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REVIEW

Head and neck paragangliomas

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ABSTRACT

Head and neck paragangliomas (HNPGL) are rare, slowly growing tumours, presenting as a painless mass in the neck. Multiple genetic mutations are associated with HNPGL; screening can have an important role in patients of a young age and/or with a positive family history and/or malignant HNPGL. The choice of treatment should be made individually, based on the patient's condition, the risk of complications and the aim of therapy. Observation can be a logical choice given the low incidence of malignancy. In the case of intervention, surgery and radiotherapy show comparable results for local control. For definitive eradication, surgery would be the treatment of choice, involving however high risks of complications.

KEYWORDS

Paraganglioma, carotid body tumour, SDHD, radiotherapy, genetic testing

INTRODUCTION

Paragangliomas (PGL) are rare tumours arising from neural crest cells associated with autonomic ganglia along the sympathetic trunk. A small percentage of PGL are located in the head/neck region. Of PGL in the head/neck region, 65% are located in the carotid body; these are called carotid body tumours (CBT). PGL are mostly benign, slowly growing tumours and were first described by Von Haller in 1743.[1-3] They are also known as chemodectomas, because they act directly as chemoreceptors or by the secretion of catecholamines in response to stress.
Head and neck paragangliomas (HNPGL) are an important differential diagnosis for a mass in the neck region. During the last decade, more has been discovered about genetic mutations in HNPGL. Also, therapeutic regimens have been altered over the years. Hence we present two cases and give an overview on current concepts of HNPGL.

CASE 1

In our outpatient clinic a 48-year-old man, with no past medical history, presented with a painless, slowly progressive mass on the left side of the neck, which had been there for two months. He reported no other symptoms. A cousin had been treated for CBT. On physical examination we found a solid mass of 3-4 cm on the left side of the neck. Ultrasound and later magnetic resonance imaging (MRI) of the neck showed a CBT along the left side of the carotid bifurcation (*figure 1*). Urine analysis demonstrated no excess of metanephrines. The CBT

Figure 1. *MRI neck: CBT on the left side of the carotid bifurcation*

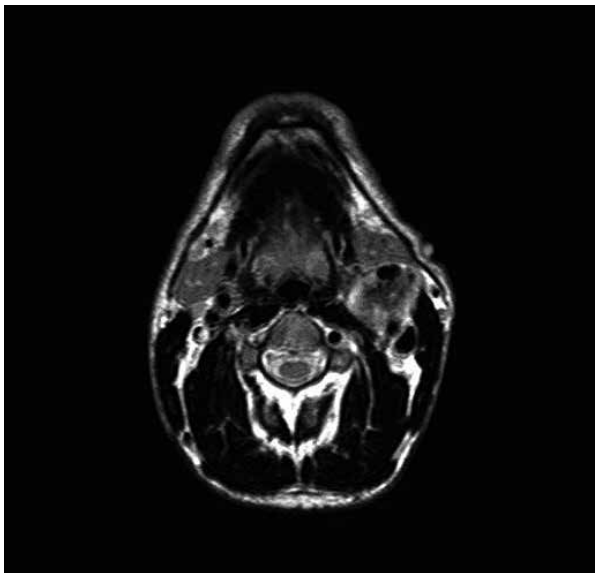
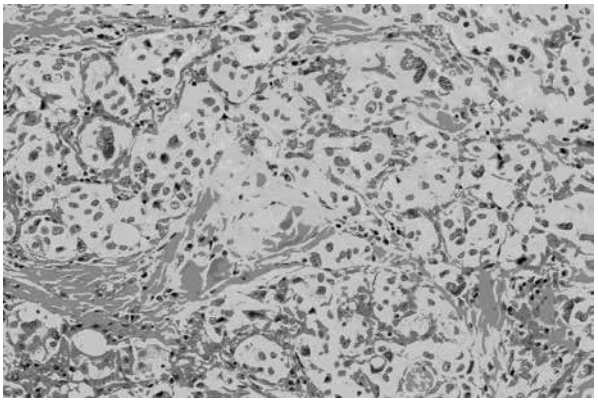


