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Systematic Review

Sex differences according to ethnic presentation in carotid body tumors: a systematic literature review

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ABSTRACT

Compare through a systematic literature review, the sex distribution of patients with carotid body tumors in Mexico and Latin America with the rest of the world. The eligibility criteria included retrospective cohort studies of more than 15 patients with a diagnosis of carotid body tumor (regardless of Shamblin's classification or clinical manifestations), which also reported the number of women and men affected, as well as their mean age. We divided the countries where the studies were conducted into regions (Latin America, USA, and Europe/Asia). The sex ratio difference between regions was calculated using a chi-square test. A $p<0.05$ was considered statistically significant. Thirty-eight studies met the eligibility criteria. Latin America had 1,345 cases, the United States had 808, and Europe/Asia had 672. Mexico had the most cases (1125), followed by the United States. The rest of the countries had less than 30 cases each. We found a statistically significant differences when we compared Latin American countries with the United States and Europe/ Asia ($p<0.001$). However, the most significant difference was observed when we compared Mexico with the United States, Europe/Asia, and other Latin American countries. When comparing other Latin American countries with Europe/Asia, we found a statistical difference ($p=0.01$); however, there was no statistical difference ($p=0.05$) when we compared other Latin American countries with the United States. Mexico has the highest number of reported cases of carotid body tumors in the world. Women account for 90% of cases.

Keywords: Systematic review, Carotid body tumor, Carotid body paraganglioma, Head and neck paraganglioma, Paraganglioma

INTRODUCTION

Paragangliomas can occur anywhere in the body; however, 65% of cases occur in the head and neck, where carotid body tumors are the most common type.[1] The male-to-female ratio in non-Latin American countries is 1:1.9, but several papers have shown a greater difference (1:11) in Latin America, Some explanations and risk factors have been proposed: high-altitude cities, hormone receptors, hypoxia, and genetic differences.[2-7] Our objective is to compare, through a systematic literature review, the sex distribution of patients with carotid body tumors in Mexico and Latin America with rest of world.

LITERATURE REVIEW

A systematic literature review was conducted according to the Cochrane methodology and PRISMA (Preferred reporting items for systematic reviews and meta-analysis) guidelines. We queried specialized health databases, such as Medline, PubMed, Embase, ClinicalKey, and the Cochrane Library, using following terms: carotid body

tumor, carotid body paraganglioma and head and neck paraganglioma. We reviewed 123 articles in June 2020. The eligibility criteria included retrospective cohort studies of more than 15 patients with a diagnosis of carotid body tumor (regardless of Shamblin's classification or clinical manifestations), which showed number of women and men affected and their mean age.

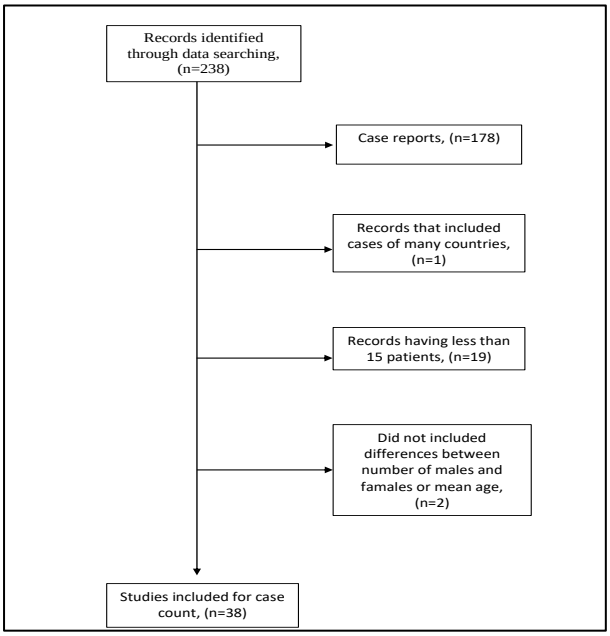

Figure 1: Literature search results using keywords in healthcare databases.

After full-text review, 38 articles written in English/ Spanish met the inclusion criteria. We excluded articles with less than 15 patients/case reports and no information on sex distribution or mean age. Multi-center studies involving different countries also excluded to provide data by regions instead of multi-national contributions, which could have confused purpose of our review. If a single institution had published several articles, we selected articles with more patients (Figure 1).

