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The epidemiology of neuroendocrine tumours. The dimension of a problem, a problem of dimension

L'epidemiologia dei tumori neuroendocrini. La dimensione di un problema, un problema di dimensione

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Summary

Neuroendocrine tumours (NETs) are rare neoplasias with a clinical mean incidence of 1 case/100,000/year. On the basis of the numerous data gathered by our General Surgery Unit over the last 14 years, it is clear that the clinical and epidemiologic dimension of the problem related to NETs cannot be immediately assessed, on the one hand because there is a prevalence of asymptomatic tumours and, on the other, because, data on the clinical incidence of the disease are, in some cases, in contrast with those of *post-mortem* prevalence. A particularly sensitive factor derives from the clinicians' degree of knowledge about the issue and from the fact that neuroendocrine tumours, being rare, may arouse little interest in the scientific community, thus leading to an underestimation of the problem. Selective screening for some typical aspects of the symptomatic tumours may help to give a more realistic epidemiological picture. For this reason, it will be necessary in the future to exploit all possible resources, in order to obtain data which are more and more realistic and less and less approximate. Eur. J. Oncol., 10 (1), 55-62, 2005

Key words: **neuroendocrine tumours, carcinoid, epidemiology, screening, diarrhoea**

Riassunto

I tumori neuroendocrini (NETs) sono neoplasie rare con una incidenza clinica media pari a 1 caso/100.000/anno. Da numerosi dati raccolti dalla nostra Unità Operativa di Chirurgia Generale nel corso degli ultimi 14 anni, si può osservare che la dimensione clinica ed epidemiologica del problema NETs non si presta ad una valutazione immediata, da un lato per la preponderanza di tumori asintomatici, dall'altro perché i dati di incidenza clinica della malattia contrastano in alcuni casi con quelli di prevalenza autoptica. Un fattore particolarmente sensibile deriva dal grado di conoscenza del problema da parte del clinico e dal fatto che i tumori neuroendocrini, in quanto rari, possono destare scarso interesse da parte della comunità scientifica, col risultato di una sottostima del problema. Lo screening selettivo su alcuni aspetti che caratterizzano i tumori sintomatici potrebbe aiutare a dare una immagine epidemiologica più vicina alla realtà. Per tale motivo sarà necessario in futuro utilizzare tutte le risorse in nostro possesso allo scopo di ottenere dati sempre più realistici e sempre meno approssimativi. Eur. J. Oncol., 10 (1), 55-62, 2005

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Introduction

Neuroendocrine tumours (NETs) are hormonal neoplasias with a low incidence (approximately 1 case/ 100,000/year), commonly known as rare disorders.

In most cases, NETs are well-differentiated tumours associated with a low grade of malignancy and long survival, and they are often characterized by an unpredictable clinical course, due to the presence of disabling symptoms which are difficult to control (e.g. refractory chronic diarrhoea); relapses sometimes occur after long time.

On the contrary, in 20-30% of cases, NETs are advanced malignancies with metastases, primarily to the liver. In other cases, they are poorly differentiated tumours with an unfavourable short-term prognosis, being able to metastasize even to the skin.

NETs may be a sporadic condition or a familial disease diagnosed in patients belonging to families who are known to have hormonal disorders.

From 1990 to date, our General Surgery Unit has studied 151 cases of neuroendocrine gastroenteropancreatic tumour, 17 cases of bronchial carcinoid tumour, 10 cases of Merkel cell carcinoma, 6 cases of adrenal pheochromocytoma, 3 cases of medullary thyroid carcinoma, as well as NETs in other regions (soft tissues, paranasal sinuses, breast, paraganglions).

These findings have induced us to consider the epidemiologic aspects of NETs, since the large number of our case studies lets us suppose that epidemiologic relevance of these tumours has changed over the last ten years. One reason may be identified in the fact that our Unit has become a national benchmark for this disease over the years; but there have also been important technological developments, recorded over the last 15 years, both in nuclear medicine and radiological imaging, and in laboratory techniques, all of which have facilitated the diagnosis of these tumours. Another reason may be associated with the multifactorial origin (genetic and environmental) which may have caused an increase in the incidence of these tumours.

Based on these premises, we have thought it might be necessary to verify historical, epidemiologic, diagnostic and cultural criteria which may contribute to a correct quantification of NETs, in order to identify the basic tools which may demonstrate that this disease is less rare than expected.

Diffuse neuroendocrine system

More than 60 years ago, Feyrter[1] had postulated the presence of a diffuse neuroendocrine system, which might be affected by tumours with identical morphologic and secretory characteristics - the so-called "*helle zelle*" (cells endowed with a light cytoplasm) distributed throughout the human body - by reworking hypotheses which had been already suggested by Heidenhain in 1870 and then by Gosset and Masson in 1914[2] and Hamperl in 1932.

