

Paraneoplastic syndromes secondary to neuroendocrine tumours

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Abstract

Neuroendocrine tumours may be either benign or malignant tumours, and have the ability to synthesise and secrete biologically active substances characteristic of the cell of origin that can cause distinct clinical syndromes. The term 'paraneoplastic syndromes' (PNSs) is used to denote syndromes secondary to substances secreted from tumours not related to their specific organ or tissue of origin and/or production of autoantibodies against tumour cells; such syndromes are mainly associated with hormonal and neurological symptoms. Appreciation of the presence of such syndromes is important as clinical presentation, if not identified, may delay the diagnosis of the underlying neoplasia. Conversely, early recognition can allow for more rapid diagnosis, particularly as the coexistence of a neoplasm with a clinical or biochemical marker offers an additional determinant of tumour status/progression. PNSs can complicate the patient's clinical course, response to treatment, impact prognosis and even be confused as metastatic spread. Their diagnosis involves a multidisciplinary approach, and detailed endocrinological, neurological, radiological and histological studies are required. Correct diagnosis is essential as the treatment of choice will be different for each disorder, particularly in the case of malignant tumours; it is therefore important to develop appropriate means to correctly identify and localise these tumours. Clinical awareness and the incorporation into clinical practise of ¹¹¹In-octreotide scintigraphy, chromogranin A and other evolving biochemical marker measurement techniques have substantially contributed to the identification of patients harbouring such syndromes. Disease-specific medical therapies are mandatory in order to prevent recurrence and/or further tumour growth. Owing to their rarity, central registration of these syndromes is very helpful in order to be able to provide evidence-based diagnostic and therapeutic approaches.

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Introduction

Neuroendocrine tumours (NETs) are derived from cells that have the unique ability to synthesise, store and secrete a variety of metabolically active substances, peptides and amines, which can cause distinct clinical syndromes. These secretory products are characteristic of the tissue of origin, and such secretory tumours are denoted 'functioning' in order to be distinguished from tumours originating from NE cells not producing any substances associated with clear clinical syndromes. The latter tumours are termed 'non-functioning' and cause symptoms, along with functioning tumours, due to mass effects (Kaltsas *et al.*

2004b, Modlin *et al.* 2008), although they may in fact also be secretory without causing any well-described syndrome. The universal non-specific immunohistochemical markers, chromogranin A (CgA) and synaptophysin, have been used to substantiate the NE nature of these tumours, and in this context, tumours expressing these markers are regarded as NETs, and as such will be considered in the present review (Table 1). The recently introduced WHO and European Neuroendocrine Tumour Society (ENETS) classifications have identified NETs as either benign, unknown potential, well or poorly differentiated endocrine

Table 1 Tumours regarded as NETs on the basis of the immunohistochemical expression of markers of NE differentiation

CgA-positive neuroendocrine tumours by immunohistochemistry

Anterior pituitary tumours
NFPA
PRLoma (CgB positive)
GH
ACTH
TSH
FSH/LH
Parathyroid tumours
Medullary thyroid carcinoma
Merkel cell tumour
Neuroendocrine gastroenteropancreatic tumours (GEP tumours)
Carcinoids (foregut, midgut and hindgut)
ECL-oma
Non-functioning pancreatic neuroendocrine tumours
Gastrinoma
Insulinoma
VIP-oma
Glucagonoma
Somatostatinoma
Phaeochromocytoma
Paraganglioma
Neuroblastoma and ganglioneuroma
Small/large cell lung carcinoma

CgA, chromogranin A; NET, neuroendocrine tumours; NFPA, non-functioning pituitary adenoma; PRL, prolactin; CgB, chromogranin B; ECL, enterochromaffin-like.

carcinomas; all these histopathological entities have the ability to synthesise and secrete characteristic (of the cell of origin) biologically active products (Rindi et al. 2000, Modlin et al. 2008).

Patients with neoplastic, mostly malignant, tumours may occasionally present with symptoms that cannot be explained by the presence of the neoplastic lesion in a specific anatomic site or by a clinical syndrome attributed to a secretory product derived from the specific cell of origin (Keffer 1996). The term ‘paraneoplastic syndromes’ (PNSs) is used to denote an array of symptom complexes that are manifested systemically as the result of the production of hormones, growth factors, cytokines and/or other substances by the tumour cells (Baylin & Mendelsohn 1980, Agarwala 1996). A significant number of these syndromes are caused by the secretory products, mainly peptide hormones, of NE cells that are widely dispersed throughout the lung, gastrointestinal (GI) tract, pancreas, thyroid gland, adrenal medulla, skin, prostate and breast (Agarwala 1996, Modlin et al. 2008). The clinical manifestations of these ectopic hormonal secretion syndromes are similar to those caused when the secretory product is derived from the expected site of origin, eutopic hormonal secretion, and can cause diagnostic and therapeutic dilemmas (Keffer 1996; Fig. 1). Additionally, symptoms may result from autoantibodies produced against the tumour cells that may cross-react with a variety of normal cellular constituents (Agarwala 1996). The majority of such PNSs are associated with ectopic hormonal and neurological symptoms due to the production of autoantibodies against neurological tissues (Pierce 1993, Agarwala 1996, DeLellis & Xia 2003; Table 2). The overall prevalence is 15% of malignancies, mostly involving the lungs, GI system and breast (Pierce 1993,

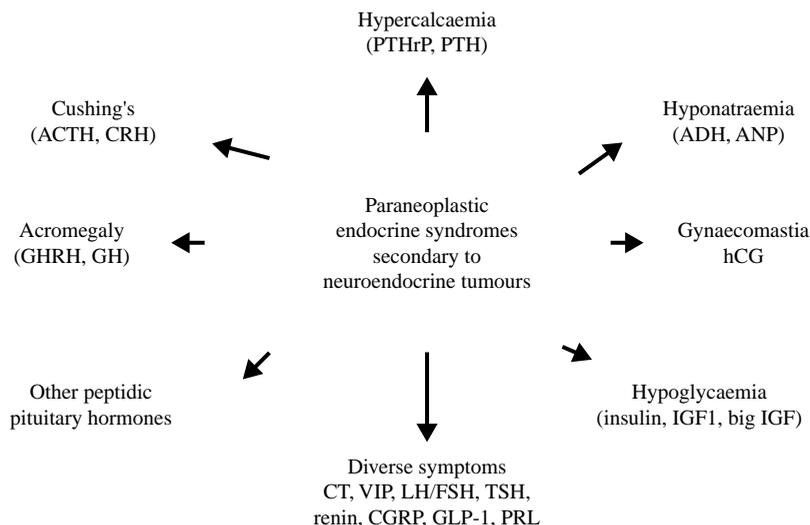


Figure 1 Spectrum of paraneoplastic humoral syndromes secondary to NETs. CT, calcitonin; PTHrP, parathyroid hormone related peptide; CGRP, calcitonin gene related peptide; GLP, glucagon like peptide; ANP, atrial natriuretic peptide; VIP, vasointestinal peptide.

Table 2 Pathophysiology of common NET-related paraneoplastic syndromes

Tumour production and secretion of biologically active peptide hormones → endocrine diseases
Tumour production of cytokines → fever, fatigue, weight loss and cachexia
Tumour stimulation of antibody formation → neurological syndromes

NET, neuroendocrine tumour.

Agarwala 1996, Bollanti *et al.* 2001). It is therefore critical to recognise the presence of a PNS as it may 1) lead to the diagnosis of an underlying, previously unsuspected neoplasm, 2) dominate the clinical picture and therefore be misleading in terms of tumour origin and type, and 3) be useful in following and monitoring the clinical course of the underlying disease (Pierce 1993, Bollanti *et al.* 2001).

