



Carotid Paraganglioma Synchronous with another Ipsilateral Carotid Disease: A Systematic Literature Review

Francisco S Lozano-Sánchez^{1,4,5}, Angel Muñoz², José A de las Heras³, Carola Rubio Taboada^{1,4} and María Begoña García-Cenador^{1,5*}

¹Department of Surgery, University of Salamanca, School of Medicine, Spain

²Service of Otorhinolaryngology, University of Salamanca, School of Medicine, Spain

³Service of Radiology, University of Salamanca, School of Medicine, Spain

⁴Service of Angiology and Vascular Surgery, University Hospital, Spain

⁵Salamanca Institute of Biomedical Research (IBSAL), Spain

Abstract

Carotid paragangliomas are infrequent tumors whose biology and natural history are unpredictable in a significant number of cases. Such infrequency and the different ways they manifest themselves pose a diagnostic/therapeutic challenge that is reflected in the final outcomes.

Seventy-five percent of carotid paragangliomas adopt simple forms (single tumors measuring <4 cm, defined and resectable, non-secretory and benign); with expert treatment, this normal presentation leads to excellent results. The remaining 25% are complex forms (bilateral, large, attached to the carotids, functional, malign, associated with other pathologies, etc); morbidity and mortality rates in these cases are clearly different. Within this complex group, there are a number of carotid pathologies (e.g., symptomatic stenosis or aneurysms) that are synchronous and ipsilateral to the paraganglioma.

This review sets out to address these situations in a unitary manner, with its references being very widely distributed in the literature, with the aim being to highlight their idiosyncrasies of diagnostic and therapeutic interest. This has involved a systematic literature review of the Medline and Cochrane Library databases, up to 1 November 2019. This has located 12 articles with a total of 15 patients.

Conclusion: Patients with these exceptional combinations are more complex and constitute a twin challenge: a) diagnostic (search for associations), and b) therapeutic (surgical times and prioritizations), with the aim being to avoid errors and achieve the best end results.

Keywords: Carotid body tumor; Carotid paraganglioma; Carotid stenosis; Carotid aneurysm; Carotid endarterectomy; Carotid stent

Abbreviations

ECCA: Extracranial Carotid Artery Aneurysm; CA-FMD: Carotid Artery Fibromuscular Dysplasia; CAS: Carotid Artery Stenting; CEA: Carotid Endarterectomy; CBT: Carotid Body Tumor or Carotid Paraganglioma; CSG: Covered Stent Graft; ICA: Internal Carotid Artery; ICA-S: Internal Carotid Artery Stenosis; PG: Paraganglioma; PTA: Percutaneous Transluminal Angioplasty; TIA: Transient Ischemic Attacks

Introduction

A Carotid Paraganglioma (CPG) is an infrequent tumour that affects between 1/30,000 and 1/100,000 people; of neuroectodermic origin (neural crest), these tumors are more frequent among woman in their fifties [1,2].

Most CPGs are simple forms: Single tumors that are small (<4 cm), defined and resectable (they do not affect the carotid axis), non-secretory and benign; with expert treatment, this normal form has excellent therapeutic results. Nevertheless, the unpredictable biology and natural history of PGs may produce complex forms (large tumors, attached to the carotids, bilateral, functional, malign, residual, associated with other pathologies, etc.) which have very different rates of morbidity and mortality to the simple forms [3-5].

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*Correspondence:

María Begoña García Cenador,

Department of Surgery, University of Salamanca, School of Medicine, Spain,

Tel: 34 923294500;

E-mail: mbgc@usal.es

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A subgroup of the complex forms involves those CPGs that are synchronously and ipsilaterally associated with other carotid pathologies (e.g., carotid stenosis) [6]. These situations present two characteristics: a) a low rate, which means surgical teams have little experience of them, and b) issues of a diagnostic nature (detection) and therapeutic nature (complexity); both issues clearly pose a challenge for surgeons as this lack of knowledge may compromise the final outcome.

This review seeks to adopt a unitary approach to the diverse literature on CPGs that develop synchronously with another ipsilateral extracranial carotid pathology, with the aim being to analyze their idiosyncrasies of diagnostic and therapeutic interest.

Systematic literature review

This review involved methodological aspects of the PRISMA statement for a systematic approach [7].

