Detecting Neuroendocrine Cancer

PURPOSE OF THIS GUIDE: To shorten the time to diagnosis of neuroendocrine tumors (NETs).

- The average time to diagnosis for symptomatic patients is 6 years. (incalliance.org/scan)
- The only curative intervention is surgery, but only if the diagnosis is made early enough.
- Neuroendocrine neoplasms (NENs)* are highly likely to metastasize.
- Small primary tumors may generate large metastases.
- The incidence of NENs has risen faster than the incidence of malignant neoplasms overall.

THREE PATTERNS OF PRESENTATION

1. ASYMPTOMATIC

Many NENs are discovered incidentally when imaging is done (e.g., for injury or routine colonoscopy)

2. ACUTE SYMPTOMS CAUSED BY TUMOR GROWTH

Obstruction, bleeding, or pain may come from both the primary tumor and the metastases (lymph nodes, liver, bone)

3. FUNCTIONAL (HORMONAL) TUMOR SYNDROMES

About a third of patients experience symptoms from the excess production of hormones caused by the tumors. These patients are likely to repeatedly seek a doctor's help. Symptoms of NETs are varied and typically occur in other more common diseases, which makes diagnosis a challenge.

A PATIENT JOURNEY

Gayle Morell began having symptoms in 1994, when she was in her early 20s and in pharmacy school. She was unable to get from her dorm to her classes because of digestive issues and related panic attacks. Gayle was misdiagnosed for 18 years before a doctor suspected a functional neuroendocrine tumor. She has been experiencing a much higher quality of life for the past 10 years and is forever grateful to the doctor who found the answer.

A WOLF IN SHEEP'S CLOTHING

Neuroendocrine cells are widely distributed in the body and NENs have a wide range of primary sites with significant variation in presentation. The symptoms in the chart reflect this range of sites.

- 63% originate in the digestive tract (small intestine, rectum, pancreas, stomach, etc.)
- 23% originate in the lungs
- 14% unknown primary and rare sites (uterus, ovary, testis, breast, adrenal glands, etc.)

SYSTEM	FEATURES OF FUNCTIONAL NENS	FREQUENTLY DIAGNOSED AS
GASTROINTESTINAL	Diarrhea, jaundice, abdominal pain and swelling, recurrent ulcers, intestinal obstruction, GI bleeding, gallstones, heartburn	Irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), peptic ulcer, hiatal hernia, gallstones
DERMATOLOGICAL	Flushing, rashes	Menopause, drug reactions
CARDIOPULMONARY	Right-sided heart failure and valvular dysfunction, palpitations, wheezing, blood clots	Anxiety, stress, asthma, primary cardiac disease
ENDOCRINE	Hypoglycemia or hyperglycemia	Diet-related blood sugar problems, diabetes
NEUROPSYCHIATRIC	Mood changes, syncope	Anxiety, depression
RENAL	Electrolyte disturbances, dehydration	Infectious diarrhea

**Neuroendocrine neoplasm (NEN) is an umbrella term that encompasses low and high grade well differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinomas (NECs).*

NEUROENDOCRINE TUMOR SYNDROMES & DIAGNOSTIC TESTING

Differentiating NETs from other disease states is helped by the patterns of the hormonal syndromes in the chart below, e.g., if persistent watery stool is accompanied by dry flushing or wheezing, carcinoid syndrome may be present as opposed to the far more common irritable bowel syndrome or inflammatory bowel disease.

Imaging Studies support the diagnosis and establish the extent of disease.

CT and/or MRI are typically the first studies pursued if NEN is suspected.

- Arterial phase CTs are important due to robust vascularization of tumors.
- MRIs with contrast have slightly higher yield than triple-phase CT scans in detecting liver metastases.

DOTATATE-PET CTs

- The gold standard for detecting well-differentiated NETs, usually performed at specialized centers
- Often negative for poorly differentiated NECs or very small functional tumors

FDG PET-CTs

- Often high yield for poorly differentiated NECs (but low for NETs)

Pathologic Biopsy confirms the diagnosis of neuroendocrine cancer.

For information about management of neuroendocrine cancer:

- thehealingnet.org/topics-nets
- nanets.org/net-guidelines-library
- nccn.org/guidelines/category_1

SYNDROME *(frequency)* *Scan QR code to view related Case Presentation*	**SYMPTOMS**	**DIAGNOSTIC TESTING***
CARCINOID SYNDROME *(most common)* *Case #1*	Flushing, diarrhea, night sweats, wheezing, pellagra, heart valve damage	5-HIAA (preferred) plasma or urine Blood/serum serotonin can be considered
ZOLLINGER ELLISON SYNDROME *Gastrinoma* (*frequent*) *Case #2*	Diarrhea, peptic ulceration (usually duodenal), heartburn, abdominal pain	Serum gastrin (Proton pump inhibitor use can falsely elevate levels but should only be discontinued in a controlled setting.)
INSULINOMA (*frequent*) *Case #3*	Hypoglycemia, (neuroglycopenia or sympathetic overdrive), obesity	Fasting plasma insulin, proinsulin, c-peptide
PHEOCHROMOCYTOMA adrenal PARAGANGLIOMA extra-adrenal (*rare*)	Hypertension, headache, sweating, palpitations	Plasma free metanephrines, 24-hr urine catecholamines, metanephrines
ACTHOMA OR ECTOPIC CUSHINGS (*rare*)	Bruising, proximal myopathy, central weight gain, striae, glucose intolerance	Plasma cortisol, ACTH
GLUCAGONOMA (*rare*)	Diabetes/hyperglycemia, cachexia/weight loss, necrolytic migratory erythema, anemia, venous thrombosis	Plasma glucagon
VIPOMA (*rare*)	Watery secretory diarrhea, electrolyte disturbances, hypokalemia, achlorhydria	Plasma VIP

**False negatives and positives can occur with these tests.*

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