Figure 2. *Histology CBT: Organoid growth pattern of the tumour cells with an intervening stromal component and supporting sustentacular cell population at the periphery of the cell nests ('zellballen'). (Pathologist Dr. H.H. van Boven, Netherlands Cancer Institute, Antoni van Leeuwenhoek)*

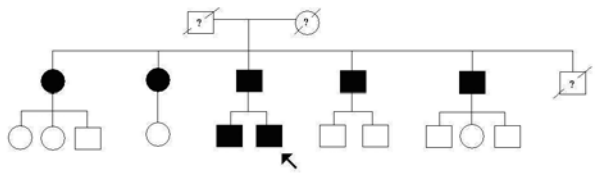


was surgically removed without complications. Typical histopathological images of CBT were seen (*figure 2*). Genetic evaluation is in progress.

CASE 2

Another man, aged 46 years, who was remotely related to the first patient, presented to the outpatient clinic with a mass on the left side of the neck; he had no past medical history and a positive family history for PGL (*figure 3*). MRI proved the mass to be a CBT (3.5-4 cm) along the left side of the carotid bifurcation, which was surgically removed. A small PGL along the right jugular artery was left in situ. Two years later the patient returned with complaints of a dystrophic tongue, caused by a PGL in the left jugular foramen, for which he received gamma knife therapy. During follow-up, more PGL evolved, namely one along the glomus tympanicum dextra (12 x 6 mm), two along the right side of the vagal glomus (24 x 7 mm and 28 x 20 mm) and one along the left side of the vagal glomus (36 x 18 mm). These HNPGL were all observed over time. Genetic evaluation of this patient and his relatives is in progress. Notably, during follow-up a prolactinoma was diagnosed on the left side of the pituitary gland.

Figure 3. *Family tree of patient 2*



CLINICAL PICTURE

Patients with HNPGL typically present at the age of 40-70 years with a gradually enlarging mass in the neck; 84% of HNPGL are painless. Sometimes hoarseness, dysphagia, and more seldom vertigo and coughing may occur, resulting from pressure on the vagus nerve or sympathetic nerves. Some patients present with hypertension, sweating and headache, due to vasoactive catecholamines produced by HNPGL.[1,4]

HNPGL are more prevalent in women than in men (1-5:1).[3,4] They grow less than 1-2 mm per year and malignancy occurs in less than 5% of the cases. However, for malignant HNPGL, ten-year survival is less than 50%.[2,5] The differential diagnosis of a mass in the neck other than HNPGL includes lymph node pathology, thyroid gland pathology, saliva gland pathology, neurofibromas and carotid artery aneurysms.

AETIOLOGY

There are two known forms of HNPGL, the sporadic form and the familial form. Thirty-five percent of all HNPGL are familial.[3] It is thought that the sporadic form is triggered by hypoxia. Research has shown that patients living at high altitude, and therefore enduring a more or less chronic form of hypoxia, have a larger carotid body.[6]

The familial form of HNPGL is less strongly related to hypoxia and more strongly associated with genetic mutations. Genetic mutations can also occur spontaneously; however, most patients with genetic mutations have a positive family history. For example, a study done in the United Kingdom found a prevalence of genetic mutations of 92% in patients with a positive family history.[7] Penetration of genetic mutations and existence of environmental factors (such as hypoxia) predispose to the development of HNPGL.

Several genetic mutations are known to be associated with HNPGL, namely SDHB, SDHC, SDHD, VHL, NF-1, RET, TMEM127, SDHAF, SDHA, MAX.[7] Generally, HNPGL are associated with mutations in the succinate dehydrogenate complex (SDH) subunit B and D (SDHB and SDHD). SDH is an enzyme complex, bound to the inner membrane of the mitochondria. Frequency of mutations is variable among different populations. For example, in the UK 27% of HNPGL have a detectable mutation in SDHB and 35% in SDHD.[7] While in the Netherlands 87% of genetic mutations in HNPGL are SDHD. The dominance of SDHD mutations is unique to the Netherlands. Altogether 88.8% of the Dutch HNPGL SDH mutation carriers have one of six Dutch founder mutations in SDHD, SDHB or SDHAF2 (SDHAF2 c.232G>A, SDHB c.423+1G>A SDHB

c.201-4429_287-933del, SDHD c.274G>T SDHD c.416T>C p.Leu139Pro SDHD c.284T>C).[8]

