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 neoplasms 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 paraganglionic tissue deriving from stem cells of the Neural Crest1,2. 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 A P U D (Amine Precursor Uptake Decarboxylation) system which includes cells able to free nerve regulating substances4. 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 fibres5.

The different clinical symptoms caused by these tumours may be due to the secretion of catecholamines (functional tumours) or to growth and eventual localised infiltration2,4,5. However, they are generally slow-growth tumours and rarely develop into malignant ones6,7. 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 catecholamines5. 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 origin2.

The relationship with Multiple Endocrine Neoplasms (M E N) 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 system7,8.

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 parangangiomas and 41 for left vagal parangangioma. 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 E nolase) 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 recurrrental paralysis in a patient operated on for vagal paraganglioma; a recurrrental paralysis and temporary dysarthria in the patient affected by multiple familial paraganglioma and operated on both carotid bodies, vagus nerve and hypoglossum nerve. A nother 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-operative diagnosis as to the nature and size of the neoplasm by means of such imaging techniques as Ultrasoundony, Computed Tomography and/or M agnetic R esonance mainly for diagnosis of site and extension, A ngiography and M agnetic R esonance A ngiography 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 A spirated Biopsy (F NAB) has proved to be extremely efficacious. This technique, were feasible and if Computed Tomography or M agnetic R esonance guided, enables to take a cyto logical sample without the risk of lesions to
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 neoplasm4. 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 indispensable9. 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 insurgery 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 onco-
logical 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 en-
larged 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 mi-
crosurgery enable to reconstruct the nerve fi-
bres. 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 dis-
ease. Unless these tumours secrete enough
catecholamines to determine evident symp-
toms, 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 discov-
ery of a silent retroperitoneal mass is usually
due to some incidental factor.

Greater knowledge has not substantially
modified the criteria of treatment. The proba-
bility of remission is undoubtedly linked to the
amplitude of surgical act and so far the effica-
cy 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 genet-
ic factors and in staging of the disease. The rel-
atively limited number of cases of paragan-
glioma in cervical pathology does not allow
exclusion of this possibility when conducting a
differentiated diagnosis of an otherwise un-
specifed 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 dis-
ease. In actual fact, recognition of one of these
rare sporadic forms is possible only after exhaust-
ive screening even using the most specific tech-
niques and, in some cases, absolute certainty only
comes after examination of the removed tissue.

In addition to highlights in the literature stud-
ies 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 in-
vestigation, along with the rest of his family.

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