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The Diagnosis of Neuroendocrine Tumours: An Endocrine Perspective

Nöroendokrin Tümörlerin Tanısına Endokrin Bakış

Mehtap Çakır, Ashley B. Grossman*

Kent Hospital, Division of Endocrinology, İzmir
*Emeritus Professor of Endocrinology, University of Oxford and Consultant NET Endocrinologist, NET Centre of Excellence, Royal Free Hospital, London

Abstract

Neuroendocrine tumours are functioning or non-functioning tumours which are derived from neuroendocrine cells scattered throughout the body. The clinical presentation of neuroendocrine tumours depends mainly on the site of the primary tumour and whether it is secretory in nature and thus causing specific symptoms. neuroendocrine tumour patients may be consulted in endocrinology outpatient clinics with complaints of flushing and sweating, hypoglycaemia, or due to ectopic hormone production-related symptoms, or may be referred from gastroenterology or general surgery units due to incidentally-found gastric neuroendocrine tumours, diabetes, pancreatic lesions, abdominal pain and/or diarrhoea. The current review will focus on presentation, symptomatology and diagnostic markers of tumours arising from the diffuse NE cell system, principally gastroenteropancreatic neuroendocrine tumours. The aim is to present a practical approach for the endocrinologist facing the large numbers of available laboratory tests, and will emphasise the relationship of these tumours with some genetic syndromes such as multiple endocrine neoplasia type 1 (MEN1).

Keywords: Neuroendocrine tumors; gastroenteropancreatic; carcinoid syndrome; ectopic; multiple endocrine neoplasia

Özet

Vücutta pek çok organ sistemi ve dokuya dağılmış olarak bulunan nöroendokrin hücrelerden köken alan, aktif hormon salgısı olan/olmayan tümörlere nöroendokrin tümörler adı verilmektedir. Nöroendokrin tümörlerin kliniğe başvurusu primer tümörün köken aldığı organa, hormon salgısı olmasında ve böylece hormona özel bulguların olup olmamasına göre değişmektedir. Nöroendokrin tümörü olan hastalar endokrinoloji polikliniklerinde yüz kızarması ve terleme atakları, hipoglisemi ya da salgılanan ektopik hormona bağlı bulgular ile görülebilmekte veya gastroenteroloji/genel cerrahi polikliniklerinden tesadüfen saptanan gastrik nöroendokrin tümör, diyabet, pankreas kitlesi ve/veya diyare ile konsülte edilebilmektedirler. Bu çalışmada, difüz nöroendokrin sistem kaynaklı tümörlerin ama özellikle gastroenteropankreatik nöroendokrin tümörlerin polikliniğe geliş şikâyetleri, bulgular ve laboratuvarda tanısal belirteçler anlatılmıştır. Amaç, sık görülmeyen bu hastalara tanı koyması en muhtemel uzman hekim olmakla birlikte, çok sayıda laboratuvar testi ile karşı karşıya olan endokrinologlara pratik bir yaklaşım sunmak ve bu tümörlerin bazı genetik sendromlarla, özellikle multipl endokrin neoplazi tip 1 (MEN1) ile olan bağlantısını vurgulamaktır.

Anahtar kelimeler: Nöroendokrin tümörler; gastroenteropankreatik; karsinoid sendrom; ektopik; multipl endokrin neoplazi

Introduction

Neuroendocrine tumours (NETs) are functioning or non-functioning tumours which are derived from neuroendocrine (NE) cells scattered throughout the body. NE cells can form glands (adenohypophysis, parathyroid, adrenal medulla, paraganglia) or may be found in a diffuse/disseminated way throughout the body in the skin, thyroid, lung, thymus, pancreas, gastrointestinal, biliary and urogenital tracts (1). NETs are capable of storing and secreting different peptides and amines, some of which may cause specific clinical syndromes. NET patients may be consulted in endocrinology outpatient clinics with complaints of flushing and sweating, hypoglycaemia, or due to ectopic hormone production-related symptoms, or may be referred from gastroenterology or general surgery units due to incidentally-found

Address for Correspondence: Mehtap Çakır, Kent Hospital, Division of Endocrinology, İzmir, Turkey
Phone: 00 90 232 398 11 00 **E-mail:** mehtapcakir@gmail.com **Received:** 08/02/2018 **Accepted:** 22/02/2018

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gastric NETs, diarrhoea, abdominal pain and/or pancreatic lesions. From this point of view, the current review will focus on the presentation, symptomatology and diagnostic markers of tumours arising from the diffuse NE cell system, principally gastroenteropancreatic neuroendocrine tumours (GEP-NETs). The aim is to present a practical approach for the endocrinologist facing the large numbers of available laboratory tests, and will emphasise the relationship of these tumours with some genetic syndromes such as multiple endocrine neoplasia type 1 (MEN1).

Epidemiology and Classification

NETs are rare tumours but their incidence and prevalence are increasing owing to increased diagnosis of early stage tumours, and possibly a true increase in incidence. According to a recent retrospective analyses of the SEER database from the USA, the age-adjusted annual incidence of NETs is 60-70 cases per million which indicates an 6.4 fold increase in rate between 1973 and 2012 (2). The prevalence of NETs, which was estimated to be 171,321 cases in 2014 in the USA, is higher than the combined 2013 estimates of other common gastrointestinal malignancies, including oesophageal cancer (36,857 patients), gastric adenocarcinoma (79,843 patients), and pancreatic adenocarcinoma (49,620 patients) (3). About two-thirds of NETs are GEP-NETs, mostly ariseing from the small intestine: small intestinal NETs are most frequently located in the distal ileum (4). On the other hand, as NE cells are distributed all around the body, there are many reports indicating diverse locations such as the sphenoid sinus (5), middle ear (6,7), renal pelvis (8), mediastinum (9), retroperitoneum (10), medulla spinalis (11), cavernous sinus (12), lymph nodes (13), fallopian tubes (14) and the parotid gland (15). NETs may be benign when small (usually <1 cm), but when malignant (representing less than 2% of gastrointestinal malignancies) they metastasise often before becoming symptomatic, generally when the tumour is larger than 2 cm. They frequently metastasise to regional lymph nodes, liver and less commonly to bone, although the latter site is becoming more obvious with newer imaging techniques. In terms of primary tumour site, unpredictable combinations occur such as thymic carcinoids to the myopericardium (16), gastrointestinal carcinoids to the orbit (17), bronchial carcinoids to the spinal cord (18), lung carcinoids to the choroid (19) or breast (20), and visceral carcinoids to the skin (21). However, it does seem that NETs have a general predisposition to metastasise to non-classic sites such as the myocardium, breast and eye. Essentially, histology strongly correlates with specific primary sites; in a registry database from the Netherlands, while grade 1 NETs mostly originate from the gastrointestinal tract, grade 2 NETs often originate from the lung (22), although there is much overlap. According to the SEER data the best prognosis has been reported for rectal and appendiceal carcinoids (often when small and discovered incidentally), and worst for pancreatic and lung NETs (2).

In terms of pathological diagnosis, it is important to ask for an immunohistochemical analysis of biopsy materials in order not to miss the diagnosis of a NET. Tumours may be labelled mistakenly as adenocarcinoma, which may affect the management and treatment protocol and patient prognosis. While there are a number of NE markers, chromogranin A (CgA) and synaptophysin are the principal ones used in diagnostic pathology (Figure 1). CgA is widely used as an immunohistochemical marker in NETs and is recognised as the most useful (23). Importantly, as synaptophysin can be examined in formalin-fixed tissues, it is possible to reevaluate the tumour if it is not considered neuroendocrine initially. The use of Neuron Specific Enolase (NSE) has been discouraged in a recent ENETS consensus guideline due to its low specificity (24).

There are a few proposed classification systems for NETs. Tumour behaviour, secretory patterns, and type of secretory products are similar between NETs of same embryological site. Based on this, NETs have been classified as (25):

Foregut NETs (bronchus, lung, thymus, oesophagus, stomach, liver, biliary system, pancreas, first portion of duodenum)

Midgut NETs (second portion of duodenum, jejunum, ileum, appendix, right colon, proximal transverse colon)

Hindgut NETs (distal transverse colon, left colon, rectum).

On the other hand, although this classification system was introduced both for ease of understanding and gaining a systematic approach to these rare tumours, because of the wide spectrum of their presentations and changing characteristics, neither diagnosis nor designation of a treatment algorithm is valid for all types of NETs. As an example, the molecular profiling of gastrointestinal NETs (GI-NETs) and pancreatic NETs

(pNETs) have demonstrated different genetic changes, such that these tumours should be regarded as different tumour entities and managed accordingly (26). Thus, the putative embryonic derivation is no longer used, and instead the newer World Health Organization (WHO) classification is used in addition to the standard TNM classification (27). Indeed, neuroendocrine neoplasms (NEN) are heterogeneous tumours now classified into fundamentally two groups: well-differentiated, low-proliferative NENs, called NETs, and poorly-differentiated, highly proliferative NENs, called small- or large-cell neuroendocrine carcinomas (NECs) (28). This dichotomy may be due to an origin from different progenitor cells. The latest WHO classification of gastrointestinal NENs uses the Ki-67 proliferation index to grade NETs as G1 (Ki-67<2%) or G2 (Ki-67 2-20%), and NECs as G3 (Ki-67>20%) (In the 2017 WHO nomenclature, it is suggested that the threshold for pNETs should be changed from 2% to 3%, but other NETs remain unchanged) (Figure 2). In the pancreas, NETs and NECs may overlap in their proliferation index, making the distinction between them difficult and leading to therapeutic uncertainties (28). Because of this, the 2017 WHO Classification of pancreatic NENs introduced a new NET G3 category: well-differentiated G3 tumours with a Ki-67 usually in the range 20-55% are referred to as G3 NETs, while poorly-differentiated G3 tumours with a Ki-67 >55-100% are to be referred to as G3 NECs. At present, this classification officially only applies to pancreatic NETs, but can probably be applied informally to all NETs (27).

