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Neuroendocrine Tumors

A guide to common tests for diagnosis and monitoring

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A word about neuroendocrine nomenclature

This brochure uses the nomenclature established in the 2010 *WHO Classification of Tumours of the Digestive System*[1] to classify different types of neuroendocrine neoplasms.

The WHO naming convention categorizes these neoplasms into 2 groups:

- Neuroendocrine tumors (NETs): well-differentiated neoplasms that can be divided into grade 1 (G1) and grade 2 (G2) depending on proliferation and histology
- Neuroendocrine carcinomas: poorly differentiated grade 3 (G3) neuroendocrine neoplasms

Introduction

The diagnosis and monitoring of neuroendocrine tumors (NETs) can be challenging.[2] NETs can form in multiple locations throughout the body,[3] and although they share a number of common features, the clinical presentation may vary according to site of origin, secretory potential, and histologic subtype.[4]

Patients may be asymptomatic or present episodically with nonspecific symptoms that can be mistaken for other more common conditions,[2] including irritable bowel syndrome (IBS), diabetes, and asthma.[2,3] Symptoms may include diarrhea, hypoglycemia, dramatic weight loss, and wheezing depending on the site and characteristics of the tumor.[2]

It is not unusual for patients to suffer for years before NETs are diagnosed. In fact, the estimated time to diagnosis of certain NETs can reach 5 to 7 years.[5] NETs are often diagnosed after they metastasize, and 50% of all patients with G1 and G2 NETs have regional or distant metastases at diagnosis.[6] For patients with G1 and G2 NETs with distant metastases the 5-year survival rate is only 35%.[6]

A number of tools are available to help physicians identify, diagnose, and monitor NETs.[7] This brochure provides an overview of commonly used tests that may help to diagnose and monitor patients with NETs.

Imaging techniques

Computed tomography (CT)

Rationale

- CT is a widely available tool for the localization, staging, and monitoring of solid neoplasms, including NETs[8]

Methodology

- CT images may be obtained with a helical or spiral scanner using different contrast agents.[8-10] NETs and their metastases may appear to be isodense depending upon the phase of contrast.[8] In patients with metastatic NETs, triphasic CT scans should be used[11]

Advantage

- CT scanners are widely available,[8] offer good resolution for both intrahepatic and extrahepatic disease, and may help identify bone metastases[12]

Disadvantage

- CT may be less sensitive than MRI in identifying small-volume hepatic disease[9,13,14]

Magnetic resonance imaging (MRI)

Rationale

- MRI is a well-recognized imaging technique, useful in the localization and monitoring of NETs and their metastases[8,9,14]

Methodology

- MRI is a reasonable alternative to CT, as neoplasms can be visualized without contrast using T1 and T2 images, reducing the variability sometimes seen on contrast CT[15]

Advantage

- The sensitivity of MRI in detecting hepatic metastases may be superior to that of CT[14]

Disadvantage

- MRI may not be as useful as other modalities in identifying and following extrahepatic disease[14,15]

Imaging techniques

Octreoscan™

Rationale

- Octreoscan is a whole-body imaging technique that identifies primary NETs and metastases that express somatostatin receptors[3]

Methodology

- Patients are intravenously administered a radiolabeled somatostatin analog (SSA) (^{111}In-octreotide or ^{111}In-pentetreotide) prior to scintigraphy with a large-field gamma camera[13,16]

Advantages

- Octreoscan may identify disease sites not previously identified with cross-sectional imaging[15]
- Octreoscan provides information on somatostatin receptor status[3]

Disadvantages

- Octreoscan does not identify neoplasms that are not somatostatin receptor-positive (approximately 10% of NETs)[3]
- The resolution of Octreoscan for neoplasms ≤7 mm is limited[9]
- Octreoscan may be associated with false positives. Uptake can be seen in normal bowel tissue and in other conditions (including lymphomas and lung cancer)[3]