We obtained the total population diagnosed with carotid body tumors, as well as their age and sex. We divided the countries where the studies were conducted into regions (Latin America, USA, and Europe/ Asia). The sex ratio difference between regions was calculated using a chi-square test. $P<0.05$ considered statistically significant. Analyses were performed using Stata version 14.

RESULTS

Out of 38 studies, Mexico had the most cases (1125), followed by the United States (808). The rest of the countries had less than 30 cases each. Some countries occasionally showed slightly higher figures, as shown in Table 1.[1-4,6,8-39] To compare them, we classified countries by regions: Latin America (1,345 cases), the United States (808), and Europe/ Asia (672). Moreover, comparisons were made using sex and age at presentation. Age at presentation did not show a statistical difference between populations (Table 1). We found a statistical difference when comparing Latin American countries with the United States and Europe/ Asia ($p<0.001$). Most significant difference was observed when we compared Mexico with the United States, Europe/ Asia and other Latin American countries. There also a statistical difference between other Latin American countries and Europe/ Asia ($p=0.01$). However, no statistical difference observed between other Latin American countries and US ($p=0.05$) (Table 2).

Table 1: Cases by region.

Authors	Regions	Female, N (%)	Male, N (%)	Age (years) (Mean)
Latin America				
Bizueto Rosas[4]	Mexico	887 (92)	77 (8)	55
Enríquez Vega[6]	Mexico	23 (92)	2 (8)	55.1
Gutiérrez-Carreño[18]	Mexico	44 (77)	13 (23)	52
Rodríguez-Cuevas[2]	Mexico	107 (89)	13 (11)	49
Luna-Ortiz[3]	Mexico	64 (97)	2 (3)	50.2
Lechter[10]	Colombia	16 (69)	7 (31)	59.5
Casarim[16]	Brazil	14 (63)	8 (37)	43
Silva[36]	Ecuador	20 (73)	6 (27)	57
Pacheco-Ojeda[33]	Ecuador	14 (74)	5 (26)	52.5
Saldaña[35]	Peru	20 (87)	3 (13)	31
Total	1345	1209 (90)	136 (10)	45.2
USA				
Hushang[24]	USA	15 (62)	9 (38)	46
Douglas[29]	USA	21 (51)	18 (49)	49
Neterville[32]	USA	17 (65)	13 (35)	42
Kraus[25]	USA	11 (73)	4 (27)	45
Williams[39]	USA	20 (67)	10 (33)	54
Anderson [12]	USA	8 (53)	7 (47)	Not reported
Bishop[14]	USA	17 (61)	11 (39)	47

Continued.

Authors	Regions	Female, N (%)	Male, N (%)	Age (years) (Mean)
LaMuraglia[28]	USA	12 (70)	5 (30)	44
Anand[41]	USA	11 (60)	7 (40)	39
Patetsios[19]	USA	19 (65.5)	10 (34.5)	43
Lack[26]	USA	22 (52)	21 (48)	46
Cobb[15]	USA	350 (64)	170 (36)	54
Total	808	523 (65)	285 (35)	46.2
Europe/Asia				
Paridaans[22]	Netherlands	23 (56)	18 (44)	38
Atefi[13]	UK	19 (68.5)	6 (31.5)	54
Sajid[31]	UK	63 (66)	32 (34)	55
Papaspyrou[34]	Germany	81 (67.5)	39 (32.5)	42
Lamblin[27]	France	27 (55)	22 (45)	54
Muhm[30]	Austria	14 (58)	10 (42)	51
Fruhmann[17]	Austria	33 (66)	17 (34)	54.5
Dorobisz[40]	Poland	19 (40)	28 (60)	45
Boscarino[21]	Italy	14 (80)	6 (20)	55
Amato[11]	Italy	19 (56)	12 (44)	48
Dematte [1]	Italy	26 (65)	14 (35)	52
Inan[23]	Turkey	13 (65)	7 (35)	45.65
Y. Ünlü[38]	Turkey	23 (82)	5 (18)	50.6
D.Sanghvi[37]	India	6 (30)	14 (70)	38
Al-Harthy[9]	Saudi Arabia	27 (59)	19 (41)	43
Gwon[20]	South Korea	11 (69)	5 (31)	41.7
Total	672	418 (62)	254 (38)	47.9

Table 2: Comparative analysis between regions.