Because NE cells can produce a number of hormonal peptides and neuroamines (29,30), another classification system for NETs may be based on secretory products. However, a NET may start as a silent tumour then become secretory, may co-secrete several hormones/amines (31), and on recurrence may secrete another product (32); even its metastases may secrete different peptides from the parent tumour. As a corollary, clinical symptoms and signs may

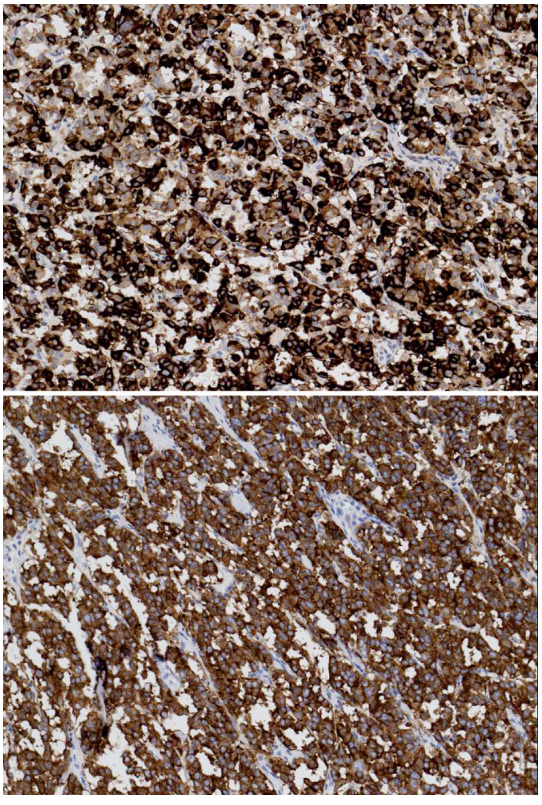

Figure 1: Chromogranin A (upper) and synaptophysin (lower) staining in a NET.

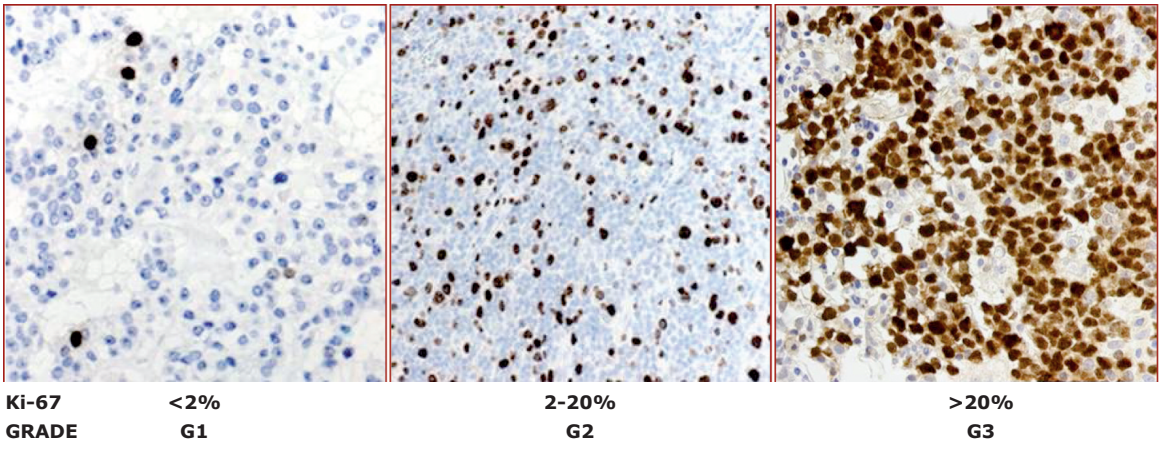

Figure 2: Grading gastrointestinal NETs using Ki-67 according to WHO (27).

change over time due to the secreted peptides (33). Additionally, NETs may secrete substances not related to their cell of origin, such as cytokines and autoantibodies which result in paraneoplastic syndromes (34,35). Although a few of the secreted compounds may be used more generally, there is no ideal NET marker, and the clinician needs to make a choice according to the clinical presentation keeping in mind that the sensitivity and specificity of serum levels differ for each marker.

The complexity and diversity of NETs make the diagnosis of these rare tumours quite difficult. But as mentioned above, although the clinician should expect the "unexpected", it is of utmost importance to take into consideration the rates and common locations of these tumours before starting laboratory tests and/or imaging studies to prevent useless costs. As an example, for a patient who presents with the carcinoid syndrome (CS), the diagnostic work-up should initially target the small intestine as hindgut NETs are generally silent and non-secretory. On the other hand, secretory pancreatic NETs are most commonly insulinomas, gastrinomas and PPomas, the remaining tumours comprising around 1% of pancreatic NETs. Thus, for a patient with a silent pancreatic mass without diabetes, it is not particulary helpful to start laboratory workup with plasma somatostatin and/or glucagon levels.

Clinical Presentation

The clinical presentation of NETs depend mainly on the site of the primary tumour and whether it is secretory in nature and thus causing specific symptoms. To present an overview of clinical presentation, tumour type and location, secreted hormones and diagnostic markers have been listed in detail in Table 1. Corresponding references have also been added not for common but for rare tumour locations and secretory products.

NETs are the most common gut endocrine tumours; while they comprise less than 2% of gastrointestinal malignancies, 71% of midgut NETs have metastatic disease at presentation (36). As the most common primary site is the small intestine, around one-third of patients present with many years' history of intermittent abdominal pain and vague abdominal symptoms (37), and are often misdiagnosed as 'irritable bowel syndrome'. NETs are slow-growing tumours and the patient may thus be followed as 'irritable bowel syndrome' for years (38). Additionally, NETs may present with symptoms due to CS (Table 2), ectopic hormone production, mechanical complications, or more rarely with paraneoplastic conditions.

Although once considered to occur in less than 10% of patients with NETs, in a recent population-based study from the SEER database excluding patients with pancreatic tumours, small and large cell lung cancers, the frequency of CS at NET diagnosis was reported as 19% (39). In this study, NETs presenting with CS were most commonly duodenal, jejunal or ileal in origin. Additionally, CS was significantly associated with tumour stage, grade and primary tumour site, and led to shorter overall survival.

CS occurs due to secretion of several vasoactive substances such as serotonin, histamine, tachykinins and prostaglandins by the tumour (Table 1). Symptoms of classic CS consist of flushing (occuring in 84%), diarrhoea (70%), abdominal cramping, carcinoid heart disease, telangiectasia, and bronchospasm presenting with wheezing (uncommon) (25,40). The relationship of flushing to diarrhoea is variable. Carcinoid heart disease, which mainly involves the right side of the heart, occurs in more than 50%, and is the initial presentation in 20% of patients with CS (41). Fibrous endocardial thickening occurs mainly in the tricuspid and pulmonary valves which may lead to regurgitation or stenosis (41). Left-sided valvular problems tend to occur when there is a patent foramen ovale. N-terminal pro-brain natriuretic peptide (NT-pro-BNP) is a valid marker in the clinical evaluation of carcinoid heart disease (23,42,43). Additionally, paraneoplastic neuropathy, myopathy, arthropathy, increased skin pigmentation, and peripheral oedema may occur (40). In CS the essential amino-acid tryptophan is mainly used as the precursor for serotonin, leaving inadequate amounts of tryptophan for conversion to niacin (Figure 3). Pellagra may develop due to deficiency of niacin (vitamin B3) with components of dermatitis, diarrhoea, dementia, stomatitis, glossitis and angular cheilitis (40,43). A patient with CS presenting with anaemia, urticaria and angioedema has also been described (44).

The extent and frequency of symptoms of CS vary and may change according to tumour location due to the difference in secreted products. It is important to note that, in midgut NETs, CS is only possible with hepatic metastases or peritoneal seeding as otherwise the secreted products will be catabolised by the liver (hepatic first-pass effect) (40,45). Additionally, midgut

Table 1. Symptoms, associated syndromes, secretory products and tumor locations of NETs with special emphasis on GEP-NETs *(Modified from Vinik AI & Chaya C. Hematol Oncol Clin N Am 2016;30:21-48)(40)*.

