Biochemical Testing in Neuroendocrine Tumors

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KEYWORDS

• Neuroendocrine tumor • Carcinoid • Tumor marker • Diagnostic test
• Prognostic indicator • Disease monitoring

KEY POINTS

- Neuroendocrine tumors secrete chemicals that can be used as circulating biomarkers.
- Tumors originating from different sites may differ in the tumor markers secreted.
- All tumor markers have potential for false-positive and false-negative results.

Neuroendocrine cells are widely distributed throughout the body. They are characterized by the ability to produce, store, and secrete peptides and biogenic amines, in response to neural, chemical, and other stimuli. Most tumors arising from these cells are found in the intestine (particularly the jejunoileum), pancreas, and lung. As with tumors arising in other endocrine organs, the neuroendocrine tumors (NET) may be functional (secreting 1 or more products associated with a clinical syndrome) or nonfunctional. Nonfunctional tumors either fail to secrete any known product, or may secrete a product with no known associated clinical outcome. Diagnosis of NET involves analysis of the patients' clinical features, imaging (including somatostatin receptor-based imaging), biomarkers, and biopsy. Blood or urine concentrations of amines and peptides secreted by NET have proved to be useful biomarkers for the diagnosis and monitoring of these tumors. Although biomarkers may include cellular, biochemical, or molecular alterations that are measurable in biological media such as human tissues, cells, or fluid, we focus herein on currently available biochemical testing of blood or urine for gastroenteropancreatic (GEP) and lung NET.

Timely diagnosis of NET can be challenging for multiple reasons:

1. The incidence of these tumors is low, although it does seem to be increasing. Incidence of NET from all sites was 5 in 100,000 in 2004, increased from 1 in 100,000 in 1973.[1]

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2. The primary tumor may be very small and is often metastatic at the time of diagnosis. Data from US and European cancer registries suggest that 30% to 75% of patients have distant metastases at the time of diagnosis.[1–3]
3. Clinical presentation may vary depending on the site of origin of the primary tumor. Traditionally, NET are described as arising from the foregut (bronchopulmonary, thymus, gastric, proximal duodenum, pancreas), midgut (distal duodenum, jejunum, ileum, ascending colon), or hindgut (distal colon, rectum). Primary tumors arising from these different anatomic zones differ in their tumor secretions (Table 1). For example, tumors originating in the midgut secrete serotonin and are more likely than tumors of other origins to present with carcinoid syndrome. Carcinoid syndrome, when present, may include the following symptoms: flushing (94%), diarrhea (78%), abdominal cramping (50%), valvular heart disease (50%), telangiectasia (25%), wheezing (15%), or edema (19%).[4–6] Pulmonary tumors are less likely to secrete serotonin (although they may secrete the serotonin precursor, 5-hydroxytryptophan) and more likely to secrete histamine. Although foregut tumors can present with flushing and wheezing, the full carcinoid syndrome with diarrhea is unusual. Hindgut tumors rarely secrete serotonin or cause carcinoid syndrome.
4. The clinical presentation may vary between tumors of the same originating site, based on the tumor grade and stage. Some biochemical tests have been suggested as markers of tumor grade or differentiation, for example, neuron-specific enolase. Although only about 10% of NET present with features of carcinoid syndrome, this number increases with greater tumor bulk (later stage), especially when liver metastatic disease increases.

Because of the low incidence, early diagnosis requires highly sensitive and specific biomarkers. It should be noted, however, that although the incidence of NET is low, the prevalence is relatively high because of slow tumor progression. The estimated prevalence is 3-fold that of pancreatic cancer and is greater than that of esophageal and gastric cancers combined.[1] Because of relatively slower progression and prolonged follow-up period, markers of tumor growth, response to therapy, prognosis, and differentiation state are important.

Table 1
Neuroendocrine tumor sites of origin, potential associated symptoms, and specific biomarker tests

Primary Tumor Location	Symptom	Test
Bronchopulmonary and thymic	Local symptoms Flushing, wheezing Cushing syndrome	CgA, serotonin, 5-HIAA, 5 hydroxytryptophan ACTH, cortisol
Jejunoileal	Local symptoms Carcinoid syndrome	Serotonin CgA Pancreastatin NKA
Colorectal	Local symptoms Incidental findings	CgA
Pancreaticoduodenal		
Nonfunctional	Local symptoms/incidental	CgA, (serotonin), PP
Functional (see Table 2)	Specific syndrome	See Table 2

Abbreviations: 5-HIAA, 5-hydroxyindoleacetic acid; ACTH, adrenocorticotrophic hormone; CgA, chromogranin A; NKA, neurokinin A; PP, pancreatic polypeptide.