is present include: other syndromic features, bilateral or multicentric tumors, metastasis, young age at diagnosis, or a family member with tumors related to a neoplastic syndrome. In total, 41.5%

had at least one of these reasons to be tested, 9.8% had two reasons, and 2.0% had three reasons and 0.4% had four reasons, representing 53.7% of the patients that would be candidates to a germline mutation screening.

PERIOPERATIVE MANAGEMENT

Only 6.3% of the patients received alpha blockade before surgery with prazosin, 13.4% received beta blockade with metoprolol, and 2.9% received verapamil. In total, 69.2% had surgery and 4.6% were waiting for this treatment. The remaining 26.3% were not considered to be candidates for surgery, refused it or were lost to follow-up. Radiotherapy was performed on 10.5% of the patients, 4.2% of them as primary treatment, the rest as an adjuvant therapy. No patients had been treated with I-131-metaiodobenzylguanidine (MIBG), although one has been a candidate for this treatment. Other radionuclide therapies are not currently available in our center.

COMPLICATIONS

The data regarding intraoperative blood pressure and complications were not available in 185 patients. The data available showed that hypertension during surgery was present in 14.6%, hypotension in 8.1% (half of the cases presented without previous hypertension during surgery), and 2.9% required attention by the Intensive Care Unit after their procedures.

Persistent dysphonia was present in 10.2% of the patients, dysphagia was reported by only 1 patient, 2.5% had a clinically significant cerebrovascular event, one had pulmonary thromboembolism, two patients had cardiogenic shock during surgery, and 2.4% had persistent cranial nerve palsies.

Two patients died as a direct consequence of a cerebral hemorrhagic event after surgery, both female with carotid body PGN. The first patient was a 54-year-old woman with previous hypertension and hyperlipidemia, her tumor was 4.7 cm tall and involved both carotids, she did not have any preparatory hormone testing. The second patient was a 27-year-old woman, with hypothyroidism, and a family history for hypertension, heart disease, and non-specified neoplasias. She had hypotension spells and tachycardia, her total urinary catecholamines were 2.2 times the ULN and received alpha- and beta-blockade before undergoing embolization and surgery for her 7.6 cm tall tumor.

PATHOLOGY RESULTS

Pathology reports were available for 96 patients. The ear tumors were biopsies which were reported as "glomus tumor" without any additional information. In 39 cases of neck PGN, there was invasion to the capsule, 17 cases had vascular invasion and eight had lymphatic invasion, and one case had necrosis. Thirty-one patients had at least one lymphatic ganglion removed; only one patient had one metastatic ganglion. Other metastases were detected by nuclear medicine or biopsy. Immunohistochemistry for Ki-67 reported 0% in 11 cases, and 15 had 3% or less and eight cases were classified between 4 and 10%. One tumor was considered to be moderately differentiated, while the others were well differentiated.

DISCUSSION

Our results show that HNPGN are more frequent than expected in our center and a large proportion of them needs a multidisciplinary evaluation due to their location, size, hormone production or complications. We expected to evaluate 81 new cases in 3 years and found 114. In total, 246 patients were evaluated for these tumors during the study time, but the other 132 had been diagnosed earlier and were in follow-up, 9.3% did not complete their evaluation or refused surgery and were lost to follow-up. We consider this to be partially related to the

COVID-19 pandemic since elective surgeries were suspended for several months in our center.

The previous studies regarding HNPGN show lower incidences due to the restrictions given by previous neuroendocrine neoplasias classifications, which lead to sub-registry. Studies in Mexico showed low incidences like a report of 41 cervical PGN in a 21-year evaluation by Rodriguez-Cuevas and collaborators in 1986[17]. In 2005, The audiology department of the National Institute of Neurology and Neurosurgery identified 62 patients with "glomus tumors," mostly jugulotympanic, but they also included five intratympanic and four carotid tumors, in which neurologic symptoms were frequent and treatment complications, but with a 60% of stable tumors using surgery and radiotherapy[18]. In 2012, Gutierrez-Carreño et al. published their 35-year experience with vascular surgery in 57 neck PGN, although it is not clear if the study was multicentric or the characteristics of the center[19]. Other reports in our country report mainly isolated and difficult cases, in which treatment has been successful, but larger series have been published in Europe and the United States, with multicentric efforts and long periods of time. The high incidence reported in our center, despite the limitations imposed by the COVID-19 pandemic, may be related to several factors, the first of them being the wide search performed using all the names registered for these tumors; second, the inclusion of cases evaluated by all the specialists involved and not only the ones evaluated by endocrinology or internal medicine; third, the fact that a large proportion of the Mexican population lives at high altitudes (> 2000 m above the sea level), which has been reported to increase the likelihood of having HNPGN by 10 times and explains the female predominance of these tumors in this series[20]. These results show that female predominance was present in all tumors, but it was significantly higher in neck PGN.

The patients with head PGN were younger compared to the patients with neck tumors, earlier diagnosis may be related to the compressive and neurologic symptoms (such as nerve palsies, hypoacusis, and vertigo), which presented more frequently in head PGN compared to neck tumors. Cardiovascular symptoms were similar among groups, except for the higher frequency of hypertension in young people in head PGN than in the neck, but catecholamine production could not be ascertained in most cases. Glucose metabolism abnormalities were higher in the patients with neck PGN, which may be related to their older age since their body mass indexes were similar.

