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Glomus jugular foramen tumours. A review

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Introduction

Paragangliomas (PGL) are rare neuroendocrine tumours arising from neuroectodermally derived paraganglionic cells scattered throughout the body. The tumours can be divided into 2 groups: those related to the sympathetic system, predominantly located in the posterior mediastinum and retroperitoneum, along the thoracolumbar paravertebral region, the most typical being phaeochromocytomas arising from the adrenal medullar; and those associated with the parasympathetic system, located in the head and neck (HN) and anterior mediastinum. The 3 main locations of HN-PGL are the carotid body, the vagus nerve and the jugular bulb regions.

This chapter focuses on jugular PGL tumours arising from paraganglia or glomus cells situated in the adventitia of the jugular bulb beneath the floor of the middle ear. It provides an overview of the clinical features of the disease, with special emphasis on malignant, genetic and therapeutic issues.

Various terms have been used for PGL in the literature, which has resulted in some confusion. In the initial description, in 1945, Rosenwasser[1] used the term "carotid body" tumours of the middle ear and mastoid, whereas later authors mentioned "chemodectomas".[2] This latter term should be reserved for carotid body tumours, the only aortic PGL exhibiting a chemoreceptor function. "Glomus" tumour was used in 1948 by Winship *et al.*[3], probably by analogy to cutaneous tumours arising from vascular pericytes. Also mentioned are "glomerocytomas", "receptomas" or "non-chromaffin tumours"[4] referring to the capacity of hematoxylin but not potassium dichromate to stain PGL, but use of the terms is inconsistent and nonspecific.

General characteristics

PGL are rare (incidence estimated at 1 in 1.3 million people[5,6]), slow growing (doubling time of 13.8 years and annual growth rate of 0.79 mm/year),[7] and most of the time benign. They affect more women than men, with the mean age at presentation between 40 and 60 years.[8]

The natural history of PGL is notable in 3 ways. First, it is locally aggressive, linked to the trend to infiltrate connective tissue planes and to erode bone, following the path of least resistance, including mastoid air cell tracts, vascular channels, and neural foramina. The second is the secretion of catecholamines, so PGL are part of the sympathoadrenal neuroendocrin system.[9] As such, PGL secrete neurohormones and express receptors at the surface of their cells, especially receptors to somatostatin (see below). Finally, they are multicentric and hereditary or familial in nature in 10% to 50% of cases. Multicentricity ranges from a mean of 30% to 40% in familial forms, and averages 10% in sporadic cases (see genetic data).

Occasionally PGL may be associated with other tumour types such as astrocytomas,[10] thyroid carcinomas[11] and may be part of multiple endocrine neoplasms type II or associated with medullary thyroid carcinomas, hyperparathyroidism, pheochromocytomas and parathyroid adenomas.[12,13]

Clinical aspects

Jugular PGL remain silent for a long time.[14] Revealing symptoms are of 3 types. The first is *otologic*, such as unilateral pulsatile tinnitus, hearing loss, aural fullness, and dizziness. These symptoms reflect invasion of the tympanic cavity, as demonstrated by findings of a reddish retrotympanic mass. The second is *neurologic,* including swallowing disorders, hoarseness and dysphonia, shoulder weakness, lingual paralysis, and Horner sign. These symptoms reflect impaired lower cranial and sympathic nerves. Facial paralysis

is usually a late sign. The third is *cervical*, as in a retromandibular or subdigastric mass. Occasionally, tachycardia, cephalalgia, sweating, arterial hypertension, diarrhea and flush may be revealing or associated. Finally, jugular PGL may be asymptomatic and discovered by screening relatives.

Radiological evaluation

Besides the usual cochleovestibular testing and determination of urinary catecholamine levels,[15-17] extension of the PGL and delineation of the likely boundaries for surgical resection should be revealed by both CT and MRI.[18]

High-resolution, thin-section axial and coronal CT images with bone windows allows for delineating the exact extent of bone destruction, dehiscence of the floor of the tympanic cavity, protrusion in the tympanum, erosion of the carotid canal and fallopian canal, destruction of the bony labyrinth and extension into the cerebellopontine angle. Axial and coronal T1- and T2-weighted MRI after gadolinium enhancement and/or fat-suppression sequences reveals the typical "salt-and-pepper" pattern and the soft-tissue involvement. Both CT and MRI can demonstrate the highly suggestive hallmark of paraganglioma (i.e., strong enhancement with contrast), indicative of hypervascularity.

MRI angiography and venography are essential in identifying the feeding vessels from the external, carotid and vertebral arteries and, of major importance, the venous flow, especially a possible jugular thrombosis and contralateral venous drainage.