Following the continuing rise in the prevalence of NETs, it is expected that the prevalence of PNSs related to such tumours will also rise (Modlin *et al.* 2008). However, to date, there has been no systemic documentation of the PNSs related to NETs. The body of literature and medical knowledge relevant to the PNSs secondary to NETs is widely dispersed, and has long been the subject of personal experience more than coordinated reports (Keffer 1996, Bollanti *et al.* 2001, DeLellis & Xia 2003). The emphasis is usually related to selected tumours or selected hormones, more rarely to other non-humoral PNSs, and the published literature is not fully inclusive or exclusive (Keffer 1996). Given the diversity of hormonal expression encountered in these syndromes, a practical and realistic approach employing screening with selective cost-effective identification of functional activity is required.

The scope of the current review is to record common and uncommon PNSs related to such tumours, provide information regarding their clinical presentation, natural history and overall prognosis, and to identify features that distinguish them from the eutopic hormonal secretion-related syndromes. A vigorous attempt has been made to include all possible distinct presentations; however, due to the numerous syndromes attributed to the secretory products of NETs, relevant review papers have also been included along with original descriptions. As the diagnosis and distinction of PNSs from syndromes related to eutopically secreted hormones are difficult and often require complex biochemical and imaging procedures, only consensus statements published from a number of medical societies dealing with these issues will be provided. Treatment of PNSs usually relates to that of

the underlying NET for which updated and consistent guidelines have recently been formulated (Falconi *et al.* 2006, Pacak *et al.* 2007, Ahlman *et al.* 2008, Eriksson *et al.* 2008, Kloos *et al.* 2009). Where specific PNS-directed therapy is required, this will be outlined.

Classification

Based on clinical presentation, the great majority of NET-related PNSs are classified as follows:

- 1) Humoral PNSs
- 2) Neurological PNSs
- 3) Other less common manifestations of PNSs.

Pathogenesis

The exact pathogenesis that leads to the development of these syndromes is not known. All cells in the human body contain the same genetic information, of which only a proportion is expressed under normal situations (Pierce 1993, Agarwala 1996). It is clear that neoplastic transformation is linked or caused by the activation of certain cellular events that control cell growth related to alterations of oncogenes, tumour suppressor genes and/or apoptotic mechanisms (Pierce 1993, Isidori *et al.* 2006). The same mechanisms that lead to neoplastic formation could also initiate PNSs, i.e. by activating hormone production, by changing the activity of genes that regulate the expression of genes involved in hormonal synthesis, or by antibody formation (Pierce 1993, Odell 1997, Bollanti *et al.* 2001). A still unsolved issue is whether the gene expression responsible for hormonal secretion leading to the ectopic hormone syndrome is switched on before or after the neoplastic transformation of the cell, and whether the cell of origin of the tumour has this 'ectopic' capacity intrinsically (Odell 1997; Table 2).

Humoral PNSs

Ectopically produced substances are mainly peptides or glycoproteins and extremely rarely steroids, biogenic amines or thyroid hormones. Occasionally malignant or inflammatory tissues may be capable of metabolising steroid or thyroid hormones, leading to an alteration in biological activity and causing distinct clinical syndromes (Pierce 1993). The humoral PNSs are produced by the direct secretion of these substances from a tumour arising from tissue other than the endocrine gland or tissue that normally produces them.

Table 3 Criteria for defining ectopic hormonal syndromes

Endocrine or metabolic disturbance in a patient with a NET
Remission after successful treatment
Return of endocrine syndrome with tumour recurrence
Abnormally regulated elevated hormone levels
Significant gradient between hormone concentration in the venous effluent from the tumour and arterial hormone levels
Extracts from tumour exhibit bio- and/or immunoreactive hormone
Relevant hormone mRNA can be identified in tumour tissue
Synthesis and secretion of relevant hormone by tumour cells <i>in vitro</i>

This view may not be strictly correct, as many of these substances can be produced in low quantities or inadequately processed forms in several tissues acting as paracrine signals or cytokines (Agarwala 1996, Odell 1997). However, the phrase ‘ectopic hormonal production’ leading to a PNS is used whenever these substances are secreted in such quantities that can be related to a clinical syndrome and be measurable (Agarwala 1996, Odell 1997; Table 2).

Since some of these PNSs can occur rather frequently, they constitute part of the differential diagnosis of many endocrine syndromes. A number of NETs are more frequently associated with ectopic hormone secretion; this is clinically relevant as secretory products can be used as tumour markers for either early detection or relapse of such a tumour, as well as for monitoring the response to treatment.

Neurological PNSs

These syndromes are secondary to antibody formation induced by the expression of immunoaccessible antigens by various neoplasms. When the neuronal tissue expresses antigens that are also recognised by the antibodies directed against the tumour antigens, characteristic neurological symptoms develop (Table 2).

Criteria for ectopic hormone production

There are several modes of secretion of bioactive tumour products, namely autocrine, paracrine and endocrine; however, only the endocrine type of secretion is associated with ectopic humoral PNSs (Table 3, Fig. 2). It is generally accepted that the term ectopic hormone production is employed whenever these substances are secreted from different tissues from the site of origin into the bloodstream where they can be measured in sufficient quantities that they cause clinical syndromes (Keffer 1996, Bollanti et al. 2001). The criteria for the latter comprise demonstration of the synthesis, storage and secretion of the particular compound by the tumour using *in situ* hybridization

to detect that substance’s mRNA and immunohistochemistry to demonstrate its protein presence in the tumour tissue (Pierce 1993). Furthermore, an arterio-venous gradient in the concentration of a substance or its release from cultured tumour cells provides additional evidence (Pierce 1993, Keffer 1996; Table 3, Fig. 2). In the presence of an ectopically secreted substance, its secretion is usually aberrantly regulated, as shown by the distinct responses to endocrine dynamic function testing (Pierce 1993, Keffer 1996, DeLellis & Xia 2003). Occasionally, a substance is synthesised and/or processed in a different way, and appears in the circulation in molecular forms that are distinct from the eutopically secreted substance (Pierce 1993, Keffer 1996, DeLellis & Xia 2003). Furthermore, successful tumour treatment leads to clinical remission of the syndrome, whereas tumour recurrence leads to reappearance of the syndrome; in parallel, these changes are accompanied by changes in hormonal levels (Keffer 1996, Bollanti et al. 2001).

Methods for diagnosing NET-related PNSs

Given the diversity of hormonal expression and neurological manifestation in these syndromes, a practical and realistic approach employing screening with selective cost-effective identification of functional activity is required. This task requires physicians to become familiar with the clinical presentation of PNSs, maintaining a high level of clinical suspicion, utilising specific imaging information and

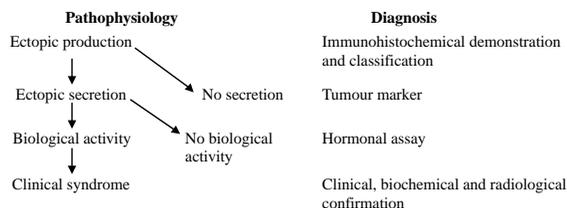


Figure 2 Pathophysiology and diagnosis of ectopic humoral syndromes.

measurement of serum markers, and finally performing a direct examination of the neoplastic cells. Over the last few decades, important advances in imaging modalities, namely scintigraphy with ^{111}In -labelled octreotide and serum estimation of the universal NET marker CgA, have contributed substantially to this field. Conventional imaging modalities such as computerised tomography (CT) and magnetic resonance imaging (MRI) are used for delineation of the anatomical localisation of the tumours (Fig. 3).