In the sixties, Pearse[3] also made his contribution to the classification of NETs, by identifying a system known with the acronym APUD (Amine Precursor Uptake and Decarboxylation), including cells with similar ultrastructural, cytochemical and metabolic characteristics, as well as with the same embryologic origin from the neural crest.

Refined chimerism tests, performed by Fontaine and Le Douarin[4], Le Dourain[5] and Andrews in the seventies, showed the presence of neuroendocrine cells having also an embryologic endodermal origin, thus confuting Pearse's concept of the APUD cell and extending the classification for this group of tumours.

More recently, tissue staining procedures, molecular biology techniques and the research on some specific cellular markers have enabled us to identify some important criteria for defining a neuroendocrine cell[6]:

- neuroendocrine cells produce a neurotransmitter, a neuromodulator or a neurohormone;
- these chemical agents, which are inside cytoplasmic vesicles, are released through exocytosis in response to external stimuli;
- neuroendocrine cells differ from nerve cells for the absence of axons and specialized nerve endings;
- many neuroendocrine cells express the same type of protein marker.

Thanks to these original ideas, the concept of the neuroendocrine cell has developed and changed over almost one Century, so that nowadays prostatic[7-10], ovarian[11, 12], testis[13], renal[14, 15], breast[16], thymic[17-19] and laryngeal[20-23] endocrine tumours may be discussed, without arousing great amazement. Moreover, the old barrier between what is endocrine and what is not may be removed, supporting a novel concept of the endocrine cell. This original idea poses new problems relating to its classification and epidemiology, and leads on to consider the dimensions of the problem related to NETs which, at this point, may be unlimited and certainly different from those conceived up to now.

Somatostatin and its analogues

In vivo research on receptors for somatostatin and its analogues has highlighted new useful elements to define the characteristics of neuroendocrine cells.

At the beginning of the nineties, Lamberts *et al* [24] demonstrated *in vivo* the presence of specific receptors

for analogues of somatostatin even on cells which were not closely related to the neuroendocrine system, using a labelled analogue (^{111}In pentetreotide)[24]. Lamberts made a personal reassessment of Feyrter's concept of a diffuse neuroendocrine system, in order to provide clinicians with a novel diagnostic and therapeutic instrument, but he also posed a new problem relating to the classification: do neuroendocrine cells share the same hormonal receptors? Or, is the presence of these receptors enough to define NETs in any case?

Sensitivity to ^{111}In pentetreotide is very high (75%) in breast carcinoma, whereas it is extremely high (85%) in infiltrating ductal carcinoma[25]. Small cell lung carcinoma has several characteristics in common with NETs, such as the tissue expression for Neuron Specific Enolase (NSE), chromogranin A and synaptophysin[26], as well as sensitivity and specificity to ^{111}In pentetreotide corresponding to 100% of cases[27]. The same can be said both for meningioma, which in some works in the literature[24, 28, 29], has shown high sensitivity to ^{111}In pentetreotide (100%), and for some lymphoproliferative disorders, whose sensitivity to ^{111}In pentetreotide ranges from 13% to 100% of cases[30-36].

The problem is becoming more complicated.

Epidemiology

By turning on the computer and connecting to one of the most famous scientific search engines (such as PubMed), it is possible to find a variety of items relating to NETs: approximately 50,000 just for therapy, more than 20,000 for surgery, and 10,000 for chemotherapy. It is the same both for scientific protocols created over the last 15 years, and for the large number of international meetings on this disease.

These figures indicate how the problem relating to NETs is being discussed in the literature and how the scientific community has realized the need for a better understanding of this issue.

These tumours are undoubtedly rare, based on published data about their incidence. In fact, the mean incidence of NETs is around 1 case/100,000/year[37-55] (Table 1).

However, a great discrepancy explaining clinicians' difficulty in diagnosing these tumours is observed, when comparing data of clinical incidence with those of *post-mortem* prevalence, estimated at 8.4 cases/100,000/year[56] and at 1,500 cases/100,000/year[57] in relation to carcinoids and to endocrine pancreatic tumours, respectively, although these results are not statistically comparable.

This is certainly due to the fact these tumours are asymptomatic (non functioning) in 80% of cases. And, even in the case of a symptom or a syndrome being distinctive of this disease (chronic diarrhoea is a typical example), clinicians are inclined to believe that the low frequency of these tumours may represent a good reason to exclude them *a priori* from diagnostic suppositions.