In patients with HNPGL, the chances of finding a genetic mutation are higher in patients with a positive family history, multiple paragangliomas, malignant disease and patients of a younger age. The median age of genetic HNPGL is 38.5 years versus 62 years in non-genetic HNPGL.[7,8] Of the described genetic mutations, SDHB is most strongly associated with metastatic disease.[9] In addition to HNPGL, a variety of other tumour types have been reported to be associated, or potentially associated, with *SDHB* or *SDHD* mutations. Case 2 described an HNPGL and a concurrent prolactinoma. To our knowledge there is only one other case published and it has not yet been associated with genetic mutations.[7]

Given the strong association of genetic mutations in HNPGL with a positive family history, occurrence of multiple tumours and young age, screening might be useful in these patients. A German study by Erlic *et al.* proposed an algorithm for genetic testing.[10] However, given the variable mutations in different populations, genetic screening should be adjusted to the population under study. This might lead to a specific Dutch screening program for the six founder genes in selected (high-risk) HNPGL patients.

DIAGNOSIS

The first step in evaluating a mass in the neck is Doppler ultrasound. If clinical suspicion of HNPGL exists, further imaging of the tumour and its relation to environmental structures is necessary. Both computer tomography (CT) and MRI are valuable methods for this purpose and can sometimes be used complimentarily. CT provides more information on bone destruction by the HNPGL than MRI, while MRI provides more detailed information about the relation of the HNPGL with surrounding vascular and bone structures. If surgery is considered, angiography remains the golden standard to evaluate the vasculature of the HNPGL.[4,11] Lastly, research has been done to evaluate position emission tomography (PET)/MRI for imaging of HNPGL. However PET/MRI is a costly and difficult technique and further research is needed to evaluate the use of PET/MRI in the diagnostic evaluation of HNPGL.[12]

Imaging techniques of HNPGL are highly specific; therefore, biopsy is not necessary to confirm the diagnosis and is relatively contraindicated because of a high risk of haemorrhage on the biopsy site. Moreover, based on histology, it is difficult to differentiate between benign and malignant HNPGL.[3] The best proof of malignancy is radiological evidence of metastatic spread.

TREATMENT

Several treatment modalities are available for HNPGL: observation, surgery and radiotherapy. As mentioned before, small HNPGL are often very slow growing and rarely demonstrate to be malignant.[2,5] Therefore, small (<3 cm), asymptomatic HNPGL can be observed over time. For elderly patients with bilateral tumours and/or a high surgical risk, observation is probably also the best policy. For large and/or symptomatic tumours surgery or radiotherapy is indicated.

Historically, surgical resection was the treatment of choice. Surgery offers a good prognosis and chances of recurrence or metastatic spread are very low. However, there are high risks associated with surgery of HNPGL, including haemorrhage, cerebral ischaemic events and cranial nerve damage.[13] The complication rate can be reduced by performing embolisation within 48 hours before surgery.[13-16] However, embolisation can provoke thrombosis. Despite embolisation, surgery for large HNPGL is still significantly associated with high risks.

Radiotherapy is an interesting option if patients have a high surgical risk, if a large lesion is unresectable or if a large haemorrhage is anticipated. There is increasing evidence that radiotherapy gives comparable prognostic results to surgery, without the risk of surgery-associated complications. Observational studies demonstrate long-term control rates (defined as stable disease or partial regression with no evidence of growth) for HNPGL of 95-96%.[17,18] Given the rarity of the condition, there are no randomised controlled trials yet to compare surgery with radiotherapy for HNPGL.

CONCLUSION

HNPGL are rare, slowly growing tumours, presenting as a painless mass in the neck. Multiple genetic mutations are associated with HNPGL, screening can have an important role in patients of young age and/or with a positive family history and/or malignant HNPGL. The choice of treatment modality should be made individually, based on the patient's condition, the risk of complications and the aim of therapy. Observation can be a logical policy, given the low incidence of malignancy. In the case of an intervention, surgery and radiotherapy show comparable results for local control. For definitive eradication, surgery is the treatment of choice, however associated with high risks of complications.

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