Search methods: Two researchers (FSL and BGC) and a librarian (MMB) conducted a search in Medline (through Pubmed) and the Cochrane Library (through Wiley) from their first records through to the end of the search (1st November 2020). No language restrictions have been applied, nor in terms of type of publication or date of the same. The search was conducted in English.

Inclusion criteria: The following keywords (MESH terms) were used: “Carotid Body Tumour”, “Carotid Paraganglioma”, “Carotid stenosis”, “Carotid endarterectomy”, “Carotid stenting”, “Fibromuscular dysplasia”, and “Carotid aneurysm”.

Data collection and analysis: The search found 245 potential publications, of which 90 were duplications. A reading of the titles and abstracts of the remaining 155 publications, examined separately by two researchers (FSL and BGC), led to 138 references being discarded. This meant that only 17 articles were considered relevant for our review. Following a reading of the full manuscripts, a further five articles were discarded because they dealt with aspects that were collateral to the search’s core purpose. Finally, this review considered 12 publications (Figure 1). This low number, which is in turn spread across three pathologies, does not permit the application of criteria of meta-analysis.

Results

The 12 articles selected involve a total of 15 patients with a CPG associated with another synchronic and ipsilateral carotid pathology (Table 1) [8-18].

The articles included are basically reports on individual cases (six in the US and three in Europe), and two short series (US and Spain). Except for two written in Russian and Spanish, all the others are in English. The article in Russian was translated in full into English. The review is completed by a US record [6].

This review is divided into three groups: 1) CPG and stenosis of the internal carotid artery of arteriosclerotic origin (n=11); 2) CPG and fibromuscular dysplasia of the carotid artery (n=1), and 3) CPG and aneurysms of the extracranial carotid artery (n=3).

Discussion

CPGs may coincide in time with other pathologies involving the same carotid artery affected by the PG. Three pathologies of the extracranial carotid (stenosis of atheromatous origin, fibromuscular dysplasia, and aneurysms) have been described in synchrony with

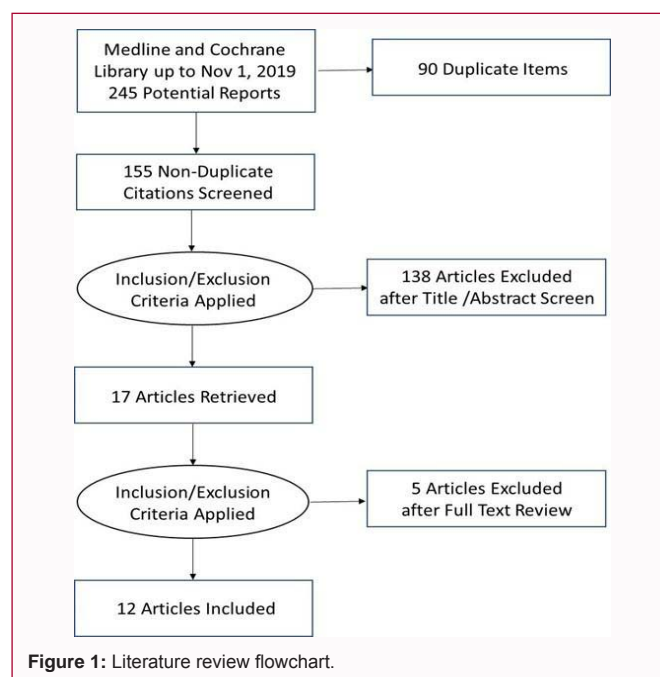


Figure 1: Literature review flowchart.

an ipsilateral PGC. Our review provides data on 11 cases of severe stenosis, one of fibromuscular dysplasia, and three of aneurysms.

Internal carotid artery stenosis (ICA-S)

It is widely known that arteriosclerosis is often located in the carotid bifurcation. The tromsø population study (6,727 people aged 25 to 84) detected a rate of carotid stenosis of 3.8% and 2.7% among men and women, respectively [19]. A subsequent study (over three million people of different ethnic origins, and aged between 40 and 100) used Eco-Doppler to detect a rate of ICA-S >50% among 4.2% (men) and 3.4% (women) [20].

The coexistence of a carotid stenosis symptomatic with a CPG is a possibility of unknown frequency; regarding this association, we have found one record [6], two short series and reports on individual cases [9-11,13,14, 17,18].