Because of the remarkable performance of CT and MRI, diagnostic angiography is no longer useful. This exam is now performed before embolization or to assess the contralateral arterial supply if the internal carotid artery is sacrificed.

Finally, evaluation should systematically include somatostatin receptor scintigraphy (SRS) because of the intrinsic characteristic of PGL to express somatostatinergic receptors. Numerous studies[19-22] have shown SRS to be a reliable non-invasive diagnostic tool to: i) confirm the diagnosis of PGL in patients with clinically suspected PGL but inconclusive results of conventional imaging; ii) stage or assess multicentricity in patients considered on conventional imaging to have head or neck PGL; and iii) screen asymptomatic relatives of patients. A limitation of SRS is that it reveals specific somatostatinergic receptors and therefore cannot differentiate PGL from other tumours expressing such receptors, particularly meningiomas.

Genetic features

Recent advances in molecular genetics have established hereditary PGL associated with mutations of the mitochondrial succinate dehydrogenase (SDHx) enzyme gene, located at the crossroads between the Krebs cycle and the mitochondrial respiratory chain, encoding 3 subunits (SDHD, SDHC, SDHB) and that malignant forms are frequently related to a B-subunit mutation.[23] The SDH genes are tumour-suppressor genes that induce an abnormal stimulation of the hypoxia-angiogenesis pathways, thus leading to the classical intense and particular vascularisation of PGL.[24] According to Neumann *et al.*,[23] 4 different PGL syndromes should be distinguished: PGL1 associated with SDHD mutation; PGL4 associated with SDHB mutation; PGL3 associated with SDH C mutation; and PGL2, unknown susceptibily to a gene.

In hereditary or familial HN-PGL, which represent 9.5% to 50% of HN-PGL, the mutation concerns essentially the SDHD subunit, then the SDHB subunit, whereas in sporadic forms, mutation rates are variable across studies, ranging from 11% to 29%, with a predominance of SDHD mutation.[24-26]

The transmission is autosomal dominant for SDHB, SDHC and SDHD mutations.[23] However, the autosomal dominant transmission of the SDHD mutation is associated with maternal genomic imprinting.[8] Consequently, tumours could develop in SDHD carriers only when they have inherited the SDHD mutation from their paternal branch, whatever their gender.

Clinically, patients with inherited PGL are usually younger than those without mutations and frequently have bilateral or multiple tumours. In addition, a germline SDHB mutation is associated with a high risk of malignancy and poor prognosis, although some patients with an SDHD mutation could show malignancy.[27,28]

Large international genetic studies proposed specific genetic testing in all patients with HN-PGL and clinical criteria.[24,29] With paternal family history and/or multiple HN-PGL, the SDHD gene should be screened first, and the SDHB gene should be screened first with malignant PGL. A positive genetic test offers the opportunity to propose a pre-symptomatic genetic testing to first-line relatives and thus, to detect small tumours in mutation carriers. The test can also

lead to a search in the index case for other tumours of the hereditary PGL spectrum such as catecholamine-secreting PGL, non-functional PGL or pheochromocytomas in the thorax, abdomen or pelvis.

Few cases of HN-PGL have been described in the context of von Hippel Lindau disease type 2, and genetic testing for von Hippel Lindau would be indicated with the association of HN-PGL and another lesion such as retinal or central nervous system hemangioblastomas, clear-cell renal cancer or pancreatic endocrine tumours.[30,31]

Screening for hereditary syndromes is an important part of the initial work-up for affected patients. Finally genetic testing and genetic counselling should be considered in all patients with PGL.

Malignant PGL

Currently, we lack validated histological criteria for malignancy. For some authors, malignancy relies on some abnomalities such as multiple mitosis, nuclear polymorphism, or capsular invasion.[9] For Lack *et al.*,[32] 3 criteria argue for malignancy: central necrosis as described by Zellballen, vascular and lymphatic invasion, and abnormal mitosis, 2 of these criteria being sufficient. For other authors**,** the destructive potential and recurrence are sufficient.[33,34]

At present, malignancy in PGL is defined as the presence of metastatic lesions (i.e., chromaffin tissue in non-chromaffin organs).[35] The rate of malignancy ranges from 6% to 24% for all extra-adrenal PGL[26,36] and is estimated at 5% for jugular and carotid body PGL[5,37] but 10% to 19% for vagal PGL.