Octreotide scintigraphy

One of the most important characteristics of NE cells and NETs is the expression of various receptors on their cell surface, particularly somatostatin receptors (SSTRs; Lamberts *et al.* 1996). Although these receptors are not restricted only to NETs, scintigraphy with ^{111}In -labelled octreotide (Octreoscan) has offered a highly sensitive tool which, when used in the relevant clinical setting, identifies and localises the tumour in patients with NETs (Krenning *et al.* 1993, Olsen *et al.* 1995, Kaltsas *et al.* 2004a; Fig. 4). The Octreoscan achieves a sensitivity that ranges between 67 and 100%, depending on the tumour type, and can be used for the diagnosis, staging and follow-up of patients with NETs (Krenning *et al.* 1993, Kaltsas *et al.* 2004a,b); occasionally, false positive results have been reported (Kwekkeboom & Krenning 2002). A number of NETs may still not be identified with this technique, most probably due to their small tumour size or less expression of the relevant SSTR subtypes 2 and 5; ^{68}Ga coupled to octreotide or ^{64}Cu -TETA-octreotide have also recently been used as tracers for positron emission tomography (PET) scanning, and has demonstrated more lesions than ^{111}In -octreotide in patients with NETs (Hofland & Lamberts 2001).

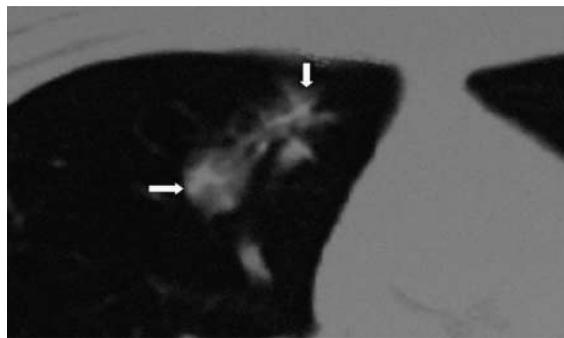


Figure 3 High-resolution CT scan of the chest in a patient with Cushing's syndrome due to ectopic ACTH secretion from a typical carcinoid tumour with surrounding atelectasis.



Figure 4 Octreoscan (scintigraphy with ^{111}In -octreoscan). Anterior view in a patient with Cushing's syndrome due to ectopic ACTH secretion revealing increased areas of uptake in the left upper lung, both clavicles and sternum, which proved to be metastases from an atypical bronchial carcinoid tumour.

Serum markers in NET (chromogranin measurements)

The various cell types of the NE cell system can secrete specific products, such as peptides and biogenic amines, which are tumour specific and may serve as markers for the diagnosis, prognosis and follow-up of treatment (Kaltsas *et al.* 2004b). A number of other compounds specific for all NE cells found within secretory granules or as cytosolic proteins can also be used as tumour markers that are applicable to all NETs; among these, the chromogranin family is the one most commonly used (Facer *et al.* 1985, Lamberts *et al.* 2001). Cgs A, B and C form a group of acidic monomeric soluble proteins that are localised within secretory granules, in which they are co-stored and co-secreted with the locally produced peptides (O'Connor & Deftos 1986, Eriksson *et al.* 2000, Baudin *et al.* 2001, Taupenot *et al.* 2003, Kaltsas *et al.* 2004b). CgA is the granin mostly used in clinical practice, although the other Cgs are relevant, particularly as CgA negative, but CgB positive, tumours are increasingly being recognised (Eriksson *et al.* 2000, Baudin *et al.* 2001, Kaltsas *et al.* 2004b). Plasma CgA is found to be elevated in a variety of NETs, including pheochromocytomas, paragangliomas, midgut 'carcinoids' and pancreatic islet cell tumours (PICT), medullary thyroid carcinomas (MTCs), parathyroid and pituitary adenomas, and at low levels in small cell lung carcinomas (SCLCs; Nobels *et al.* 1998, Kaltsas *et al.* 2004b, Vinik *et al.* 2009). Both tumour burden and secretory activity should be considered when interpreting CgA results, with a sensitivity and specificity that varies between 10–100 and 68–100% respectively (Nobels *et al.* 1998, Eriksson *et al.* 2000, Baudin *et al.* 2001, Kaltsas *et al.* 2004b). As CgA is found to be elevated in the great majority of NETs, elevated CgA levels in the absence of conditions that are associated with false positive results, such as renal

insufficiency and hypergastrinaemia (especially in response to antacid preparations, where levels can be remarkably elevated), constitute a useful indicator of the presence of a PNS in a relevant clinical setting (Baudin *et al.* 2001). Although CgA can also be used as a prognostic factor as it correlates with tumour burden, particularly in GI NETs, there is a lack of correlation between absolute CgA levels and symptom frequency and severity (Janson *et al.* 1997, Woltering *et al.* 2006). In the presence of uncertainty, the highly specific and sensitive pancreastatin assay can detect small tumour load, being up to 100-fold more sensitive and specific than CgA assays (O'Dorisio *et al.* 2010).

Specific antibodies for neurological PNSs

There are several autoantibodies that have been shown to be of diagnostic significance in neurological PNS. These will be discussed below.

Humoral PNSs in NET

Cushing's syndrome

The association between Cushing's syndrome (CS) and various cancers was recognised as early as 1928, but was first fully characterised by Liddle in 1965 (Table 4; Brown 1928, Wajchenberg *et al.* 1994, Keffer 1996, Bollanti *et al.* 2001). This PNS develops secondary to tumoral ACTH and less often CRH production, and accounts for 10–20% of the total cases of CS (Howlett *et al.* 1986, Newell-Price *et al.* 2006). Large amounts of biologically active ACTH are found in tumour tissue, although immunoreactive ACTH may also be found at high concentrations in tumour extracts from patients without clinical manifestations of CS (Howlett *et al.* 1986, Oldfield *et al.* 1991). ACTH is usually produced in its high-molecular weight precursor form, 'big-ACTH', and/or involves abnormal posttranslational processing of precursor peptides with different bioactivity (Stewart *et al.* 1994). Owing to excessive ACTH production, severe hypercortisolism may occasionally be induced (Newell-Price *et al.* 1998).

NETs associated with CS are often derived from the lung, thymus, pancreas, thyroid (MTC), chromaffin cell tumours (phaeochromocytomas, paragangliomas and neuroblastomas) and rarely from the ovary or prostate (Ilias *et al.* 2005, Isidori *et al.* 2006). Bronchial carcinoids (typical and atypical) account for 36–46% of these cases, whereas the highly malignant SCLC accounts for 8–20% of clinically