When we consider that the number of CPGs published in Medline/PubMed does not exceed 5,000 patients and that this review has found 11 cases of carotid stenosis ipsilaterally and synchronically associated with a CPG [3,21], the frequency of this approach could be placed at around 0.2% of the overall CPGs. Nevertheless, this percentage does not correspond to the US record reported by Maxwell et al. [6], whereby out of 4,601 operations involving CPG, 855 cases (18.65) also involved a thromboendarterectomy (CEA); nevertheless, the database used in this record poses several issues: 1) it does not distinguish between an ipsilateral or contralateral lesion to CPG, 2) neither does it distinguish whether the surgeries were concomitant or sequential, and 3) in our view of greatest importance, this study does not specify whether the CEA performed was due to a symptomatic or asymptomatic carotid stenosis. In two series (three CEAs/15 CPG resections) and (3/29) the percentages of CEA + CPG resection were 20% and 10.3%, respectively [10,14]. None of the patients in our series manifested significant carotid stenosis that was symptomatic (>50%) or asymptomatic (>60%) (In the imaging tests performed) [21].

The prevalence of this association is therefore unknown, although it may be assumed that given the prevalence of carotid stenosis of arteriosclerotic origin, the association is higher than that reflected in

Table 1: Carotid Paraganglioma (CPG) synchronous with another ipsilateral carotid disease. Literature review.

Author/s year [reference]	#	Age/ Sex	CBP*	Synchronic Pathology[clinic]	Simultaneous Surgery	Sequential Surgery	Morbidity	Mortality
CPG + Internal carotid Artery Stenosis (high-grade)								
Cromartie et al. [9]	1	62/F	I/I	Right Carotid Stenosis-80% (S)	1 st RS [®] +2 nd CEA	4 months later = RS (L)	NO	0
Knight et al. [14]	3	NR	I	Carotid Stenosis-high grade (1S/2A)	RS+CEA (1 shunt)		NO	0
Diaz et al. [10]	3	NR	NR	Carotid Stenosis-high grade (3NR)	RS+CEA (3 Patch)		NO	0
Smeds & Jacobs [18]	1	60/M	II	Bilateral Carotid Stenosis-80% (S)		1 st CAS (L), 2 nd CEA [®] , 3 rd RS (L)**	NO	0
Fokin et al. [11]	1	62/M	II	Left Carotid Stenosis-90% (S)	1 st RS+2 nd EversionCEA		NO	0
Hinojosa et al. [13]	1	62/M	II	Left Carotid Stenosis-70% (S)	1 st CEA (shunt; patch)+2 nd RS		NO	0
shah et al. [17]	1	66/M	II	Left Carotid Stenosis-75% (S)	1 st CEA (patch)+2 nd RS		NO	0
CPG+Carotid Artery Fibromuscular Dysplasia								
Han et al. [12]	1	54/F	II	Bilateral dysplasia (A)	RS(L) + Medical treatment		NO	0
CPG + Carotid Extracranial Aneurysm								
Al-Jarrah et al. [8]	1	76/F	I	Right internal Carotid aneurysm-2.5 cm (S)	1 st Aneurysm resection+ 2 nd RS		YES (transient)	0
Mutul & Ogul [15]	1	66/F	II	Left internal Carotid aneurysm-1.8 cm (S)	Embolization + Patient refused RS		NO	0
Rohlfing et al. [16]	1	60/M	I	Left internal Carotid aneurysm-1.87 cm (S)	CSG + Avoided RS**		NO	0

Shamblin grade: I, II, III (I/I: Bilateral Cases); ** between 1st-2nd (6 weeks); between 2nd-3rd (4 weeks); *** Significant reduction in size of CPG post-CSG.
 NR: Not Reported; M: Male; F: Female; A: Asymptomatic; S: Symptomatic; L: Left; R: Right; RS: Resection CPG sub/periadventitial; CEA: Carotid Endarterectomy; CAS: Carotid Stenting; CSG: Covered Stent Graft
 Frequency note: Knight et al. = 3 cases/15 CBP (20%); Merino et al. = 3/29 (10.3%)

Table 2: Certain carotid diseases associated with CPG. Summary.