Clinical data from the literature are scarce but suggest that patients with malignant HN-PGL are of either sex and most have primary carotid bodies, followed by vagal and jugular lesions (of interest is that tympanic PGL are almost never malignant). As compared with non-malignant patients, patients with malignant disease are younger at diagnosis and show a higher rate of secreting tumours in one-quarter of cases and multicentric tumours in one-half.

Bone and lymph nodes are the main sites of metastases.[37-39] Bone metastases predominate in the spine but may affect the iliac and cranial bone, ribs, and sternum. They manifest as expansive lesions with cortical destruction and soft-tissue involvement or as nodular lesions. These nodular lesions display a remarkable feature on radiography of a central low-signal intensity surrounded by a single halo of fat-like signal intensity or a double halo with a fat-like inner ring and an edema-like outer ring.[40] Follow-up may evidence decreased size of the oedema-like area and increased size of the fat-like area, which suggests a partially fatty regression of tumour foci.

Metastatic cervical lymph nodes are detected by palpation or imaging techniques as masses present in an area distinct from the carotid body or subdigastric regions.

Functional imaging does not seem fully reliable to reveal bone metastases. ^{111}In-pentetreotide, as well as $^{123/131}$I-MIBG show weak performance.[40-42] Positron emission tomography has recently been proposed for staging PGL, but ^{18}F-FDA gives better performance in detecting non-metastatic than metastatic PGL.[41,43] ^{18}F-DOPA has high sensitivity in detecting non-metastatic HN-PGL[44] but weak sensitivity in detecting metastases, especially in carriers of SDHB. The weak performance of these specific agents could be explained by a dedifferentiation of metastatic SDHB-related PGL. This fact could explain the superiority of ^{18}FDG found in a cohort of 30 patients with SDHB-associated PGL, 29 with metastatic disease.[41]

As a result, staging of disease in PGL patients at risk should include whole-body scintigraphy and spine MRI.

The delay between diagnosis of the primary tumour and metastases may be long and thus justifies long-term follow-up, especially for high-risk patients. If the overall 5-year survival rate reported for malignant pheochromocytoma or PGL ranges from 40% to 74%,[45] the individual prognosis is unpredictable. In our study, all patients except one (with SDHB mutation) were alive at the last follow-up. Havekes *et al.*[46] reported on one patient with multiple PGL who died after a 32-year follow-up; the woman had bone and lymph node metastases and SDHD mutation. In our series, the longest follow-up was 29 years in a patient with SDHD mutation.

Surgery and/or radiotherapy are the established treatment for PGL, but management of malignant forms remains controversial. Metabolic radiotherapy with specific agents linked to tumour cells coupled with a radiotracer for electron-dose delivery [such as ^{131}I-MIBG, Octreotide labeled with 90Ytrium, ^{111}In-pentetreotide with high activity (7 GBq)] have been proposed as palliative treatment for metastases, which leads to symptomatic relief.[43,47,48] However, metastatic lesions must bind the tracer, which is actually an uncommon feature.[40] Combination chemotherapy led to

improved symptoms and short remissions.[48,49] More recently, Sunitinib, an oral multitargeted receptor tyrosine kinase inhibitor with antiangiogenic and antitumoural activity, has been used in a few cases with promising results.[50] Because metastase is not necessarily associated with poor short-term prognosis and because patients with disease may survive for decades, active treatment should be adapted to symptoms.

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Management

Treatment of jugular PGL remains controversial. Two modalities are currently advocated: surgery with prior embolization, and radiotherapy (or a combination).

Surgery

Surgery has been long considered the treatment of choice because it was the only way to remove the tumour completely, a potential cure. Since the first description by Rosenwasser,[1] in 1945, jugular PGL have been managed by various surgical techniques. The infratemporal fossa (ITF) type A described by Fisch *et al.*[52] is now considered the standard procedure. Still, technical debates are ongoing concerning 3 anatomical structures: facial nerve, internal carotid artery, and posterior fossa.

Facial nerve

The classical ITP approach includes anterior transposition of the facial nerve from the stylomastoid foramen to the geniculate crest, which is supposed to improve access to the jugular foramen, the infralabyrinthine compartment and the ascending carotid artery, as well as to the posterior fossa. Such mobilization may cause some degree of paresis in experienced hands,[52-54] but complete facial paralysis leading to long-term cosmetic sequelae seems more frequent and more severe in other hands.[55,56] These observations are indirectly attested by the numerous articles reporting surgical and technological refinements aimed at limiting the occurrence of facial paralysis. Such refinements include mobilization of the mastoid portion only, en bloc displacement of the mastoid portion of the facial nerve with its surrounding connective tissue and with the posterior belly of the digastric muscle, replacement of the mobilized portion at the end of surgery in its original position, and permanent electromyography recording. Other authors described the "fallopian bridge technique"[57] and found, in most cases, satisfactory exposure without facial nerve rerouting (for review see[56]). To summarize this issue, mobilization should probably be reserved for selected cases.

