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Paragangliomas of the carotid body and other rare localisation

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Abstract. – **Cervical paragangliomas are uncommon benign or malignant neoplasms, originated by stem cells of neural crest. It is not easy nowadays to define properly their biological behaviour, the possible multiple location and the association with Multiple Endocrine Neoplasms. After a wide review about recent diagnostic, pathological and clinical acquisition, authors report their caseload of 10 patients affected by sporadic paragangliomas and 1 by familial multiple neoplasm localised in carotid bodies of both sides, left vagus nerve and left hypoglossus nerve. All patients but one were treated by a curative resection of the neoplasm. In one case only an explorative laparatomy was possible because of the visceral and vascular involvement.**

Key Words:

Paraganglioma, Carotid body tumours.

Introduction

Paraganglioma originate from the paragangliar tissue deriving from stem cells of the Neural Crest[1,2]. Compared to other tumours of the head and neck area, they occur less frequently (ratio 1:30.000)[3]. These tumours attach themselves to the APUD (Amine Precursor Uptake Decarboxylation) system which includes cells able to free nerve regulating substances[4]. They are localised in the adrenal and extra-adrenal glands in close relationship with the ganglia and cranial nerves. They can therefore be found in any part of the body where there are sympathetic ganglia including chemoreceptors, suprarenal medulla, retroperitoneal ganglia and the most extreme branches of the vagus fibres[1].

The different clinical symptoms caused by these tumours may be due to the secretion of catecholamines (fuctional tumours) or to growth and eventual localised infiltration[2,4,5]. However, they are generally slow-growth tumours and rarely develop into malignant ones[6,7]. The most evident symptom of tumours with neuro-endocrine effects is phaeochromocytoma present in 80% of the cases of suprarenal medulla paraganglioma and only in 20% of extra-suprarenal paraganglioma secreting catecholamines[2]. In any case, the quantity of urinary catecholamines in malignant paraganglioma is usually above normal even if it stays within sub-clinical levels. The multiple location of tumours in sporadic paraganglioma (10%) is related to the widespread organisation of the paraganglion system and or the common embryonic origin[2].

The relationship with Multiple Endocrine Neoplasms (MEN) is also due to the same origin. This is considered particularly important and occurs in 42% of the cases of familial neoplasms of the paraganglion system[7,8]. In this paper the problems in diagnosing and treating Paragangliomas of the carotid body and other rare localisation are discussed.

Materials and Methods

The sample studied between 1970-1995 consisted of 11 patients (age 28-57 years, median age 42 years). Ten patients presented single sporadic paraganglioma, one patient presented multiple familial paraganglioma. Localisation were as follows: eight patients were affected by carotid paraganglioma (five females, three males); one patient was affected by left vagal paraganglioma; one patient by retroperitoneal paraganglioma; one patient by familial paraganglioma as well as a tumour of the carotid body on both sides and a left vagal paraganglioma.

Ten years after surgery to remove these paraganglioma, the patient returned with a paraganglioma originating in the left hypoglossal nerve. A sister of this patient was operated on for a tumour of the right carotid at the age of 21, at age 40 for a right vagal paragangliomas and 41 for left vagal paraganglioma. Surgery was performed elsewhere, but post-operative complications were bilateral paralysis of the recurrent nerves, first requiring tracheotomy then arytenopexy. A brother of this patient is currently in good health.

Preoperative determinations of arterial blood pressure, hematic and urinary catecholamines are normal (with slight increasing of arterial blood pressure in aged patients). Surgery consisted in radical operation for the eight patient with tumours of the carotid body; resection of the carotid sinus was necessary for one patient, with a end-to-end internal carotid graft. For the single sporadic paraganglioma of the left vagal nerve, surgery involved discontinuation of the nerve fibres; there was a paralysis of the recurrent nerve on this side. Surgery on the retroperitoneal paraganglioma consisted essentially in an explorative laparatomy given the extensive infiltration of the voluminous mass into the vena cava. In surgery biopsy was performed which showed a neoplasm of the paragaglion, positive to NSE (Neuronal Specific Enolase) and Chromogranine (these immunohistochemical tests were possible only in this last and most recent case in 1995). A dual-flow implantable system for chemotherapy was positioned. First surgery on the multiple paraganglioma (1983) consisted in removal of carotid tumours on both sides and excision of a left vagal paraganglioma with paralysis of the recurrent nerve on the left side.