Imaging techniques

^{131}Iodine metaiodobenzylguanidine (MIBG) scintigraphy

Rationale

- MIBG scintigraphy is an imaging test that uses injected radioisotope and a specialized scanner to locate, confirm the presence of, and monitor primary and/or metastatic pheochromocytoma and neuroblastoma, and certain other NETs[17-19]

Methodology

- Prior to scintigraphy with a planar gamma camera, patients are intravenously administered MIBG, which attaches to cells of the neoplasm[19,20]

Advantages

- MIBG scintigraphy may help localize primary and/or metastatic pheochromocytomas and neuroblastomas[17]
- Results of one study support the use of dual-tracer imaging with MIBG, especially in identifying functioning metastases[18]

Disadvantages

- MIBG scintigraphy may be less effective for identifying primary pheochromocytoma than for identifying metastases[21]
- Only a minority of other NETs are MIBG-avid; MIBG typically is not used as a standard imaging technique for NETs, apart from pheochromocytoma[18]

Imaging techniques

Positron emission tomography (PET)

Rationale

- PET may be useful for identifying small NETs. Chemical tracers are used to detect metastasis[5]

Methodology

- ^{18}Fluorodeoxyglucose (FDG)-PET is commonly used in the staging of many malignancies. A newer form of PET using a gallium-68 (^{68}Ga)-labeled somatostatin analog (SSA) is currently under investigation for NETs[5]

Advantages

- PET may be helpful in patients with pheochromocytoma and in this setting may be more sensitive than MIBG or cross-sectional imaging[5]
- ^{68}Ga PET is investigational in NETs and may be useful in their detection[22]
- Other investigational techniques include ^{11}C-labeled and ^{18}F-labeled amine precursors, such as serotonin and levodopa[5]

Disadvantages

- FDG-PET is often not helpful in NETs due to their low metabolic activity[5]
- The use of newer PET techniques in this patient population is still under investigation[23]

Endoscopic techniques

Endoscopy

Rationale

- Endoscopy can be a valuable tool for the discovery and monitoring of NETs in the gastrointestinal (GI) tract, particularly in the stomach, duodenum, and rectum.[3] It is not unusual for an asymptomatic NET to be an incidental finding during routine endoscopy[3]

Methodology

- Flexible endoscopes can be used to view both the upper and lower GI tracts from the pharynx to the upper duodenum and from the anus to the terminal ileum[24]
- Double-balloon enteroscopy (DBE) is a procedure in which a latex balloon is affixed to the distal ends of both endoscope and overtube. Coordinated inflation and deflation of the balloons aid in the advancement of the endoscope deep into the small intestine[25]
- Capsule endoscopy (CE) (also called video capsule endoscopy) is a reliable, noninvasive imaging technique that allows for visualization of the entire small bowel. In studies, patients swallowed a small, pill-shaped capsule that transmitted video images as it traveled through the GI tract[25,26]

Advantages

- Most endoscopic procedures provide an opportunity to biopsy the lesion[24]
- CE is minimally invasive compared with other endoscopic techniques and may allow visualization of the small intestine[25]
- DBE has been shown to localize lesions that were missed in prior CE[25,26]

Disadvantages

- CE is relatively insensitive in identifying small-bowel NETs; one study suggests that it identifies tumors in only about 33% of cases[25]
- In general, with the exception of CE, endoscopic examination can be difficult to perform in the evaluation of neoplasms arising in the small intestine[25]
- Some endoscopic techniques, such as DBE, are demanding and require specialized training[26]
- Many endoscopic procedures require sedation[24]

Endoscopic techniques

Endoscopic ultrasound (EUS)

Rationale

- EUS is a relatively noninvasive procedure that may be useful in the localization and diagnosis of pancreatic NETs[27,28]

Methodology

- This specialized endoscopic examination is performed using an echoendoscope. For the visualization of pancreatic NETs, the echoendoscope is advanced to the descending duodenum and then slowly withdrawn to the stomach[27]