<p>Carotid Artery Stenosis [19,20,22]</p> <ul style="list-style-type: none"> -Frequency (ICA stenosis >50%): 3.8% to 4.2% (men) and 2.7% to 3.4% (women). -Increase with age and the number of cardiovascular risk factor (e.g., tobacco). -Type of patients: asymptomatic and symptomatic (TIA, strokes). <p>Treatment:</p> <ul style="list-style-type: none"> -CEA in symptomatic patients with severe stenosis (>50%). -CAS alternative to CEA. -optimal medical treatment: Symptomatic (<50%) and asymptomatic (<60%).
<p>Carotid Artery Fibromuscular Dysplasia(CA-FMD) [12,23,24]</p> <ul style="list-style-type: none"> -Narrowing of the arterial lumen non-inflammatory, nonatherosclerotic disorder. -Disease of the medium-sized arteries: renal (60% to 75%), carotid (25% to 30%). -Etiology: Unclear. Inherited in autosomal-dominant pattern? -Frequency: 3.4% about 2,000 carotid operations. -Epidemiology: Women (60% to 90%). Age <50. Bilateral presentation (40% to 80%). -Most often asymptomatic. Symptomatic and untreated --> TIA, strokes, dissection. -Overall, patients with FMD have a favourable prognosis. <p>Treatment:</p> <ul style="list-style-type: none"> -Asymptomatic patients = antiplatelet agent. -Symptomatic patient = PTA or open surgery.
<p>Carotid Artery Extracranial Aneurysm (CA-EA) [16,25-27]</p> <ul style="list-style-type: none"> -various etiologies. The most common cause is atherosclerosis (42%). -Frequency: 0.1% to 2.4% of all carotid procedures. 0.9% of all artery aneurysm. 0.4% to 4% of all peripheral artery aneurysms. -Symptom: Cranial nerve compression and cerebrovascular event (embolization). -Treatment: Symptomatic and asymptomatic patients. -option techniques: Endovascular and open surgery.

CPG: Carotid Paraganglioma; ICA: Internal Carotid Artery; TIA: Transient Ischemic Attacks; PTA: Percutaneous Transluminal Angioplasty

the few studies on the matter. It would therefore be important for the handful of studies on CPG in which an eco-Doppler is systematically performed to reflect the percentages of this association, as well as the degree of stenosis.

Nonetheless, what is initially important about the association between ICA-S and ipsilateral CPG is that both are detected and quantified. Subsequently, if surgery is recommended in both pathologies [10,22], it is advisable to begin with CEA and then perform the resection of the CPG during the same procedure; this sequence avoids the possibility of an intraoperative ictus (due to a distal embolism during the mobilization/resection of the PG). This

was the procedure followed by Arrants et al. [9], Hinojosa et al. [13] and Shah et al. [17] when addressing a severe/symptomatic carotid stenosis and a Shamblin Grade I or II CPG; the results were satisfactory in all cases. In turn, Smeds and Jacobs [18] chose to insert a stent (CAS) instead of a CEA prior to the resection of the CPG. In the authors' opinion, this is the first case reported in the literature. The outcome was equally satisfactory.

By contrast, Fokin et al. [11] modified the aforementioned surgical sequence. In the same surgical procedure, they first performed the resection of the CPG; they then administered 5000 UI of unfractionated heparin, and finally performed a CEA by eversion.

Table 3: CPG and other ipsilateral and synchronic carotid diseases. Relevant aspects.

Very infrequent associations, but situations do exist. Need for more knowledge.
No links. Casual associations.
Non-existence of specific diagnostic and therapeutic protocols.
Need for a preoperative diagnosis of both lesions. Prevent intraoperative injuries.
Therapeutic priorities:
CPG + Internal Carotid Artery Stenosis (high-grade): first CEA or CAS (prevent intraoperative embolism).
G + Internal Carotid Artery Extracranial Aneurysm: better CSG than open surgery. First CSG, then resection of CPG.
Planning. Interdisciplinary collaboration across departments (otolaryngology, vascular radiology and vascular surgery).

CPG: Carotid Paraganglioma; CEA: Carotid Endarterectomy; CAS: Carotid Stenting; CSG: Covered Stent Graft

In this case, too, the result was satisfactory.