Internal carotid artery

This vital structure may be infiltrated in case of anterior extension, corresponding to the C type in the Fisch classification. In any case, CT and angio-MRI are mandatory to carefully assess the status of the internal carotid artery (ICA): erosion of the bony canal, irregularities of the wall, narrowing of the lumen, etc. Manipulation of the artery and dissection from the adventitia are feasible with limited involvement, but with massive encasement of the artery, sometimes removing the tumour without high risk of rupture is impossible.

Therefore a balloon occlusion test is systematically performed before making any decision. When this test is well tolerated as assessed both in terms of clinical tolerance and the venous phase of angiography, and should surgery be decided, then 3 possibilities exist: i) permanent occlusion of the ICA by coils (because of the risk of secondary migration of the very slippery and unstable balloons), which allows for safe sacrifice of the ICA and facilitates the removal of the tumour; ii) by-pass of the temporal ICA, a complex and sophisticated procedure; and iii) stenting of the arterial lumen. This technique, advocated by some authors, appears promising.[58] The major drawbacks are the need for life-long anti-thrombosis therapy and the risk of late occlusion of the stent.

The posterior fossa

Invasion of the posterior fossa raises two questions. First, should the neurosurgical step be realized at the same time as the ITF approach or should it be delayed? Most authors recommend staging the procedure to minimize the risk of cerebrospinal fluid leak and secondary meningitis.[59-61] Second, What approaches should be used? Countless techniques have been proposed, including juxta-condylar, extreme lateral trans-condylar, supra-condylar, infra-petrosal, and infra-labyrinthine trans-sigmoid approaches.[62] All differ by some subtle and minimal techniques but provide a good overview of the CPA and allow for complete resection of the intracranial extension.

Finally, marked advances in embolization and nerve monitoring have improved the ability to remove jugular PGL formerly

considered unresectable, with tumour control rates of about 90%.[56,63,64] However, total resection presents the inescapable risk of neurological complications, including facial paralysis, dysphonia or swallowing problems, with permanent disability up to 10%. Such consequences are hardly acceptable for a benign tumour, especially in patients with no pre-operative abnormalities.

Radiotherapy

Substantial disability with surgery, along with the increasing concern for quality of life, has rendered radiotherapy a valid alternative treatment. Indeed, an increasing number of reports have emphasized the effectiveness of radiotherapy in controlling tumour growth while minimizing permanent disability.

External beam radiotherapy delivering 45-55 Gy in 20-25 fractions was introduced as an alternative to minimize post-surgical morbidity.[65-67] However, in some rare instances, it could induce severe side effects, including temporal bone osteoradionecrosis, cranial nerve paralysis, abcess, and occasionally radiation-induced malignancy. With conformational radiotherapy, results improved, with 90% to 100% tumour control rate and minor complications.[68]

More recently, radiosurgery delivering a single high dose (about 13 Gys) of stereotactically guided beams on a specific well-defined target have been used with promising results, probably because it is effective on the vasculature supporting the tumour, a characteristic of PGL. Moreover, it provides significant advantages in reducing the time of treatment, limiting the exposure of adjacent cerebral and cranial nerves, and improving indirect benefits, such as medical costs, lost working days, travel and housing expenses.[69-71]

A recent literature review of the use of gammaknife, LINAC and Cyberknife,[72] suggests excellent tumour and symptom control ranging from 71% to 100% and from 88% to 100%, respectively, as well as lower morbidity than with surgery. Transient side effects include tinnitus, hearing loss, facial nerve palsy, and cephalalgia.

Accordingly, radiosurgery could be recommended for tumours <3 cm in diameter or residual or recurrent tumours after surgery. In addition, fractionated radiosurgery delivering small doses of radiation over 30 fractions, equivalent to a single 15-16 Gy margin dose, seems interesting for larger unresectable tumours.[73,74] Contraindications include a mass effect on the brain stem, tumours >3 cm in diameter and marked extension below the skull base.

Management decisions

Selecting the most appropriate form of therapy should rely on patient and tumour-specific factors.[68]

1. Age of the patient

In "young" patients, surgery should be proposed, whereas radiotherapy or follow-up should be considered for "older" patients for three main arguments: i) young patients usually have no medical factors contraindicating aggressive surgery and cope more easily with post-operative neurologic deficits; ii) radiotherapy may stabilize the tumour growth for 10 to 15 years (the older the patient, the lower the risk of recurrence); and iii) the risk of radiotherapy-induced malignancy, if any, does not occur until years after the completion of irradiation. During such a period, older patients may be affected by other conditions.