Advantages

- EUS is able to localize small neoplasms, such as those in the pancreatic head, as well as detect neoplasms in the duodenal wall[8,27,28]
- The detection of lymph node enlargement during EUS may aid in staging[8]

Disadvantage

- EUS requires specialist training and may not be available at all facilities[8]

Echocardiogram

Rationale

- An echocardiogram can help assess patients for carcinoid heart disease[11]
  - Cardiac heart disease occurs in 11% to 66% of patients with carcinoid syndrome
  - An echocardiogram should be considered to assess these patients

Biomarkers

Please note: For diagnostic accuracy, as well as continued disease management, preliminary biomarker results should be confirmed with imaging and endoscopic techniques, along with histopathologic analysis, when appropriate.[2]

Chromogranin A (CgA)

Rationale

- CgA is a general circulating NET marker that is elevated in up to 90% of patients with NETs,[29,30] and levels are independent of hormone secretion.[30,31] Despite certain limitations, CgA is a useful circulating marker for GEP-NETs.[29,32]

Methodology

- CgA can be measured in either plasma or serum.[33] Most test kits measure CgA levels by radioimmunoassay (RIA) or enzyme-linked immunosorbent assay (ELISA)[34]

Interpretation of results

- Elevated CgA levels may indicate the presence of NETs and may have prognostic significance. They can also be used to help monitor disease progression and may be correlated with disease burden and survival.[35,36] Patients with certain metastatic NETs may even have very high levels (up to 1000 times normal ranges) of CgA.[37] The clinician should keep in mind that CgA may be elevated in a number of conditions not related to NETs. These include concomitant use of PPIs, and renal and liver diseases[32]

Advantages

- Across all NET types, the sensitivity of CgA ranges from 60% to 90% and specificity ranges from 68% to 100%[32]
- CgA levels are independent of hormone secretion[31]
- When monitoring disease, CgA levels may start to increase before changes in neoplasm size can be seen on CT or MRI[38]

Disadvantages

- Some conditions can increase CgA levels without a NET being present. For example, patients receiving proton pump inhibitor (PPI) therapy, and those with chronic gastritis, inflammatory chronic diseases, renal or hepatic dysfunction, and arterial hypertension, may have elevated CgA levels[2,32]
- Test results vary among laboratories and assays,[34] and levels of CgA secretion differ by neoplasm type. CgA values should not be compared across studies[34]

Biomarkers

5-Hydroxyindoleacetic acid (5-HIAA)

Rationale

- 5-HIAA, the primary metabolite of serotonin, has diagnostic and prognostic value in NETs associated with carcinoid syndrome.[2,3,39] Carcinoid syndrome can occur in 8% to 35% of NETs[39]

Methodology

- 5-HIAA is measured by high-performance liquid chromatography in a 24-hour urine sample[32]

Interpretation of results

- The normal range for 5-HIAA is 2 to 8 mg per 24 hours. Elevations in 5-HIAA are predictive of poor outcome[40] and progressive carcinoid heart disease[41]

Advantage

- 5-HIAA has diagnostic and prognostic value in NETs associated with carcinoid syndrome[2,3,39]

Disadvantages

- Only a minority of NETs secrete serotonin. Therefore, the sensitivity of 5-HIAA in NETs ranges from 5% to 50% (65%-85% in ileal NETs), and 5-HIAA is not elevated in NETs that do not secrete serotonin[2,32]
- 5-HIAA may be falsely elevated and possibly increased by ingestion of foods high in serotonin, such as avocados, bananas, pineapples, walnuts, and kiwifruit. Certain medications, including guaifenesin, acetaminophen, salicylates, and L-dopa, may also affect 5-HIAA. Patients should be instructed to avoid these foods and medications before and during urine collection[3]
- The measurement of 5-HIAA requires the collection of urine over a 24-hour period,[32] which patients may find inconvenient

Neuron-specific enolase (NSE)