Clinical presentation	Syndrome	Tumor type	Tumor location	Mediator peptides and hormones	Diagnostic markers
Flushing	Carcinoid syndrome	NET	Foregut, midgut, rarely hindgut, pancreas, testes (109), presacral (110), pituitary (111)	Serotonin, prostaglandins, kinins, pro-gastrin-releasing peptide (112), VIP, calcitonin gene-related peptide, histamine (45), 5-HTP, substance P, neurotensin, motilin, neurokinin A, kallikrein, neuropeptide K, somatostatin, dopamine (38)	CgA, 24-hour urinary 5-HIAA
	MTC, C-cell hyperplasia	C-cell	Thyroid (38,113)	Calcitonin	Calcitonin
	Phaeochromocytoma/ paraganglioma	Chromaffin cell	Adrenal medulla, sympathetic nervous system	Adrenalin, noradrenalin, rarely dopamine	Plasma or 24-hour urinary metanephrines, normetanehrines, dopamine
Diarrhoea/abdominal pain, dyspepsia	Carcinoid syndrome	NET	Foregut, midgut, appendix (114), rarely hindgut, pancreas, testes (109), presacral (110)	As above	CgA, 24-hour urinary 5-HIAA
	Zollinger-Ellison syndrome (ZE)	Gastrinoma	Duodenum (70%), pancreas (25%), other sites (5%) (40,115)	Gastrin	CgA, gastrin, PP
	Pancreatic polypeptide	PPoma	Pancreas	PP	CgA, PP
	MTC NET	C-cell NET	Thyroid Lung (116), pancreas (116,117), stomach (116), appendix (116)	Calcitonin	Calcitonin
	WDHHA (Verner-Morrison syndrome)	VIPoma Secretinoma	Pancreas (90%, adult), other (10%, neural, phaeochromocytoma, periganglionic) (118-121) Pancreas (122)	VIP, neurotensin Secretin	CgA, VIP Secretin (tissue immunohistochemistry)
Wheezing, dermatitis, heart disease	Carcinoid syndrome	NET	Foregut, midgut, rarely hindgut, pancreas	Substance P, histamine, 5-HT (38)	CgA, 24-hour urinary 5-HIAA
Ulcer, dyspepsia, epigastric pain	ZE	Gastrinoma	Duodenum (70%), pancreas (25%), other sites (5%) (40,115)	Gastrin	CgA, gastrin, PP
Hypoglycaemia (123)	Whipple's triad	Insulinoma/ nesidioblastosis	Pancreas (~98%) Ectopic insulinoma (~2%)(124)	Insulin	Glucose, insulin, C-peptide
		Ectopic insulin secreting NET	Ovary (125), kidney (126), paraganglioma (127), liver (32), cervix NET (SCC) (128), bronchial carcinoid (129), appendix (114)	Insulin	Insulin
		Proinsulinoma	Pancreas (130)	Proinsulin	Proinsulin

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Clinical presentation	**Syndrome**	**Tumor type**	**Tumor location**	**Mediator peptides and hormones**	**Diagnostic markers**
	Non-islet cell tumour hypoglycemia (NICTH)	IGF2-oma	Gastric NET (131), bronchial carcinoid, phaeochromocytoma (132), pancreas (67)	Big IGF2	IGF2 isoforms (thin-layer chromatography) (29) (accompanying low insulin, GH and IGF-1)
		IGF1-oma	Large cell Ca of lung (133)	IGF-1	IGF-1
		GLP-1 secreting NET	Pancreas (68), ovary (134)	GLP-1	GLP-1
Silent pancreatic mass or diarrhea, liver metastases	Silent	PPoma	Pancreas	PP	CgA, PP
Diabetes, diarrhoea, steatorrhoea, cholelithiasis, deep vein thrombosis	Somatostatin	Somatostatinoma	Pancreas (55%), duodenum/ small intestine (44%) (40), kidney (135), ovary (136)	Somatostatin	CgA, somatostatin
		Phaeochromocytoma	Adrenal medulla (137)	Somatostatin, adrenalin, noradrenalin	Somatostatin, 24-hour urinary or plasma metanephrine, normetanephrine
		C-cell	Thyroid (138)	Somatostatin, calcitonin	Somatostatin, calcitonin
Diabetes, diarrhea, necrolytic migratory erythema, pellagra (somatitis, glossitis, angular cheilitis)	Glucagonoma	Glucagonoma NET	Pancreas Foregut, midgut, rarely hindgut, pancreas	Glucagon As above	CgA, glucagon CgA, 24-hour urinary 5-HIAA
Fever	With weight loss	All (especially pheochromacytoma)	All	Cytokines (IL-1, IL-6, TNF-α, IFN-γ)	
Acromegaly	Acromegaly	GHRH-secreting NET	Lung (54%), pancreas (30%), jejunum (7%), other (e.g.thymus) (13%) (40,139)	GHRH	GHRH, GH, IGF-1 (pituitary hyperplastic/normal on imaging)
		Phaeochromocytoma/ paraganglioma	Mediastinal paraganglioma (61), adrenal medulla (140)		
		GH-secreting NET	Pancreas (141), bronchial carcinoid (142)	GH	GH, IGF-1
		GH and IGF-1 secreting NET	Pulmonary carcinoid (52)	GH, IGF-1	

Table 1. Symptoms, associated syndromes, secretory products and tumor locations of NETs with special emphasis on GEP-NETs *(Modified from Vinik AI & Chaya C. Hematol Oncol Clin N Am 2016;30:21-48)(40) (continued)*.

Clinical presentation	**Syndrome**	**Tumor type**	**Tumor location**	**Mediator peptides and hormones**	**Diagnostic markers**
Cushing's syndrome	Cushing's syndrome	ACTH-secreting NET (50% of ectopic Cushing syndrome are due to lung) Phaeochromocytoma C-cell	Foregut (143), midgut, appendix (114), rectum (144), pancreas (59,60, 145-150), bladder, prostate SCC (151), ovary (152) Adrenal medulla (153) Thyroid (154)	ACTH	ACTH, midnight salivary cortisol, 24-hour urinary free cortisol, dynamic tests
		ACTH and/or CRH secreting NET C-cell	Thymus (155), Pancreas (156) Thyroid (157)	ACTH, CRH	
Anorexia, nausea, vomiting, abdominal pain	Hypercalcemia	PTHrP-oma Phaeochromocytoma	Pancreas (62, 158,159), thymus (160), liver (161), Phaeochromocytoma (162)	PTHrP	PTHrP
		PTH-oma	Lung (163), MTC (164), ovary (165), pancreas (166), neck NET (167), paraganglioma (168), gastric NET (169)	PTH	PTH
		1,25-dihydroxyvitamin D secreting NET	Pancreas (158, 170)	1,25-dihydroxyvitamin D	1,25-dihydroxyvitamin D
Weakness, lethargy, apathy	Hyponatremia, SIADH	ADH-secreting NET	Larynx (171), Lung (172), rectum (173), cervix (174), pancreas (175,176), prostate (177)	ADH	ADH
		ADH/ANP-secreting NET	Lung (178), thymus (54)	ADH and ANP	ADH and ANP
Hypertension	Severe hypertension	Phaeochromocytoma/ paraganglioma	Adrenal medulla Sympathetic nervous system	Adrenaline, noradrenaline, dopamine	Plasma or 24-hour urinary metanephrines, normetanehrines, dopamine
		NET Adrenal	Pancreas (66), bronchial carcinoid (179) Phaeochromocytoma (180)	Renin	Plasma renin activity, prorenin
Hyperandrogenism,virilization	LHoma	pNET	Pancreas (65)	LH	LH
Constipation		NET	Ovary (51)	Peptide YY	
			Unknown origin (181), intraabdominal mass (182)	GLP-1, GLP-2, peptide YY	
Ovarian hyperstimulation	FSHoma	NET	Mediastinal (183), pancreas (184)	FSH	FSH
Gastroparesis	Ghrelinoma	NET Pancreas	Stomach (185), presacral region (53) Pancreas (70,186)	Ghrelin	Ghrelin
Diarrhea, peptic ulcer, bile stone attacks	CCKoma	pNET	Pancreas (69)	CCK	CCK
Polycythemia		pNET	Pancreas (73)	Erythropoietin	Erythropoietin

Table 1. Symptoms, associated syndromes, secretory products and tumor locations of NETs with special emphasis on GEP-NETs *(Modified from Vinik AI & Chaya C. Hematol Oncol Clin N Am 2016;30:21-48)(40) (continued)*.