2. Natural history and growth rate

Most PGL have a slow growth rate. This feature resembles that found in vestibular schwannomas and gives support to a "wait and scan" policy as a primary option in asymptomatic patients.

However, with the increasing life expectancy, even a slowly growing tumour left untreated in a young patient may progress on the long-term and cause cranial nerve and brain-stem injury. Furthermore, some jugular PGL seem more aggressive, especially in patients younger than 20 years of age.

3. Presence of symptoms

Symptomatic patients should receive treatment. Pre-operative neurologic paralysis makes the surgical decision easier, because surgery will not add further neurologic deficits. Conversely, adopting a conservative attitude in asymptomatic patients seems reasonable. However, in asymptomatic patients with PGL detected by genetic counselling in families, surgically removing small asymptomatic tumours seems advisable.

Surgical removal of the hormone-secreting localization is usually indicated.

4. Tumour size and extent of disease

For small tumours, types B or C1, surgery should be proposed if it carries an acceptable risk of complications. Similarly, surgery should be proposed for "complex" PGL: those with giant size, massive intracranial or petroclical extension

with mass effect on the brain stem; previously irradiated; with suspected malignancy; or too large for safe irradiation. In these instances, treatment with subtotal resection can be followed by radiotherapy.

Bilateral tumours may represent a contraindication to surgery because bilateral paralysis of the lower cranial nerves results in permanent and severe disabilities. However, surgery may be indicated to first excise a small contralateral vagale or carotid body to ensure that functions of the X and XII nerves are preserved.

5. Patient consent

Sometimes patients are unwilling or not able to undergo surgery, whereas others are not able to cope with the idea of radiotherapy and retaining a tumour. In general, patients are increasingly demanding less-invasive methods of treatment.

In providing information about the above-mentioned benefits and risks, the physician should be aware that most patients are now self-informed – if not over-informed – because of the Internet, and physicians must clearly explain that the goals of surgery and radiotherapy differ and that the resulting quality of life cannot be compared.

Tentative treatment algorithm

Taking into account criteria of success differences (surgery aims at eradicating tumour, any remnant being considered as failure, whereas radiotherapy stabilizes or reduces the volume of the tumour), treatment of jugular PGL should always be tailored to each case. However, the 4 following strategies can be proposed.[68]

1. Wait and scan policy

An undisputed indication for such strategy would be asymptomatic PGL developing within the jugular foramen, or extending slightly beyond, in an elderly patient. The slow annual growth rate and the exceptional accuracy of MRI in detecting volume increase favour this choice. The same indication seems legitimate for young relatives of affected patients who present a small tumour. In both instances, regular imaging follow-up is mandatory, with secondary surgery or radiotherapy proposed should the tumour increase in size.

2. Surgery

Surgical resection can be reasonably proposed under one or more of the following conditions: i) young age (perhaps younger than 45 years of age); ii) pre-operative neurologic deficits, including paralysis of the facial or lower cranial nerves; iii) tumour resectable with minimal risk of complications; iv) intracranial extension of PGL; v) unilateral PGL occasionally associated with ipsilateral vagale or carotid body localizations; vi) evolving and aggressive PGL as demonstrated by successive imaging or bone erosion with risk of cranial-nerve damage; vii) major petroclival extension with encasement of the internal carotid artery and positive results of well-tolerated balloon occlusion test; or viii) tumour recurrence after irradiation.

3. Radiotherapy

Recommendations for radiation as a primary treatment are: i) age older than 60 years; ii) surgical contraindications including medical or personal reasons; iii) inextirpable or bilateral large tumour; iv) major vascular risk as seen by negative results of balloon occlusion test or unique venous outflow; or iv) absence of neurologic deficits.

4. Combined radio-surgical approach

This approach can be discussed in some instances, as in when a patient suitable for surgery presents a large tumour, with no neurological deficits, and who is not ready to accept post-operative disabilities. Here, the planned combination of subtotal surgical resection followed by radiotherapy seems attractive. Indeed, such an approach does not fully satisfy the surgeon with the challenge of a particularly delicate operation but meets the patient's desire (i.e., to control a benign tumour; improve symptoms such as tinnitus, pain or hearing loss; or to avoid further neurologic compromise). Radiotherapy may be undertaken systematically after surgery or if the tumour remnant regrows.

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