Rationale

- NSE is a blood marker located in neuroendocrine cells[42] that is elevated in patients with functional as well as nonfunctional neoplasms. It is not a secretory protein but, rather, is located in cell cytoplasm,[43] entering the circulation as a result of neoplasm lysis[44]

Methodology

- NSE is used to confirm the presence of neuroendocrine cells and the diagnosis of neuroendocrine neoplasms. Due to its lack of sensitivity, NSE should be used in correlation with other indicators of neuroendocrine cells[45]

Advantages

- Highly specific indicator used to identify neuroendocrine cells and neoplasms. One study showed 100% specificity[45]
- Commonly used in the diagnosis and monitoring of small cell lung carcinomas or neuroblastomas[43]

Disadvantage

- Lacks sensitivity. One study showed 33% sensitivity[45]

Synaptophysin (SNAP)

Rationale

- Synaptophysin is a 38 kilodalton protein molecule that is a component of the membrane of presynaptic vesicles. Widely distributed in neurons and neuroendocrine cells and their neoplasms, SNAP is a reliable broad-spectrum neuroendocrine marker and a fairly sensitive indicator for both low- and high-grade malignancies[42]

Methodology

- SNAP can be used to help confirm a diagnosis of a neuroendocrine neoplasm, although SNAP should be used with CgA and not as the sole test for NETs[42]

Advantages

- Highly sensitive
- SNAP is expressed independent of other neuronal differentiation markers[46]

Disadvantages

- Lacks specificity[42]
- The occurrence of SNAP in many, though not all, NETs is not completely understood[46]

Specific biochemical tests for functional NETs

Overview

- In addition to broad markers such as CgA, some biochemical substances secreted by NETs are specific to the type of neoplasm.[2] Excessive levels of these substances may suggest the presence of a NET. In general, biochemical evidence of a NET is not sufficient to make a diagnosis, and histologic confirmation of a NET is required[2]

Insulinomas

- A history of hyperinsulinemic-hypoglycemic syndrome is a diagnostic indicator[47]
- Standard 72-hour fasting test should be used to measure glucose (<45 mg/dL) and insulin (>30 pmol/L) levels and to exclude all differential diagnoses of insulinoma, except for very rare conditions[10,47,48]
- Measurement of proinsulin and C-peptide levels may be helpful[49]

Note: Insulin levels are increasingly being measured by immunochemiluminescent assays or specific immunoradiometric assays that do not cross-react with proinsulin. These assays result in lower insulin values that will not compare accurately with results from radioimmunoassay.[49]

Gastrinomas

- Diagnosis often begins with determination of fasting serum gastrin (≥1000 pg/mL) levels and gastric pH (<2.5)[10]
- Stop proton pump inhibitor (PPI) therapy at least 1 week prior to testing[50,51]
- Over repeated testing, <0.5% of patients with Zollinger-Ellison syndrome (ZES) will have normal values[47,48]

Note: PPI withdrawal in patients with ZES may induce severe hypersecretion and should be done by experts in a controlled setting.[51]

Glucagonomas

- Diagnosis can be made when plasma glucagon levels are increased to 500 to 1000 pg/mL (normal range <50 pg/mL)[49]
- Symptoms include glucose intolerance, weight loss, and erythematous rash[49]

Specific biochemical tests for functional NETs

VIPomas

- Diagnosis is based on elevated levels (>200 pg/mL) of plasma vasoactive intestinal peptide (VIP) in patients with large-volume secretory diarrhea (>700 mL/d)[49,52]

Somatostatinomas

- Symptoms include diabetes mellitus, gallbladder disease, diarrhea, weight loss, anemia, and steatorrhea[49]
- Diagnosis can be confirmed by elevated plasma somatostatin levels in the setting of histologically confirmed NET[49]

Other types of functional NETs

- Other hormones secreted by NETs include growth hormone-releasing hormone (from GHRHomas) and adrenocorticotropic hormone (from ACTHomas)[49]

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