apparent cases (Limper *et al.* 1992, Newell-Price *et al.* 1998). However, up to 30% of SCLCs hypersecrete ACTH that may be bio-inactive following incomplete processing and thus not capable of inducing a clinical syndrome, or possibly the time course may be insufficiently long for the syndrome to be manifest (Limper *et al.* 1992, Newell-Price *et al.* 1998). Typically, bronchial carcinoids produce a clinical and biochemical syndrome that resembles pituitary-dependent CS (Cushing's disease, CD). In contrast, patients with CS secondary to SCLCs do not typically exhibit the classical manifestations of prolonged and sustained hypercortisolaemia but rather those of the underlying malignancy (Bollanti *et al.* 2001, Ilias *et al.* 2005, Isidori *et al.* 2006). Weight loss rather than weight gain, and slight changes in body fat distribution and hyperpigmentation constitute early reported symptoms/signs (Bollanti *et al.* 2001, Ilias *et al.* 2005, Isidori *et al.* 2006); due to excessive cortisol secretion, mineralocorticoid effects and glucose intolerance are often present in patients with SCLCs (Ilias *et al.* 2005, Isidori *et al.* 2006). In such cases, the diagnosis is readily suspected due to the rapid onset of symptoms, related to the degree of malignancy of the tumour, and is based on clinical, biochemical and radiological features (Newell-Price *et al.* 1998, Alwani *et al.* 2009). However, in cases of CS due to bronchial carcinoids where imaging does not immediately reveal the source, 'covert' CS, several endocrine tests may be necessary including inferior petrosal sinus sampling (IPSS) to exclude CD; as such tumours may be small and elude radiological detection, in ~8–19% of cases, medical or surgical control of hypercortisolaemia and prolonged follow-up may be necessary to establish the diagnosis (Oldfield *et al.* 1991, Kaltsas *et al.* 1998, Tsagarakis *et al.* 2003, Ilias *et al.* 2005, Isidori *et al.* 2006, Newell-Price *et al.* 2006). In some cases, the source may be hidden for many years or may never be revealed, so-called 'occult' CS. The incidence of CS secondary to MTCs is <1%, with ~100 cases being reported, whereas CS due to chromaffin cell tumours is even rarer with <30 reported cases (Barbosa *et al.* 2005, Nijhoff *et al.* 2009). Occasionally, cyclic or periodic production may render this diagnosis of the PNS extremely difficult (van Dam *et al.* 2002, Arnaldi *et al.* 2003).

Rarely, CS may result from CRH production from SCLCs, MTCs, carcinoids, PETs, chromaffin cell tumours or hypothalamic tumours (Upton & Amatruda 1971, Oldfield *et al.* 1991, Muller & von Werder 1992, DeLellis & Xia 2003, Markou *et al.* 2005); in many of these cases, tumours may produce both ACTH and CRH (DeLellis & Xia 2003, Zangeneh *et al.* 2003).

Table 4 Ectopic humoral syndromes secondary to NETs: differences in clinical, basal biochemical, endocrine function tests and radiological features in ectopic humoral paraneoplastic syndromes (PNSs) compared with the ectopically secreted substances

Syndrome	Mediator	Tumour	Features which distinguish PNS from ectopic syndromes		
			Clinical–biochemical	Endocrine testing	Radiological
Hypercalcaemia	PTHrP, PTH and growth factors/cytokines	SCLC PICT, carcinoid and pheochromocytoma	↑Ca, ↓P, } ↑cAMP urine	↓PTH ↑PTHrP ↑TGFβ, ↑IL, PG	(–) Parathyroid imaging, (+) lesion elsewhere, conventional imaging, (+) octreoscan [#]
Cushing's syndrome (CS)	ACTH and CRH	SCLC Carcinoid tumour PICT MTC Pheochromocytoma	Hypo-K, cachexia Cushing's phenotype Cushing's phenotype Cushing's phenotype Cushing's phenotype	↑ACTH (isoforms) CRH/DDAVP test	Normal pituitary MRI IPSS (–) Lesion elsewhere (+) Octreoscan (+) MIBG scan
Acromegaly	GHRH and GH	Carcinoid tumour PICT, carcinoid and pheochromocytoma	Acromegalic features Acromegalic features	↑GH, IGF1, failure to suppress GH on OGTT	Normal pituitary MRI Lesion elsewhere (+) Octreoscan
Hyponatraemia (SIADH)	ADH and ANP	SCLC	Hypo-Na, ↑plasma, ↓urine osmolarity	Water deprivation test	(+) Radiology (–) Octreoscan
Hypoglycaemia	Insulin IGF1 IGF2 (pro-IGF2)	Carcinoid tumour	Autonomic and neurological symptoms of hypoglycaemia	↑Insulin ↑IGF1, N pro-IGF2, ↑pro IGF2	Normal pancreas EUS Lesion elsewhere (+) Octreoscan
Other pituitary hormones	LH/FSH TSH PRL	PICT	Hyperandrogenism Hyperthyroidism Gynaecomastia ?	↑LH, androgens ↑fT ₄ , T ₃ , TSH ↑PRL	Normal pituitary MRI Lesion elsewhere (+) Octreoscan
Vasoactive peptides	CGRP CT	SCLC, PICT and pheochromocytoma	Vasodilation Hypotension ? Flushing	↑CT Ca/pentagastrin stimulation	(–) Thyroid imaging Lesion elsewhere (+) Octreoscan
Gynaecomastia, menstrual irregularity	hCG HPL	SCLC, PICT SCLC, pheochromocytoma	Gynaecomastia, menstrual irregularity and precocious puberty	↑Androgens ↑hCG	Normal adrenal, ovarian imaging Lesion elsewhere (+) Octreoscan
Hypertension	Renin	Paraganglioma and carcinoid	Malignant hypertension Hypokalemia alkalosis	↑Pro-renin, aldosterone	(+) Radiology (+) Octreoscan
Gut hormones	Ghrelin Gastrin VIP GLP-1,2	Carcinoid and PICT PICT PICT and pheochromocytoma PICT	Unknown clinical phenotype Zollinger–Ellison Pancreatic, cholera Hypoglycaemia?	↑Ghrelin ↑Gastrin ↑VIP	(+) Radiology (+) Octreoscan (+) Radiology (+) Octreoscan Endoscopy, EUS (+) Radiology (+) Octreoscan

PTH, parathyroid hormone; PTHrP, parathyroid hormone-related peptide; SCLC, small cell lung carcinoma; TGF, tumour growth factor; IL, interleukin; PG, prostaglandin; PICT, pancreatic islet cell tumour; DDAVP, desmopressin; MRI, magnetic resonance imaging; MTC, medullary thyroid carcinoma; MIBG, meta-iodo-benzyl-guanidine; ADH, vasopressin; ANP, atrial natriuretic peptide; hCG, chorionic gonadotrophin; IGF, insulin growth factor; CT, calcitonin; EUS, endoscopic ultrasound; VIP, vasointestinal peptide; fT₄, free thyroxine; T₃, triiodothyronine; HPL, human placenta lactogen; CGRP, calcitonin gene-related peptide; GLP, glucagon-like peptide; PRL, prolactin; N, normal. [#]usually negative in poorly differentiated tumours.

In such cases, patients have high CRH levels in plasma and tumour tissue, whereas plasma ACTH levels are also increased; CS due to CRH production does not have a distinctive presentation, and endocrine testing may represent an interplay between ectopic and eutopic production (DeLellis & Xia 2003, Zangeneh *et al.* 2003, Markou *et al.* 2005).

It has been suggested that no single endocrine test and/or imaging procedure are accurate enough to diagnose and localise ectopic ACTH/CRH-producing bronchial carcinoids, particularly as false positive IPSS results may occasionally be obtained, albeit very rarely (Young *et al.* 1998, de Herder & Lamberts 1999, Baudin *et al.* 2001, Loli *et al.* 2003). In such cases, scintigraphy with ¹¹¹In-octreotide, particularly after correction of hypercortisolaemia, and PET using several novel tracers can be used to reveal confounding cases eluding localisation (de Herder *et al.* 1994, Tsagarakis *et al.* 2003, Kaltsas *et al.* 2004b, Markou *et al.* 2005). The recent finding that dopamine receptors are expressed in NETs associated with CS, and that the dopamine agonist cabergoline could be effective in controlling cortisol excess in a subgroup of such patients, provides further medical therapeutic options to control the hypercortisolism while awaiting definitive diagnosis (Newell-Price *et al.* 2006, Pivonello *et al.* 2007). Mifepristone, an antagonist of both progesterone and glucocorticoid receptors, has also been used to control excessive hypercortisolaemia secondary to disseminated NETs (Cassier *et al.* 2008). However, as its effects can only be monitored clinically and it is associated with hypertension and hypokalaemia, its use is generally limited to the short term (Cassier *et al.* 2008).