Our study is limited by the low number of patients that had biochemical and genetic testing before treatment as well as a full pathology report. At present, there is debate among different specialists regarding which patients need to have their metanephrines and normetanephrines tested before treatment. Previous guidelines limited the evaluation to the patients with the "classic triad" (headache, sweating, and heart palpitations), as well as those with severe hypertensive crisis, adrenal incidentalomas or that had a germline mutation related to these tumors. However, recent publications show that some tumors may be clinically silent, but they can produce catecholaminergic symptoms during surgery[21]. Furthermore, the biochemical profile of these tumors as well as their location are predictive of the genes involved in their pathogenesis, a characteristic that improves the cost-benefit balance of genetic testing algorithms. Evidence suggests that measurements of plasma free or urinary fractionated metanephrines are superior to other tests of catecholamine excess in PGN[22]. These tumors show slightly elevated catecholamines, unlike functioning intra-adrenal PGN (or pheochromocytomas) and the tests must be carefully prepared with a special diet and drug control to get the best results. This study was also limited by the fact that the patients that were not evaluated by an endocrinologist were not instructed to follow these recommendations. Additional limitations include the retrospective nature of the study and the fact that our center is a referral center for complicated diseases; this can be a source of bias for our results.

Genetic testing is gaining popularity among the specialists treating PGN, because 20-40% of them have hereditary mutations[12]. Succinate dehydrogenase genes (*SDHx* A to F), *MAX,* and *TMEM127* are novel genes have been related to "emerging hereditary PHEO/PGN syndromes," which may be more frequent than the traditionally known genes that

cause cancer susceptibility syndromes, such as *VHL*, *NF-1* (neurofibromin 1), and *RET* (ret proto-oncogene)[23]. New algorithms suggest that HNPGN should be tested for *SDHD*, *SDHC*, *VHL*, *SDHB,* or *SDHAF2* sequentially, unless other characteristics are present (multicentricity, specific syndrome, or family history or malignant behavior)[24]. The results may lead to a differential monitoring for the patient and genetic counseling for family members; therefore, it needs an informed consent and the participation of a geneticist. These procedures are standard practice in advanced countries, but they are limited elsewhere due to the costs, but may be necessary to improve the overall outcomes. Alvarez-Morujo et al. reported 162 tumors in 126 patients in a retrospective analysis from 178 to 2014, 88 were jugulotympanic tumors, 53 carotid tumors, and 21 vagal PGN, with multicentricity in 19.1% and germline mutations in *SDHD* and *SDHB* genes in Madrid Spain[25]. A study published in 2017 with 197 patients from Michigan, USA evaluated from 2000 to 2017, 51 patients underwent genetic testing and they found mutations in 43 (20 SDHD, 13 SDHB, 7 SDHC and one of each SDHA, SDHAF2, and NF1)[26]. A Mexican study by Enríquez-Vega et al., in 2018, evaluated succinate dehydrogenase D mutations in 25 patients with carotid tumors, which were detected in a 5 year period, where they detected a female predominance of 92%, and also, 92% of the cases were considered to be invasive, 20% were bilateral, and 16% were multicentric[27]. This is, to the best of our knowledge, the largest series of HNPGN in a single center performed in a short period of time. This study shows that these tumors are much more frequent than expected and need to be systematically registered and evaluated by a multidisciplinary team to avoid sub-registry and, eventually, promote the need for genetic testing among healthcare authorities in developing countries. The inclusion of all PGN in a single group, regardless of their location or hormonal production, using the new classifications will help to avoid these limitations in future studies. Considering the characteristics of the tumors reported in our series, genetic testing should be considered in 53.7% of our population. Larger genetic studies in patients with similar characteristics will lead to better characterization of the most prevalent genes and better follow-up algorithms, which are not currently in place in most institutions in our country. Performing the basic laboratory tests suggested by international guidelines in optimal pre-test conditions is necessary for a complete evaluation of these cases, especially for the patients with high-risk tumors. Additional tests such as dopamine (which was elevated in a third of patients in our series), chromogranin A or specific catecholamines and metabolites may be necessary in selected cases. Increasing awareness about these neoplasms among endocrinologists and other specialists is essential to achieve the goal of having multidisciplinary approaches that will benefit the patient and their families, as well as the healthcare systems.

CONCLUSIONS

HNPGN are neuroendocrine neoplasms with a higher-than-expected incidences, that have been related to hereditary syndromes in more than 20% of the cases. Genetic testing is not widely available in developing countries, but careful clinical, biochemical, and imaging evaluation is useful to detect cases that may be hereditary. In populations with several risk factors, increased awareness among physicians is necessary to detect these neoplasms and treat them using the best available resources.

FUNDING

The authors received funding from the Sociedad Mexicana de Nutrición y Endocrinología A. C.

CONFLICTS OF INTEREST

Authors FHA y CRR are part of the editorial committee of Revista Mexicana de Endocrinología, Metabolismo y Nutrición. FHA, CRR and NLJ are members of Sociedad Mexicana de Nutrición y Endocrinología.

ETHICAL DISCLOSURES

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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