Clinical presentation	**Syndrome**	**Tumor type**	**Tumor location**	**Mediator peptides and hormones**	**Diagnostic markers**
Neurological / muscular paraneoplastic syndrome	Painful axonal polyradiculoneuropathy, autonomic neuropathy	Mostly SCLC	Lung (187,188)	CRMP5 (collapsin response-mediator protein-5)	
	Myopathy	NET	Lung (189)		
	Myasthenia gravis	NET	Lung (190), Small intestine (191), ileum (192), thymus (193)	AChR Ab (anti-acetylcholine receptor Ab)	
	Paraneoplastic cerebellar degeneration	Mostly SCLC, also NET	Oropharynx (194), stomach (195), pancreas (196), lung (197), thymus (198), midgut NET (199)	Anti-Yo Ab (Purkinje cell cytoplasmic Ab type 1-PCA1), Anti-Ri Ab (anti-neuronal nuclear Ab type 2-ANNA-2), anti-GAD Ab (glutamic acid decarboxylase Ab)	
	Limbic encephalitis	Mostly SCLC, NET	Pancreas (200), midgut (201), bronchus (199), thymus (202), lung (203), tonsil (204)	Anti-Ma2 Ab, anti-Hu Ab, anti-Ri Ab	
	Lambert-Eaton syndrome	Mostly SCLC, NET	Lung (205,206), oropharynx (194), larynx (171)	P/Q type voltage-gated calcium channel Ab	
	Autoimmune retinopathy	Mostly SCLC, NET	Lung (206), small bowel (35)	Antirecoverin Ab	
	Neuromyelitis optica spectrum disorder	NET	Stomach (34), small bowel (207)		
	Axonal Guillian-Barre-like syndrome	Mostly SCLC	Lung (208)		
	Sensory neuropathy	Mostly SCLC, NET	Lung (206), bronchus (199), duodenum (209)	Anti-Hu Ab	
	Visceral neuropathy (chronic gastrointestinal pseudoobstruction)	Mostly SCLC, NET	Lung (210), bronchial NET (211)	Anti-Hu Ab, Anti-CV2 Ab	
	Neuromyotonia, amyotrophic lateral sclerosis, multifocal hypertrophic mononeuropathy	SCLC	Lung (212-214)		
	Brainstem encephalitis	NET	Rectum (215)	Anti-Ri Ab	
	Paraneoplastic encephalomyelitis	NET	Lung (216)		
	Paraneoplastic neuropathy	NET	Cecum (217)		
Miscellaneous				HCG (218), CGRP (219), motilin (220,221), dopamine (64), neuropeptide K (222), neurotensin (72), neurokinin A (223)	

Table 2. Site of NET – CS relationship *[Modified from Halperin DM et al. Lancet 2017; 18: 525-534 (39)].*

SITE	WITH CS	WITHOUT CS
Appendix	2%	2%
Caecum	5%	3%
Colon or rectum	10%	17%
Lung, bronchus, larynx, trachea or other respiratory organ	13%	36%
Other	30%	22%
Duodenum, jejunum, or ileum	40%	19%

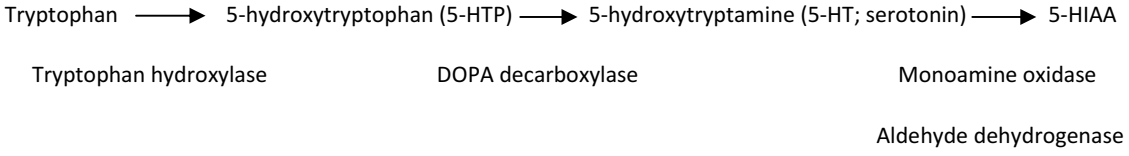

Figure 3: Serotonin metabolism.

NETs have a high 5-hydroxytryptamine (5-HT) content, rarely secrete 5-hydroxytryptophan (5-HTP), and may present with classic CS. However, for some foregut NETs (bronchus, lung, thymus, oesophagus) and gonadal NETs (ovarian and testicular carcinoids) the vasoactive substances can be released into the bloodstream before inactivation, and thus metastases are not essential for CS to occur (40,45,46,47). Foregut NETs have a low content of serotonin and often secrete the serotonin precursor 5-HTP and histamine (40). These differences also reflect in the clinical picture and diagnostic tests of midgut and foregut NETs (see below).

As a common presenting symptom of CS is flushing and these patients are seen in endocrinology outpatient clinics, it is often the endocrinologist who will consider NET as a preliminary diagnosis in these patients. In the work-up of the patient referred with a complaint of flushing, the endocrinologist should obtain a thorough history and perform a physical examination for the differential diagnosis (45,48). Firstly, the absence or presence of sweating should be asked for, as pathophysiology differs between "wet" and "dry" flushing; neurally-mediated flushing is frequently associated with sweating (wet flushing) which can be due to events at both central and peripheral sites, while isolated (dry) flushing is mainly due to circulating vasodilator substances (40,45,48). Additionally, associated symptoms during the attack and triggering events should be sought (emotions, food, alcohol), and importantly a careful drug history is mandatory as flushing can occur as a side effect of several drugs (Table 3). Four types of carcinoid flushing have been described; erythematous, violaceous, prolonged and bright-red (45). The flushing of foregut NETs are described as a bright-red "geographic" flush but bronchopulmonary carcinoids are associated with prolonged flushing lasting several hours to some days which may result in telengiectasia and hypertrophy of the skin of the face and neck (45). The face may take a leonine appearance resembling acromegaly after repeated episodes (40). On the other hand, the flushing of midgut tumours is erythematous, and involves the face and upper trunk down to the nipple line (40). Ileal NETs as part of a midgut syndrome seem to show a patchier and more violaceus flush. Flushing of CS may be spontaneous or triggered by certain foods rich in serotonin (blue cheese, sherry, beer, nuts, avocado, banana, fermented foods, chocolate, red wine, red sausage), alcohol, palpation of the liver, general anaesthesia, and increased adrenergic activity as occurs with pain, anger, embarrassment or exertion (45).

On the other hand, in post-menopausal flushing Tepper and colleagues have described four distinct trajectories which may well explain the spectrum of onset and frequency of symptoms seen in these patients; early onset (onset about eleven years before the final menstrual period with decline after menopause), late onset (onset near the final menstrual period with later decline), high frequency (onset early with persistently high frequency) and low frequency (persistently low frequency) (49). In phaeochromacytoma generally pallor occurs due to the pe-

Table 3. Differential diagnosis of flushing (45,48).

Carcinoid syndrome
Phaeochromocytoma, paraganglioma
Medullary thyroid cancer
Renal cell carcinoma (due to secretion of gonadotrophin-like hormones)
Systemic mastocytosis
Pancreatic NETs
Cushing's syndrome
Autonomic neuropathy
Post-menopausal hot flashes (80% of post-menopausal women)
Medical or surgical castration for prostatic cancer (more than 65% of men)
Malignant histiocytoma, neuroblastoma, ganglioneuroma (due to VIP secretion)
Anxiety, panic attacks
Simultaneous ingestion of alcohol and chlorpropamide
Drugs (nitroglycerine, nitro-derivatives, phosphodiesterase-5 inhibitors, calcium channel blockers-mainly dihydropyridine, cholinergic drugs, prostaglandin D2 and E, non-steroidal antiinflammatory drugs, nicotinic acid, vancomycine, rifampicin, cyclosporine, cisplatin, dacarbazine, TRH, bromocriptine, morphine, opioids, triamcinolone, metoclopramide, isoflurane, fentanyl, serotonin reuptake inhibitors-can cause night sweats, radiologic contrast agents)

ripheral vasoconstrictive affect of catecholamines but flushing may also rarely occur. In medullary thyroid carcinoma (MTC) the most prominent hormone-mediated symptom is secretory diarrhoea with or without flushing (48). In systemic mastocytosis, in addition to flushing pruritus, nausea, diarrhoea, abdominal pain and even vasodilatory shock may occur due to the release of mast cell mediators (45,50).

Table 1 summarises a number of secretory products and associated symptoms which will not be discussed here in detail. However, it may be important to note that, with the progress in both laboratory and imaging techniques in the last decades, there has been a noticeable increment in the discovery of secretory products and NET locations such as ovarian strumal carcinoid presenting with constipation due to peptide YY secretion (51), a GH and IGF-1 co-secreting pulmonary carcinoid (52), and a presacral 'ghrelinoma' causing gastroparesis (53). Patients may also present with acromegaly secondary to secretion of GH-releasing hormone (Table 1).

Mechanical complications in NETs may occur according to the location of the tumour. Obstructive pneumonia, dyspnoea and cough have been reported for bronchial NETs (54). Midgut NETs may cause obstruction in the small bowel but ischaemia may also occur due to mesenteric fibrosis and vessel compression even in the absence of an obvious mass (55). While hindgut NETs are generally silent tumours and rarely cause CS, they may present with bleeding, pain and intestinal obstruction.

In terms of paraneoplastic syndromes, a number of newly-defined neurological conditions and corresponding antibodies have been defined (Table 1), but there also are anecdotal case reports in which the mechanism of the paraneoplastic condition can not be readily explained such as a Budd-Chiari syndrome induced by a stage IV rectal carcinoid (56).

From another point of view, GEP-NETs may also be discovered as incidental masses detected at imaging or endoscopy in gastroenterology outpatient clinics, or with the irritable bowel syndrome-like symptoms. Among these, pNETs and gastric NETs will be mentioned here in detail, particularly because of their relationship with the MEN1 syndrome.