Regions	N (%)	Females, N (%)	Males, N (%)	Chi², p
Latin America vs USA	1385 (100) 808 (100)	1247 (90) 523 (65)	138 (10) 285 (35)	<0.001
Latin America vs Europe/ Asia	1385 (100) 672 (100)	1247 (90) 418 (62)	138 (10) 254 (38)	<0.001
Mexico vs other Latin American countries	1232 (100) 113 (100)	1125 (90) 84 (74)	107 (10) 29 (26)	<0.001
Mexico vs USA	1232 (100) 808 (100)	1125 (90) 523 (65)	107 (10) 285 (35)	<0.001
Mexico vs Europe/ Asia	1232 (100) 672 (100)	1125 (90) 418 (62)	107 (10) 254 (38)	<0.001
Other Latin American countries vs Europe/ Asia	113 (100) 672 (100)	84 (74) 418 (62)	29 (26) 254 (38)	0.01
Other Latin American countries vs USA	113 (100) 808 (100)	84 (74) 523 (65)	29 (26) 285 (35)	0.05
Europe/ Asia vs USA	672 (100) 808 (100)	418 (62) 523 (65)	254 (38) 285 (35)	0.3

DISCUSSION

Paragangliomas are extra-adrenal tumors originating from the neuroectoderm. They can occur anywhere in the body; however, more than 50% are found in the head and neck region, and they account for 0.03% of all human tumors. In 1943 Haller described that their main function was related to blood pressure and oxygen receptors.[6] Hence, chronic hypoxia induced hypertrophy, which resulted in sporadic (non-hereditary) tumor growth. Thus, cities located at over 1500 m above sea level had a higher prevalence. Rodríguez-Cuevas et al stated, without evidence, that chronic hypoxia and erythrocyte loss during menstruation caused carotid body tumors to develop more often in Mexican women.[2] After finding that patients had normal hemoglobin levels, Luna-Ortiz et al indicated a genetic factor.[3] It is now known that more than 30% of paragangliomas are related to germline mutations associated with the mitochondrial succinate dehydrogenase complex (SDHD, SDHB, SDHC, or SDHAF2). Patients with any of these mutations should be closely monitored during neck, chest, abdominal, or pelvic MRI scans, and their family should be screened too.[6] In a mutation study of 25 Mexican patients living at 2,200 m above sea level, 92% were women, 8% had a family history, bilateral tumors of 20% and 16% with a

tumor in other regions. The p81L SDHD (11q23) gene mutation was found; 16% of patients were heterozygous, twice as much as what has been reported in the United States.[5,40,41] This could explain to some extent why there is a larger number of cases in women.[3]

As mentioned in the literature, carotid body tumors are generally benign, and seldom pose an imminent risk of death. Malignant tumors occur in non-neuroendocrine tissues, such as lymph nodes, liver, bone, kidneys, lungs, breasts, pancreas, retroperitoneum, and thyroid gland.[3,13,42] However, there are no reported series of patients with carotid body tumors to identify genetic differences.

Based on our findings, we observed a higher incidence in Latin American women ($p<0.001$). Mexico and, to a lesser extent, Peru show a significantly higher incidence compared with the rest of the world ($p<0.001$). The difference was also observed when we compared Mexico with other Latin American countries, which demonstrates that carotid body tumors are more common in Mexico. The populations of other Latin American countries and the United States showed a similar pattern; thus, we consider there could be a population bias because many Latinos live in the United States. The American series could have included Latino patients. In that case, such series could be similar to those of other Latin American countries, which would be an instance of the Will Rogers phenomenon.[43] Finally, we did not find differences between the United States and Europe/Asia. Genetic studies are warranted to determine if it is a racial phenomenon.

CONCLUSION

Mexico has the highest number of reported cases of carotid body tumors in the world. Women account for 90% of cases. Peru shows similar numbers. Contrary to the rest of the world, carotid body tumors are more common in Mexican women than men. The incidence is higher in Latin American countries, compared with the United States and Europe/Asia. If we exclude Mexico from the Latin American countries, their sex difference is similar to that reported in the United States, whose large Latino population may create a bias. The United States and Europe/Asia behave similarly, and the incidence is almost the same between men and women.

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