Hypercalcaemia

Although humoral hypercalcaemia is one of the commonest of the PNSs, and ~5% of patients with malignant tumours may develop hypercalcaemia, it has not been commonly described in patients with NETs (Pierce 1993, DeLellis & Xia 2003). As the main secretory products of NETs are peptides or amines, almost all cases of NET-related hypercalcaemia are associated with hypophosphataemia suggesting a parathyroid hormone (PTH)-like effect, implicating as mediators either PTH or PTH-related protein (PTHrP; DeLellis & Xia 2003). PTHrP was first isolated in 1987 from cancer cell lines and a tumour associated with hypercalcaemia, and is now considered to be the main mediator of humoral hypercalcaemia of malignancy (Suva *et al.* 1987, Strewler 2000). PTHrP is present in a very wide variety of normal cells and tissues, and has a wide spectrum of functions;

hypomethylation of the promoter has been suggested as a possible underlying mechanism by which the gene is expressed (Strewler 2000). PTHrP has been shown to be secreted by NETs. The first case of a PTHrP-producing malignant NET was described in a pancreatic islet cell tumour presenting with severe hypercalcaemia during pregnancy (Abraham *et al.* 2002); however, benign pheochromocytomas can also secrete PTHrP and cause hypercalcaemia (Fukumoto *et al.* 1991). Several reports have now demonstrated either biochemical and/or immunohistochemical PTHrP-related hypercalcaemia in ~25 patients with PICTs (Mao *et al.* 1995, Srirajakanthan *et al.* 2009). The majority of these tumours are well-differentiated stage III–IV carcinomas, and this entity should be considered in the differential diagnosis of all patients with NETs presenting with hypercalcaemia and a disproportionately low PTH. In contrast to other PTHrP-secreting malignancies that have a mostly abysmal prognosis, patients with NET-related PTHrP secretion have a much better outcome (DeLellis & Xia 2003, Srirajakanthan *et al.* 2009). It is possible that the exact prevalence of PTHrP-secreting NETs may well be underestimated as the assay is difficult to perform, and may not always be requested (Srirajakanthan *et al.* 2009). Very few cases of ectopic PTH secretion from NETs have been documented, two from an SCLC and one from an MTC (Weiss *et al.* 2006, Demura *et al.* 2009). A further case secondary to a small cell carcinoma of the ovary has also been described; although hypercalcaemia is encountered in 70% of patients harbouring such tumours, almost all are secondary to PTHrP secretion (Chen *et al.* 2005). Furthermore, hypercalcaemia due to ectopic PTH secretion from a poorly differentiated pancreatic NET has been described, in which transactivation of the PTH gene was found (VanHouten *et al.* 2006). Interestingly, serum PTHrP was also elevated and detected immunohistochemically in the tumour specimen (VanHouten *et al.* 2006). Although successful treatment of the underlying neoplasm usually suffices to control the clinical symptoms and systemic sequelae of hypercalcaemia, in cases of severe, residual or recurrent disease, medical treatment of hypercalcaemia is also required (Makras & Papapoulos 2009).

Acromegaly

Acromegaly secondary to non-pituitary tumours is rare, and accounts for <1% of cases of acromegaly (Melmed 2006). This PNS is more commonly related to GHRH-hypersecretion and rarely to GH itself; however, its rarity may be related to the fact that

clinical presentation is usually subtle, and GHRH measurement is not widely available (Biermasz *et al.* 2007). NETs most commonly associated with GHRH hypersecretion are carcinoids, PICTs, SCLCs and pheochromocytomas, with ~70 cases having been described (Thorner *et al.* 1984, Faglia *et al.* 1992, Biermasz *et al.* 2007, Vieira *et al.* 2007). However, GHRH tumoral immunoreactivity without clinically obvious acromegaly is found in up to 17% of gastroenteropancreatic NETs (Dayal *et al.* 1986). Clinical presentation is not different to that of pituitary origin, although co-secretion of other substances by the tumour may increase clinical suspicion (Losa *et al.* 1993); endocrine testing does not reliably distinguish these tumours from pituitary adenomas (Biermasz *et al.* 2007). In contrast to the presence of pituitary adenomas in patients with classical acromegaly, the pituitary pathology in patients with ectopic GHRH secretion and acromegaly is GH-cell hyperplasia (except in patients with hypothalamic GHRH-producing tumours where adenomatous lesions may also be found; Sano *et al.* 1988, Biermasz *et al.* 2007). Only a few patients with GHRH-producing secondary to PICTs from patients with the multiple endocrine neoplasia-1 (MEN-1) syndrome have been described (Sano *et al.* 1987, Ramsay *et al.* 1988, Biermasz *et al.* 2007). A further two cases of ectopic GH secretion, one from a PICT, have also been described (Melmed *et al.* 1985, Beuschlein *et al.* 2000). Treatment is that of the underlying tumour, and relates to the extent of the disease; in GI NETs, long-acting somatostatin analogues can also be useful for the treatment of both the tumour and the PNS in the case of residual disease (Kaltsas *et al.* 2004b).

Ectopic vasopressin and atrial natriuretic peptide secretion

Vasopressin (ADH) is produced within the hypothalamus and stored in nerve terminals of the posterior pituitary and from a subset of normal pulmonary NE cells (Gainer & Wray 1992). Additional processing of ADH also occurs in SCLC cells that can also synthesise and secrete oxytocin (OXT) and its corresponding neurophysin; cosecretion of ADH and OXT may be related to linkage of encoding genes (Sausville *et al.* 1985). Both ADH and OXT exert autocrine/paracrine signalling activities, and have been implicated in the initiation and growth of SCLCs (Pequeux *et al.* 2002, DeLellis & Xia 2003). A syndrome of renal sodium loss and hyponatraemia resulting from inappropriate ADH secretion (SIADH) has been described since the 1950s (Schwartz *et al.* 1957). Although ADH levels are increased in up to 50% of patients with SCLCs, only

15% develop the syndrome; however, some patients exhibit abnormalities following water loading (Moses & Scheinman 1991). Increased plasma OXT levels occur in up to 20% of patients with SCLCs. (Moses & Scheinman 1991). Atrial natriuretic peptide (ANP) is a peptide synthesised from the cardiac atria that can cause natriuresis and hypotension (Kangawa *et al.* 1984, Marchioli & Graziano 1997). It has also been implicated in the development of some cases of hyponatraemia related to malignancy, and both ANP and ADH can be synthesised and produced contributing to the hyponatraemia by the same tumour cells (Shimizu *et al.* 1991); however, severe cases of hyponatraemia are more clearly associated with SIADH (Marchioli & Graziano 1997, DeLellis & Xia 2003). In contrast to the majority of chronic causes of hyponatraemia that may develop gradually and be relatively asymptomatic, hyponatraemia secondary to ectopic hormonal production can develop abruptly and be associated with severe symptoms (Adrogue & Madias 2000). Although there are no established guidelines for evaluating and treating such patients, the diagnosis is readily made by demonstrating a urinary osmolality that exceeds 100 mOsm/kg of water in the presence of low effective plasma osmolality in an euvoalaemic individual (Adrogue & Madias 2000). Treating the underlying neoplasm is the definitive means of correcting the hyponatraemia (Ellison & Berl 2007). In the absence of symptoms, gradual correction of the hyponatraemia is appropriate, and involves adequate solute intake and fluid restriction (Adrogue & Madias 2000, Ellison & Berl 2007). In the presence of symptoms, increasing serum sodium by 0.5–1 mmol/l per h for a total of 8 mmol/l during the first day may suffice to render the patient asymptomatic; this can be enhanced by promoting free-water excretion with furosemide (Ellison & Berl 2007). Alternatively, the management of SIADH may be enhanced by the recent introduction of the ‘vaptans’, ADH antagonists; however, the clinical experience with these agents remains limited (Ghali *et al.* 2006, Schrier *et al.* 2006).