Pancreatic NETs

PNETs are divided into functional (10-30%) and non-functional groups (70-90%)(57). Non-functional pNETs are malignant in 60-90% of cases and CgA and pancreatic polypeptide (PP) levels are elevated (57). Insulinomas are the most common functional pNETs (58), and in decreasing order of frequency gastrinomas, glucagonomas, vasoactive intestinal peptide secreting-tumours

(VIPomas) and somatostatinomas may be seen (40). Rarely, other ectopic hormones are produced such as adrenocorticotropic hormone (ACTH) (59,60), growth hormone-releasing hormone (GHRH) (61), PTH-related peptide (PTHrP) (62) and serotonin (63). More rarely, dopamine (64), luteinising hormone (LH)(65), renin (66), insulin-like growth factor II (IGF-II)(67), glucagon-like peptide-1 (GLP-1)(68), cholecystokinin (CCK)(69), ghrelin (70), calcitonin (71), neurotensin (72) or erythropoietin (73) have all been reported. PNETs may be associated with four autosomal dominant disorders: MEN1 (seen in 30-80% of MEN1 patients in different series) (see below) (74), Von-Hippel Lindau disease (VHL) (seen in 11-17% of these patients), von Recklinghausen disease (neurofibromatosis type 1, seen in 10%) and occasionally tuberous sclerosis (40,75,76). Germline mutations in the VHL gene trigger overexpression of hypoxia-inducible factor (HIF) proteins and cause VHL disease characterised by various tumours and cysts, such as multiple phaeochromocytomas/paragangliomas, haemangioblastomas of the retina and central nervous system, kidney cysts, pancreatic cysts (50%) and NETs, renal cell carcinoma and polycythaemia (77,78).

Patients with insulinoma and non-insulinoma pancreatogenous hypoglycemia syndrome (NIPHS)/ nesidioblastosis may present with complaints of hypoglycaemia and are in large part seen in endocrinology outpatient clinics. As the cases of obesity and prediabetes have been on the rise, several patients experiencing postprandial hypoglycaemia quite frequently present nowadays. As opposed to postprandial hypoglycaemia, insulin-related hypoglycaemia classically occurs with fasting either early in the morning or may be exercise-induced (79), but in 5% of patients with insulinomas the hypoglycaemia may be purely post-prandial. Insulin-induced hypoglycaemia generally results in a combination of neurologic (diplopia, blurred vision, confusion, abnormal behaviour and amnesia, seizures, coma) and autonomic (sweating, weakness, hunger, tremor, nausea, feelings of warmth, anxiety, palpitations) symptoms, while post-prandial hypoglycemia is rarely associated with neurologic symptoms. However, importantly NIPHS patients usually present postprandially but with neuroglycopenic symptoms (within four hours of meal ingestion). NIPHS, which was previously quite rare, is now being seen more frequently as it is most commonly seen after gastric bypass surgery (40).

Patients with gastrinoma are generally seen in gastroenterology outpatient clinics due to epigastric pain, dyspepsia, reflux oesophagitis, recurrent ulcers and diarrhoea associated with steatorrhoea. Diarrhoea is due to the high gastric acidic content extending to the small intestine which precipitates bile salts, stimulates release of secretin and inactivates lipase, amylase and trypsin. Accordingly, diarrhoea generally improves with a proton pump inhibitor (PPI) or histamine-2 (H2) receptor blockers. More than 80% of gastrinomas arise within the triangle defined as the confluence of the cystic and common bile duct superiorly, the second and third portions of the duodenum inferiorly, and the neck and body of the pancreas medially. Rarely, primary tumours also occur in a variety of ectopic sites, including the jejunum (80), lymph nodes (81), heart (82), liver (83), omentum (84), common bile duct (84), and ovary (84). Duodenal wall gastrinomas have been identified in 40-50% of patients and are frequently small and multiple. Gastrinomas in patients with MEN1 tend to develop within the duodenal submucosa (70-100%) and 20-25% of these patients also develop type 2 gastric NETs due to gastrin stimulation (see below) (58,85). Sporadic tumours occurring in the pancreas tend to be solitary and have a greater malignant potential as compared to duodenal gastrinomas. The triad of non-beta islet cell tumours of the pancreas (gastrinomas), hypergastrinaemia and severe ulcer disease was described by Zollinger and Ellison in 1955, and named as the Zollinger-Ellison syndrome (ZES). Elevated fasting serum gastrin (FSG) levels (>1000 pg/mL), accompanying low gastric pH in a normocalcaemic patient with normal renal function, in the absence of fundic atrophic gastritis (which would elevate the gastric pH) or medication, confirms the diagnosis of ZES (23,40).

Patients with glucagonoma (previously called the Sweet syndrome) may be initially diagnosed by a dermatologist when evaluated for the typical rash (necrolytic migratory erythema) characterised by raised erythematous pathches beginning in the perineum and subsequently involving the trunk and extremities (40) (Figure 4). Although typical, this rash is not specific for glucagonoma and may occur with cirrhosis, pancreatitis and coeliac disease (38). Patients clinically have diabetes accompanied by the '4D' syndrome: dermatosis, depression, diarrhoea and deep vein thrombosis. VIPomas are also called pancreatic cholera or

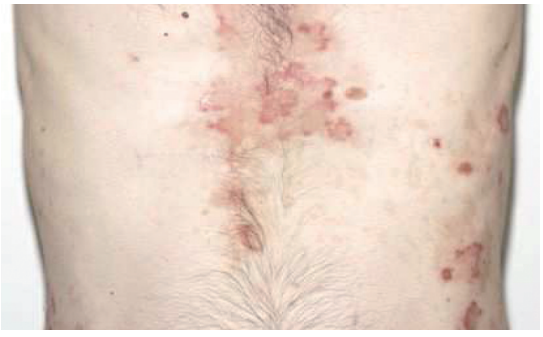

Figure 4: Necrolytic migratory erythema in a patient with glucagonoma.

WDHA (watery diarrhoea, hypokalaemia and achlorhydria) syndrome. VIPomas cause a large amount of stool (>700 mL/day), hypercalcaemia is frequent, and marked metabolic acidosis with bicarbonate and potassium wasting is characteristic of the VIPoma syndrome (40). As noted above, other endocrine causes of diarrhea include CS, MTC, C-cell hyperplasia syndrome, ZES or gastrinoma (38). Diarrhoea in NETs is always secretory, while diarrhoea from other gastrointestinal causes is usually malabsorptive (38). Thus, the key question to ask is whether the diarrhoea persists with fasting, thus clarifying its secretory nature. Importantly, diarrhoea may occur at night (38). Secretory diarrhoea may also be idiopathic or due to a secreting villous adenoma of the rectum or surreptitious laxative abuse (38). Although irritable bowel syndrome also causes abdominal pain and discomfort, it typically does not disturb sleep, and bleeding, fever, weight loss and persistent severe pain are not features of IBS. It should also be noted that the use of somatostatin analogues changes the character of the diarrhoea from secretory to malabsorptive statorrhoea in NETs (38). The stools become foul smelling, there is an inability to flush the toilet, and the stools float on the surface of the water and contain undigested food particles as somatostatin analogues cause inhibition of pancreatic enzyme secretion and intestinal absorbtion (38). However, even in patients with NETs one should always consider other possibilities such as short-bowel syndrome after surgery, bile salt malabsorption, or blind-loop syndrome with bacterial overgrowth.

Although a very rare tumour, patients with diabetes, diarrhoea, steatorrhoea, gallbladder disease and weight loss should raise suspicion of a somatostatinoma. Somatostatin inhibits the secretion of numerous hormones (insulin, PP, glucagon, gastrin, secretin, gastric inhibitory peptide-GIP, motilin) and peptides of endocrine and exocrine function, which leads to decreased gastric acid secretion, slowing of the gastrointestinal transit time, and malabsorption of fat and calcium (40). Somatostatinomas arising from the pancreas, intestine and extrapancreatic sites seem to differ both clinically and in terms of laboratory tests. Diabetes, gallbladder disease, diarrhoea, hypochlorhydria and weight loss are much more common in pancreatic-type compared to intestinal somatostatinomas (38). Mean somatostatin-like immunoreactivity (SLI) concentration in patients with pancreatic somatostatinoma is fifty times higher than normal, while intestinal tumours have only slightly elevated or normal SLI concentrations, which may explain the clinical difference(38). Patients presenting with massive gastrointestinal bleeding (86) and extreme hypoglycaemia (87) have also been reported. Recently, a new dyad/triad including somatostatinomas informally named the Pacak-Zhuang syndrome have been defined (78). The syndrome occurs due to somatic mutations in *HIF2A* affecting PHD hydroxylation and subsequent VHL degradation, and includes paraganglioma and/or somatostatinoma associated with polycythaemia (78). Duodenal somatostatinomas are also associated with neurofibromatosis type 1.

Gastric NETs

There are three types of gastric NETs: type I gastric NETs represent around 70-80% and are associated with chronic atrophic gastritis (85). Partial or complete atrophy of parietal cells lead to hypo- or achlorhydria. Through a feedback mechanism loss of gastric acid secretion results in gastrin (G) cell hyperplasia and hypergastrinaemia ensues. Gastrin is trophic to enterochromaffin-like (ECL) cells in the stomach, and especially at levels higher than 1000 pg/mL induces the development of small gastric NETs as polyps or tumours. Premature graying of the hair, anti-parietal cell or intrinsic factor antibodies, pernicious anemia and associated autoimmune conditions may be seen. Type II gastric NETs, comprising around 5-10%, develop from ECL cells in response to constitutively high gastrin levels from a gastrinoma, and are associated with ZES (85). Both type I and II gastric NETs are multifocal and primarily arise in the corpus (85). Type III gastric carcinoids, which are sporadic and solitary, represent approximately 10-15% of

lesions and have the highest risk of metastasis (85). They are not associated with hypergastrinaemia but an atypical CS due to histamine release may occur: extended episodes of flushing, headache, shortness of breath and lacrimation may be seen (rarely). The flushing may be deep purple and last for hours. It may be followed by increased blood flow to the limbs and trunk (40).