Table 1 - Clinical incidence and frequency of neuroendocrine tumours

Tumour	Incidence or frequency[a]
Midgut carcinoid	0.8-2.1/100,000/year
Gastric carcinoid	< 1% overall gastric tumours
Large bowel carcinoid	< 1% overall bowel tumours
Rectal carcinoid	1-2% overall rectal tumours
Pancreatic endocrine tumours	0.4/100,000/year
insulinoma	1/1,000,000/year
glucagonoma	0.2/1,000,000/year
gastrinoma	0.05-2/1,000,000/year
VIPoma	0.05-0.2/1,000,000/year
Typical bronchial carcinoid	2% overall lung tumours
Phaeochromocytoma	0.8/100,000/year
Medullary thyroid carcinoma	< 10% overall thyroid tumours
Merkel cell carcinoma	0.2/100,000/year

[a] Data on these tumours are very scarce. The Table provides the data which are available

In Italy, an important project, the GEP Project (data base on gastroenteropancreatic endocrine tumours) was carried out to verify the number of cases of digestive NETs in this country: it involved 45 centres located in 32 towns, it collected 470 cases from 1995 to 1998, including a retrospective analysis of appropriately documented cases since 1960[58, 59], and it was concluded in 1998 (fig. 1).

NETs have been proven to exist: it is necessary to learn how to detect them.

Laboratory

It is a well-known fact that the laboratory diagnosis of NETs is linked to the measurement of some plasma peptides and other markers, including NSE and chromogranin A, an acid protein that belongs to the family of granins.

Several studies suggest that the measurement of chromogranin A is very useful in patients with NETs – such as phaeochromocytoma, neuroblastoma, midgut carcinoid tumour and small cell lung tumour – with an increase in plasma values in 50-100% of cases.

It is a well known fact that the measurement of plasma chromogranin A in patients with NETs provides a consid-

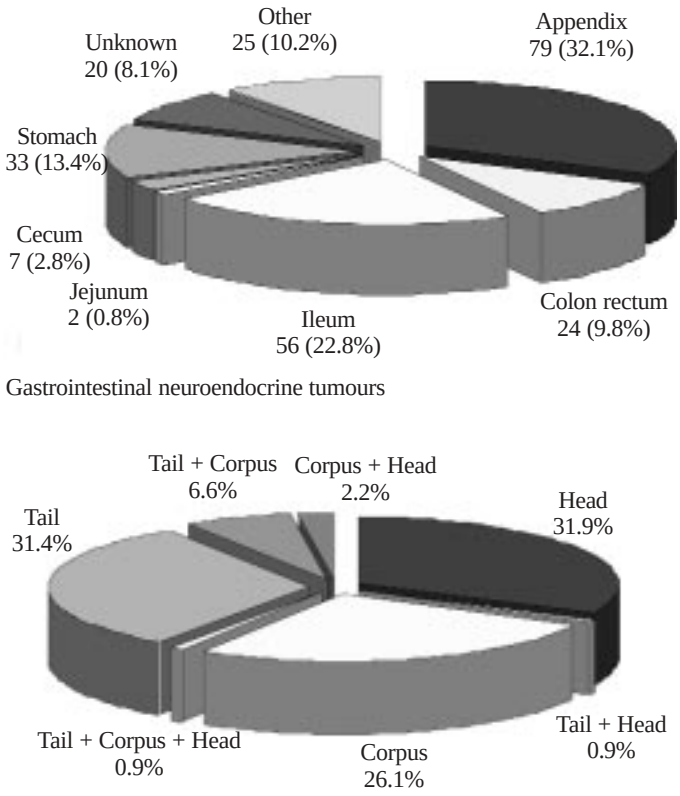

Fig. 1. GEP Project: frequency of digestive neuroendocrine tumours. From De Angelis *et al.*, 2002[58, 59], modified

erable diagnostic accuracy, with a sensitivity of 70-90% and specificity of 70-80%[60-71].

These findings have aroused interest in NETs and have contributed to further extend the epidemiologic dimension related to biology, evidencing high chromogranin A plasma levels even in tumours which are not usually considered as neuroendocrine disorders, such as prostatic tumour[72, 73].

Moreover, tissue immunohistochemical tests now allow a modern approach to the pathological diagnosis of NET, including the use of several parameters of evaluation, such as angioinvasivity, mitotic index, cell proliferation index (Ki67), and the expression of specific proteins, such as chromogranin A, NSE, synaptophysin and vimentin[74-82], which have enabled us to exceed the diagnostic limit imposed by the grading, increasing the number of new diagnoses and consequently modifying the epidemiologic dimension of the problem.

This issue becomes broader and more complicated, if considering the problem in relation to molecular biology, highlighting the hypothesis of genetic involvement not only for hereditary forms[83]. This fact has new implications for the classification. It will soon be necessary to revise the latest classifications for NETs, using new parameters of identification, and to recognize the ploidy status as a prognostic indicator[84].

Imaging

The technological developments in nuclear medicine and radiological imaging have allowed a better understanding of NETs, identifying an ever-increasing number of lesions and the subsequent escalation in their diagnosis[85-90].