In 1993 further surgery was necessary to remove a paraganglioma of the left hypoglossal nerve, prior to which highly selective periangiographic embolization of the blood vessels at the base of the skull was performed to limit in-surgery bleeding. This left the patient with a temporary motor deficit of the tongue and considerable difficulty in swallowing.

Results

There is no mortality. There are no modifications in arterial blood pressure and catecholamines values in all patients. The complications were: a recurrential paralysis in a patient operated on for vagal paraganglioma; a recurrential paralysis and temporary dysarthria in the patient affected by multiple familial paraganglioma and operated on both carotid bodies, vagus nerve and hypoglossum nerve. Another patient operated on for carotid body paraganglioma showed a cerebral ischaemic lesion (left temporal lobe) which caused a slight transitory facial-brachial motor deficit on the right side and a speech impairment. At two months from operation it had completely regressed. None of the patients undergoing surgery for cervical paraganglioma revealed regional recurrences of the neoplasm nor metastases (follow-up: 2-25 years).

The patient who underwent surgery for retroperitoneal neoplasm, judged inoperable because of the size and the aggressive behaviour of the mass, is being treated with chemotherapy. At the end of the cycle of therapy, the mass has not increased his volume and the patient is still alive at eighteen months from diagnosis. The patient affected by multiple familial paragangliomas does not presently show any sign of recurrence or further localisation of the disease (Table I).

Discussion

Today it is possible to carry out a pre-operatory diagnosis as to the nature and size of the neoplasm by means of such imaging techniques as Ultrasonography, Computed Tomography and/or Magnetic Resonance mainly for diagnosis of site and extension, Angiography and Magnetic Resonance Angiography for a more accurate topographic evaluation and for diagnosis of the kind of tumour, even if only indicative. The search for multiple growths or metastases can be carried out by means of immunoscintigraphy with radioisotope markers (Meta Iodo Benzyl Guanidine and Octreotide, similar to Somatostatin)[5].

Besides biopsy and needle-biopsy to diagnose the kind of tumour, Fine-Needle Aspirated Biopsy (FNAB) has proved to be extremely efficacious. This technique, were feasible and if Computed Tomography or Magnetic Resonance guided, enables to take a cytological sample without the risk of lesions to

Table I.

	Age	Sex	Tumour(s)	Surgery	Complication(s)	FOD	Survival
G.P.	41 aa	male	left carotif body p.	resection	no	yes	25 years
F.L.	37 aa	female	right carotid body p.	resection + graft	no	yes	22 years
A.C.	35 aa	female	right carotid body p.	resection	no	yes	19 years
A.D.	39 aa	male	left carotid p.	resection	no	yes	11 years
G.F.	48 aa	male	right carotid p.	resection	no	yes	9 years
M.E.	42 aa	female	left carotid p.	resection	no	yes	8 years
B.G.	45 aa	female	left vagal p.	resection	recurrential palsy	yes	5 years
P.D.	37 aa	female	multicentric familial p.	resections (iterative)	recurrential palsy; transitory dysarthria	yes	3 years
M.F.	45 aa	female	left carotid body p.	resection	no	yes	3 years
A.M.	39 aa	female	left carotid body p.	resection	transitory right facial-brachial deficit	yes	2 years
G.D.	57 aa	female	retroperitoneal p.	laparotomy	no	no	18 months

the thick vascular network that characterises these neoplasm. On the other hand, owing to the limits of this sample-taking technique, to obtain accurate diagnostic data FNAB must be supported by immunohistochemical data.

The use of NSE immunohistochemical marker, Chromogranine and S-100 protein enables a more accurate diagnosis of the nature of the growth and, furthermore, to recognise fairly accurately the biological characteristic of the neoplasm[4]. This type of evaluation is extremely difficult if only the histological data are considered. Given the not-to-be underestimated aggressiveness of familial disease, early diagnosis of eventual recurrences and metastases is indispensable[9]. Familial paraganglioma is just like any other system disease; in fact, the presence of PGL (Predisposing Genetic Locus) is a high-risk factor for recurrence and new growths. Furthermore, it has been observed that the first signs of the neoplasm appear later at age twenty-thirty years, indicating a different growth rate of the tumoral mass. It is advisable to test other members of the same family for siblings possibly affected by malignant paraganglioma. They can only benefit from an early diagnosis of the disease. The technique used to identify the PGL is still difficult to put into the practice, also due to the fact that its position in the genome is not always the same. It does not seem justified to use this technique clinically except for specific cases. Follow-up of these patients must be at precise and short intervals.