Multiple Endocrine Neoplasia Syndrome Type 1

MEN1 is an autosomal dominant disorder occuring due to mutations in the tumour suppressor gene *MEN1* which encodes a protein called menin. MEN1 is characterised by the occurence of parathyroid, pancreatic islet (NE) and anterior pituitary tumours. In a patient having any of these tumours, the other two organ systems should be checked by obtaining a careful medical history and additional laboratory workup. The incidence of MEN1 has been reported to be 1-18% in patients with primary hyperparathyroidism, 16-38% in patients with gastrinoma and less than 3% in patients with pituitary tumours (74). The diagnosis of MEN1 may be established by one of three criteria (74): (1) the development of tumours in two or more primary MEN1-associated endocrine organs [parathyroid adenoma (90-95%), enteropancreatic tumour (30-70%), pituitary adenoma (30-40%)], (2) the occurence of one of the MEN1-associated tumours in a first-degree relative of a patient with a clinical diagnosis of MEN1 (3), or identification of a germline MEN1 mutation in an individual who may be asymptomatic (74). It should be kept in mind that, although it is a familial disorder, genetic studies have shown that *de novo* MEN1 mutations comprise approximately 10% of MEN1 patients (88). In other words, it is possible that the identified patient (index case) may not have a family history regarding MEN1-associated tumours. MEN-1 associated pNETs present at an earlier age compared to patients without MEN1 (sporadic insulinomas generally present between 40 and 45 years while the mean age of gastrinomas is 48-55 years)(58), are multiple, and their behaviour is uncertain (74). In terms of enteropancreatic tumour subgroup rates, gastrinoma (40%), insulinoma (10%), nonfunctioning and PPoma (20-55%), glucagonoma (<1%) and VIPoma (<1%) may be seen. Some MEN1 patients may also develop adrenocortical tumours (40%), gastric NETs (10%), bronchopulmonary NETs (2%), thymic NETs (2%), meningiomas (8%), angiofibromas (85%), collagenomas (70%), lipomas (30%), and very rarely phaeochromocytomas (<1%) (74). However, these rates and differences in gender predisposition seem to change according to ethnicity. In association with MEN1, bronchial carcinoids occur predominantly in women, while thymic carcinoids occur predominantly in men (at least in Europe) (74,89). In a recent case series from China, the prevalence of thymic NETs was 7.4% in patients with MEN1, and 55% were in women (90). Compared to sporadic tumours of the same organ, MEN1-associated tumours may be larger, more aggressive and resistant to treatment. As parathyroid tumours are the most common feature of MEN1, patients presenting with primary hyperparathyroidism before the age of 30 years, or multigland hyperparathyroidism, should raise suspicion in terms of genetic predisposition. On the other hand, gastrinomas generally occur in patients who are older than 30 years and many insulinomas occur in patients younger than 20 years (74). Genetic screening is recommended for the index case who meet the clinical criteria of MEN1, who are suspicious for MEN1 (multiple parathyroid adenomas before the age of 40 years, recurrent hyperparathyroidism, gastrinoma or multiple pancreatic NETs at any age) or atypical for MEN1 (development of two nonclassical MEN1-associated tumours, e.g. parathyroid and adrenal tumour) and first-degree relatives of a MEN1 patient even if they are asymptomatic (74). Untreated, patients with MEN1-related endocrine tumours are associated with an earlier mortality. Thus, patients who are found to have MEN1 germline mutations should be screened at least annually for the development of MEN1-associated tumours. An algorithm for tumour screening in patients with known mutation can be found in detail in the guidelines by Thakker *et al.* which were published in 2012 (74).

How to Choose Relevant Laboratory Tests?

Most NE cells have secretory dense core granules. In the diagnosis of NETs both the stored secretory products (bioactive peptides or amines) and the capsular proteins (e.g. CgA) of these granules can be used as diagnostic markers. 5-hydroxy-indole acetic acid (5-HIAA) is the metabolite of serotonin which is formed by monoamine oxidases in the liver, lungs and brain (Figure 3). The biomarkers and/or hormones to be measured should be chosen according to the patient's presentation, symp-

toms, physical examination and preliminary diagnosis, as noted (Table 1). Currently-used biomarkers are CgA, urinary/plasma 5-HIAA, pancreastatin, PP, NSE, serotonin and neurokinin A (91) (see section below). However, biomarkers are insufficient to identify the primary tumour site so tissue confirmation is necessary for the diagnosis (40,91). For some of the hormones, a cause and effect relationship is clear and the hormone may be used both in diagnosis and follow-up. In others, biomarkers such as CgA need to be identified and used in conjunction with symptoms and imaging during follow-up. It should be noted that CgA is useful for follow-up but is relatively insensitive for diagnosis.

To adopt a problem-oriented approach may be easier if the patient is symptomatic. In terms of *endocrinology* referrals , the patient with a possible NET may be seen in endocrinology outpatient clinics due to two main symptoms, hypoglycaemia and flushing. Secondly, the patient may be referred on from a gastroenterology clinic due to a gastric NET or a pancreatic mass.

Hypoglycaemia

Obtaining a careful history will generally rule out insulin-related fasting hypoglycaemia. In a well patient with documented hypoglycaemia, inappropriate levels of insulin, C-peptide and pro-insulin will suggest either an insulinoma or factitious hypoglycaemia due to drug ingestion. Suppressed levels of insulin, C-peptide and pro-insulin during hypoglycaemia may indicate the presence of an IGF-II-secreting tumour. Post-oesophagectomy or post-bariatric surgery hypoglycaemia should be obvious from the history (40). Whipple's triad of hypoglycaemia comprises symptoms of hypoglycaemia, a documented plasma glucose level ≤40 mg/dL (2.2mmol/L) and relief of symptoms with administration of glucose. Recently published ENETS Consensus Guidelines recommend concomitant measurements of blood glucose ≤40 mg/dL and an insulin level >6 μU/L (or ≥3 μU/L by ICMA) (if available a β–hydroxybutyrate level ≤2.7 mmol/L will confirm inappropriate insulin release on fasting) during a hypoglycaemic episode to reveal a diagnosis of insulinoma without additional tests (23). According to the 2009 Endocrine Society Guidelines plasma glucose concentrations of glucose less than 55 mg/dL, insulin of at least 3 μU/mL, C-peptide of at least 0.6 ng/mL and proinsulin of at least 5 pmol/L documents endogenous hyperinsulinism (79). However, we consider this glucose threshold is too high and currently prefer the 40 mg/dL. Differential diagnosis includes other possible causes such as counter-regulatory hormone deficiency, autoimmune (insulin antibodies), drug-induced and factitious hypoglycaemia (38).

Flushing

It is also vital in a patient with flushing to obtain a good history, as mentioned in the clinical presentation section (Table 3). The laboratory work-up of unexplained flushing should basically include serum fasting CgA and 24-hour urinary 5-HIAA. If CS is excluded, 24-hour urinary metanephrine and normetanephrine, serum calcitonin, and serum total tryptase levels for systemic mastocytosis, should be measured. In general, total tryptase levels are greater than 20 ng/mL in systemic mastocytosis and this is a minor criterion in WHO diagnostic criteria for systemic mastocytosis (50). However, in cutaneous mastocytosis, monoclonal mast cell activation syndrome and systemic mastocytosis limited to bone marrow, tryptase values may be lower (45).

Patient referred from gastroenterology clinic

In gastroenterology clinics patients may be seen with symptoms such as dyspepsia, epigastric pain and/or diarrhoea. Furthermore, a gastric NET diagnosed in upper gastrointestinal endoscopy or a pancreatic mass detected on abdominal imaging may be the reason necessitating further laboratory work-up. In these instances the physician needs to choose necessary laboratory tests according to patient's history and coexisting symptoms. In gastric NETs, measurement of 5-HIAA levels is not recommended as CS is not common. Increased plasma CgA levels are seen in all gastric NETs, and may be used for follow-up and also have prognostic value in patients with metastatic disease. Fasting gastrin levels are elevated in both type I and type II gastric NETs, but there is hypo- or achlorhydria in type I and high acidity in type II gastric NETs. Thus, in a patient having clinical signs and symptoms of ZES, measurement of gastrin and gastric pH levels are necessary (92). As chronic PPI use also leads to high gastrin levels, PPIs must be withheld at least three weeks prior to measuring FSG and gastric pH level as a washout period, if this can be done safely (92). If the gastric pH is above 2 or, regardless of gastric pH, if the fasting gastrin level is normal, than ZES is ef-

fectively excluded. In subjects with low gastric pH and gastrin levels >1000 pg/mL then a gastrinoma is in most situations confirmed in the absence of medication (23), [some authors use gastric pH levels ≤2 with accompanying fasting gastrin levels >10x ULN (upper limit of normal) as a criteria] (92). However, in a recent prospective analysis up to two-thirds of gastrinoma patients were found to have gastrin values below 10-fold normal (93). If fasting gastrin levels are between 1-9.9xULN in a subject with gastric pH ≤2, than the gold standard approach is to perform a secretin test (23,92). Gastrinomas ectopically express secretin receptors and intravenous administration of secretin characteristically causes an exaggerated release of gastrin. Recent ENETS Consensus Guidelines recommend the secretin test for FSG levels between 200-1000 pg/mL, and explains the method of secretin test in detail (23). Gastrin levels also may be elevated in other conditions with hyperchlorhydria such as *H. pylori* infection, gastric outlet obstruction, renal failure, antral G cell syndromes, short bowel syndrome, and retained gastric antrum (23).