Ectopic calcitonin

Elevated calcitonin levels are considered a valuable biochemical marker for both sporadic and familial forms of MTCs (Kloos *et al.* 2009). An elevated basal value >50 pg/ml, and/or a five- to tenfold peak following pentagastrin or calcium stimulation are both highly suggestive of an MTC (Kloos *et al.* 2009). However, in the majority of cases, such values are not associated with a secretory syndrome and, therefore, do not fulfil the prerequisites for a PNS

(DeLellis & Xia 2003). A number of other tumours have also been shown to exhibit plasma calcitonin immunoreactivity (Coombes *et al.* 1974). Several cases of PICTs and carcinoid tumours with elevated calcitonin levels associated with no clinical symptoms but causing diagnostic confusion have been described; such cases usually do not exhibit a calcitonin rise in response to pentagastrin or calcium stimulation (Engelbach *et al.* 1998, Schneider *et al.* 2009).

Human placental lactogen

Human placental lactogen is normally produced in the latter part of gestation, and stimulates the mammary gland, but has been shown to be secreted by SCLCs and pheochromocytoma; its secretion may be associated with gynaecomastia (Weintraub & Kadesky 1971).

Hypoglycaemia

Tumours not derived from pancreatic islets may produce recurrent fasting hypoglycaemia, a condition called non-islet cell tumour hypoglycaemia (NICTH; Seckl *et al.* 1999). In such cases, hypoglycaemia may be induced by substances that interfere with insulin metabolism (such as insulin receptor antibodies, cytokines, catecholamines and secretion of insulin-like growth factor 1, IGF1), and particularly by tumours that secrete partially processed precursors of IGF2. In the latter case, the IGF2 precursor is not cleaved, producing increased amounts of 'big IGF2' (molecular mass, 10–17 kDa, in contrast to mature IGF2 of 7.5 kDa), which cannot bind to its cognate-binding protein (Megyesi *et al.* 1974, Daughaday *et al.* 1993). Diagnosis is by measurement of the IGF2 isoforms, most easily by thin-layer chromatography. Big IGF2 impairs formation of a heterotrimeric 150 kDa IGF-binding protein complex in the circulation that binds the majority of IGFs (Daughaday & Trivedi 1992, Zapf *et al.* 1992, Seckl *et al.* 1999). Normally, IGFs are prevented from displaying their insulin-like potential by their sequestration in this large complex; however, this mechanism is impaired when big IGF2 is produced, and IGF bioavailability is increased leading to enhanced peripheral consumption and suppressed hepatic glucose production (Seckl *et al.* 1999, de Groot *et al.* 2007). The majority of tumours presenting with such a syndrome are tumours of mesenchymal or epithelial origin, but rare cases of NETs have also been described (Gorden *et al.* 1981, Daughaday *et al.* 1993, Marks & Teale 1998). Typically, serum insulin is low and serum GH levels

suppressed contributing further to hypoglycaemia; IGF1 levels are usually also low (Seckl *et al.* 1999, de Groot *et al.* 2007). The diagnosis should always be suspected in patients presenting with hypoglycaemic symptoms, particularly in the presence of a malignant tumour; acromegaloid skin changes have also been described in patients with NICTH (Marks & Teale 1998). As elevated serum levels of total IGF2 have been described in acromegalic patients, it is probable that prolonged activation of the IGF1 receptor by IGF2 can lead to these symptoms (de Groot *et al.* 2007). Although in almost half of all patients, hypoglycaemia was the initial symptom leading to the diagnosis of a tumour, this probably reflects the majority of mesenchymal and epithelial tumours and does not apply for the few NETs described to date (Marks & Teale 1998, Seckl *et al.* 1999, de Groot *et al.* 2007). Although big IGF2 is expressed in a broad spectrum of tumours and may act as an autocrine growth factor binding to the IGF2 receptor or the A isoform of the insulin receptor, it has not been established whether it stimulates tumour progression (Baserga *et al.* 2003).

Ectopic insulin

The possibility of hypoglycaemia due to insulin secretion from NICTs is controversial (Gorden *et al.* 1981, Furrer *et al.* 2001). Although primary hepatic carcinoid tumours are extremely rare, most probably reflecting tumours with unidentified primaries that have metastasised to the liver, a well-documented case has been described of a probable primary hepatic carcinoid that was manifest initially as extrapituitary acromegaly and a typical carcinoid syndrome, and later on as a hyperinsulinaemic hypoglycaemic syndrome (Furrer *et al.* 2001). The hepatic origin of hyperinsulinism was demonstrated by selective arterial calcium stimulation and insulin and C-peptide immunoreactivity by the tumour cell (Furrer *et al.* 2001). A further case of ectopic insulin production from an apparently primary ovarian carcinoid tumour associated with episodic hyperinsulinaemic hypoglycaemia has also been described (Morgello *et al.* 1988). The diagnosis was biochemically proven, and at autopsy, the ovarian tumour exhibited secretory granules on electron microscopy and insulin immunoreactivity on immunohistochemistry, while there was a suggestion that this developed in the context of MEN-1 syndrome (Morgello *et al.* 1988). Following that original report, a further case of an insulin-secreting NET of the cervix, and two paragangliomas, has also been described (Seckl *et al.* 1999, Uysal *et al.* 2007).

Ectopic IGF1

A rare case of a large cell lung carcinoma with recurrent hypoglycaemia, low insulin and big IGF2 levels, and increased IGF1 levels, has recently been described (Nauck *et al.* 2007). Although no acromegaloid features were found in that particular patient, hypoglycaemia did not recur and IGF1 levels decreased following successful treatment (Nauck *et al.* 2007).

Treatment relates to that of the underlying neoplasm, stage and grade of the disease. Patients with NICTH may undergo complete remission following surgical removal of the tumour; even partial removal often may reduce or abolish the hypoglycaemia (Marks & Teale 1998). This is followed by a rise in IGF1 levels, restoration of the IGF2/IGF1 ratio, blood glucose and plasma insulin levels (Perros *et al.* 1996, Marks & Teale 1998). Both hGH and prednisolone can induce a substantial and seemingly specific effect in alleviating the symptoms of hypoglycaemia (Mitchell *et al.* 1968, Teale *et al.* 1992, Perros *et al.* 1996). Although a therapeutic role of long-acting somatostatin analogues seems feasible, they should be used with caution as they may inhibit other counter-regulatory responses to hypoglycaemia hormones (Kaltsas *et al.* 2004b).

Other ectopic pituitary hormone secretion

Although extremely rare, a few cases of ectopic LH production from PICTs have been described (Brignardello *et al.* 2004, Piaditis *et al.* 2005). An interesting case was reported of ectopic bioactive LH production from a PICT in a woman presenting with symptoms/signs of hyperandrogenism and markedly elevated serum androgen and LH levels, leading to hyperthecosis and bilateral luteinised granulosa–thecal cell tumours of the ovaries (Piaditis *et al.* 2005). No definite case of ectopic TSH has been clearly described, although some anecdotal cases have been mentioned in the literature; ectopic TSH-secreting pituitary adenomas have occasionally been described (Bollanti *et al.* 2001, Pasquini *et al.* 2003). The paraneoplastic production of prolactin has been reported in association with SCLCs (Turkington 1971).