There is some controversy over whether patients should periodically repeat the total-body immunoscintigraphy. It must be considered that, compared to the side effects of this technique, once eliminated the capturing areas formed by the clinically obvious neoplasms, it is able to identify very small growths and in region's difficult to investigate with conventional diagnostic systems. Moreover, the high degree of specificity eliminates any doubts as to the nature of eventual small growths such as a fibrous pulmonary nodules or small angiomas, shown up by the Computed Tomography or Magnetic Resonance and therefore to be suspect.

The elected treatment of paraganglioma is surgery. In carotid localisations it is often possible to perform a sub-adventitial dissection which enables preservation of the contiguous vascular ramifications. Were this is not possible, it is necessary to perform vascular resection followed by graft. The possibility of involving nerve ramifications, which happens only rarely, calls this type of surgery. Highly-selective peri-angiographic embolization of the neoplasm may be performed to limit in-surgery bleeding. We choose this technique for the patient affected by paraganglioma of the hypoglossal nerve because adhesions on the arteries in proximity of the base of the skull were presumed difficult to control during surgery performed via cervical approach. Good haemostatic control during dissection of the mass was achieved. Localisation along the cranial nerves determines a more or less evident neurological deficit.

The typical growth develops within the nerve fibres, dislocating, compressing and sometimes infiltrating them. Surgical removal of these tu-

mours must be performed according to oncological criteria, but also trying to preserve as much as possible the healthy nerve fibres around the site of the neoplasm. Sometimes, however, it is impossible to isolate the tumour from the nerve itself or the growth is so enlarged as to embrace nearby cranial nerves or it may extend beyond the cranial base through the foramina. In these cases up-stream and down-stream resection of the nerve may be necessary. Were feasible, the techniques of microsurgery enable to reconstruct the nerve fibres. With regards to retroperitoneal growths, the patient in our sample, who appeared to be in good health but was already inoperable, confirm the biological malignancy of this disease. Unless these tumours secrete enough catecholamines to determine evident symptoms, they remain silent for a long time until the mass compresses or infiltrates the nearby organs. Rarely do above-normal levels of catecholamines create the suspicion that there is a growth originating in the paraganglion. In most cases of retroperitoneal paraganglioma the rarity of the disease is such that the discovery of a silent retroperitoneal mass is usually due to some incidental factor.

Greater knowledge has not substantially modified the criteria of treatment. The probability of remission is undoubtedly linked to the amplitude of surgical act and so far the efficacy of supplementary treatment, in terms of survival, has not been proved. On the other hand, the last ten years have revealed the practical importance of advanced diagnostic techniques, both in the identification of genetic factors and in staging of the disease. The relatively limited number of cases of paraganglioma in cervical pathology does not allow exclusion of this possibility when conducting a differentiated diagnosis of an otherwise unspecified swelling on the side of the neck. This requires careful evaluation of site and nature, starting with an ordinary ultrasonography and, if the doubts are confirmed, proceeding with more sophisticated techniques.

Clearly other types of paraganglioma (cervical, mediastinal, retroperitoneal etc) require greater diagnostic effort for early diagnosis of the disease. In actual fact, recognition of one of these rare sporadic forms is possible only after exhaustive screening even using the most specific techniques and, in some cases, absolute certainty only comes after examination of the removed tissue.

In addition to highlights in the literature studies on familial forms have greatly improved our knowledge over the years and, together, make diagnosis of suspect familial disease easier.

We can even venture to say that any type of cervical, mediastinal or retroperitoneal swelling in persons belonging to a genetically prone family must be first of all considered a possible paraganglioma. For this reason the patient with more than one growth of this type, whether synchronous or not, must undergo genetic investigation, along with the rest of his family.

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