A pancreatic mass work-up needs to be done according to additional disease states and symptomatology (Table 1). For all masses CgA should be measured; with accompanying diarrhoea, duodenal ulcers or ZES, additionally fasting gastrin values, in diabetic patients with accompanying rash plasma glucagon levels, and in patients with severe watery diarrhoea plasma VIP levels (in VIPomas >200 pg/mL), may be added to CgA (25). The diagnosis of a glucagonoma requires demonstration of increased fasting plasma glucagon levels (generally 500-1000 pg/mL) accompanied by a typical clinical presentation (38). Glucagon values may be elevated in other conditions such as diabetes mellitus, burn injury, acute trauma, bacteraemia, cirrhosis, renal failure or Cushing's syndrome, but it is generally below 500 pg/mL (40). Although rare, it should be remembered that serotonin-secreting pancreatic NETs may also present with CS, and urinary 5-HIAA measurement in pancreatic masses may be helpful in this small group of subjects. In a recent study evaluating the incidence and prognostic value of serotonin secretion in 255 patients with pNETs, 0.8% were diagnosed with CS and 7.8% had a serotonin-secreting pNET without symptoms (63). In the literature somatostatinomas are usually diagnosed incidentally and the events leading to the diagnosis usually occured in reverse order (38). However, in a patient with a pancreatic or duodenal mass, a combination of diabetes, gallbladder disorder and unexplained steatorrhoea may be a sign of the tumour and plasma somatostatin levels may be measured.

For foregut or hindgut NETs and pNETs that do not secrete serotonin, 5-HIAA is not as useful as a marker compared to CgA in terms of diagnosis, evaluating possible progression and treatment response (38). In patients with foregut NETs the urine contains relatively little amounts of 5-HIAA but large amounts of 5-HTP. It is presumed that these tumours are deficient in dopa-decarboxylase which impairs the conversion of 5-HTP into 5-HT. CgA is positive 80-100% in foregut, midgut and hindgut tumours whereas 5-HIAA detects only 30% of foregut and around 70% of midgut tumours, but fails to recognise the presence of a hindgut tumour.

Biochemical Markers

Thus, the two critical biomarkers are CgA and 5-HIAA. As all laboratory measurements, NET-related biomarkers have their own limitations. CgA, the most important biomarker, is secreted from NETs including foregut, midgut, hindgut gastrointestinal NETs, phaeochromocytomas, neuroblastomas, MTC, some pituitary tumours, functioning and non-functioning pNETs and other NETs (23). However, the sensitivity of CgA is moderate while its specificity is dependent on primary site, grade and status of disease (91,94). CgA is almost universally elevated in patients with gastrinomas, and is often high in midgut NETs and non-functioning pNETs (23). CgA values do not correlate with symptoms but may correlate with tumour type and burden; thus, small tumours may present with normal values while significantly higher levels are found in NET patients with liver metastases, with the highest levels in patients with functioning ileal NET and CS (95,96). There are several available immunoassays for CgA, but with a high level of variability between CgA kits and international standardisation is lacking (91). Individual CgA immunoassays tend to be poorly correlated with each other, making inter-assay assessments difficult (97). In a prospective analysis CgA was underlined as a practical marker in patients with NETs with limited diagnostic power (98). Using ROC curves, a cut-off of 53 ng/mL for IRMA and 16 U/L for ELISA for discriminating between

healthy controls and NET patients yielded moderate sensitivities (71.3% and 83%, respectively) and specificities (71% and 85%, respectively) (98). False-positive CgA due to heterophile antibodies (HAb) which can bind to animal antigens has also been reported, and may be present in up to 40% of the normal population (98). In the CgA immunometric assays HAb interference may be obviated by using HAb-blocking tube (100). CgA needs to be measured under fasting conditions in the morning in plasma or serum and ideally in the same laboratory with the same assay. As CgA is expressed in healthy tissue as well, several neoplastic and non-neoplastic factors may cause elevated CgA levels, but very high levels are rarely found outside the setting of NETs with the exception of gastric acid secretory therapy or those with hypergastrinaemia (Table 4) (4,23,91). PPI therapy may increase CgA concentration just five days after its first intake (45). If the patient is on PPI treatment, measurement needs to be made at least two weeks after stopping the drug and possibly three weeks is the safest (leaving a clearance of at least 3 half-lives, e.g. the half-live of lansoprazole is 12.9 hs and pantoprazole is 45.9 hs) (23,45,92). However, in a patient with a high likelihood of gastrinoma such omission of therapy may be life-threatening and anti-acid therapy and H2-receptor antagonist treatment may be commenced. In this situation measurement can be made after these periods but discontinuing H2-receptor treatment for at least 24 hours (45). It should be kept in mind that somatostatin analogues decrease CgA levels significantly, and thus an increase under treatment may signal loss of control. In patients under somatostatin analogue treatment serial CgA measurements should be made at the the same interval from injection of the drug. In conclusion, CgA may be helpful when there is a known NET and may be a good marker of response to therapy, but it does not have prognostic value, has poor assay reproducibility, moderate sensitivity, and several factors other than NETs may elevate CgA (23,40,101).

As serum serotonin levels changes during the day depending on activity and stress, urinary 5-HIAA as a serotonin degradation product is a useful marker if the tumour is secreting serotonin. It is measured in 24-hour urine specimens collected in hydrochloric acid and usually measured via liquid chromatography tandem mass spectrometry (LC-MS/MS) or high performance liquid chromatography (HPLC) (23). Although not widely available, plasma values have been proven as accurate as urine analysis with suitable care, but they are not routinely available (25,102). In the presence of CS the specificity of 5-HIAA is 90% and sensitivity 70% (23). Urinary 5-HIAA values may found to be normal in non-metastatic tumours, in patients with CS who possibly secrete other biologically-active molecules, and rarely in some CS patients without diarrhoea, while a small number of normal individuals may have elevated urinary 5-HIAA (probably due to diet) (23). It may be used both for diagnosis and follow-up but it has weak cor-

Table 4. Factors increasing CgA levels in the absence of GEP-NET *(adapted from Verbeek WHM et al. EJE 2017;174:R1-R7)* (23).

Organ System or Condition	Causes
Renal system	Renal insufficiency (CKD 2-3)
Cardiovascular	Acute coronary syndrome, cardiac insufficiency, giant-cell arteritis, essential hypertension, untreated hypertension and pregnancy
Gastrointestinal	Chronic atrophic gastritis, pancreatitis, inflammatory bowel disease, irritable bowel syndrome, liver cirrhosis, chronic hepatitis, colon cancer, pancreatic adenocarcinoma, hepatocellular carcinoma
Endocrine	Pheochromocytoma, hyperparathyroidism, pituitary tumors, medullary thyroid carcinoma, hyperthyroidism, Cushing's syndrome
Inflammatory disorders	Rheumatoid arthritis, chronic bronchitis, systemic inflammatory response syndrome
Non-gastrointestinal cancers	Small-cell lung, prostate, breast, ovary, testis, neuroblastoma
Drugs	Steroid treatment, proton-pump inhibitors, H2-receptor antagonists
Other	Parkinson disease, food intake, exercise shortly before measurement

relation with severity of CS and is not accepted as a consistently reliable prognostic factor (23). Correct determination of 5-HIAA in urine requires avaidance of certain foods and drugs 72 hours before and during the day of urine sampling (Table 5) (23).

PP is a non-specific biochemical marker which is a hormone secreted by islet cells of ventral pancreas and NE cells of colon (40). Levels are increased after meals and exercise, and falsely elevated values are detected with laxative abuse, age, inflammatory processes of gut and chronic renal disease (25), and thus it rarely offers any additional benefit (91).

Pancreastatin is a post-translational processing fragment of CgA; its levels are elevated in 58-81% of NETs (91). It is not affected by PPI use, is more stable, not associated with tumour functionality, and is a good marker for GI-NETs (91). Pancreastatin has been claimed as a better predictor of tumour growth than CgA but medications, food ingestion, diabetes and hyperparathyroidism may alter test results and there are only few assays available (23,91,103).

NSE is elevated in 30-50% of NETs and mainly in poorly differentiated ones, in which case CgA may be normal (23,25). Despite its high sensitivity (nearly 100%) in ruling-out disease, due to its low specificity (in diagnosing new disease, 32.9%) the use of NSE is limited to the follow-up of patients with known diagnosis of NETs (40,104). Haemolysis can lead to significant artefactual NSE elevations as erythrocytes contain a large amount of NSE (25).