The diagnostic approach with ^{111}In pentetreotide, having sometimes a higher sensitivity than the radiological one, has enabled us to change the clinical and therapeutic approach, so avoiding the surgical approach when unnecessary in a large proportion of cases (21-47% of cases) [91-94].

The recent development of diagnostic procedures, such as Positron Emission Tomography (PET)[95], along with X-ray imaging fusion, has allowed further improvement in the therapeutic approach to NETs in up to 30% of cases, extending the role of imaging in the diagnostics of these tumours[96-99].

A cultural dimension of the problem

In addition to explicit epidemiologic and classificatory aspects, there is also a cultural dimension of the problem related to NETs, which should not be underestimated and is related to the clinicians' degree of knowledge about this issue.

In fact, NETs belong to the group of rare neoplasias and, for this reason, they may be disregarded by clinicians, who are more involved in organisational and operating aspects related to more common neoplastic disorders.

Patients are often addressed to centres, where the knowledge of NETs is partial, and technological resources used for the diagnosis and opportunities to find a correct treatment are very limited. The presence of centres with a different degrees of experience has induced a great and constant drift of patients in search of certainty, both in terms of diagnosis and therapy. Moreover, in many cases, it is not easy for patients to obtain some certainty, compelling them to support an additional burden, not only in terms of expense[100].

This drift of patients represents another issue: the same subject may be included in several databases, thus creating subsequent problems related to the epidemiologic interpretation of data as well as an incorrect dimension of the problem.

Lastly, data dispersion prevents the collection of adequate samples, which are consequently poorly statistically significant.

New terms have been already included in the medical vocabulary, such as Diagnosis Related Groups (DRG), an instrument whose improper use may reduce the interest in NETs, since these types of tumour do not produce the benefits associated with more common oncologic diseases, thus underestimating the problem.

Screening for epidemiology

Screening for NETs may appear to make little sense. In fact, the high proportion of non-functioning cases prevents these tumours from being clinically recognized and, as previously stressed, despite the evidence of common symptoms associated with this disorder, such as chronic diarrhoea and relapsing peptic disease, there is no incentive to proceed with targeted investigations in most cases.

Taking for granted the relevance of screening for familial diseases, which has consolidated its own rationale of use[83] for long time, the question is whether to recognize screening as being useful for those symptoms (namely, gastritis, relapsing peptic disease and chronic diarrhoea) which may mask a hormonal neoplasm, as well as whether this fact may alter the epidemiologic dimension of NETs.

Gastrinoma is one of the most common and most investigated hormonal disorders[43, 101]. It is a well-known fact that peptic disease is usually observed in 93% of cases with Zollinger-Ellison syndrome[102]. The indiscriminate use of antisecretory agents (H_2 antagonists, protonic pump inhibitors) has led to the masking of early clinical manifestations[103], thus reducing the presence of peptic disease to just 18-25% of cases in recent studies[104] and extending, inevitably, the mean time between the onset of symptoms and the diagnosis of the disease by up to 6 years[105]. In our opinion, even if gastrinoma is only observed in 0.1-1% of all patients with peptic ulcer disease[106], the determination test of plasma gastrin level in all dyspeptic disorders may be extremely useful both for the early determination of hormone-related forms and for the correct assessment of the epidemiology of gastrinoma.

There are many forms of disease associated with chronic diarrhoea, as well as many NETs correlated with diarrhoeal events. In a small study, we enrolled diarrhoeic patients in order to verify how many of them really suffered from NETs. Patients were experiencing diarrhoeal events from at least 3-4 weeks (frequency: not less than 6 loose stools a day), and they were refractory to common antidiarrhoeal drugs. These patients underwent the determination test for plasma gastrin (a common marker of many neuroendocrine diseases), NSE and 5-HIAA urine level[107].

The findings from this study were not high (true-positive tests <3%), but confirm that early diagnosis of some functioning NETs allows resources to be saved, a better quality of life for patients to be ensured and, in terms of epidemiology, a more realistic dimension for the problem of NETs correlated with chronic diarrhoea to be defined.

Conclusions

The dimension of the issue relating to NETs has many aspects. The quantification of the problem cannot be immediately assessed, because there is a prevalence of asymptomatic tumours and data about the disease-related clinical incidence are in contrast with those of *post-mortem* prevalence in some cases. A particularly sensitive factor derives from the clinicians' degree of knowledge about the issue and from the fact that NETs, being rare, may arouse little interest in the scientific community, thus underestimating the problem.

Selective screening for some typical aspects of the symptomatic tumours may help to give a more realistic epidemiological picture.

NETs represent a current condition. It is therefore necessary to exploit all possible resources in order to obtain data which are more and more realistic, and less and less approximate.

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