Ectopic secretion of other peptide hormones

Tumour-associated β -human chorionic gonadotrophin (hCG) production has been demonstrated in SCLCs and PICTs clinically associated with gynaecomastia in men, menstrual irregularity and virilisation in women, and precocious puberty in children (Braunstein *et al.*

1972, DeLellis & Xia 2003, Yaturu *et al.* 2003, Mehta *et al.* 2008). An hCG-like protein is also found in a variety of normal tissue, and there is evidence to suggest that the α -hCG subunit may exert a paracrine effect on the growth of tumour cells (Rivera *et al.* 1989), whereas β -hCG has been thought to act as a growth factor in SCLCs (Szturmowicz *et al.* 1995). An interesting case of a patient with an ovarian metastasis from an ACTH-producing carcinoid tumour and androgen hypersecretion by steroid-producing cells of the ovary has been described (Netea-Maier *et al.* 2006). It was thought that high ACTH levels induced androgen hypersecretion, which was gonadotrophin sensitive (Netea-Maier *et al.* 2006).

Ectopic renin secretion

This PNS is extremely rare, and only very few cases of renin hypersecretion related to NETs (SCLC, paraganglioma and carcinoid) have been described (Dayal *et al.* 1986). Clinically, these patients present with hypertension and hypokalaemia, whereas an increased ratio of pro-renin to renin is found due to inefficient processing of renin by the tumours (Leckie *et al.* 1994).

Ectopic gut hormonal and vasoactive peptide secretion

Clinical syndromes associated with the ectopic production of gut hormones by tumours are very rare, but vasoactive intestinal polypeptide (VIP) causing typical watery diarrhoea has been described (Said 1976). Tumours of the lung (SCLC), MTC, pheochromocytoma and NETs arising from the kidney have also been reported to produce VIP (Said & Faloona 1975, Tischler *et al.* 1984). Calcitonin gene related peptide (CGRP) is derived from the calcitonin gene as a result of alternative processing of calcitonin mRNA; this is widely distributed in the thyroid and neural tissues of brain, gut and perivascular tissue (Herrera *et al.* 1992), whereas VIP is the major product in the central and peripheral nervous system (Herrera *et al.* 1992). Both peptides are potent vasodilators, and may produce flushing and hypotension (Sundler *et al.* 1988, Herrera *et al.* 1992). Although the presence of peptide immunoreactivity is not always associated with clinical manifestations, several cases of pheochromocytomas presenting with flushing, hypotension or normal blood pressure plus excessive catecholamine secretion and elevated CGRP and/or VIP levels have been described (Fisher *et al.* 1987, Takami *et al.* 1990, Herrera *et al.* 1992). CGRP-producing NETs secrete

larger forms of calcitonin than MTC (DeLellis & Xia 2003). Although ectopic gastrin production from PETs lead to the characteristic Zollinger–Ellison syndrome, this clinical entity has traditionally not been considered as being truly ectopic.

Ghrelin is a 28-amino acid peptide that was first identified in rat stomach and is found abundantly in the human stomach with gradually decreasing amounts throughout the GI tract (Kojima *et al.* 1999, Gnanapavan *et al.* 2002). It acts through the GH-secretagogue receptors to strongly stimulate GH secretion, and plays a major role in energy balance by enhancing appetite and food intake (Howard *et al.* 1996). It has been found in excess in the serum of a patient with a PICT and a carcinoid of the stomach without obvious clinical symptoms and/or acromegaly features (Corbetta *et al.* 2003, Tsolakis *et al.* 2004). Gastrin-releasing peptide is present in highest concentration in SCLCs and, besides gastrin hypersecretion, may act as an autocrine growth factor (Cuttitta *et al.* 1985). Glucagon-like peptides (GLPs) 1 and 2 are derived from the post-translational processing of proglucagon in the intestinal L cells that influence intestinal motility and small bowel growth respectively; GLP-1 is also an insulinotropic hormone released in response to a meal that contributes significantly to glucose homeostasis (Baggio & Drucker 2004). Synthetic GLP-1 analogues and/or drugs that inhibit its degradation have recently been incorporated into the therapeutic algorithm of diabetes mellitus (Nauck 2004). A case of a GLP-1 and somatostatin-secreting NET has been described, presenting with reactive hypoglycaemia and hyperglycaemia subsequently cured by surgery (Todd *et al.* 2003). A further NET of unknown primary origin was described in a patient who presented with diffuse metastases, constipation and nocturnal itching; histology revealed a well-differentiated NET (Grade1), with positive immunostaining for CgA, GLP-1, GLP-2 and polypeptide YY (PYY). Jejunal biopsy demonstrated marked intestinal mucosal hypertrophy. HPLC analysis combined with RIA of tumour and serum extracts revealed that the tumour was producing and releasing GLP-1 and GLP-2, as well as PYY (Byrne *et al.* 2001).

Cytokines

There is increasing evidence indicating that several cytokines, particularly interleukin-6 (IL-6), can be secreted directly by NETs (Fukumoto *et al.* 1991). IL-6 plays an important role in the development of inflammatory reactions by stimulating the production

of acute phase proteins, such as C-reactive protein, serum amyloid and fibrinogen, while inhibiting albumin synthesis (Gauldie *et al.* 1987, Fukumoto *et al.* 1991). In addition, as IL-6 synthesis is induced by other cytokines, such as IL-1 and tumour necrosis factor- α (TNF α), and because the latter cytokines cannot directly stimulate acute phase proteins synthesis, it is likely that inflammatory reactions caused by these cytokines are mediated by IL-6. A PNS presenting with fever and increased acute phase proteins has been shown to be associated with elevated IL-6 levels (Dawson & Harding 1982, Yoshizaki *et al.* 1989, Fukumoto *et al.* 1991) and related tumours to secrete IL-6 (Tabibzadeh *et al.* 1989, Fukumoto *et al.* 1991). In this context, several patients with pheochromocytoma, pyrexia, marked inflammatory signs and elevated IL-6 levels have been described, in all of whom symptoms subsided by removal of the tumour; IL-6 expression was demonstrated in the tumours (Fukumoto *et al.* 1991, Suzuki *et al.* 1991). A case of co-secretion of ACTH and IL-6 has been described, implicating a stimulatory effect of IL-6 on ACTH secretion (Suzuki *et al.* 1991). Hypoglycaemia occurring in patients with metastatic disease has not been clearly defined and is usually attributed to liver infiltration and failure by the tumour (Teale & Marks 1998). An equally plausible explanation is that this could be mediated by various cytokines such as these that can be produced by NETs (Fitzpatrick *et al.* 1995).

Osteogenic (hypophosphataemic) osteomalacia

Osteogenic hypophosphataemic osteomalacia is a rare PNS with <100 cases reported (DiMeglio *et al.* 2000, DeLellis & Xia 2003). It is clinically manifest by muscle weakness and bone fractures secondary to decreased mineralisation of newly formed bone; the clinical and biochemical findings are of osteomalacia and marked hypophosphataemia, increased levels of alkaline phosphatase, and normal levels of calcium and PTH. The syndrome has been most commonly associated with mesenchymal tumours that abate following resection of the tumour (Weidner & Santa 1987, Terek & Nielsen 2001, DeLellis & Xia 2003). The mediator of oncogenic osteomalacia has been identified as fibroblast growth factor-23 (FGF-23); levels of FGF-23 mRNA and protein are overexpressed in such tumours, and serum levels are raised (Shimada *et al.* 2001, Terek & Nielsen 2001). Although to date there is no direct association of this PNS with NETs, its presence has for the most part not been actively sought.