Neurokinin A is a tachykinin, predominantly secreted by midgut NETs, which has prognostic value and correlates strongly with poor outcomes in small intestinal NETs (25,105,106). Other granins, CgB and CgC, have been evaluated but

Table 5. The foods and medications that should be avoided 72 hs prior to the test and conditions that affect 5-HIAA collection result are listed below (recommendations differ and the list below may not be definitive) (23,25,38,40,45,224,225). To avoid degradation, preservatives should be used (generally hydrochloric acid) to keep the pH around 3 (224). Although many laboratories recommend keeping urine sample at 4°C in the refrigerator, there is no published data reporting degradation of 5-HIAA in acidified urine at room temperature (224). Drugs and food avoidance has been recommended for two days (224) or five days (45) before urine collection by different authors. Reference values change between laboratories but is approximately 2 to 8 mg/day (23,25,38,40,45,224,225).

Moderate elevations due to foods that contain serotonin and tryptophan- bananas (23,25,38,224), plantains (38,224), pineapple (23,25,38,224), kiwis (38,224), walnuts (23,224), almond (224), cashews (224), macadamia nuts (224), plums (23,38,224), tomatoes (38,224), tomato products (38,224), avocado (23,25,38,224), pecans (23), cantaloupe (38), dates (38), grapefruit (38), honeydew melon (38), meat, milk, cheese, chocolate (23), tea and coffee (23), black olives (38), spinach (38), broccoli (38), cauliflower (38), figs (38), eggplant (included in 23,38, excluded in 224).
Drugs that increase 5-HIAA– acetaminophen (23,25), fluorouracil (23), melphalan (23), mephenesin (23), methamphetamine (23), methysergide maleate (23), phenmetrazine (23), caffeine (23,25), acetanilide (23,38), reserpine (23,38), phenacetin (38), glyceryl guaiacolate (38), some over-the-counter sleep medications that include 5-HTP (Happy Days, Sweet Dreams)(225). [Although included in the interfering drug lists in the given references, guaifenesin (23,25), L-DOPA (23), methocarbamol (23,38), salicylates (23) and mesalamine (25) do not interfere with 5-HIAA measurements in using electrochemical or mass spectrometric assays (224)].
Drugs that decrease 5-HIAA- ethanol (25), chlorpromazine (23,38), corticotropin (23), p-chlorophenylalanine (23), heparin (23,25,38), imipramine (23,38), isoniazide (23,38), methenamine maleate (23,38), methyldopa (23,25,38), promethazine (38), tricyclic antidepressants (38,45), MAO inhibitors (25,38,45). [Although included in the interfering drug lists in the given references, L-dopa (25,38,45), phenothiazines (38,45) do not interfere with 5-HIAA measurements in using electrochemical or mass spectrometric assays (224)].
Conditions that decrease 5-HIAA- Renal impairment, being on haemodialysis
Conditions that increase 5-HIAA- Untreated patients with malabsorption (celiac disease, tropical sprue, Whipple disease, intestinal stasis, cystic fibrosis)

they are less reliable than CgA (91). Some authors recommend complementary measurement of CgB with CgA as it does not have false positivity problem (40).

As mentioned above, NT-pro-BNP seems to be an excellent biomarker for carcinoid heart disease (42).

More recent developments have focused on the use of novel technologies to quantify circulating tumor cells. Among these multianalyte technologies based on NE tumour genomics, especially the *NETest* (a multianalyte qRT-PCR assay based on fifty-one marker genes with algorithmic analysis) has a high sensitivity (>95%) and specificity (>95%) in the detection of GEP-NETs (94). However, further study is required, especially in view of its likely expense, although it does seem to offer a novel and exciting approach to assessing tumour burden.

Imaging

Imaging is used in the diagnosis, staging and monitoring treatment in NETs. In patients with hormonal hypersecretion syndromes e.g. CS, positive laboratory tests are not enough to establish the diagnosis and imaging is required to locate the potential tumour (107). On the other hand, when a tumour is identified incidentally by imaging for other purposes, the characteristics of the tumour may give helpful clues to the potential diagnosis (107).

Ultrasonography (US) frequently provides the initial diagnosis of liver metastases and contrast-enhanced US is excellent in characterisation of liver lesions that remain equivocal on CT/MRI (108). US is useful for guiding the biopsy in histopathological NET diagnosis.

Imaging modalities may be divided as anatomic, which includes computed tomography (CT, including CT enterography) and magnetic resonance imaging (MRI), and functional which includes In-111-octreotide scanning and Ga-68 somatostatin analogue PET (107). In terms of anatomic imaging, CT is better for imaging of lung NETs, while MRI is better for the assessment imaging of hepatic NET metastases. For biopsy of thoracic NET lesions CT-guided biopsy is used. CT and MRI enterography are both satisfactory for the diagnosis of small bowel NETs and may detect mucosal NETs as small as 0.5 cm (107). In functional imaging, the In-111-octreotide scan – *Octreoscan*- has been in clinical use for about thirty years and was the gold standard for NET functional imaging until recently (Figure 5). In-111-labeled octreotide binds to any tissue expressing somatostatin receptor subtype 2 (sst-2) and somewhat to 5 (sst-5). Although the octreotide scan can detect large NETs it can not reliably detect NETs less than 1 cm. PET scans using a positron-emitting radioisotope-labelled somatostatin analogue (SA) have been developed to overcome the limits of the octreotide scan. Additionally, PET is usually combined with CT to provide better signal localisation. Currently, two Ga-68 labelled tracers, DOTATATE (tetraazacyclododecane tetraacetic acid-octreotate) and DOTATOC (DOTA^0-D-Phe^1-Tyr^3-octreotide) are in use. Both are used with approximately equal accuracy, while DOTATATE has around 10-fold higher affinity to sst2. Ga-68 SA PET is certainly superior to octreotide scanning in localising NETs, and should be used whenever available (107). As most NETs do not exhibit high standardised uptake values they are negative on FDG-PET so it is not routinely used for NET imaging. However, positive uptake on an FDG-PET signals a high

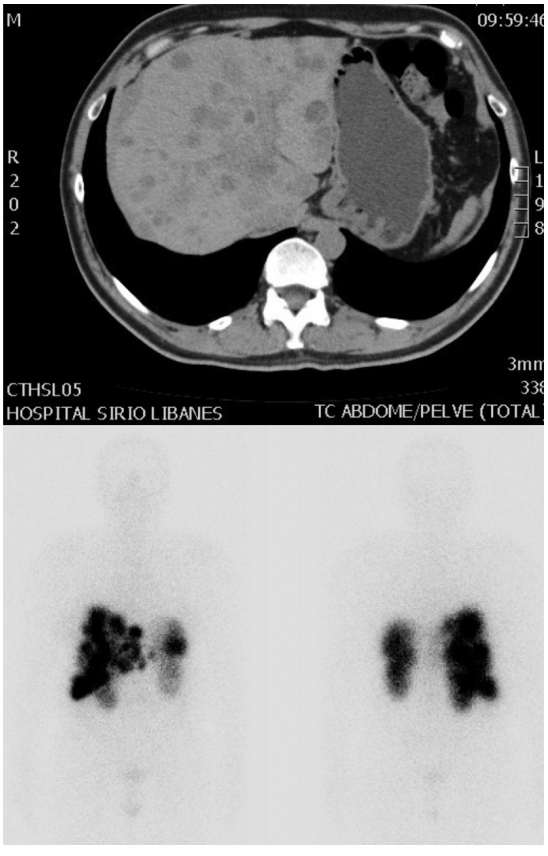

Figure 5: A CT scan showed multiple hepatic metastases, deemed unresectable by the surgeon. A new Octreoscan showed significant uptake in the liver nodules: no extrahepatic disease was detected.

proliferative potential and can be useful in choosing the optimal therapeutic strategy, and some would advise complementary FDG- and Ga-68-DOTATATE scanning in most patients, especially those with a high Ki-67 index or more which are rapidly progressive.

In the work-up of GI tract NETs, endoscopy and endoscopic ultrasound (EUS) imaging can directly examine mucosal and mural lesions and can biopsy lesions in the upper (oesophagus, stomach and duodenum) and lower (colon and rectum) GI tract; capsule endoscopy and double balloon enteroscopy are used for the same purpose in the jejunum and ileum (107). Endoscopic EUS is the most sensitive method to diagnose pancreatic NETs and is also suitable for cytology or biopsy (108). Recently, *ENETS* has released a useful guideline for the imaging of NETs (108).

Conclusions

The huge interpatient heterogeneity of NETs and their rarity render their understanding by the clinician complex unless one sees such patients on a regular basis. Endocrinologists need to be alert to the complaints of the patients which may occur over a wide spectrum. In patients with a clinical suspicion but with negative laboratory tests, follow-up may be more appropriate than immediately ruling out a NET, as the biological behaviour of the tumour may be unpredictable and diagnosis may become possible in the long term. While NETs may be seen in several outpatient clinics, a multidisciplinary network may not be available in every centre. In this situation, endocrinologists should still have contact with cardiologists for patients with right-sided cardiac disease, gastroenterologists need to consider NETs as a cause of diarrhoea and 'IBS', and dermatologists should consider NETs in patients presenting with sweating, flushing and unexplained rashes. All biomarkers may not be available in every laboratory, but a good history, physical examination, basic biomarkers and imaging studies may help the clinician to avoid missing the diagnosis and consequent delay in initiating adequate and effective therapy. It is ideal that when a NET is confirmed, they should be seen at a multidiciplinary centre where all the required diagnostic and therapeutic techniques are available.

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