Despite the zero-mortality rate among the 11 cases reviewed [9-11,13,14,17,18], account should be taken of the results reported by Maxwell et al. [6], where by between 1988 and 1999 (ten years) their review of the US data on CPG revealed that 4,601 operations were associated with 855 CEAs. Despite this study’s aforementioned limitations, the authors should like to mention the impact that a possible combined or sequential surgical procedure (even during the same admission) has on mortality, as this rose from 2.0% (sole treatment of CPG) to 8.8% (combined surgery with CEA). This is evidence that a fourfold increase in the mortality rate is much more noticeable with patients’ age: 7% between 61 and 70, and 12.4% between 71 and 80.

By contrast, Knight et al. [14], who associated a CEA in 20% of their series (3/15 cases), report that mortality is very low or non-existent when performed in the most straightforward cases (Shamblin I).

Carotid Artery Fibromuscular Dysplasia (CA-FMD)

FMD is a rare disease, described in 1938 by Lead better and Burkland. Its most salient aspects are featured in Table 2.

In 2010, Han et al. [12] reported an interesting case, the first and so far only one in the medical literature, of a left-side CPG (non-functional) associated with a bilateral carotid FMD, with a further highlight being a family history of CPG (three sisters). They successfully removed the CPG and began a medical treatment (aggregation inhibition) for the FMD. The authors stressed the need in these combined situations to take the utmost care in the surgical procedure: Mobilization of the tumour during CPG resection.

There is no documented link, either anatomically or genetically, between CPG and FMD [23,24].

Extracranial carotid artery aneurysm (ECCA)

ECCAs are rare [25,26], which is why the ipsilateral association of a case inked to CPG is of some significance [8,15,16]. The main features of ECCAs are shown in Table 3. In the series reported by Taylor et al. [26] (334 consecutive carotid surgical procedures) only 14 cases (4.2%) were non-CEA, including two aneurysms (0.6%); two CPGs (0.6%) and one FMD (0.3%), none associated with CEA.

Al-Jarrah et al. [8] have reported the first case mentioned in the literature of a CPG and an ECCA. It involves a symptomatic aneurysm (cerebral embolism) of the extracranial ICA associated with an ipsilateral CPG. The initial plan was to insert a Covered Stent Graft (CSG) and then treat the CPG; as the endovascular technique was not technically possible, the strategy was changed to simultaneous open surgery: The first step involved repairing the aneurysm, which was followed by the resection of the CPG (Shamblin Grade I). Mutlu and Ogul [15] have subsequently reported an ECCA (albeit of the external

carotid) associated with a CPG. Finally, Rohlfing et al. [16] have presented another case of concomitance of a CPG with an internal ECCA. The authors inserted a CSF, and when they found that the CPG was not as big as it initially seemed, they chose to monitor the PG.

The synchronism of these two pathologies is important because any failure to detect the presence of an aneurysm of the internal carotid prior to the resection of a PGC may lead to an iatrogenic vascular lesion (hemorrhage, cerebrovascular accident or death). It is therefore vital to identify this underlying vascular pathology for a safe treatment and know what needs to be prioritized. The insertion of a CSG is an excellent option [27], especially when it means subsequently removing the CPG with greater assurances.

There is no etiological link between CPG and ECCA, although hypertension may be a common denominator between the two pathologies. Accordingly, Inci and Bertan [28] present a functional CPG (catecholamine secretor) associated with an intracranial aneurysm (middle cerebral artery), and their review of the literature reveals four cases of intracranial aneurysms or of the internal carotid associated with pheochromocytomas.

In short, CPGs are infrequent tumors, and their synchronism with another ipsilateral carotid pathology is extremely rare. It is important in these situations to have pre-op knowledge of both lesions and the therapeutic planning (priorities pathologies, treatment in stages or sequential), as well as the essential cooperation between specialisms: Otorhinolaryngology, vascular surgery and vascular radiology. Due to the low frequency and variability, patients carrying these exceptional combinations are more complex and undoubtedly pose a diagnostic and therapeutic challenge for physicians. This review attempts to gather experiences in order to overcome this challenge.

Conclusions

1) Patients with these exceptional combinations present major clinical complexity; 2) they pose a medical challenge, with the diagnostic strategy being vitally important together with the therapeutic process (surgical times and priorities); and 3) there must be interdisciplinary cooperation across the different medical specialism’s involved.

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