Neurological PNSs of NET

Lambert–Eaton myasthenic syndrome

More than 50% of well-documented cases of Eaton–Lambert syndrome, an uncommon presynaptic neuromuscular junction disorder, have been reported in association with SCLC (Table 5; Marchioli & Graziano 1997). This PNS presents as subacute or chronic proximal muscle weakness, mainly of the pelvic and shoulder girdle muscles, and more rarely involvement of the cranial nerves, that may improve with movement; it has been estimated that the incidence of this syndrome may be as high as 3–6% in such patients (Deleu & De Geeter 1991, Marchioli & Graziano 1997). A very few cases of Lambert–Eaton myasthenic syndrome in association with atypical carcinoid tumours that remit following treatment have been described (Burns *et al.* 1999). It has been established that voltage-gated calcium channels, which function in the release of acetylcholine from presynaptic sites, particularly the P/Q-type, are the targets of antibodies produced in the presence of the tumour cells (Marchioli & Graziano 1997).

Paraneoplastic cerebellar degeneration

This PNS is rare, and usually presents as an ataxic gait, which may make the patient unable to walk (Brain & Wilkinson 1965). Other relevant symptoms such as loss of coordination, dysarthria and nystagmus may develop limiting ambulation, vision and coordination (Brain & Wilkinson 1965, Posner 1993). It has mainly been linked to SCLCs, and its pathogenesis relates to autoantibody-induced destruction of Purkinje cells (Posner 1993). Although occasionally patients may respond to treatment of the underlying disease and/or administration of i.v. immunoglobulin, the majority of cases suffer considerable deficits due to rapid cerebellar damage, unless the diagnosis is readily made and treatment started at an early stage (Marchioli & Graziano 1997). Very few cases of other non-SCLC

NET-related paraneoplastic cerebellar degeneration cases have been described (Balducci *et al.* 1999).

Limbic encephalitis

Limbic encephalitis (LE) is a multifocal inflammatory disorder characterised by personality changes, irritability, memory loss, seizures and, in some cases, dementia (Davis & Ravenel 2008). In more than 60% of cases, this occurs as a PNS predating the diagnosis of malignancy by an average of 3–5 months, and can be associated with a number of malignancies, the most common being SCLCs (Gultekin *et al.* 2000). In the majority of cases, it results from an autoimmune reaction to onconeural antigens including anti-neuronal nuclear antibody type 1 (anti-Hu) antibodies (SCLC) and anti-Ma2 antibodies (germ cell tumours; Gultekin *et al.* 2000, Davis & Ravenel 2008). Recently, a case of LE associated with a thymic carcinoid has been described (Davis & Ravenel 2008). While thymic carcinoid tumours may be clinically silent, they can also be associated with humoral PNSs, the most common being CS, whereas neurological PNSs are distinctly unusual (Davis & Ravenel 2008). In general, these tumours are relatively aggressive; about 80% of cases show aggressive behaviour with local or distant metastases, particularly in the presence of a PNS (Davis & Ravenel 2008).

Although peripheral neuropathy has commonly been the presenting or even preceding symptom in patients with neoplasms, it has not distinctively been described in patients with NETs. However, several authors have recently identified a series of antibodies reactive with neurons of the myenteric plexus in the sera of patients with paraneoplastic intestinal obstruction, defined as a syndrome of GI obstruction in the absence of mechanical blockage (Gerl *et al.* 1992). The presence of enteric neuronal autoantibodies (type 1 anti-neuronal nuclear antibodies; Lennon *et al.* 1991), along with other autoantibodies in such patients, suggests an autoimmune pathogenesis of the

Table 5 Neurological paraneoplastic syndromes related to NETs

Neurological PNS	Responsible Auto-Ab	NET
Lambert–Eaton myasthenic syndrome (LEMS)	Anti-voltage-gated calcium channels (P/Q type)	SCLC, carcinoid
Cerebellar degeneration	–	SCLC
Limbic encephalitis	Anti-Hu, anti-Ma2	SCLC, carcinoid
Visceral plexopathy	Type 1 anti-neuronal nuclear antibodies	SCLC
Cancer-associated retinopathy	Anti-23 kDa CAR antigen	SCLC
Autonomic dysfunction	–	SCLC, carcinoid

PNS, paraneoplastic syndromes; NET, neuroendocrine tumours; SCLC, small cell lung carcinoma.

paraneoplastic visceral neuropathy (Gerl *et al.* 1992). Chronic intestinal pseudo-obstruction has been recognised as a PNS in patients with SCLC and bronchial carcinoids (Lennon *et al.* 1991). Initial symptoms are mostly non-specific; they can occasionally mimic mechanical bowel obstruction and present as achalasia and/or constipation (Gerl *et al.* 1992, Marchioli & Graziano 1997). In such cases, exploratory laparotomy characteristically does not identify any macroscopic changes, although full thickness biopsy of the involved part of the gut allows the diagnosis of paraneoplastic visceral neuropathy (Gerl *et al.* 1992). In the few cases where an autoimmune process was considered treatment with steroids, immunosuppressive drugs or even plasmapheresis was not successful most probably due to irreversible damage of involved neurons (Gerl *et al.* 1992). The possibility of treating such patients with biological agents such as TNF inhibitors can also be considered, although experience is still limited (Vinik & Ziegler 2007). Alternatively, such syndromes could possibly be secondary to the ectopic production of opioid-like peptides (Pullan *et al.* 1980).

Other less common manifestations

The association of photoreceptor degeneration and SCLC, termed cancer-associated retinopathy (CAR), develops secondary to autoantibodies produced by malignant cells that react with a 23-kDa retinal antigen termed 23-kDa CAR antigen (Thirkill *et al.* 1993). Clinical findings include the triad of photosensitivity, ring scotomatous visual field loss, and attenuated arteriole calibre, that are usually evident long before the diagnosis of cancer is made (Thirkill *et al.* 1993). Treatment includes the use of steroids and treatment of the underlying malignancy (Marchioli & Graziano 1997). Cases of orthostatic hypotension secondary to autonomic dysfunction and nephrotic syndrome have also been reported in patients with SCLCs and carcinoid tumours (Becker *et al.* 1996, Marchioli & Graziano 1997, Luyckx *et al.* 2002). An unusual case of Quincke's oedema in a patient with long-standing carcinoid syndrome that improved following combined treatment with selective histamine-1 and -2 antagonists has been described (Wymenga *et al.* 1995).

Conclusions

The term PNS refers to the ability of some tumours to produce signs and symptoms at a distance from the site

of the primary tumour or metastases, and which may well develop before the tumour becomes apparent. NETs which are composed of multipotent cells, and that have the ability to synthesise and secrete biologically active compounds constitute a very common cause of humoral and less commonly neurological PNS; the latter develop as a result of autoantibodies elicited by malignant cells that cross-react with nerve cells leading to neurological sequelae. Although several secretory products, mainly peptides, can be detected in the plasma of many patients with NETs, clinically significant syndromes are less frequent. Current diagnostic tools, serum CgA measurement, and scintigraphy with ¹¹¹In-octerotide, are widely used to diagnose well-characterised NET-related PNSs, and identify others less well-described attributed to such tumours. Documentation and registration of these syndromes may be anticipated to increase tumour awareness and estimate their exact prevalence and associations with NETs. Current existing diagnostic and therapeutic guidelines may be employed for the management of PNSs and their secretory tumours.

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